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Vaccination in Chronic Kidney Disease

Snigdha Reddy
Henry Ford Health, SREDDY5@hfhs.org

Chandrika Chitturi
Henry Ford Health, cchittu1@hfhs.org

Jerry Yee
Henry Ford Health, JYEE1@hfhs.org

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Vaccination in Chronic Kidney Disease

Snigdha Reddy, Chandrika Chitturi, and Jerry Yee

Infections after cardiovascular disease are the second most common cause of death in the chronic kidney disease population. Vaccination is an important component of maintaining health and wellness in patients with kidney disease. There is a changing epidemiologic landscape for several vaccine-preventable illnesses from childhood to adulthood and unfounded public perception of safety concerns. Several mechanisms have been proposed to cause inadequate vaccine protection in this high-risk group with chronic kidney disease. These have led to recent advances in new designs for vaccination strategies in kidney disease. In this article, we discuss the current evidence and recommendations for vaccination in those with kidney disease and needing renal replacement therapy (dialysis and transplant).

Key Words: Vaccines, Chronic kidney disease, Immunizations

The high morbidity and mortality of patients with end-stage renal disease (ESRD) led to the development of various guidelines for improving the care of patients on dialysis and, more recently, the care of patients with early stages of chronic kidney disease (CKD). Although much focus has been placed on cardiovascular disease, infectious disease is the second most common cause of death in patients suffering from late-stage CKD.[1] According to the US Renal Data System Annual Data Report, more than 660,000 Americans are being treated for kidney failure, of which 468,000 are patients on dialysis and more than 193,000 have a functioning kidney transplant.[2] Infections with bacteremia and/or septicemia in patients with CKD who are on dialysis and patients with kidney and other organ transplants contribute to a proportion of hospitalizations in addition to cardiovascular events and bacterial pneumonias.[3-5] Vaccine-preventable diseases account for only a fraction of the infectious burden in patients with CKD and ESRD. Centers with vaccination protocols have demonstrated reduced infection rates and resultant decreased morbidity and mortality.[6] It could be surmised that widespread vaccination would reduce the total cost of kidney disease patient care and potentially improve patient well-being. Nonetheless, patients with CKD are immunized less frequently than the general population.[7,8] Patients with CKD, regardless of etiology, are known to be vulnerable to vaccine-preventable infections because of impaired immunity, immunosuppressive treatments, and dialysis. Attempts to improve vaccine administration rates in these patients have been hampered by reduced efficacy of vaccines and safety concerns for transplant candidates or recipients.[9]

IMMUNE FUNCTION IN CKD

Over the last decade several developments in understanding immunologic response have led to advances in new designs for vaccination strategies. Children with immature immune function and the elderly with comorbidities are uniquely at risk for infection-related complications, and CKD may be a risk multiplier. Reduction in vaccine effectiveness across the stages of CKD has not been attributed to a single abnormality in immune function but a host of disturbances in innate and adaptive immunity.[10] Innate immunity involves dendritic cells, T lymphocytes (both T helper and cytotoxic), and B lymphocytes (responsible for immunoglobulin generation and class switching).[11] In advanced CKD, innate immunity may be responsible for inadequate vaccination response. In addition, malfunction of adaptive immunity with impaired B and T cells with decreased monocyte functioning results in faulty antigen presentation to the antigen-presenting cells for their destruction. This generates impaired memory cells and inadequate antibody production to vaccines.[12] Decrease in the population of the aforementioned cells is noted in late-stage CKD (Stages 4 and 5).[10,12] Increased health care utilization and exposure to infections in these patients has also been proposed as another factor. Uremic toxins, malnutrition, and various aspects of the host defense system contribute to suboptimal immune function. To name a few, decreased function of neutrophils such as chemotaxis, phagocytosis, and decreased oxidative metabolism are worsened by dialysis.[4,12] Both patients on hemodialysis (HD) and patients on peritoneal dialysis have disruption in the protective cutaneous barriers against infections predisposing them to bacteremia, exit-site infections, and peritonitis. Immunoglobulin loss in peritoneal dialysis has been suggested for increased risk. Immunosuppressive treatments in idiopathic and autoimmune glomerulopathies as well as transplant recipients have major suppression of major defense mechanisms. Because the response to many vaccines is diminished in organ failure, transplant candidates should be immunized early in the course of their disease.

It is recommended that vaccination status ideally be documented at the pretransplant clinic visit and the patient referred for the appropriate vaccines at the time of listing.[13] Studies have underscored that early stage disease

From the Division of Nephrology and Hypertension, Henry Ford Hospital, Detroit, MI.

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Address correspondence to Snigdha Reddy, MD, Henry Ford Hospital, 2799 West Grand Blvd, CFP-523, Detroit, MI 48202. E-mail: snigdhatreddy@gmail.com

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does not seem to elicit as significant an impairment in immune function as late-stage disease.[9,14]

BARRIERS TO VACCINATION IN PATIENTS WITH CKD

There is no clear explanation for the low vaccination rates among patients with CKD, in particular patients on dialysis, because most have coverage of vaccinations through Medicare. Genetic and CKD-related factors as well as logistic problems with providing the recommended vaccination schedules have been implicated in lower immunization rates in CKD compared with the general population. Social and financial status, health care access, personal perception of vaccination, and increased skepticism of vaccines in the general population consequently affect patients with CKD.[15] Variation in recommendations often stating "guidelines derived from small or controversial studies" or being suggested as an "expert opinion" leads to confusion and reluctance both among providers and patients. Health care providers should be encouraged to discuss safety of vaccination for the patient's condition and address concerns. Specialists caring for these patients with CKD may overlook vaccination because of lack of adequate knowledge on immunizations deferring it to the general practitioner, who in turn may not want to interfere in CKD care and regard vaccination as a specialist's responsibility.[16] Unique issues with vaccination after transplantation such as induction of graft rejection or autoimmunity have been suggested but not supported by the current literature. Recent studies have discussed the safety of live-attenuated vaccines (LAVs) in transplant recipients, but these data are not sufficient for universal recommendations. Opportunities should not be missed in immunizing children needing dialysis at an early age and subsequently being transplanted.

CLINICAL SUMMARY

- Patients with chronic kidney disease are known to be vulnerable to vaccine-preventable infections because of impaired immunity, immunosuppressive treatments, and dialysis.
- Several barriers have been identified for low vaccination rates among patients with chronic kidney disease.
- The current immunization strategies available must be aggressively promoted in the kidney disease population.

VACCINATION RECOMMENDATIONS IN CKD AND ESRD

Immunization guidelines for CKD vary between regions and health authorities. In addition, patients with CKD at high risk for poor immune response or rapidly waning immunity cannot be easily identified. Some general considerations for vaccination approaches include

- Patients with early stage CKD have minimal immune impairment and can be safely vaccinated.
- Patients with ESRD should not be excluded from routine vaccination practices for risk of disease with LAVs.
- The immune status of transplant candidates must be reviewed, and complete age-appropriate vaccination must be recommended in the pretransplant period at least 1 month before transplant.
- Safety of LAVs such as measles, mumps, and rubella (MMR) and varicella zoster virus (VZV) has not been secured in transplant recipients. However, they can be safely vaccinated with inactivated ones.
- Every effort should be made to ensure that transplant candidates, their household members, and health care workers have completed the full complement of recommended vaccinations before transplantation.

Current recommendations of vaccinations in adults with CKD and ESRD (Table 1) are reviewed.

Hepatitis B

Hepatitis B virus (HBV) is transmitted through percutaneous or mucosal exposure to infectious blood or body fluids. HBV is highly infectious, can be transmitted in the absence of visible blood,[17] and remains viable on environmental surfaces for at least 7 days. Persons with chronic infection (eg, those with persistent hepatitis B surface antigen [HBsAg] in the serum for at least 6 months after acute infection) serve as the main reservoir for HBV transmission. Persons with chronic HBV infection are at increased risk for cirrhosis and liver cancer. HBV has long been a threat for patients with CKD especially those undergoing HD, because of transfusions and contamination of dialysis equipment. There is heterogeneity in practices for prevention and prevalence of HBV infection across the world.[18] Unlike healthy adults, HBV infection in patients undergoing dialysis becomes chronic (positive serum HBsAg) in 30% to 60% compared with 10% in nonuremic patients.[19,20] The incidence of HBV infection among patients undergoing HD has declined since the initiation of hepatitis B vaccination and additional infection control precautions, such as segregation of seropositive patients and their equipment, decreased need for transfusions with the use of erythropoietin, and routine screening for hepatitis B in dialysis centers. Since 1995, the annual incidence has been stable and HBsAg seroprevalence has remained at 1%.[18] HBV vaccination is advised in patients with progressive CKD and immunization in Stage 4 CKD. In "late" Stage 5 CKD there is lower rate of seroconversion, consequently HBV-antibody responses to HBV are less intense and less durable.[18,21] Immunocompetence, measured by achievement of a titer of >10 mIU/mL antibody to hepatitis B surface antigen (anti-HBs) after 3 doses of vaccine at 0-, 1-, and 6-month intervals is usually achieved in most healthy adults. This response has been observed in about 50% to 70% of patients with ESRD. HBV vaccines are derived from inactivate viral particles and hence contraindicated in people with yeast allergy. Commonly used US commercial brands are Recombivax and Engerix-B. Patients undergoing HD require higher doses. Current recommendations for adults on dialysis are either 40 μg of Recombivax administered at

Table 1. Recommended Immunization Schedule for Adults With Renal Disease

Vaccine	Dosing and Schedule		Booster
	CKD Stages 3 and 4	CKD Stage 5 and ESRD	
Hepatitis B-recombinant	Recombivax 10 μg: 3 doses (0, 1, and 6 mo) Engerix-B 20 μg: 4 doses (0, 1, 2, and 6 mo) Heplisav-B: 2 doses (0 and 1 mo)	Recombivax 40 μg: 3 doses (0, 1, and 6 mo) Engerix-B 40 μg: 4 doses (0, 1, 2, and 6 mo) Heplisav-B: 2 doses (0 and 1 mo)	Boost when anti-HBs titer <10 mU/mL
Hepatitis A-inactivated	No clinical trials. Administer based on risk. Two-dose series of single antigen hepatitis A vaccine (Havrix at 0 and 6-12 mo or Vaqta at 0 and 6-18 mo; minimum interval, 6 mo)		
Influenza-inactivated (quadrivalent or high-dose trivalent)	1 dose annually before onset of influenza season		
Diphtheria-tetanus (TT or Td)	Primary: 3 doses (0,1, and 6-12 mo)		Every 10 y Can substitute Td + acellular pertussis for 1 booster
MMR	Administer if no evidence of immunity: 2 doses of MMR at least 28 d apart		
VAR	Administer if no evidence of immunity: 2 doses of VAR vaccine 4-8 wk apart if not previously received If previously received 1 dose, administer 1 dose of VAR at least 4 wk after the first dose		
RZV ZVL	Administer 2 doses of RZV 2-6 mo apart to adults >50 y regardless of past episode of herpes zoster or ZVL Administer 2 doses of RZV 2-6 mo apart to adults who previously received ZVL at least 2 mo after ZVL For adults >60 y or older, administer either RZV or ZVL (RZV is preferred)		

Abbreviations: anti-HB, antibody to hepatitis B surface antigen; MMR, measles, mumps, and rubella; RZV, recombinant zoster vaccine; VAR, varicella; ZVL, zoster vaccine live.

0, 1, and 6 months or 40 μg of Engerix-B administered at 0, 1, 2, and 6 months. This is a greater dose than the regular dose of 10 μg of Recombivax HB or 20 μg of Engerix-B administered at 0, 1, and 6 months to patients who are immunocompetent. The HBV-antibody titer should be evaluated 1 to 2 months after the final dose.[18] If the anti-HBs titer is <10 mIU/mL, repeating the entire dosing series is suggested with determination of the antibody response in 1 to 4 months.[22,23] For patients on HD, the need for booster doses should be assessed by annual testing of the anti-HB levels. A booster dose should be administered when anti-HB levels decline to <10 mIU/mL (Fig 1). Other vaccines like Elovac B, Genevac B, and Shanvac B are available worldwide. The Food and Drug Administration recently approved the use of Heplisav-B, a yeast-derived vaccine prepared with a novel adjuvant, administered as a 2-dose series (0 and 1 month) for use in persons aged ≥18 years. Safety and efficacy of Heplisav-B have not been entirely established in adults on HD.[24] To assess response to vaccination and the need for revaccination, postvaccination serologic testing using a method that allows determination of the protective level of anti-HBs (≥10 mIU/mL) 1 to 2 months after the final dose of vaccine is recommended. Alternative strategies for vaccination in nonresponders include intradermal administration, coadministration with immunostimulatory agents such as levimasole or granulocyte-macrophage colony stimulating factor (GM-CSF), and use of third-generation vaccines; use of newer adjuvant agents have been proposed but not yet universally recommended.[25]

Influenza Vaccines

Epidemics of influenza have been responsible for thousands of deaths over the years in the US. Of the available vaccinations, influenza vaccinations have clear benefits in the ESRD population.[26,27] Patients with ESRD who are vaccinated had significantly lower infection-related hospitalization rates and mortality than those who were not vaccinated.[26-28] Adequate influenza vaccination response rates have been reported among patients on dialysis and after kidney transplantation, but rates of seroconversion and comparisons relative to patients without CKD vary across reports and by influenza viral strain.[29] Several formulations that are updated yearly are now available, including standard dose intramuscular, high-dose intramuscular, intradermal, adjuvant, and live attenuated.[30] Routine annual influenza vaccination for all persons aged ≥6 months who do not have contraindications has been recommended by the Centers for Disease Control and Prevention (CDC) and the Advisory Committee on

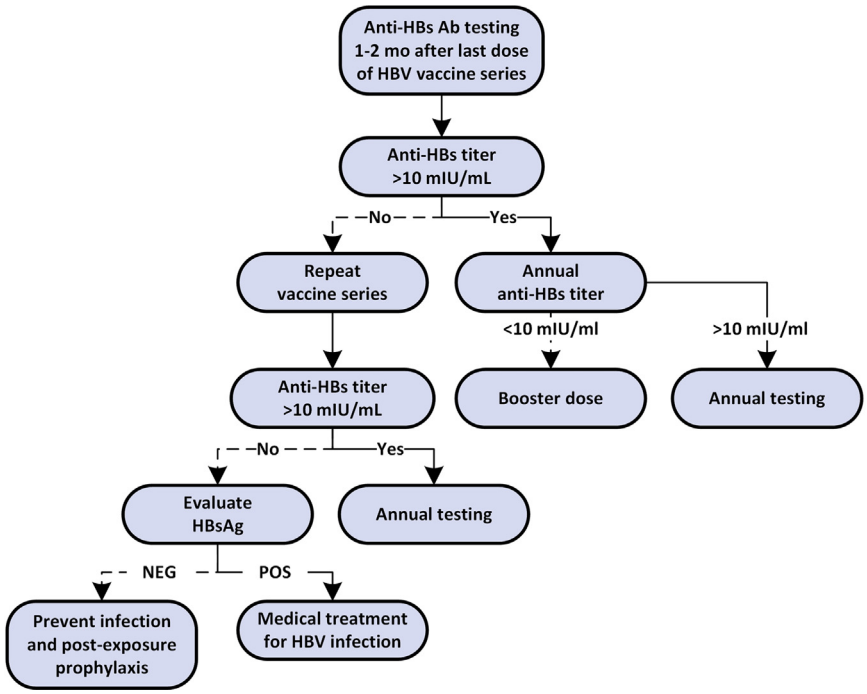

Figure 1. Hepatitis B serologic testing and surveillance in in-center patients on hemodialysis. Anti-HB, antibody to hepatitis B surface antigen; HBsAg, hepatitis B surface antigen; HBV, Hepatitis B virus; NEG, negative; POS, positive.

Immunization Practices (ACIP) since 2010. Optimally, vaccination should occur before onset of influenza activity in the community; however, it should be offered throughout the influenza season (ie, as long as influenza viruses are circulating in the community). In the United States, the Centers for Medicare and Medicaid Services recommend that all patients, including transplant recipients, be immunized before discharge from hospital. This may lead to some patients being immunized very early after transplant and decreased immune response to vaccine. Revaccination 3 to 6 months after transplant could be considered if still within the influenza season. Although the rates of influenza have increased over the past decade, there are disparities because of demographic and socioeconomic factors.

Quadrivalent influenza vaccine comprises 2 "A" (1 is H1N1) and 2 "B" virus strains and may be coadministered with pneumococcal vaccines. Alternatively, a high-dose trivalent vaccine may be substituted in patients aged $>$ 65 years. Persons with a history of egg allergy of any severity may receive any licensed, recommended, and age-appropriate influenza vaccine.

The CDC recommends a 0.5 mL dose of inactivated influenza vaccination for all patients with kidney dysfunction and close contacts (household contacts, physicians, nurses, and personnel in hospital and outpatient care settings). Live-attenuated cold-adapted quadrivalent influenza vaccine (FluMist) should not replicate in normal body temperature. However, because of the small theoretical risk, it is not approved for use in high-risk conditions such as after transplant and has not been tested in CKD, ESRD, or in organ transplantation.[13,30] FluMist could be given to persons awaiting transplant; however, at least 2 weeks should elapse before transplant.

Pneumococcal Vaccines

Patients with CKD remain particularly vulnerable to invasive pneumococcal infection because of waning immune protection. Children with nephrotic syndrome and elderly on dialysis are at highest risk.[31] *Streptococcus pneumoniae* is the most commonly identified bacterial cause among patients on dialysis and in kidney transplant recipients with community-acquired pneumonia. The use of the 23-valent pneumococcal polysaccharide vaccine (PPSV23) has long been suggested for the protection of these groups, but with modest efficacy.[32] PPSV23 (Pneumovax 23, Merck & Co, Inc) contains 12 of the serotypes included in 13-valent pneumococcal conjugate vaccine (PCV13; Prevnar 13, Wyeth Pharmaceuticals, Inc, a subsidiary of Pfizer, Inc), plus 11 additional serotypes. Given the high burden of invasive pneumococcal disease caused by serotypes in PPSV23 but not in PCV13, broader protection might be provided through use of both pneumococcal vaccines. The PCV13 has been included in the vaccination recommendations of immunocompromised individuals including patients with CKD in combination with the PPSV23 vaccine as it helps reduce pneumococcal pneumonia in addition to invasive pneumococcal disease.[5]

The current ACIP PPSV23 recommendations call for vaccination of adults 19 to 64 years at the time of CKD diagnosis. Figure 2 outlines the current recommendations. A one-time revaccination dose of PPSV23 is recommended 5 years after the first dose. ACIP recommends that adults with CKD aged $\geq$19 years who have not previously

received PCV13 or PPSV23 should receive a dose of PCV13 first, followed by a dose of PPSV23 at least 8 weeks later. Specifically, a second PPSV23 dose is recommended 5 years after the first PPSV23 dose for these persons. In addition, those who received PPSV23 before age 65 years for any indication should receive another dose of the vaccine at age 65 years, or later if at least 5 years have elapsed since their previous PPSV23 dose. Persons with CKD who previously received ≥1 dose of PPSV23 should be given a PCV13 dose ≥1 year after the last PPSV23 dose was received. For those who require additional doses of PPSV23, the first such dose should be given no sooner than 8 weeks after PCV13 and at least 5 years after the most recent dose of PPSV23.[33]

Tetanus, Diphtheria, and Pertussis

In the United States, reported tetanus and diphtheria cases are rare. Although vaccine coverage is high among infants, children, and adolescents, serologic and survey data indicate that adults are undervaccinated against tetanus and diphtheria.[4] Maintaining seroprotection against tetanus and diphtheria through adherence to the ACIP-recommended schedule of booster doses of vaccine is important for adults of all ages.

In contrast to tetanus and diphtheria, the incidence of reported pertussis in the United States has been increasing despite high infant and childhood coverage with tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis (TdaP) vaccines.[4] Although vaccine-induced protection provided by acellular pertussis vaccines wanes over time, vaccination remains the best protection available against pertussis. In the United States, 1 TdaP product is licensed for use in adults and adolescents. Adacel (Sanofi-Pasteur, Toronto, Ontario, Canada) is used in persons aged 11 to 64 years as a single dose active booster vaccination against tetanus, diphtheria, and pertussis. One dose of TdaP should be administered to adults who previously did not receive a dose as an adult or child (routinely recommended at age 11-12 years), followed by a dose of tetanus and diphtheria toxoids (Td) booster every 10 years.[6]

Hepatitis A

Endemic hepatitis A viral infections are low in the United States, hence vaccination to hepatitis A virus (HAV) is not universally recommended. However, with increased international food trade, a change may occur in the frequency of HAV infections. Infection with HAV usually provides lifelong immunity in most healthy adults and vaccination offers about 99% seroconversion.[34] Persons with CKD and ESRD who have increased risk, that is, those with travel or residence to known endemic areas, chronic liver disease, hepatitis C or HIV, homosexual males, and intravenous drug abusers, should be considered for HAV vaccination to mitigate the associated increased morbidity and mortality. The Food and Drug Administration has licensed 2 inactivated vaccines, Harvix (GlaxoSmithKline, London, United Kingdom) and Vaqta (Merck) offered in a 2-dose series. Twinerix (combination inactivated HAV [720 ELISA units] and purified HBV surface antigen [20 mg]; GlaxoSmithKline, London, United Kingdom) can be offered to those at risk at 0, 1, and 6 months.[23] There are no studies of the safety and efficacy of HAV vaccine in patients with CKD.

Live-Attenuated Vaccines

Few data are available on the safety and efficacy of LAVs in the CKD population. MMR and varicella immunizations are recommended in children with CKD. Immigration from endemic areas and antivaccine beliefs may cause resurgence of these vaccine-preventable illnesses

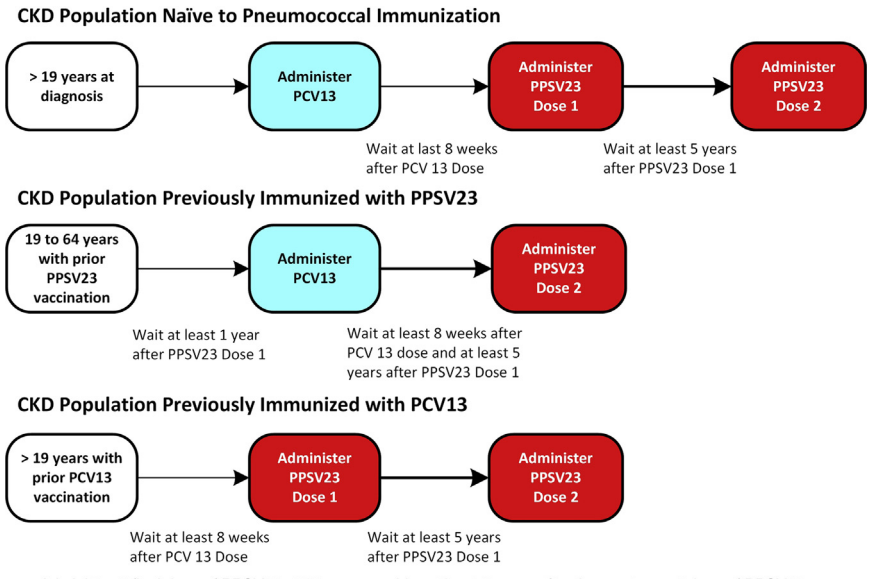

Figure 2. Vaccination schedule for prevention of pneumococcal disease. PCV13, 13-valent pneumococcal conjugate vaccine; PPSV23, 23-valent pneumococcal polysaccharide vaccine.

especially in this vulnerable CKD population.[6] Primary infection with VZV causes chickenpox, wherein VZV replicates in multiple organs, particularly the skin. VZV can be latent and present as herpes zoster in the elderly causing a severe illness especially if immunocompromised.[35]

These LAVs are contraindicated in transplant recipients.[13,23,36] MMR and varicella serology should be checked before transplant and transplant candidates should be immunized. One or 2 doses of MMR and varicella with serologic testing to determine immune status should be done. If seroconversion does not occur, the dose can be repeated once if time permits before transplantation. Because of known interference of blood products such as intravenous immunoglobulin with response, ideally MMR and varicella vaccine should be delayed for 3 to 11 months after the receipt of such depending on the indication for which the blood product is being used.[37] In addition, 2 live vaccines (eg, MMR and varicella) can be administered on the same day; however, if not done on the same day, the second live vaccine should be administered ≥28 days later. Because tuberculin skin test (TST) is also part of the pretransplant workup, it should be noted that live vaccines can interfere with the TST response. The TST can be done on the same day as the live vaccine injection; however, if not done on the same day, it should be done 4 to 6 weeks later.[13] Herpes zoster vaccine has been shown to decrease shingles and postherpetic neuralgia.[38] Two doses of recombinant zoster vaccine 2 to 6 months apart to adults aged 50 years or older regardless of past episode of herpes zoster or receipt of zoster vaccine live are recommended.[1,9,23]

CONCLUSION

Vaccination remains an important yet frequently overlooked component in caring for patients with CKD. In advanced CKD, vaccine-induced serconversion rate is seldom observed in more than 90% of vaccines.[4,21] Various strategies have been used to increase the vaccine-induced seroconversion rate in patients with advanced CKD. Traditional vaccination strategies have poor effectiveness in host responses in this population. There is a changing epidemiologic landscape for several vaccine-preventable illnesses from childhood to adulthood and increasing safety concerns. Changing the injection mode, the use of adjuvants and immunostimulants to improve the immunogenicity of existing recombinant vaccines, introduction of mammalian-cell derived vaccines (third-generation vaccines) are being tried to improve the immunization rate and efficacy.[39] Additional research is needed to compare effectiveness of combining vaccine antigens to improve protective responses and immunologic memory. Nevertheless, as we await novel vaccines, the current immunization strategies available must be aggressively promoted in the CKD population.

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