Cytomegalovirus Infection and Cardiac Allograft Vasculopathy in Children

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The relationship between viral infections, host immune responses, and long-term cardiac allograft outcomes is complex and not fully elucidated at this time. Children are exposed to many viruses, and young transplant recipients will often experience their primary infection for a given viral pathogen while under iatrogenic immunosuppression. Despite this, most viruses cause only mild clinical illness, and transplant recipients often clear infection in a fashion similar to that of their healthy (nonimmunocompromised) peers. Death or serious morbidity from acute viral infection, especially those caused by common respiratory and intestinal viruses, is very rare in children who have received heart transplants. Serious morbidity and mortality may, however, follow infection with human herpes viruses.

Article p 1798

Human herpes virus infections occur in most children during the course of childhood, and the viruses persist in the body indefinitely. Many primary infections carry no symptoms, and the presence of prior infection is identified through evidence of seroconversion at the time of evaluation for transplantation. Symptomatic disease is more common when primary viral infection occurs in the immunocompromised host. Primary Epstein–Barr virus infection posttransplantation poses significant risk for the development of posttransplantation lymphoproliferative disorders. Cytomegalovirus (CMV) may also cause severe infection, especially if primary infection occurs in the early weeks or months after transplantation. This risk appears low, however, in the modern era.

Prevention commonly involves early postoperative use of intravenous ganciclovir and/or oral administration of valganciclovir, with or without immunoglobulin preparations. The length of therapy varies widely between centers. Pretransplantation seropositive status for CMV is generally considered to carry lower risk of severe acute infection, but antiviral prophylaxis is still generally used in most centers.

With the recognition that acute CMV infection now poses low risk for serious early morbidity and mortality after heart transplantation, increasing attention is being focused on the possible role of viral persistence as a risk factor for the development of chronic graft vasculopathy (transplant coronary artery disease [CAD]), chronic graft dysfunction, and late graft loss. In adults, substantial evidence exists that CMV infection plays an important role in the pathogenesis of chronic graft vasculopathy/CAD. The importance of this observation lies in the fact that CAD is the most common cause of death beyond the first year after transplantation. Evidence to support a role for CMV in the pathogenesis of CAD comes from epidemiological observations, pathophysiological studies, and from therapeutic effects of anti-CMV antiviral therapy in animal models and in human clinical trials. In contrast to adults, the role of CMV infection in the determination of cardiac allograft outcomes after pediatric transplantation has received little attention.

In the current issue of Circulation, Hussain and colleagues investigate the role of pretransplantation CMV serostatus and posttransplantation CMV infection on CAD in a pediatric heart transplantation population. A total of 165 children were studied retrospectively with the primary outcome measures of development of graft CAD, mortality or graft loss beyond 6 months from transplantation, and death or graft loss caused by CAD. Of these children, 32 developed laboratory evidence of CMV infection, but only 6 developed CMV disease or syndrome. Recipient-positive CMV serostatus pretransplantation was the only independent predictor of all 3 outcomes measures. The authors also noted that recipients who were seronegative for CMV pretransplantation had less CAD, irrespective of donor serology.

This important study has some limitations, several of which are noted by the authors. The overall sample size is modest (though large for a pediatric study), and 22 cases were excluded from the multivariate analysis because of missing risk factor data. The data collection was retrospective, and there were inconsistent approaches to CMV prophylaxis and diagnosis over time. Importantly, no surveillance protocol for CMV infection is given, and it seems likely that screening for viremia may have differed among different “at-risk” groups as well as over time. The number of variables analyzed as risk factors was limited, and some variables known to be risk factors for the development of CAD, such as older donor age, were excluded. A number of the variables studied were closely correlated (eg, recipient and donor age and CMV serostatus), and the multivariate analysis may not be able to unravel all these confounders in a limited population of patients. Older recipients are more likely to be CMV-seropositive and are known to have a greater risk of development of CAD on the basis of multicenter experience of >1000 pediatric heart transplant recipients. Older recipients are also more likely to receive organs from older donors, also known to be an important risk factor for the development of...
graft CAD in children (but not evaluated in this study).\textsuperscript{11} Finally, the accuracy of pretransplantation recipient and donor CMV serologies as markers of prior infection is unknown. For example, infants will frequently be seropositive because of placental transmission of maternal CMV IgG antibodies. Others may be positive as a result of blood transfusions or therapy with immunoglobulin preparations that might predate referral for transplantation evaluation. Donor serologies may also be unreliable in a significant number of cases caused by transfusion of blood products during resuscitation before declaration of brain death and formal donor evaluation. It is not clear in this study what percentage of donor and recipient serologies were performed in the absence of these confounding variables.

Despite these limitations inherent in a retrospective study, the data certainly suggest that CMV-positive serostatus at transplantation is an important risk factor for graft vasculopathy and graft loss in children. This suggestion supports the mounting literature in adults, which bears similar conclusions.\textsuperscript{1} On the basis of this retrospective analysis alone, caution should be exercised in concluding that recipient seronegative status with positive donor CMV serology is not a risk factor for graft CAD. Primary CMV mismatch certainly increases the risk of symptomatic primary CMV infection and the risk of viremia. In adults, the latter may be a risk factor for the development of coronary endothelial dysfunction, subsequent CAD, and reduced patient survival.\textsuperscript{12} The data in this study are certainly sufficiently interesting to justify prospective analysis with uniform CMV antigen surveillance protocols and posttransplantation prophylactic management. Unfortunately, the prevalence of angiographically defined CAD in children is likely insufficient to power randomized trials of prophylactic antiviral therapy, even if performed in the setting of a multicenter study. Coronary intravascular ultrasound is potentially an excellent surrogate marker for the study of CMV infection on graft CAD, but it is currently used in very few pediatric centers and is not suitable for use in infants and very small children. In the interim, it seems likely that pediatric transplantation physicians will be guided by the results of prospective studies and clinical trials of CMV prevention performed by our adult colleagues.

Finally, we should note that other viruses may be the cause of acute and chronic graft dysfunction. Though enteroviruses, adenoviruses, and parvoviruses are less studied than CMV, increasing evidence exists that they may infect the cardiac allograft and be the cause of late graft dysfunction and loss.\textsuperscript{13,14} Of particular relevance to pediatric practice, the detection of an adenoviral genome (and other viruses) from endomyocardial biopsy samples strongly predicts subsequent transplantation CAD and graft loss. It is clear that viruses may be critical determinants of long-term allograft outcomes, even though death as a result of acute viral infection is a very rare event. Much is still to be learned about the interactions between viruses, the allograft, and the immune response of the immunocompromised heart transplant recipient.

**Disclosures**

None.

**References**


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