Chapter 12: Vaccination

12.1: We recommend giving all KTRs approved, inactivated vaccines, according to recommended schedules for the general population, except for HBV vaccination. *(1D)*
- **12.1.1: We suggest HBV vaccination (ideally prior to transplantation) and HBsAb titers 6–12 weeks after completing the vaccination series. *(2D)***
  - **12.1.1.1: We suggest annual HBsAb titers. *(2D)***
  - **12.1.1.2: We suggest revaccination if the antibody titer falls below 10 mIU/mL. *(2D)***

12.2: We suggest avoiding live vaccines in KTRs. *(2C)*

12.3: We suggest avoiding vaccinations, except influenza vaccination, in the first 6 months following kidney transplantation. *(2C)*
- **12.3.1: We suggest resuming immunizations once patients are receiving minimal maintenance doses of immunosuppressive medications. *(2C)***
- **12.3.2: We recommend giving all KTRs, who are at least 1-month post-transplant, influenza vaccination prior to the onset of the annual influenza season, regardless of status of immunosuppression. *(1C)***

12.4: We suggest giving the following vaccines to KTRs who, due to age, direct exposure, residence or travel to endemic areas, or other epidemiological risk factors are at increased risk for the specific diseases:
- **rabies, *(2D)***
- **tick-borne meningoencephalitis, *(2D)***
- **Japanese B encephalitis—inactivated, *(2D)***
- **Meningococcus, *(2D)***
- **Pneumococcus, *(2D)***
- **Salmonella typhi—inactivated. *(2D)***

12.4.1: Consult an infectious disease specialist, a travel clinic or public health official for guidance on whether specific cases warrant these vaccinations. (*Not Graded*)

KTRs, kidney transplant recipients; HBsAb, antibody to hepatitis B surface antigen; HBV, hepatitis B virus.

Background

Recommended vaccinations are those approved and suggested by local and national health authorities for their constituent populations. These may vary by country of origin and geographic location. The efficacy of hepatitis B vaccination is determined by the prevention of hepatitis B infection, which is indirectly measured by the development of antibody to hepatitis B surface antigen (HBsAb) titers >10 mIU/mL. Individuals who are at increased risk include those with direct exposure, or residence in or travel to an endemic geographic area. In the case of meningococcal infection, patients who have undergone splenectomy are at increased risk.

Rationale

- The harm of different infections, and thereby the potential benefits of vaccinations, vary by geographic region.
- Little or no harm has been described with the use of licensed, inactivated vaccines in KTRs.
- Most vaccines produce an antibody response, albeit diminished, in immunocompromised individuals, including KTRs.
- The potential benefits outweigh the harm of immunization with inactivated vaccines in KTRs.
- Serious infection can result from live vaccines in immunocompromised patients, including KTRs.
- In the absence of adequate safety data to the contrary, it should be assumed that the harm of live vaccines outweigh their benefits in KTRs.
- Vaccinations are most likely to be effective when immunosuppression is lowest, when KTRs are receiving the lowest possible doses of immunosuppressive medication.
- Influenza vaccination needs to be provided on an annual basis in advance of the onset of the annual influenza season. Even while KTRs are receiving high levels of immunosuppression, the benefits of timely vaccination outweigh the risks of delaying vaccination.
- Some KTRs are at increased risk to develop disease attributable to one or more (rare) pathogens based upon direct exposure from residence in, or travel to, endemic areas. Although limited efficacy data are available for these inactivated vaccines to rare pathogens, potential benefits likely outweigh harm.

Inactivated vaccines

The American Society for Transplantation's Guidelines for the Prevention and Management of Infectious Complications of Solid Organ Transplantation provides guidance on immunizations relevant to their patient populations (289). While these recommendations may be appropriate for North America, they may not apply to KTRs worldwide.

Although only a limited number of studies evaluating the safety and efficacy of inactivated vaccines have been performed in solid-organ transplant recipients in general, and in KTRs in particular, available evidence suggests that inactivated vaccines are safe. There is no evidence that vaccinations lead to an increased risk of rejection.

Unfortunately, data on the efficacy of individual inactivated vaccines are limited. In general, existing data suggest that the response to vaccination in KTRs is diminished compared to immunization prior to transplantation. Accordingly, the optimal timing for immunizing KTRs is prior to transplantation. However, this is not always possible and, in some cases, repeated vaccinations after transplantation are necessary. A number of studies have been performed in organ transplant recipients that demonstrate immunogenicity of several inactivated vaccines after solid-organ transplantation. Influenza vaccination is among the most thoroughly evaluated in organ transplant recipients. Although response to influenza vaccination may vary among KTRs and from year to year, 30–100% of immunized KTRs will achieve protective hemagglutination-inhibiting serum antibody titers. Of note, the efficacy of influenza vaccination appears to be superior in pediatric compared to adult KTRs (290). Data are also available supporting the use of the 23-valent polysaccharide pneumococcal vaccine for KTRs >2 years of age. In contrast, hepatitis B vaccine has significantly diminished immunogenicity in organ transplant recipients compared to organ transplant candidates (291). Specific data regarding the immunogenicity of most of the remaining inactivated vaccinations are not available for solid-organ transplant recipients. Although data are lacking, most experts agree that the benefits outweigh the risks of immunization with inactivated vaccines (289).

There are sufficient data in KTRs indicating that the risk of vaccination with inactivated vaccines is minimal. The risk of infection, on the other hand, is higher in KTRs than in the general population. Therefore, vaccination with inactivated vaccines is warranted (Table 12).

Table 12: Recommended vaccines after kidney transplantation

Diphtheria—pertussis–tetanus
Haemophilus influenza B
Hepatitis A*
Hepatitis B
Pneumovax
Inactivated polio
Influenza types A and B (administer annually)
Meningococcus: administer if recipient is in high risk
Typhoid Vi

*For travel, occupational or other specific risk, and edemic regions.
Consider providing booster polysaccharide pneumococcal vaccination every 3–5 years.

Live vaccines

The currently licensed live vaccines use either attenuated viral strains that have been manipulated to reduce their virulence while attempting to maintain their immunogenicity, or, as in the case of Bacillus Calmette-Guérin (BCG), substitute a related bacterium that is thought to be less pathogenic, but still able to provide cross-reacting immunity to the target pathogen. While data are limited, significant concern exists for the use of live vaccines in immunocompromised patients. To date, only a limited number of studies have evaluated the use of live viral vaccines in organ transplant recipients (292). The high incidence of infections in KTRs is ample cause for concern that live vaccinations may cause infection in KTRs. While limited published experience is available describing the use of some live viral vaccines in organ transplant recipients (292), the limited number and small sample sizes included in these studies raise concerns about both the safety and efficacy of these vaccines in KTRs. Accordingly, most experts agree that, in general, the risks outweigh the potential benefits of using live vaccines in KTRs (293).

A number of live vaccinations licensed for use in the general population are contraindicated in KTRs (Table 13).

Vaccination timing

The reduced antibody response to different vaccines in KTRs is most likely due to immunosuppressive medication. Although there are no RCTs, it is reasonable to assume that giving vaccines when the amount of immunosuppressive medications patients are receiving is lowest is most likely to maximize the response to the vaccine (289)

Immunosuppressive medication amounts are usually highest in the first few months after transplantation, when the risk of acute rejection is also the greatest. Some time during the first 6–12 months, the amount of immunosuppressive medication is generally reduced to the lowest maintenance levels, if there is no acute rejection, and this is likely to be the best time for vaccination. This time of minimal maintenance immunosuppressive medication, and optimal time for vaccination, may be different in patients treated for acute rejection.

Table 13: Contraindicated vaccinations after transplantation

Varicella zoster
BCG
Smallpox
Intranasal influenza
Live oral typhoid Ty21a and other newer vaccines
Measles (except during an outbreak)
Mumps
Rubella
Oral polio
Live Japanese B encephalitis vaccine
Yellow fever

BCG, Bacillus Calmette-Guérin.

Influenza infection is a potentially important cause of morbidity and mortality in KTRs. The use of influenza vaccination has been demonstrated to be safe and generally effective in organ transplant recipients, including KTRs (294,295). In particular, it is worth noting that there is no proven association between the use of influenza vaccination in organ transplant recipients and the development of rejection. Accordingly, annual use of influenza vaccination is recommended for both KTRs and their household contacts. Because acquisition of influenza will occur during annual seasonal epidemics, it may not be possible to delay giving this vaccine until the patient is out far enough from transplant or on low levels of immunosuppression. Given that this is an inactivated viral vaccine, the major consequence of using this too early is that the immunization will not work. Given the potential benefit of providing the vaccine, it is recommended to give this vaccine prior to the onset of the annual influenza season, as long as the recipient is at least 1-month posttransplant. This timing is chosen as the vaccine is least likely to work during the first month after transplant, especially if the KTR has received induction therapy.

Hepatitis B revaccination

The need for hepatitis B vaccination booster is controversial and the practice varies from country to country. Patients with impaired immune function tend to have lower peak HBsAb levels compared to immunocompetent individuals. There are few data on durability of immunologic memory in immunocompromised hosts. However, there have been reports of clinically significant infection due to hepatitis B virus (HBV) in previously immunized dialysis patients in whom production of HBsAb was no longer measurable (296).

Serial measurements of HBsAb levels to inform the use of a booster dose of hepatitis B vaccine has been recommended for dialysis patients by the US Advisory Committee on Immunization Practices (296). In addition, the European Consensus Group on Hepatitis B immunity has expanded this recommendation to include patients with impaired immune function (297). Immunological memory wanes faster in immunocompromised renal transplant recipients. A level above 10 mIU/mL is generally taken to be protective, but transplant recipients with titers less than 100 mIU/mL tend to lose them rapidly. The potential for low anti-HBs levels to mask significant infection (indicated by hepatitis B surface antigen (HBsAg)) and the rapid decline led a European Consensus Group to suggest booster vaccination at titers below 100 mIU/mL. Although there is no clear evidence to support this recommendation, given the relative risk–benefit ratio of hepatitis B vaccine, it seems prudent to assess annually the need for a booster dose of this immunization.

Additional vaccines

Kidney transplant recipients may be at increased risk for vaccine-preventable pathogens through residence or travel to endemic areas, or due to inadvertent exposure. Recommendations for individuals traveling to certain geographic locations frequently include receipt of one or more immunizations against these pathogens. These recommendations would logically apply to KTRs, as long as the recommended vaccinations are inactivated, for example salmonella typhi Vi polysaccharide vaccine, or meningococcal vaccine. Consultation with an infectious disease specialist, travel clinic or public health official is recommended to clarify appropriate use of vaccinations for scenarios where travel or exposure may warrant use of these additional vaccinations.

Although efficacy data may not be available in KTRs, inactivated vaccines are generally safe. In contrast, some immunizations typically recommended for travelers are available only as live-attenuated vaccines. The use of these vaccines cannot be recommended, as neither safety nor efficacy data are available in this patient population.

Research Recommendations

Studies are needed to determine:

- the optimal timing of immunization in KTRs;
- the durability of immunologic response in KTRs vaccinated before and after transplantation.