Cytomegalovirus in the Pediatric Transplant Recipient: Where Are We Now?

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Cytomegalovirus (CMV) has long been recognized as one of the most important infections to complicate organ transplantation.¹ In the early era of transplantation, it led to disease in 40% of pediatric liver recipients.² Disease was particularly severe for those who were naïve to the virus prior to transplantation.^{2,3} In addition to direct viral damage, CMV has been implicated in a number of indirect adverse effects including rejection, vascular complications and a risk for other infections, although these indirect effects have mostly been noted in adult recipients.⁴⁻⁶

The availability of ganciclovir starting in the late 1980s changed the outcome for patients suffering from CMV disease, improving survival as well as decreasing morbidity.³⁻⁶ Ganciclovir was superior to previous antiviral agents, such as acyclovir, as a preventive strategy and helped to mitigate disease or at least postpone it until later after transplantation when the immunosuppression burden was minimized.^{3,7,8} The development of laboratory assays for monitoring the virus in transplant recipients coupled with the availability of valganciclovir, a bioavailable form of ganciclovir, permitted more nuanced strategies for prevention and treatment.^{9,10}

Taking advantage of both valganciclovir and sensitive quantitative viral load assays in the peripheral blood of transplant recipients has led to a number of studies conducted to evaluate prophylaxis or preemptive administration of antiviral agents, but mostly in adult recipients.¹⁰ One pediatric liver transplant study directly compared the sequential strategy of using a 30-day course of universal prophylaxis followed by preemptive therapy to preemptive therapy alone.¹¹ This study involved only 21 subjects and was discontinued early after an interim analysis found the

outcomes for CMV disease to be comparable, but that the prophylaxis group had a much greater exposure to ganciclovir. The transplant center subsequently adopted a preemptive strategy for all patients undergoing liver transplantation. In this issue of the *Transplantation*, Nicastro and colleagues,¹² build on their previous work and retrospectively describe results of using preemptive therapy alone in 100 children after liver transplantation. Although retrospective in nature, its large sample size (for a pediatric cohort) furthers the knowledge of CMV in the pediatric population, but likewise raises some questions for further study. Importantly, they showed that although 61 of the children had CMV viremia, using an intensive surveillance strategy, very few children required preemptive treatment (N = 19), only 3 of the children had actual disease, and no child died from CMV. Not surprisingly, they showed that the highest risk for having CMV viremia was based on the mismatch, Donor+/Recipient-, CMV serostatus. Intriguingly, this group did not have a higher risk for disease or for the need for preemptive treatment; rather the group to require preemptive intervention most frequently was the Donor+/Recipient+ CMV serostatus group. The study also looked for evidence of indirect effects of CMV but did not find any difference in short or long term complications, such as acute cellular rejection, graft dysfunction, sepsis, Epstein Barr virus infection, or biliary or vascular complications between those children with or without CMV viremia. Sample size could play a role in this or it is possible that the pediatric population does not have the same indirect effects that are seen in the adult population. In addition, the preemptive therapy itself may have mitigated the development of indirect effects. The authors compared their preemptive strategy to the historical control group who had the sequential short course of ganciclovir prophylaxis followed by serial monitoring of CMV viral load. Although there were no statistically significant differences in CMV disease or clinical outcome, they noted that the historical controls required greater amounts of antiviral therapy. The small sample size of the historical control (N = 16), and the much greater percent of mismatch patients in the control group necessitates caution in interpretation.

The authors convincingly demonstrated that with a rigorous weekly screening for 90 days, they could safely intervene with antiviral therapy in those with elevated viremia. However, not all institutions will have the luxury or ability to perform such intensive screening once patients leave the transplant hospital. Because only approximately 10% of the transplant population fall within the pediatric age group (United Network for Organ Sharing database), single-center studies, although offering insight into CMV infection, may not

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be of sufficient size to identify whether there truly are indirect effects in the pediatric population or to determine if some populations are at greater risk for more severe disease. The time has come for a concerted effort to have multicenter prospective trials that can be sufficiently powered to determine optimal preventive strategies in the pediatric transplant population.

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