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Vaccination strategies in patients with solid organ transplant: evidences and future perspectives

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Solid organ transplant recipients need emphases on immunization that result in certainly decrease the risk of vaccine preventable diseases. Organ transplant candidate should complete the recommended full vaccination schedule as early as possible during the courses of underlying disease because the patients with end stage liver or renal disease have reduced immune response to vaccine. Furthermore, live attenuated vaccines are generally contraindicated after transplantation. This review summarizes current information and the evidences regarding the efficacy and safety of immunization in adult solid organ transplant candidates and recipients.

Keywords: Vaccines, Immunization, Organ transplantation

Current Information on Immunization in Organ Transplant Recipients

Organ transplantation is one of the most effective therapeutic modalities for patients with acute or chronic end-stage liver or kidney disease, but infectious complications significantly impact the morbidity and mortality among organ transplant recipients. Some of these infectious complications are vaccine-preventable diseases; thus, vaccination of organ transplant recipients should not be overlooked. Current guidelines support the completion of a vaccination schedule prior to transplantation because the efficacy and safety of vaccines are lower in solid organ transplant (SOT) recipients than in immunocompetent individuals as a result of their underlying chronic disease and the administration of post-transplantation immunosuppressive therapy, which can decrease the immune response of these patients to a vaccine [1-4]. Compared with post-transplant primary vaccination, pre-transplant immunization reduces morbidity and increases protective antibody titers [5]. Thus, vaccination should be scheduled as early as possible when transplantation is planned.

Vaccines in Organ Transplant Candidates and Recipients

Influenza vaccine

Influenza is one of the common endemic viral diseases that is associated with higher morbidity and mortality in SOT recipients than in immunocompetent patients. Following infection with pandemic influenza A H1N1, 57%-70% of organ transplant patients required hospital admission, and the resulting mortality was 4%-21% [6-8]. Fur-

thermore, influenza infection was related to graft rejection in 19.5% of kidney transplant recipients [8]. Although estimates of the immunogenicity of influenza vaccine vary between studies, some reports indicated that organ transplant recipients have poorer antibody responses to influenza vaccination than patients on dialysis or healthy controls [9-11]. The types of immunosuppressive agents, the intensity of immunosuppression, age, and early period after transplant was associated with lower antibody responses [12-14].

The definite evidence to guide the optimal timing of influenza vaccination is still lacking. Administration of the inactivated seasonal influenza vaccine is recommended annually in pre- and post-transplantation periods; however, it should not be administered any earlier than 3-6 months after transplantation [15]. The Kidney Disease/Improving Global Outcomes (KDIGO) guidelines suggest that patients who are at least one month post-transplantation should receive an influenza vaccination before the start of the influenza season [16]. The live attenuated influenza vaccine (LAIV) is administered intranasally by spray and can cause mild to severe respiratory symptoms related to viral replication, therefore LAIV is contraindicated for immunosuppressed patients including SOT recipients. Several trials concerning a booster dose, a higher dose, or the use of adjuvant or intradermal vaccination are evaluated for their ability to overcome the relatively low immunogenicity of inactivated influenza vaccines in transplant recipients. Unfortunately, the booster strategy after a single standard dose of influenza vaccine did not significantly improve the immunogenicity of this vaccine in transplant recipients [17,18]. A recent randomized controlled trial comparing high dose intradermal versus standard intramuscular influenza vaccination showed that high dose intradermal vaccination has the potential to enhance immunogenicity in certain groups [19]. Further studies will be needed to improve the immunogenicity of influenza vaccines in transplant recipients.

Pneumococcal vaccines

The estimated incidence of invasive pneumococcal disease in transplant recipients is 28-36 per 1,000 patients per year, which is higher than that in the general population [20,21]. Currently, the pneumococcal polysaccharide 23-valent vaccine (PPSV23) and pneumococcal conjugate 13-valent vaccine (PCV13) are licensed for use globally. Unfortunately, there have been reports that PPSV23 has low immunogenicity in organ transplant recipients, and one study showed that both the total antibody concentration and the number of serotypes with protective antibodies significantly decrease by 15 months after PPSV23 vaccination [22-24]. Advisory Committee on Immunization Practices (ACIP) of United States recommended that adults aged ≥19 years who have immunocompromising conditions, including SOT recipients, and 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. Subsequent doses of PPSV23 should follow current PPSV23 recommendations for high risk adults [25]. However, there have been few well-designed studies on the effectiveness of conjugated pneumococcal vaccines in SOT recipients (Table 1) [26-29]. One randomized, double-blind, placebo-controlled trial found no enhancement of pneumococcal vaccination immunogenicity by priming the recipients with the pneumococcal conjugate 7-valent vaccine before administering PPSV23, compared with that of a single dose of PPSV23 [26,27]. In contrast, a cost effectiveness analysis found that the addition of one dose of PCV13 to the previously recommended PPSV23 doses for adults with immunocompromised conditions potentially reduces both the risk of disease and the costs of related treatments [30].

Table 1. Conjugated pneumococcal vaccine studies in organ transplant recipients

Transplant organ	Vaccine	Efficacy	Reference
Kidney	PCV7 vs. PPSV23	Conjugate vaccine does not improve the durability of response	[21]
Liver	PCV7/PPSV23 vs. PPSV23	Similar (85.7% vs. 91.2%)	[26]
Heart, lung	PCV7/PPSV23	No benefit from the additional PPSV23 dose	[29]
Kidney	PCV7/PPSV23 vs. PPSV23/PPSV23	Similar (87.5% vs. 87.1%)	[27]

PCV7, pneumococcal conjugate 7-valent vaccine; PPSV23, pneumococcal polysaccharide 23-valent vaccine.

Hepatitis A vaccines

Fulminant hepatitis due to hepatitis A virus may develop in patients with chronic hepatitis or end stage liver disease [31,32]. Guidelines recommend hepatitis A vaccination in all seronegative patients with end-stage liver disease or renal disease [33]. Ideally, the serologic studies for hepatitis A should be performed prior to transplantation. Hepatitis A vaccines show reduced efficacy in patients with dialysis or end-stage liver disease compared with that in healthy control subjects, and the antibody titers in these patients may decrease rapidly

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over time [34,35]. The seropositive rate in liver and kidney transplant recipients after two doses of the hepatitis A vaccine was initially high at 97.4%, but it declined to 59.3% two years later [36]. It is not clear if these low antibody titers result in a lack of clinical immunity; further studies are needed to evaluate this question.

Hepatitis B vaccines

Hepatitis B virus (HBV) reactivation has been observed in SOT recipients due to immunosuppression [37]. Routine HBV vaccination is recommended for all seronegative patients with end-stage liver disease or renal disease because HBV can be transmitted by organ transplant or transfusion and because vaccine immunogenicity may be suboptimal after transplantation [33]. HBV vaccines have a lower efficacy in patients with end-stage renal disease or end-stage liver disease than they do in healthy control subjects [38,39]. Moal et al. [40] reported a considerable decrease in anti-HBV antibody titers and a loss of protective HBV immunity during the first year following kidney transplantation, especially in patients with an initial anti-HBV antibody titer of <100 IU/L. A HBV vaccination schedule with a higher dose of vaccine showed a better antibody response rate in patients with end-stage liver disease. Furthermore, the administration of four doses of the intramuscular recombinant HBV vaccine led to seroconversion in 88% of patients who were on dialysis; in contrast, the traditional three-dose schedule is associated with low seroconversion rates of 65%-76% [41-43].

Varicella-Zoster vaccine

Herpes zoster results from a reactivation of latent varicella-zoster virus (VZV) infection. The risk of fatal complications, such as disseminated VZV, is greater in immunosuppressed individuals than in immunocompetent persons. A live attenuated virus vaccine for VZV (Zostavax) has recently been introduced, and this vaccine is effective in preventing herpes zoster in older patients [44]. Among patients aged ≥60 years with end-stage renal disease, receipt of the herpes zoster vaccine was associated with a lower incidence of herpes zoster (adjusted hazard ratio, 0.49; 95% confidence interval, 0.29 to 0.85) [45].

Generally, the use of live-attenuated vaccines is not recommended after transplantation because of the possibility of vaccine-related viral disease. Live vaccines should be administered at least four weeks prior to transplant [4,46]. After VZV vaccine administration in a group of pediatric liver transplant recipients, 97% of patients remained seroprotected at follow-up (median follow-up time, 1.7 years), and no VZV-related diseases were reported [47]. However, there is a case report about fatal disseminated varicella zoster infection following zoster vaccination in an immunocompromised patient [48]. A clinical trial for an inactivated zoster vaccine is ongoing, and this formulation may play a pivotal role in the post-transplant setting.

Tetanus, diphtheria toxoid and pertussis

High response rates to tetanus vaccination have been observed in transplant recipients, ranging from of 85%-100%. However, patients who are immunosuppressed via treatment with an anti-CD20 monoclonal antibody show lower immune responses to tetanus vaccination than patients receiving conventional immunosuppressive medication [11]. Additionally, short-term response rates to diphtheria vaccination were as high as 88.5% in SOT recipients [11]. However, a rapid loss of anti-tetanus and anti-diphtheria antibodies has been observed after transplantation [49-51].

Pertussis is a highly contagious infectious disease caused by *Bordetella pertussis*, and transplant recipients have a higher chance of contracting this disease from health care workers or family members. ACIP in United States recommends that adults aged 19-64 years who have not previously received a dose of tetanus, diphtheria toxoid, and pertussis vaccine (Tdap) receive a single dose of Tdap [52,53]. They also recommend that persons aged 65 years or older who have or who anticipate having close contact with an infant aged less than 12 months (e.g., grandparents, child-care providers, and healthcare practitioners) and who previously have not received Tdap should also receive a single dose of Tdap, both to protect against pertussis and to reduce the likelihood of its transmission to babies with underdeveloped immune systems. After the initial Tdap vaccination, all persons should continue to receive a booster of tetanus-diphtheria vaccine every 10 years throughout life, whether or not they are organ transplant patients.

Varicella

Most adult transplant candidates already have immunity to varicella from natural infection or childhood vaccination; however, this disease is potentially life-threatening in patients who are immunosuppressed following organ transplantation [54-56]. The ACIP recommends the routine vaccination of children and of susceptible persons who have close contact

with persons at high risk for serious complications of varicella [57]. The varicella vaccine is a live attenuated vaccine that is contraindicated for immunocompromised patients. SOT candidates should take a varicella serologic test before transplantation, and varicella vaccine should be administered before transplantation to any candidates who are seronegative for anti-varicella antibodies [1,2,4]. There are some reports about the safety and effectiveness of varicella vaccination in pediatric transplant patients receiving low-dose immunosuppression (Table 2) [47,58,59]. The seroprotection rate for varicella following post-transplant immunization in a group of pediatric living donor liver transplant recipients was 32%, and the seroprotection rate after second-dose vaccination for recipients with primary vaccine failure was 50% [58].

Table 2. Varicella vaccine studies in organ transplant recipients

Transplant organ	Median age (mo)	Efficacy (%)	Side effect	Reference
Liver, intestine	26	86	Disseminated rash 25%	[59]
Liver	15.6	97	Local: 54.8% Systemic: 64.5%	[47]
Liver	17	32	No serious adverse events	[58]

Measles, mumps, and rubella

SOT candidates who are identified by serologic tests as not having antibodies against measles, mumps, or rubella should complete vaccination with the measles, mumps, and rubella vaccine (MMR) before transplantation. MMR is a live attenuated vaccine, so it is contraindicated after transplantation, especially in adults. Immunity to rubella is especially important in female transplant candidates who are of childbearing age because of the risks for congenital rubella syndrome if these patients contract rubella while pregnant. There are some reports about the safety of the MMR vaccine in pediatric SOT recipients; however, no data are available in adult SOT recipients [60,61].

Table 3. Recommended vaccine schedule in adult solid organ transplant recipients

	Plan		Comment
	Evaluation	Vaccination plan	
Pre-transplant	Serologic test for measles IgG Mumps IgG Rubella IgG	MMR if seronegative	MMR should be completed at least I month prior to transplantation (not recommended if emergency listing for transplant within 4 weeks)
	HAV IgG	HAV vaccine as schedule	2 doses, 0, 1 month (titer follow up needed)
	HBsAb	HBV vaccine as schedule	3 doses, 0, 1, 6-12 months (titer follow up needed)
	Varicella IgG	Varicella vaccine if seronegative	Varicella should be completed at least I month prior to transplantation (not recommended if emergency listing for transplant within 4 weeks)
	Herpes zoster	Possible	Contraindication in patients with previous varicella vaccinated or varicella naïve
	No need for serologic test, check vaccine history	Tdap (if no history of Tdap with 10 years)	Age of <64, first dose of Tdap, then Td every 10 years
		Pneumococcal vaccines	PCV13 1 dose followed by a dose of PPSV23 at least 8 weeks later
Post-transplant	Serologic test for HAV, HBV	HAV, HBV if needed	Same as pre-transplant periods
			Vaccine start 2-6 months after transplant except annual influenza
	Catch-up vaccination according to vaccine history and serology	Tdap (or Td)	Age of <64, first dose of Tdap, then Td every 10 years
		Pneumococcal vaccine	PCV13 1 dose followed by a dose of PPSV23 at least 8 weeks later if PPSV23 vaccinated first, can re-vaccine PPSV23 at least 5 years later or PCV13 at least 1 year later if high risk for pneumococcal infection (limited data)
		Herpes zoster	Contraindication
Annual vaccine		Influenza	Live influenza vaccine is contraindication, others are strongly recommended
Special vaccination		Meningococcal disease	Splenic dysfunction, conjugate vaccine is preferred
		HPV	Recommended but limited data
		Haemophilus influenza type B (Hib)	Not recommended routine adult SOT recipients
		Yellow fever	Contraindication

MMR, measles, mumps, and rubella vaccine; HAV, hepatitis A virus; HBsAb, hepatitis B surface antibody; HBV, hepatitis B virus; Tdap, tetanus, diphtheria toxoid, and pertussis vaccine; Td, tetanus-diphtheria vaccine; PCV13, pneumococcal conjugate 13-valent vaccine; PPSV23, pneumococcal polysaccharide 23-valent vaccine; HPV, human papillomavirus; SOT, solid organ transplant.

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Immunization for Healthcare Workers and Close Contacts of Transplant Recipients

Healthcare workers and close contacts of transplant recipients should be immunized against all vaccine preventable diseases to provide the transplant recipient with additional protection from these diseases [4]. Healthcare workers and close contacts can receive all indicated vaccines, including live attenuated vaccines. However, viral shedding has been reported after the administration of some live attenuated vaccines, so frequent handwashing should be maintained for a two-week period following vaccination with these types of vaccines [3,4,62,63].

Conclusion

SOT recipients have a higher risk of vaccine-preventable diseases than the general population especially if they have not been properly immunized prior to receiving the transplant. Although the immune response may be suboptimal in transplant recipients, immunization is crucial to decreasing the morbidity and mortality from vaccine-preventable diseases in these patients. Whenever possible, physicians should consider scheduling vaccination early in the course of end-stage organ disease and postponing the transplantation (Table 3). Live attenuated vaccines are generally contraindicated after transplantation, although there are increasing data regarding the safety of the varicella vaccine, especially in pediatric transplant recipients. Based on the beneficial effect of herd immunity, the vaccination of health care workers and close contacts of transplant patients is important to protect immunocompromised patients from diseases.

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