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What is the Practical Differences Between Vaccine Recommendations for Solid Organ Transplantation and Hematopoietic Stem Cell Transplantation?

Çocuklarda Solid Organ Transplantasyonu ve HSCT Hastalarındaki Aşı Önerileri Arasındaki Pratik Farklılıklar Nedir?

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Question: *What are the practical differences between vaccine recommendations for solid organ transplantation and hematopoietic stem cell transplantation?*
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Answer (Zeynep Gizem Ergün Özdel, MD; Mustafa Hacımustafaoğlu, MD)

The transplantation in children is a long and tiring process that carries significant health risks, both for patients, their relatives and also physicians. The transplantation process carries high health risks, especially in terms of infection. From this point, prevention of common and vaccine-preventable diseases is highly important for the transplant patients. So, it is necessary to evaluate the patient carefully, both before and after the transplantation procedure. There are a few prospective randomized controled trials about transplant vaccination and its timing. The quality evidence for these recommendations are usually Grade 2 or 3. Most of the clinical trials have been planned as adult study and most suggestions can be used reflectively for children.

In general, transplantation can be evaluated in two main groups as solid organ transplantation (SOT) or bone marrow stem cell transplantation (Hematopoietic stem cell transplantation; HSCT). Although the general evaluation and follow-up approaches are similar in regard of the transplant vaccinations, there are some differences between them. These differences are largely due to differences in immunological status among these patients.

Vaccination practices in adult and pediatric transplant recipients share similar principles. In adults, varicella zoster vaccine (inactivated recombinant vaccine) is also administered, and the human papilloma virus (HPV) vaccine is no longer recommended over a certain age. Only vaccination of pediatric transplant recipients will be discussed in this article.

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General issues and evaluations about SOT and HSCT transplant vaccinations

General post-transplant vaccination approaches: SOT recipients are constantly at risk of infection due to their lifetime use of immunosuppressive drugs. Post-transplant vaccination of inactivated vaccines are usually administered ≥3-6 months after transplantation, if there is no additional contraindication (graft rejection, intensive immunosuppressive therapy, etc.). Depending on the age of patient, inactivated vaccines are completed if missing. In some cases, additional vaccine doses (such as influenza, pneumococcus, HBV) are administered. Principally, live viral vaccines are not recommended after SOT (some authors may recommend some viral attenuated live vaccines, especially if the immunological status is appropriate after carefully evaluation).

In allogeneic HSCT recipients, after transplantation, recipient's immune system is mainly replaced with the donor's immune system. In the most HSCT transplant recipients, the recipient's immunity is largely lost as if recipient is never vaccinated. Therefore, all or most vaccinations after HSCT should be re-administered on an appropriate schedule. After successful transplantation, HSCT recipients (unlike SOT recipients); they eventually reconstitute their immune systems, usually by 3-6 months, and therefore may not require lifelong immunosuppressive therapy. Inactivated vaccines can be scheduled in HSCT recipients if there is no additional contraindication (Graft Versus Host reaction, intensive immunosuppressive therapy, relapse of the disease, etc.) ≥6-12 months after transplantation. For live attenuated viral vaccines, HSCT recipients are generally considered to become immunocompetent ≥24 months after transplantation. And live attenuated viral vaccines can be administered if there are no additional contraindications (Graft Versus Host reaction, intensive immunosuppressive therapy, etc.), and the vaccine schedule is incomplete or serology is negative.

It is recommended to evaluate the transplant recipient's serological status for vaccine-preventable diseases (HBV, Hepatitis A, tetanus, diphtheria, Hemophilus influenza Type B (Hib), measles, rubella, mumps, varicella, pneumococcal specific antibodies, etc.) before planning and initiating the post-transplant vaccination schedule. Then a vaccination schedule can be planned. While the individual vaccination plan is being scheduled, some inactivated vaccines (such as influenza, pneumococcal, HBV, DBaT-IPV vaccines) should be given priority in the vaccination plan. After post-transplant vaccination schedule is completed, response of the some vaccines should be reassessed with serology. According to serologic levels (such as HBV, HAV, tetanus, etc), revaccination may be required.

General pre-transplantation evaluation in regard of vaccination: In transplant candidates (SOT or HSCT), all age-appropriate vaccines are recommended to be administered by a certain period of time before transplantation. Inactivated vaccines should be completed ≥2 weeks before transplantation, and live attenuated vaccines ≥4 weeks. If the recipient has administered blood and blood products, and antibodies such as IVIG, especially in live attenuated vaccine applications such as MMR and varicella should be considered to have passed the recommended time. ≥4 weeks after completion of pre-transplant vaccines, serologic evaluation of vaccines (HBV, Hepatitis A, tetanus, diphtheria, Hemophilus influenza Type B (Hib), measles, rubella, mumps, varicella, pneumococcal specific antibodies, etc.) is recommended. In case of negative serological response, additional vaccination can be administered, if there is still appropriate time period before transplantation. It is recommended that the transplant donor, as well as the recipient, should be completed all their recommended vaccinations in an appropriate period (at least four weeks before live attenuated vaccines, at least two weeks before inactivated vaccines) prior to transplantation. Also, individuals in the close contact of the transplant recipient (such as family members, caregivers, long-term associates) should be vaccinated appropriately against all vaccine-preventable diseases, and missing vaccines, if any, should be completed, preferably before the transplant. In addition, pets living in the close environment of the transplant recipient should also be vaccinated appropriately.

Practical differences of vaccination for post-transplant SOT and HSCT recipients: Inactive vaccines of SOT recipients after transplantation: In SOT recipients, inactivated vaccines can be administered after ≥3-6 months after transplantation, unless there is an additional contraindication to the vaccine. However, as an exception, the influenza vaccine can be administered earlier; it can be administered at the beginning of the influenza season and ≥1 month after transplantation. The influenza vaccine can be repeated (four weeks apart, for a total of two doses). In adults, high-dose influenza vaccine may be preferred for stronger immune response, but use of high dose in children has not been adequetly studied yet. Other inactivated vaccines are completed according to the vaccination program and in accordance with the age if the schedule is not completed. However, pneumococcal vaccine in children aged 2-5; an additional dose of 13-valent pneumococcal conjugated vaccine (PCV-13) is administered, even if full doses have been given previously. The 23-valent polysaccharide pneumococcal vaccine (PPV-23) is administered eight weeks after the last dose of PCV-13. PPV-23 administration. PPV-23 should be repeated after five years. Even if the full dose of HBV vaccines

has been administered before, if the serological antibody titer is low (<10 I/mL), the HBV vaccine series are repeated (three doses in total; at 0-1-6 months). Other inactivated vaccines (Hepatitis A, diphtheria, pertussis, tetanus, polio virus, Hib, human papilloma virus, 4-valent conjugated meningococcal ACYW; MCV-4, 4-antigen meningococcal B and rabies when indicated, etc.) can be administered to SOT recipients at the recommended age, number of doses, and dose ranges as healthy children, ≥3-6 months after transplant. In SOT recipients, assesing the vaccination schedule, among the inactivated vaccines; influenza, pneumococcal, HBV DBT-IPV vaccines should be given priority.

Live attenuated vaccination of SOT recipients after transplantation: Live attenuated vaccines are still not recommended in patients undergoing SOT.

Inactive vaccination of HSCT recipients after transplantation: Inactivated vaccines are generally started ≥6-12 months after HSCT. Influenza vaccine and conjugated pneumococcal vaccines can be administered earlier (≥3 months after transplantation), if needed. When influenza vaccine is given at the beginning of the influenza season, a second influenza vaccination is recommended four weeks later. In HSCT recipients (unlike SOT recipients), inactivated vaccines are repeated as full dose (number) according to age. Post-transplant inactivated vaccine and its doses in HSCT recipients can be summarized as follows:

Influenza vaccine; It can be administered ≥3 months after transplantation, two doses should be administered with four weeks apart during the influenza season,

Pneumococcal vaccine; at ≥6 months (or ≥3-6 months) after transplantation, three doses of PCV-13 are administered at two-month intervals. PPA-23 is administered (or 4th dose of PCV-13) 6-8 months later.

DPaT, DPaT-IPV, DPaT–IPV–Hib, dpat (selected by age group) vaccine(s); ≥3 doses (according to age group) are administered, starting at ≥6 months (≥6-12 months) after transplantation. Doses are administered two months apart (three doses), if a 4th dose is required according to the age group, the 4th dose can be administered ≥6 months later. Some authors may prefer vaccines containing DPaT after seven years of age, as it has better antigenic responses.

HBV vaccine; starting at ≥6 months (≥6-12 months) post-transplant. Three doses (0-1-6 schedule) are administered.

Hepatitis A virus vaccine (routinely recommended in our country); two doses are administered, starting at ≥6 months (≥6-12 months) post-transplant and 6-12 months apart.

Hib vaccine; if it is not performed with DBaT, three doses are administered, starting at ≥6 months (≥6-12 months) after the transplantation, and with 1-2 month intervals.

Human papilloma virus (HPV) vaccine; Starting at ≥6 months (≥6-12. months) after transplant, taking into account age (≥9 years old), three doses (at 0, 1-2, six months) are administered. The two-dose reduced schedule is not recommended.

MCV-4 vaccine is administered at appropriate doses and intervals according to age and MCV-4 vaccine types, starting at ≥6 months (≥6-12 months) after transplant. However, at the age of ≥ 2 years, two doses are administered with an interval of two months.

Meningococcal B vaccine (four component); is administered according to the recipients age ≥6 months (>6-12 months) after transplantation. In children two years and older, it is administered as two doses with an interval of two months.

Among the inactivated vaccines; influenza, pneumococcal, HBV, DPaT-IPV vaccines should be given priority while scheduling.

Live attenuated vaccination of HSCT recipients after transplantation: Post-transplantation live attenuated vaccines (such as MMR, varicella) in HSCT recipients can be summarized as follows:

MMR vaccine; If serology is negative and there is still no significant immunosuppression (such as graft versus host reaction, significant immunosuppressive therapy, not taking rituximab therapy, etc.), two doses are administered one month apart, starting at ≥24 months after transplantation. If recipient has received blood and blood products or antibodies such as IVIG, it should be ensured that the recommended time has passed after the administration.

Varicella vaccine; if serology is negative, two doses are administered 1-3 months apart, starting ≥24 months after transplantation. If the recipient has previously received blood and blood products containing antibodies, such as IVIG, it should be noted that the recommended time has passed after the administration.

In conclusion: To briefly summarize the answer to our colleague's question, the pre-transplant vaccination principles are similar in SOT and HSCT recipients (also donor vaccination, vaccination of families and close contacts). The difference is mainly noticeable in post-transplant vaccination. Taking into account the current ages of the child and missing vaccines, after SOT, the all missing vaccines of recipients should be completed ≥3-6 months after transplantation. However, in pneumococcal vaccination, in children between ages 2-5, an additional dose of PCV-13 and PPV-23 is given, even if the vaccines are complete. And PPV-23 vaccine is repeated five years after. In patients with the complete vaccination history, additional booster doses are recommended for inactivated vaccines

if the serology is negative. Post-transplant live attenuated vaccines are not recommended to SOT recipients after transplantation. In HSCT recipients, post-transplant inactivated vaccines (assuming never been given before) are administered ≥6-12 months after transplantation, at full dose (number) and at appropriate intervals according to age. In HSCT recipients, live attenuated vaccines such as MMR and varicella can be administered ≥24 months after transplantation, if the serology is negative and if there is still no significant immunosuppression and the immunological parameters are adequate.

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