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Infectious Complications After Umbilical Cord Blood Transplantation for Hematological Malignancy

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Background. Umbilical cord blood transplant (UCBT) is used for patients who do not have a matched donor, but engraftment often takes longer than with a standard allogeneic transplant, likely increasing the risk for infection. We characterized specific infections and outcomes in adults undergoing UCBT at our 2 centers.

Methods. All adults who underwent UCBT between January 1, 2006 and December 31, 2015 were included. Infectious episodes from 6 months before to 2 years after UCBT were reviewed.

Results. Fifty-seven patients underwent UCBT; 47 had neutrophil engraftment. A total of 179 infectious episodes occurred in 55 patients, 73 (41%) within 30 days post-UCBT. Viruses caused 85 (47%) infections. Cytomegalovirus caused 32 infectious episodes and was most common from day 30 to 100. Human herpesvirus 6 occurred in 28 episodes, was most common within 30 days, and caused 1 death. Bacteria were responsible for 82 (46%) infections, most commonly bacteremias due to *Staphylococcus* spp, *Enterococcus* spp, and *Enterobacteriaceae*. Of 11 invasive fungal infections, 9 were aspergillosis, 4 of which were fatal. Overall mortality was 56% in the first year. Thirteen deaths were from infection; 11 occurred in the first 100 days and 7 in the first 30 days post-UCBT. Of 10 patients who never engrafted, 9 died, 6 from infection, within 100 days post-UCBT.

Conclusions. Infectious complications were common after UCBT, especially in the first 30 days. Deaths from viral infections were fewer than expected. Delayed engraftment and nonengraftment continue to convey increased risk for fatal bacterial and fungal infections post-UCBT.

Keywords. CMV; HHV-6; infections; umbilical cord blood transplant.

Umbilical cord blood (UCB) cells are a suitable source of stem cells for patients who require hematopoietic cell transplantation (HCT) and who do not have a matched donor [1]. The use of UCB cells has been mostly studied in children with hematological malignancies, but it has extended to the adult population because of the paucity of related or matched donors [1, 2]. Advantages to using UCB cells for HCT include the ability to use human leukocyte antigen (HLA)-mismatched cells without significant adverse effects on graft function and the decreased incidence of graft-versus-host disease (GVHD) after transplantation [1, 3]. However, both the decreased quantity of cells available for transplantation and the immunological immaturity of UCB cells have been linked to delayed engraftment after UCB transplant (UCBT) [3, 4].

Prolonged neutropenia is a well recognized risk factor for severe infections [5]. Patients receiving UCBT appear to be at increased risk compared with allogeneic HCT recipients, perhaps due to delayed engraftment [6–8]. Infection is estimated to cause 35%–50% of nonrelapse mortality in patients after UCBT, compared with 8%–22% after allogeneic HCT [2, 5, 6, 9–12]. Viral infections, especially cytomegalovirus (CMV), and human herpesvirus 6 (HHV-6), have been associated with increased morbidity and mortality post-UCBT [6, 13]. We sought to characterize the infectious complications and outcomes of patients who received a UCBT in our institutions over a 10-year period.

METHODS

This retrospective study was conducted at the University of Michigan Health System (Ann Arbor, MI) and Karmanos Cancer Center (Detroit, MI). Approval was granted by the institutional review board at each center.

All adult patients ≥18 years of age who underwent UCBT at the 2 study centers between January 1, 2006 and December 31, 2015 were included in this study. Medical records were reviewed to identify infectious complications from 6 months before UCBT and for 2 years after transplantation; demographic information, underlying hematologic diseases, conditioning

regimens, prophylaxis, time to engraftment, episodes of infection, their treatment, and outcomes were collected. Patients who experienced relapse of underlying malignancy after UCBT were excluded from further analysis from the date relapse was documented. Study data were collected and managed using REDCap electronic data capture tools.

Infectious episodes were defined as episodes of fever or hemodynamic instability for which antimicrobial therapy was initiated and which were separated by at least 48 hours from previous episodes. Day of episode was counted as the first day of antimicrobial administration. The timing of neutrophil engraftment after UCBT was defined as the first of 3 consecutive days

Table 1. Demographics, Underlying Conditions, and Pretransplant Conditioning Regimens of 57 Patients Who Received an Umbilical Cord Blood Transplant

Demographic Information	n (%)
Female	34 (59.6)
Age (years), mean ± standard deviation	43.1 ± 13.6
BMI (kg/m^2), mean ± standard deviation	26.3 ± 5.7
Hematological Malignancy	
Acute leukemia or myelodysplastic syndrome	39 (68.4)
Lymphoma[a]	12 (21.1)
Multiple myeloma	4 (7.0)
Chronic myeloid leukemia	1 (1.8)
Myelofibrosis	1 (1.8)
Prior Hematopoietic Cell Transplant	
Autologous stem cell transplant	10 (17.5)
Umbilical cord blood transplant	1 (1.8)
Infections Within Prior 6 Months[b]	23 (40.4)
Bacteremia[c]	12 (21.1)
Clostridium difficile infection	9 (15.8)
Pneumonia	5 (8.8)
Intraabdominal infection	5 (8.8)
Urinary tract infection	5 (8.8)
Respiratory viral infection	1 (1.8)
Invasive aspergillosis	5 (8.8)
Hepatosplenic candidiasis	1 (1.8)
Conditioning Type	
Myeloablative	31 (54.4)
Reduced-intensity	26 (45.6)
Conditioning Regimen	
Total body irradiation	54 (94.7)
Busulfan/fludarabine	28 (49.1)
Cytarabine/fludarabine	17 (29.8)
Cytarabine	8 (14.0)
Other[d]	4 (7.0)
Antithymocyte globulin	3 (5.3)
Rituximab	3 (5.3)

Abbreviations: BMI, body mass index.

[a]Follicular lymphoma (3), diffuse large B-cell lymphoma (3), marginal zone lymphoma (2), anaplastic large cell lymphoma (1), angioimmunoblastic T-cell lymphoma (1), Hodgkin lymphoma (2).

[b]Many patients had more than 1 infection.

[c]*Enterococcus* spp (3), *Klebsiella pneumoniae* (2), *Escherichia coli* (1), *Staphylococcus aureus* (3), *Enterobacter cloacae* (1), *Micrococcus luteus* (1), *Streptococcus* spp (2), *Staphylococcus epidermidis* (2).

[d]Fludarabine/melphalan (1), etoposide (2), carmustine/etoposide/cytarabine/melphalan (1).

when the absolute neutrophil count was >500/µL. Graft-versus-host disease, veno-occlusive disease, and other complications related to the transplant, including infection, were defined in accordance with NCCN Guidelines [14]. Conditioning regimens were classified as either myeloablative or reduced-intensity using criteria proposed by Bacigalupo et al [15]. National Institute of Allergy and Infectious Diseases Mycoses Study Group criteria were used for the definition of invasive fungal infections [16]. Cytomegalovirus infection and end-organ disease were defined by current consensus definitions [17]. Routine screening for CMV viremia was not performed; molecular testing for CMV, HHV-6, and Epstein-Barr virus was performed with febrile episodes.

Patients received antibacterial prophylaxis, typically with a fluoroquinolone, starting on the day of transplant and continuing until engraftment; antibacterial prophylaxis was restarted with subsequent neutropenia or GVHD. Antifungal prophylaxis was initiated by day 5 posttransplant and was continued through engraftment. Viral prophylaxis with acyclovir was started on the day of transplant and continued for at least 1 year; routine prophylaxis for CMV was not given. *Pneumocystis* prophylaxis with either pentamidine or trimethoprim/sulfamethoxazole was started at day 30, provided neutrophil engraftment had occurred.

We conducted descriptive data analyses for all variables. Student's *t* test, Fisher's exact test, and one-way analysis of variance were used to determine differences between groups. All statistical analyses were completed using SPSS software, version 24.0 (SPSS, Inc., Chicago, IL).

RESULTS

Pretransplant Patient Characteristics

There were 57 adult patients who underwent UCBT from January 2006 through December 2015. The mean age was 43 ± 13.6 years; 34 (60%) were women. Thirty-nine (68%) patients received a UCBT for myelodysplastic syndrome or acute myeloid leukemia, 12 for a lymphoid malignancy and 6 for another hematological malignancy (Table 1).

Ten patients had a prior autologous HCT, and 1 patient had a prior UCBT at a different institution. Twenty-three (40%) patients had an infection in the preceding 6 months before UCBT (Table 1). Bacteremia and *Clostridium difficile* infection were the most common documented infections before UCBT. Twenty-seven (47%) patients had at least 1 episode of febrile neutropenia in the 6 months before transplant. Thirty-eight (67%) patients were CMV antibody positive before transplant.

Conditioning was myeloablative in 31 (54%) patients and reduced-intensity in 26 (46%) (Table 1). A double-unit UCBT was received by 35 (61%) patients, and a single-unit UCBT was received by 21 (37%) patients. For 1 patient, the number of units received was not recorded. The median UCB cell volume

infused was 4.2×10^7 cells (range, 1.4×10^7–35.7×10^7 cells), with a median of 5.5×10^5 nucleated cells per kilogram body weight. Forty-eight (84%) patients had >1 HLA mismatch.

Posttransplant Patient Characteristics

Fifty-six patients were on antibacterial prophylaxis at the time of and after UCBT; for 45, this consisted of a fluoroquinolone (Table 2). Ten patients received a β-lactam and 1 received clindamycin. Three of the 10 patients on a β-lactam were given secondary prophylaxis for infection that occurred before transplantation. All patients received antiviral prophylaxis with acyclovir, 400 mg twice daily. Antifungal prophylaxis consisted of an azole or an echinocandin (Table 2). Forty-seven patients (82%) received *Pneumocystis* prophylaxis after engraftment; the remaining 10 patients did not have neutrophil engraftment. All patients received GVHD prophylaxis, with tacrolimus/mycophenolate mofetil (n = 52), cyclosporine/mycophenolate mofetil (n = 3), tacrolimus alone (n = 1), or sirolimus/mycophenolate mofetil (n = 1).

All patients developed profound neutropenia and thrombocytopenia post-UCBT. Forty-seven (82%) patients had neutrophil engraftment at a mean of 20.8 ± 7.0 days. Of the 10 patients who never achieved engraftment, 9 died within 100 days of UCBT, and 1 was lost to follow up at day 60. Platelet engraftment occurred in 40 patients with a mean time of 47.9 ± 34.2 days. Time to engraftment did not differ between patients who received a single versus a double UCBT.

Graft-versus-host disease occurred in 35 (61%) patients. Twenty-seven had acute GVHD (14 with skin involvement and 18 with gastrointestinal involvement) and 3 had chronic GVHD (1 with skin involvement and 2 with gastrointestinal

involvement); 5 additional patients had acute followed by chronic GVHD. Mean time to development of acute GVHD was 40 ± 27 days and for chronic GVHD was 218 ± 79 days.

Infectious Episodes

A total of 179 episodes of infection were reported in 55 patients; the median number of episodes per patient was 3 (range, 0–11). The greatest number of infections occurred within 30 days post-UCBT (73 episodes in 50 patients). Among these early infections, 57 (78%) occurred before neutrophil engraftment. Although fewer in number, infections continued to occur throughout the 2-year follow-up period post-UCBT; there were 51 episodes between days 30 and 100 and 55 episodes after day 100. Viral infections were most common, followed by bacterial and fungal infections. There were no episodes of infection with protozoal or helminthic pathogens. Several different infections were present concurrently in 64 (36%) of infectious episodes, irrespective of the time posttransplant. The mean number of infectious episodes per patient ranged between 2 and 3.8 per year over the 10-year period of the study.

Viral Infections.

Eighty-five episodes of viral infection were identified in 39 patients (Table 3). Cytomegalovirus and HHV-6 were the most common viral infections, but their onset varied post-UCBT.

Cytomegalovirus infection was uncommon early after transplant, but it was the most common pathogen found from days 31 to 100 post-UCBT. Of the total of 32 episodes of CMV noted in 22 patients over all time periods, 24 were characterized by viremia alone, and 8 involved end-organ disease, which included colitis in 3, pneumonia in 4, and both in 1. Antiviral treatment with either foscarnet or ganciclovir was administered in 31 of the 32 episodes (97%). In 21 episodes, CMV infection occurred concurrently with other infections; most commonly, the coinfection was with vancomycin-resistant *Enterococcus* (VRE), which occurred in 5 episodes. All 22 patients who developed CMV infection had antibodies to CMV before UCBT. The remaining 16 seropositive patients, including 2 who had received antithymocyte globulin (ATG), did not develop CMV infection.

Human herpesvirus 6 was the most common infection noted within the first 30 days post-UCBT. Twenty-eight episodes of HHV-6 infection were identified in 21 patients; 18 occurred within the first 30 days post-UCBT, and 11 occurred before neutrophil engraftment. The manifestations of infection were viremia alone in 24 episodes, meningitis 2, and pneumonia and posttransplant acute limbic encephalitis, each in 1 episode. Treatment was initiated in 25 episodes; treatment consisted of foscarnet in 21 episodes and ganciclovir in 4 episodes. Human herpesvirus 6 infection occurred concomitantly with another infection in 18 episodes; the most common coinfections were CMV viremia and BK viruria in 4 patients each. Among the 10 patients who did not engraft neutrophils, only 1 developed HHV-6 infection. Time

Table 2. Antimicrobial Prophylaxis Regimens in 57 Patients Who Received an Umbilical Cord Blood Transplant

Prophylaxis	n (%)
Bacterial	
Fluoroquinolone	45 (78.9)
β-lactam[a]	10 (17.5)
Clindamycin	1 (1.8)
Viral	
Acyclovir	57 (100)
Fungal (Yeasts and Molds)	
Voriconazole	22 (38.6)
Fluconazole	16 (28.1)
Posaconazole	9 (15.8)
Micafungin	9 (15.8)
Itraconazole	1 (1.8)
Fungal (Pneumocystis)	
Pentamidine (inhaled or intravenous)	32 (56.1)
Trimethoprim/sulfamethoxazole	8 (14.0)
Atovaquone	4 (7.0)
Dapsone	3 (5.3)

[a]Penicillin VK (1), cefpodoxime (2), cefepime (6), aztreonam (1).

Table 3. Eighty-Five Viral Infectious Episodes, Grouped by Date of Onset, in 39 Patients Who Had Received an Umbilical Cord Blood Transplant

Virus/Infection	Episodes Occurring 1–30 Days After UCBT[a] (n = 26)	Episodes Occurring 30–100 Days After UCBT[a] (n = 36)	Episodes Occurring >100 Days After UCBT[a] (n = 23)	Total Episodes
Cytomegalovirus	3	21	8	32
Viremia	3	21	6	30
Colitis	1	2	1	4
Pneumonia	0	2	3	5
Human herpesvirus 6	18	9	1	28
Viremia	18	9	1	28
Meningitis	1	1	0	2
Pneumonia	0	1	0	1
Encephalitis	0	0	1	1
Herpes simplex virus[b]	3	4	1	8
Respiratory virus[c]	2	5	12	19
BK virus	8	9	1	18

Abbreviations: HSV, herpes simplex virus; UCBT, umbilical cord blood transplant.

[a]Patients often had more than 1 infection per episode.

[b]Includes both HSV-1 and HSV-2.

[c]Includes adenovirus, coronavirus, human metapneumovirus, influenza A, influenza B, parainfluenza, and respiratory syncytial virus.

to engraftment did not differ significantly between patients with HHV-6 viremia and those without HHV-6 viremia.

Other viral infections were seen less commonly than CMV and HHV-6. BK virus infection was noted in 18 episodes and was characterized by viruria in all 18 and hemorrhagic cystitis in 10. All 57 patients were on acyclovir prophylaxis for HSV, but 8 infectious episodes involved HSV reactivation, 2 of which were severe; 1 patient had meningoencephalitis, and the other had widespread dissemination with a virus that became increasingly resistant to acyclovir and foscarnet. Most other viral infections involved the respiratory tract, most occurred >100 days post-UCBT, and only 1, a coronavirus infection, was severe.

Bacterial Infections.

A total of 82 episodes of bacterial infection were reported in 41 patients (Table 4). The most common bacterial infection

Table 4. Eighty-Two Bacterial Infectious Episodes, Grouped by Date of Onset, That Occurred in 41 Patients Who Received an Umbilical Cord Blood Transplant

Organism/Infection	Episodes Occurring 1–30 Days After UCBT[a] (n = 30)	Episodes Occurring 30–100 Days After UCBT[a] (n = 18)	Episodes Occurring >100 Days After UCBT[a] (n = 34)	Total Episodes
Coagulase-negative *Staphylococcus* BSI	8	6	7	21
van-R *Enterococcus*	9	5	5	19
Bacteremia	4	3	3	10
UTI	5	2	1	8
Intraabdominal	0	0	1	1
Enterobacteriaceae[b]	2	3	9	14
Bacteremia	1	2	2	5
UTI	1	1	7	9
Pseudomonas species	1	0	4	5
Bacteremia	0	0	2	2
Pneumonia	1	0	1	2
UTI	0	0	1	1
Other BSI[c]	3	4	1	8
Clostridium difficile infection	10	4	7	21
Tuberculosis	0	1	0	1
NTM pneumonia	0	1	2	3

Abbreviations: BSI, bloodstream infection; NTM, nontuberculous mycobacterium (includes *Mycobacterium chelonae*, *Mycobacterium abscessus*, and *Mycobacterium avium*); UTI, urinary tract infection; van-R, vancomycin resistant.

[a]Patients often had more than 1 infection per episode.

[b]Includes *Escherichia coli*, *Klebsiella* spp, *Citrobacter* spp, *Enterobacter* spp, and *Proteus* spp.

[c]Includes *Acinetobacter baumanii* (n = 3), *Clostridium perfringens* (n = 1), *Micrococcus* spp (n = 1), and *Streptococcus* spp (n = 3).

after UCBT was bloodstream infection (BSI), occurring in 41 episodes in 29 patients. Central line-associated BSIs (CLABSI) accounted for 22 (54%) BSIs. The predominant organism was coagulase-negative *Staphylococcus*, accounting for 21 episodes, 17 of which were CLABSI. Vancomycin-resistant *Enterococcus* was the pathogen in 10 BSI episodes, 4 of which were CLABSI, and Gram-negative bacilli accounted for another 7 BSI episodes, including 5 CLABSI. Polymicrobial bacteremia was noted on 8 occasions.

Clostridium difficile infection accounted for 21 (26%) episodes in 16 patients. There was a trend for VRE infections and *C difficile* infections to occur more often in the first 30 days posttransplant, but time to occurrence was not significantly different for any bacterial pathogen. Other bacterial infections are noted in Table 4.

Three patients had mycobacterial infection. One patient, an immigrant from Malaysia, developed fulminant pulmonary tuberculosis 83 days after UCBT and died several weeks later. Two patients had pneumonia due to nontuberculous mycobacteria; 1 patient, whose course was complicated by bronchiolitis obliterans syndrome, developed pulmonary infection with *Mycobacterium avium* 1.5 years after UCBT and then pulmonary infection with *Mycobacterium abscessus* 6 months later. Another patient developed pneumonia 32 days after UCBT, and bronchoalveolar lavage cultures yielded *Mycobacterium chelonae* after her death.

Fungal Infections.

Eleven episodes of invasive fungal infections were recorded in 10 patients after UCBT. Invasive aspergillosis was noted in 9 patients. One other patient had 2 episodes of *Candida glabrata* fungemia. The median time from UCBT to the diagnosis of aspergillosis was 16 days (range, 4–102 days), and the 2 episodes of candidemia occurred on day 38 and day 140 after UCBT. Aspergillosis was defined as proven in 3, probable in 2, and possible in 4; 8 patients had pulmonary infection, 1 with spread to the central nervous system, and 1 had isolated central nervous system infection. Of the 9 patients who developed invasive aspergillosis, 4 had received fluconazole for antifungal prophylaxis, 2 had received micafungin, 2 initially had received voriconazole but had been switched to micafungin before development of infection, and only 1 had received voriconazole throughout the post-UCBT period.

Recurrent Infections.

Of the 23 patients who had infections before UCBT, only 4 had documented recurrence of that same infection in the first 30 days post-UCBT. One patient had recurrence of *C difficile* infection, and another had recurrent VRE urinary tract infection. Two patients had recurrent BSI, with VRE and *Escherichia coli* in one and *Streptococcus* spp in the other. One additional patient was treated for possible invasive aspergillosis in the setting of pneumonia 3 months before UCBT, and a computed tomography scan demonstrated full resolution of airspace opacities before transplant; she later developed probable invasive aspergillosis on day 18 after UCBT while on micafungin prophylaxis.

Outcomes

Overall mortality in the first year post-UCBT was 56% (32 patients); 3 additional patients died in year 2. Thirteen of the 35 (37%) deaths were attributed to infection (Table 5). Malignancy relapse occurred in 18 patients, and death from relapse occurred in 14, including the 3 patients who died in year 2. Other causes of death were complications of severe/

Table 5. Death Attributed to Infection After Umbilical Cord Blood Transplant

Patient Age, Sex	Underlying Malignancy	Conditioning	Days to Neutrophil Engraftment After UCBT	Days to Diagnosis of Infection After UCBT	Infection	Days to Death After UCBT
56, F	MDS	RIC	No	48	Invasive pulmonary aspergillosis	49
51, F	AML	RIC	No	26	Invasive pulmonary aspergillosis, *Stenotrophomonas* bacteremia	52
61, F	B-cell lymphoma	MA	No	16	VRE bacteremia	26
34, F	AML	MA	No	12	Disseminated aspergillosis	18
59, F	MDS	RIC	No	12	CNS aspergillosis	20
33, F	ALL	MA	No	20	Septic shock	22
44, F	Follicular lymphoma	RIC	25	32	*Mycobacterium chelonae* pneumonia	45
55, M	CML	MA	22	99	HSV-2 meningoencephalitis	105
52, M	MM	MA	21	28	Disseminated HSV-1	97
54, M	ALL	MA	21	201	*Enterobacter cloacae* and coronavirus pneumonia	205
48, F	AML	RIC	18	21	*Escherichia coli* and VRE bacteremia	38
54, M	B-cell lymphoma	RIC	16	83	Pulmonary tuberculosis	106
55, F	AML	RIC	7	120	HHV-6 limbic encephalitis	128

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CML, chronic myelogenous leukemia; CMV, cytomegalovirus; CNS, central nervous system; HHV-6, human herpesvirus 6; HSV, herpes simplex virus; MA, myeloablative; MDS, myelodysplastic syndrome; MM, multiple myeloma; RIC, reduced-intensity conditioning; UCBT, umbilical cord blood transplant; VRE, vancomycin-resistant *Enterococcus*.

refractory GVHD in 5, sinusoidal obstruction syndrome in 1, graft failure in 1, and hemophagocytic lymphohistiocytosis in 1. The median time from UCBT to death from infection was 49 days (range, 18–205), and the median time to death from malignancy relapse was 223 days (range, 21–468) (*P* = .002). Among the 10 patients who never achieved neutrophil engraftment, 9 died within 100 days of UCBT, 6 of those from infection between days 18 and 52 post-UCBT. Seven of the 13 infections that led to death occurred in the first 30 days post-UCBT, and 4 patients who died developed infection between days 30 and 100 post-UCBT. Patients who died <100 days after UCBT (n = 17) had more early infections due to invasive fungi (*P* = .04), VRE (*P* = .03), and *Enterobacteriaceae* (*P* = .03) compared with those who survived more than 100 days after transplant (n = 40). Even though CMV and HHV-6 were the most common infections post-UCBT, only 1 death, in the patient with HHV-6 limbic encephalitis, was attributed to these viruses.

DISCUSSION

In the current study, we describe the burden of infectious complications in adult patients after UCBT. Prior studies have demonstrated the high infection risk in children after this procedure, but there are contradictory studies regarding the risk of infection in adult patients after UCBT [5, 6, 18].

Viral infections have been associated with excess morbidity and mortality after UCBT [6, 13, 19]. Cytomegalovirus reactivation has been of particular concern. Positive CMV serostatus of the recipient and use of ATG or monoclonal T-cell antibodies during conditioning are known risk factors for CMV reactivation and increased mortality after UCBT [6, 20–22]. Previous studies of infection after UCBT found rates of CMV reactivation from 21% to 64% and noted that these rates were higher than those noted after allogeneic HCT [13, 18, 22–24]. The use of ATG at conditioning in UCBT recipients has previously been associated with increased risk of CMV reactivation [13]. In our study, CMV reactivation was not associated with ATG use, but only 3 patients had received this agent. Cytomegalovirus infection did not contribute to the death of any patient in our cohort.

In our cohort, HHV-6 was the second most frequent pathogen observed, consistent with prior reports [6, 13]. Most often, HHV-6 presented as viremia without end-organ disease and occurred early after UCBT. The clinical significance of asymptomatic HHV-6 viremia remains controversial; however, HHV-6 reactivation has been independently associated with graft failure after UCBT [25]. We did not find a significant relationship between HHV-6 and graft failure in our patients. With the onset of viremia, patients were treated with foscarnet, and this may have blocked the development of end-organ disease due to HHV-6. Human herpesvirus 6 was responsible for the death of 1 patient, who developed limbic encephalitis more than 100 days after UCBT; this patient had been previously treated with foscarnet

for 2 episodes of HHV-6 viremia, 1 of which was accompanied by pneumonitis. Receipt of an UCBT has been described previously as a risk factor for the development of limbic encephalitis; this condition is associated with high plasma HHV-6 viral loads, which were observed in this patient [26].

Universal prophylaxis for HSV is a common practice after UCBT, and all 57 patients in our study were on standard-dose acyclovir. Despite appropriate antiviral prophylaxis, we observed 8 episodes of HSV reactivation, 2 of which were severe and led to the patient's death. Acyclovir resistance was confirmed in 1 patient who died of disseminated HSV-1 infection. Acyclovir resistance appears to be more common after HCT, particularly in the setting of T-cell depletion, and may be related to prolonged use of acyclovir for prophylaxis [27, 28]. None of our patients were on high-dose acyclovir, which is used at some centers for antiviral prophylaxis after HCT; this raises the question of whether this prophylaxis strategy might have prevented these fatal herpesvirus infections [29].

Increased emphasis on screening for reactivation of CMV and HHV-6 whenever fever occurred and prompt treatment is likely responsible for decreased mortality from viral pathogens, but deaths due to bacterial and fungal pathogens remained high after UCBT. Six of the 13 infectious deaths in our patient population were due to bacteremias or invasive aspergillosis that occurred in the first 30 days after transplantation.

Not surprisingly, bacterial infections were common throughout all time periods, and many were likely related to the presence of indwelling catheters. Infections with *Enterobacteriaceae* and VRE within the first 30 days after UCBT were associated with increased mortality. The prolonged time to neutrophil engraftment after UCBT increases the period at which recipients are at high risk of life-threatening bacterial infections. Although antibacterial prophylaxis is standard of care after HCT, increasing antimicrobial resistance limits the efficacy of several existing oral prophylactic regimens [30]. In some centers, VRE has become the most common cause of bacteremia in allogeneic HCT recipients and also has emerged as a problem among UCBT recipients in some centers [13, 30–34].

Infections with mycobacteria are uncommon among HCT recipients. The reported frequency of nontuberculous mycobacterial infections is 0.4%–4.9% in several reports, and most cases have been related to infection of central venous catheters [35]. Structural lung changes, such as bronchiectasis associated with bronchiolitis obliterans syndrome, likely predispose patients to infection with nontuberculous mycobacteria late after transplant, as was the case in one of our patients [35]. Pulmonary tuberculosis is less common after HCT with estimated rates between 0.1% and 0.5%, although one report from Japan noted an incidence of 2.5% among UCBT recipients [36, 37].

Invasive mold infections were a major cause of death in our cohort, but invasive *Candida* infections were rare; only 1 patient had 2 episodes of candidemia. The widespread use of azoles for

prophylaxis for allogeneic HCT recipients likely has changed the epidemiology of invasive fungal infections in this population [19, 38]. The 4 patients in our cohort who died of invasive aspergillosis did so before neutrophil engraftment, and none were receiving prophylaxis with a mold-active azole. This high burden of disease early after UCBT underscores the need for aggressive surveillance for fungal infections and the need for mold-active azole prophylaxis.

Despite prior pediatric studies that have demonstrated decreased risk of GVHD after UCBT, we saw a high rate of GVHD in our cohort (61%), and 5 patients died from sequelae of severe/refractory GVHD [3]. We observed a higher rate of acute GVHD than chronic GVHD in this population, as has been previously described [39]. It is possible that higher rates of acute GVHD after UCBT are associated with greater HLA mismatch; however, the exact mechanisms remain unclear [39, 40].

The limitations of our study include its retrospective nature and the relatively small sample size. In addition, over the 10-year time span of our study, changes in practice, particularly regarding prophylaxis and infection monitoring protocols, likely impacted the risk for and outcomes of infection.

CONCLUSIONS

In summary, the implementation of the strategy to screen for infection with CMV and HHV-6 with the onset of fever and to treat promptly has evolved over time, changing the landscape of infectious complications after UCBT. Cytomegalovirus and HHV-6 were common after UCBT, but they were not associated with increased mortality. Delayed neutrophil engraftment increases the risk for bacterial and fungal infections early after UCBT and is associated with increased mortality. Multiple concurrent infections were present in more than one third of episodes, and diagnosis of one infection should not prohibit further testing for other possible infections.

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