1084. Epidemiology and Long-term Outcomes of Cytomegalovirus (CMV) in Pediatric Liver Transplant Recipients (PLTR) at Texas Children's Hospital (TCH)

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Session: P-49. Infections in Immunocompromised Individuals

Background. Despite widespread use of prevention strategies, CMV DNAemia remains common in PLTR. Contemporary data, however, is limited. We sought to determine the frequency of, risk factors for, and long term outcomes of CMV DNAemia in a large, single center cohort of PLTR.

Methods. A retrospective cohort study of PLTR < 22 yrs of age transplanted from 2011-2018 was completed. Per protocol, CMV prophylaxis with ganciclovir/valganciclovir was universally implemented; high risk (HR)(D+/R-) and intermediate risk (IR)(R+) patients received 6 months while low risk (LR)(D-/R-) patients received 3 months. Primary outcomes included any CMV DNAemia, CMV DNAemia >1000 IU/mL and long term outcomes including rejection, graft failure, hepatic steatosis (HS), and de novo autoimmune hepatitis (AIH). Associations with CMV DNAemia were measured using Fisher exact and multivariate regression. Survival analysis, time to CMV infection, and time to PLTR long term outcomes were assessed using Kaplan-Meier plots.

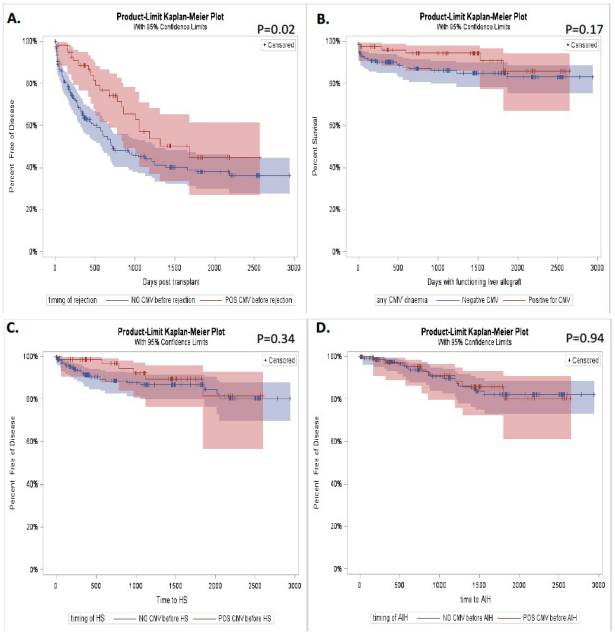
Results. Among 270 PLTR, 81 (30%) had quantifiable CMV DNAemia; 36 (13%) had CMV DNAemia >1000 IU/mL. Fifty (19%) developed CMV DNAemia while on prophylaxis. Median time (range) to CMV DNAemia was 162 days (5-2213). HR (OR 4.18; 95% CI 1.84-9.49, p< 0.01) status was associated with CMV DNAemia and time to CMV DNAemia. CMV DNAemia was not associated with age at transplantation or cold ischemic time.

Eight PLTR (3%) developed CMV syndrome (4 HR, 3 IR, 1 LR), the median peak (range) DNAemia was 2133 IU/mL (202-58000) for these patients. No PLTR developed CMV tissue invasive disease.

CMV DNAemia was not associated with rejection (15% vs. 33%, p=0.62), graft failure (7% vs. 13%, p=0.17), HS (8% vs. 12%, p=0.32), or AIH (10% vs. 8%, p= 0.68). CMV DNAemia was associated with a longer time to rejection (p=0.02). Time to development of graft failure, HS, and AIH were not associated with CMV DNAemia (Figure 1). Finally, there was no difference in survival during the study follow-up period (1 – 9 yrs) for PLTR with vs. without CMV DNAemia (p=0.58).

Figure 1

Figure 1: A. Kaplan- Meier curve of % free from rejection by developing any CMV DNAemia versus no CMV DNAemia B. Kaplan-Meier curve of % free from graft failure by developing any CMV DNAemia versus no CMV DNAemia C. Kaplan-Meier curve of % free from hepatic steatosis by developing any CMV DNAemia versus no CMV DNAemia D. Kaplan Meier curve of % free from alloimmune hepatitis by developing any CMV DNAemia versus no CMV DNAemia



Conclusion. This large cohort of PLTR demonstrates high rates of CMV DNAemia but low rates of CMV disease. HR status remains associated with CMV DNAemia. CMV DNAemia did not increase the risk of long term adverse outcomes such as rejection, graft failure, HS, and AIH.

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1085. Epidemiology and Outcomes of Histoplasmosis in Transplant Recipients

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Session: P-49. Infections in Immunocompromised Individuals

Background. Histoplasmosis in transplant recipients is understudied. We reviewed a large cohort of histoplasmosis in patients with solid organ and stem cell transplants in an endemic area to describe the epidemiology, clinical findings and outcomes.

Methods. We performed a single-center retrospective cohort study of patients diagnosed with histoplasmosis between 2002 and 2017. Demographic data, clinical findings, diagnostic methods, treatment, and mortality were collected. We compared the characteristics of patients with history of transplant to non-transplant (NT) patients.

Results. We identified 261 patients with histoplasmosis. Of those, 28(11%) were transplant recipients; 8(29%) liver, 8(29%) lung, 6(21%) kidney, 3(11%) heart, and 3(11%) stem cell.

Median time from symptom onset to diagnosis was 6 vs 34 days in transplant vs NT groups (p=0.001). Lung was the most common organ involvement (89% in transplants vs 78% in NT, p=0.168). Spleen involvement was more commonly found in transplant patients (29 vs 14%, p=0.039). In patients with disseminated disease, urine antigen was 100% sensitive in transplant patients compared to 78% in the NT group (p=0.038). Duration of treatment was 13 vs 6 months in transplant vs NT patients (p= 0.003). Mortality was comparable between groups (14 vs 15% in transplant vs NT, p=0.918).

Median time from transplant to diagnosis was 4.21 years. However, five patients (18%) developed histoplasmosis within 6 months. For these early diagnosed patients, ICU admission rate was 80 vs 30% (p=0.04) and rate of mechanical ventilator use was 80 vs 22% (p=0.011) compared to patients diagnosed later.

Table 1: Patient characteristics

Variables	Transplant N=28 (%)	Non-transplant N=233 (%)	P value
Age, years (median, IQR)	54 (33,62)	50 (36, 62)	0.855
Male sex	17 (61)	139 (60)	0.914
Race			0.481
White	24 (86)	173 (74)	
African American	2 (11)	48 (21)	
Other	1 (4)	7 (3)	
Unknown	1 (4)	5 (2)	
Organ transplant			
Liver	8 (29)		
Lung	8 (29)		
Kidney	6 (21)		
Heart	3 (11)		
Stem cell	3 (11)		
Symptoms			
Cough	17 (61)	92 (39)	0.096
Fever	15 (54)	112 (48)	0.818
Dyspnea	14 (50)	86 (37)	0.373
Gastrointestinal symptoms	11 (39)	73 (31)	0.663
Night sweat	7 (25)	47 (20)	0.793
Weight loss	5 (18)	75 (32)	0.252
Chest pain	1 (4)	52 (22)	0.055
Skin nodules	1 (4)	2 (1)	0.397
Asymptomatic lung nodule(s)	1 (4)	24 (10)	0.069
Days from symptom onset to diagnosis, days, median (IQR)	16 (10,33)	34 (17, 101)	0.001

Table 2: Organ involvement

	Transplant N=28 (%)	Non-transplant N=233 (%)	p-value
Disseminated disease	18 (64)	116 (50)	0.147
Organ involvement			
Lung	25 (89)	182(78)	0.168
Blood	7 (25)	47(20)	0.551
Spleen	8 (29)	32 (14)	0.039
Liver	4 (14)	24 (10)	0.520
Gastrointestinal tract	3 (11)	8 (3)	0.079
Skin	1 (4)	12 (5)	0.826
Central nervous system	1 (4)	12 (5)	0.717
Adrenal gland	1 (4)	7 (3)	0.869
Lymph node	-	20 (9)	0.236
Oral cavity	-	11 (5)	0.233
Bone marrow	-	23 (10)	0.190
Others	-	8 (3)	0.319
Time from transplant to diagnosis, years, median (range)	4.21 (0.02 – 19.33)	-	
Diagnosis of histoplasmosis in the first six months of transplant	5 (18)	-	

Table 3: Diagnostic test positivity

Diagnostic method	Transplant N (%)	Non-transplant N (%)	P value
Isolated pulmonary disease	10 (36)	117(50)	
Urine antigen	4/8 (50)	37/81 (46)	0.815
Serum antigen	1/1 (100)	7/12 (58)	0.411
Antibody	3/7 (43)	41/60 (16)	0.179
Disseminated disease	18 (64)	116(50)	
Urine antigen	16/16 (100)	75/96 (78)	0.038
Serum antigen	6/7 (86)	13/20 (65)	0.302
Antibody	5/9 (56)	33/52 (63)	0.651

Conclusion. Transplant recipients with histoplasmosis are likely to be diagnosed early and be treated longer. Urine antigen is highly sensitive for diagnosis of disseminated disease. Histoplasmosis that occurs within the first 6 months after transplantation tends to be more severe.

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1086. Epidemiology, Risk Factors, and Effect of Antifungal Prophylaxis on Early Invasive Fungal Infection in Heart Transplant Recipients

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Session: P-49. Infections in Immunocompromised Individuals

Background. Invasive fungal infection (IFI) in heart transplant recipients is associated with increased mortality and poor outcome. Reports have estimated the risk of 1-year IFI to be 3.4-8.6% with renal replacement therapy, delayed chest closure, and reoperation suggested as risk factors. However, the role of antifungal prophylaxis is unclear, though previous studies have suggested a reduced incidence of invasive *Aspergillosis*. The transplant program in Mayo Arizona provides 6 months of universal azole prophylaxis for *Coccidioides*, while Rochester and Florida only provide prophylaxis to high risk patients. We sought to define epidemiology and risk factors for 1-year IFI and determine the effect of antifungal prophylaxis.

Methods. We conducted a retrospective cohort study of patients undergoing single-organ heart transplantation at Mayo Rochester, Florida, or Arizona from January 2000 to March 2019. We identified baseline characteristics, details of transplant hospitalization such as need for renal replacement therapy, open chest, reoperation, and operative time, receipt of antifungal prophylaxis, and diagnosis of IFI. Multivariable Cox analysis was performed to identify risk factors of time to 1-year IFI.

Results. A total of 966 heart transplant recipients were identified with a median age of 56 years (IQR 47, 62) and 72% male. 444 patients received antifungal prophylaxis which included 32% fluconazole, 34% itraconazole, 18% voriconazole, 15% echinocandin, and < 1% amphotericin or posaconazole. Over 1-year follow-up, 62 patients developed IFI with a cumulative prevalence of 6.4%. The most common organisms were *Aspergillus* (50%) and *Candida* (27%). In a multivariable model, factors associated with 1-year IFI were post-transplant renal replacement therapy (HR 3.34, 95% CI 1.69-6.60; P < 0.001) and antifungal prophylaxis (HR 0.32, 95% CI 0.11-0.96; P=0.042). Operative time, recent hospitalization, open chest, and post-transplant mechanical circulatory support were not associated with 1-year IFI.

Conclusion. Renal replacement therapy after transplantation is associated with 1-year IFI. Antifungal prophylaxis appears to be protective and further prospective study is warranted to verify this finding.

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1087. Evaluation of Risk Factors for Infection among Patients Receiving Ibrutinib

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Session: P-49. Infections in Immunocompromised Individuals

Background. Ibrutinib is a small-molecule inhibitor of Bruton tyrosine kinase (BTK) approved for various B-cell malignancies and cGVHD. Rates of serious infection—defined as requiring hospitalization or parenteral antimicrobials— and invasive fungal infection (IFI) in patients on ibrutinib are as high as 11.4% and 4.2% respectively (Varughese T, et al. *Clin Infect Dis* 2018;67(5):687-92), which may be related to off-target inhibition of interleukin-2-inducible T-cell kinase or macrophage function.

Methods. We retrospectively reviewed infection complications in patients receiving ibrutinib at our institution between 06/01/2014 and 08/31/2019, including patients who received single-agent or combination ibrutinib. In this study, serious infection was defined as above, or a diagnosis of pneumonia regardless of hospitalization or parenteral antimicrobial therapy. Logistic regression was used to identify risk factors.

Results. Baseline characteristics of 134 included patients are in Table 1. Infection and serious infection occurred in 96 (72%) and 48 (36%) patients, respectively. When pneumonia was not included as a criterion for serious infection, the serious infection rate was 22%. Prior allogeneic stem cell transplant (allo-HSCT) (OR 4.50; 95% CI 1.19 – 17.00) and corticosteroid use (OR 5.42; 95% CI 1.49 – 19.82) were significant risk factors for serious infection without pneumonia (Table 2).

Of 37 patients (28%) who received primary HSV/VZV prophylaxis with acyclovir, there was one case of suspected herpes zoster infection (3%). IFI developed in 7 patients (5%): 5 with *Pneumocystis jirovecii* pneumonia (PJP), 1 with invasive aspergillosis, and 1 with a filamentous fungus, species unknown. Other identified organisms are detailed in Figure 1. Classical risk factors for IFI, including diabetes, allo-HSCT, and concurrent corticosteroid use, were not significant predictors in this group.

Table 1. Baseline Characteristics

Table 1. Baseline Characteristics, N=134	n (%)
Age, median (SD), y	71 (11)
Male	105 (78)
Indication	
Chronic lymphocytic leukemia (CLL)	90 (67)
Mantle cell leukemia (MCL)	16 (12)
Waldenstrom macroglobulinemia (WM)	12 (9)
Chronic graft-versus-host disease (cGVHD)	7 (5)
Marginal zone lymphoma (MZL)	2 (1)
Small lymphocytic leukemia (SLL)	6 (4)
Other	
Diffuse large B-cell lymphoma	3 (2)
Primary CNS lymphoma	3 (2)
Cancer therapies or immunosuppressants concurrent or within 3 months prior to ibrutinib initiation	
Ibrutinib monotherapy	76 (57)
In combination with rituximab-containing regimen	31 (23)
In combination with selinexor	9 (7)
In combination with other agents	18 (13)
Initial ibrutinib dose	
140 mg	5 (4)
280 mg	2 (1)
420 mg	106 (79)
560 mg	19 (14)
840 mg	2 (1)
Diabetes	26 (19)
COPD	7 (5)
Autoimmune disorder	7 (5)
Corticosteroid use (prednisone ≥ 20 mg equivalent for ≥ 4 weeks)	11 (8)
Prior hematopoietic stem cell transplant (HSCT)	
None	113 (84)
One – autologous (auto-HSCT)	11 (8)
One – allogeneic (allo-HSCT)	9 (7)
Two – both allogeneic	1 (1)

Table 2. Risk Factor Analysis

Table 2. Risk Factor Analysis	Serious Infection (Excluding Pneumonia)		Invasive Fungal Infection	
Parameter	Odds Ratio (95% CI)	p-value	Odds Ratio (95% CI)	p-value
Age	1.01 (0.97 –1.04)	0.64	1.00 (0.94 – 1.08)	0.85
Indication: CLL	0.62 (0.28 –1.37)	0.24	0.63 (0.14 – 2.97)	0.56
Initial ibrutinib dose	1.00 (0.99 –1.00)	0.18	1.00 (0.99 – 1.01)	0.85
Diabetes	0.75 (0.27 –2.03)	0.57	1.71 (0.31 – 9.34)	0.53
COPD	1.05 (0.19 –5.67)	0.95	3.36 (0.34 – 32.5)	0.30
Autoimmune disorder	1.05 (0.19 –5.67)	0.95	N/A	
Prior auto-HSCT	0.55 (0.11 –2.72)	0.47	N/A	
Prior allo-HSCT	**4.50 (1.19 –17.00)**	**0.03**	2.18 (0.24 – 20.18)	0.49
Concurrent cancer tx or within 3 mos	1.61 (0.54 –2.49)	0.70	3.49 (0.65 – 18.68)	0.14
Corticosteroid use*	**5.43 (1.49 –19.82)**	**0.01**	5.24 (0.89 – 30.92)	0.06

* Defined as prednisone ≥ 20 mg equivalent for ≥ 4 weeks