Epidemiology of Cytomegalovirus (CMV) in Pediatric Solid Organ Transplant Recipients (SOTR) at Texas Children's Hospital (TCH)

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Abstract

Background: Despite widespread use of prevention strategies, CMV remains a common opportunistic infection in SOTR. Contemporary data regarding CMV in pediatric SOTR is limited. We sought to determine the frequency of and risk factors for CMV infection and disease in a large single-center cohort of pediatric SOTR.

Methods: A retrospective cohort study of patients < 22 yr of age who received lung, heart, liver, kidney, or multi-organ transplants at TCH between 2011-2018 was completed. Universal CMV prophylaxis was used based on risk status. Primary outcome was quantifiable CMV DNAemia. Associations with CMV DNAemia were measured using Fisher exact, Kruskal-Wallis, and multivariate logistic regression. Survival analysis and time to CMV infection were assessed using Kaplan-Meier plots.

Results: Among 719 SOTR, 172 (24%) developed CMV DNAemia; this included 32/90 (36%) lung, 80/260 (31%) liver, 38/166 (23%) heart, 2/14 (14%) multi-organ, and 20/189 (11%) kidney recipients. 63 (37%) SOTR had early-onset CMV reactivation while on antiviral prophylaxis. Post-prophylaxis, 109 (63%) SOTR had CMV reactivation and 12 (7%) had primary infection. Median time to any DNAemia was 302 days post-transplant for lung, 200 for liver, 186 for heart, and 338 for kidney (p=0.04), reflecting differences in prophylaxis strategies. High-risk CMV status (D+/R- for heart, liver, kidney and D+ and/or R+ for lung) and type of organ transplanted were associated with CMV DNAemia (p<0.01). DNAemia was not associated with age at transplantation or the use of induction immunosuppression. There was no difference in survival during the study follow-up period (1 – 8 yr) for SOTR with vs. without DNAemia.

Overall 29/719 (4%) SOTR had CMV disease, 8 (9%) lung, 7 (4%) heart, 7 (3%) liver, 1 (11%) multi-organ, and 7 (4%) kidney recipients. 25 had CMV syndrome and 6 had tissue invasive disease. Median (range) maximum viral loads were 27,700 IU/mL (233-4,200,000) for SOTR with vs. 760 IU/mL (760-112,000) for SOTR without CMV disease (p<0.01).

Conclusions: This large contemporary cohort of pediatric SOTR on universal prophylaxis demonstrates low overall rates of CMV DNAemia and CMV disease. High-risk CMV status remains associated with CMV DNAemia, suggesting that further interventions targeting this group may be warranted.

Background

- Despite prophylaxis, CMV DNAemia occurs in up to 23% of SOTR during the first year post-transplant.
- Previously reported risk factors for developing CMV DNAemia and disease include high risk CMV status (D+/R-), young age at time of transplant, receiving induction therapy with anti thymocyte globulin, and receiving a small bowel or lung transplant.
- CMV DNAemia has negative direct effects on SOTR including CMV syndrome and CMV tissue invasive disease as well as indirect effects including chronic allograft rejection, decline in graft function/graft loss, and opportunistic infections.
- Limited contemporary pediatric data regarding CMV DNAemia in SOTR exists.

Hypotheses/Methods

- We hypothesized that 20-25% percent of children who undergo SOT at Texas Children's Hospital will develop CMV DNAemia.
- We hypothesized that SOTR who receive immunosuppressive induction therapy, who have high risk CMV status (D+/R-), or are <1 year of age at time of transplant will have a higher incidence of CMV DNAemia.
- A retrospective review of first time SOTR < 22 years of age at TCH from January 1, 2011 - December 31, 2018 was performed to determine the epidemiology and variables which may impact rates of CMV infection and disease in SOT recipients.
- Primary Outcome: CMV DNAemia
- Universal CMV prophylaxis was used based on organ and risk status:

Organ	Serostatus	Risk Status	Prophylaxis
Lung	D+/R- R+ D-/R-	High High Low	12 mo of ganciclovir/valganciclovir + CMV Ig 12 mo of ganciclovir/valganciclovir 3 mo of ganciclovir/valganciclovir
Heart	D+/R- R+ D-/R-	High Intermediate Low	3 mo of ganciclovir/valganciclovir + CMV Ig 3 mo of ganciclovir/valganciclovir + CMV Ig None
Liver	D+/R- R+ D-/R-	High Intermediate Low	6 mo of ganciclovir/valganciclovir 6 mo of ganciclovir/valganciclovir 3 mo of ganciclovir/valganciclovir
Kidney	D+/R- R+ D-/R-	High Intermediate Low	6 mo of ganciclovir/valganciclovir + CMV Ig 6 mo of ganciclovir/valganciclovir 6 mo of ganciclovir/valganciclovir

Statistics: Demographic and transplantation characteristics were compared using c^2 or Fisher exact tests for categorical data. Associations with CMV DNAemia were measured using Fisher exact test, Kruskal-Wallis, and multivariate logistic regression. Survival analysis and time to CMV infection were assessed using Kaplan-Meier calculations. All statistical analyses was completed with SAS v 9.4.

Results

Table 1: Patient Demographics and Clinical Characteristics

	No CMV DNAemia N=547 pts	CMV DNAemia N=172 pts	P value
Sex (female)	263 (48.1%)	82 (47.7%)	0.93
Organ			**<0.01**
Liver	180 (32.9%)	80 (46.5%)	
Heart	128 (23.4%)	38 (22.1%)	
Kidney	169 (30.9%)	20 (11.6%)	
Lung	58 (10.6%)	32 (18.6%)	
Multi	12 (12.2%)	2 (1.2%)	
Risk			**<0.01**
High risk (D+/R-)	208 (38%)	100 (58.1%)	
Intermediate risk (R+)	168 (30.7%)	60 (34.9%)	
Low risk (D-/R-)	171 (31.3%)	12 (7.0%)	
All-cause mortality	58 (10.6%)	13 (7.6%)	0.50
Age at transplant			0.80
<1 year	82 (15.0%)	26 (15.1%)	
1-5 years	137 (25.0%)	49 (28.5%)	
6-10 years	98(17.9%)	31 (18.0%)	
11-17 years	188 (34.4%)	56 (32.6%)	
18+ years	42 (7.7%)	10 (5.8%)	
Race			0.69
African American	83 (15.2%)	32 (18.6%)	
Asian	15 (2.7%)	6 (3.5%)	
Hispanic	153 (28.0%)	49 (28.5%)	
White	274 (50.1%)	79 (45.9%)	
Unknown/Other	22 (4%)	6 (3.5%)	

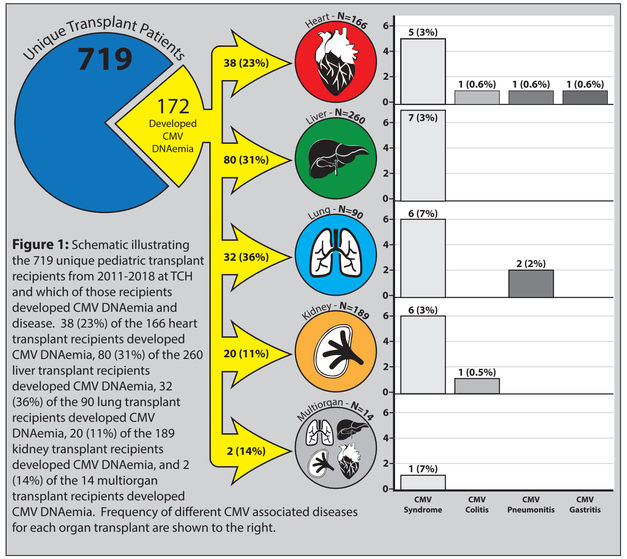

Figure 1: Schematic illustrating the 719 unique pediatric transplant recipients from 2011-2018 at TCH and which of those recipients developed CMV DNAemia and disease. 38 (23%) of the 166 heart transplant recipients developed CMV DNAemia, 80 (31%) of the 260 liver transplant recipients developed CMV DNAemia, 32 (36%) of the 90 lung transplant recipients developed CMV DNAemia, 20 (11%) of the 189 kidney transplant recipients developed CMV DNAemia, and 2 (14%) of the 14 multiorgan transplant recipients developed CMV DNAemia. Frequency of different CMV associated diseases for each organ transplant are shown to the right.

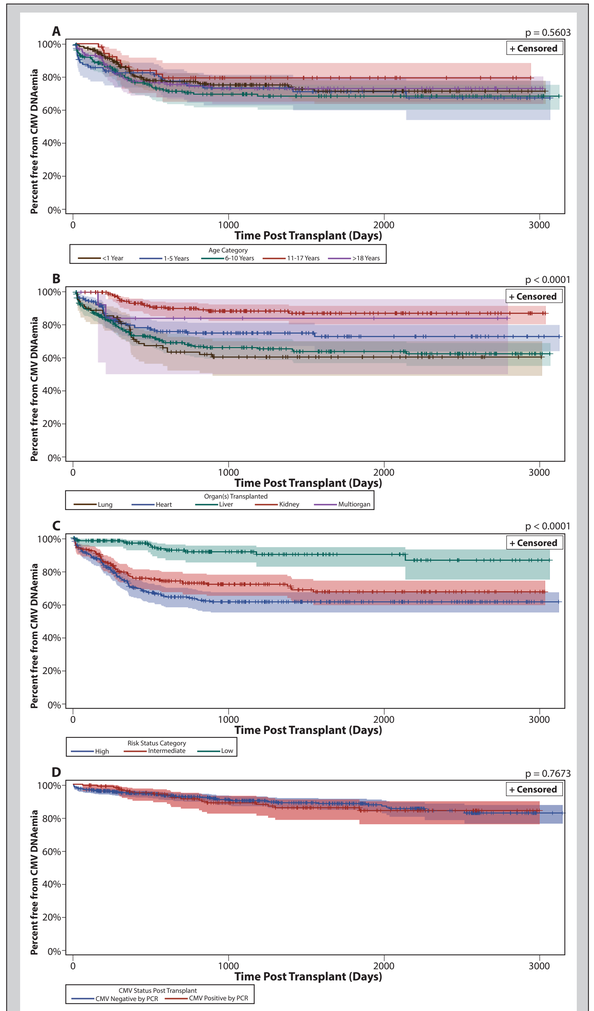

Figure 2: A. Kaplan-Meier curve of % of SOTR free from CMV DNAemia by age B. Kaplan-Meier curve of % of SOTR free from CMV DNAemia by organ transplanted C. Kaplan-Meier curve of % of SOTR free from CMV DNAemia by risk status D. Kaplan-Meier curve of survival in SOTR with and without CMV DNAemia

Table 2: Level and Timing of CMV DNAemia

	CMV DNAemia < 1,000 N=91 pts	CMV DNAemia ≥ 1,000 N=81 pts
Organ		
Liver (N=260 pts)	50 (19%)	30 (12%)
Heart (N=166 pts)	17 (10%)	21 (13%)
Kidney (N=189 pts)	7 (4%)	13 (7%)
Lung (N=90 pts)	16 (18%)	16 (18%)
Multi (N=14 pts)	1 (7)%	1 (7%)
Timing of CMV DNAemia		
On primary prophylaxis	36 (40%)	27 (33%)
CMV reactivation post-prophylaxis (D+ or R+)	85 (93%)	75 (93%)
Primary CMV DNAemia (D-/R-)	6 (7%)	6 (7%)

Table 3: Associations with CMV DNAemia

	Odds Ratio	95% CI	P-value
Risk Status			
High risk	6.63	3.56-12.35	<0.01
Intermediate risk	5.93	3.06-11.49	<0.01
Low risk	1	(ref)	
Organ			
Heart	3.96	1.60-9.80	0.32
Lung	7.36	3.44-15.77	<0.01
Liver	5.32	1.90-14.87	0.08
Multi-organ	1.73	0.33-9.14	0.36
Kidney	1	(ref)	

* Donor age, recipient age, immunosuppressive induction, and organ transplanted were not associated with CMV DNAemia

Table 4: Signs/Symptoms of CMV Syndrome

Sign/Symptom	# of Patients (N=25)
Fever> 38°C for 2 days	17 (68%)
New of increased malaise	11 (44%)
Leukopenia or neutropenia	13 (53%)
Greater than or equal to 5% atypical lymphocytes	0 (0%)
Thrombocytopenia	7 (28%)
Elevated AST/ALT	5 (20%)
Mean DNAemia	27,700 IU/mL

Table 5: Median time to CMV DNAemia post-transplant

Organ	Median time to DNAemia post-transplant
Lung	302 days
Heart	186 days
Liver	200 days
Kidney	338 days

Conclusions

- CMV DNAemia occurred in 24% of SOTR with 11% being > 1,000 which is consistent with the literature.
- High and intermediate risk CMV status and receiving a lung transplant are associated with CMV DNAemia.
- Donor age, recipient age, and induction immunosuppression were not associated with CMV DNAemia.
- CMV DNAemia occurs post prophylaxis in the majority of patients.
- 16% of SOTR who developed CMV DNAemia had CMV syndrome and 2% had CMV invasive disease.
- CMV infection and disease continues to occur in pediatric SOTR despite routine prophylaxis.
- More effective prevention strategies aimed at higher risk SOTR are still needed.

References

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