1744. CMV Infection and Management Among Pediatric Solid-Organ Transplant Recipients

Anna Sharova, MPH[1]; Despoina M. Galetaki, MD[1];
Molly Hayes, PharmD, BCPS[1]; Lauren Gianchetti, BS[2];
Laura A. Vella, MD, PhD[1]; Kevin J. Downes, MD[2]; Kevin J. Downes, MD[2]; [1]Children's Hospital of Philadelphia, Philadelphia, Pennsylvania; [2]The Children's Hospital of Philadelphia, Philadelphia, Pennsylvania

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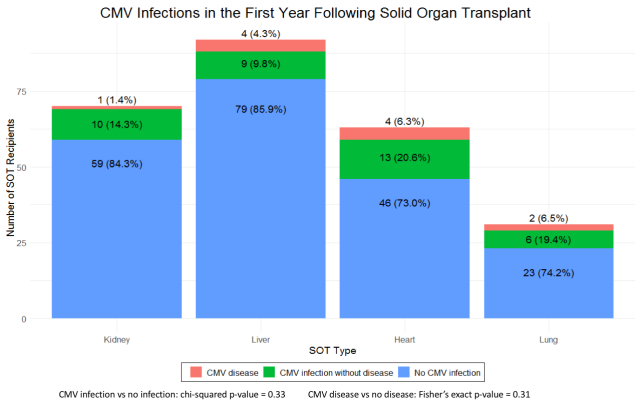
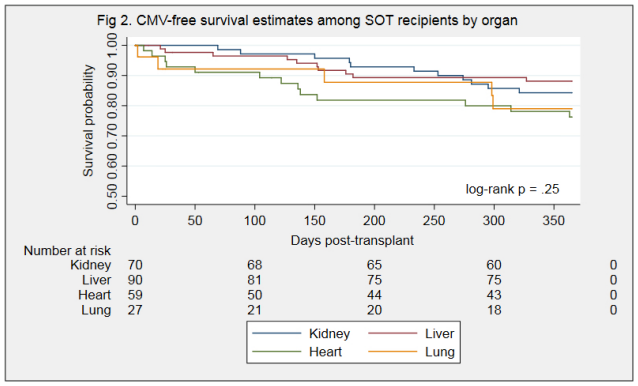
Background. Our institution provides universal CMV prophylaxis (PPX) for all high (D+/R-) and medium risk (R+) solid-organ transplant (SOT) recipients. We sought to evaluate this practice by assessing CMV infection and disease within the first year of SOT.

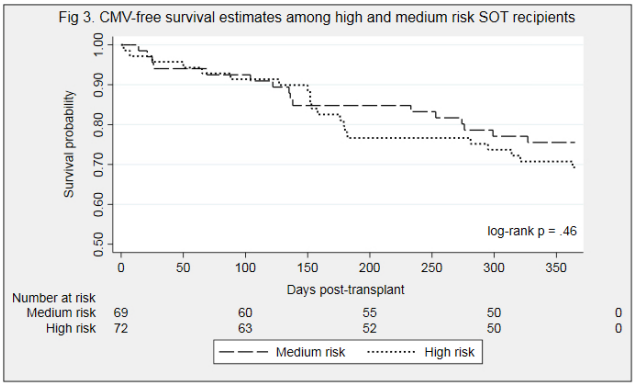
Methods. Retrospective cohort study of all children undergoing first SOT at Children's Hospital of Philadelphia from January 2012 to October 2017. We identified recipients with CMV infection (detection of CMV DNA in body fluid/tissue with or without symptoms) and disease (symptomatic or tissue-invasive infection) in the first year after SOT. We calculated the rate of CMV infection and compared CMV-free survival based on SOT type and CMV risk using log-rank tests.

Results. 244 children received 246 SOTs: 90 liver, 70 kidney, 59 heart, 27 lung. In total, 39 children (16%) had 49 CMV infections in the first year after SOT, including 29% of high (n = 21/72) and 23% of medium risk recipients (n = 16/69). The fraction of each organ type with CMV infection was similar (Figure 1, P = 0.33). Among high and medium risk recipients, all of whom received PPX, the incidence rate of CMV infection in the first year post-SOT was similar: 10.1 vs. 7.8/10,000 days (P = 0.22). There were no differences in CMV-free survival by organ (Figure 2, log-rank P = 0.25) or between high and medium risk recipients (Figure 3, log-rank P = 0.46). In total, 22% (n = 10/45) of CMV infections in high/medium risk patients occurred while on PPX; half were in the setting of reduced PPX dosing or within 2 weeks of SOT. Of the 35 CMV infections post-PPX, the median time to detection of CMV after PPX was 39 days (IQR 28–98). There were 11 cases (6 high, 5 medium risk) of CMV disease: 6 CMV syndrome, 2 hepatitis, 2 pneumonitis, 1 GI disease. Valganciclovir was more often used for treatment of asymptomatic infections than for CMV disease (79% vs. 33%, P = 0.03). All-cause mortality in the first year post-SOT was similar among those with and without CMV infections (7.7 vs. 6.3%, P = 0.76) and among those with and without CMV disease (9.1 vs. 5.2%, P = 0.57).

Conclusion. CMV infection was common in high and medium risk SOT recipients in the first year following SOT, and most infections occurred off of PPX. Our data suggest that the highest risk period for CMV infection is in the first months after PPX, and that monitoring may be most useful after PPX has been stopped or when PPX doses are reduced.







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1745. Retrospective Cohort Analysis to Determine the Incidence of CMV Infection and Disease in Allogeneic Hematopoietic Cell Transplant Recipients at an Academic Children's Hospital

Despoina M. Galetaki, MD[1]; Molly Hayes, PharmD, BCPS[1];
Alexander Newman, MD[2]; Craig L. K. Boge, MPH[1];
Caitlin W. Elgarten, MD, MSCE[1]; Jason L. Freedman, MD, MSCE;
Timothy S. Olson, MD PhD[1]; Brian T. Fisher, DO, MPH, MSCE[1,3]; [1]Children's Hospital of Philadelphia, Philadelphia, Pennsylvania; [2]Ann and Robert H Lurie Children's Hospital of Chicago, Chicago, Illinois; [3]Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania

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Background. Data on cytomegalovirus (CMV) infection and disease by donor (D)/recipient (R) status or prophylaxis regimen in pediatric hematopoietic cell transplant (HCT) recipients are limited. There is an absence of data on adverse events (AE) attributable to prophylaxis.

Methods. A single-center cohort (N = 352) of allogeneic HCT episodes between January 2004 and June 2017 was assembled. Exclusion criteria were CMV PCR positivity 30 days before HCT, lack of CMV surveillance (<2 blood PCRs in the 30 days post HCT), or unknown D/R CMV status. CMV prophylaxis was recommended for CMV D+ or R+ patients with ≥1 of the following factors: T-cell depletion, cord blood product, or exposure to distal alemtuzumab. The CMV prophylaxis regimen was standard-dose acyclovir from day −7 to +7, then foscarnet to engraftment, and then valganciclovir to day +100 (acyc → fos → valgan). If a patient did not meet criteria for CMV prophylaxis but was HSV IgG positive then standard-dose acyclovir was given from day −7 to the end of study follow-up (SD-acyc). All remaining patients did not receive antiviral prophylaxis. Outcomes of CMV infection and CMV disease by day +180 were captured. AEs attributable to antiviral prophylaxis were also identified. An AE was attributed to an antiviral prophylaxis medication if the dose was reduced or stopped. AEs were only reported in HCT episodes with complete medical records (n = 221).

Results. The CMV infection rate was 26.7%, with a median time to detection of 23.5 days (range: 4–146). CMV infection was common in D+/R+ (58.9%) and D−/R+ (34.6%) patients. Just under 11% of CMV infections progressed to disease (Figures 1 and 2). Breakthrough CMV infection occurred in 49.1% of patients despite acyc → fos → valgan (Figure 3) at a median of 11 days from HCT (range: 4–132). The attributable AE rate was 13.4% and 36.8% for SD-acyc and acyc → fos → valgan, respectively (Figure 4).

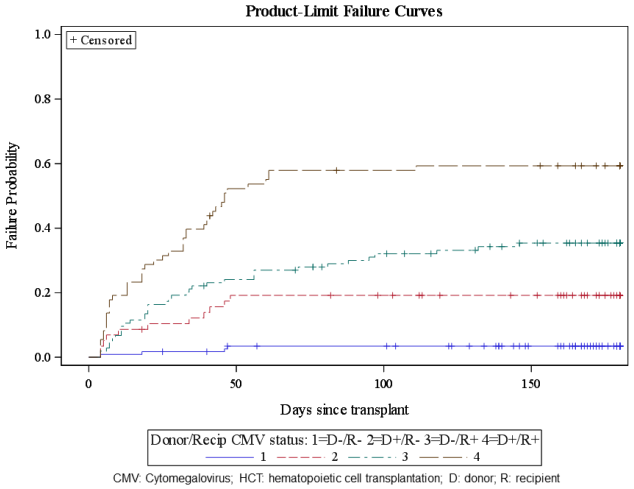
Conclusion. CMV infection was common in D+/R+ and D−/R+ patients, and a substantial proportion progressed to disease. Breakthrough infection persisted despite acyc → fos → valgan prophylaxis and AEs attributable to this regimen were common. CMV infection in R+ patients was frequent even in the absence of additional risk factors. Studies of novel prophylaxis approaches are needed and should include R+ patients regardless of other factors.

Figure 1. CMV infection and disease rates, in pediatric allogeneic HCT recipients under CMV surveillance.

		Donor/Recipient CMV Serology Status			
	All (n=352)	D-/R- (n=117)	D+/R- (n=58)	D-/R+ (n=104)	D+/R+ (n=73)
CMV infection, n (%)	94 (26.7)	4 (3.4)	11 (19.0)	36 (34.6)	43 (58.9)
Time from transplant to reactivation in days, median (range)	*23.5 (4–146)*	*32 (4–47)*	*20 (4–48)*	*26.5 (4–146)*	*22 (4–111)*
Specimen where CMV first detected, n (%)					
Blood	*91 (96.8)*	*4 (100)*	*11 (100)*	*34 (94.4)*	*42 (97.7)*
Bronchoalveolar lavage	*2 (2.1)*	*0 (0)*	*0 (0)*	*1 (2.8)*	*1 (2.3)*
Stool	*1 (1.1)*	*0 (0)*	*0 (0)*	*1 (2.8)*	*0 (0)*
Progression to CMV disease, n (%)	*10 (10.6)*	*1 (25.0)*	*2 (18.2)*	*1 (2.8)*	*6 (14.0)*
CMV disease type first detected					
Gastrointestinal disease	*2*	*1*	*0*	*1*	*0*
Gastrointestinal disease AND hepatitis	*1*	*0*	*1*	*0*	*0*
Hepatitis	*1*	*0*	*0*	*0*	*1*
Pneumonitis	*6*	*0*	*1*	*0*	*5*

CMV: Cytomegalovirus; HCT: hematopoiietc cell transplantation; D: donor; R: recipient

Figure 2. Kaplan-Meier failure curves of time from transplant to first CMV detection by PCR, by donor/recipient CMV status.



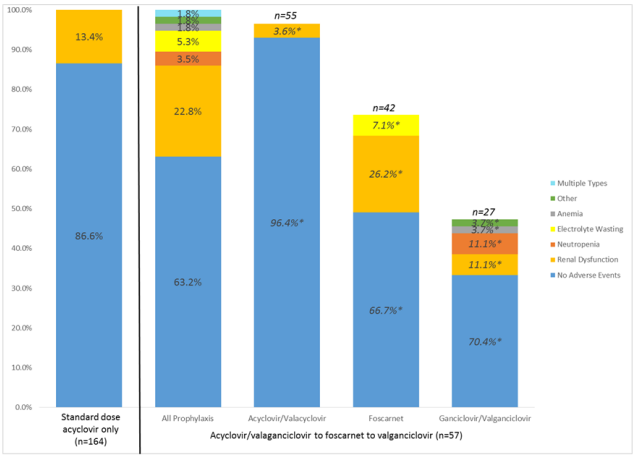
CMV: Cytomegalovirus; HCT: hematopoietic cell transplantation; D: donor; R: recipient

Figure 3. CMV infection rates by intended prophylactic regimen in pediatric allogeneic HCT recipients under CMV surveillance.

		Donor/Recipient CMV Serology Status			
	All (n=245)	D-/R- (n=75)	D+/R- (n=44)	D-/R+ (n=77)	D+/R+ (n=49)
No prophylaxis, n (%)	24 (9.8)	12 (16.0)	5 (11.4)	3 (3.9)	4 (8.2)
CMV infection	*6 (25.0)*	*0 (0)*	*2 (40.0)*	*1 (33.3)*	*3 (75.0)*
Prophylaxis, n (%)					
SD acyclovir only	164 (66.9)	63 (84.0)	34 (77.3)	33 (42.9)	34 (69.4)
CMV infection during this prophylaxis regimen	*34 (20.7)*	*4 (6.4)*	*5 (14.7)*	*9 (27.3)*	*16 (47.1)*
SD acyclovir to day + 7, foscarnet to engraftment, valganciclovir to day + 100 *	57 (23.3)	0 (0)	5 (11.4)	41 (53.3)	11 (22.5)
CMV infection during this prophylaxis regimen	*28 (49.1)*	--	*2 (40.0)*	*17 (41.5)*	*9 (81.8)*

*Includes 4 subjects on "Valganciclovir to day +7, foscarnet to engraftment, valganciclovir to day +100" prophylaxis regimen
CMV: Cytomegalovirus; HCT: hematopoietic cell transplantation; SD: Standard dose; D: Donor; R: Recipient

Figure 4. Rates of adverse events detected during prophylaxis administration, by intended prophylaxis regimen and specific antiviral agent.



*Proportions are relative to total number of subjects receiving the specific antiviral(s)

Disclosures. **All authors:** No reported disclosures.

1746. Prevalence and Resistance Patterns of Cytomegalovirus Viremia in Immunocompromised Patients

Edward Kim, MD[1]; Basim Asmar, MD[2]; Ronald Thomas, PhD[3]; Nahed M. Abdel-Haq, MD[2]; [1]Children's Hospital of Michigan, Detroit, Michigan; [2]Children's Hospital of Michigan/Wayne State University, Detroit, Michigan; [3]Children's Research Center of Michigan/Wayne State University, Detroit, Michigan

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Background. We noted a recent increase in the number of patients with CMV viremia among immunocompromised children at our institution. The study was undertaken to determine the prevalence of CMV viremia and to evaluate factors associated with the development of antiviral drug resistance.

Methods. A retrospective study of immunocompromised hosts 0–21 years of age who had CMV viremia (2007–2017). We collected demographic data as well as details of antiviral therapy and resistance testing.

Results. A total of 31 patients were identified including 10 (32%) during the last 2 years. The age range was 3 months to 20 years (median 12.6 years); 23 (74%) were male and 12 (39%) were African American. Among the 31 patients, 18 had hematopoietic stem cell transplantation, 5 had primary immunodeficiency (2 common variable immunodeficiency, 1 SCID, 1 Langerhans cell histiocytosis, 1 DiGeorge syndrome), 4 had malignancies receiving chemotherapy, 3 with heart transplantation and one 17 year old with newly diagnosed HIV infection who presented with CMV pneumonia and viremia. Antiviral resistance testing was performed on 7 CMV isolates: 5 due to persistent viremia (> 1 months) despite treatment, and 2 prior to starting antiviral therapy. CMV resistance was identified in 3 patients including 2 with CVID and one with Hodgkin's disease status post bone marrow transplantation. The 2 CVID patients had other comorbidities including chronic diarrhea and malabsorption and were TPN dependent. Both were diagnosed with CMV colitis and one also had pneumonitis. One had received a prolonged oral valganciclovir course (> 1 year) prior to diagnosis of resistance and the other received long-term intermittent oral valganciclovir courses. The patient with Hodgkin's disease received a prolonged IV ganciclovir course. All 3 tested positive for UL97 mutation and one had both UL97/UL54 gene mutations.

Conclusion. Most of our patients with CMV viremia were transplant patients. Antiviral drug resistance was detected among 3 of 31 (10%) of our patients during the study period. Two had malabsorption that may have resulted in sub-therapeutic blood levels. Treatment with oral valganciclovir should be avoided in patients with poor gut absorption because it may increase risk of drug resistance.

Disclosures. **All authors:** No reported disclosures.

1747. Impact of Inappropriately Low Cytomegalovirus (CMV) Prophylaxis Dosing on CMV Outcomes Among Lung Transplant (LT) Recipients

Corey Watts, BA; Emily Blumberg, MD, FIDSA; James Lee, MD; Tamara Claridge, PharmD; Maria Crespo, MD; Judith A. Anesi, MD; Judith A. Anesi, MD; University of Pennsylvania, Philadelphia, Pennsylvania

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Background. Valganciclovir (VGCV) and ganciclovir (GCV) are commonly used to prevent CMV in at-risk lung transplant recipients (LTRs). Because renal function changes frequently in the post-transplant setting, antiviral under-dosing may occur. We sought to determine the frequency of GCV/VGCV under-dosing and its impact on CMV-related outcomes among LTRs.

Methods. We conducted a retrospective cohort study of all adult LTRs with a CMV seropositive donor (D+) between 2014 and 2016 at the Hospital of the University of Pennsylvania. Exposed patients were those with exposure to inappropriately low-dose GCV/VGCV. Unexposed patients were those whose antiviral dosing was consistently appropriate for their creatinine clearance. We employed a multivariable Cox proportional hazard analysis to determine the impact of low-dose prophylaxis on time to CMV infection post-transplant; prophylaxis dosing was incorporated as a time-varying covariate in this survival analysis.

Results. 108 adults underwent CMV D+ LT during the study period. 46 (43%) experienced low prophylaxis dosing at some point during their prophylaxis course. 47 (43%) LTRs developed CMV viremia, of which 10 (9%) were still on prophylaxis. 20 (19%) LTRs developed CMV disease and 6 (6%) had ganciclovir-resistant CMV. In the multivariable Cox analysis, we found that there was not a significant association between exposure to any low-dose prophylaxis and the hazard of CMV infection (HR = 1.001, 95% CI 0.99–1.01, $P = 0.75$; Table 1), even among CMV seronegative recipients (D+/R–) (HR = 1.002, 95% CI 0.99–1.01, $P = 0.68$). When only those who received > 28 days of low-dose prophylaxis ($N = 6$, 6%) were evaluated, there was a trend toward an increased hazard of CMV infection (HR = 1.001, 95% CI 0.999–1.004, $P = 0.18$; Table 2).

Conclusion. CMV D+ LTR are frequently exposed to inappropriately low CMV prophylaxis dosing. This does not appear to significantly increase the risk for CMV infection, though prolonged subtherapeutic exposure merits further exploration as a risk factor for CMV outcomes in higher-risk patients.

Table 1. Multivariable Cox analysis of time to CMV infection with exposure to inappropriately low prophylaxis

Exposure	HR	95% CI	P value
Any low GCV/VGCV dosing	*1.001*	*0.99-1.01*	*0.75*
Recipient CMV seropositive (D+/R+)	0.28	0.13-0.58	0.001
Days of CMV prophylaxis	0.97	0.96-0.98	<0.001
Chronic obstructive pulmonary disease (COPD) as indication for LT	0.56	0.22-1.37	0.2
Bronchiolitis as indication for LT	2.41	0.65-8.87	0.19

Table 2. Multivariable Cox analysis of time to CMV infection with prolonged exposure to inappropriately low prophylaxis

Exposure	HR	95% CI	P value
>28 days of low GCV/VGCV dosing	*1.001*	*0.999-1.004*	*0.18*
Recipient CMV seropositive (D+/R+)	0.25	0.12-0.54	<0.01
Days of CMV prophylaxis	0.97	0.96-0.98	<0.01
COPD as indication for LT	0.49	0.19-1.24	0.13
Bronchiolitis as indication for LT	2.49	0.67-9.20	0.17

Disclosures. **All authors:** No reported disclosures.