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Characteristics of Late Fatal Infections after Allogeneic Hematopoietic Cell Transplantation

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A B S T R A C T

We analyzed late fatal infections (LFIs) in allogeneic stem cell transplantation (HCT) recipients reported to the Center for International Blood and Marrow Transplant Research. We analyzed the incidence, infection types, and risk factors contributing to LFI in 10,336 adult and 5088 pediatric subjects surviving for ≥2 years after first HCT without relapse. Among 2245 adult and 377 pediatric patients who died, infections were a primary or contributory cause of death in 687 (31%) and 110 (29%), respectively. At 12 years post-HCT, the cumulative incidence of LFIs was 6.4% (95% confidence interval [CI], 5.8% to 7.0%) in adults, compared with 1.8% (95% CI, 1.4% to 2.3%) in pediatric subjects; $P < .001$). In adults, the 2 most significant risks for developing LFI were increasing age (20 to 39, 40 to 54, and ≥55 years versus 18 to 19 years) with hazard ratios (HRs) of 3.12 (95% CI, 1.33 to 7.32), 3.86 (95% CI, 1.66 to 8.95), and 5.49 (95% CI, 2.32 to 12.99) and a history of chronic graft-versus-host disease GVHD (cGVHD) with ongoing immunosuppression at 2 years post-HCT compared with no history of GVHD with (HR, 3.87; 95% CI, 2.59 to 5.78). In pediatric subjects, the 3 most significant risks for developing LFI were a history of cGVHD with ongoing immunosuppression (HR, 9.49; 95% CI, 4.39 to 20.51) or without ongoing immunosuppression (HR, 2.7; 95% CI, 1.05 to 7.43) at 2 years post-HCT compared with no history of GVHD, diagnosis of inherited abnormalities of erythrocyte function compared with diagnosis of acute myelogenous leukemia (HR, 2.30; 95% CI, 1.19 to 4.42), and age >10 years (HR, 1.92; 95% CI, 1.15 to 3.2). This study emphasizes the importance of continued vigilance for late infections after HCT and institution of support strategies aimed at decreasing the risk of cGVHD.

INTRODUCTION

Late fatal infections (LFIs) occurring ≥2 years after HCT remain a significant contributing factor to mortality post-HCT [1]. However, data are limited on the incidence of LFI, the types of infections responsible for death, and recipient-, disease-, and HCT-related risk factors associated with LFI in adult and pediatric patients surviving for ≥2 years after HCT. Previous studies addressing LFI after HCT were limited by small sample size, response bias, inadequate follow-up, and incomplete data reporting from transplantation centers. To address this knowledge gap, we performed a detailed analysis of LFI in HCT recipients reported to the Center for International Blood and Marrow Transplant Research (CIBMTR), including the incidence, types of infections, and risk factors.

METHODS

Data Source

The CIBMTR includes a network of more than 450 transplantation centers worldwide that contribute data on consecutive transplantations performed at each center to a centralized registry. All patients are followed longitudinally until lost to follow-up or death. The quality of the data reported by all participating centers is monitored by computerized error checks, physician data review, and periodic onsite patient record audits.

Study Design

The study population consisted of subjects with hematologic malignancies and nonmalignant conditions who underwent HCT between January 1, 1995, and December 31, 2011. To minimize selective reporting bias, patients were selected only from centers with a team follow-up completeness index ≥80% at 4 years (n = 344 centers and n = 43,345 patients). The completeness index is defined as the ratio of total observed person-time to the potential person-time of follow-up [2]. Subjects who received stem cells grafts from syngeneic donors or multiple donors (n = 583) were excluded. Approximately 57% (n = 24,420) of the patients were then excluded for death or relapse within 24 months of HCT. Subjects missing baseline, 100-day, or disease-specific forms (n = 193) and without available consent (n = 638) were excluded. Subjects with severe combined immunodeficiency and other immune system disorders associated with incomplete immune reconstitution after HCT (n = 1017) were excluded from the analysis. Subjects with nonmyeloma plasma cell disorders (n = 7) were also excluded owing to low numbers. Previous autologous HCT (n = 759) was permitted for study inclusion. Subjects who were lost to follow-up (n = 549) and subjects with missing survival data (n = 19) or cause of death data (n = 495) were excluded from the analysis. A total of 15,424 patients were included in the final study population, with 10,336 adult and 5,088 pediatric patients.

Statistical Analysis

Pediatric patients age 0 to 17 years and adult patients age 18 to 79 years were analyzed separately because of differences in disease biology, pretransplantation treatment, graft source, conditioning regimen, overall post-transplantation mortality, and causes of post-transplantation mortality. Relapse or second HCT at ≥2 years after the initial HCT was reported in 1263 adult patients (12%) and in 297 pediatric patients (6%), who were censored at the event. In a multivariate analysis of the pediatric population, 1 patients with multiple myeloma age <18 years and 64 patients missing data on graft-versus-host disease (GVHD) were excluded.

Potential risk factors for late death from infection included age at HCT, sex, race, geographic region of the center, Karnofsky or Lansky Performance Score at HCT, disease, previous autologous HCT, CIBMTR disease risk index, time from diagnosis to HCT, human immunodeficiency virus (HIV) status, donor type, HLA match, stem cell source, donor/recipient cytomegalovirus (CMV) status, conditioning regimen, dose of total body irradiation (TBI), GVHD prophylaxis regimen, use of T cell depletion, year of HCT, presence of fungal infections before HCT, and development of acute GVHD (aGVHD) and chronic GVHD (cGVHD) within the first 2 years after HCT. The effect of these covariates on mortality due to infection was analyzed by marginal Cox regression models, which allow for adjustment for clustering within centers.

All potential risk factors were checked with time-dependent covariates to ensure that assumptions of proportionality were met. Backward elimination procedures were used to identify significant variables to include in the final model. Interactions between donor source and GVHD status at 2 years, as well as conditioning and GVHD status at 2 years, were evaluated in the regression models for adult population. A similar assessment was not possible for the pediatric population owing to the low number of events in this cohort. A

significance level of $\alpha = .05$ was used. Analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC).

RESULTS

Patient Characteristics

The final study population included 10,336 adult patients from 267 transplantation centers and 5088 pediatric patients from 202 centers. Patient, disease, and transplantation characteristics are shown in Table 1. The median age at HCT was 44 years (range, 18 to 79 years) years in the adult patients and 9 years (range, <1 to 17 years) in the pediatric patients. The median follow-up intervals were 97 months (range, 24 to 251 months) in the adult patients and 100 months (range, 24 to 247 months) in the pediatric patients.

Table 1
Characteristics of the Study Population: HCT Recipients Who Were Disease-Free at Least 24 Months after Transplantation

Variable	Population	
	Adult (≥18 yr)	Pediatric (<18 yr)
Number of patients	10,336	5088
Number of centers	267	202
Patient age at HCT, yr, median (range)	44 (18-79)	9 (<1-17)
Sex, n (%)		
Male	5888 (57)	2898 (57)
Female	4448 (43)	2190 (43)
Performance score, n (%)		
≥90	7124 (69)	4148 (82)
<90	2689 (26)	750 (15)
Missing	523 (5)	190 (4)
Disease, n (%)		
AML	4134 (40)	1162 (23)
Acute lymphoblastic leukemia	1363 (13)	1607 (32)
Other leukemia	574 (6)	98 (2)
Myelodysplastic syndrome	865 (8)	182 (4)
Other myeloproliferative neoplasms	701 (7)	252 (5)
Non- Hodgkin lymphoma	1335 (13)	94 (2)
Hodgkin lymphoma	173 (2)	13 (<1)
Multiple myeloma	237 (2)	1 (<1)
SAA	821 (8)	826 (16)
Inherited abnormalities of erythrocyte diff/function	133 (1)	853 (17)
Interval from diagnosis to transplantation, mo, median (range)	9 (<1-540)	10 (<1-210)
Conditioning regimen, n (%)		
Myeloablative	6807 (66)	4064 (80)
Reduced intensity/nonmyeloablative	3339 (32)	977 (19)
Missing	190 (2)	47 (1)
Graft source, n (%)		
BM	3479 (34)	3395 (67)
Peripheral blood	6347 (61)	553 (11)
Cord blood	510 (5)	1140 (22)
Donor type, n (%)		
HLA-identical sibling	4509 (44)	2003 (39)
Other relative	290 (3)	249 (5)
HLA-matched unrelated donor	3774 (37)	1042 (21)
HLA-mismatched unrelated donor	984 (10)	422 (8)
Unrelated donor missing HLA data	269 (3)	232 (5)
Cord blood	510 (5)	1140 (22)
History of aGVHD (at 2 yr post-HCT), n (%)		
No	6668 (65)	3509 (69)
Yes	3559 (34)	1522 (30)
Missing	109 (1)	57 (1)
Composite history of GVHD (before 2-yr starting point), n (%)		
No GVHD	3054 (30)	2755 (54)
Acute only	932 (9)	696 (14)
cGVHD, on immunosuppression at 2 yr	3325 (32)	563 (11)
cGVHD, off immunosuppression at 2 yr	1415 (14)	566 (11)
cGVHD, unknown immunosuppression status at 2 years	1506 (15)	444 (9)
Missing all GVHD data	104 (1)	64 (1)
Follow-up of survivors, mo, median (range)	97 (24-251)	100 (24-247)

Pretransplantation Infections, Graft Sources, and GVHD

Among 10,336 adult subjects, 884 (9%) had a clinically significant fungal infection before HCT, and 318 (3%) were HIV-seropositive. Graft sources included bone marrow (BM) in 3479 patients (34%), granulocyte-colony stimulating factor-mobilized peripheral blood stem cells in 6347 (61%), and cord blood in 510 (5%). Myeloablative conditioning was used in 6807 patients (66%), and reduced-intensity/nonmyeloablative conditioning was used in 3339 patients (32%). A history of aGVHD, limited, or extensive cGVHD by 2 years post-HCT was reported in 3559 (34%), 1315 (13%), and 4912 (48%) patients, respectively.

Among 5088 evaluable pediatric subjects, 418 (8%) had a clinically significant fungal infection before HCT, and 75 (1.5%) were HIV seropositive. Graft sources included BM in 3395 (67%), granulocyte-colony stimulating factor-mobilized peripheral blood stem cells in553 (11%), and cord blood in 1140 (22%). Myeloablative conditioning was used in 4064 patients (80%), and reduced-intensity/nonmyeloablative conditioning was used in 997 (19%). A history of aGVHD, limited cGVHD, and extensive cGVHD within 2 years of HCT was reported in 1522 (30%), 109 (2%), and 858 (17%) patients, respectively.

LFI in the Context of Other Causes of Death

In the study population, 2245 adult patients (22%) died from various causes, including 839 patients (37%) who had a post-HCT relapse or underwent a second HCT. These latter patients were censored at that date. In the remaining 1406 patients, the leading primary causes of death were cGVHD (n = 340; 24%), organ failure (n = 335; 24%), and infection (n = 311; 22%). Infection was reported as a contributing cause of death in 185 patients (13%). A total of 377 pediatric patients (7%) died from various causes, including 151 patients (40%) who had a post-HCT relapse or a second HCT and were censored at that date. Among the remaining 226 patients, the leading causes of death were organ failure (n = 48; 21%), subsequent malignancy (n = 44; 19%), and GVHD (n = 43; 19%). Infection was reported as a primary cause of death in 41 patients (18%) and as a contributory cause of death in 27 (12%).

Types of Infections at ≥2 Years Post-HCT

Types of infection as causes of death in the adult and pediatric patients are listed in Table 2. Bacterial infections were the most common primary or contributing causes of LFI after HCT in both age groups. A substantial proportion of patients in both groups had unspecified infections or infections without a definitive reported pathogen.

The Risk of LFI at ≥2 Years Post-HCT

There was a continuous increase in the risk of LFI over time beyond 2 years post-HCT. As shown in Figure 1, in adults there was a progressive rise in the cumulative incidence of LFI after 2 years, from 1.8% at 3 years (95% confidence interval [CI], 1.5% to 2.0%) to 5.3% (95% CI, 4.9% to 5.8%) at 8 years and 6.4% (95% CI, 5.8% to 7.0%) at 12 years. In contrast, in children, the increase in LFI over time was significantly smaller, .4% (95% CI, .3% to .6%) at 3 years, 1.3% (95% CI, 1.0% to 1.7%) at 8 years, and 1.8% (95% CI, 1.4% to 2.3%) at 12 years ($P < .001$).

Risk Factors for Infectious Death

In adult patients age ≥20 years, male sex and receipt of a matched unrelated donor (MUD) or mismatched unrelated donor (MMUD) HCT were independently associated with an increased risk of LFI in multivariate analysis (Table 3). Older age cohorts were associated with incrementally higher LFI rates (Table 3). Patients with a history of cGVHD with ongoing immunosuppression at 2 years post-HCT had a significantly increased risk of LFI (hazard ratio [HR], 3.87; $P < .0001$) and a higher cumulative incidence of LFI ($P < .0001$) compared with patients without any reported GVHD (Table 3 and Figure 2A). In contrast, there was no statistically significant increased risk of LFI in patients with aGVHD (HR, 1.09; $P = .7310$) or in patients with a history of cGVHD without ongoing immunosuppression by 2 years post-HCT (HR, 1.25; $P = .3610$) (Table 3). Other factors, including primary disease, Karnofsky Performance Score, race and ethnicity, disease diagnosis, previous autologous HCT, preexisting fungal infection, HIV seropositivity, CIBMTR Disease Risk Index, time from diagnosis to HCT, conditioning regimen intensity, use of TBI, graft source, use of ATG or alemtuzumab before HCT, donor/recipient CMV serostatus, geographic region, and year of HCT, were not significantly associated with an increased risk for LFI.

In pediatric subjects age ≥10 years, receipt of MUD or MMUD HCT and inherited abnormalities of erythrocyte function (AEF) were independently associated with an increased risk of LFI (Table 4). In contrast, severe aplastic anemia (SAA) was associated with a decreased risk of LFI in multivariate analysis. Compared with patients without any reported GVHD, a history of cGVHD with ongoing immunosuppression at 2 years post-HCT (HR, 9.49; $P < .0001$) and a history of cGVHD without ongoing immunosuppression by 2 years post-HCT (HR, 2.79; $P = .0395$), but not history of aGVHD (HR, 2.07; $P = .16$), were significantly associated with a significantly increased risk of LFI (Table 4) and a higher cumulative incidence of LFI ($P < .001$) (Figure 2B). Karnofsky/Lansky Performance Score, race and ethnicity, sex, previous autologous HCT, preexisting fungal infections, HIV seropositivity, CIBMTR Disease Risk Index, time from diagnosis to HCT, conditioning regimen intensity, graft source, use of TBI, use of ATG or alemtuzumab before HCT, donor/recipient CMV serostatus, geographic region, and year of HCT were factors that did not increase the risk of LFI.

Table 2
Types of LFI in HCT Recipients Who Were Disease-Free for at Least 24 Months after Transplantation

Parameter	Value	
	Adult	Pediatric
Patients who died from infection, n*	496	68
Infection listed as the primary cause of death, n (%)	311	41
Bacterial	108 (35)	13 (32)
Viral	29 (9)	0
Fungal	35 (11)	7 (17)
Protozoal	1 (<1)	0
Unspecified	116 (37)	20 (49)
Multiple types reported	22 (7)	1 (2)
Infection listed as contributing cause of death, n (%)	185	27
Bacterial	85 (46)	10 (37)
Viral	29 (16)	5 (18)
Fungal	20 (11)	4 (15)
Protozoal	0	0
Unspecified	49 (26)	8 (30)
Multiple types reported	2 (1)	0

* Patients with relapse or second HCT occurring ≥2 years after HCT were censored at the event and excluded from this analysis.

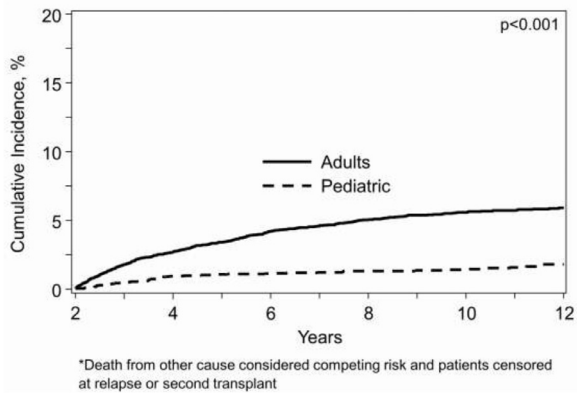

Figure 1. Cumulative incidence of death from infection after 2 years of survival in adult and pediatric patients. *Death from another cause was considered a competing risk, and patients were censored at relapse or second transplantation.

Identified Pathogens Causing Death

In 195 adult patients, an identified pathogen was listed as a primary cause of death, including bacterial infections in 108 (55%), viral infections in 29 (16%), fungal infections in 35 (18%), and multiple infections in 22 (11%). These infections included vaccine-preventable infections in 13 patients (7%; *Streptococcus pneumoniae*, influenza, hepatitis B) and drug-preventable infection in 1 patient (.5%; *Pneumocystis jirovecii* pneumonia). In the pediatric cohort, pathogens as a primary cause of death were identified in 21 patients, including bacterial infections in 13 (62%), fungal infections in 7 (33%), and multiple infections in 1 (5%). These included vaccine-preventable infections in 2 patients (10%; *S. pneumoniae*) and drug-preventable infections in 3 patients (15%; *Candida* species, *P. jirovecii* pneumonia).

Table 3
Multivariate Analysis of Factors Associated with LFIs in the Adult Population (N = 10,336)

Variable	Number	HR (95% CI)	*P* Value
Age, yr			
18-19	498	1.00	<.0001*
20-39	3849	3.12 (1.33-7.32)	.0089
40-54	3730	3.86 (1.66-8.95)	.0017
55+	2259	5.49 (2.32-12.99)	.0001
Sex			
Male	5888	1.00	.0168
Female	4448	.79 (.65-.96)	
Donor			
Matched sibling	4509	1.00	<.0001*
Other relative	290	1.04 (.56-1.92)	.9067
Matched unrelated	3774	1.65 (1.34-2.05)	<.0001
Mismatched unrelated	984	1.88 (1.35-2.62)	.0002
Unrelated, match unknown	269	1.60 (.99-2.59)	.0563
Cord blood	510	.80 (.37-1.74)	.5778
History of GVHD within 2 yr of HCT			
None	3052	1.00	<.0001*
aGVHD only	932	1.09 (.67-1.76)	.7310
cGVHD, immunosuppression at 2 yr	3325	3.87 (2.59-5.78)	<.0001
cGVHD, off immunosuppression by 2 yr	1415	1.25 (.77-2.02)	.3610
cGVHD, unknown immunosuppression at 2 yr	1506	4.14 (2.82-6.09)	<.0001
Missing	106	4.90 (2.61-9.17)	<.0001

* Overall *P* value.

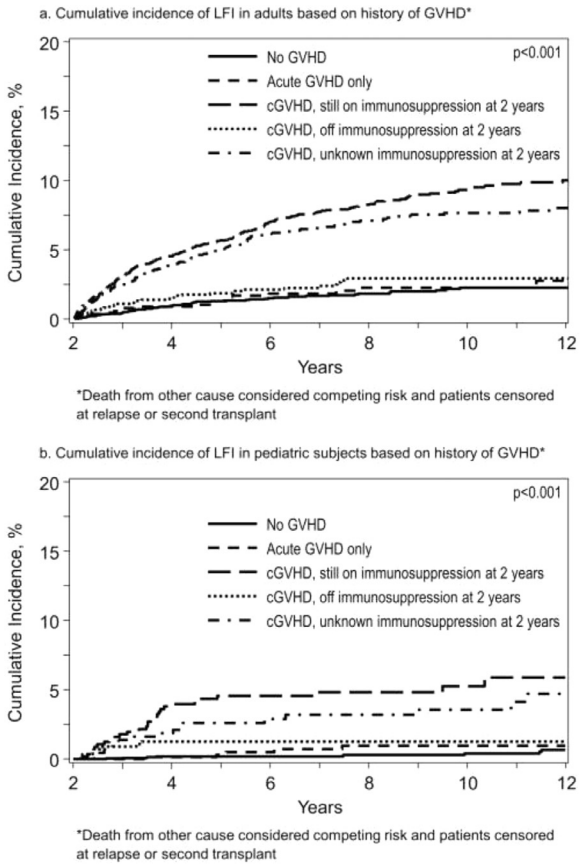

Figure 2. (A) Cumulative incidence of LFI in adults based on history of GVHD. (B) Cumulative incidence of LFI in pediatric patients based on history of GVHD.
*Death from another cause was considered a competing risk, and patients were censored at relapse or second transplantation.

Table 4
Multivariate Analysis of Factors Associated with LFIs in the Pediatric Population (N = 5053)

Variable	Number	HR (95% CI)	*P* Value
Age, yr			
0-9	2885	1.00	.0122
10-17	2138	1. 92 (1.15-3.2)	
Donor			
Matched sibling	1980	1.00	.0216*
Other relative	246	1.24 (.41-3.73)	.6986
Matched unrelated	1025	1.98 (1.02-3.86)	.0440
Mismatched unrelated	418	3.51 (1.73-7.08)	.0005
Unrelated, match unknown	231	1.60 (.57-4.46)	.3711
Cord blood	1123	1.38 (.70-2.75)	.3554
History of GVHD within 2 years of HCT			
None	2755	1.00	<.0001*
aGVHD only	696	2.07 (.75-5.72)	.1600
cGVHD, immunosuppression. at 2 yr	562	9.49 (4.39-20.51)	<.0001
cGVHD, off immunosuppression by 2 yr	566	2.79 (1.05-7.43)	.0395
cGVHD, unknown immunosuppression at 2 yr	444	9.68 (4.38-20.51)	<.0001
Disease			
AML	1146	1.00	.0027*
Acute lymphoblastic leukemia	1588	.85 (.47-1.52)	.5719
Other leukemia	96	1.56 (.38-6.46)	.5428
Myelodysplastic syndrome	179	.62 (.14-2.71)	.5222
Other myeloproliferative neoplasms	247	.88 (.30-2.55)	.8064
Lymphoma	104	1.11 (.24-5.02)	.8965
SAA	817	.22 (.05-.94)	.0409
AEF	846	2.30 (1.19-4.42)	.0129

* Overall *P* value.

DISCUSSION

In this study, we performed an analysis of LFI in the largest group of HCT survivors with long-term follow-up reported to date. Because disease relapse and relapse-directed interventions significantly increase the risk of severe infections, we censored patients with relapse or second HCT occurring after 2 years after initial HCT to analyze the impact of other less well-known factors on LFI in long-term survivors. This is the first analysis to analyze LFI separately in adult and pediatric patients and to estimate the impact of both GVHD and immunosuppression on LFI.

Although the cumulative incidence of LFI was low in HCT recipients, it contributed to one-third of all deaths occurring at least 2 years after HCT in both pediatric and adult patients. Older age, HCT from unrelated donors, male sex, and history of cGVHD with ongoing immunosuppression at 2 years post-HCT were associated with an increased risk of LFI in adult patients. This is the first comprehensive analysis of LFI in a large cohort of pediatric patients. Despite differences in primary diseases, intensity of conditioning regimens, graft sources, and lower incidence and severity of cGVHD and late mortality rate compared with adult patients, LFI contributed to one-third of all deaths at ≥2 years post-HCT in pediatric patients, similar to adult patients. Age ≥10 years, history of cGVHD either with or without ongoing immunosuppression at 2 years post-HCT, and AEF were associated with an increased risk of LFI in pediatric patients. A significantly reduced risk of LFI in pediatric patients with SAA requires further studies; it may be speculated that patients with SAA predominantly receive BM transplants from sibling donors, which is associated with a lower risk of cGVHD compared with other donor sources [3]. In our study, pediatric patients with SAA had a significantly lower incidence of cGVHD at 2 years post-HCT compared with patients with acute myelogenous leukemia (AML) (22% versus 34%; $P < .0001$).

Several previous studies have demonstrated that long-lasting impairment of the immune system can lead to increased risk of late infections after HCT [4-6]. Older age at HCT is associated with impaired recovery of $CD4^+$ T cells following HCT, leading to an increased risk of opportunistic infections [7] and a decreased response to vaccination [8]. One of the first published analyses of late infection after HCT included 89 patients with aplastic anemia and acute leukemia who survived for ≥6 months after allogeneic or syngeneic HCT [9]. In that study, conducted decades ago, bacterial infections of the respiratory tract and skin and bacteremia represented more than one-half of all reported infections, and 9% of affected patients died from infectious complications. cGVHD was the sole variable significantly associated with increased risk for late infections [9]. The incidence of and risk factors for late infections were retrospectively evaluated in a larger study that included 196 recipients with aplastic anemia, chronic myelogenous leukemia, and AML who underwent HCT from matched related donors, with a median follow-up of 8 years [10]. Late severe bacterial infections were the most frequent infections, with an 8-year cumulative incidence of 15%, and the development of extensive cGVHD was identified as a risk factor for the development of these infections [10]. A large single-center retrospective study focused on long-term survival of 389 HCT recipients surviving disease-free at 1 year after HCT identified late infections, cGVHD, and relapsed disease as the top 3 causes of mortality beyond the first year post-HCT [11]. Patients with cGVHD requiring immunosuppression at 1 year after HCT had significantly higher mortality compared with those not on immunosuppression; however, the role of infections in patients who

died from cGVHD is not reported in this study [11]. Even in long-term survivors surviving for ≥5 years after HCT, life expectancy continues to be lower than expected due to increased nonrelapse mortality, including infections, which were the third most common cause of mortality and constituted 12% of all deaths [12].

In a large single-center study including 429 HCT recipients who received myeloablative conditioning and who were alive and free of their original disease for ≥2 years post-HCT, 16% patients developed recurrent respiratory tract infections, 1% had recurrent urinary tract infections, and only 1 patient developed pulmonary aspergillosis [13]. The largest study reported to date focusing on late complications of HCT included 10,632 patients who were alive and disease-free at 2 years after receiving myeloablative conditioning HCT for AML, acute lymphoblastic leukemia, myelodysplastic syndrome, and lymphoma [1]. In that study, the rate of late death remained higher than expected for each disease compared with an age-, sex-, and nationality-matched general population. Deaths due to infection, which included only those infections occurring without active GVHD or ongoing GVHD therapy, varied from 4% to 17% of all deaths depending on disease diagnosis at the time of HCT and the duration of post-HCT follow-up. In our study, the risk of LFI was not higher in cord blood graft recipients compared with sibling donor graft recipients, but it was higher in unrelated donor transplant recipients. We hypothesize that the increased risk of LFI in unrelated donor transplants, but not in cord blood transplants in both pediatric and adult recipients, is associated with increased incidence and or severity of cGVHD in these patients.

In the present study, an increased risk of LFI in long-term survivors after HCT was associated with older age and history of cGVHD, which adversely impact immune reconstitution for many years after HCT. Despite the introduction of novel antimicrobial therapies to the clinic and the development of supportive care guidelines, the year of HCT had no significant impact on the risk of LFI in our study. Therefore, a stronger emphasis on post-HCT vaccinations, avoidance of infectious exposures, and increased awareness of primary providers of the possibility of LFI and infection control should be advocated in long-term survivors after HCT. HCT survivors themselves should be educated about increased risk of LFI and instructed to promptly alert healthcare provides if they develop symptoms suggestive of LFI. We showed that pediatric patients with inherited AEF had an increased risk of LFI. In our study, 21% of these patients had sickle cell disease (SCD). Previously, Gluckman et al. reported similar observation of increased fatal infections in patients with SCD post-HCT [14]. Although data on previous splenectomy or functional hyposplenism were not available for these patients, an increased risk of LFI suggests an increased importance of prolonged antimicrobial prophylaxis and vaccination in this group of patients. Vaccine- and drug-preventable LFI were low in our study, which may suggest that majority of transplantation centers included in our study were following protocols for post-HCT vaccinations and antimicrobial prophylaxis.

Our study has several limitations. Despite our strong emphasis on the completeness of data reporting, some important information was not available for analysis. Although the study was adjusted for center effect, several data elements related to center practices, such as vaccination schedules, use of antimicrobials for prophylaxis, and therapy for LFI were not collected and were not evaluated in this study. Although most reports noted the category of infection (bacterial, viral, fungal), the majority of specific causative pathogens were not captured in the reporting forms. Rates of preventable infections are underestimated in the present analysis owing to the large number of unspecified infections for both adult and pediatric subjects. Detailed information is lacking on the activity of cGVHD and therapy with systemic immunosuppression at the time of development of LFI.

In conclusion, this study demonstrates that in both adult and pediatric HCT recipients surviving for 2 years post-HCT LFI contributed to one-third of all deaths. This emphasizes the importance of continued long-term monitoring for infections, and the education of primary health care teams to decrease risk of LFI in long-term HCT recipients. Future studies should examine data on immune reconstitution, immunoglobulin levels, vaccinations, and postvaccination titers.

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REFERENCES

1. Wingard JR, Majhail NS, Brazauskas R, et al. Long-term survival and late deaths after allogeneic hematopoietic cell transplantation. *J Clin Oncol*. 2011;29:2230–2239.
2. Clark TG, Altman DG, De Stavola BL. Quantification of the completeness of follow-up. *Lancet*. 2002;359:1309–1310.
3. Yagasaki H, Takahashi Y, Hama A, et al. Comparison of matched-sibling donor BMT and unrelated donor BMT in children and adolescent with acquired severe aplastic anemia. *Bone Marrow Transplant*. 2010;45:1508–1513.
4. Antin JH. Immune reconstitution: the major barrier to successful stem cell transplantation. *Biol Blood Marrow Transplant*. 2005;11(2 suppl 2):43–45.
5. Storek J, Dawson MA, Storer B, et al. Immune reconstitution after allogeneic marrow transplantation compared with blood stem cell transplantation. *Blood*. 2001;97:3380–3389.

6. Storek J, Joseph A, Espino G, et al. Immunity of patients surviving 20 to 30 years after allogeneic or syngeneic bone marrow transplantation. *Blood*. 2001;98:3505–3512.
7. Small TN, Papadopoulos EB, Boulad F, et al. Comparison of immune reconstitution after unrelated and related T-cell-depleted bone marrow transplantation: effect of patient age and donor leukocyte infusions. *Blood*. 1999;93:467–480.
8. Roux E, Dumont-Girard F, Starobinski M, et al. Recovery of immune reactivity after T cell-depleted bone marrow transplantation depends on thymic activity. *Blood*. 2000;96:2299–2303.
9. Atkinson K, Storb R, Prentice RL, et al. Analysis of late infections in 89 long-term survivors of bone marrow transplantation. *Blood*. 1979;53:720–731.
10. Robin M, Porcher R, De Castro Araujo R, et al. Risk factors for late infections after allogeneic hematopoietic stem cell transplantation from a matched related donor. *Biol Blood Marrow Transplant*. 2007;13:1304–1312.
11. Solh MM, Bashey A, Solomon SR, et al. Long term survival among patients who are disease free at 1-year post allogeneic hematopoietic cell transplantation: a single center analysis of 389 consecutive patients. *Bone Marrow Transplant*. 2018;53:576–583.
12. Martin PJ, Counts Jr GW, Appelbaum FR, et al. Life expectancy in patients surviving more than 5 years after hematopoietic cell transplantation. *J Clin Oncol*. 2010;28:1011–1016.
13. Abou-Mourad YR, Lau BC, Barnett MJ, et al. Long-term outcome after allo-SCT: close follow-up on a large cohort treated with myeloablative regimens. *Bone Marrow Transplant*. 2010;45:295–302.
14. Gluckman E, Cappelli B, Bernaudin F, et al. Sickle cell disease: an international survey of results of HLA-identical sibling hematopoietic stem cell transplantation. *Blood*. 2017;129:1548–1556.