Practical Guide to Vaccination in All Stages of CKD, Including Patients Treated by Dialysis or Kidney Transplantation

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Infection is a major cause of morbidity and mortality in patients with chronic kidney disease (CKD), including those receiving maintenance dialysis or with a kidney transplant. Although responses to vaccines are impaired in these populations, immunizations remain an important component of preventative care due to their favorable safety profiles and the high rate of infection in these patients. Most guidelines for patients with CKD focus on the importance of the hepatitis B, influenza, and pneumococcal vaccines in addition to age-appropriate immunizations. More data are needed to determine the clinical efficacy of these immunizations and others in this population and define optimal dosing and timing for administration. Studies have suggested that there may be a benefit to immunization before the onset of dialysis or transplantation because patients with early-stage CKD generally have higher rates of seroconversion. Because nephrologists often serve as primary care physicians for patients with CKD, it is important to understand the role of vaccinations in the preventive care of this patient population

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Clinical Vignette

A 50-year-old man with hypertension and stage 5 chronic kidney disease (CKD) due to autosomal polycystic kidney disease is in your office to discuss kidney replacement therapy (KRT) options. He thinks that preemptive kidney transplantation would be his preference. He has 1 potential donor undergoing evaluation. If transplantation is not an option, he has decided on peritoneal dialysis (PD). He is starting to develop uremic symptoms, having anorexia and morning nausea. He denies shortness of breath or chest pain but notes night-time leg cramping and occasional pruritus.

On examination, the patient is a well-developed man in no acute distress. Blood pressure is 130/80 mm Hg and weight is stable at 160 pounds. His abdomen is distended with palpable kidneys and the lower extremities have pitting edema (2+). Laboratory test results show the following values: potassium, 5.2 mEq/L; creatinine, 5.6 mg/dL (previous value, 4.7 mg/dL); albumin, 3.2 mg/dL; and phosphorus, 5.0 mg/dL. Current medications include amlodipine, 10 mg, once daily; losartan, 50 mg, once daily; sodium bicarbonate, 1,300 mg, 3 times daily; and sevelamer, 800 mg, 3 times daily with meals.

Given the patient's uremic symptoms and worsening kidney function, you recommend that he start KRT and refer him for PD catheter insertion pending the donor's workup. The patient states that he is up to date on childhood vaccinations but has not had other immunizations in recent history. What vaccines would you recommend at this time?

Background

Infection is among the leading causes of morbidity and mortality in patients with underlying CKD, including those with kidney failure treated by dialysis or transplantation.[1] CKD results in a state of immunosuppression that is likely multifactorial due to a combination of innate and adaptive immune system dysfunction, chronic inflammation, endothelial cell dysfunction, and uremia.[2,3] The incidence of infection and infection-related hospitalizations has been shown to increase as kidney function declines, although the risk remains poorly characterized by individual stage of CKD.[3] High rates of infection among patients with end-stage kidney disease (ESKD) and earlier stages of CKD are also a consequence of advancing age, comorbid conditions such as diabetes, and high rates of hospital admissions.[4] Risk for infection in transplant recipients is compounded by the need for immunosuppressive agents.

Immunization is an important component of preventative care for patients with kidney disease. Unfortunately, patients with advanced kidney disease and/or using immunosuppressing agents generally have lower rates of seroconversion, lower antibody titers, and a less sustained response after immunization compared with healthy controls.[5] Some studies have demonstrated that the response to vaccines decreases with advancing kidney disease and dialysis treatment,[6,7] suggesting that earlier immunization may be beneficial. Additional clinical outcome data are needed to define optimal timing for administration.

In Practice is a focused review providing in-depth guidance on a clinical topic that nephrologists commonly encounter. Using clinical vignettes, these articles illustrate a complex problem for which optimal diagnostic and/or therapeutic approaches are uncertain.

Vaccination rates are improving but overall are underused in patients with CKD despite proven benefits and recommendations by major professional societies.[8] This is an area in which nephrologists can potentially have a major impact on care because they often serve as primary care providers for their patients.

Non–KRT-Dependent CKD Patients and Those Treated by Maintenance Dialysis

Overview

Adult patients with non–KRT-dependent CKD and those receiving maintenance dialysis should receive all routinely recommended vaccinations based on their age group and other risk factors.[4,9] The Advisory Committee on Immunization Practices (ACIP) has put a special emphasis on hepatitis B, influenza, and pneumococcal immunizations for this population.[9] There are limited data for the effectiveness of other vaccinations. The optimal timing of immunizations in patients before the initiation of dialysis is uncertain because cost benefit and clinical outcome data in early-stage CKD (stages 1-3) has not been well studied. Live vaccinations are generally considered appropriate in this population if inactivated vaccines are unavailable, but safety data are limited. Though the true benefit of routine immunization in this population is poorly defined, these vaccines are safe and infection risk is high, which warrants universal immunization practices (Table 1).[10] The same guidelines apply to patients requiring immunosuppressive therapy for their kidney disease with special emphasis on pneumococcal vaccination. Patients receiving immunosuppression should avoid live vaccines.[9]

Hepatitis B

Recommendations

- There are no specific recommendations for immunization of patients with CKD stages 1 to 3 but vaccination may be considered

Table 1. Immunization Recommendations for Adult Patients with Kidney Disease

	Non–KRT-Dependent CKD	Maintenance Dialysis	Kidney Transplant Recipients	Safe in Contacts of Kidney Transplant Recipients
Cholera	Usual recommendation	Usual recommendation	Contraindicated[a]	Precaution[a]
Hepatitis A	Usual recommendation	Usual recommendation	Usual recommendation	Yes
Hepatitis B[b]	Recommended[c]	Recommended	Usual recommendation	Yes
Hib	Usual recommendation	Usual recommendation	Usual recommendation	Yes
HPV[d]	Usual recommendation	Usual recommendation	Usual recommendation	Yes
JEV	Usual recommendation	Usual recommendation	Usual recommendation	Yes
Influenza				
IIV/RIV	Recommended	Recommended	Recommended	Yes
High dose	Recommended ≥65 y	Recommended ≥65 y	Recommended ≥65 y	Yes
LAIV	Precaution	Precaution	Contraindicated	Yes[e]
Meningococcal	Usual recommendation	Usual recommendation	Usual recommendation	Yes
MMR	Usual recommendation	Usual recommendation	Contraindicated	Yes
Pneumococcal[f]	Recommended	Recommended	Recommended	Yes
Rabies	Usual recommendation	Usual recommendation	Usual recommendation	Yes
Tdap/Td[g]	Usual recommendation	Usual recommendation	Usual recommendation	Yes
Typhoid	Usual recommendation	Usual recommendation	Usual recommendation[h]	Yes[h]
Yellow fever	Usual recommendation	Usual recommendation	Contraindicated	Yes
VZV				
RZV	Usual recommendation	Usual recommendation	Usual recommendation[i]	Yes
LZV	Usual recommendation	Usual recommendation	Contraindicated	Yes[j]
Varicella	Usual recommendation	Usual recommendation	Contraindicated	Yes[j]

Note: Based on information in the KDIGO CKD guidline[4] and Kim et al.[9]
Abbreviations: CKD, chronic kidney disease; Hib, *Haemophilus influenzae*; HPV, human papilloma virus; IIV, inactivated influenza vaccine; JEV, Japanese encephalitis virus; KRT, kidney replacement therapy; LAIV, live attenuated influenza vaccine; LZV, live zoster vaccine; MMR, measles, mumps, rubella; RIV, recombinant influenza vaccine; RZV, recombinant zoster vaccine; Td, tetanus, diphtheria; Tdap, tetanus, diphtheria, acellular pertussis; VZV, varicella zoster virus.
[a]Vaxchora (oral live attenuated cholera vaccine) is contraindicated in immunocompromised patients. The vaccine strain can be shed for 7 days. Killed whole-cell vaccines can be used in immunocompromised patients but are not available in the United States.
[b]Energix-B high dose (40 μg) at 0, 1, 2, and 6 months; Heplisav standard dose at 0 and 1 month; Recombivax-HB high dose (40 μg) at 0, 1, and 6 months. See Table 2.
[c]Recommended in patients with stages 4 to 5 CKD, consider in patients with earlier-stage CKD.
[d]HPV vaccine is currently recommended for men and woman (starting as early as 9 years old) until age 26 years for women and 21 years for men (26 years if high risk), although the vaccine is approved by the US Food and Drug Administration for patients up to 45 years of age. There are no specific recommendations in patients with CKD but small studies have indicated the antibody response appears appropriate.[83]
[e]Only use if no injectable vaccine is available.
[f]Recommended in patients with CKD, nephrotic syndrome, receiving immunosuppression, and diabetes. See Table 3 for dosing.
[g]Administer at least 1 dose of Tdap if not previously done, followed by either Tdap or Td booster every 10 years.
[h]Live vaccine contraindicated in transplant recipients. Administer inactivated typhoid if needed.
[i]No recommendations for use of RZV by Advisory Committee on Immunization Practices (see text for data regarding efficacy and safety in transplant recipients).
[j]Transplant recipients should avoid contact with injection site if visible vesicles.

- Patients with CKD stages 4 to 5 who are at risk for progressive kidney disease should receive the hepatitis B series
- Patients receiving dialysis who are not already immune should receive the hepatitis B series

Summary of Evidence

Current rates of hepatitis B virus (HBV) infection are low in the United States among patients with CKD (<2%).[11,12] However, sporadic outbreaks in hemodialysis (HD) units remain a concern and patients receiving dialysis are more likely to become chronic carriers.[13-16] Immunization remains an important strategy to protect patients with ESKD and the staff who care for them. Unfortunately, rates of seroconversion decrease with advancing kidney disease: 44.3% of those with ESKD, 89.7% of patients with stages 3 to 4 CKD, and 96.2% of healthy controls after 4 doses of a high-dose HBV vaccine.[7] Variability in the rate of seroconversion is attributed to individual host factors, including CKD stage, age, presence of diabetes, nutritional status, and differences in formulations, dosage, number of doses, adjuvants, and administration (ie, intradermal vs intramuscular).[6,7,17-20] Although there are limited clinical outcome data, vaccinated patients have a 70% decreased risk for acquiring HBV infection and those who seroconvert have reduced all-cause mortality. The ability to achieve seroconversion could also be a reflection of overall health status.[15,20]

There are 3 recommended hepatitis B vaccines available in the United States at this time, including the second-generation vaccines, Recombivax-HB (Merck) and Energix-B (GlaxoSmithKline), and a third-generation vaccine with an immune adjuvant, Heplisav-B (HepB-CpG; Dynavax; Table 2). HepB-CpG was approved by the US Food and Drug Administration in 2017 after studies demonstrated improved immunogenicity, especially in groups known to have low responses historically.[21-25]

Patients with CKD who received a 3-dose series of HepB-CpG had an 89.9% response rate of seroprotection compared with 81.8% of patients who received a 4-dose series of Energix-B.[24] Both groups had similar declines in antibody titers over time, resulting in higher levels at a 1-year follow-up in the HepB-CpG group. Further evaluation of adverse reactions is being evaluated in postmarketing studies.

After administration of the hepatitis B series, patients should have titers checked 1 to 2 months after the last dose. If the hepatitis B surface antibody (anti-HBs) titer is <10 IU/mL, it is recommended to revaccinate with a full series. Anti-HBs titers are known to decline more rapidly in this population, leaving patients vulnerable to disease acquisition.[14] The need for a booster dose should be assessed annually with quantitative titers. A single dose should be administered if the anti-HBs titer declines to <10 IU/ML.

Seroprotection against HBV infection is important for patients receiving HD and may be best achieved by administering before ESKD. Despite a suggested benefit of earlier vaccination, Medicare part B coverage for immunization against HBV only applies to patients with ESKD, so cost may also need to be taken into consideration.

Table 2. Dosing Schedule for Hepatitis B Immunizations in Adult Patients With Kidney Disease

Vaccine	Dose	Schedule
Energix-B[a]	High dose (40 μg)	0, 1, 2, and 6 mo
Heplisav[b]	Standard dose	0 and 1 mo
Recombivax-HB[a]	High dose (40 μg)	0, 1, and 6 mo

Note: Based on information in Kim et al.[9]
Abbreviations: CKD, chronic kidney disease; ESKD, end-stage kidney disease.
[a]High-dose vaccine recommended in advanced kidney disease and for patients receiving maintenance dialysis. Optimal dosing in early-stage kidney disease not well defined. Titers should be checked to ensure appropriate response.
[b]To date there are no specific dosing recommendations for Heplisav in patients with ESKD or earlier stages of CKD, so dosing is extrapolated from general guidelines. Of note, trials specifically evaluating patients with ESKD or earlier stages of CKD used a 3-dose series.

Influenza

Recommendations

- The inactivated seasonal influenza vaccine should be administered to adults annually, including those with all stages of CKD, whether or not these patients are treated by dialysis or kidney transplantation
- The high-dose influenza vaccine is recommended for patients 65 years or older

Summary of Evidence

Patients receiving dialysis who develop influenza are at increased risk for complications, including hospital admission and death.[26] Rates of seroprotection after influenza vaccine administration in dialysis patients vary in the literature and have been reported to be from 33% to 80%.[27-30] It is uncertain whether the decreased humoral response results in higher rates of disease or worse outcomes clinically. Observational studies of large cohorts have demonstrated that patients receiving maintenance dialysis who are administered the influenza vaccine have decreased risk for hospitalization and all-cause mortality compared with nonvaccinated controls.[10,31-33] These studies must be interpreted carefully because influenza vaccination could be a reflection of overall higher quality of care. There are fewer data for patients receiving PD, but a large Taiwanese study demonstrated a similar reduction in mortality of 34% in patients who received the influenza vaccine compared with controls.[33] Efficacy in the non–KRT-dependent CKD population needs to be investigated.

Further research is required to define optimal dosage and administration in patients with CKD. Additional areas of study include use of adjuvant vaccinations, higher doses of antigen, or boosters. Repeated yearly administration may help increase response rates[33] but has not been consistently demonstrated to alter rates and duration of seroconversion. The benefit of a high-dose influenza vaccine in elderly patients is well established[34,35] and raises

the question of whether patients with CKD would also benefit from higher doses of antigen. In a recent comparative analysis of HD patients who had received the traditional influenza vaccine versus the high dose, patients receiving the high-dose vaccine had a lower hospitalization rate but no change in mortality during 2016 to 2017. This effect was more pronounced in patients older than 65 years.[36] Although high-dose vaccine is not currently recommended in patients younger than 65 years, further study is needed.

Importantly, no specific adverse events due to the influenza vaccine have been reported in patients with CKD. Given the severity of influenza and the safety of the vaccine, the relevant major professional societies recommend annual immunization. Rates of influenza vaccination among patients with CKD are low but have been increasing. During the 2005 to 2006 season, an estimated 52% of eligible patients received the vaccine in the United States compared to 71% in the 2014 to 2015 season.[8] Interventions such as enhanced education, quality improvement reporting, and automated order sets can help increase the vaccination rate within a dialysis unit.[37]

Pneumococcal Disease

Recommendations

- Pneumococcal immunization is recommended for patients with non–KRT-dependent CKD and those treated by maintenance dialysis
- Pneumococcal immunization is recommended for those with nephrotic syndrome or those requiring immunosuppression. It is also worth mentioning that the presence of diabetes, a frequent comorbid condition in this population, also warrants administration of the pneumococcal vaccine

Summary of Evidence

Pneumonia is the second most common infection in the ESKD population after bloodstream infections and is associated with increased mortality and overall poor long-term prognosis.[38,39] *Streptococcus pneumoniae* remains the most common bacterial pathogen isolated.[40] There are limited data for pneumococcal vaccine effectiveness in the CKD and ESKD populations. In small studies, patients with CKD have demonstrated a decreased antibody response to the 23-valent pneumococcal capsular polysaccharide vaccine (Pneumovax 23 [Merck], or PPSV23) compared with healthy controls.[41,42] In one study, 21% of patients had a suboptimal serologic response and these patients were at higher risk for developing invasive pneumococcal disease compared with patients with CKD with appropriate seroconversion and healthy controls.[42] Although seroconversion in dialysis patients occurs ~94% of the time within the first weeks postvaccination, protective antibody titers wane at a much more rapid rate than in the general population.[43] A retrospective study looking at more than 110,000 incident HD patients found a marginal but statistically significant overall survival benefit of pneumococcal vaccination despite no clear benefit from infectious death.[44]

Few data exist for the 13-valent pneumococcal conjugate vaccine (Prevnar 13 [Pfizer], or PCV13) in this population. A small study assessing the immunogenicity of the vaccine revealed a >53% response rate at 2 months but this waned to 23.5% at a year.[45] Interestingly, PCV13 appeared to be more immunogenic than PPSV23, especially in PPSV23-naive patients.[46] In addition, some serologic strains were more likely to result in an immune response than others. No data exist for the effect of PCV13 on morbidity and mortality.

Although overall efficacy in this population is poorly defined, immunization is strongly recommended due to the high mortality associated with invasive pneumococcal disease and low risk for vaccine adverse reactions. Vaccination schedule is complex and depends on which of the 2 pneumococcal vaccines is given first to an individual patient (Table 3).

Herpes Zoster

Recommendations

- The zoster vaccination is approved for adults 50 years and older (Shingrix [GlaxoSmithKline], a recombinant zoster vaccine [RZV]) or 60 years or older (Zostavax [Merck]; a live zoster vaccine [LZV]).

Summary of Evidence

Almost a third of patients will develop herpes zoster (HZ) at some point in their lifetime, with age being the most important risk factor for development of the disease. CKD, including ESKD, has also been shown to independently increase the risk for shingles.[47] There is some observational evidence that patients with CKD who develop an episode of HZ are at higher risk for progressing to ESKD. Whether HZ accelerates progression to ESKD or the development of HZ is a marker for chronic illness is unknown.[48] In a population-based comparative study in Taiwan, there is some evidence that the incidence of HZ is higher among patients receiving PD than those receiving HD, although

Table 3. Dosing Schedule for Pneumococcal Immunizations in Adult Patients With Kidney Disease

Initial Vaccine	Subsequent Vaccination Needs
PCV13	8+ wk later give PPSV23, then 5 y later give a second dose of PPSV23
PPSV23[a]	1 y later give PCV13 and 5 y after initial PPSV23 vaccine give second dose of PPSV23
Either	All patients should get an additional PPSV23 vaccine at age 65 y if initial vaccine series started before age 65

Note: Based on information in Kim et al.[9] PCV13 is the preferred initial vaccine. Subsequent PPSV23 vaccines should be given a minimum of 5 years after the prior dose.
Abbreviations: PCV13, 13-valent pneumococcal conjugate vaccine; PPSV23, 23-valent pneumococcal capsular polysaccharide vaccine.
[a]Either previously vaccinated with PPSV23 or first dose given is PPSV23.

the explanation for this difference is not clear.[49] In the population receiving HD, steroid therapy increases the HZ rate, as would be expected, although there may be a protective role for intravenous vitamin D analogues and intravenous iron.[50] Limited data suggest that vaccination is safe and may be efficacious in this population. In a Kaiser cohort of patients receiving dialysis,[51] those who received the vaccine were less likely to develop HZ compared with those not vaccinated.

There are currently 2 recommended shingles vaccines in the United States, including RZV, a nonlive recombinant glycoprotein E vaccine with adjuvant, administered as a 2-dose series (at least 2 months apart) at 50 years or older, and LZV, a live attenuated vaccine administered at 60 years or older. Either vaccine can be administered to patients with CKD, although RZV is generally recommended over LZV due to greater efficacy and prolonged immunity in general.[9] Limitations of RZV include the need for a 2-dose series, increased rate of minor side effects, and lack of long-term follow-up data.

Special Considerations

Data for the use of other vaccines in patients with non–KRT-dependent CKD and those receiving maintenance dialysis are scarce. Patients should receive other routine immunizations (ie, human papilloma virus, tetanus, etc) if otherwise indicated. Travel vaccines (ie, yellow fever, typhoid, etc) should be administered if indicated in patients without contraindications (Table 1).

Kidney Transplant Recipients

Overview

Kidney transplant recipients remain at increased risk for infectious complications from vaccine-preventable diseases. Because vaccine responses are typically reduced in transplant recipients, every effort should be made to optimize vaccination before transplantation.[52] Further, given the reduced responses in transplant recipients, careful attention to vaccination of household members, close contacts, and health care workers who care for the recipients, who should be vaccinated as per standard ACIP guidelines, with particular attention to annual influenza vaccination.[53,54]

Although the optimal time to give vaccines after transplantation is not well studied, responses are expected to be reduced, particularly early posttransplantation, after treatment for rejection, or receipt of rituximab.[55-57] As such, most centers will wait 3 to 6 months after transplantation or treatment for rejection to vaccinate patients. If there is a community outbreak of an infection (ie, influenza), consideration should be given to vaccinate even if transplantation occurred within 3 months. Most inactivated vaccines can be safely given posttransplantation without significant risk for rejection. Vaccination may be associated with the development of de novo anti-HLA antibodies. Typically these are not donor specific and are generally not associated with adverse outcomes.[58-60]

However, live vaccines such as measles-mumps-rubella (MMR), varicella, live zoster, and yellow fever are generally not recommended posttransplantation because of the risk for ongoing replication in the setting of immunosuppression. There is limited experience in clinical trials of giving MMR or varicella vaccines posttransplantation to children without adequate vaccination pretransplantation. In studies of MMR posttransplantation, serologic response ranged from 41% to 62% in the year posttransplantation without evidence of developing clinical disease.[61,62] Likewise, studies of varicella vaccine posttransplantation, typically given late (8 months to 6 years), were associated with excellent humoral (87%-100%) and cell-mediated (86%-97%) immunity.[63-66] Some patients developed fever and vesicular lesions that responded to acyclovir. Disseminated varicella zoster virus has been described after vaccination in transplant recipients, with one case being proved due to the vaccine strain.[67,68] Despite the growing safety data, posttransplantation live virus vaccination is generally restricted to research studies.

Influenza

Recommendations

- All transplant recipients, their close contacts, and health care workers caring for them should get an inactivated influenza vaccine annually
- For patients 65 years or older, the high-dose inactivated influenza vaccine is preferred
- Vaccination should be given optimally 3 to 6 months after transplantation or treatment of rejection; if a local epidemic requires earlier vaccine, consideration for a booster dose 4 to 6 weeks after the initial dose should be considered

Summary of Evidence

A number of different formulations of influenza vaccine are available. Although studies have generally been small, all formulations of inactivated vaccine have been demonstrated to be effective in preventing influenza. In general, live-attenuated influenza vaccine should be avoided in kidney transplant recipients unless it is the only option for vaccinating the patient. Kidney transplant recipients on ≥2 g of daily mycophenolate mofetil and who are 65 years and older generally have reduced humoral responses.[69] MF59-adjuvanted influenza vaccine does not appear to significantly improve vaccine responses compared with standard vaccines.[70,71]

Repeat vaccination, typically 4 to 8 weeks after the initial vaccine, is another approach to improve responses to standard-dose vaccines in transplant recipients and is commonly used in individuals needing vaccination shortly after transplantation. This approach is associated with a consistent but modest improvement in seroconversion and seroprotective humoral responses (10%-12% increase in seroprotection with the second vaccine).[72] Inactivated high-dose influenza vaccine contains 4 times the

hemagglutinin protein and has also been studied in the transplantation population. In the largest study to date, high-dose vaccine was associated with a much higher seroconversion rate (influenza A, subtype H1N1: 40.7% vs 20.5%; A/H3N2: 57.1% vs 32.5%; B: 58.3% vs 41.6%), although there were no significant differences in seroprotection rates, likely due to high prevaccination titers.[73] If additional studies demonstrate similar superiority, high-dose vaccine may become standard of care for all transplant recipients. Due to costs and insurance limitations, high-dose vaccine is generally recommended only for patients 65 years or older, for whom it is specifically indicated.[74]

Pneumococcal Disease

Recommendations

- All transplant recipients should be given PCV13 and PPSV23 according to current ACIP recommendations
- Repeat dosing of the pneumococcal conjugated vaccine should be given at 65 years of age

Summary of Evidence

As in other patients with kidney disease, pneumococcal conjugated vaccine (PCV13) is recommended in kidney transplant recipients and is generally followed by a boosting dose of pneumococcal polysaccharide vaccine (PPSV23). Unlike the evidence supporting the prime-boost approach in healthy individuals, studies in transplant recipients have not clearly demonstrated a significant increase in serotype-specific functional antibody concentrations. Most studies did not assess cellular responses.[75] Nonetheless, studies of the currently approved 13-valent conjugate have demonstrated a median 1.1- to 1.7-fold increase in antipneumococcal immunoglobulin G antibody concentrations for all 13 serotypes. Further, the vaccine has been consistently found to be safe with no de novo anti-HLA antibodies and no episodes of biopsy-proven rejection reported.[76]

Herpes Zoster

Recommendations

- RZV, the inactivated adjuvanted HZ vaccine, should be given to all kidney transplant recipients ideally 6 to 12 months posttransplantation

Summary of Evidence

Transplant recipients are at greater risk for developing HZ and related complications. As such, approaches to reduce the incidence of HZ infection are greatly needed. The live attenuated zoster vaccine (LZV) is contraindicated in transplant recipients. RZV, the recently approved adjuvanted inactivated varicella zoster vaccine, has been demonstrated to reduce the risk for zoster and related complications in a healthy elderly cohort. In a large study of autologous hematopoietic stem cell transplant recipients, RZV was 63.8% effective in preventing HZ infections.[77] A 2-dose series of the inactivated vaccine was studied in kidney transplant patients (121 vaccine, 119 placebo) and was found to be safe and have a vaccine response rate of 80.2%, while 71.2% of vaccinated people had varicella zoster virus–specific cell-mediated immunity detected.[78] Future studies will have to demonstrate whether pretransplantation vaccination retains protection, particularly in the setting of lymphocyte depletion and/or rituximab use.

Special Considerations

Meningococcal Disease

Patients with an indication for eculizumab should receive both MenACWY (the vaccine against *Neisseria meningitidis* serogroups A, C, W, and Y) and MenB (against serogroup B) at least 2 weeks before initiation (Table 1). Patients who are predicted to need eculizumab, either due to preexisting antibodies or atypical hemolytic uremic syndrome, should be given meningococcal vaccines. Because many transplant recipients receive eculizumab in the setting of an acute event (ie, antibody-mediated rejection or hemolytic uremic syndrome) that is treated with intravenous immunoglobulin and enhanced immunosuppression, response to vaccine is generally poor, typically in the range of 20% with the first dose.[79] Even with a second dose of vaccine, ~50% remain without protective antibodies. As a result, prophylaxis is typically continued until a second dose of vaccine is given and immunity is confirmed. Optimizing vaccination is important because breakthrough infections occur, likely due to inadequate immunization. The Centers for Disease Control and Prevention identified at least 16 cases of meningococcal disease in eculizumab recipients in the United States from 2008 to 2016, most (14 [88%]) of whom had received at least 1 dose of meningococcal vaccine. All had meningococcemia and 6 had meningitis; 4 cases were caused by serogroup Y and 11 by nongroupable *N meningitidis*.[80]

Cytomegalovirus

While cytomegalovirus vaccines in development are immunogenic, their ability to reduce the frequency of cytomegalovirus replication and end-organ disease is limited. As such, no cytomegalovirus vaccines are currently approved for use.[81]

Travel

For transplant recipients with plans to travel to regions of increased risk for infection, routine vaccinations (eg, hepatitis B) and travel-specific vaccinations should be provided along with routine pretravel advice. Live attenuated vaccines, such as yellow fever, oral *Salmonella typhi* (Vivotif [PaxVax Berna]), and cholera vaccine (Vaxchora [PaxVax Inc]) are not recommended for transplant recipients.[55] Inactivated vaccines, including Japanese encephalitis and intramuscular *Salmonella typhi* (Typhim Vi [Sanofi Pasteur]) can be safely given to transplant

recipients. Unvaccinated transplant recipients should be strongly advised against traveling to areas where there is a true risk for yellow fever. If travel to an area where yellow fever vaccine is recommended cannot be avoided, these patients should be informed of the risk for yellow fever, given detailed information on how to avoid mosquito bites, and be provided with a vaccination medical waiver.[82]

Vaccination of Close Contacts of Transplant Recipients

Use of vaccines in health care workers, close contacts, and pets of transplant recipients are generally recommended and may reduce the risk for transmission and disease in the recipient. Although live virus vaccines are contraindicated in transplant recipients, health care workers, close contacts, and pets of transplant recipients can be safely given any vaccine except for smallpox vaccine.[55] Live attenuated cholera vaccine may be shed in the stool for a week after vaccination so caution should be taken by household contacts. Most live virus vaccines require no special precautions. Transplant recipients who care for infants who receive the rotavirus vaccine should practice good handwashing practices after diaper changes for 2 weeks after vaccination. Inactivated influenza vaccine is preferred but if unavailable (ie, in the setting of a pandemic), live-attenuated influenza vaccine can be given to contacts.

Case Review

The nephrologist caring for the patient in this vignette should administer the seasonal influenza vaccine when available and PCV13 followed by PPSV23 at 8-plus weeks later. If the patient is not immune to HBV infection, he should receive the full series with a repeat titer 1 to 2 months postvaccination. At age 50 years, he would be a candidate for a 2-dose series of the inactivated zoster vaccine. The nephrologist should also ensure that the patient is up to date on routine adult immunizations, including Tdap/Td (tetanus and diphtheria or tetanus, diphtheria and pertussis) and MMR.

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