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Economic Burden of *Cytomegalovirus* infection in CMV-Seropositive Hematopoietic Stem Cell Transplant Recipients Managed with Pre-Emptive Therapy: A Single Center Experience

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Introduction: *Cytomegalovirus* (CMV) infection is a common viral infection in allogeneic hematopoietic stem cell transplantation (HCT) recipients, especially in the first 100 days post HCT. Preemptive therapy (PET) proved to be effective in managing CMV but led to prolonged antiviral use and associated toxicities. Limited data exist on the economic burden of PET use and cost of care among HCT recipients.

Objectives: We aimed to compare direct all-cause or CMV-related inpatient healthcare resource use and costs in those who received or did not receive PET through 180 days (D180) post HCT.

Methods: Study cohort comprised of adults, CMV R+ allogeneic HCT recipients of first peripheral blood or marrow allograft at a single center from 3/2013 to 12/2017. HCT recipients were routinely monitored for CMV using quantitative PCR assay and administered PET as per the standards of care. Data on clinical characteristics, CMV outcomes, PET administration, reasons and dates of hospitalizations were extracted from the electronic medical records. Inpatient hospital charges were obtained from the Vizient billing database from date of HCT to D180 post HCT. Charges data were converted to costs using cost-to-charge ratios, wage index and inflation rate to 2017 US Dollars. CMV-related readmissions were identified as readmissions for initiation of PET, work up or management of CMV End Organ Disease and any readmission where PET was initiated during D180 post HCT.

Table 1
Healthcare resource utilization and total inpatient costs between PET and NO PET group from date of HCT to day+180 post-HCT

	PET N=208	No PET N=160	p-value
Total hospital length of stay mean (SO)			
Transplant (index) admission LOS	34.3 (18.6)	29.9 (15.5)	**00001**
Readmission LOS	28.9 (34.8)	25.8 (54.1)	0.6581
Readmissions, N (%)			
Number of patients with resdmissions	112 (54%)	53 (33%)	**000005**
Total number of readmissions	180 (100%)	78 (100%)	-
CMV-related readmissions	67 (37%)	-	-
Non CMV-related readmissions	113 (63%)	78 (100%)	-
Inpatient Healthcare Costs S, mean (SD)			
Index admission costs (N= 368)	$184,230 (179,059)	$150,938 (84,283)	**0.0304**
All-cause readmission costs (N= 368)	$105,676 (196,628)	$51,444 (129,038)	**0.0032**
All-cause readmission costs among those who had > 1 admission (N= 165)	$196,255(233,732)	$155,302 (185,671)	0.2654
Readmission cost per episode (n= 180)	$122,384 (174,082)	$105,526 (140,759)	0.4517
CMV-related readmission costs per episode (n=67)	$167,701 (227,028)	-	-
Non CMV-related readmission per episode (n=113)	$96,941 (130,061)	$105,526 (140,759)	0.6645

Abbreviations: CMV: *cytomegalovirus*; HCT: hematopoietic stem cell transplantation; LOS: length of stay; PET: preemptive therapy; SD: standard deviation

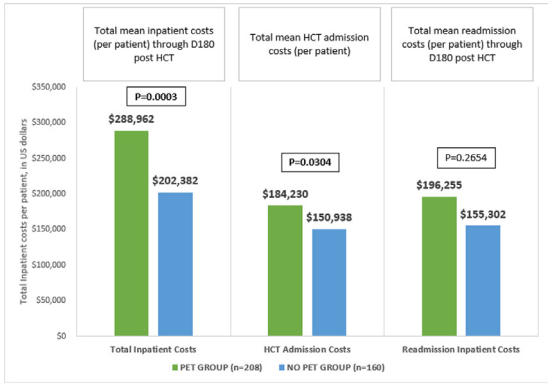

Figure 1. Comparison of total mean inpatient costs (per patient per episode) by HCT admission and readmissions by PET and NO PET group.

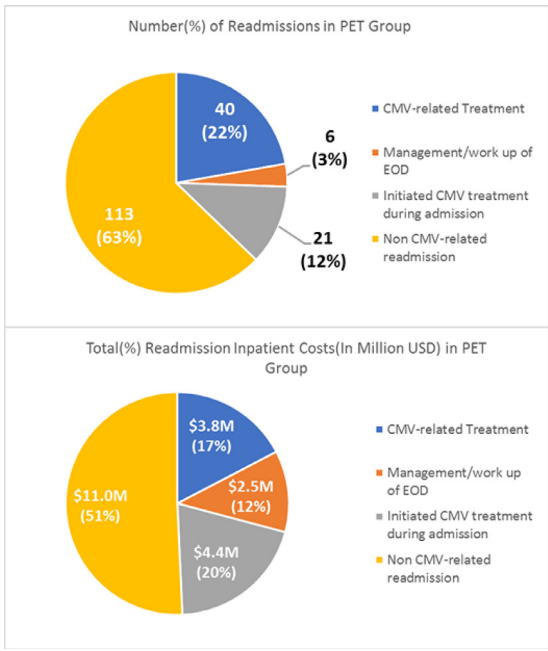

Figure 2. Reasons of readmissions and total readmission costs in PET group (readmissions were categorized as CMV-related or non CMV-related).

Results: Of 368 HCT recipients, 176 (48%) received unmodified graft from matched related or unrelated donors (low CMV risk); and 192 (52%) received either ex vivo T-cell depleted or conventional graft from mismatched donors (high CMV risk). Overall, 208 (57%) HCT recipients received PET; and 72% of them were high risk. PET recipients had longer length of stay for index admission (p=0.0001) and a greater proportion required readmission at D180 (p=0.00005) (Table 1); greater average inpatient costs for index admission ($184,230 vs. $150,938, p=0.0304) and for readmissions through D180 ($105,676 vs. $51,444, p=0.0032) (Table 1) as compared to those who did not receive PET. PET recipients also had higher costs for CMV-related readmissions per episode than non CMV-related readmissions ($167,701 vs. $96,941, p=0.0089) (Table 1). CMV-related readmissions comprised of 37% of total all-cause readmissions and incurred 49% of total all-cause readmission costs in PET recipients (Figure 2).

Conclusion: PET recipients had higher overall inpatient resource use and costs as compared to those who did not receive PET. CMV-related readmissions had disproportionate share of total inpatient readmissions costs in PET recipients. Future studies are needed to examine the cost-effectiveness of alternative strategies for CMV management.

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Invasive Atypical Mycobacterial Infection in Allogeneic Pediatric HSCT

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Introduction: Infection is a major cause of morbidity and mortality following hematopoietic stem cell transplant (HSCT). Atypical or nontuberculous mycobacterial (NTM) infections are known to occur at higher rates in patients with a compromised immune system and a study by Unal et al. reported a 6.4% incidence of NTM infections in pediatric allogeneic HSCT recipients. Disease severity with NTM infections is broad and can range from asymptomatic line infections to disseminated disease. Antimicrobial therapies for NTM infections are variable and typically multiagent. Limited data are available describing the impact of these infections and their associated therapies on HSCT outcomes in children.

Methods: We retrospectively reviewed outcomes for pediatric allogeneic HSCT recipients between 2014 and 2019 whose courses were complicated by symptomatic invasive NTM infection. Metrics analyzed include underlying disease, conditioning regimen, antimicrobial therapies, survival and donor engraftment.

Results: 5 patients were diagnosed and started on multidrug therapy for NTM surrounding HSCT. Presenting symptoms for each patient are described in Figure 1. Patient demographics and NTM details are shown in Table 1. All 5 patients received myeloablative conditioning (MAC) with busulfan and fludarabine, in addition to thiotepa (n=1), ATG (n=1) and alemtuzumab (n=1) in select patients. All patents engrafted $\leq$ 20 days with at least 99% donor chimerism. Patient 3 showed mixed chimerism on day 25, eventually resulting in graft loss requiring re-transplantation. Four out of five patients (80%) are alive today with median follow up time of 4.3 years (range 3.4 – 5.3 years).

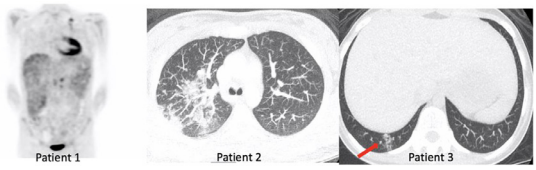

Figure 1. Patient 1 had disseminated disease with spleen, liver, lymph node and lung involvement which is appreciated in part on this PET CT image (left). She initially presented with fevers, cough, dyspnea and abdominal pain. NTM was identified in the blood and sputum; symptoms improved with NTM therapy. Following transplant, NTM therapy was briefly stopped due to transaminitis but resulted in return of cough, dyspnea and fevers, prompting resumption of therapy. Patient 2 had recurrent chest pain, cough and dyspnea that repeatedly improved with azithromycin despite initially negative workup; NTM was ultimately isolated from sputum. Her initial chest CT is shown in the center image. NTM-therapy was weaned off at 5 months post transplant, however she then developed chest pain and dyspnea with CT findings of new infectious infiltrate. Symptoms improved with resumption of NTM-therapy. Patient 3 developed worsening PFTs and a new infiltrate on chest CT (shown in right image) following HSCT. Diagnostic BAL grew NTM and therapy was initiated with symptom improvement. Patient 4 developed night sweats, fevers, pericardial effusion and productive cough 1-month after her first HSCT. NTM was isolated from sputum sample and treatment yielded improvement of symptoms. Patient 5 was found to have a sacral abscess needing incision and drainage and NTM was isolated on culture.

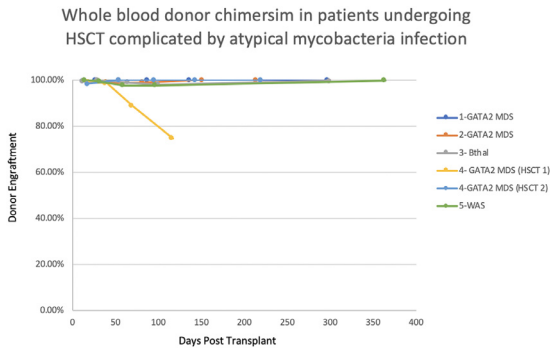

Figure 2. Kinetics of engraftment in the first year after transplant. Patient 4 underwent a second HSCT due to primary graft failure.

Conclusion: Our experience suggests that children undergoing HSCT complicated by NTM infections have favorable outcomes. NTM directed multi-drug therapy was well tolerated and did not immediately appear to affect engraftment. Recurrence of symptomatic invasive NTM infection occurred in two patients post-HSCT after stopping NTM therapy, while a third patient developed a first-time symptomatic invasive NTM infection after HSCT. This observation advocates for continuation of antimicrobial therapy through immune reconstitution.

Table 1
NTM organism, treatment and transplant details for patients with NTM infections. Patient 1 and Patient 2 had recurrence of symptomatic invasive NTM infection post-HSCT after stopping NTM therapy. Patient 2 continues on therapy to date. Patient 3 repatriated prior to completion of therapy with plan to continue for 1 year total duration. Patient 4 died while still taking NTM therapy

Patient	Sex	Age at HSCT	Diagnosis	Donor	NTM Infection	NTM Disease Prior to HSCT	NTM Disease Location	Source of NTM culture	NTM Therapy During HSCT	NTM Therapy Duration
1	F	19y/o	GATA2 MDS	MSP	M.lonsasii M. intracellulare	Yes	Disseminated	Blood Sputum	Rifampin, Ethambutol, Clarithromycin	4 years
2	F	21v/o	GATA2 MDS	MSD	M. fortuitum	Yes	Lungs	Sputum	Rifampin, Ethambutol, Azithromycin	4 years
3	F	13v/o	Beta Thalassemia	MRD	M. gordonae	No	Lungs	Sputum	None	1 year
4	F	18y/o	GATA2 MDS	HSCT1. MUD HSCT2: MUD	Mycobacterium NOS	HSCT 1: No HSCT 2: Yes	lungs	Sputum	HSCT 1: None HSCT2 : Azithromycin	2 years
S	M	Sy/o	WAS	MSD	M. fortuitum	Yes	Sacrum	Absccss	Azithromycin, Moxifloxacin	1 year