Epidemiology of Acute Infections among Patients with Chronic Kidney Disease

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The objectives of this review were (1) to review recent literature on the rates, risk factors, and outcomes of infections in patients who had chronic kidney disease (CKD) and did or did not require renal replacement therapy; (2) to review literature on the efficacy and use of selected vaccines for patients with CKD; and (3) to outline a research framework for examining key issues regarding infections in patients with CKD. Infection-related hospitalizations contribute substantially to excess morbidity and mortality in patients with ESRD, and infection is the second leading cause of death in this population. Patients who have CKD and do not require renal replacement therapy seem to be at higher risk for infection compared with patients without CKD; however, data about patients who have CKD and do not require dialysis therapy are very limited. Numerous factors potentially predispose patients with CKD to infection: advanced age, presence of coexisting illnesses, vaccine hyporesponsiveness, immunosuppressive therapy, uremia, dialysis access, and the dialysis procedure. Targeted vaccination seems to have variable efficacy in the setting of CKD and is generally underused in this population. In conclusion, infection is a primary issue when caring for patients who receive maintenance dialysis. Very limited data exist about the rates, risk factors, and outcomes of infection in patients who have CKD and do not require dialysis. Future research is needed to delineate accurately the epidemiology of infections in these populations and to develop effective preventive strategies across the spectrum of CKD severity.


Recent data have reinforced the growing public health burden of chronic kidney disease (CKD). Between 1999 and 2004, an estimated 13% of the US adult population had CKD as compared with 10% in 1988 through 1994 (1). In 2005, approximately 485,000 people received renal replacement therapy, 340,000 of whom were receiving maintenance dialysis (2). It is currently projected that there will be approximately 710,000 prevalent end-stage renal disease (ESRD) patients by the year 2015 (3). The importance of this information on the changing epidemiology of kidney disease is that the advanced stages of CKD and ESRD (stage 5 CKD requiring renal replacement therapy) are associated with a marked increase in the risk for all-cause and cardiovascular morbidity and mortality (2,4). For patients who have ESRD and initiate maintenance dialysis, the overall 1-yr mortality rate is 20%, and the 5-yr mortality rate exceeds 60% (2). Importantly, there is a graded, increased risk in the annual incidence of all-cause mortality with declining glomerular filtration rate (GFR) among patients with mild to moderate CKD (4). Of interest, acute infections (bacterial, viral, and fungal) contribute substantially to the high rates of hospitalization and mortality in patients with ESRD (2). Limited existing data suggest that annual mortality rates in the dialysis population are increased by 10-fold for pneumonia and 100-fold for sepsis compared with the general population (5,6). Even less is known about the role of infections among patients with mild to moderate CKD.

In this review, we examine the risks and associated complications of acute infections in patients with CKD and ESRD and discuss a proposed framework for addressing existing knowledge gaps in this area. For the purposes of this review, CKD refers to patients who are not receiving renal replacement therapy (i.e., dialysis or transplant), and ESRD refers to patients who have stage 5 CKD and are receiving maintenance dialysis (hemodialysis or peritoneal dialysis). Although the physiologic effects of kidney dysfunction are a continuum, a distinction between CKD requiring compared with not requiring dialysis therapy is made because the population characteristics and risk factors for infection differ in these populations, and outcomes among patients who receive dialysis are affected by both the underlying kidney disease and the dialysis therapy. The kidney transplant population is a separate subgroup of patients with ESRD, with unique risk factors for infection, and is not discussed in this review.

For this review, we searched PubMed for relevant articles using the following keywords: “infection” “chronic kidney disease,” “end-stage renal disease,” “chronic renal failure,” “dialysis,” “vaccination,” “influenza vaccine,” “hepatitis B vaccine,” and “pneumococcal vaccine” through December 31, 2007. On
the basis of a review of the titles and the abstracts of identified articles, articles were selected for full review. In addition, references from reviewed articles were hand searched for additional articles. Included in this review are the articles that we considered to be informative and relevant to the epidemiology of infections and efficacy of vaccinations in the setting of kidney disease.

Epidemiology of Infections
Incidence and Prevalence of Acute Infections in CKD and ESRD

CKD. Very few studies have examined the incidence or prevalence of infections among patients with CKD, and no published data describe CKD stage-specific infection rates. Among Medicare beneficiaries aged ≥66 yr, patients with diagnosed CKD seem to have substantially higher rates of hospitalization for diagnoses of pneumonia and sepsis compared with patients without diagnosed CKD (2). In addition to an increased incidence of being hospitalized with infections, patients with CKD have longer lengths of hospital stay during infection-related admissions compared with patients without CKD (7).

ESRD. Acute infection is a common cause of hospitalization in patients with ESRD. Despite that hospitalization rates have stabilized in the ESRD population since 1993, the relative contribution of infection-related hospitalizations has increased (2). Between 1996 and 2001 among a US Medicare cohort of patients who newly started dialysis, the 1-yr incidence of infection-related hospitalizations was 32% for those who received hemodialysis and 24% for those who received peritoneal dialysis; the 3-yr incidence exceeded 50% in both groups (8).

The Hemodialysis (HEMO) Study provides further insights into the risk for infections and associated complications in patients who receive long-term hemodialysis. The HEMO Study was a randomized trial that examined the effect of dialysis dose and membrane flux on hemodialysis outcomes among 1846 patients and secondarily evaluated infection-related hospitalizations and deaths (9). Overall, the study cohort was younger, consisted of more black patients, and had a lower prevalence of dialysis catheters compared with the general population of patients who received hemodialysis in the United States during the study period; in addition, patients with significant comorbidity or low serum albumin at entry were excluded (10). Despite potential limited generalizability of these findings, the HEMO Study provided important information about infections in this population and is one of the few studies to provide an in-depth examination of the range of infections in the setting of maintenance hemodialysis. During a mean follow-up of 2.8 yr, 1696 infection-related hospitalizations were identified, which corresponded to a very high annual infection rate of 35% (10). The HEMO Study found that infection-related hospitalizations were not related to vascular access in 77% of identified cases. Rather, the most common reason was hospitalization for an infection of unknown source, which included sepsis, bacteremia, and abscess not classifiable into other organ-specific infections (e.g., cardiac, respiratory, hepatobiliary), accounting for 35% of all infection-related hospitalizations. The next most common infections were vascular access related and respiratory, which were responsible for 23% and 22% of all infection-related hospitalizations, respectively, in this sample (10).

Among US Renal Data System (USRDS) Wave 2 Study participants with Medicare as the primary payer, the rates of first hospitalization for septicemia and/or bacteremia that did not require hospitalization were examined during a median follow-up of 3.2 yr. In this sample, >40% of patients were receiving peritoneal dialysis. The rate (per 100 person-years) was 7.0 for first episode of septiceemia that required hospitalization, 5.9 for first episode of bacteremia that did not require hospitalization, and 10.4 for either event (11). In a previous study that examined incident dialysis patients during a mean follow-up of 7 yr, the risk for hospitalization for septicemia was 11.7% for hemodialysis patients and 9.4% for peritoneal dialysis patients (12).

It is interesting that in a single-center cohort study of 181 incident dialysis patients identified between 1999 and 2005, peritoneal dialysis and hemodialysis patients had similar overall crude rates of infection, but the type and timing of infections differed by modality. Among peritoneal dialysis patients, peritonitis accounted for a significant portion of infections, and no episodes of bacteremia were observed. Among hemodialysis patients, bacteremia accounted for a significant portion of infections (13).

As highlighted in the above literature, the majority of studies examined only infections that required hospitalization. Given the outpatient management of many serious infections with intravenous and intraperitoneal antibiotics in patients who receive maintenance dialysis, the reported rates likely substantially underestimate the true burden and impact of infections in the ESRD population (13).

Outcomes of Infection in CKD and ESRD

Hemodialysis. Among participants in the HEMO Study who died during follow-up, infection was the primary assigned cause of death in 23%. The overall probability of death during an infection-related hospitalization was 15% (10). The likelihood of death during hospitalization varied with respect to the cause of infection, ranging from as low as 7% for vascular access-related infections to as high as 30% for cardiac-related infections (10). Older age, comorbidity burden, dialysis vintage, and lower serum albumin were associated with an increased risk for infection-related death (10). When examining the first infection-related hospitalization, a severe outcome (defined as death, intensive care unit stay, or hospitalization ≥7 d) was observed in 58% of participants (14).

Peritoneal Dialysis. It is interesting that few comparable studies describing infection-related outcomes are available among peritoneal dialysis patients. Although numerous studies have examined the risk for peritonitis and associated outcomes such as hospitalization, catheter loss, and technique failure, few studies have examined the broader spectrum of acute infections in the setting of peritoneal dialysis. For example, peritoneal dialysis patients seem to have similar rates of hospitalization for peritonitis as for other types of infection (13), and this
highlights the need for additional investigation into the outcomes across the range of acute infections in this population.

**Risk Factors for Infection in CKD and ESRD**

Numerous risk factors predispose patients with CKD and ESRD to infection (Figure 1). Potential risk factors for infection among patients with CKD or ESRD include advanced age, high burden of coexisting illnesses, hypoalbuminemia (10,15), immunosuppressive therapy (16), nephrotic syndrome (17), uremia, anemia, and malnutrition (18,19). Once maintenance dialysis is initiated, additional potential risk factors for infection include vascular access used for dialysis, the dialysis procedure itself, and iron overload (18,19). In fact, ESRD may be considered a state of acquired immunodeficiency (18). Although many of these risk factors have been previously studied in the ESRD population, they may also convey excess risk among those with moderate to advanced CKD (not yet requiring dialysis) given that kidney disease is a continuum and many of these conditions (e.g., anemia, malnutrition) are present well before the initiation of dialysis.

**Demographic Characteristics and Comorbidity Burden.**

The CKD and ESRD populations are characterized by older age and high rates of diabetes and a substantial burden of coexisting illnesses (2,4). In addition, there is a high prevalence of functional disabilities such as dementia, extremity amputation, and limb paresis or paralysis (2), which may further predispose to acute infections. Among HEMO Study participants, diabetes, other coexisting illnesses, and low serum albumin were associated with a higher risk for acute infection (10).

**Cause of Kidney Disease and Selected Therapies.**

Nephrotic syndrome, especially in children, has been associated with serious bacterial infections (20–22). Peripheral edema, urinary loss of alternative complement pathway factors, and defective leukocyte and splenic function contribute to the risk for infection in nephrotic syndrome (17). A number of kidney diseases, including idiopathic glomerular diseases and autoimmune-related kidney diseases, are managed with systemic immunosuppressive therapy. As expected, immunosuppressive therapy, particularly cytotoxic therapy, predisposes to infection (23,24), and immunosuppressive therapy has been associated with an increased risk for bacteremia in maintenance hemodialysis patients (16).

**Alterations in the Immune System.**

Alterations in the host immune response have primarily been studied in the ESRD population. In these patients, the function of polymorphonuclear white blood cells, lymphocytes, and monocytes is altered, resulting in an impaired host response to infection (25–27). Malnutrition, increased intracellular calcium, iron overload, dialysis membranes, and uremic toxins (i.e., circulating factors that inhibit granulocytes) contribute to impaired polymorphonuclear leukocyte function (18,26). In the setting of kidney failure, T lymphocyte (28), monocyte, and monocyte-derived dendritic cell function is also impaired (29); however, these issues have not been adequately investigated in patients with CKD.

**Reduced Responsiveness to Vaccines.**

Patients with ESRD have a reduced response to vaccinations, which is ascribed to alterations in the immune system (27). In general, patients with kidney dysfunction have been observed to have lower rates of vaccine response and a more rapid decline of antibody levels after vaccination (30). Although lower vaccine responsiveness has been widely recognized in the ESRD population, to what extent moderate to advanced CKD modifies vaccine responsiveness remains unclear (31,32).

**Vascular or Peritoneal Dialysis Access.**

Recurrent needle sticks of arteriovenous fistulas/grafts or dialysis catheters (peritoneal or vascular) are a potential risk factor for infection because they disrupt the protective cutaneous barrier (18). Although all forms of dialysis access are a potential source of

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**Figure 1. Risk factors and outcomes of infection in kidney disease. AVF, arteriovenous fistula; AVG, arteriovenous graft.**
infection, certain types of access are associated with significantly higher risks for infectious morbidity and mortality. Compared with arteriovenous fistulas, dialysis catheters are associated with a nearly two-fold increased risk for bacteremia or sepsis (11) and a more than two-fold increased risk for infection-related death (10).

Enhanced Exposure to Pathogens through Excess Health Care Use. No published study has directly addressed whether frequent health care utilization in patients with CKD or ESRD is a potential risk for acute infections; however, rates of hospitalization increase markedly as kidney function declines (4), and the number of physician visits increases substantially before the initiation of renal replacement therapy (33). Physician visits, emergency department visits, hospitalizations, and routine care in dialysis centers increase an individual’s exposure to infections from other patients, health care providers, and medical facilities and may contribute to the high rates of acute infection in CKD and ESRD populations.

Preventive Strategies

Given the risks and associated complications of infections in patients with CKD and ESRD, strategies to prevent infections effectively are of paramount importance. Unfortunately, many of the risk factors for infection and poor outcomes related to infections are not easily modified (e.g., demographic characteristics, cause of kidney disease), and studies are needed to demonstrate whether better management of coexisting illnesses and use of particular therapies for the management of CKD and ESRD can favorably alter the risk for acute infection; however, selected approaches could be adopted, including reducing unnecessary exposure to pathogens (e.g., avoiding unnecessary phlebotomy and hospitalizations) and the potentially effective preventive strategy of vaccination.

Vaccination

In the general population, targeted vaccination of children and adults has been shown to reduce potentially severe or life-threatening infections (34,35); however, the efficacy of vaccinations specifically in CKD and ESRD has not been widely studied. Although a review of all adult vaccinations is beyond the scope of this article, the following highlights research that is relevant for understanding either commonly used vaccines or the prevention of common infections in the setting of kidney disease.

Vaccine studies in patients with kidney disease have primarily examined antibody response and rate of antibody decline after vaccination as opposed to vaccine efficacy for preventing infection (36). How these alterations in the surrogate outcomes of vaccine responsiveness help to explain observed variation in rates of clinical events as compared with the general population is not well understood. Studies that have examined vaccination in the setting of CKD or ESRD have been limited by small study size, variable follow-up, and ascertainment of surrogates for vaccine effectiveness. Direct comparison of the various studies is difficult secondary to differences in study population, variation in vaccine composition, vaccination schedule (e.g., 14-valent versus 23-valent pneumococcal vaccine, three versus four doses of Engerix B), the definition of vaccine response, and the outcomes of interest (e.g., antibody levels against specific capsular types as opposed to total antibody levels).

Influenza Vaccination. Patients with ESRD have significantly lower response rates to influenza vaccine as compared with healthy control subjects but nonetheless have been shown to develop protective antibody levels to the majority of influenza strains examined (37). Among patients with ESRD, response rates to influenza vaccination (defined as a four-fold increase in titers) have been reported in some studies to vary from 7 to 44%, whereas protection rates (defined as hemagglutination inhibition titer ≥40) in these same studies has ranged from 46 to 93% depending on the dialysis modality and specific strain titer measured (e.g., H3N2, H1N1, type B) (37,38). Administration of the same antigenic vaccine in two influenza seasons has been associated with protective antibody rates of 100% in the second season (an increase from 50 to 62% in the first season of vaccination) (39). Among patients who received maintenance hemodialysis, vaccination against influenza A and B was associated with a reduced risk for infection-related hospitalizations, hospitalizations for influenza or pneumonia, all-cause mortality, infection-related mortality, and cardiac-related mortality (40). Among patients who received peritoneal dialysis, influenza vaccination was associated with a lower risk for all-cause mortality (40).

Pneumococcal Vaccination. After immunization with the pneumococcal vaccine, children with steroid-responsive nephrotic syndrome have been shown to develop anti-pneumococcal antibodies to most capsular types comparable to healthy children. In contrast, children with steroid-resistant nephrotic syndrome have been observed to have significantly lower levels of anti-pneumococcal antibodies to numerous specific capsular types as compared with healthy children (41). It is interesting that revaccination of children and young adults who have kidney disease (both CKD and ESRD) who lose protective titers 1 yr after initial vaccination has been associated with a lower response rate and more rapid loss of protective antibody titers as compared with the initial vaccination (42).

As compared with healthy adults, patients with advanced CKD and ESRD seem to have reduced responsiveness to pneumococcal vaccination, although findings have been inconsistent across studies (43,44). Patients who have kidney disease and are vaccinated with the pneumococcal vaccine seem to develop different serotype-specific titers, develop lower levels of antibody titers, and have a more rapid loss of antibody titers as compared with healthy control subjects (36,44,45).

Hepatitis B Vaccination. Hepatitis B vaccination has been widely studied in the ESRD population, and numerous studies have examined how the dosage, total number, and route of administration affect antibody response (generally defined as >10 mUI/ml) (46–49). In patients with ESRD, studies using Engerix B have shown variable response rates ranging from approximately 60 to 80% depending on the dosage, number of vaccinations, route of administration (intradermal versus intramuscular), and study population (46–49). Among patients with moderate to advanced CKD, vaccine responsiveness has also been shown to range from approximately 60 to 80% depending
on the dosage, number of administered vaccines, and study population (31,32). Findings have been inconsistent as to whether level of estimated GFR affects vaccine responsiveness in patients with CKD (31,32).

Staphylococcus aureus Vaccination. StaphVAX has not been shown to be efficacious in reducing the risk for Staphylococcus aureus bacteremia in hemodialysis patients, although it may confer some benefit during the first 40 wk after administration (50). Although administration of a booster dose of StaphVAX a mean of 958 d after the initial vaccination was shown to increase antibody levels, whether this same response would be observed if the vaccine were administered earlier is unclear (51). Further studies are needed to determine whether an effective immunization strategy can be developed using S. aureus vaccination.

Current data suggest that vaccination is an underused prevention strategy in the CKD and ESRD populations (33,40). In a Medicare cohort of individuals who were ≥67 yr of age and subsequently initiated renal replacement therapy, the rates of influenza and pneumococcal vaccination before renal replacement therapy were somewhat lower as compared with a contemporaneous Medicare-eligible cohort without diagnosis codes for kidney disease (46 versus 49% for influenza [P < 0.0001]; 9 versus 14% for pneumococcal vaccination [P < 0.0001]). Conversely, hepatitis B vaccination was notably higher in the cohort with CKD as compared with the cohort without kidney disease (24 versus 0.1%; P < 0.0001) (33). On the basis of USRDS data as of 2005, rates of vaccination were also low in the ESRD population. The overall influenza vaccination rate was 58%, the overall 2-yr rate for pneumococcal vaccination was 19%, and the overall hepatitis B vaccination rate was 21% (2).

In general, potential barriers to achieving more optimal immunization rates include inadequate access to preventive care (52), suboptimal rates of provider recommendation for vaccination (53), other issues predominating clinic visits, patient concerns about vaccine safety, inadequate physician reimbursement, and incomplete immunization history (54). These and other potential barriers to immunization that are specific to the CKD and ESRD populations have not been systematically examined, although some of these barriers should be minimized in the setting of ESRD that is treated with maintenance dialysis.

Health Care Resource Use Related to Infection

Few published data are available about how acute infections in CKD and ESRD affect both health care resource use and overall costs and whether preventive strategies are cost-effective or even possibly cost-saving. The high cost of providing renal replacement therapy is well documented, with annual direct medical costs for ESRD care an estimated $32.5 billion in 2004 (55). The average cost of a hospitalization for S. aureus bacteremia is high, with an estimated range of $20,000 to $24,000 per patient (56,57). Yet the overall contribution of infections to the cost of ESRD care is unknown, and whether reducing infections would have a substantial impact on costs in ESRD and the much larger CKD population is not known.

Future Directions

Comprehensive studies of the absolute rates, risk factors, clinical course, and outcomes of different types of clinically relevant infections across the spectrum of CKD are not available, and our understanding of these issues among patients with ESRD remains limited. Although relatively more data have been collected about infections in the ESRD population as compared with the CKD population, there are significant gaps in our knowledge of infections in patients with ESRD. The majority of the current data are derived from the USRDS or selected randomized, controlled trials. Although it is nationally representative, the USRDS is an administrative database of patients who receive renal replacement therapy, is limited to Medicare-eligible individuals, depends on submitted claims for potential outcomes, and does not include patients who have low kidney function and do not receive renal replacement therapy. Randomized, controlled trials of ESRD, such as the HEMO Study (9), include a highly selected population that generally was healthier and may not be completely representative of the broader target population of ESRD. In addition, further study of the range of infections (e.g., pneumonia, cellulitis, abscesses) is needed to determine the burden of individual types of infections in this population. Some of the important understudied questions among patients with ESRD receiving dialysis include the following:

- What are the types, rates, and patterns of acute infection?
- What are the risk factors for specific types of infection, and how do these factors relate to dialysis modality and vintage?
- What are the short- and long-term clinical and functional outcomes after acute infections?
- What health care resources are used for the diagnosis (e.g., abdominal and chest computed tomography scans, bronchoscopy) and management (e.g., change of permanent dialysis catheter, extremity amputation, nursing home placement for antibiotics) of infections, and what are the associated direct and indirect costs?

Among patients with CKD, few data exist on many aspects related to acute infections. Given that kidney dysfunction is a continuum and the high apparent burden of non–vascular access–related infections in the dialysis population, acute infections likely play an important role in the observed morbidity and mortality of patients with CKD. Some of the key unanswered questions among patients at different stages of CKD include the following:

- What are the incidence and prevalence of acute infections in patients with CKD, and how do the rates of infection vary by stage of CKD?
- What are the primary risk factors that predispose to acute infection in patients with CKD (e.g., estimated GFR, proteinuria, previous or current immunosuppression, age, comorbid medical illnesses, diabetes, malnutrition, inflammation)?
- What are the short- and long-term outcomes of acute infections in the CKD population?
What is the efficacy and safety of various vaccines in the setting of CKD, and how does the severity of CKD affect vaccine responsiveness?

Conclusions
With the expanding population of patients with CKD and ESRD globally and the associated excess morbidity and mortality, greater efforts are needed to identify potentially modifiable risk factors to reduce this burden to patients, families, and the health care system. On the basis of limited data, acute infections seem to occur more frequently in the setting of kidney disease and are associated with poorer outcomes compared with the general population. Our understanding about useful preventive strategies for infection in those with CKD and ESRD is even more limited. Greater insights into the epidemiology and contribution of infections (overall and disease specific) to overall mortality in CKD and ESRD are clearly needed to prevent and treat infections in these populations and hopefully improve overall clinical outcomes.

Disclosures
None.

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