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Infection Prophylaxis Patterns Following Pediatric Autologous Hematopoietic Stem Cell Transplantation: A Survey of Pediatric Transplant and Cell Therapy Consortium (PTCTC) Centers

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Abbreviations:

ANC	absolute neutrophil count
Auto-HSCT	Autologous Hematopoietic Stem Cell Transplantation
Allo-HSCT	Allogeneic Hematopoietic Stem Cell Transplantation
CMV	Cytomegalovirus
EBV	Epstein Barr Virus
EFS	event free survival
HSV-1	Herpes Simplex Virus-1
HHV-6	Human Herpes Virus-6
HLA	Human Leukocyte Antigen
PTCTC	Pediatric Transplant and Cellular Therapy Consortium

Introduction

Autologous hematopoietic stem cell transplantation (auto-HSCT), also referred to as high-dose chemotherapy with hematopoietic stem cell rescue, is frequently incorporated into

pediatric treatment protocols for neuroblastoma, malignant brain tumors, and relapsed lymphomas. Administration of myeloablative doses of chemotherapy is followed by autologous stem cell infusion in order to ensure hematopoietic recovery and to reduce the duration of pancytopenia. Use of auto-HSCT has improved outcomes for children with these malignancies, with high risk neuroblastoma demonstrating the most marked improvement. Children with neuroblastoma undergoing a single auto-HSCT experienced improved 3-year event free survival (EFS) from 30% to 52% [1]. The addition of a second auto-HSCT transplant (tandem transplant) further improved outcomes with a reported three-year EFS of 61% [2]. Similarly, use of auto-HSCT has resulted in improved EFS for patients with relapsed Hodgkin lymphoma from 34% to 55% [3].

Despite the documented benefits of auto-HSCT, this therapy also has well-described toxicities, including post-transplant infections. Infection following auto-HSCT has been reported as the primary cause of death in 8% of auto-HSCT patients [4]. Post auto-HSCT patients are at risk of developing bacterial, viral, and fungal infections similar to allogeneic hematopoietic stem cell transplantation (allo-HSCT) recipients. Therefore, in an effort to decrease infectious complications, post-transplant antimicrobial prophylaxis is frequently employed. Currently, there is still little known about the time period of overall infection risk in pediatric patients after auto-HSCT and there are no expert consensus recommendations regarding infectious prophylaxis duration for these patients [4].

Infection prophylaxis for patients receiving auto-HSCT has largely been extrapolated from treatment of patients receiving allo-HSCT, where post-transplant infections account for 17-20% of deaths [4]. However, autologous and allogeneic HSCT differ in the pattern of immune reconstitution. Therefore, we hypothesized that given the lack of guidelines available, there would be significant variation in infection prophylaxis protocols following auto-HSCT among pediatric HSCT centers. To address this, we conducted a survey of pediatric HSCT programs that participate in the Pediatric Transplant and Cellular Therapy Consortium (PTCTC) to assess institutional practices and help guide future studies in identifying optimal prophylaxis strategies and determining guidelines for care in the auto-HSCT setting.

Methods

A web-based, multiple-choice survey consisting of 21 questions was developed using REDCap software and distributed by email to Pediatric Transplant and Cellular Therapy Consortium centers. The survey assessed institutional practices for post auto-HSCT infection prophylaxis in pediatric patients, including duration of prophylaxis, medications used for prophylaxis, viral screening practices, and immune reconstitution monitoring (**Supplemental Figure 1**). Pneumocystis jiroveci prophylaxis practice was not included in the survey, as this is standard of care for oncology patients undergoing chemotherapy as well as HSCT patients and we did not anticipate significant variances in practice patterns. Approval for the development of the survey was obtained from the University of Alabama at Birmingham Institutional Review Board.

The survey was distributed by email in March of 2017 to principal investigators at pediatric HSCT centers within the United States who participate in the PTCTC (n = 98). The PTCTC is the largest clinical trials group focused on pediatric HSCT and includes centers in the United States, Canada, New Zealand, and Australia along with affiliated members in Europe, Asia, and South America. The purpose of the survey and assurance of anonymity for participating centers was included in the email. Physicians did not receive any honorarium for completion of the survey. The same web-based survey was redistributed four weeks later to capture additional responses. Fisher's exact test was used to compare prophylaxis practices among primary providers.

Results

A total of 33 centers responded, accounting for approximately one-third of pediatric HSCT centers participating in the PTCTC. Each institution supplied only one survey response. Thirty-two of the responding centers completed the entire survey. The HSCT team remained the primary service during and after hospital discharge for auto-HSCT at the majority of centers (n=23, 69%). At the remaining centers, the oncology team managed all auto-HSCTs after hospital discharge. Of the 23 centers where HSCT remained the primary service, 17 (74%) of them did so for <3 months, three (13%) for 3-6 months, one (4%) for 6-12 months, and 2 (8%) for > 12 months. Infectious prophylaxis practices were as follows: 30 (91%) centers give viral prophylaxis, 31 (94%) give fungal prophylaxis, and 14 (42%) give bacterial prophylaxis after

auto-HSCT. There was no significant association between the primary service and duration of fungal, viral, or bacterial prophylaxis (p= 0.33, 0.28, 0.07, respectively).

Bacterial Prophylaxis

Thirteen (39%) of the 33 responding institutions administered bacterial prophylaxis after auto-HSCT as standard therapy. Of the other centers, 18 (54.5%) did not give bacterial prophylaxis, one (3%) center gave prophylaxis only in the setting of a clinical indication (i.e., asplenia), and one (3%) center did not respond to the question (**Figure 1A**). Eight (57%) of the thirteen centers administering bacterial prophylaxis used cefepime, levofloxacin at four centers (31%), and two centers (14%) did not disclose a primary antibiotic choice (**Figure 1B**). Bacterial prophylaxis was discontinued once the patient's absolute neutrophil count (ANC) reached greater than 500 cells/μL at 12 centers (86%). The remaining center that administered bacterial prophylaxis did not report the duration of prophylaxis.

Viral Prophylaxis and Screening

Thirty (91%) of the 33 responding transplant centers reported use of prophylaxis for prevention of herpes simplex virus (HSV) reactivation. Acyclovir was the agent of choice at all reporting centers that utilized HSV prophylaxis. Three (9%) centers reported use of valacyclovir in place of acyclovir in specific settings, but the nature of these situations was not reported. For those centers indicating use of HSV prophylaxis, a marked variation in duration was noted, with sixteen of the 30 reporting centers (53%) utilizing HSV prophylaxis for less than 3 months, nine (30%) for 3-6 months, and four (13%) 6 to 12 months or greater. One institution (3%) did not indicate the duration of HSV prophylaxis (**Figure 1C**).

Viral screening was routinely performed by 17 (52%) institutions after auto-HCST, all on a weekly basis. Cytomegalovirus (CMV) screening was most common, occurring at 15 institutions (45%). Twelve institutions (36%) screened for CMV alone, two (6%) screened for CMV, adenovirus, and Epstein Barr virus (EBV), and a single center reported screening for CMV, adenovirus, EBV, and human herpes virus 6 (HHV-6). Two institutions (6%) did not screen for CMV, with one screening for adenovirus only and one for EBV, adenovirus, and HHV-6 (**Figure 1D**).

Fungal Prophylaxis

Fungal prophylaxis medications were administered following auto-HSCT at 31 (94%) of the 33 responding centers. Fluconazole alone was the agent of choice at 29 (94%) of these 31 centers. Micafungin and voriconazole combination therapy were utilized at one center, with another center using a combination of micafungin and fluconazole. Thirty (30) centers provided additional details regarding the duration of prophylaxis with 22 of 30 centers (73%) administering prophylaxis for less than 3 months, 7 (23%) for 3-6 months, and one for greater than 12 months (**Figure 1E**).

Immune Reconstitution Monitoring

Seven institutions (21%) monitored immune reconstitution after auto-HSCT. Three (43%) of these seven institutions measured antibody levels, lymphocyte subsets ($CD3^+$, $CD4^+$, $CD8^+$, and $CD19^+$ cells), and performed mitogen stimulation testing after auto-HSCT. One institution performed these evaluations and also tested for vaccine response to Tetanus and Diphtheria vaccination. Two (29%) institutions reported only measuring lymphocytes subset numbers ($CD3^+$, $CD4^+$, $CD8^+$, and $CD19^+$ cells). A single (14%) institution reported antibody level measurements and specific levels of $CD4^+$ and $CD8^+$ cells (**Figure 1F**). Importantly, only two of these institutions relied on immune reconstitution to determine length of prophylaxis following auto-HSCT, using $CD4^+$ count >200 cells/μL as a target. There was no significant association noted between immune reconstitution monitoring and the primary team following auto-HSCT patients (HSCT versus Oncology, p= 0.16).

Discussion

Despite marked improvements in screening methodologies and treatments, infection remains a significant cause of morbidity and mortality in pediatric patients following HSCT. To address this issue, the pediatric transplant community has established evidence-based clinical practice guidelines for infection prophylaxis following allogeneic HSCT [4]. However, a similar guideline does not exist for management of pediatric patients following autologous HSCT. The results of

our survey suggest marked practice variations among U.S. pediatric HSCT centers and highlight the absence of clear standards for preventing infection in these patients.

Bacterial infection is the most common infectious complication following autologous and allogeneic HSCT, but the risk decreases significantly upon resolution of neutropenia. In our survey, 41% of responding institutions utilized bacterial prophylaxis following auto-HSCT, and all of these responders discontinued prophylaxis upon neutrophil recovery (defined as ANC > 500 cells/μL). A meta-analysis of 17 prospective, randomized trials including 1453 autologous and allogeneic HSCT recipients revealed that primary antibiotic prophylaxis reduced the incidence of bacteremia compared to no prophylaxis, but did not have a significant impact on mortality [5]. However, patients receiving systemic antibiotic prophylaxis also experienced a greater incidence of adverse events, including renal and hepatic toxicity [5]. More recently, additional studies have demonstrated a benefit from bacterial prophylaxis in the auto-HSCT setting, including reductions in ICU transfers and mortality in patients receiving antibiotic (fluoroquinolone) prophylaxis [6, 7]. These studies did not report significant toxicities or the emergence of resistant organisms, but this remains a concern for the pediatric transplantation and infectious disease communities [8]. Larger prospective studies in the auto-HSCT population are required to determine the safety and utility of bacterial prophylaxis.

Lymphocyte immune reconstitution following allogeneic and autologous HSCT typically follows a similar kinetic pattern with absolute numbers reaching equivalent levels at post-transplant time points. Expansion of the lymphocyte populations in both graft types occurs secondary to homeostatic proliferation, as well as other mechanisms [9, 10]. Previous studies have demonstrated that B- and T-lymphocytes, including $CD4^+$ and $CD8^+$ cells, achieve normal ranges at similar time points [11-13]. Not surprisingly, earlier studies that demonstrated differences in lymphocyte recovery were often explainable by the increasing use of growth factor–mobilized peripheral blood stem cells for autologous HSCT over bone marrow, which is commonly used as the graft source of choice for pediatric allogeneic HSCT [13-15]. Peripheral blood stem cell grafts have been shown in both the autologous and allogeneic setting to hasten lymphocyte recovery [9, 16].

Despite a similar period of lymphopenia, there is evidence for a role of memory T cells contained within the autologous graft in controlling viral infections. A subset of $CD8^+$ T cells has previously been demonstrated to survive intensive chemotherapy and retain function [17]. The

repeated induction of profound lymphopenia in patients undergoing multiple cycles of cytotoxic chemotherapy, a common occurrence in auto-HSCT, infrequently results in severe viral infections suggesting that a population of memory T cells persist and, at least partially, restores immunity [17, 18]. It is hypothesized that the function of these memory T cells in the context of autologous Human Leukocyte Antigen (HLA) presentation are critical for controlling viral reactivation in the autologous host, in contrast to the allogeneic setting, where the foreign HLA can abrogate complete functional activation of these cells.

A recent analysis of pediatric and adult patients undergoing auto-HSCT demonstrated a low level of viral reactivation by multiplex PCR [19]. HHV-6 reactivation was the most common, occurring in approximately 40% of patients. Reactivation of EBV and CMV occurred in less than 5% of patients. HSV reactivation was not noted, but all patients received post-transplant acyclovir prophylaxis [19]. Of reporting centers, over half utilized viral screening following auto-HSCT, with CMV being the most common screening performed. The utility of CMV screening following auto-HSCT remains uncertain. While research has indicated a significant incidence of CMV reactivation occurring within the auto-HSCT population [20, 21], the benefit of routine screening and the risk of potential overtreatment is not established [22].

The use of acyclovir or a similar agent appears justified due to the risk of HSV reactivation following autologous HSCT [23, 24]. The duration of time necessary for prophylaxis, however, is not established. Previous studies have reported use until engraftment or greater than one year following auto-HSCT [23, 24]. Similarly, our survey results suggest a marked variation in practice patterns for HSV prophylaxis. It should be noted that acyclovir prophylaxis offers some protection from varicella-zoster virus reactivation, and could also influence the practice patterns of some centers.

Among auto-HSCT recipients, the risk of invasive candidiasis and fungemia decreases significantly once neutropenia and mucositis have resolved. Although patients remain at risk to certain fungi, mainly aspergillus and pneumocystis, until cellular and humoral immunity is restored. The period of neutropenia is typically shorter for auto- versus allo-HSCT recipients with most resolving by 21 days after transplant. In one study, no cases of invasive fungal infections were identified after auto-HSCT, even in those patients that did not receive fungal prophylaxis [6]. This evidence suggests that fungal prophylaxis may not need to be continued upon hospital discharge. Our survey results, however, revealed that nearly 25% of institutions

continue prophylaxis beyond three months post auto-HSCT. Further studies are needed to better identify patients at increased risk for fungal infections and to determine the appropriate length of prophylaxis.

We conclude that following auto--HSCT, infection prophylaxis practices are highly variable among PTCTC participating institutions. The data supports a need for research studies in this subset of transplant patients to help better define the timing and nature of infectious complications in order to develop standardized clinical practice guidelines for these patients.

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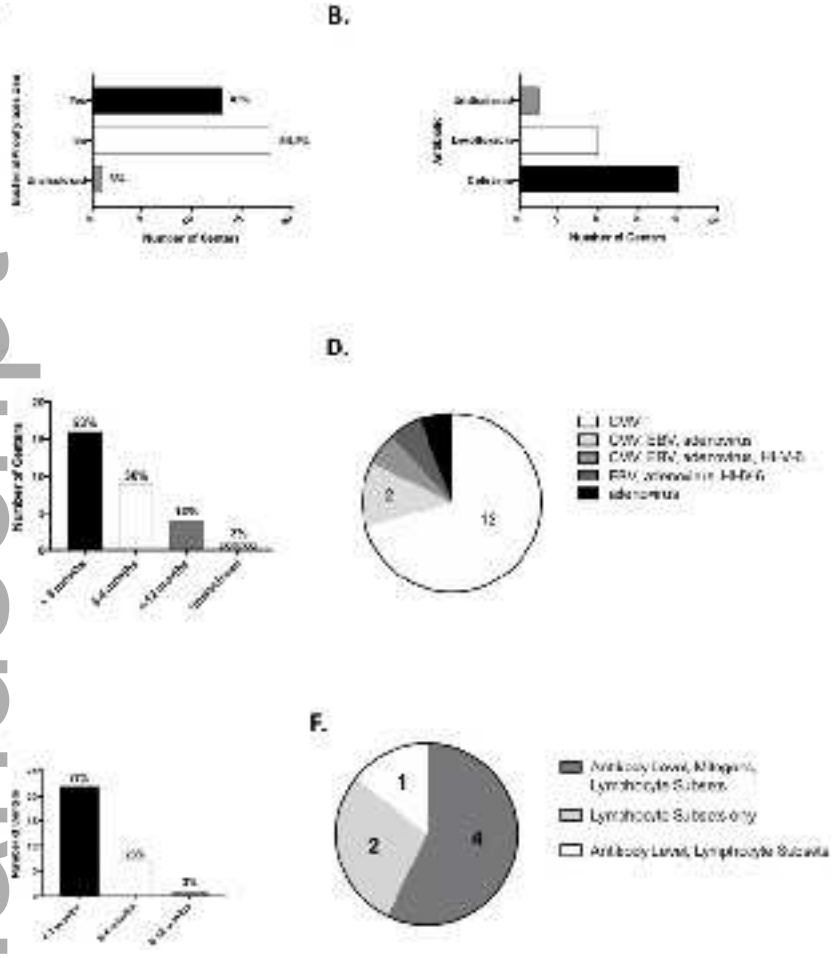
Figure Legends

Figure 1. Infection Prophylaxis Patterns following autologous HSCT amongst centers within the PBMTC. Survey results are shown for infection prophylaxis patterns among the 33 responding PBMTC centers. Shown in (A) are responses to the use of bacterial prophylaxis following auto-HSCT, percentages are calculated from the total 33 responding centers. For the 13 centers using bacterial prophylaxis, the choice of agent is shown in (B). Thirty (30) centers indicated use of HSV-1 prophylaxis in patients following auto-HSCT, shown in (C) is the reported duration of antiviral use, with percentages calculated from the 30 total centers using prophylaxis. Seventeen (17) centers reported viral screening following autologous HSCT. The

specific viral screens performed are shown in (D), with the number of centers shown for CMV alone (12) and CMV, EBV, and adenovirus (2). All other viral screens were reported by a single center. Anti-fungal prophylaxis was utilized at 94% of responding centers. Thirty (30) centers reported duration of anti-fungal use, and these results are shown in (E). Percentages are calculated from the 30 centers reporting duration. Seven institutions reported monitoring immune reconstitution following auto-HSCT. The specific tests utilized are shown in (F), with the number of centers performing the tests indicated.



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