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Clinical and Economic Impact of Cytomegalovirus Infection among Children Undergoing Allogeneic Hematopoietic Cell Transplantation

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A B S T R A C T

The literature on the impact of cytomegalovirus (CMV)-related hospitalization in pediatric allogeneic hematopoietic cell transplantation (alloHCT) recipients is limited. The aim of this study was to determine utilization and outcomes of CMV-related hospitalization in alloHCT recipients using a single-center clinical database. This was a retrospective study of 240 children aged 3 months to 21 years (median age, 9.5 years) who underwent alloHCT between 2005 and 2016. The impacts of CMV-related length of stay (LOS) and total healthcare costs were quantified. Factors associated with prolonged CMV viremia (>25 days' duration) were also examined. In at-risk patients with CMV infection, the incidence of CMV viremia was 38% (59 of 155), the median time to onset was 33 days (range, 0 to 292 days), and the median time to resolution was 25 days (range, 3 to 48 days; n = 53). CMV infection was associated with a 23.3-day increase in LOS ($P = .004$) and added hospital costs of $45,443 ($P = .162$) compared with patients without CMV infection. In multivariable analysis, receipt of alemtuzumab ($P = .027$) was associated with CMV viremia of >25 days' duration. Our data show that CMV viremia is associated with prolonged LOS and higher hospital costs and indicate the need for improved and cost-effective CMV prevention strategies. Further studies of patient outcomes and costs in pediatric alloHCT recipients is needed.

INTRODUCTION

Allogeneic hematopoietic cell transplantation (alloHCT) is a curative treatment for various malignant and nonmalignant diseases in children [1]. Although HLA-matched siblings are the preferred donors for most alloHCT, they are available for only 18% of patients. For the remaining patients, alternative donor sources (ie, unrelated donors, umbilical cord blood, or partially matched family donors) are used [2,3]. For alternative donors, some centers administer serotherapy, such as antithymocyte globulin (ATG) or alemtuzumab to prevent graft rejection and acute graft-versus-host disease (aGVHD). This can lead to an increased risk of CMV reactivation, ultimately resulting in poor outcomes [4,5]. Although the burden of CMV infection and disease in alloHCT recipients has been documented, little is known about the effect of CMV infection on utilization of healthcare resources.

In adult patients with inflammatory bowel disease, CMV infection is associated with higher in-hospital mortality (odds ratio [OR], 7.09; 95% confidence interval [CI], 3.38 to 14.85), prolonged hospital length of stay (LOS) (7.77 days; $P < .0001$), and higher cost of hospitalization ($66,495; $P < .0001$) compared with patients without CMV infection [6]. In the United Kingdom, children with viral reactivation after alloHCT, including with CMV, had a prolonged LOS and higher costs of transplantation [7]. CMV infection post-alloHCT can result in pneumonitis, colitis, and other organ dysfunction and can lead to death, all of which can result in prolonged hospitalization and ultimately drive up the cost of alloHCT. However, there is limited information about the cost of alloHCT in the US for pediatric patients and little data on the effect of CMV viremia or other modifiable risk factors that can result in greater health care utilization.

Understanding the cost and healthcare utilization associated with CMV treatment is particularly important as new agents become available as alternatives for CMV prevention and treatment such as letermovir and anti-CMV cytotoxic T lymphocytes

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[8]. We hypothesize that CMV infections post-alloHCT will result in increased hospital LOS and higher healthcare costs. We examined the associations among CMV infection, LOS, and total healthcare costs in children undergoing alloHCT for malignant and nonmalignant diseases. The results of this study will help identify potentially modifiable factors in greater healthcare utilization.

METHODS

This was a retrospective study of 240 pediatric patients who underwent alloHCT for malignant and nonmalignant diseases at Columbia University Medical Center. Patients ranged in age from 3 months to 21 years and underwent transplantation between 2005 and 2016. Allogeneic hematopoietic cell sources included bone marrow, peripheral blood stem cells (unmanipulated and $CD34^+$-selected), and umbilical cord blood. For this analysis, eligible patients were identified from a transplantation database, and clinical data were collected from electronic medical records. This study was approved by the center's Institutional Review Board.

Clinical Definitions

Patients were classified as positive CMV risk status if donor, recipient, or both were CMV IgG positive pretransplantation. Patients were considered to have a post-transplantation viral reactivation with values of >600 CMV copies/mL on 2 consecutive polymerase chain reaction (PCR) analyses in blood measured within a 1-week interval.

Definitions of CMV disease were those described previously by Marty et al. [9]. A diagnosis of CMV pneumonia required the presence of signs or symptoms of pulmonary disease along with CMV viremia or detection of CMV in bronchoalveolar fluid or lung tissue samples. CMV gastrointestinal disease required the presence of clinical symptoms along with laboratory confirmation of CMV on gastrointestinal biopsy. CMV hepatitis was defined by elevated bilirubin or liver enzyme levels with concomitant detection of CMV viremia. Central nervous system CMV disease was defined by the detection of CMV in cerebrospinal fluid.

CMV Monitoring and Treatment

Prospective quantitative PCR monitoring for CMV reactivation was performed weekly from day 0 to 180 days post-transplantation. After day +180, CMV PCR was performed based on the clinical symptoms or at the physician's discretion. CMV PCR was performed at Columbia University Medical Center in accordance with the manufacturer's protocol (Roche Diagnostics, Risch-Rotkreuz, Switzerland) [10]. Prophylaxis for patients at risk for CMV was initiated at an absolute neutrophil count (ANC) $>.75 \times 10^9$/L for 2 days post-alloHCT with ganciclovir/foscarnet or valganciclovir and continued daily until at least day +100 [10].

Patients with a positive CMV PCR were preemptively treated with ganciclovir (induction dose of 5 mg/kg i.v. every 12 hours, followed by maintenance dose of 5 mg/kg i.v. daily for at least 4 weeks) or, if the patient was cytopenic at the time of CMV reactivation, foscarnet 180 mg/kg/day [11]. Induction treatment was continued until CMV PCR was negative, but it could be modified based on the viral clearance, ANC, or renal function. Patients with 2 consecutive CMV PCR values <600 copies/mL were considered to have resolution of CMV viremia.

Transplantation Characteristics

Myeloablative conditioning regimens consisted of either total body irradiation (12 Gy) or busulfan 12.8 to 16 mg/kg plus cyclophosphamide 120 mg/kg/melphalan 135 mg/m^2 with or without rabbit ATG (r-ATG) 8 mg/kg, busulfan 12.8 to 16 mg/kg/fludarabine 150 to 160 mg/m^2, and alemtuzumab 54 mg/m^2 or fludarabine 150 mg/m^2/cyclophosphamide 200 mg/kg/r-ATG 8 mg/kg. Reduced-intensity conditioning regimens contained busulfan 6.4 to 8 mg/kg, fludarabine 150 to 180 mg/m^2 with or without r-ATG 8 mg/kg [12].

Myeloid engraftment was defined as the first day of 3 consecutive days with an ANC $>.5 \times 10^9$/L. The time to platelet engraftment was the first day postnadir with a platelet count $>20 \times 10^9$/L for 7 consecutive days without transfusion. Primary graft failure was defined as failure to achieve a donor-derived ANC $>.5 \times 10^9$/L by day +42 [12]. GVHD prophylaxis was as provided in accordance with a previous study by our center [13]. aGVHD was graded by clinicians according to the Seattle criteria [14].

Transplantation admission (ie, first admission) was defined as the period from the initiation of the conditioning regimen to first discharge from the hospital post-alloHCT.

Kidney and liver injury were defined based on creatinine and total bilirubin levels through day +100. Liver injury was defined as total bilirubin >2 mg/dL. Kidney injury was defined as a >50% decrease in creatinine clearance over the pretransplantation baseline value [14].

Outcomes: Cost and Healthcare Utilization

Our primary outcomes of interest were hospital LOS and total cost in patients with and without CMV reactivation. Secondary outcomes included incidence, time of onset, days to resolution of CMV viremia, number and LOS of hospitalizations after CMV reactivation, and effect of antiviral therapy on hepatic and bone marrow function. One-year overall survival and incidence of transplantation-related mortality were compared between patients with and those without CMV reactivation. Transplantation-related mortality was defined as death due to any transplantation-related cause other than disease relapse. Overall survival analysis included patients who were alive with or without their original disease.

Inpatient charges were obtained from the US Pediatric Health Information System Database, a confidential patient database including data from 50 tertiary care children's hospitals. Participating hospitals submit deidentified data, and an encrypted medical record code permits identification of readmissions at the same hospital. Inpatient charges were divided into 4 categories: clinical, pharmacy, laboratory, and imaging services. Outpatient charges were obtained from the pediatric financial services of the study institution [15,16]. Costs were estimated using institution-specific cost-to-charge ratios, published annually in the *Federal Register*, and adjusted for inflation using the medical component of the Consumer Price Index to 2016 US Dollars. Health care utilization was assessed based on hospital LOS and intensive care unit admission [17].

Statistical Analyses

SAS version 9.3 (SAS Institute, Cary, NC) was used to perform all analyses. Continuous variables were summarized as median with range, and categorical variables were summarized as number and percentage. Patients were analyzed in 2 categories, those with CMV reactivation and those without CMV reactivation. The groups were compared using the Wilcoxon rank-sum test for continuous variables and either the χ^2 or Fisher exact test for categorical variables, as appropriate. A P value $\leq$.05 was considered significant. Simple and multiple linear regressions were used to evaluate the effect of CMV infection on LOS and total costs. Univariable analyses were conducted to assess the relationships between risk factors (CMV infection, age at alloHCT, sex, disease, transplant type, cell source, HLA match, conditioning regimen, pretransplantation CMV serostatus, performance status, aGVHD, liver injury by day +30, and kidney injury by day +30) and the outcomes of LOS and costs separately. Variables found to be significant on the univariable analyses were then adjusted for in the multivariable analysis.

Two post hoc analyses were also conducted. In the first analysis, we examined cost and healthcare utilization using a matched pair analysis in patients with CMV viremia. The controls were identified from the patients without CMV viremia, matched by age (within 1 year), disease status, conditioning regimen, and donor source. In the second analysis, we compared data between patients who developed CMV viremia during the first transplantation admission and those who never developed CMV viremia.

According to Tomblyn et al. [18], 7 to 14 days is the standard protocol for ganciclovir induction for preemptive treatment of CMV, but the median time to CMV resolution in our cohort was 25 days. We performed a post hoc analysis on patients whose CMV viremia took >25 days to resolve. Univariable logistic regression analyses were used to evaluate the risk factors for prolonged CMV viremia of >25 days' duration and multivariable model adjusted for variables that were found to significant with a P value $\leq$.10 in univariate analysis.

RESULTS

Patient Demographics and Characteristics

Between 2005 and 2016, 240 pediatric patients aged <21 years underwent alloHCT; 1 patient who transferred care to another center was excluded from our analysis. In the total cohort (N = 240), 124 patients (51.9%) had malignant disease, 141 (59%) had an unrelated donor, 187 (78.2%) received myeloablative conditioning, and 52 (21.8%) received reduced-intensity conditioning.

Indications for transplantation included malignant diseases such as acute leukemia (n = 95; 40%), lymphoma (n = 26; 18.5%), and solid tumors (n = 6; 2.5%), and nonmalignant diseases, such as hemoglobinopathies (n = 61; 25%), bone marrow failure (n = 22; 9%), and others (n = 29; 12%).

CMV Incidence and Resolution

The overall incidence of CMV viremia in all patients from day 0 post-alloHCT was 25% (n = 59 of 239). The incidence of CMV viremia among patients at risk was 38% (n = 59 of 155).

All patients who developed CMV viremia had a positive pretransplantation CMV risk status, and the incidence of CMV viremia was 0% among CMV serology-negative patients who had a CMV serology-negative donor. The incidence of CMV viremia among patients with malignant disorders was comparable to that among patients with nonmalignant disorders (24% versus 26%; P = .60). Comparing clinical characteristics, the patients with CMV viremia were younger and had a higher rate of myeloablative conditioning compared with those without CMV viremia (Table 1). Other key demographics and baseline characteristics of the transplant recipients are summarized in Table 1.

The median time to the onset of CMV viremia was 33 days (range, 0 to 292 days; n = 59). The median peak CMV copy number was 5430 (range, 749 to 261,780; n = 59). The median time to resolution of CMV viremia was 25 days (range, 3 to 148 days; n = 53). Among the patients with CMV reactivation (n = 53), the median time to resolution of viremia was significantly longer in those who received ATG (17 days, range 7-48) or alemtuzumab (31 days, range 3-121), compared with those who received neither drug (12.5 days; range, 4 to 35 days; P = .004). The median hospital LOS after onset of viremia was 33 days (range, 1 to 237 days). Six patients with CMV viremia died and did not clear viremia before death and thus were excluded from the analysis for CMV viremia resolution.

CMV Treatment and Nephrotoxicity

Among the 59 patients with CMV infection, 21 (35.6%) were treated with 1 drug (ganciclovir or foscarnet), 22 (37.3%) were treated with 2 drugs (ganciclovir and foscarnet), 9 (15.3%) were treated with 3 drugs (ganciclovir, foscarnet, and CMV immunoglobulin), and 7 (11.9%) were treated with 4 drugs (ganciclovir, foscarnet, cidofovir, and CMV immunoglobulin). Three patients received anti-CMV cytotoxic T lymphocytes. In the majority of patients, ganciclovir, foscarnet, and cidofovir were not administered simultaneously but instead were delivered consecutively owing to inadequate response or toxicity. Eight patients had a recurrence of CMV viremia. Six patients were treated with ganciclovir, and 2 patients were treated with foscarnet. Given the potential nephrotoxicity of these antiviral medications, kidney injury was evaluated. The incidence of kidney injury at was 8.8% at 2 weeks, 13.2% at 4 weeks, and 20.4% at 8 weeks.

Overall Survival

Among the patients with CMV reactivation, 19 developed viral CMV disease (32.2%). Among the 19 patients with CMV disease, 16 patients had CMV pneumonitis, and 1 patient each had colitis, hepatitis, and encephalitis. The 1-year overall survival was not significantly different between patients with CMV viremia and those without CMV viremia (61.0% ± 6.4% versus 68.3% ± 3.5%; P = .457, log-rank test). The overall survival was lower for patients who developed CMV disease compared with those who did not develop CMV disease (47.4% ± 11.5% versus 67.5% ± 7.4%; P = .134, log-rank test), but the difference did not reach statistical significance.

HOSPITALIZATION AND HEALTHCARE UTILIZATION

The median LOS for transplantation admission was longer in patients with viremia compared with those without viremia (53 days [range, 25 to 260 days] versus 44.5 days [range, 23 to 281 days]; $P < .001$) (Table 2). Similarly, the median hospital LOS in the first year post-alloHCT was longer in the patients with viremia (101 days [range, 25 to 319 days] versus 72 days [range, 26 to 354 days]; $P < .001$). The median cost of transplantation admission was significantly higher in the patients

Table 1
Univariate Analysis of Baseline Characteristics among Bone Marrow Transplantation Recipients

Characteristic	All (N = 239)	CMV viremia (N = 59)	No CMV viremia (N = 180)	*P* Value
Age, yr, median (range)	9.52 (.26-21)	7.85 (.31-21.0)	10.1 (.26-21)	.026
Sex, n (%)				.05
Female	92 (38.5)	29 (49.2)	63 (35)	
Male	147 (61.5)	30 (50.9)	117 (65)	
Disease, n (%)				.63
Malignant	124 (51.9)	29 (49.2)	95 (52.8)	
Nonmalignant	115 (48.1)	30 (50.9)	85 (47.2)	
Transplant type, n (%)				.33
Related	98 (41)	21 (35.6)	77 (42.8)	
Unrelated	141 (59)	38 (64.4)	103 (57.2)	
Cell source, n (%)				.40
Cord blood	57 (23.9)	13 (22.0)	44 (24.4)	
Unmanipulated PBSCs	34 (14.2)	11 (18.6)	23 (12.8)	
Bone marrow	115 (48.1)	30 (50.9)	85 (47.2)	
CD34 selected	33 (12.8)	5 (8.5)	28 (15.6)	
HLA match, n (%)				.85
Mismatch	112 (46.9)	27 (45.8)	85 (47.2)	
Full match	127 (53.1)	32 (54.2)	95 (52.8)	
Conditioning regimen, n (%)				.30
Myeloablative	187 (78.2)	49 (83.1)	138 (76.7)	
Reduced intensity	52 (21.8)	10 (16.9)	42 (23.3)	
Pretransplantation CMV serostatus, n (%)				<.001
Negative	84 (35.2)	0 (0)	84 (46.7)	
Positive	155 (64.8)	59 (100)	96 (53.3)	
Karnofsky Performance Status, n (%)				.36
<90	66 (27.6)	19 (32.2)	47 (26.1)	
≥90	173 (72.4)	40 (67.8)	133 (73.9)	
ATG use, n (%)	93 (38.9)	20 (33.9)	73 (40.6)	.36
Alemtuzumab use, n (%)	103 (43.1)	31 (52.5)	72 (40)	.09

PBSCs indicates peripheral blood stem cells.
HLA full match is defined as a 6/6 or 8/8 match; otherwise classified as mismatch. CMV-positive serostatus is defined as either patient or donor being CMV IgG-positive before transplantation.

Table 2
Hospital Healthcare Utilization and Costs

	All Patients with and without CMV Viremia				Matched-Pair Analysis				CMV Viremia during First Transplant Admission versus No CMV Viremia			
Parameter	All (N = 239)	CMV Viremia (N = 59)	No CMV Viremia (N = 180)	*P* Value	All (N = 139)	CMV Viremia (N = 52)	No CMV Viremia (N = 87)	*P* Value	All (N = 227)	CMV Viremia during First Admission (N = 47)	No CMV Viremia (n = 180)	*P* Value
Duration of transplantation admission, d, median (range)	47 (23-281)	53 (25-260)	44.5 (23-281)	<**.001**	50 (23-281)	56 (25-260)	46 (23-281)	**.016**	47 (23-281)	56 (25-260)	44.5 (23-281)	<**.001**
Total hospital length of stay, d, median (range)	79 (25-354)	101 (25-319)	72 (26-354)	<**.001**	85 (25-354)	105.5 (25-319)	78 (26-354)	**.011**	78 (25-354)	106 (25-319)	72 (26-354)	<**.001**
Cost of transplantation admission, $, median (range)	159,432 (13,126-1,471,698)	183,308 (13,126-1,471,698)	149,661 (63,026-1,149,262)	**.015**	164,542 (13,126-1,471,698)	215,657 (13,126-1,471,698)	160,328 (83,876-810,367)	**.044**	(N = 176) 72 (27-354)	(N = 29) 109 (31-319)	(N = 135) 66 (27-354)	<**.001**
Overall cost, $, median (range)	332,322 (117,830-1,471,698)	387,540 (117,830-14,711,698)	307,957 (119,002-1,191,131)	**.005**	349,076 (117,830-1,471,698)	402,771 (117,830-14,711,698)	299,254 (125,228-900,155)	**.023**	160,328 (13,126-1,471,698)	213,674 (13,126-1,471,698)	149,661 (63,026-1,149,262)	**.014**
Outpatient costs, $, median (range)	(N = 207) 43,328 (2-208,680)	(N = 50) 9520 (959-208,680)	(N = 157) 43,242 (2-147,361)	.790	(N = 119) 41,225 (2-208,680)	(N = 43) 43,791 (959-208,680)	(N = 76) 40,309 (2-116,672)	.287	322,332 (117,830-1,471,698)	385,588 (117,830-14,711,698)	307,957 (119,002-1,191,131)	**.014**

Significant *P* values are in bold type.

Table 3
Multivariable Linear Regression Analysis of the Associations between CMV Infection and LOS and Total Costs

		LOS		Total Costs	
Variables	n	Days (SE)	*P* Value	Dollars (SE)	*P* Value
CMV infection					
Negative	180	Reference		Reference	
Positive	59	23.3 (7.90)	.004	47,360.3 (32,980)	.152
Age at transplantation	239	-.514 (.599)	.39		
Sex					
Male	147			Reference	
Female	92			44,326.6 (29,141.9)	.130
Disease					
Nonmalignant	115			Reference	
Malignant	124			26,907.8 (30,851.7)	.384
Transplant type					
Related	98	Reference		Reference	
Unrelated	141	6.34 (8.91)	.48	19,333.2 (37,696.6)	.609
Cell source					
Cord blood	57	Reference		Reference	
Unmanipulated PBSCs	34	-32.3 (12.2)	.009	-74,611.8 (52,637.8)	.158
Bone marrow	115	-26.7 (10.5)	.012	-82,571.4 (42,840.9)	.055
CD34-selected PBSCs	33	-20.3 (11.9)	.09	-21,364.3 (47,319.2)	.652
HLA match					
Mismatch	112	Reference		Reference	
Full match	127	-22.6 (8.03)	.005	-87,022.9 (34,082.7)	.011
aGVHD	80	45.4 (7.37)	<.001	173,833.8 (31,306.6)	<.001
Liver injury by day 30	70			85,022.1 (29,033.9)	.004
Kidney injury by day 30	85			52,849.5 (28,537.4)	.065

with CMV viremia ($183,308 [range, $13,126 to $1,471,698] versus $149,661 [range, $63,025 to $1,149,261]; P = .015). Overall 1-year costs were also statistically significantly different between patients with CMV viremia and patients without CMV viremia (P = .005) (Table 2). Matched-pair analysis focusing on patients who developed CMV viremia during the transplantation admission compared with those without CMV viremia yielded findings similar to the foregoing results (Table 2). We also compared patients who had CMV viremia during the first admission (n = 47) and never developed CMV viremia (n=180) and found similar results (Table 2).

In regression analyses examining the association between CMV infection and LOS, the unadjusted association between CMV infection and LOS was 27.4 days (P = .003). In multivariable analysis, LOS was an average of 23.3 days longer in patients with CMV infection compared with those without infection when adjusted for age at transplantation, transplant type, all cell sources, HLA matching, and aGVHD (P = .004) (Table 3). In multivariable linear regression matched-pair analysis among patients with and without CMV viremia, LOS was 20 days longer on average in the patients with CMV viremia (P = .02) (Table 4). CMV viremia was not associated with a significant increase in total costs when adjusted for other risk factors (Tables 3 and 4).

Multivariable Analysis for Days to Clear CMV

Finally, simple and multiple logistic regressions were performed to examine risk factors associated with CMV viremia of >25 days' duration. In multivariable analysis, use of alemtuzumab (OR, 25.1; 95% CI, 1.437 to 437; P = .027) was associated with CMV viremia of >25 days' duration (Table 5). Our analysis included only risk factors found to be significantly associated in univariate analyses (P < .10).

DISCUSSION

The results of our single-center analysis show that the duration of transplantation admission and cumulative hospital LOS in the first-year post-transplantation were significantly longer in patients with CMV infection compared with those without CMV infection. Similarly, transplantation-associated hospitalization costs and overall costs were also higher in patients with CMV viremia, supporting our hypothesis. Our findings are consistent with those of previous studies in which CMV infection was associated with significantly increased LOS when controlling for significant risk factors [7,19,20]. However, to the best of our knowledge, no previous study has examined the costs associated with CMV infection specifically.

Jain et al. [19] reported an average of 13.9 additional days of hospitalization for patients treated with antiviral therapy and estimated average additional costs of $58,000 to $74,000 per patient. Although we found higher costs in patients with CMV infection, the difference did not reach significance in multivariable analysis, possibly explained by the smaller sample size. Other studies have reported similarly higher costs in patients with CMV infection [7,20]. Ghantoji et al. [20] estimated an average direct cost of $38,658 associated with CMV infections across 9 major US cancer centers in 2016. Some studies have proposed that increased costs are often related to the frequency of CMV monitoring and duration, as well as the treatments provided [3,21,22].

The fact that almost one-fourth of our patient population had CMV viremia is consistent with previous reports [23–26]. A study of alloHCT conducted by the Center for International Blood and Marrow Transplant Research indicated that CMV reactivation remains associated with poor outcomes post-transplantation [27]. Similarly, in our study, patients who developed CMV disease had a 20% lower overall survival rate compared with those who did not, which was not statistically significant but was clinically meaningful. Surprisingly, the overall survival of patients with viremia was similar to that of patients without viremia, which might be related to close monitoring of PCR copy numbers of viremia in our cohort. It is possible that our use of a lower threshold viral copy number of 600 copies/mL allowed for more rapid treatment initiation and better outcomes compared with the use of 10,000 copies/mL for CMV [4,7].

Table 4
Multivariable Linear Regression Analysis of the Association between CMV Infection and LOS and Total Costs (Matched-Pair Analysis)

		LOS		Total Costs	
Variables	n	Days (SE)	*P* Value	Dollars (SE)	*P* Value
CMV infection					
Negative	87	Reference		Reference	
Positive	52	20.4 (8.73)	.021	34,857.8 (36,065.3)	.336
Age at transplantation	139	-1.316 (.827)	.114		
Sex					
Male	90			Reference	
Female	49			49,517.1 (36,233.6)	.174
Transplant type					
Related	58	Reference		Reference	
Unrelated	81	1.992 (10.89)	.855	-9673.7 (43,710.8)	.825
Cell source					
Cord Blood	40	Reference		Reference	
Unmanipulated PBSCs	13	-28.6 (18.7)	.128	-14,595.3 (68,978.9)	.833
Bone marrow	76	-26.9 (12.4)	.032	-78,538.0 (47,228.5)	.099
CD34 selected PBSCs	10	-40.4 (18.4)	.030	-105,232.7 (69,345.5)	.132
HLA Match					
Mismatch	62	Reference		Reference	
Full match	77	-20.0 (10.9)	.068	-125,963.1 (42,190.6)	.003
aGVHD	44	52.0 (9.76)	<.001	175,303.4 (38,546.2)	<.001
Liver injury by day 30	40			85,717.6 (39,396.3)	.031
Kidney injury by day 30	49			28,541.1 (37,356.6)	.446

In the present study, the use of ATG and use of alemtuzumab were individually found to significantly increase the time to resolution of viremia compared with administration of neither drug (P = .004). These results were in accordance with those of Schonberger et al. [23], which identified ATG treatment as an independent risk factor for viremia, along with recipient CMV seropositivity, stem cell source, and HLA mismatch. Given the median time to viremia resolution in this study of 25 days, we examined risk factors associated with CMV viremia of >25 days' duration. Notably, the use of alemtuzumab was significantly associated with CMV viremia of >25 days' duration [28–30], a finding that was not unexpected given alemtuzumab's potent in vivo T cell-depleting properties. The use of novel anti-CMV prophylactic and therapeutic strategies, such as letermovir or CMV-specific cytotoxic T cell infusion, could potentially decrease the incidence and/or duration of viremia in high-risk patients post-alloHCT.

Other studies have indicated that preemptive CMV treatment, which uses costly and toxic antiviral drugs, can cause renal damage and necessitate further treatment and hospitalization [28,29]. In our cohort, the incidence of renal injury was 20% at 8 weeks after the initiation of anti-CMV treatment. Improving CMV prevention strategies is crucial to avoiding higher costs and clinical toxicity. A recent randomized Phase III clinical trial reported that letermovir prophylaxis resulted in a significantly lower risk of clinically significant CMV infection compared with placebo after alloHCT in adults [9]. Letermovir is the first Food and Drug Administration-approved drug for CMV prophylaxis, and although currently approved only for adults aged >18 years, it could have important implications for decreasing preemptive CMV therapy-related myelosuppression and kidney injury, healthcare utilization, and costs. Schelfhout et al. [31] recently reported that letermovir reduced the rate of CMV infection requiring preemptive treatment at 24 weeks post-transplantation, with an incremental cost-effectiveness ratio of $29,110 per quality-adjusted life-year (QALY) gained; the probabilistic sensitivity analysis indicated that letermovir was cost effective in 93.5% of iterations at $100,000 per QALY gained, which was well within the commonly accepted incremental cost-effective ratio threshold. At $195 per letermovir tablet and $270 per injection, the cost of letermovir prophylaxis would range from $16,380 to $22,680 for 3 months. This projected cost range is far lower than the difference in hospital costs between our patients with and without CMV infection ($45,443), suggesting that letermovir is a more cost-effective option compared with current treatment approaches. As it stands, letermovir has great potential to reduce CMV-related costs, improve QALYs, and reduce mortality; however, future studies of letermovir use in patients using alemtuzumab are needed, given alemtuzumab's frequently use in pediatric patients.

Our study was limited by the fact that it is from a single center in which transplantation care was provided by small group of physicians, nurse practitioners, and medical staff and based on clinical practice guidelines. The costs that we have detailed reflect inpatient and outpatient costs only and do not include the costs associated with outpatient oral medications, i.v. medications, and i.v. fluids administered at home. Our patient population also had a variety of diagnoses and individually tailored conditioning regimens and therapies. Nevertheless, we were able to obtain charges for both initial hospitalizations for transplantation and cumulative 1-year post-transplantation, inclusive of inpatient and outpatient care, and to provide accurate estimates of costs. The fact that medical centers use multiple unstandardized methods of viral load thresholds, detection

Table 5
Multivariable Logistic Regression Analysis of Risk Factors Associated with CMV Viremia of >25 Days' Duration (Median)

Factor	OR	95% CI	*P* Value
Karnofsky Performance Status			
<90	Reference		
90	.085	.007-1.093	.059
ATG use			
No	Reference		
Yes	3.065	.168-56.0	.450
Alemtuzumab use			
No	Reference		
Yes	25.1	1.437-437	.027

mechanisms, and management likely results in increased healthcare costs and makes it difficult to compare costs of CMV-related hospitalizations across sites.

A limitation in our cost analysis is that we studied only 10 variables, whereas many other factors, such as mucositis, veno-occlusive disease, and severe hemorrhagic cystitis, can affect the cost of alloHCT.

Although many potential factors can impact hospital LOS and cost, in our cohort, the major contributors to higher costs of alloHCT were aGVHD ($P < .001$), liver injury by day 30 ($P = .004$), and HLA mismatch ($P = .01$). In our study, aGVHD was the principal driver of cost; it is likely that aGVHD-related symptom management and the side effects of steroids led to prolonged hospitalizations, which ultimately resulted in higher cost and healthcare utilization. As expected, costs were lower in patients who received an HLA-matched transplant, possibly related to a lower incidence of aGVHD. Interestingly, we noted that liver injury resulted in significant cost increases, which we suspect is related to veno-occlusive disease occurring in the first 30 days post-alloHCT.

Although prevention of CMV recurrence with newer treatment modalities may potentially decrease healthcare utilization and costs, our data indicate that aGVHD is a primary driver of increasing costs, and thus optimal strategies to prevent and treat aGVHD are greatly needed. If successfully administered, these new strategies could potentially improve alloHCT outcomes and decrease associated costs.

Although preemptive CMV therapy in adults has proven valuable in controlling or preventing CMV disease and other complications [9], we conclude that CMV viremia remains associated with prolonged hospitalization. The present study highlights the need for prospective studies of CMV monitoring strategies, cost-effective prophylaxis, and other CMV-directed treatment options for patients with CMV reactivation.

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