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EDITORIAL

Optimizing virus protection in lung transplant recipients: Don't drop the ball

The SARS-CoV-2 pandemic has brought the threat of viral infections to the fore. Even seemingly healthy, young individuals can die if they contract the virus,[1] and immunocompromised individuals may be at greater risk of a fatal outcome should they become infected.[2] But many other viruses pose potential threats to the well-being of solid organ transplant recipients. Chief among viral threats to lung transplant recipients are cytomegalovirus and community-acquired respiratory viruses. Fortunately, we have developed strategies to prevent or blunt the impact of cytomegalovirus on lung transplant recipients,[3] but a high degree of vigilance must be maintained to screen and prevent the passage of transmissible viruses from donor to recipient.[4]

Since the advent of highly effective vaccines against common childhood illnesses (Table 1), measles, mumps, German measles, and chicken pox outbreaks and epidemics have almost completely disappeared from the United States and most other developed countries. Nonetheless, even fully vaccinated individuals could still contract and develop infections from these viruses, but the herd immunity attained by universal childhood vaccination programs makes it very unlikely that a significant outbreak or epidemic can arise. However, increasing hostile attitudes in a substantial segment of the population toward childhood vaccination and the unfounded notion that childhood vaccines are linked to autism[5] may abrogate the protection that herd immunity provides and lead to outbreaks or even epidemics that can threaten the well-being of immunocompromised transplant recipients, even if they have received vaccinations prior to transplantation. If vaccines are available to protect patients who must receive intense posttransplant immunosuppression, but using live attenuated virus vaccines, such as measles, mumps, rubella (MMR) and Varicella, in immunosuppressed transplant recipients is considered to be contraindicated—it seems logical that it is important to screen solid organ transplant candidates for evidence of protective, virus-specific immune responses. Then, if needed, these vaccines can be given to candidates prior to transplantation. However, emerging data in pediatric solid organ recipients suggest that live virus vaccinations may be given safely to carefully selected, clinically stable patients following transplantation.[6]

Hostetler et al[7] performed a retrospective analysis of virus-specific antibody levels in 1025 candidates who underwent first-time evaluations for lung transplantation at their center to determine whether serologic evidence of humoral immunity against measles, mumps, and varicella-zoster (VZV) could be detected. They found that a small, but not negligible, number of patients lacked detectable IgG antibodies against these viruses. Those with undetectable anti-virus IgG titers tended to be younger patients, especially those with a diagnosis of cystic fibrosis (CF).

Attenuated live virus vaccines against measles and mumps were licensed in the United States in the 1960s, and these were combined with the MMR vaccine in 1971, which became mandatory in pediatric vaccination recommendations. Subsequent accumulated data showed that the vast majority of vaccinated children appear to attain lifelong immunity as reflected by seropositivity, similar to individuals who developed active infections prior to the introduction of these vaccines. Data also indicate that active infection in unvaccinated individuals can lead to higher titer, sustained IgG levels later in life. However, both total antibody levels and antibody avidity for antigen can wane over time in non-immunocompromised populations.[8,9] Therefore, it is perhaps not surprising that evaluation of solid organ transplant candidates by other investigators have found individuals who appear to lack virus-specific immunity to measles, mumps, and Varicella.[10]

The report by Hostetler et al[7] and others raise important questions concerning the evaluation and care of lung transplant candidates as well as the sustainability of immune responses to the MMR and Varicella vaccines. Although one would suspect that individuals with unmeasurable virus-specific antibody titers are likely to have significantly impaired ability to respond to a specific infectious agent, might previously vaccinated individuals with undetectable antibody titers still retain some degree of immunologic memory? Could such individuals still have an ability to rapidly generate antibodies via immunologic recall or have latent T cell responses that can be ramped up to provide protection should they become infected with one of these viruses? Are children with CF somewhat less likely to adequately respond to childhood vaccinations with the MMR or Varicella vaccines, and are their immune responses more likely to wane over time? Additionally, should lung transplant centers routinely screen all candidates for serologic immunity to these viruses, and should seronegative candidates be vaccinated with appropriate live virus vaccines if they are not immunocompromised? We suggest that screening for immunity to measles, mumps, and rubella should be a routine part of the pretransplant evaluation, and vaccinating appropriately prior to transplant should be done by all centers.

TABLE 1 Virus infections for which live virus vaccines are typically given in early childhood

Virus	Disease	Virus type	Major potential complications of active infection	Vaccine efficacy[a]	Year vaccine first available[c]
Measles morbillivirus (Rubeola)	Measles	SS RNA	Pneumonia, encephalitis, immune suppression, secondary infection	1st dose – 93% 2nd dose – 97%	1963
Mumps orthorubulavirus (Mumps)	Mumps	SS RNA	Deafness, encephalitis, meningitis, pancreatitis	1st dose – 78% 2nd dose – 88%	1967
Rubivirus rubella (Rubella)	German measles	SS RNA	CNS infection; internal bleeding Congenital rubella syndrome[b]	>90% for at least 15 years	1969
Varicella-zoster (VZV)	Chickenpox (acute primary infection)	DNA (Herpes family)	Pneumonia, encephalitis, internal bleeding, disseminated disease	95% after 10 years (2 doses)	1995

Abbreviations: CNS, central nervous system; SS, single-stranded.

[a]Vaccine efficacy varies slightly according to live virus strain, country where assessed, quality of assessment, and definition of efficacy.

[b]Congenital rubella syndrome risk greatest in first trimester of pregnancy (fetus can develop deafness, heart defects, CNS, ocular abnormalities, etc.).

[c]Year licensed in United States.

Because assumptions are made that if children receive two vaccinations with the MMR and Varicella vaccines they have lifelong protection, IgG responses are rarely checked later in life. Therefore, there are few data pertaining to long-term antibody levels in specific populations such as young adults with CF. The recent finding that the MMR II vaccine may provide long-term, cross-protective immunity against COVID-19[11] provides another reason to ascertain whether past vaccinations are accompanied by serologic evidence of sustained efficacy. Re-vaccination, if evidence of serologic immunity is lacking, may not only protect against measles, mumps, and rubella but also provide some protection against SARS-CoV-2 as its evolving variants continue to ricochet throughout world populations.

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DISCLOSURE

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