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A Multicenter Study of Bacterial Blood Stream Infections in Pediatric Allogeneic Hematopoietic Cell Transplantation Recipients: The Role of Acute Gastrointestinal Graft-versus-Host Disease

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A B S T R A C T

Blood stream infections (BSI) caused by enteric organisms are associated with a particularly high mortality rate in allogeneic hematopoietic cell transplantation (alloHCT) recipients. We conducted a retrospective multicenter study aiming to analyze the risk factors associated with antibiotic resistance and impact of BSI on transplantation-related mortality (TRM) in children after alloHCT. During the study period from 2004 to 2014, 395 children (mean age, 9.4 years) with at least 1 BSI were included. The incidences of resistant gram-negative rods were 20.7% to piperacillin-tazobactam, 10.9% to cefepime, 21% to ceftazidime, 11.4% to levofloxacin, and 8.16% to meropenem. Thirty-eight percent of *Enterococcus spp*. isolates were resistant to vancomycin. More than 1 episode of BSI was associated with significant increase in the risk of resistance to piperacillin-tazobactam, cefepime, and vancomycin. On multivariate analysis of risk factors for TRM, achievement of neutrophil engraftment by day 30 was associated with lower TRM ($P = .002$). However, infection with an antibiotic-resistant organism was not associated with TRM. Development of enteric bacterial BSI after the onset of acute gastrointestinal graft-versus-host disease (GVHD) was the strongest predictor of TRM (hazard ratio, 4.786; 95% confidence interval, 2.833 to 8.087; $P < .001$). In patients with acute gastrointestinal GVHD who subsequently developed enteric bacterial BSI, the incidence of 1-year TRM was 33.4% (SE = 7%), compared with 15.3% (SE = 2%) for those without acute gastrointestinal GVHD ($P = .004$). Primary prevention of a first episode of BSI is arguably the most important intervention to decrease antibiotic resistance. It is also imperative that we develop strategies to maintain gastrointestinal health, especially in patients with gastrointestinal GVHD, in an effort to prevent subsequent enteric bacterial BSI and improve survival.

INTRODUCTION

Over the last 3 decades, transplantation-related mortality (TRM) has significantly decreased in children and adults after allogeneic hematopoietic cell transplantation (alloHCT) [1,2]. These improved outcomes are because of numerous advances in care, including better HLA matching, targeted treatment for acute graft-versus-host disease (aGVHD), refinement of conditioning regimens, molecular diagnostic testing for viral infections, and more effective antimicrobial agents [3]. Despite these advances, bacterial infections remain common and are associated with poor outcomes in this population. Bacterial infections caused by enteric organisms are associated with a particularly high mortality rate of 24% to

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40% in alloHCT recipients [4]; this high mortality rate could be associated with antibiotic-resistant blood stream bacterial infections. A few small studies have characterized the incidence of antibiotic resistance in bacterial infections in this population [5-7]. However, there are minimal data regarding risk factors associated with antibiotic resistance or its impact on TRM in children.

AlloHCT-related factors, such as conditioning regimen, acute gastrointestinal graft-versus-host disease (GVHD), antibiotics, and use of total parenteral nutrition in place of enteral feeds, likely contribute to gastrointestinal mucosal injury and alteration of gastrointestinal microbiome, increasing the likelihood of transmission of enteric bacteria into the blood stream [8-12]. We have demonstrated previously that acute gastrointestinal GVHD is associated with an increased risk of enteric bacterial (EB) blood stream infections (BSI) in pediatric alloHCT recipients [13]. However, because of sample size limitations, we were unable to demonstrate the impact of these episodes of EB-BSI on TRM.

One of the challenges in the field of pediatric alloHCT is the generally small number of patients per center, making it difficult to perform single-center retrospective studies with sufficient statistical power to draw conclusions worthy of changing practice. Thus, we conducted a retrospective multicenter study aiming to analyze the risk factors associated with antibiotic resistance and the impact of infections on TRM in children after alloHCT.

METHODS

Study Design and Patient Population

We performed a multicenter retrospective cohort study among pediatric recipients of alloHCT. The following 6 institutions participated in this study: Columbia University (2004 to 2012), Children's Hospital of Philadelphia, Philadelphia, PA (2005 to 2011), UCSF Medical Center-Mission Bay, San Francisco, CA (2008 to 2011), Ann and Robert H. Lurie Children's Hospital of Chicago, Chicago, IL (2008 to 2013), Hackensack University Medical Center, Hackensack, NJ (2010 to 2014), and The Steven and Alexandra Cohen Children's Medical Center of New York, New Hyde Park, NY (2007 to 2011). Patients with at least 1 positive blood culture were included in this study. Various myeloablative and reduced-intensity conditioning regimen were utilized. Conditioning regimens were as classified as published by Center for International Blood and Marrow Transplant Research [13]. The institutional review board of each center approved this study with a waiver of informed consent.

Blood Cultures and Antimicrobial Susceptibility

All positive bacterial blood cultures from days –10 to +365 surrounding alloHCT were reviewed. As per the treating clinician, blood cultures were obtained at onset of fever (>38°C) or if a patient showed signs of clinical decompensation. Isolation of the same bacterial species over 7 days apart was considered 2 BSI. Antibiotic susceptibilities were performed using the most current Clinical and Laboratory Standards Institute guidance. Bacteria reported as "intermediate" were considered resistant (clsi.org-Clinical and Laboratory Standards Institute Microbiology Standards).

Study Definitions

The diagnosis and grades of aGVHD are as defined by Glucksberg et al. [14]. EB-BSI were defined as gram-positive and gram-negative bacteria that resides in the lower gastrointestinal tract. *Absolute neutrophil count* was defined as the product of the white blood cell count (cells/L) and the fraction of polymorphonuclear cells and bands. *Neutrophil engraftment* was defined as the achievement of absolute neutrophil count $> .5 \times 10^9$/L for 3 consecutive days after alloHCT. *TRM* was defined as death from any transplantation-related cause other than disease relapse [13].

Statistical Methods

The continuous variables were summarized as mean ± standard deviation, median, and Q1 and Q3 (quartiles); categorical variables were summarized as percentages. Age was analyzed as both a continuous and categorical variable to identify which age group was at highest risk for antibiotic resistance and TRM. The comparisons between 2 groups were done by *t*-test for continuous variables and by chi-square test or Fisher's exact test for categorical variables. *P* values of <.05 were considered significant. Variables assessed for antibiotic resistance and TRM are shown in Tables 1 and 2. Only variable with a *P* value <.05 were included in the multivariate analysis.

The logistic regression analysis was done to examine risk factors for EB-BSI. The cause-specific hazards regression models were used to identify risk factors for the time to TRM by treating relapse as a competing event after alloHCT. Neutrophil engraftment, onset of aGVHD, and onset of infections were treated as time-varying variables in the analysis of TRM. *P* values <.05 were considered significant. The analysis was carried out in SAS 9.3 (Cary, NC).

RESULTS

Patient Characteristics

Only patients with at least 1 positive blood culture were included in this study. For all patients, the mean age was 9.4 ± 7 years, quartile 1 was 2.42 years, and quartile 3 was 16 years. Demographic and transplantation characteristics of patients are summarized in Table 1.

The median time to neutrophil engraftment was 17.4 days (range, 7 to 49), with 85% of patients engrafting by day +30. The incidence of grades I to IV aGVHD was 49%, grades II to IV aGVHD was 41%, and grades III or IV aGVHD was 27%. The incidence of acute gastrointestinal GVHD was 24.8%. Median time to onset of aGVHD was 28 days (range, 7 to 91 days).

Bacterial BSI

During the study period, 848 positive blood cultures were identified among 395 patients. Among these cultures, 496 (58.5%) were gram positive and 352 (41.5%) were gram negative. Fifty-seven (6.7%) of these occurred from day –10 to day 0, among 42 patients.

Among 395 patients, 307 (77.7%) experienced at least 1 gram-positive infection. Among all patients, individuals averaged 1.26 gram-positive infections per person. Among gram-positive isolates, the proportion of *Staphylococcus epidermidis*

Table 1
Demographic and Transplantation Characteristics of Patients

Characteristic	Value
No. of patients	395
Age, mean, yr	9.4 ± 7
Males	252 (64%)
Malignant disease	239 (60.5%)
Acute myeloid leukemia	104
Acute lymphoid leukemia	87
Lymphoma	21
Others	27
Nonmalignant disease	156 (39.5%)
Hemoglobinopathies	49 (31.4%)
Immunodeficiency	40 (25.6%)
Bone marrow failure including severe aplastic anemia	34 (21.7%)
Metabolic disorders	26 (16.6%)
others	7 (4.4%)
Donors	
HLA matched siblings	114 (29%)
HLA-matched (8/8,10/10) unrelated donors	83 (21%)
HLA mismatched unrelated donors	198 (50%)
Stem cell sources	
BM	138 (35%)
PBSC	162 (41%)
UCB	95 (24%)
Conditioning regimens	
MAC	284 (72%)
RIC	111 (28%)
TBI	142 (36%)
MAC	127 (89.5%)
RIC	15 (10.5%)

Data presented are n (%) unless otherwise indicated.
BM indicates bone marrow; PBSC, peripheral blood stem cells; UCB, umbilical cord blood; MAC, myeloablative conditioning; RIC, reduced-intensity conditioning; TBI, total body irradiation.