

Vaccinations in Kidney Transplant Patients: Searching for Optimal Protection

Camille Nelson Kotton

Clin J Am Soc Nephrol 6: 2099–2101, 2011. doi: 10.2215/CJN.07330711

Adults tend to be significantly undervaccinated, and many patients on hemodialysis or who have undergone kidney transplantation often miss this opportunity for protection. Clinicians, leery of doing harm and not fully appreciating the risks and benefits of vaccination, may defer indicated immunizations for their patients. Unfortunately, this renders these already vulnerable patients more susceptible to preventable infections. Hemodialysis and kidney transplant patients should receive many of the routine vaccines as per national and local guidelines, as well as necessary travel-related and other immunizations (1–3). In general, although live attenuated vaccines should be deferred in this population, including those against attenuated (intranasal) influenza, varicella, zoster, measles, mumps, rubella, yellow fever, Bacille Calmette Guerin, and oral *Salmonella typhi*, most other routine vaccines are recommended.

Clinicians are often concerned about the efficacy of vaccination in kidney transplant recipients who are on chronic immunosuppression or on hemodialysis. In this study by Crespo *et al.* (4), of subjects with low prevaccination titers ($<1:40$), seroconversion rates were low and not statistically different in both renal transplant (42%) and hemodialysis (33%) patients, but were much higher in healthy controls (82%). For the entire group, seroconversion was associated with younger age. For the transplant subgroup, seroconversion was associated with a longer time after transplantation and proteinuria (according to Crespo *et al.*, a surrogate marker of length of time after transplantation). Numerous other factors, including type of immunosuppression, did not influence response to vaccination. In the hemodialysis group, only younger age was associated with response. No severe adverse events or cases of clinical influenza were detected or reported, and serum creatinine remained stable in the transplant recipients at 6 months of follow-up. Other studies have also shown reduced rates of seroconversion in immunosuppressive hosts, which is not surprising. They excluded the 12% who had seroprotection in the initial sample; thus, these data are not broadly applicable to all transplant and hemodialysis patients, but only to those who had no prior seroprotection. Whether reaching the seroconversion definition is imperative for true clinical protection or

whether some immunologic protection even below the seroconversion threshold may be partially protective in immunocompromised hosts remains to be determined.

Optimal timing of vaccination after solid organ transplant has been shown to be important in optimizing the immunologic response in multiple studies: generally, the further out from transplant, the better the response. The potent immunosuppression given at the time of organ transplant (especially cytolytic induction therapies) seems likely to result in muted immunologic responses to vaccination for at least several months. Most vaccine trials exclude patients who underwent organ transplant within the previous 2 to 6 months. One early study of mixed organ transplant recipients saw no difference in the time after transplant in vaccine nonresponders *versus* responders (5), whereas in another series of 51 liver transplant recipients who underwent influenza vaccination, vaccine response corresponded to length of time after transplant: within 4 months of transplantation, 1 of 7 (14%) responded; within 4 to 12 months, 6 of 9 (67%) responded; and after 12 months, 30 of 35 (86%) responded to the H1 strain. Overall more than 55% of the subjects vaccinated 4 to 12 months after transplantation had adequate antibody seroconversion to the three strains of the influenza vaccine (6). A recent study showed lower antibody titers in kidney transplant recipients vaccinated within 6 months of transplantation (7). One-third of the 53 transplant recipients were 6 months or less from the time of kidney transplantation. The muted response to vaccination was more marked with respect to seroresponse (fourfold increase in antibody titer) than with seroprotection (titer $\geq 1:32$).

In the absence of strong evidence to drive the clinical decision, programs develop local protocols. A recent survey of 239 United Network for Organ Sharing–certified kidney transplant programs showed that the majority of the respondents began posttransplant vaccination within the first 6 months, with 42% of programs giving influenza vaccine within the first 3 months, 43% at 3 to 6 months, 13% at 6 to 12 months, and 3% more than 12 months after transplant (8). Guidelines from the American Society of Transplantation Infectious Dis-

Transplant and Immunocompromised Host Infectious Diseases, Infectious Diseases Division, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts

Correspondence: Dr. Camille Nelson Kotton, Transplant and Immunocompromised Host Infectious Diseases, Infectious Diseases Division, Massachusetts General Hospital, Harvard Medical School, 55 Fruit Street, Cox 5, Boston, MA 02114. Phone: 617-724-0082; Fax: 617-726-7653; E-mail: ckotton@partners.org

eases Community of Practice suggest that centers restart vaccination 3 to 6 months after transplant (1). With pandemic H1N1, expert guidelines suggested that transplant recipients begin to receive H1N1 vaccine as soon as 1 month after transplant (9), balancing the risk of infection during a pandemic with the likelihood of an immunologic response. Further studies are needed regarding optimal timing of vaccination with respect to clinical protection after solid organ transplantation.

Acceptance for vaccination of transplant patients has increased. In the aforementioned survey, 95% of respondents at 239 United Network for Organ Sharing–certified kidney transplant centers recommended influenza vaccination in 2009, up from 84% in 1999 (8). For the minority of centers that do not recommend vaccination, two-thirds cited a concern about lack of efficacy, and close to one-third cited safety concerns. In a recent trial of two prospectively followed independent cohorts of 92 and 59 kidney-transplanted patients, assessing their anti-HLA antibodies before, 6 weeks, and 6 months after H1N1 vaccination, 16 of 92 (17.3%) and 7 of 59 (11.9%) patients developed anti-HLA antibodies (detected using single antigen bead technology) (10). This included both donor-specific and non-donor-specific antibodies, mostly at low levels. Two of the 20 patients followed at 6 months had clinical events possibly related to *de novo* anti-HLA antibodies. The authors expressed concern that multiple doses of annual influenza vaccine may lead to the production of anti-HLA antibodies in some kidney transplant recipients. The study highlights the complexity in demonstrating an association between rejection and immunization. Further scrutiny of alloimmune response after vaccination may be helpful in evaluating this important question.

Adjuvants are used to stimulate the immune system by attracting greater number of antigen-presenting cells to the site of vaccination; as potent stimulators of both cellular and humoral responses, they augment the response to immunization. The use of adjuvants in immunocompromised transplant recipients is relatively unstudied; there has been theoretical concern about adjuvants increasing the risk of rejection. Recent guidelines suggested, “If only adjuvanted H1N1 vaccine is available, this should be given to solid organ transplant recipients.... There is no evidence that adjuvants increase the risk of allograft rejection.” (9) In the study by Crespo *et al.* (4), two different adjuvants were used in the two different vaccines. Both are proprietary adjuvants, with AS03 in *Pandemrix*, and MF59 in *Focetria*, and contain squalene as well as other ingredients. During the H1N1 outbreak, adjuvanted vaccines were not recommended for use in young children and pregnant women due to unclear consequences. Although adjuvanted vaccines were used in Europe and Canada, unadjuvanted vaccines were used in the United States. Whether adjuvants can be safely used in organ transplant recipients is another area ripe for study.

Whether multiple doses of vaccination should be given to transplant recipients remains unclear. One recent study in HIV-positive patients showed a significant augmentation of the immunologic response after repeat

vaccination; the rate of seroconversion after the first dose of an adjuvanted H1N1 influenza A vaccine was 68% and increased to 92% after a second dose (11), and the authors conclude that repeat vaccination may be indicated as a means to augment immunity. Clinicians may want to consider this, especially in individual patients who seem less likely to respond to a primary vaccine based on the factors described by Crespo *et al.* (4). In addition, if the influenza season lasts longer than usual, repeat vaccination may be helpful in providing longer protection.

Numerous studies have shown that although vaccination in this population may result in a less robust immunologic response, it is nonetheless generally worthwhile to vaccinate because many patients develop some type of immunologic response and protection against disease. To achieve the optimal response to vaccination, clinicians should consider timing after transplant, because the first few months after transplant are likely to result in a reduced response to vaccination. The clinicians must balance the potential lack of immunogenicity with the risk of acquisition of clinical disease. Additionally, they should consider giving more frequent booster doses of vaccines because immunity wanes more rapidly in immunocompromised hosts. If vaccines are given during periods of potent immunosuppression, clinicians may want to repeat the vaccination once the immunosuppression has lightened.

Disclosures

None.

References

1. Danzinger-Isakov L, Kumar D: Guidelines for vaccination of solid organ transplant candidates and recipients. *Am J Transplant* 9 [Suppl 4]: S258–S262, 2009
2. Kotton CN, Hibberd PL: Travel medicine and the solid organ transplant recipient. *Am J Transplant* 9: S273–S281, 2009
3. Recommended adult immunization schedule for United States 2011. *MMWR Morb Mortal Wkly Rep* 60, 1–4, 2011 Web site: www.cdc.gov/vaccines/recs/schedules/downloads/adult/mmwr-adult-schedule.pdf
4. Crespo M, Collado S, Mir M, Cao H, Barbosa F, Serra C, Hidalgo C, Faura A, Montero M, García de Lomas J, Horcajada JP, Puig JM, Pascual J: Efficacy of influenza A H1N1/2009 vaccine in hemodialysis and kidney transplant patients. *Clin J Am Soc Nephrol* 6: 2208–2214, 2011
5. Blumberg EA, Albano C, Pruett T, Isaacs R, Fitzpatrick , Bergin J, Crump C, Hayden FG: The immunogenicity of influenza virus vaccine in solid organ transplant recipients. *Clin Infect Dis* 22: 295–302, 1996
6. 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* 4: 1805–1809, 2004
7. Birdwell KA, Ikizler MR, Sannella EC, Wang L, Byrne DW, Ikizler TA, Wright PF: Decreased antibody response to influenza vaccination in kidney transplant recipients: A prospective cohort study. *Am J Kidney Dis* 54: 112–121, 2009
8. Chon WJ, Kadambi PV, Harland RC, Thistlethwaite JR, West BL, Udani S, Poduval R, Josephson MA: Changing attitudes toward influenza vaccination in U.S. Kidney transplant programs over the past decade. *Clin J Am Soc Nephrol* 5: 1637–1641, 2010
9. Kumar D, Morris MI, Kotton CN, Fischer SA, Michaels MG, Allen U, Blumberg EA, Green M, Humar A, Ison MG, AST

- Infectious Diseases Community of Practice and Transplant Infectious Diseases Section of TTS: Guidance on novel influenza A/H1N1 in solid organ transplant recipients. *Am J Transplant* 10: 18–25, 2010
10. Katerinis I, Hadaya K, Duquesnoy R, Ferrari-Lacraz S, Meier S, van Delden C, Martin PY, Siegrist CA, Villard J: De novo anti-HLA antibody after pandemic H1N1 and seasonal influenza immunization in kidney transplant recipients. *Am J Transplant* 11: 1727–1733, 2011
 11. Bickel M, von Hentig N, Wieters I, Khaykin P, Nisius G, Haberl A, Stephan C, Herrmann E, Doerr HW, Brodt HR, Allwinn R: Immune response after two doses of the novel split virion, adjuvanted pandemic H1N1 influenza A vaccine in HIV-1-infected patients. *Clin Infect Dis* 52: 122–127, 2011
- Published online ahead of print. Publication date available at www.cjasn.org.
- See related article, “Efficacy of Influenza A H1N1/2009 Vaccine in Hemodialysis and Kidney Transplant Patients” on pages 2208–2214.