Infectious complications following hematopoietic cell transplantation in patients with primary immunodeficiency diseases

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Abstract

Background: Hematopoietic cell transplantation (HCT) has significantly improved long- term survival for children with primary immunodeficiency diseases (PID). Little is known about specific risk factors for infections after HCT in PID patients specifically. Factors impacting success of HCT in PID include age at HCT, underlying genetic defect, type of donor, hematopoietic stem cell source, and conditioning regimen, and importantly, the presence of pre-existing infections. Here we describe the epidemiology of bacterial, viral and fungal infections in patients undergoing HCT for PID.

Methods: After IRB approval, medical records of patients undergoing HCT at Seattle Children's Hospital for PID between 1998 and 2017 were reviewed. Data collected included donor and stem cell source, conditioning regimen, graft versus host disease (GVHD) and mortality. Timing, character, and details of each incident infection during 12 months post-HCT were also collected. Primary outcomes included mortality and infection free survival. Kaplan-Meier curves were used to examine infection free survival, by diagnosis and by HCT era.

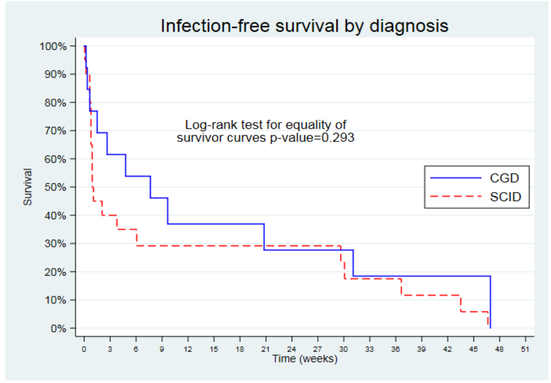
Results: 69 children and adults with PID underwent HCT during the study period. Median age at HCT was 2.2 years and varied by underlying PID. Altogether, 24 patients (34.8%) had severe combined immune deficiency (SCID), 14 (20.3%) had chronic granulomatous disease (CGD), 9 (13%) had combined immune deficiency (CID), 6 (8.7%) had Hyper IgM syndrome and 16 (23%) had other forms of PID. Twenty patients (29%) received HLA-matched related grafts and thirty-six received matched unrelated (52%) grafts. 7 patients (10%) received umbilical cord blood grafts. Acute GVHD grade II-IV developed in 46 (67%) patients. Bacterial infections were the most common infection post-HCT in all time periods, followed by respiratory and herpes viral infections. Overall mortality at 1 year was 19%, of which at least 50% was infection related.

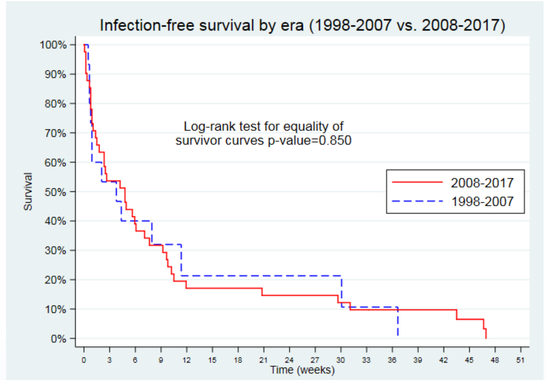
Conclusions: Infections occur frequently and contributes to morbidity and mortality in patients undergoing HCT for PID. Understanding the timing of infections and contributing risk factors could help develop preemptive and monitoring strategies to improve outcomes in this patient population.

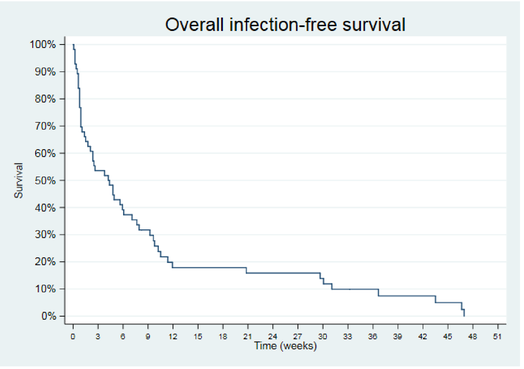
Patient characteristics

Characteristic, N (%)	Total patients N=69
Age at HCT in years, median (range)	2.2 (0.2-46)
HLA Matched	56 (81%)
Related	20 (29%)
Unrelated	36 (52%)
Source of cells	
Bone marrow	54 (79%)
Cord blood	7 (10%)
PBSC	7 (10%)
Underlying primary immunodeficiency	
SCID	24 (35%)
Chronic Granulomatous Disease (CGD)	14 (20%)
Combined Immune Deficiency	9 (13%)
Hyper IgM syndrome	6 (9%)
Wiscott Aldrich syndrome	3 (4%)
Cartilage-hair hypoplasia	3 (4%)
Combined variable immune deficiency	3 (4%)
Other B cell immune deficiency*	5 (7%)
Other T cell immune deficiency**	2 (3%)
Acute GVHD (Grades II, III, IV)	46 (67%)
Conditioning Intensity	
None	2 (3%)
Nonmyeloablative	41 (59%)
Myleoablative	26 (38%)
CMV Status (n=65)	
D+/R+	16 (25%)
D+/R-	9 (14%)
D-/R+	26 (40%)
D-/R-	14 (22%)
Mortality at 12 months	13 (19%)
Infection related mortality	7/13 (54%)

***includes NEMO, congenital neutropenia, IL 10 receptor defect, X linked agammaglobulinemia**
**** includes DiGeorge syndrome**







Conclusions

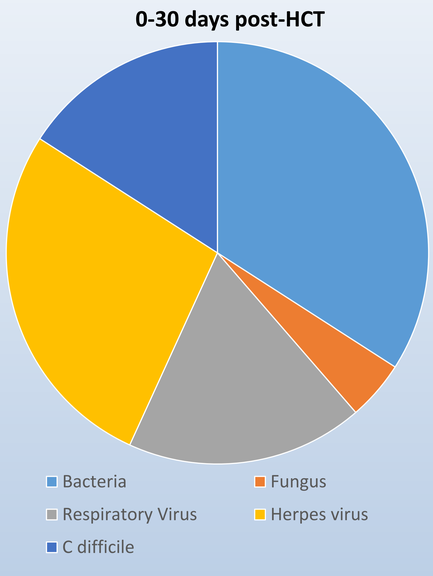
- Bacterial and viral infections occur frequently in all time periods post HCT in PID patients and infection is a significant contributor to mortality in these patients.
- Infection-free survival has not significantly improved in the recent decade and does not significantly differ between CGD and SCID patients post HCT.
- Understanding the timing of infections and contributing risk factors could help develop preemptive and monitoring strategies to improve outcomes in this patient population.

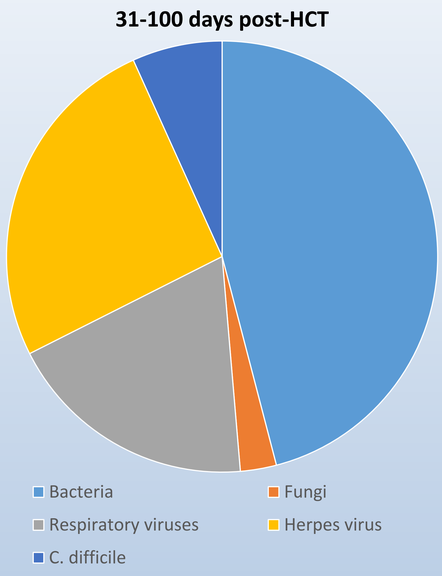
- FUTURE WORK:
  - Understanding the impact of pre-HCT infections on risk of infection post HCT
  - Recognizing the effect of other risk factors for infection (conditioning, GVHD, CMV status, etc)

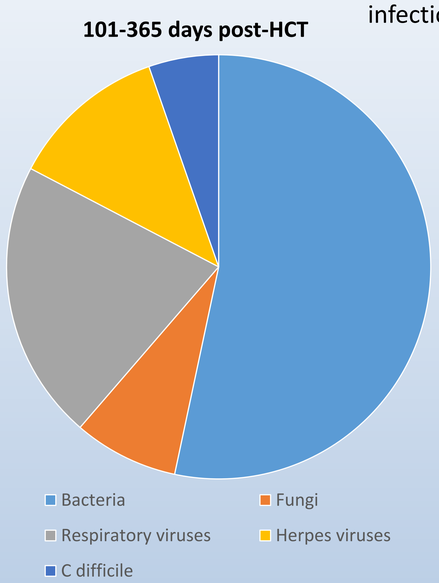
Introduction

- Pediatric patients with PID are adversely impacted by infections, which may jeopardize the chances of a successful HCT to treat their underlying disease.
- Newborn screening for SCID has resulted in early identification and HCT.
- An expanding number of non-SCID PIDs are also being treated with HCT.
- Though existing literature describes HCT outcomes for PID patients, little is known about the specific risk factors for development of infections after HCT.
- We hypothesized that these disorders may carry disease-specific risks that increase their infection-related risk for morbidity and mortality following HCT
- This study was performed to better understand infections in specific PID populations and inform our guidelines and practices for HCT in these high-risk patients.

Types of Infection by Time Post-HCT







Limitations

This is a retrospective review with a small number of patients which can not establish any causality

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