Vaccination of Solid-Organ Transplantation Candidates

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Verifying immunization status and updating vaccinations are important steps in the evaluation of patients who are solid-organ transplant candidates because the potential benefits of vaccination outweigh the risk of adverse events. Because patients with end-organ disease, such as end-stage renal disease and cirrhosis, have reduced immune responses to many vaccines, vaccination should be performed as early as possible during the course of these diseases. Furthermore, it is particularly important for live vaccines to be updated during the pretransplant assessment because such vaccines are contraindicated once a patient is maintained on immunosuppression. Current information on vaccination for adult solid-organ transplant candidates is reviewed.

Among recipients of solid-organ transplants (SOTs), immunosuppression, underlying comorbidities, and exposure to health care increase the occurrence and severity of infection and the risk of related complications. Some infections have been associated with an increased risk of graft rejection and dysfunction [1–8]. Consequently, posttransplantation infections are a major determinant of the patient’s and the organ’s prognosis, making prevention of infection an attractive strategy. Commonly used interventions to prevent infection include vaccination, antimicrobial prophylaxis, and preemptive antimicrobial therapy.

Multiple observational studies have demonstrated the safety of vaccines in patients with end-stage renal disease (ESRD) and/or end-stage liver disease (ESLD) and in patients after SOT with inactivated and killed microorganisms [9–13]. Although there is some evidence that administration of live-virus vaccines (varicella and measles) in pediatric SOT populations is safe [14–17], current adult vaccination guidelines consider live-virus vaccines after transplantation to be contraindicated because of the risk of developing disease from the vaccine viral strain [1, 18–21]. Viral replication after the receipt of live-virus vaccines can be enhanced in patients who are immunosuppressed [22, 23]. According to evidence from the varicella vaccine literature, viral replication persists for 4–5 weeks after vaccination. We therefore propose that live-vaccine administration should occur only in those transplant candidates whose possibility for undergoing transplantation is not imminent (within 2 months) [24–26].

In general, compared with antibody titer response after vaccination in healthy control subjects, antibody titer response after vaccination in patients with ESRD and/or ESLD is lower and in patients after SOT is lowest [9, 10, 12, 13, 27–36]. Furthermore, patients with both organ failure and SOT have more rapid decreases in antibody titers compared with the decreases in antibody titers of control populations [34–42]. This decreased immune response in end-organ disease has led to increased-potency preparations of the hepatitis B vaccine for dialysis patients [20, 43]. In a recent review article by Plotkin [44], a correlate of vaccine-induced immunity has been defined as a specific immune response that is closely related to protection against infection or disease. In many cases, the true correlate of protection from infection is unknown or difficult to measure and protective levels of serum antibody titers do not always correlate with effective prevention from infection. In a few studies, SOT recipients have demonstrated cellular immune responses after vaccination that are comparable with those of control subjects; however, such assays are available only in research settings [16, 45, 46].

The timing of vaccination administration in relation to stage of end-organ disease and transplant status is a key determinant of immunity development. Immunosuppressive regimens used after transplantation may severely decrease immune responses to vaccines. For optimal host immune responses, vaccinations should therefore be administered before transplantation. Because ESRD and ESLD reduce immune responses to many vac-
cines, vaccination should be performed as early as possible during the course of these diseases; however, to our knowledge, no data exist on the minimum or maximum interval between vaccination and transplantation. A careful evaluation of immunity status before transplantation includes assessing the history of varicella and other infections for which vaccines may be used, obtaining a complete vaccination history, and measuring titer of hepatitis B surface antibodies and immunoglobulin G against hepatitis A, varicella, measles, mumps, and rubella. When available, antibody titers should be rechecked after vaccination to assess the need for booster doses, especially if ESRD or ESLD is already present [18].

In addition to the enhanced immune response to vaccination, other secondary benefits of administering vaccines to SOT candidates before development of end-organ disease and before transplantation exist. These benefits include avoiding vaccine-related febrile reactions that can complicate the clinical management of an SOT recipient and avoiding the possibility of developing clinical infection from live vaccines once immunosuppression has occurred. There are also theoretical concerns that vaccination could potentially trigger a cellular allograft rejection response [47]. Data in the literature, however, do not support this concept and rather confirm the safety of vaccination in SOT recipients [2, 48–50].

To reduce the risk of morbidity and mortality from vaccine-preventable disease, physicians who care for potential adult transplant recipients should monitor the immunization status of their patients and keep abreast of changes in the recommended immunization guidelines. Several new vaccines were recently approved for use in adults and recommendations for use of the influenza, pneumococcal, and pertussis vaccines were recently updated. Current information on vaccination for adult SOT candidates is reviewed.

**HEPATITIS B VACCINE**

SOT recipients may have more severe and more rapidly progressive hepatitis B virus (HBV) infection and may also reactivate latent disease while receiving immunosuppression [51]. Vaccination against hepatitis B may provide protection against donor-derived infection also [52]. The Advisory Committee of Immunization Practices (ACIP) currently recommends hepatitis B vaccination for patients with ESLD and/or ESRD [20]. Because patients with ESRD who are receiving hemodialysis may have a decreased serologic response to vaccination, higher-dose vaccine formulations have been developed for such patients (Recombivax HB, 40 µg, 3 doses [at 0, 1, and 6 months] and Engerix-B, 40 µg, 4 doses [at 0, 1, 2, and 6 months]) [43]. Standard-dose hepatitis B vaccines include Recombivax HB (10 µg) and Engerix-B (20 µg). There is also the option of Twinrix, the combined hepatitis A and hepatitis B vaccine. Patients with ESLD also produce lower antibody titers in response to vaccination and may benefit from the higher-dose hepatitis B vaccine [53–55]. Hepatitis B surface antibody titers should be assessed 1–3 months after completion of the primary HBV vaccine series [12, 54, 56]. For patients who do not respond to the initial HBV series (ie, who have antibody titers ≤10 IU/L), administration of an additional 3- or 4-dose series is recommended [57]. Although antibody titers may decrease after SOT, higher rates of protection are seen when vaccination occurs before SOT compared with rates of protection when vaccination occurs after SOT [34, 36]. Hepatitis B surface antibody titers should be monitored after SOT and booster doses given once titers decrease below 10 IU/L [58].

**HEPATITIS A VACCINE**

Severe disease and fulminant hepatitis can be caused by hepatitis A virus (HAV), especially in patients with chronic viral hepatitis and ESLD [59–61]. Vaccination against hepatitis A is recommended by ACIP for patients with ESLD [20]. There are 2 single-antigen vaccines (Havrix and Vaqta) that yield antibody responses. As mentioned above, there is also a combined hepatitis A and B vaccine for use in adults (Twinrix). As with hepatitis B vaccination, antibody titers in response to hepatitis A vaccination are lower in patients with ESLD and after renal and liver transplantation compared with antibody titers in healthy control subjects, and antibody titers may decrease after SOT [9, 10, 30, 37, 39]. Although, to our knowledge, there are no data specific to HAV vaccination, some experts would follow the same approach as for HBV. HAV serologic response should be assessed 1–3 months after completion of the primary HAV vaccine series and a single HAV booster dose should be administered to nonresponders [12, 54, 56, 57].

**PNEUMOCOCCAL VACCINE**

Invasive pneumococcal infection can cause significant morbidity and mortality in SOT recipients [62]. Pneumococcal vaccination is currently recommended in patients with chronic organ disease, including cardiovascular, renal, and liver disease, as well as in SOT candidates and recipients [20]. ACIP recommends one additional dose given 5 years after the first vaccination to those patients who received the initial vaccination before the age of 65 years and to immunosuppressed patients. Additional doses should be avoided to prevent the possible development of immune tolerance (hyporesponsiveness) [63]. As with other vaccines, protective antibody titers are known to decrease with time in patients with ESRD and/or ESLD and after SOT [35, 42, 64]. Available vaccines include the polysaccharide 23-valent vaccine (PPV-23) and the newer heptavalent conjugate vaccine (PCV-7). PCV-7 is not indicated for adult use. In one study by Kumar et al [40, 65], the PPV-23 and the PCV-7 vaccines demonstrated similar antibody responses; however, the effect of additional doses was not studied. Again,
pretransplant vaccination is preferred given that the antibody response in SOT recipients is lower than that of patients with end-organ disease, whose response is lower than that of control subjects [13, 33, 64].

**TETANUS, DIPHTHERIA, AND ACELLULAR PERTUSSIS VACCINE**

To our knowledge, there are no data on the incidence or severity of tetanus, diphtheria, or pertussis in transplant recipients. Tetanus and diphtheria vaccination appears to be safe and immunogenic in pediatric populations with ESRD and/or ESLD and in pediatric SOT recipients [66–68]; however, accelerated loss of diphtheria antibodies has been seen in the early posttransplant period [41]. In 2005, a tetanus, diphtheria, and acellular pertussis (Tdap) vaccine was licensed for use in the United States for persons aged 11–64 years. The ACIP currently recommends a single dose of Tdap booster for adults aged <65 years, which may be given ≤2 years after the last tetanus and diphtheria vaccine in high-risk individuals, such as those who are SOT candidates [69].

**HUMAN PAPILLOMAVIRUS VACCINE**

Immunosuppressed individuals, including recipients of SOTs, who have anogenital human papillomavirus (HPV) infection are at substantially increased risk of developing cervical and anogenital cancers [70]. In 2006, a quadrivalent capsid protein HPV vaccine was licensed in the United States for use in females aged 9–26 years [4]. The ACIP currently recommends vaccination for all females aged 11 or 12 years and catch-up vaccination for those aged ≤26 years. To our knowledge, the efficacy of this vaccine has never been studied in end-organ disease or SOT populations; however, we advise administration of this vaccine to SOT candidates who are female and aged 9–26 years.

**INFLUENZA VACCINE**

Influenza infection in SOT recipients is associated with increased morbidity and mortality, including severe pulmonary and extrapulmonary complications [3, 71–73]. In patients with cirrhosis, influenza infection may lead to further hepatic decompensation [74]. Immunosuppressed patients with influenza infection have prolonged viral shedding [75, 76] and are at increased risk of allograft rejection [6, 8, 73]. There have been theoretical concerns about influenza vaccination and development of allograft rejection [47]; however, the literature has not validated these concerns [31, 45, 49, 77, 78], and the influenza vaccine has been shown to be safe and to yield adequate antibody responses in SOT recipients [11, 27, 29, 31, 45, 46, 48, 77, 79–83]. There are currently 2 influenza vaccines available: the trivalent inactivated vaccine given intramuscularly and the live attenuated intranasal vaccine. To our knowledge, the safety of the live attenuated intranasal vaccine has not been studied in patients with ESRD and/or ESLD or in SOT recipients and should be avoided until more data are available. The administration of the live attenuated intranasal vaccine is contraindicated in immunosuppressed patients. Studies have revealed both adequate and impaired immune responses to the influenza vaccine in renal, heart, and liver transplant recipients [11, 27, 29, 31, 45, 46, 48, 77, 79–86]. Given that the risks of the trivalent inactivated vaccine are minimal, this vaccine should be administered annually to transplant candidates as well as recipients. This recommendation is supported by the ACIP guidelines that recommend influenza vaccination in all patients with chronic cardiovascular disease or with chronic renal or hepatic disease and in those who are immunosuppressed [20].

**MEASLES, MUMPS, AND RUBELLA VACCINE**

Most adult transplant candidates are already immune to measles, mumps, and rubella; however, because measles and rubella are live attenuated vaccines, every effort should be made to complete measles, mumps, and rubella (MMR) vaccination before transplantation in those adults who are not immune by serologic testing. In the general adult population, patients who were born before 1957 are assumed to be immune to measles, mumps, and rubella, and MMR vaccination is not recommended for them [20]. In contrast, SOT candidates reflect a population in whom live attenuated vaccines will soon be contraindicated and whose immunity to measles, mumps, and rubella should be verified. Serologic testing for measles, mumps, and rubella is therefore recommended in all SOT candidates. Moreover, because measles and rubella vaccines are live attenuated vaccines, MMR vaccination should be completed before transplantation in those adults who are seronegative. Immunity to rubella is particularly important in female transplant candidates who are of childbearing age because the risks of congenital rubella syndrome in those who may become pregnant outweigh the risks of the vaccine. Indeed, the MMR vaccine has been proven to be safe in bone marrow transplant recipients and in patients with human immunodeficiency virus (HIV) infection [87, 88]. HIV infection is currently not a contraindication to the MMR vaccine according to the ACIP except in those who are severely immunocompromised (ie, CD4+ cell count <200 cells/μL) [20].

**VARICELLA VACCINE**

As with measles, mumps, and rubella, most adult transplant candidates are already immune to varicella; however, varicella is known to cause severe disease in immunocompromised hosts [89]. Documented or physician-confirmed varicella disease is rarely available in the medical record of transplant candidates, unlike varicella-zoster virus (VZV) serology, which is both
widely and readily available. The ACIP gives special consideration for VZV vaccination to those at high risk for VZV disease, such as nonpregnant women of childbearing age [20]. Similarly, transplant candidates can be considered to be another high-risk group for whom VZV vaccination is highly recommended. In addition, the varicella vaccine is a live attenuated vaccine that is contraindicated for use in immunocompromised patients [20]. Therefore, we advise that all SOT candidates should have varicella serologies assessed, even those candidates who report a history of varicella disease, and all transplant candidates who are seronegative to varicella should be vaccinated before transplantation. Varicella vaccination has been studied in pediatric renal-transplant candidates with good safety and effectiveness [2, 90]. Varicella vaccination has also been studied in pediatric SOT recipients and has demonstrated safety and effectiveness [14, 16]; however, in the study by Zamora et al [17], a few children did develop mild varicella disease after vaccination. To our knowledge, the safety and effectiveness of the varicella vaccine has never been studied in adult SOT recipients. Use of the varicella vaccine in adults after SOT needs further study before it can be recommended for use in SOT recipients [91, 92].

**VARICELLA-ZOSTER (SHINGLES) VACCINE**

Reactivation of VZV after primary infection, or herpes zoster infection (shingles), occurs with increased incidence in immunocompromised hosts, including SOT recipients [93–95]. These patients are also more likely to develop more severe disease or disseminated herpes zoster infection. Not only is the incidence of herpes zoster infection known to increase with age, but also older individuals are receiving SOTs and the age of SOT recipients is likely to increase as the rest of the general population ages.

A live attenuated herpes zoster vaccine has been approved in the United States for use among individuals aged ≥60 years to prevent shingles [96]. The ACIP recently recommended routine single-dose vaccination of all persons aged ≥60 years, including those who report having previous episodes of zoster. Specific contraindications include immunodeficiency, immunosuppressive therapy, and previous receipt of the varicella vaccine. The ACIP also gives a recommendation specifically for “persons anticipating immunosuppression” [97]. They suggest that the zoster vaccine be administered ≥14 days before immunosuppressive agents are initiated with the caveat that some experts advise a period of 1 month between administration of live vaccines and immunosuppression [98]. As with other live vaccines, the herpes zoster vaccine is currently contraindicated after transplantation; thus, every effort should be made to complete zoster vaccination before transplantation.

A recent article by Cohen [99] summarizes points to consider when thinking about herpes zoster vaccination in immunocompromised patients. The new zoster vaccine is composed of the same viral strain (Oka) as the varicella vaccine but is distinctly composed with a 14-fold higher virus titer [96], and vaccination with the zoster vaccine could result in more adverse events in immunocompromised hosts than the varicella vaccine. However, if the zoster vaccine is given to immunocompromised individuals who already have some cellular and humoral immunity to VZV infection as measured by VZV antibodies, vaccination with the live-virus vaccine might be less dangerous. Regardless, immunocompromised patients were excluded in the Shingles Prevention Study [96] and, to our knowledge, there are no published data on the safety of the herpes zoster vaccine in immunocompromised hosts. The safety of herpes zoster vaccination in SOT recipients and other immunocompromised individuals warrants careful evaluation. We currently recommend that the herpes zoster vaccine be given to all adult SOT candidates with evidence of immunity to varicella, regardless of age, if transplantation is not imminent (within 2 months).

**CONCLUSIONS**

In summary, robust data in the form of large-scale vaccine clinical trials of patients with end-organ failure and SOT are lacking and these studies are unlikely to be conducted because of ethical and technical difficulties. Our review is mainly based upon observational studies and a few small clinical trials of particular vaccines. Some of our recommendations are extrapolated from data derived from healthy volunteers and pediatric populations. Nonetheless, despite this lack of data, most vaccines are considered to be safe and the potential benefit of conferring immunity to infection or disease in such a vulnerable patient population as SOT recipients is of great advantage. In contrast, any vaccine that is not administered to a patient is, by definition, 100% ineffective. Therefore, we view any patient encounter as an opportunity for vaccination, especially if SOT is a potential future consideration. Timing of vaccination is of utmost importance so patients may have the best opportunity to mount an appropriate immune response. Vaccination early in the course of end-organ disease is preferred to waiting until the pretransplant evaluation for the organ wait list. Influenza vaccine is an exception because it should be given annually both before and after transplantation.

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**References**


