

REVIEW

Recommended Vaccination in Solid Organ Transplantation

Theodoros Voulgaris, MD, Vassilios A. Sevastianos, MD, PhD

*Fourth Department of Internal
Medicine, “Evangelismos” General
Hospital, Athens, Greece*

ABSTRACT

Patients with end-stage organ diseases, as well as solid organ transplantation recipients have reduced immune response to many vaccines. Thus, vaccination should be performed as early as possible during the natural course of their primary disease. Verifying immunization status and updating vaccinations are important steps in the evaluation of patients who are on a waiting list for solid organ transplantation. Potential benefits of vaccination outweigh the vaccine-related adverse events. According to current literature, there is no association between rejection episodes and previous exposure to vaccination. Furthermore, several viral infections have been reported to trigger graft rejection. This suggests that infectious agents, more commonly than vaccines, are a cause of graft rejection episodes, and effective immunization may be protective. Current information on vaccination for adult solid organ transplant candidates is reviewed in this article.

KEY WORDS: *rejection; solid organ;
transplantation; vaccination*

INTRODUCTION

Clinical course and survival of patients after solid organ transplantation have greatly improved over the last 20 years. Consequently, novel preventive and effective health measures are needed for the maintenance of the general health, not only for this fragile and vulnerable group of patients, but also for the community which is the source of solid organ grafts.¹ Anti-rejective immunosuppressive treatments expose these patients to a higher risk of life-threatening infections. At the same time, antimicrobial agents often exhibit poorer effectiveness in comparison to the one observed in the immunocompetent.² Therefore, prevention of infections in these patients is of fundamental importance.

Vaccinations can prevent diseases and reduce the proliferation and spread of various infectious agents. Nevertheless, even if active immunization is the key mechanism to preventing infections, many solid organ transplant recipients, who are under long-term immunosuppressive treatment, cannot achieve protective immune response even after the execution of a complete vaccination timetable. Moreover, vaccination with live attenuated vaccines carries with it the risk of an uncontrolled proliferation of the strain included in the vaccine and consequently such vaccination is avoided in solid organ transplant recipients.

It is important to clearly distinguish the documented contraindications for the

Correspondence to:
Vassilios Sevastianos, MD,
4th Department of Internal Medicine,
“Evangelismos” General Hospital,
Athens, Greece;
Tel./Fax: +30-210-6919912;
Mobile: +30-6973-795493;
e-mail: vsevastianos@gmail.com

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administration of a vaccine derived from strong clinical or bibliographic data, from those warnings emanating from mainly theoretical interpretations and sometimes personal thoughts of some clinicians. Not infrequently, the decision to offer a vaccine should be supported by the balance between two factors; first, the benefit, resulting from vaccination, following the prevention of an infectious disease and second the adverse effects or the risk of developing a life-threatening infection, from the wild strain of the pathogenic microorganism that may be contained in the vaccine.³

The risk of the development of an infectious disease and the failure to prevent it by active immunization is directly related to the immune competence of each patient. The greatest the degree of the therapeutic immunosuppression, the less possible to obtain an adequate response following active immunization. Recipients of solid organs, at least for the first two months after transplantation, are among the individuals with severe immunosuppression.³ Factors that contribute to the negative modification of the recipient's immune competency include underlying diseases, e.g., renal or hepatic insufficiency, a history of allograft rejection episode and the type of immunosuppressive therapy administered after transplantation.

A number of reasonable questions arise in clinical practice for transplanted individuals, concerning a) the effect of immunosuppression during vaccination exposure before transplantation, b) the efficacy of vaccinations after transplantation, c) the side effects of vaccines that contain live or inactivated strains in immunocompromised patients, and d) the effect of the vaccines on grafts function.⁴

GENERAL PRINCIPLES

Candidates for solid organ transplantation demonstrate an increased risk of infective complications. A variety of these transmissible complications can be effectively prevented if the appropriate vaccination schedule is carried out prior to transplantation. Therefore, an urgent need is emerging for health authorities before performing a transplantation; they should certify that the full timetable of planned vaccinations has been executed with respect to the transplantation candidate, his/her relatives and those health care professionals who support him/her (Table 1).

For example, the response to vaccination of patients with end-stage renal and/or liver disease is poor, while the one applied to solid organ transplant recipients is even poorer, in comparison to the one detected in healthy individuals. In addition, several studies reported that patients with organ failure and/or solid organ transplantation exhibit a faster reduction of serum antibody response titles after vaccination. The decrease of immune response in persons with underlying terminal illness was the fact that led to the modification of hepatitis B vaccine preparations available in the market, pointing to the group of patients with end-stage renal disease under hemodialysis (Recombivax HB, 40 mg, 3 doses at 0, 1 and 6 months; and Engerix-B, 40 mg, 4 doses at 0, 1, 2, and 6 months). Nevertheless, published studies present data where solid organ transplant recipients exhibited cellular immune response after a completed vaccination schedule, comparable to the response observed in the control groups.⁵

TABLE 1. Vaccinations in Patients with Solid Organ Transplantation.⁷

Vaccine	Recommendations
BCG	Contraindicated
Diphtheria, Tetanus, Pertussis	Before and after transplantation
Haemophilus influenzae	Before and after transplantation
Hepatitis A	For travelers to endemic areas before and after transplantation
Hepatitis B	Before and after transplantation
Influenza	Patients and family members before and after transplantation
MMR	Before transplantation
Pneumococcal	Before and after transplantation
Polio (oral)	Contraindicated
Vaccinia	Contraindicated in patients, household members, transplant health-care workers
Varicella	Controversial
Yellow Fever	Contraindicated

BCG= Bacillus Calmette-Guérin, MMR= Measles, Mumps, Rubella vaccine

Vaccination requirements for solid organ transplant candidates should be documented during patients' initial assessment and vaccination coverage must be completed before their inclusion in the transplant register. Indeed, in many organ transplant centres serological testing for infections that can be prevented by vaccination is routinely performed, including hepatitis B, chickenpox, measles, mumps and rubella with the goal to provide individualized recommendations to each applicant before transplantation.

It is generally accepted that due to the therapeutic immunosuppression received by solid organ transplant recipients, their immune system is unable to respond effectively. Most immunosuppressive regimens used in this group of patients include combinations of steroids and calcineurin inhibitors such as cyclosporine and tacrolimus. Consequently, both T- and B-cells' response is disturbed, firstly because of the inhibition of their proliferation, which is normally induced by antigen stimulation and secondly as a result of the interruption of cytokine production after such a stimulation.

Corticosteroids are potent cytokine inhibitors (interleukin 1, 2, 6, tumor necrosis factor and interferon gamma) and T-cell proliferation blockers. However, the degree of immunosuppression achieved merely by taking steroids, does not seem to fully disrupt immune response after the administration of a vaccine.

Calcineurin inhibitors directly inhibit T-cell proliferation induced by interleukin 2, while halting the production of interleukin 4 and 5 from T-cells, that subsequently have an inhibitory effect on B-cell activity and antibody production. Azathioprine and mycophenolate mofetil, which are used as third line immunosuppressive agents, interfere with purine synthesis, whereas they inhibit T- and B-cell proliferation at different stages.⁴

However, the above figures of immunosuppressive interventions are often supplemented by the co-administration of the recombinant humanized (daclizumab) or the chimeric (basiliximab) monoclonal antibodies (IgG1), which exhibit their activity without destroying activated T-lymphocytes, or by the co-administration of antibodies such as monoclonal antibody OKT-3 or antithymocyte globulin (ATG) with destructive effect on T-cells and in case of rituximab on B-cells.⁶

The combination of these mechanisms leads to the significant disturbance of the metabolic cascade resulting from the presentation of an antigen to the immune system cells. However, it is not known whether the use of these specific immunosuppression agents or the total burden of the received immunosuppression contribute more to the inadequate immune response to vaccination.

Furthermore, hypogammaglobulinemia, which is often observed after transplantation, seemingly plays an important role in the decrease of immune response to vaccination. This observation was documented in transplant heart, kidney and lung recipients and was associated with the development of

recurrent infections. Indeed, in a study involving patients with hypogammaglobulinemia, a protective response to pneumococcal vaccination was absent in 30%, to diphtheria in 15%, and to tetanus in 19% of cases. Patients with immunoglobulin levels <400 mg/dL had a poorer survival rate and a higher risk of invasive infections from cytomegalovirus. Therefore, the lack of innate immunity and the impaired antibody related response to vaccination may lead to an insufficient immune protection after solid organ transplantation.

The production of new memory cells and the survival of those cells acquired before transplantation are of critical importance for the expression of a capable response to vaccination. The effect of therapeutic immunosuppression on memory T-cells and on their life expectancy has not been fully elucidated. However, there is evidence that the booster administration of one or more additional vaccine doses can mobilize the immune memory acquired before transplantation and support a more effective response than that achieved by initial immunization.⁴

While health care professionals should make every effort that applicants to transplantation complete the vaccination timetable prior to the procedure, it should be highlighted that vaccines containing inactivated strains are generally safe also after solid organ transplantation. Particularly where bibliographic data regarding efficiency and safety of inactivated vaccines in transplant candidates are lacking, the recommendations of the national immunization advisory committees, designed for the general population, should be strictly followed.

There is no documentation that correlates graft rejection clinical episodes and previous vaccination exposure. It is generally accepted that vaccines containing live strains should not be administered after organ transplantation. Even if the optimum time for a vaccine administration after organ transplantation has not been defined yet, most transplant centres expose transplant recipients to vaccination 3 to 6 months after transplantation, when the levels of the therapeutic immunosuppression have been reached and become constant. Additionally, it is recognized that at least 4 weeks should elapse between the administration of the vaccine and the evaluation of seroconversion on the basis of the protective titers of antibodies, which for every vaccine have been documented in the literature.⁷

OPTIMAL TIME FOR IMMUNIZATION PRE- AND POST-TRANSPLANTATION

Candidates for solid organ transplantation may remain in transplant registries for an unpredictable, often long, time period. This length of time may be used by clinicians, *inter alia* in order to preserve and enhance, with the appropriate vaccinations, the serum levels of various antibodies against a wide range of disease-causing microorganisms. Thus, there is a rising need to draft future guidelines which will incorporate

vaccination in the criteria used for pre-transplant evaluation.⁸

This proposition is reinforced by the fact that before transplantation the antigen-related response to vaccination is characterized inadequate in many instances and this response evolves even more insufficiently after transplantation.^{2,9,10} Thus, given that vaccine immunogenicity is often reduced as organ failure deteriorates, candidates for transplantation should be immunized at the earliest time point possible during the natural course of the underlying main disease.⁷ Other reasons for the timely immunization of patients before transplantation include the fact that vaccines containing live viruses, e.g. measles, mumps, rubella, varicella and intranasal flu vaccine, are ordinarily avoided after organ transplantation. National guidelines of some international organizations head towards this direction by recommending that vaccination with live strains should precede the inception of any therapeutic immunosuppression at least by four weeks and in any case it should be avoided for the first two weeks after immunosuppression exposure.³

An important question arising in clinical practice concerns the optimal time for the continuation and/or completion of immunization after solid organ transplantation. Although this time frame cannot be definitely identified based on the available literature, many transplant centers anticipate at least two months after transplantation before proceeding to vaccinations. The rationale behind this is to avoid the contribution of the high doses of immunosuppression received by patients, which may further blunt immune response to the vaccines.³

It is usual to wait three to six months after transplantation before the administration of vaccines, once maintenance levels of the therapeutic immunosuppression are archived.⁷ Exceptions are influenza epidemic cases where the objective is to administer the inactivated influenza vaccine as early as one month after transplantation.³ Therefore, the standard vaccination schedule based on the age of the recipient and the one suggested for the immunocompromised hosts, e.g., pneumococcal vaccines in adults, should be administered at least two to six months after transplantation.³

RISK OF GRAFT REJECTION

The unwillingness of the clinicians to allow vaccine administration in transplant patients stems from a variety of factors, including the fear of triggering the mechanisms of allograft rejection. This issue was raised in the literature mainly from publications of small series of patients and individual case reports with scarce documentation. Indeed, in a study where two doses of influenza vaccine were administered in heart transplant patients, rejection episodes were experienced by 4 of the 14 heart transplant recipients, but by only one of the 14 controls ($p = 0.326$).¹¹

However, almost all large studies, conducted on this topic,

failed to document an increase in graft rejection or a significant clinical dysfunction of the graft after vaccination.^{12,13} Moreover, many recent literature references contain additional documentation for the safety of certain vaccines after transplantation, such as the influenza vaccine. Two studies, where 62 and 51 liver transplant recipients were included, demonstrated the effectiveness and safety of the influenza vaccine. At the same time they pointed out that vaccination against the influenza virus was not associated with allograft rejection or transaminase flares in liver transplant recipients.¹⁴

In a randomized trial where 58 heart transplant recipients were included, at least six months before their enrolment in the study, two different but antigenically identical vaccines, which differ only for the presence of adjuvants, were administered. Influenza symptoms were observed in 33% and 29% of the vaccinated patients, in comparison to 61% of the control group. In the same study, four episodes of acute myocardial rejection were identified without differences between the three study groups.¹⁵

In another study, which included 29 vaccinated cardiac transplant recipients; vaccination against influenza did not alter the percentage of lymphoid subpopulations and did not induce the generation of anti-HLA alloantibodies. Response to vaccination was detected in 12 of 29 patients and did not correlate with rejection history, length of graft survival, or the received immunosuppressive therapy. Vaccination did not change the frequency of rejection. Flu-like symptoms were reported in one patient but the possible association is not confirmed microbiologically.¹⁶

Another study, which included 3601 heart transplant recipients from 28 transplant centers, did not detect any variances, possibly related to vaccination, in the prevalence or the seasonality of graft rejection. However, it seems that differences exist between current recommendations and clinical practice. Current practice recommends that all immunosuppressed patients should receive vaccination against influenza. In the same study, large disparities were observed between vaccination practices used by different transplant centers. An 89% of the institutions administered flu vaccines, with 7 institutions requiring adequate range of time between transplantation and the introduction of vaccination. More specifically in one centre more than three months were required in order to introduce vaccination after transplantation, in another more than six and in five centers more than 12 months. All 25 centers that vaccinated patients used trivalent inactivated vaccines. Three centres did not vaccinate their patients due to a supposed association of vaccination with an increased allograft rejection. There were no significant differences in the total number of rejection episodes (0.4% vs 0.3%, $p = 0.7$), rejection episodes by month (January 0.4% vs 0%, $p = 0.2$; February 0.5% vs 1.5%, $p = 0.08$; March 0.5% vs 0%, $p = 0.14$), all infections (0.7% vs 0.6%, $p = 0.6$) and viral infections (0.1% vs 0%, $p = 0.17$) between centers that administered flu vaccines and those that

did not, respectively. The incidence of the influenza was low in both groups.¹⁷ Additionally in a recent study where 51,730 adult kidney transplant recipients were included, vaccination against influenza in the first year after transplant was associated with lower risk of subsequent allograft loss and death.¹⁸

Furthermore, in a recent study that included 51,730 adult renal transplant recipients, vaccination against influenza conducted during the first year after transplantation was associated with lower possibility of subsequent both graft and life loss¹⁸.

CONCLUDING REMARKS

Despite a lack of powerful literature data, most vaccines are thought to be safe for patients with end-stage organ failure or solid organ transplant recipients. The potential benefit of achieving immunity against various infectious agents in such a vulnerable patient population constitutes a major medical advantage. Contrariwise, every vaccine that is not administered is by definition 100% ineffective. Therefore, every such patient should be encouraged to be vaccinated. Every chance to access a vaccination program should be provided to any single transplant candidate where solid organ transplantation is the only future prospect.

Rejection episodes are not associated in the literature with previous vaccination exposure. Furthermore, several viral infections have been reported to trigger rejection. This suggests that infectious agents, more than vaccines, are a common cause of rejection, and effective immunization may be protective.

The clinicians should aim at full vaccination coverage of both the patient and household members of patient's family before transplantation. Vaccination should be carried out as soon as possible during the natural history of the underlying disease. Finally, special attention should be paid to the vaccination of medical practitioners and nursing staff that are in close contact with such a vulnerable patient population.

REFERENCES

- Zeldin GA, Maygers J, Klein A, et al. Vaccination, screening for malignancy, and health maintenance of the liver transplant recipient. *J Clin Gastroenterol* 2001;32:148-150.
- Hibberd PL, Rubin RH. Approach to immunization in the immunosuppressed host. *Infect Dis Clin North Am* 1990;4:123-142.
- Rubin LG, Levin MJ, Ljungman P, et al. 2013 IDSA clinical practice guideline for vaccination of the immunocompromised host. *Clin Infect Dis* 2014;58:309-318.
- Duchini A, Goss JA, Karpen S, Pockros PJ. Vaccinations for adult solid-organ transplant recipients: current recommendations and protocols. *Clin Microbiol Rev* 2003;16:357-364.
- Chow J, Golan Y. Vaccination of solid-organ transplantation candidates. *Clin Infect Dis* 2009;49:1550-1556.
- Sester M, Gartner BC, Girndt M, Sester U. Vaccination of the solid organ transplant recipient. *Transplant Rev* 2008;22:274-284.
- Danziger-Isakov L, Kumar D. Vaccination in solid organ transplantation. *Am J Transplant* 2013;13:311-317.
- Martin P, DiMartini A, Feng S, Brown R, Jr., Fallon M. Evaluation for liver transplantation in adults: 2013 practice guideline by the American Association for the Study of Liver Diseases and the American Society of Transplantation. *Hepatology* 2014;59:1144-1165.
- Gangappa S, Kokko KE, Carlson LM, et al. Immune responsiveness and protective immunity after transplantation. *Transpl Int* 2008;21:293-303.
- Molrine DC, Hibberd PL. Vaccines for transplant recipients. *Infect Dis Clin North Am* 2001;15:273-305, xii.
- Blumberg EA, Fitzpatrick J, Stutman PC, Hayden FG, Brozena SC. Safety of influenza vaccine in heart transplant recipients. *J Heart Lung Transplant* 1998;17:1075-1080.
- Grekas D, Alivanis P, Kiriazopoulou V, et al. Influenza vaccination on renal transplant patients is safe and serologically effective. *Int J Clin Pharmacol Ther Toxicol* 1993;31:553-556.
- Kobashigawa JA, Warner-Stevenson L, Johnson BL, et al. Influenza vaccine does not cause rejection after cardiac transplantation. *Transplant Proc* 1993;25:2738-2739.
- Lawal A, Basler C, Branch A, Gutierrez J, Schwartz M, Schiano TD. Influenza vaccination in orthotopic liver transplant recipients: absence of post administration ALT elevation. *Am J Transplant* 2004;4:1805-1809.
- Magnani G, Falchetti E, Pollini G, et al. Safety and efficacy of two types of influenza vaccination in heart transplant recipients: a prospective randomised controlled study. *J Heart Lung Transplant* 2005;24:588-592.
- Kimball P, Verbeke S, Flattery M, Rhodes C, Tolman D. Influenza vaccination does not promote cellular or humoral activation among heart transplant recipients. *Transplantation* 2000;69:2449-2451.
- White-Williams C, Brown R, Kirklin J, et al. Improving clinical practice: should we give influenza vaccinations to heart transplant patients? *J Heart Lung Transplant* 2006;25:320-323.
- Hurst FP, Lee JJ, Jindal RM, Agodoa LY, Abbott KC. Outcomes associated with influenza vaccination in the first year after kidney transplantation. *Clin J Am Soc Nephrol* 2011;6:1192-1197.