The Value of Vaccination in Chronic Kidney Disease

Annamaria Kausz and Dilip Pahari
Department of Medicine, Division of Nephrology, Tufts-New England Medical Center, Boston, Massachusetts

ABSTRACT

There has been much attention directed toward the high mortality of patients with end-stage renal disease (ESRD), with much of the focus on cardiovascular disease. However, infectious disease is the second most common cause of death among dialysis patients. Although CKD patients are immunocompromised, some vaccines such as influenza, retain their efficacy and reduce infection rates with a standard immunization schedule. Other vaccines, such as hepatitis B and pneumococcal vaccines, require more frequent and/or higher doses to produce and maintain protective antibody levels. Attention has recently been given to the efficacy of influenza vaccination in ESRD patients in reducing morbidity and mortality. Centers with vaccination protocols have demonstrated reduced infection rates and resultant decreased morbidity and mortality. It could be extrapolated from this that widespread vaccination would reduce the total cost of ESRD patient care, and potentially improve patient well-being. However, vaccination appears to be underutilized in CKD patients, and it is a readily available intervention to improve outcomes.

The high morbidity and mortality of patients with end-stage renal disease (ESRD) have led to the development of a variety of guidelines for improving the care of patients on dialysis, and more recently the care of patients with early stages of chronic kidney disease (CKD). Much of the focus has been placed on cardiovascular disease (CVD) (1), as it is the leading cause of death among patients on dialysis (2). However, infectious diseases are the second most common cause of death among ESRD patients, accounting for approximately 25 deaths per 1000 patient-years at risk (data from the U.S. Renal Data Systems [USRDS], 1998–2000). Infections account for a large proportion of hospitalizations among patients on dialysis and patients with kidney and other organ transplants (2), and are also a common cause of hospitalization among patients with earlier stages of CKD (3).

Although a limited number of effective vaccines exist, and these diseases likely account for only a fraction of the morbidity and mortality associated with infectious disease in ESRD, the influenza vaccination rate in the ESRD population falls below targets for the general population (4). This is troubling, since this patient population has access to influenza immunization through Medicare benefits. There is no clear explanation for the low vaccination rates, but it may be surmised that a perception of reduced effectiveness due to the immune system compromise associated with uremia may be one reason. There are, however, studies suggesting benefit from a variety of vaccines, including influenza, pneumococcal, and hepatitis B vaccines (5–7).

Chronic kidney disease is considered an immunocompromised state, given that T-cell, B-cell, and monocyte/macrophage function are all diminished (8). These abnormalities are evidenced in part by the greater susceptibility to fungal and tuberculous infections. T-cell activation and proliferation are depressed, lymphokine production and antibody-dependent cell-mediated cytotoxicity are reduced, and there is increased suppressor cell activity, among other abnormalities. In addition, B-cell counts are decreased. Although total antibody production is not reduced, there is decreased IgG production in response to vaccination, probably related to impaired generation of antigen-specific helper T cells that are required for appropriate B-cell antibody synthesis in response to vaccination. Macrophages also do not function properly in uremic blood, with decreased interleukin (IL)-1 production (9).

The combination of immune system abnormalities in CKD leads to lower seroconversion rates, lower peak antibody titers, and more rapid decline of antibody levels (9–11). Vaccines thus may be potentially less effective and provide less protection from infections among patients with kidney failure. However, adequate seroresponse has been documented with standard or augmented regimens for vaccinations against influenza, hepatitis B, pneumococcus, and varicella (4,7,9,11–13), but the clinical response to vaccination is not well understood.

In addition to a decreased immune response, patients with CKD also have a greater predisposition to infections. They have a deficient mucocutaneous barrier, related to a variety of factors, including excoriations of the skin due to pruritus, epidermal and sweat gland atrophy, dryness and fissuring of the skin, ichthyosis, gastrointestinal ulcerations, and poor mucociliary and alveolar macrophage clearance (9). In addition, treatment-related repeated
vascular access in hemodialysis, permanent catheters with repeated connect-disconnect in peritoneal dialysis, and immunosuppressive drugs used for treatment of a variety of conditions associated with kidney failure contribute to the high predisposition to infections.

Influenza causes significant mortality and morbidity in the general population, with 20,000 deaths annually (14,15). The effectiveness of vaccinations varies, depending on the outcome examined. In a meta-analysis of 20 cohort studies in elderly patients, the pooled estimates of vaccine efficacy (1 odds ratio) ranged from 50% for preventing hospitalization to 68% for preventing death, while the effectiveness for preventing respiratory illness and pneumonia was intermediate (16). Influenza vaccination has also been demonstrated to be cost saving in both high-risk elderly as well as healthy adults, with the cost savings derived from reductions in hospitalizations, health care provider visits, and absenteeism from work (17). Despite smaller proportions of patients with ESRD achieving potential antibody levels compared to patients without kidney failure (and response varies depending on the particular viral antigen and whether the patient is on peritoneal dialysis or hemodialysis), there does appear to be a clinical benefit from vaccination (4,5,18,19). A recent study of Medicare billing data from the years 1997 to 1999 in the United States revealed that among hemodialysis patients vaccinated against influenza, the likelihood of hospitalization and death were consistently lower compared to unvaccinated patients; among peritoneal dialysis patients, only the likelihood of death was lower (5). Overall, vaccinated patients had lower hospitalization rates (5).

Although a cause-and-effect relationship cannot be established from such retrospective studies, they are highly suggestive. Vaccine effectiveness studies, especially those related to respiratory illness, probably underestimate effectiveness, given that not all lead to encounters with the medical system (16). In addition, interpretation of studies regarding respiratory illness is complicated by the fact that definitions for illness may vary, causative agents are often not isolated, and pneumonia may be confused with other conditions such as bronchitis and congestive heart failure. Similar problems arise with attribution of cause of death in mortality studies.

Recommendations regarding vaccination against influenza in ESRD/CKD have existed for some time (9). However, it appears that the rates of influenza vaccination in these patients lag behind the rates in the general population. The national health objective target for influenza vaccination rates was 60% in 2000. While the objective was achieved in 2000 for the general population, the vaccination rate was only 48.8% in hemodialysis patients and 39.2% in peritoneal dialysis patients in the years 1997–1999 (5). In another study of a single ESRD network, vaccination rates were substantially higher, near 75% (20). The discrepancy may be due in part to data capture, that is, some patients may be receiving vaccines without the procedure being billed to Medicare, such as through managed care plans, but also may be explained by different practice patterns. Another potential reason for low vaccination rates may be lack of awareness of the benefit of influenza vaccination. Overall, the low rates of influenza vaccination are difficult to explain, given the frequent interactions with the medical system necessitated by renal replacement therapy and universal coverage of influenza vaccination, which should adequately ensure access to this intervention.

Polyvalent pneumococcal vaccine has been used in childhood nephrotic syndrome and kidney failure for years (21), and it has also been demonstrated to be modestly efficacious in adult kidney transplant recipients (6). In one study of patients with kidney disease not on dialysis, significant antibody titers (antibody titer > 200 µg/L) were observed in only 68% of patients at 6 months and 48% at 1 year, and revaccination produced a significant immune response in only 50%, followed by a rapid decline in antibody level within 6 months (11). However, administering repeated booster doses of pneumococcal vaccine to hemodialysis and kidney failure patients resulted in virtual disappearance of pneumococcal infections over a follow-up period of 2 years (21). Thus pneumococcal vaccine, probably with repeated booster doses every 2 years, should be used in CKD patients, especially those at further risk due to splenectomy, sickle cell anemia, or nephrotic-range proteinuria, or those who will be receiving a kidney transplant (9,22).

Hepatitis B virus (HBV) infection in hemodialysis units is a serious concern. Sources of infection are blood product transfusions, contamination from dialysis equipment, and infections from other environmental sources. Thus immunization against hepatitis B is widely practiced (23). Diminished viral clearance leading to a prolonged hepatitis B carrier state, e-antigen and HBV-DNA positivity, and poor anti-HBsAg titer in response to both natural infection and vaccination have all been reported (24).

While the majority of healthy individuals develop a protective antibody titer (>10 IU/L) to three doses (20 µg/dose) of vaccine at 0-, 1-, and 6-month intervals, the seroconversion rates are much lower in the ESRD patient population (9). The protective antibody levels also fall to undetectable levels in 50% of CKD patients at 1 year, compared to 15% in healthy individuals.

Various strategies have been attempted to improve seroconversion and maintain protective antibody levels, including 1) adding one extra dose of vaccine, for a four-vaccine series (13); 2) doubling the dose of vaccine to 40 µg/dose (13); 3) repeating the vaccine at yearly intervals or when the antibody titer falls below 10 IU/L (25,26); 4) starting vaccination at an earlier stage of CKD (27); and 5) intradermal injection at more frequent intervals (13,28). In addition, the vaccine has been given in combination with a number of substances such as erythropoietin, granulocyte-macrophage colony-stimulating factor (GM-CSF), IL-2, interferon (IFN)-α, IFN-γ, and thymopentin (7). The rationale for use of these factors is that increased mobilization of the monocyte-macrophage system will result in better antigen processing. Of all the factors, GM-CSF as adjuvant therapy via intradermal injection appears to be promising (7,29). Thus routine screening and regular vaccination should be considered for reduction of HBV infection rates.

Other infections have been targeted for vaccines. Cytomegalovirus (CMV) infection is a major problem following transplantation. Live-attenuated CMV vaccine
has been tried, but although this led to a reduction in the severity of CMV infections, there was no reduction in the frequency of infection (30). While vaccination against Staphylococcus aureus has been attempted, with the goal of reduction in exit-site infection and peritonitis rate in continuous ambulatory peritoneal dialysis (CAPD) patients, a prospective randomized double blind multicenter study did not demonstrate its efficacy in reducing either infection (31). Hepatitis A vaccination has been shown to be feasible in patients on hemo dialysis (32), and thus should probably be considered for patients who will be exposed. Other vaccines recommended for the general population, such as tetanus, polio, and diphtheria, should be provided to patients with CKD, but the protection may not be optimal and may be short lived. Children awaiting kidney transplantation should receive the standard regimen of recommended childhood immunizations (22). Splenectomized adults are more susceptible to infection by capsulated organisms and should thus receive hemophilus influenza vaccination (22). Successful vaccination with live-attenuated varicella vaccine prior to transplant has led to a decrease in the incidence of herpes zoster and chickenpox in the posttransplant period (33).

In summary, patients with CKD, on dialysis, or following a kidney transplant are immunocompromised, and infection is a major concern. While some vaccines (like influenza) in usual doses provide protection, other vaccines (hepatitis B, pneumococcal) require more frequent dosing to maintain protective antibody titers. It appears that there are no added risks to immunization with nonlive vaccines, and there is the potential for deriving benefit in terms of reductions in cost and hospitalization. This has been clearly demonstrated for influenza vaccination, but it may be reasonable to expect that this would be true for pneumococcal and hepatitis B vaccination as well. There are sufficient reasons to reinforce to the medical community, nephrologists, and primary care providers alike, the importance of vaccinating CKD patients.

References