Not for publication or presentation

CIBMTR®
CENTER FOR INTERNATIONAL BLOOD & MARROW TRANSPLANT RESEARCH

A G E N D A
CIBMTR WORKING COMMITTEE FOR INFECTION AND IMMUNE RECONSTITUTION
Houston, TX
Wednesday, February 20, 2019, 12:15 – 2:15 pm

Co-Chair:	**Caroline Lindemans, MD, PhD, University Medical Center Utrecht, Utrecht, Netherlands; Telephone: +31 622879245; E-mail: c.a.lindemans@umcutrecht.nl**
Co-Chair:	**Krishna Komanduri, MD, University of Miami; Miami, FL; Telephone: 305-243-5302; E-mail: kkomanduri@med.miami.edu;**
Co-Chair:	**Miguel-Angel Perales, MD, Memorial Sloan Kettering Cancer Center, New York, NY; Telephone: 212-639-8682; E-mail: peralesm@mskcc.org;**
Scientific Director:	**Marcie Riches, MD, MS, The University of North Carolina at Chapel Hill, Chapel Hill, NC; Telephone: 919-966-3048; E-mail: marcie_riches@med.unc.edu**
Statistical Directors:	**Soyoung Kim, PhD, CIBMTR Statistical Center, Milwaukee, WI; Telephone: 414-955-8271; E-mail: skim@mcw.edu**
Statistician:	**Min Chen, MS, CIBMTR Statistical Center, Milwaukee, WI; Telephone: 414-805-0710; E-mail: minchen@mcw.edu**

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1. **Introduction**
   a. Welcome and introduction
   b. Introduction of incoming Co-Chair: Dr. Roy Chemaly, M.D. Anderson Cancer Center, Houston, Tx.
   c. Minutes and Overview Plan from February 2018 meeting (Attachment 1)

2. **Accrual summary** (Attachment 2)

3. **Studies published/submitted/Preliminary results**
   a. **IN07-01/IN11-01(a)** Ustun C, Young J-H, Papanicolau GA, Kim S, Ahn KW, Chen M, Abdel-Azim H, Aljurf M, Beitinjaneh A, Brown V, Cerny J, Chhabra S, Kharfan-Dabaja MA, Dahi PB, Daly A, Dandoy CE, Dvorak CC, Freytes CO, Hashmi S, Lazarus H, Ljungman P, Nishihori T, Page K, Pingali SRK, Saad A, Savani BN, Weisdorf D, Williams K, Wirk B, Auletta JJ, Lindemans CA, Komanduri K, Riches M. **Bacterial blood stream infections (BSIs), particularly post-engraftment BSIs, are associated with increased mortality after allogeneic hematopoietic cell transplantation.** Bone Marrow Transplantation. *doi:10.1038/s41409-018-0401-4. Epub 2018 Dec 13.* **Published.**
   b. **IN07-01/IN11-01(b)** Genovefa A Papanicolaou, Celalettin Ustun, Jo-Anne H Young, Min Chen, Soyoung Kim, Kwang Woo Ahn, Krishna Komanduri, Caroline Lindemans, Jeffery J Auletta, Marcie L Riches, **CIBMTR® Infection and Immune Reconstitution Working Committee; Bloodstream infection (BSI) due to Vancomycin-Resistant Enterococcus (VRE) is associated with increased mortality after hematopoietic cell transplantation for acute leukemia and myelodysplastic syndrome: A multicenter, retrospective cohort study**, Clinical Infectious Diseases, , ciz031, https://doi.org/10.1093/cid/ciz031. **Published.**

c. **IN13-01** Bacterial and fungal infections in patients undergoing allogeneic hematopoietic cell transplantation following non- myeloablative and myeloablative regimens (C Ustun). **Manuscript.**

d. **IN14-01** Post allogeneic hematopoietic transplant Epstein Barr Virus related Lymphoproliferative disorder following conditioning with Antithymocyte globulin or Alemtuzumab (S Naik/ C Bachier/ P Shaughnessy/ P Hari/ R Kamble). **Submitted.**

e. **IN16-01** Maheen Z. Abidi, Parameswaran Hari, Min Chen, Soyoung Kim, Minoo Battiwala, Parastoo Bahrami Dahi, Miguel Angel Diaz, Robert Peter Gale, Siddhartha Ganguly, Usama Gergis, Jaime Green, Gerhard Hildebrandt, Joshua A. Hill, Krishna Komanduri, Hillard Lazarus, David Marks, Taiga Nishihori, Richard Olsson, Sachiko Seo, Celalettin Ustun , Jean Yared, Dwight Yin, John Wingard, Baldeep Mona Wirk, Jeffrey Auletta, Caroline Lindemans, Marcie Riches, **Virus detection in the cerebrospinal fluid of hematopoietic stem cell transplant recipients is associated with poor patient outcomes: a CIBMTR contemporary longitudinal study,** Bone Marrow Transplantation, 2019 Jan 29. doi: 10.1038/ s41409-019-0457-9. **Published**

f. **IN16-02** Determination of the burden of mucosal barrier injury-laboratory confirmed bloodstream infections (MBI-LCBI) in the first 100 days after stem cell transplant (C Dandoy/P Daniels) **Manuscript** (Attachment 3)

4. Studies in progress (Attachment 4)

a. **IN17-01** Incidence and impact of cytomegalovirus and other viral infections, on post-transplant outcomes following HLA-haploidentical hematopoietic cell transplantation compared to other donor sources. (Rizwan Romee/ Anurag Singh/ Randy Allison Taplitz) **Protocol development** (Attachment 5)

b. **IN18-01** Comparison of early (by day 100) infections after haploidentical HSCT between patients receiving cyclophosphamide-based or other GVHD prophylaxis (Celalettin Ustun/Genovefa Papanicolaou) **Protocol development** (Attachment 6)

c. **IN18-02** The Incidence, and impact of Clostridium difficile infection within 100 days on Transplant outcomes after allogeneic stem cell transplant (Muthalagu Ramanathan/ Bipin Savani/ Celalettin Ustun) **Protocol development** (Attachment 7)

5. Future/proposed studies

a. **PROP 1810-10** Retrospective study of the impact of mammalian target of rapamycin inhibitors (mTORi) in the incidence of herpesvirus-associated complications after allogeneic hematopoietic cell transplantation (HCT)(J Kanakry) (Attachment 8)

b. **PROP 1811-18** The burden of infectious complications and the kinetics of engraftment and immune reconstitution in high-risk MDS vs de-novo acute myeloid leukemia in adults (A Ali/ K Larkin) (Attachment 9)

c. **PROP 1811-42** Infection with Atypical Nontuberculous Mycobacteria (NTM) after Hematopoietic Stem Cell Transplantation (HSCT) (D Melendez/J Holter-Chakrabarty/ K Williams/ S Schmidt/ S Vesely) (Attachment 10)

d. **PROP1811-59** Immune recovery predicts post-transplant outcomes (Miguel-Angel Perales) (Attachment 11)

e. **PROP1811-77** Impact of seasons on outcomes of allogenic hematopoietic cell transplantation (HCT) in North America (P Teira) (Attachment 12)

f. **PROP1811-82** Impact of antibacterial prophylaxis on outcomes after allogeneic hematopoietic stem cell transplant (C Dandoy/ P Alonso)
PROP1811-150 Clinical Impact of Pre-Engraftment Antibacterial Prophylaxis in Adult Patients Undergoing Allogeneic Hematopoietic Cell Transplantation in the Current Era (Z El Boghdadly) (Attachment 13)

g. **PROP1811-139** Impact of Early Post-Transplant Infections on Relapse Risk Following Autologous Stem Cell Transplantation for Multiple Myeloma. (C D'Angelo /A Hall) (Attachment 14)

Dropped proposed studies

a. **PROP 1811-30** To study the correlation between JC viral load, JC Viral antibody index and development of progressive multifocal leukoencephalopathy in multiple sclerosis patients following autologous stem cell transplant. *Dropped due to feasibility-the data was not been collected*.

b. **PROP 1811-43** Impact of Epstein Barr virus (EBV) infection on outcomes of allogenic hematopoietic cell transplantation (HCT) for hematologic malignancies*. Dropped due to feasibility.*

c. **PROP 1811-50** Outcomes of HIV+ Patients undergoing autologous hematopoietic cell transplantation (Auto-HCT) for Multiple Myeloma. *Dropped due to feasibility*

d. **PROP 1811-147** Comparative analysis of infectious complications occurring in stem cell transplants using alternative donor source. *Dropped due to overlap with a recently published and 2 on-going studies focused in specific infections following Haplo-identical transplant*

f. **PROP 1811-154** Does rising Human Herpes virus (HHV) 6 titers post Allogenic Stem cell transplant predict reactivation of CMV?. *Dropped due to feasibility*

g. **PROP 1811-155** Post-transplant CMV reactivation in the era of letermovir*. Dropped due to feasibility*

6. Other Business

a. Statistical method

CIBMTR®
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MINUTES AND OVERVIEW PLAN
CIBMTR WORKING COMMITTEE FOR INFECTION AND IMMUNE RECONSTITUTION
Salt Lake City, Utah
Thursday, February 22, 2018, 12:15 – 2:15 pm

Co-Chair:	**Jeffery Auletta, MD, Nationwide Children's Hospital, Columbus, OH; Telephone: 614-722-3553; E-mail: jeffery.auletta@nationwidechildrens.org**
Co-Chair:	**Caroline Lindemans, MD, PhD, University Medical Center Utrecht, Utrecht, Netherlands; Telephone: +31 622879245; E-mail: c.a.lindemans@umcutrecht.nl**
Co-Chair:	**Krishna Komanduri, MD, University of Miami; Miami, FL; Telephone: 305-243-5302; E-mail: kkomanduri@med.miami.edu;**
Scientific Director:	**Marcie Riches, MD, MS, The University of North Carolina at Chapel Hill, Chapel Hill, NC; Telephone: 919-966-3048; E-mail: marcie_riches@med.unc.edu**
Statistical Directors:	**Kwang Woo Ahn, PhD, CIBMTR Statistical Center, Milwaukee, WI; Telephone: 414-456-7387; E-mail: kwooahn@mcw.edu**
	Soyoung Kim, PhD, CIBMTR Statistical Center, Milwaukee, WI; Telephone: 414-955-8271; E-mail: skim@mcw.edu
Statistician:	**Min Chen, MS, CIBMTR Statistical Center, Milwaukee, WI; Telephone: 414-805-0710; E-mail: minchen@mcw.edu**

1. Introduction

a. Welcome and introduction

Dr. Marcie Riches moderated the introduction of the working committee followed by which all the attending co-chairs and the statisticians were introduced. She welcomed Dr. Miguel-Angel Perales as the new chair for INWC starting March 1st 2018, and thanked Dr. Jeffery Auletta for his excellent service for INWC in the past 5 years. Dr. Riches also welcomed Dr. Jan Styczynski, EBMT working party chair.

Dr. Riches reviewed the goal of the working committee is to publish high impact studies in a timely manner. The expectations of the meeting are review of the current status of ongoing studies and timelines and for members to assess and select proposals that will have a high impact on the field. Each proposal presentation was limited to 5 minutes to allow for adequate time for 10 minutes discussion.

The working committee members were asked to vote on a level of scientific impact score, 1 is the highest impact and 9 is the lowest impact score for the new proposals based on the feasibility and impact on the transplant community. Due to limited statistical hours and on-going work in the INWC, two proposals will be accepted this year.

Dr. Riches mentioned the working committee's membership is open to any individual willing to take an active role in study development and completion. She emphasized the rules of

Authorship: 1. substantial and timely contributions to conception and design, acquisition of data, or analysis and interpretation of data; 2. drafting the article or revising it critically for important intellectual content; 3. final approval of the version to be published. All three conditions must be met. The studies that are closest to submission will receive highest priority.

b. Minutes and Overview Plan from February 2017 meeting
The minutes and overview plan from the 2017 Tandem meeting held in Orlando, Florida were reviewed and approved by committee members.

2. Accrual summary

Due to the full agenda, the accrual summary of registration and research cases between 1995 and 2016 were not presented to the committee, but were available as part of the Working Committee attachments.

3. Studies in Submitted/Preliminary results

Dr. Marcie Riches also introduced the studies with preliminary results.

a. **IN07-01/IN11-01(a**) Bacterial blood stream infection (BSI), particularly post-engraftment BSI, are associated with increased mortality after allogeneic hematopoietic cell transplantation (Celalettin Ustun/ JA Young).
The paper has been submitted to BBMT on Jan 31, 2018.

b. **IN07-01/IN11-01(b)** Bloodstream infection (BSI) due to Vancomycin-resistant Enterococcus (VRE) and mortality after hematopoietic cell transplantation. A multicenter retrospective cohort study. (Genovefa A Papanicolaou) **Manuscript preparation**

c. **IN13-01** Bacterial and fungal infections in patients undergoing allogeneic hematopoietic cell transplantation following non- myeloablative and myeloablative regimens (C Usten) **Manuscript preparation**

d. **IN14-01** Post allogeneic hematopoietic transplant Epstein Barr Virus related Lymphproliferative disorder following conditioning with Antithymocyte globulin or Alemtuzumab (S Naik, C Bachier, P Shaughnessy, P Hari, R Kamble) **Manuscript preparation, the abstract was presented as a poster at this Tandem meeting**

e. **IN16-01** Viral Encephalitis in Hematopoietic Stem cell Transplant Recipients, 2007-2013 **(**M Abidi, P Hari) **Manuscript preparation, the abstract was presented as a poster at this Tandem meeting**

4. Studies in progress

Dr. Jeffery Auletta introduced the ongoing studies.

a. **IN16-02** Determination of the burden of mucosal barrier injury-laboratory confirmed bloodstream infections (MBI-LCBI) in the first 100 days after stem cell transplant (C Dandoy, P Daniels) **Data file preparation**
Dr. Christopher Dandoy updated the study.
The study specific aims: Compare TRM and OS post-SCT between patients who develop a MBI-LCBI versus those a non-MBI-LCBI BSI versus those with both an MBI-LCBI and a non-MBI-LCBI and those without any BSI occurring in the first 100 days; Determine the incidence of MBI-LCBIs in the first 100 days post SCT; Determine the risk factors for development of a MBI-LCBI in the first 100 days; Determine the timing of MBI-LCBI after SCT

MBI-LCBI will be assessed as the cumulative incidence function with death and relapse/progression as competing risks. A bloodstream infection will be classified as a MBI-LCBI if it meets both the organism criteria and the patient criteria from the NHSN: Eligible organisms include Candida species, Enterococcus species, Enterobacteriaceae, viridans group, Streptococcus species, and certain anaerobes without isolation of additional recognized pathogens or common commensal organisms; Patient Criteria are: Grade 3-4 gastrointestinal graft versus host disease or ANC < 500 within 7 days of the positive culture. Study strengths are: 1) Large sample size; 2) Contemporary; 3) Reflects the global reality of HSCT by including a large number of centers; 4)Identify MBI-LCBI burden for public health reporting. The study has public health implications and should target major public health journal such as JAMA.

Comments from the committee:

- Time of GVHD and time of infection are correlated
- Bacteria prophylaxis and treatment cannot be distinguished; although the data for both are not captured.
- Request to consider examining the number of CLABSI as well

WC Leadership:

- Acknowledged the second limitation and therefore, the study population is limited to centers having an MBI-LCBI and at least one patient in either the non-MBI-LCBI or control group to minimize variation in prophylaxis and treatment within centers

b. **IN17-01** Incidence and impact of cytomegalovirus and other viral infections, on post-transplant outcomes following HLA-haplo-identical hematopoietic cell transplantation compared to other donor sources. (Rizwan Romee/ Anurag Singh/ Randy Allison Taplitz, et al)

Protocol development

Dr. Rizwan Romee updated the study.

Objectives of the study are: Compare CMV and key viral infections in PTCy haplos, non-PTCy haplos, PTCy non-haplos and non PTCy allo-HCTs; Assess impact of CMV D/R serostatus on CMV viremia, disease and key transplant outcomes (OS, Relapse, NRM, aGvHD, cGvHD etc); Assess incidence of CMV viremia and disease on Key transplant outcomes (OS, Relapse, NRM, GvHD etc); Describe potential risk factors and determine incidence for the development of non-CMV viral infections across these donor types.

Inclusion criteria are First allo-HCT of AML, ALL and MDS, age ≥ 2 years, and HCT between 2008-2016. Exclusion criteria are mismatched unrelated donor transplants; Umbilical cord blood transplants; Lack of donor/recipient CMV serostatus.

Comments from the committee:

- Cord blood could be a potential study
- Post Cy alone group only 15 patients
- Add CMV reactivation
- Lack of information on viral prophylaxis limits study
- Should there be a separate analysis of T-cell depleted transplants
- It's not just post/Cy vs other: variables of the whole transplant platform should be taken into account including conditioning regimen

WC Leadership:

- Due to recent publication for UCBT and impact of CMV reactivation (INWC 1201) and other viral infections in cords (INWC 1001), cords are not included

5. Future/proposed studies

Dr Caroline Lindemans reported that 9 proposals were received this year and 4 will be presented.

a. **PROP1707-01** Comparison of Early (d100) Infections after Haplo HCT between patients receiving Cy-based vs other GVHD prophylaxis
Dr. Celalettin Ustun presented the proposal.
The primary objectives are: To document the incidence and infection density of 3 types (bacterial, viral, and fungal) of infections within 100 days after T-cell replete HCT followed by PTCy; To compare these infections with those occurring after allogeneic HCT with other common/traditional GVHD prophylaxis; To compare these infections with those occurring after allogeneic HCT with T-cell depleted (*in vivo or in vitro*) allogeneic HCT; To compare infections between PTCY+ additional ISP and PTCy alone.
The secondary objectives are: To compare NRM, OS, acute GVHD at 6 months and year 1; To evaluate the impact of Donor/recipient seropositivity (CMV, EBV, HSV, VZV) on viral infections.
Study population: STUDY POPULATION: First alloHCT between 1/ 2010 and 12/2016, any disease.
Viral part overlaps with IN1701 study.

Comments from the committee:

- We can use the same population of ongoing CIBMTR study IN1701, but look at bacterial and fungal infection only.
- GVHD and infection are competing risks
- Add ATG

b. **PROP 1710-06** Posa v Vori prophylaxis in patients with Allo HCT
Hypothesis: Both voriconazole and posaconazole are equally effective in preventing invasive fungal infections (IFI) post SCT.
The primary outcome is incidence of proven/probable invasive fungal infection (IFI) within 180 days. The secondary outcomes are; Proven/probable Invasive aspergillosis (IA); Proven invasive candidiasis (IC); OS, NRM; Need other IV antifungal therapy within 180 days; Cost.

Numbers are given for patients that received one of these agents as a single agent, assuming it has been prophylaxis,

Comments from the committee:

- The treatment data, cost information and diagnosis information are not available. Limited information on prophylaxis, diagnosis, and treatment are now captured on the current fungal forms released in Spring 2017.

c. **PROP1711-57** Incidence and impact of C diff infection by day 100 on allo HCT outcomes
Dr. Muthalagu Ramanathan presented the proposal.
C Diff infection is very common after SCT due to use of prophylactic antibiotics. Incidence, risk

factors and impact C diff has on transplant outcomes has not been clearly defined.
Hypothesis of the proposal is C diff infection increases risk of acute and chronic (GVHD) of gut and slows recovery leading to increased TRM in the elderly. The objective of the proposal is to determination of incidence and impact of C diff on transplant outcomes will further help develop strategies for prevention and treatment of C diff post-transplant.
The primary outcome is TRM based on C diff. The secondary outcomes are OS, Relapse, the incidence, time of onset, and severity of acute GVHD, chronic GVHD especially gut.
Eligible population: Allo HSCT 2010 - 2016.

Comments from committee:

- Patients age 2 and younger have different lack the receptor for C difficile infection and should be excluded.
- Limitations regarding lack of diagnostic testing used (PCR vs other) so should consider limited to more recent years
- Consider querying centers for year of HCT and C difficile testing method. This may be a better approach if limit to centers with a large number of patients (>20)
- Consider adding a control group (only patients from the same centers as cases)
- Consider adding frequency of bacterial BSI as an outcome

d. **PROP1711-74** Allogeneic hematopoietic cell transplantation is a feasible and effective treatment option for HIV positive patients with advanced hematological disorders.
Dr. Akash Mukherjee presented the proposal.
Hypothesis : Allo-HCT is a feasible treatment option for HIV positive patients with outcome similar to non HIV patients. Eligible patients are all patients age 18 years or more with HIV infection and had an Allo-HCT at a CIBMTR center between 2008 – 2016.
Study Aims are: Report the outcomes of allo-HCT for HIV infected patients; Report outcomes of patients based on their pre-transplant disease status and HIV status; Compare the clinical outcome between HIV infected and non HIV infected cohort; Identify patient-, disease- and transplant-factors that can predict survival and/or disease progression/relapse after HSCT.

Comments from Committee:

- Optimal analysis is comparison with HIV patients not receiving HCT
- Add disease risk index, GVHD and chimerism
- Concerns that 17 patients in the cohort of 39 are already reported in the outcomes of BMT CTN 0903

Dropped proposed studies

These proposals were not discussed during the meeting.

a. **PROP1710-13** Comparion of Cipro vs Levo in patients with AlloHCT. *Dropped due to feasibility-the data just started being requested Jan 2017*.
b. **PROP1711-17** Changing epidemiology of invasive pneumoccal infx since PCV vaccines. *Dropped due to feasibility –We do not have the data to answer these questions.*
c. **PROP1711-62** risk of CMV reactivation in Haplo patients with PTCY. *Dropped due to overlaps with ongoing study IN1701*
d. **PROP1711-73** Association between respiratory viral infection and rates of GVHD by 2 years

after HCT. *Dropped due to feasibility*

e. **PROP1711-76** Impact of TMP/SMX prophy on rates of bacterial infection and NRM following allogeneic HCT. *Dropped due to feasibility-no data for duration of prophylaxis.*

6. Other Business

Dr. Marcie Riches talked about Immune Reconstitution data issue.
We looked at CD4 counts at 100 days in all allogeneic HCT patients by center. 42(442 patients) out of 272 centers never obtained any lymphocyte subset analysis. Only 29 (1420 patients) centers report 75% or more of obtained data. It is unclear if low reporting occurs because the data managers for reporting do not understand/recognize the data. Dr. Riches suggested the committee talk with their lead data manager for education and encourage them to report the immune reconstitution data.

Comments from the committee for future immune reconstitution studies:

- Include centers who report immune reconstitution data more than 60%.

Working Committee Overview Plan for 2018-2019

a. IN07-01/IN11-01 Early bacterial infection in patients undergoing allogeneic HCT (C Ustun /J-A Young/M Robien/G Papanicolaou).

i. **VEP vs LEP BSI:** Has been submitted to BBMT in January 2018. We anticipate the paper is published by April 30, 2018. (Hour to completion: 0; Allocated by Jun 30, 2018: 0)

ii. **VRE vs Other BSI:** Plan to submit to Blood by April 30 2018. We anticipate the paper is published by June 30, 2018. (Hour to completion: 30; Allocated by Jun 30, 2018: 30)

b. IN 13-01 Bacterial and fungal infections in patients undergoing allogeneic hematopoietic cell transplantation following nonmyeloablative and myeloablative regimens (C Usten). Plan to submit to BBMT by Jun 30 2018. We anticipate paper is published by June 30, 2018. (Hour to completion: 50; Allocated by Jun 30, 2018: 50)

c. IN 14-01 (PROP 1303-03/PROP1311-19): Post allogeneic hematopoietic transplant Epstein Barr Virus related lymphproliferative disorder following conditioning with antithymocyte globulin or alemtuzumab (R Kamble/ P Hari/S Naik /C Bachier/P Shaughnessy). We anticipate paper is submitted by April 30, 2018

(Hour to completion: 30; Allocated by Jun 30, 2018: 30)

d. IN16-01 Viral encephalitis in hematopoietic stem cell transplant recipients, 2007-2013 (Maheen Abidi/ Parameswaran Hari) (PROP1510-16). We anticipate paper is published by May 30 2018. (Hour to completion: 30; Allocated by Jun 30, 2018: 30)

e. IN16-02 Determination of the burden of mucosal barrier injury-laboratory confirmed bloodstream infections in the first 100 days after stem cell transplant (Christopher Dandoy/ Paulina Daniels) (PROP 1511-85). We anticipate receiving the paper for submission by June 30, 2019. (Hour to completion: 200; Allocated by Jun 30, 2019: 200)

f. **IN17-01** Incidence and Outcomes of individuals with and without viral infections in recipients of haploidentical versus other allogeneic hematopoietic stem cell transplantation for patients with hematologic malignancies (Rizwan Romee/ Ephraim Fuchs/ Asad Bashey/ Stefan Ciurea/ Anurag Singh/ Siddhartha Ganguly/ Randy Allison Taplitz/ Carolyn Mulroney/ Richard Maziarz). We anticipate data file preparation by June 30, 2019. (Hour to completion: 290; Allocated by Jun 30, 2019: 220)

g. **IN18-01** Comparison of Early (d100) Infections after Haplo HCT between patients receiving Cy-based vs other GVHD prophylaxis (Genovefa Papanicolaou/Celalettin Ustun)(PROP1707-01). We anticipate finishing data file preparation by June 30, 2019. (Hour to completion: 290; Allocated by Jun 30, 2019: 110)

h. **IN18-02** Study the Incidence, and impact of C diff infection within 100 days on Transplant outcomes after allogeneic stem cell transplant (Muthalagu Ramanathan/ Bipin Savani)(PROP1711-57). We anticipate finishing data file preparation by June 30, 2019. (Hour to completion: 290; Allocated by Jun 30, 2019: 160)

Work Assignments for Working Committee Leadership (March 2018)	
Jeffery Auletta	**IN07-01/IN11-01**: Early bacterial infection in patients undergoing allogeneic HCT
Caroline Lindemans	**IN13-01** Bacterial and fungal infections in patients undergoing allogeneic hematopoietic cell transplantation following non- myeloablative and myeloablative regimens.
Jeffery Auletta	**IN14-01** Post allogeneic hematopoietic transplant Epstein Barr Virus related lymphproliferative disorder following conditioning with antithymocyte globulin or alemtuzumab (R Kamble/ P Hari/S Naik /C Bachier/P Shaughnessy)
Krishna Komanduri	**IN16-01** Viral encephalitis in hematopoietic stem cell transplant recipients, 2007-2013 (Mhaeen Abidi/ Parameswaran Hari)
Caroline Lindemans and Jeffery Auletta	**IN16-02** Determination of the burden of mucosal barrier injury-laboratory confirmed bloodstream infections in the first 100 days after stem cell transplant (Christopher Dandoy/ Paulina Daniels)
Caroline Lindemans and Krishna Komanduri	**IN17-01** Incidence and Outcomes of individuals with and without viral infections in recipients of haploidentical versus other allogeneic hematopoietic stem cell transplantation for patients with hematologic malignancies(Rizwan Romee/ Ephraim Fuchs/ Asad Bashey/ Stefan Ciurea/ Anurag Singh/ Siddhartha Ganguly/ Randy Allison Taplitz/ Carolyn Mulroney/ Richard Maziarz). (PROP 1611-02/1611-117/1611-134)
Miguel-Angel Perales	**IN18-01** Comparison of Early (d100) Infections after Haplo HCT between patients receiving Cy-based vs other GVHD prophylaxis (Genovefa Papanicolaou/Celalettin Ustun)(PROP1707-01).
Caroline Lindemans	**IN18-02** Study the Incidence, and impact of C diff infection within 100 days on Transplant outcomes after allogeneic stem cell transplant (Muthalagu Ramanathan/ Bipin Savani)(PROP1711-57).

Accrual Summary for Infection and Immune Reconstitution Working Committee
Donor-recipient and Infection information reported to the CIBMTR between after 2008

Variable	Allogeneic N(%)	Autologous N(%)
Number of Patients	27290	11842
Infection		
Donor/recipient CMV status		
-/-	7141 (26)	N/A
+/-	2606 (10)	
-/+	8518 (31)	
+/+	8520 (31)	
Missing/not tested	505 (2)	
Donor/recipient hepatitis B status		
-/-	8816 (32)	N/A
+/-	260 (<1)	
-/+	2263 (8)	
+/+	205 (<1)	
-/?	134 (<1)	
+/?	5 (<1)	
?/-	12451 (46)	
?/+	2870 (11)	
Both missing	286 (1)	
Donor/recipient hepatitis C status		
-/-	15517 (57)	N/A
+/-	69 (<1)	
-/+	155 (<1)	
+/+	6 (<1)	
-/?	42 (<1)	
?/-	9974 (37)	
?/+	116 (<1)	
Both missing	1411 (5)	
Fungal Infection history		
No	25120 (92)	11720 (99)
Yes	2141 (8)	120 (1)
Missing	29 (<1)	2 (<1)
Fungal Infection after starting of conditioning		
No	21476 (79)	10491 (89)
Yes	5527 (20)	829 (7)
Missing	287 (1)	522 (4)

Variable	Allogeneic N(%)	Autologous N(%)
Infection prophylaxis after starting of conditioning		
No	342 (1)	213 (2)
Yes	26268 (96)	11032 (93)
Missing	680 (2)	597 (5)
Immune Reconstitution		
IgG at 100 day		
Data not available	9638 (35)	4554 (38)
Data available	17652 (65)	7288 (62)
IgM at 100 day		
Data not available	17998 (66)	5349 (45)
Data available	9292 (34)	6493 (55)
IgA at 100 day		
Data not available	17993 (66)	5294 (45)
Data available	9297 (34)	6548 (55)
CD3 at 100 day		
Lymphocyte analyses were not performed	15725 (58)	10740 (91)
Data not available	4618 (17)	473 (4)
Data available	6947 (25)	629 (5)
CD4 at 100 day		
Lymphocyte analyses were not performed	15725 (58)	10740 (91)
Data not available	4685 (17)	459 (4)
Data available	6880 (25)	643 (5)
CD8 at 100 day		
Lymphocyte analyses were not performed	15725 (58)	10740 (91)
Data not available	4855 (18)	500 (4)
Data available	6710 (25)	602 (5)
CD20 at 100 day		
Lymphocyte analyses were not performed	15725 (58)	10740 (91)
Data not available	9781 (36)	979 (8)
Data available	1784 (7)	123 (1)
CD56 at 100 day		
Lymphocyte analyses were not performed	15725 (58)	10740 (91)
Data not available	7062 (26)	839 (7)
Data available	4503 (17)	263 (2)
Infection Prophylaxis		
Antibiotics		
No	7548 (28)	3227 (27)
Yes	19714 (72)	8604 (73)

Variable	Allogeneic N(%)	Autologous N(%)
Missing	28 (<1)	11 (<1)
Amoxicillin clavulanate oral (Augmentin)(after 2017)		
No	3274 (94)	1732 (96)
Yes	83 (2)	21 (1)
Missing	113 (3)	54 (3)
Cefdinir oral (Omnicef)(after 2017)		
No	3345 (96)	1724 (95)
Yes	12 (<1)	29 (2)
Missing	113 (3)	54 (3)
Cefpodoxime oral (Vantin)(after 2017)		
No	3348 (96)	1746 (97)
Yes	9 (<1)	7 (<1)
Missing	113 (3)	54 (3)
Ciprofloxacin IV or oral (Cipro)(after 2017)		
No	2685 (77)	1442 (80)
Yes	672 (19)	311 (17)
Missing	113 (3)	54 (3)
Ertapenem IV(after 2017)		
No	3352 (97)	1751 (97)
Yes	5 (<1)	2 (<1)
Missing	113 (3)	54 (3)
Levofloxacin IV or oral (Levaquin)(after 2017)		
No	2160 (62)	783 (43)
Yes	1197 (34)	970 (54)
Missing	113 (3)	54 (3)
Moxifloxacin IV or oral (Avelox)(after 2017)		
No	3292 (95)	1724 (95)
Yes	65 (2)	29 (2)
Missing	113 (3)	54 (3)
Vancomycin IV(after 2017)		
No	3142 (91)	1667 (92)
Yes	215 (6)	86 (5)
Missing	113 (3)	54 (3)
Other antibacterial drug(after 2017)		
No	2735 (79)	1479 (82)
Yes	622 (18)	274 (15)
Missing	113 (3)	54 (3)

Variable	Allogeneic N(%)	Autologous N(%)
Antifungal agent		
No	9469 (35)	6650 (56)
Yes	17794 (65)	5181 (44)
Missing	27 (<1)	11 (<1)
Amphotericin		
No	25277 (93)	11548 (98)
Yes	1675 (6)	72 (<1)
Missing	338 (1)	222 (2)
Caspofungin		
No	25697 (94)	11560 (98)
Yes	1255 (5)	60 (<1)
Missing	338 (1)	222 (2)
Fluconazole		
No	17333 (64)	6752 (57)
Yes	9619 (35)	4868 (41)
Missing	338 (1)	222 (2)
Itraconazole		
No	26526 (97)	11575 (98)
Yes	426 (2)	45 (<1)
Missing	338 (1)	222 (2)
Micafungin		
No	23118 (85)	11465 (97)
Yes	3834 (14)	155 (1)
Missing	338 (1)	222 (2)
Posaconazole		
No	23816 (87)	11581 (98)
Yes	3135 (11)	39 (<1)
Missing	339 (1)	222 (2)
Ravuconazole		
No	26929 (99)	11615 (98)
Yes	23 (<1)	5 (<1)
Missing	338 (1)	222 (2)
Voriconazole		
No	20593 (75)	11441 (97)
Yes	6359 (23)	179 (2)
Missing	338 (1)	222 (2)
Other systemic antifungal agent		
No	26305 (96)	11537 (97)

Variable	Allogeneic N(%)	Autologous N(%)
Yes	675 (2)	83 (<1)
Missing	310 (1)	222 (2)
Antiviral agent		
No	4701 (17)	1638 (14)
Yes	22562 (83)	10193 (86)
Missing	27 (<1)	11 (<1)
Acyclovir		
No	8507 (31)	3022 (26)
Yes	18471 (68)	8588 (73)
Missing	312 (1)	232 (2)
Foscarnet		
No	26268 (96)	11584 (98)
Yes	709 (3)	26 (<1)
Missing	313 (1)	232 (2)
Ganciclovir		
No	25437 (93)	11572 (98)
Yes	1541 (6)	38 (<1)
Missing	312 (1)	232 (2)
Valganciclovir		
No	25105 (92)	11498 (97)
Yes	1873 (7)	112 (<1)
Missing	312 (1)	232 (2)
Valacyclovir		
No	21120 (77)	9220 (78)
Yes	5858 (21)	2390 (20)
Missing	312 (1)	232 (2)
Other antiviral agent		
No	26164 (96)	11446 (97)
Yes	813 (3)	164 (1)
Missing	313 (1)	232 (2)
Pneumocystis agent		
No	3333 (12)	4366 (37)
Yes	23797 (87)	7176 (61)
Missing	160 (<1)	300 (3)
Other prophylaxis agent(Before 2017)		
No	19369 (81)	8267 (82)
Yes	2774 (12)	742 (7)
Missing	1677 (7)	1026 (10)

Variable	Allogeneic N(%)	Autologous N(%)
Disease		
Acute Leukemia/MDS	19718 (72)	172 (1)
Chronic Leukemia	834 (3)	0
Non-Hodgkin Lymphoma	1618 (6)	2834 (24)
Hodgkin Lymphoma	137 (<1)	872 (7)
Solid tumors	22 (<1)	827 (7)
Myeloma/Plasma Cell Disorder	149 (<1)	7059 (60)
Non-malignant disorders	4812 (18)	78 (<1)
Year of transplant		
2008	3258 (12)	2195 (19)
2009	2996 (11)	931 (8)
2010	1859 (7)	414 (3)
2011	1344 (5)	494 (4)
2012	1433 (5)	532 (4)
2013	2664 (10)	1192 (10)
2014	3523 (13)	1282 (11)
2015	3508 (13)	1468 (12)
2016	3235 (12)	1527 (13)
2017	2824 (10)	1350 (11)
2018	646 (2)	457 (4)

IN16-02 ASH Abstract

Title: Burden and outcomes of mucosal barrier injury-laboratory confirmed bloodstream infections (MBI-LCBI) in the first 100 days after allogeneic stem cell transplant: A CIBMTR Analysis

Background: Patients undergoing stem cell transplant (SCT) are at risk of bloodstream infections (BSI). BSI led to prolonged hospitalization, intensive care admissions, prolonged antibiotic treatment and increased mortality. Recently, the Centers for Disease Control and Prevention developed a modification of the Central line associated bloodstream infection (CLABSI) definition, termed "mucosal barrier injury laboratory-confirmed bloodstream infection" (MBI-LCBI) to differentiate BSI likely related to mucosal barrier injury. BSI are identified as an MBI-LCBI if: (1) it resulted from 1 or more of a group of selected organisms known to be commensals of the oral cavity or gastrointestinal tract and (2) occurred in a patient with signs or symptoms compatible with the presence of mucosal barrier injury such as gastrointestinal graft-versus-host disease and/or neutropenia. We utilized the CIBMTR database to determine the incidence and timing of MBI-LCBI, risk factors for development of MBI-LCBI, and compare transplant outcomes by 1 year after SCT.

Methods: We identified 16,875 pediatric and adult patients receiving first allogeneic transplant from 2009-2016. Patients were classified into 4 categories based on the occurrence of BSI in first 100 days: MBI-LCBI (n=1434; 8.5%), MBI-LCBI +other BSI (n=700; 4.1%), BSI only (n=3016; 17.8%), and control (n=11725; 69.5%) (Figure 1). Demographics and outcomes, including overall survival (OS), chronic GVHD, and transplant-related mortality (TRM, for malignant disease patients only), were compared between groups.

Results: The cumulative incidence of MBI-LCBI was 13% (99% CI: 12-13%) by day 100 whereas the probability for another BSI not meeting MBI-LCBI criteria was 22% (99% CI: 21-23%) by day 100. The median time from transplant to first MBI-LCBI was 8 days (<1-98), MBI-LCBI + other BSI 10 days (<1-99), and other BSI was 38 days (<1-100). Karnofsky/Lansky performance status <90 [RR 1.21 (99% CI: 1.06 – 1.38)], myeloablative conditioning [RR 1.45 (99% CI: 1.27-1.69)], post-transplant cyclophosphamide as GVHD prophylaxis [RR 1.83 (99% CI: 1.40 – 2.39)], and receipt of cord blood [RR 2.89 (99% CI: 2.06 – 4.06)] were associated with a significant increase in the risk of MBI-LCBI (Table 1). The 1 year OS was inferior for patients with MBI-LCBI only [59% (99% CI: 56 – 61%); RR 1.86 (99% CI: 1.65 – 2.09)], Other BSI only [60% (99% CI: 58 – 63%); RR 1.86 (99% CI: 1.70 – 2.04)], and MBI-LCBI + Other BSI [46% (99% CI: 41 – 50%); RR 2.79 (99% CI: 2.42 – 3.23)] compared to controls [72% (71 – 73); p <0.0001] (Table 2). There was no impact of MBI-LCBI only, Other BSI only, or MBI-LCBI + Other BSI compared to controls on development of chronic GVHD. As expected 1 year TRM in patients with malignant disease was increased with any BSI but was similar for patients with MBI-LCBI only [30% (99% CI: 27 – 34%); RR 2.41 (99% CI: 2.05-2.82] or Other BSI [25% (99% CI: 23 – 27%); RR 2.20 (1.94 – 2.51)] and further worsened for patients with both MBI-LCBI + Other BSI [45% (99% CI: 39 – 50%); RR 4.23 (3.53 – 5.07)] compared to controls [16% (99% CI:15 – 17%)]. Finally, infection as a cause of mortality was higher in patients with MBI-LCBI (19%), BSI only (17%), and MBI-LCBI + BSI (21%) then controls (12%).

Discussion: Our data demonstrate approximately 13% of all patients develop at least one MBI-LCBI and an additional 22% of patients develop another BSI in the first 100 days post SCT. Multivariable analysis revealed increased risk of MBI-LCBI with poor performance status, cord blood grafts, myeloablative conditioning, and post-transplant cyclophosphamide GVHD prophylaxis. BSI, whether or not MBI-LCBI, significantly decreases overall survival, primarily related to an increased TRM. The combination of MBI-LCBI and other BSI worsens both TRM and OS, but the respective impact of MBI-LCBI only was similar to Other BSI only. BSI, both MBI-LCBIs and other BSI, lead to significant morbidity and mortality and

healthcare resource utilization. Reduction in frequency of BSI should be a major public health and scientific priority.

Table 1: Variables associated with MBI-LCBI

			99% CI	99% CI		
Variables	**N**	**RR**	**Lower Limit**	**Upper Limit**	**p-value**	**overall p-value**
Karnofsky performance Status						0.0011
>=90	8568	1.00				
<90	5095	1.21	1.06	1.38	0.0002	
Missing	202	1.05	0.64	1.72	0.7888	
Conditioning regimen intensity						
RIC/NMA	5243	1.00				<.0001
Myeloablative	8622	1.45	1.27	1.69		
GVHD prophylaxis						<.0001
TAC/CSA + MTX +/- others	6474	1.00				
TAC/CSA + MMF +/- others	4453	0.83	0.69	1.00	0.0091	
TAC/CSA +/- others (except MTX, MMF)	1442	0.82	0.65	1.04	0.0354	
CD34 selection/ex vivo TCD	314	1.33	0.90	1.99	0.0628	
Cyclophosphamide	1009	1.83	1.40	2.39	<.0001	
Other GVHD prophylaxis	173	0.66	0.35	1.26	0.0989	
Graft type & Donor type						<.0001
Matched related Bone Marrow	644	1.00				
Mismatched related Bone Marrow	251	1.05	0.62	1.79	0.8075	
8/8 unrelated Bone Marrow	941	1.09	0.74	1.61	0.5601	
Mismatched unrelated Bone Marrow	221	1.47	0.86	2.51	0.0638	
Matched related Peripheral blood	3275	0.92	0.66	1.28	0.5003	
Mismatched related Peripheral blood	392	1.17	0.75	1.85	0.3614	
8/8 unrelated Peripheral blood	4049	0.88	0.63	1.23	0.3214	
Mismatched unrelated Peripheral blood	861	1.11	0.75	1.66	0.4894	
Cord blood	2731	2.89	2.06	4.06	<.0001	
missing	500	0.83	0.52	1.33	0.3133	

Table 2: Multivariate analysis of overall survival in all patients (n=16,875)

			99% CI	99% CI		
Variables	**N**	**RR of death**	**Lower Limit**	**Upper Limit**	**p-value**	**overall p-value**
Main effect						<.0001
Control	11725	1.00				
MBI-LCBI only	1434	1.86	1.65	2.09	<.0001	
Other BSI only	3016	1.86	1.70	2.04	<.0001	
MBI-LCBI and other BSI	700	2.79	2.42	3.23	<.0001	
Age at transplant, years						<.0001
<=20	4691	1.00				
21-40	2658	1.17	1.02	1.35	0.0039	
41-60	4921	1.51	1.32	1.73	<.0001	
>=61	4605	1.77	1.53	2.04	<.0001	
Karnofsky performance Status						<.0001
>=90	10835	1.00				
<90	5766	1.35	1.25	1.45	<.0001	
Missing	274	1.36	1.04	1.79	0.0034	
HCT-CI						<0.0001
0	6074	1.00				
1 – 2	4309	1.07	0.97	1.19	0.0878	
3+	6251	1.38	1.26	1.52	<.0001	
Missing	241	0.79	0.54	1.14	0.0993	
Disease						<.0001
non-malignant	3009	1.00				
AML	6885	1.56	1.34	1.81	<.0001	
ALL	2523	1.33	1.12	1.56	<.0001	
MDS	4458	1.55	1.31	1.82	<.0001	
GVHD prophylaxis						<.0001
TAC/CSA + MTX +/- others	7581	1.00				
TAC/CSA + MMF +/- others	5392	1.21	1.10	1.33	<.0001	
TAC/CSA +/- others (except MTX, MMF)	2006	1.13	0.99	1.28	0.0147	
CD34 selection/ex vivo TCD	492	1.15	0.90	1.46	0.1449	
Cyclophosphamide	1147	1.16	0.98	1.37	0.0267	
Other GVHD prophylaxis	257	1.44	1.10	1.90	0.0006	
ATG or Campath						<.0001
No	10510	1.00				

Yes	6365	1.17	1.07	1.27		
Year of transplant						<.0001
2009-2011	5006	1.00				
2012-2014	6355	0.88	0.80	0.96	0.0001	
2015-2016	5514	0.83	0.75	0.91	<.0001	
Graft type & Donor type						
Matched related Bone Marrow	1395	1.00				<.0001
Mismatched related Bone Marrow	315	1.24	0.89	1.71	0.0950	
8/8 unrelated Bone Marrow	1460	1.20	0.96	1.51	0.0319	
Mismatched unrelated Bone Marrow	374	1.57	1.16	2.12	0.0001	
Matched related Peripheral blood	3494	1.14	0.93	1.39	0.0993	
Mismatched related Peripheral blood	486	1.40	1.06	1.85	0.0021	
8/8 unrelated Peripheral blood	4172	1.07	0.88	1.31	0.3633	
Mismatched unrelated Peripheral blood	922	1.44	1.14	1.82	0.0001	
Cord blood	3627	1.53	1.25	1.87	<.0001	
missing	630	1.47	1.14	1.89	0.0001	
aGVHD grade 2-4						
No	10536	1.00				<.0001
Yes	6339	1.56	1.45	1.68		

Figure 1: Bloodstream infection classification

Figure 1: Bloodstream infection classification

1. MBI-LCBI Group: At least 1 MBI-LCBI.
Causative organism is a commensal of the oral cavity or gastrointestinal tract (e.g., enterococcus)
and
Occurs 14 days before or 60 days after Stage 3 or 4 GI acute GVHD
or
Infection occurs and ANC criteria met:
- ANC >500 never achieved
- Before ANC ≥ 500 or 7 days after ANC ≥ 500

2. BSI Other Group: At least one BSI that is not-classified as an MBI-LCBI
Any fungal or bacteria in blood by 100 days after transplant which is not in MBI-LCBI organisms

3. MBI-LCBI and BSI Group: At least one MBI-LCBI and BSI other

4. Control Group: All allogeneic transplant with no infection documented

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TO: Infection and Immune Reconstitution Working Committee Members

FROM: Marcie Riches, MD, MS, Scientific Director for the Infection and Immune Reconstitution Working Committee

RE: Studies in Progress Summary

Studies submitted

IN14-01: Post allogeneic hematopoietic transplant Epstein Barr Virus related Lymphoproliferative disorder following conditioning with Antithymocyte globulin or Alemtuzumab (S Naik/ C Bachier/ P Shaughnessy/ P Hari/ R Kamble) This study describes the characteristics and transplant outcomes of patients with EBV-positive and EBV negative PTLD following allogeneic transplant Between 2002 and 2014, 432 cases of PTLD following alloHCT were reported to the Center for International Blood and Marrow Transplant Research (CIBMTR). After excluding confounding variables, 267 cases (EBV^{pos} = 222, 83%; EBV^{neg} = 45, 17%) were analyzed. Two-hundred and eight patients (78%) received in vivo T-cell depletion (TCD) with either anti-thymocyte globulin (ATG) or alemtuzumab. Incidence of PTLD was highest using umbilical cord donors (UCB, 1.60%) and lowest using matched related donors (MRD, 0.40%). Clinical features and histology did not significantly differ among EBV^{pos} or EBV^{neg} PTLD cases except that absolute lymphocyte count recovery was slower and CMV reactivation was later in EBV^{neg} PTLD [EBV^{pos} 32 (5 – 95) days versus EBV^{neg} 47 (10 – 70) days, p=0.016]. There was no impact on survival by EBV-status in multivariable analysis [EBV^{neg} RR 1.42, 95% CI 0.94-2.15, p = 0.097], although features of conditioning and use of serotherapy remained important. **Submitted.**

Studies with Preliminary Results

IN13-01: Bacterial, viral and fungal infections in patients undergoing allogeneic hematopoietic cell transplantation (Allohct) following nonmyeloablative and myeloablative (C Ustun) This study compares infections between patients undergoing allogeneic hematopoietic cell transplantation (AlloHCT) following NMA/RIC (n=777), and MAC (n=978). Patients receiving NMA/RIC were older and transplanted more recently. The groups were similar regarding KPS, HCT-CI, and cytogenetic risk; however, patients receiving NMA/RIC had more frequent preceding myelodysplastic syndrome (MDS). Infections were common with 1045 patients [MAC = 595 (61%), NMA/RIC = 450 (58%); p = 0.21)] experiencing at least one infection. Patients receiving MAC had a greater probability of developing a bacterial infection by day 100 [MAC 46% (95% CI, (43 – 49); NMA/RIC 37% (34 – 41); p=0.0004], whereas viral infections predominated in the NMA/RIC cohort [MAC 34% (31 – 37); NMA/RIC 39% (36 – 42); p=0.046]. Fungal infection incidence was similar between the MAC and the NMA/RIC groups. Manuscript preparation is underway. Plan to submit by March 2019.

IN16-02: Determination of the burden of mucosal barrier injury-laboratory confirmed bloodstream infections (MBI-LCBI) in the first 100 days after stem cell transplant (C Dandoy/ P Daniels). This study compares TRM and OS post-SCT between patients who develop a MBI-LCBI versus those with no infection or a non-MBI-LCBI in the first 100 days with additional endpoints of MBI-LCBI incidence, onset, and risk factors. The cumulative incidence of MBI-LCBI was 13% and BSI-other 21% by day 100. Median time from transplant to first MBI-LCBI was 8 days. Multivariable analysis revealed increased risk of MBI-

LCBI with poor performance status [RR 1.21(99% CI:1.06–1.38)], cord blood unit grafts [RR 2.89(99% CI:2.07–4.04)], myeloablative conditioning [RR 1.46(99% CI:1.26-1.68)], and post-transplant cyclophosphamide graft versus host disease prophylaxis [RR 1.85(99% CI:1.42–2.40)]. One year overall survival was significantly inferior for patients with MBI-LCBI only [59% (99% CI:56–62%); RR 1.81(99% CI:1.61–2.04)], BSI-other only [60%(99% CI:58–62%); RR 1.81 (99% CI: 1.66 – 1.99)], and MBI-LCBI +BSI-other [46% (99% CI: 41–51%); RR 2.65 (99% CI: 2.29 – 3.06)] compared to controls [72% (71 – 73); p <0.0001]. Infection was more likely to be reported as a cause of death in patients with MBI-LCBI (19%), BSI only (16%), and MBI-LCBI + BSI (21%) then controls (12%). Manuscript preparation is underway. Plan to submit by May 2019.

Studies in Progress

IN17-01: Incidence and impact of cytomegalovirus and other viral infections on post-transplant outcomes following HLA-haploidentical HCT compared to other sources (R Romee/ A Singh/ RA Taplitz). This is a combined study from 2 different proposals and will include 3 separate analyses examining 1) the impact of donor/recipient CMV serostatus following Haploidentical transplant with and without post-transplant cyclophosphamide; 2) the impact of CMV reactivation on transplant outcomes for patients receiving Haploidentical transplant; and 3) describe the frequency of other, non-CMV viral infections comparing haploidentical, matched adult donor, and UCB donors. The study is under data file preparation. The goal of this study is to have analysis completed and initiate manuscript preparation by June 2019.

IN18-01 Comparison of early (by day 100) infections after haploidentical HSCT between patients receiving cyclophosphamide-based or other GVHD prophylaxis (Celalettin Ustun/Genovefa Papanicolaou) The study protocol is under development. The goal of this study is to finalize the dataset by June 2019.

IN18-02 The Incidence, and impact of Clostridium difficile infection within 100 days on Transplant outcomes after allogeneic stem cell transplant (Muthalagu Ramanathan/ Bipin Savani/ Celalettin Ustun) The study protocol is under development. The goal of this study is to finalize the dataset by June 2019.

CIBMTR IN17-01

Incidence and impact of cytomegalovirus and other viral infections, on post-transplant outcomes following HLA-haploidentical hematopoietic cell transplantation compared to fully matched related donors.

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1.0 Hypothesis:

We hypothesize that the viral infection incidence and impact on transplant outcomes differ between fully matched related donor transplants (MRD) and Haploidentical (HaploHCT) transplants with further differences associated with use of post-transplant cyclophosphamide (PTCy).

2.0 Specific aims:

2.1 Assess the impact of donor/recipient CMV serostatus on transplant outcomes

- 2.1.1 Relapse
- 2.1.2 Non-relapse mortality
- 2.1.3 GVHD
- 2.1.4 DFS
- 2.1.5 OS

2.2 Assess the impact of CMV reactivation occurring by day 180 on transplant outcomes

- 2.2.1 Relapse
- 2.2.2 Non-relapse mortality
- 2.2.3 DFS
- 2.2.4 OS

2.3 Describe the frequency and identify risk factors for development of other viral infections

3.0 Scientific impact/ justification:

Cytomegalovirus has long been associated with increased morbidity and mortality following allogeneic hematopoietic cell transplantation (alloHCT).[1–3] A recent CIBMTR analysis demonstrated that even in the current era of preemptive surveillance and treatment protocols, early CMV reactivation was associated with significantly increased non-relapse mortality (NRM) among recipients of alloHCT for AML, ALL, MDS, and CML, which translated to decreased overall survival (OS) among those with AML and ALL.[4] The association of CMV reactivation and improvement in relapse-free survival (RFS) is a well-published phenomenon among patients who received HLA-matched alloHCT for hematologic malignancies, however this CIBMTR study failed to identify any effect of CMV reactivation on relapse.[5,6,4,7]

This registry study was incredibly impactful, however Haploidentical hemaotpoeitic cell transplantation (haploHCT) were underrepresented, and less than 1% of all patients from the registry had received post-transplant cyclophosphamide (PTCy) for GVHD prophylaxis. This is likely due to the fact that the records utilized in this registry study were of those who underwent alloHCT prior to 2010, and the utilization of haploHCT has really only accelerated on an international level over the past five years.[8,9]

It is unknown if there are differences in the incidence of CMV reactivation and disease among recipients of haploHCT with PTCy in comparison to other non haplo alloHCT (MRD, MUD, and UCB) and haploHCT

receiving other GVHD prophylaxis. Identification of a higher incidence of disease and/ or earlier reactivation would allow design of more aggressive CMV surveillance and preemptive treatment protocols better suited to the specific immunosuppressive aspects of haploHCT with PTCy. Additionally, determination if CMV reactivation has any effect on relapse and mortality especially in the context of haploHCT, which would help provide prognostic information.

Recently we conducted a single-center, retrospective cohort study out of Washington University in St. Louis on 138 patients who underwent haploHCT with PTCy, receiving T-cell replete PBSC grafts, and did not detect a significant difference in cumulative incidence of relapse (CIR) or overall survival (OS) between those who did and those who did not have CMV viremia.[10] Notably, our viremia cohort experienced very early CMV viremia (median time to viremia of 24d), and an incidence of CMV disease that was higher than expected in the era of preemptive antiviral strategies. A large, registry study with similar endpoints would assess the validity of these results, and identify whether there is fundamental difference between HLA-haploidentical and other allogeneic transplantation, or a factor related to PTCy, that would predispose haploHCT with PTCy recipients to a higher risk of CMV disease and negate the relapse protection seen previously with CMV reactivation. Such results could lead to tailoring of preemptive treatment strategies and aid in prognosis of disease relapse.

In addition to CMV, we aim to describe the incidence of other viral infections, their specific end-organ effects, and their impact on relapse and mortality outcomes in recipients of haploHCT with PTCy in comparison to non-PTCy haploHCT and other alloHCT (MRD, MUD, and UCB). An understanding of the occurrence of these viruses will help identify specific risk factors following haploHCT as well as aid in the design of specific surveillance and treatment protocols tailored to this unique population.

High rates of viral infections in general have been reported after haploHCT, particularly in the setting of PTCy. There have been a few single-center studies describing the incidence of viral infections following haploHCT with PTCy, but multicenter, comparative data is lacking. Infection rates in this setting have been reported in the range of 70% at 100 days and 77% at 1 year for viral infections. CMV reactivation has been reported in up to 76% of recipients, and polyomavirus associated cystitis 19%. The CIBMTR database provides an ideal opportunity to take a broader look at viral infections after haploidentical transplants, particularly in recipients of PTCy, and identify the burden of viral and other infectious diseases, risk factors and outcomes.

4.0 Study population:

Inclusion Criteria:

- Patients receiving first allogeneic HCT for AML, ALL, and MDS between 2008 – 2016
- Age ≥ 2 years

Exclusion Criteria:

- Patients who received UCBT
- Patients receiving an unrelated donor
- Patients with only a single mismatch related donor
- Patient information that lacks post-transplant infection information

- Center restriction: Patients transplanted at centers which have no reported haploHCT patients

Patient cohorts for the general population are as follows:

1) HaploHCT with PTCy
2) HaploHCT with other GVHD prophylaxis
3) MRD with PTCy
4) MRD with other GVHD prophylaxis (Control)

5.0 Outcomes

5.1 CMV Serostatus analysis

- Relapse: death is the competing risk.
- Overall survival: time to death. Death from any cause is an event. Surviving patients are censored at time of last follow-up.
- Disease Free survival: time to relapse or death from any cause.
- Non-relapse mortality: death without evidence of disease relapse**.** Relapse is the competing risk**.**
- aGVHD grade 2 – 4: Death is the competing risk
- cGVHD, any severity: Death is the competing risk
- Total number of inpatient hospital days within first 100 days (LOS)

5.2 CMV Reactivation analysis

- Relapse: death is the competing risk.
- Overall survival: time to death. Death from any cause is an event. Surviving patients are censored at time of last follow-up.
- Disease Free survival: time to relapse or death from any cause.
- Non-relapse mortality: death without evidence of disease relapse**.** Relapse is the competing

5.3 Other Viral Infections

- Overall survival: time to death. Death from any cause is an event. Surviving patients are censored at time of last follow-up.
- Disease Free survival: time to relapse or death from any cause.
- Non-relapse mortality: death without evidence of disease relapse**.** Relapse is the competing risk**.**
- Relapse: death is the competing risk.

6.0 Variables to be described:

Patient related

- Patient age at transplant (in decades $\leq$ 10, 11-20, 21-30, 31-40, 41-50, 51-60, $\geq$ 60)

- Patient gender
- Patient race/ethnicity
- Karnofsky performance at transplant: <90% vs. ≥90%

Donor Related

- Donor age (in decades ≤ 10, 11-20, 21-30, 31-40, 41-50, 51-60, ≥ 60)
- Donor/recipient gender
- Donor/Recipient cmv serostatus

Disease/Transplant Related

- Disease
- Time from hematologic diagnosis to HCT
- Recipient HCT-CI
- Disease risk index (low vs intermediate vs high risk)
- Conditioning intensity (myeloablative vs. reduced-intensity/non-ablative)
- TBI-based conditioning (yes vs. no)
- GVHD prophylaxis
- Stem cell source (peripheral blood vs. marrow)
- Planned therapy with Growth factors (G-CSF or GM-CSF) post-transplant: yes vs. no (defined as day -3 to day +7)
- ATG/Alemtuzumab (yes vs no)

Cell counts

- Total nucleated cell dose (TNC)
- CD34 +/kg-bw
- CD3+/kg-bw cell doses
- Day 180 total white cell count
- Day 180 absolute lymphocyte count
- CD3 counts at day 100
- CD4 counts at day 100
- CD8 counts at day 100
- CD4:CD8 ratio at day 100
- CD3 counts at day 180
- CD4 counts at day 180
- CD8 counts at day 180
- CD4:CD8 ratio at day 180

Infection Related

- CMV reactivation by day 180: Yes/No
- Time to CMV reactivation from transplant
- Time to CMV end-organ disease at day 180

- Other viral infection by day 180: Yes/No
- Type of other viral infection (parainfluenza virus, influenza virus, RSV, adenovirus, hMPV, BK, EBV, HHV-6, VZV, and HSV)
- Time to other viral infection
- End-organ manifestations/viral disease versus viral detection only at 180 day
- Co-infection (yeast/mold/bacteria): Presence/absence of co-infection of any type ± 30 days of viral infection

Time dependent

- Time to neutrophil engraftment
- aGVHD grade II-IV: Yes/No
- cGVHD: Yes/No

7.0 Study design:

As noted, this study will have multiple analyses which will be performed separately using the same general cohort of patients.

- Analysis 1 CMV Serostatus analysis:
  Comparisons based upon donor/recipient CMV serostatus at time of transplant across the 4 cohorts
- Analysis 2 CMV Reactivation analysis: Comparisons based on the presence/absence of CMV reactivation occurring by day 180 post-transplant. This will be a landmark analysis starting at day 180
- Analysis 3: Non-CMV Viral infection analysis. Comparisons based on the presence/absence of any viral infection that is not just CMV only (i.e. CMV plus other viral infection = yes)

Analyses 1 and 2 will follow the previously published IN1201 study.

Patient-, disease- and transplant- related factors will be compared between groups using the Chi-square test for categorical variables and the Wilcox on two sample test for continuous variables. The probabilities of progression-free and overall survival will be calculated using the Kaplan Meier estimator, with the variance estimated by Greenwood's formula. For values for other endpoints, cumulative incidence estimates to account for competing risks will be calculated. Cox proportional hazards regression will be used for each outcome. The variables to be considered in the multivariable regression models are listed. The assumption of proportional hazards for each factor in the Cox model will be tested. When the proportional hazards assumption is violated, time-dependent variable will be added in the model. The stepwise variable selection method will be used to identify significant risk factors which associated with the outcomes. Factors significantly associated with the outcome variable at a 5% level will be kept in the final model. Interactions between main effect and significant covariates will be tested. Center effects will be tested.

8.0 References:

1. Ariza-Heredia EJ, Nesher L, Chemaly RF. Cytomegalovirus diseases after hematopoietic stem cell transplantation: A mini-review. Cancer Lett. 2014;342(1):1-8. doi:10.1016/j.canlet.2013.09.004.

2. Ljungman P, Hakki M, Boeckh M. Cytomegalovirus in hematopoietic stem cell transplant recipients. Infect Dis Clin North Am. 2010;24(2):319-337. doi:10.1016/j.idc.2010.01.008.
3. Mori T, Kato J. Cytomegalovirus infection/disease after hematopoietic stem cell transplantation. Int J Hematol. 2010;91(4):588-595. doi:10.1007/s12185-010-0569-x.
4. Teira P, Battiwalla M, Ramanathan M, et al. Early cytomegalovirus reactivation remains associated with increased transplant related mortality in the current era: a CIBMTR analysis. Blood. 2016;127(20):2427-2438. doi:10.1182/blood-2015-11-679639.
5. Elmaagacli AH, Steckel NK, Hegerfeldt Y, et al. Early Cytomegalovirus Replication After Allogeneic Stem Cell Transplantation Is Associated With a Decreased Relapse Risk in Acute Myeloid Leukemia Patients: Evidence for a Putative Virus-Versus-Leukemia Effect. Blood. 2011;118(5):1403-1412. doi:10.1016/j.bbmt.2010.12.034.
6. Takenaka K, Nishida T, Asano-Mori Y, et al. Cytomegalovirus Reactivation after Allogeneic Hematopoietic Stem Cell Transplantation is Associated with a Reduced Risk of Relapse in Patients with Acute Myeloid Leukemia Who Survived to Day 100 after Transplantation. Biol Blood Marrow Transplant. 2015;21(11):2008-2016. doi:10.1016/j.bbmt.2015.07.019.
7. Green ML, Leisenring WM, Xie H, et al. CMV reactivation after allogeneic HCT and relapse risk: evidence for early protection in acute myeloid leukemia. Blood. 2013;122(7):1316-1324. doi:10.1182/blood-2013-02-487074.
8. Bashey A, Zhang X, Sizemore CA, et al. T-Cell-Replete HLA-Haploidentical Hematopoietic Transplantation for Hematologic Malignancies Using Post-Transplantation Cyclophosphamide Results in Outcomes Equivalent to Those of Contemporaneous HLA-Matched Related and Unrelated Donor Transplantation. J Clin Oncol. 2013;31(10):1310-1316. doi:10.1200/JCO.2012.44.3523.
9. Solomon SR, Sizemore C a., Sanacore M, et al. Haploidentical Transplantation Using T Cell Replete Peripheral Blood Stem Cells and Myeloablative Conditioning in Patients with High-Risk Hematologic Malignancies Who Lack Conventional Donors is Well Tolerated and Produces Excellent Relapse-Free Survival: Biol Blood Marrow Transplant. 2012;18(12):1859-1866. doi:10.1016/j.bbmt.2012.06.019.
10. Goldsmith SR, Slade M, DiPersio JF, et al. Cytomegalovirus viremia, disease, and impact on relapse in T-cell replete peripheral blood haploidentical hematopoietic cell transplantation with post-transplant cyclophosphamide. Haematologica. 2016. doi:10.3324/haematol.2016.149880.
11. Holtan SG, DeFor TE, Lazaryan A, et al. Composite endpoint of graft-versus-host disease-free, relapse-free survival after allogeneic hematopoietic cell transplantation. Blood. 2015;125(8):1333-1339. doi:10.1182/blood-2014-10-609032.

Table 1.1 Characteristics of patients who underwent first ALLO transplants with Cy and without Cy conditioning regimen, reported to the CIBMTR, from 2008 to 2016

Variable	Mismatch related with Cy N(%)	Mismatch related without Cy N(%)	Matched related with Cy N(%)	Matched related without Cy N(%)	P value
Patient related					
Number of patients	488	315	330	3685	
Number of centers	88	82	68	117	
Gender					0.021
Male	299 (61)	202 (64)	204 (62)	2107 (57)	
Female	189 (39)	113 (36)	126 (38)	1578 (43)	
Age, median(range), years	58 (3 - 78)	57 (2 - 77)	49 (3 - 75)	53 (2 - 78)	<0.001
Age at transplant, years					<0.001
<=10	18 (4)	26 (8)	6 (2)	99 (3)	
11-20	26 (5)	32 (10)	15 (5)	196 (5)	
21-30	46 (9)	23 (7)	52 (16)	285 (8)	
31-40	28 (6)	18 (6)	47 (14)	354 (10)	
41-50	52 (11)	17 (5)	53 (16)	590 (16)	
51-60	97 (20)	67 (21)	70 (21)	1080 (29)	
61-70	167 (34)	103 (33)	78 (24)	957 (26)	
>70	54 (11)	29 (9)	9 (3)	124 (3)	
Karnofsky performance pre-Preparative Regimen					<0.001
<80	73 (15)	39 (12)	47 (14)	457 (12)	
80-89	155 (32)	72 (23)	88 (27)	934 (25)	
>=90	245 (50)	200 (63)	190 (58)	2251 (61)	
Missing	15 (3)	4 (1)	5 (2)	43 (1)	
Race/Ethnicity					<0.001
Caucasian, non-Hispanic	292 (60)	160 (51)	203 (62)	2720 (74)	
African-American, non-Hispanic	92 (19)	61 (19)	45 (14)	195 (5)	
Asian, non-Hispanic	33 (7)	44 (14)	17 (5)	235 (6)	
Pacific islander, non-Hispanic	5 (1)	1 (<1)	1 (<1)	13 (<1)	
Native American, non-Hispanic	2 (<1)	0	1 (<1)	13 (<1)	
Hispanic, Caucasian	37 (8)	27 (9)	37 (11)	317 (9)	
Hispanic, African-American	2 (<1)	1 (<1)	2 (<1)	5 (<1)	
Hispanic, Asian	1 (<1)	0	0	2 (<1)	

Variable	Mismatch related with Cy N(%)	Mismatch related without Cy N(%)	Matched related with Cy N(%)	Matched related without Cy N(%)	P value
Hispanic, Parcific islander	0	0	0	3 (<1)	
Hispanic, Native American	1 (<1)	1 (<1)	0	4 (<1)	
Missing	23 (5)	20 (6)	24 (7)	178 (5)	
Donor related					
Donor age, years					<0.001
<=10	1 (<1)	1 (<1)	5 (2)	94 (3)	
11-20	17 (3)	8 (3)	14 (4)	61 (2)	
21-30	115 (24)	72 (23)	46 (14)	290 (8)	
31-40	145 (30)	99 (31)	54 (16)	417 (11)	
41-50	126 (26)	82 (26)	63 (19)	675 (18)	
51-60	40 (8)	23 (7)	83 (25)	1069 (29)	
61-70	22 (5)	15 (5)	46 (14)	798 (22)	
>70	2 (<1)	1 (<1)	4 (1)	112 (3)	
Missing	20 (4)	14 (4)	15 (5)	169 (5)	
Donor age, median(range), years	36 (10 - 73)	37 (8 - 80)	45 (4 - 76)	52 (1 - 85)	<0.001
Donor/recipient gender match					<0.001
Male-Male	198 (41)	108 (34)	123 (37)	1147 (31)	
Male-Female	115 (24)	57 (18)	81 (25)	820 (22)	
Female-Male	101 (21)	94 (30)	81 (25)	960 (26)	
Female-Female	74 (15)	56 (18)	45 (14)	758 (21)	
Donor/Recipient CMV status					0.007
+/+	219 (45)	133 (42)	134 (41)	1472 (40)	
+/-	33 (7)	39 (12)	35 (11)	411 (11)	
-/+	136 (28)	78 (25)	85 (26)	888 (24)	
-/-	83 (17)	53 (17)	67 (20)	832 (23)	
+/?	1 (<1)	3 (<1)	0	10 (<1)	
-/?	1 (<1)	1 (<1)	1 (<1)	16 (<1)	
?/+	11 (2)	7 (2)	5 (2)	40 (1)	
?/-	4 (<1)	1 (<1)	3 (<1)	16 (<1)	
Disease related					
Disease					<0.001
AML	257 (53)	165 (52)	186 (56)	1849 (50)	
ALL	95 (19)	58 (18)	82 (25)	670 (18)	
MDS	136 (28)	92 (29)	62 (19)	1166 (32)	

Variable	Mismatch related with Cy N(%)	Mismatch related without Cy N(%)	Matched related with Cy N(%)	Matched related without Cy N(%)	P value
HCT-CI					<0.001
0	110 (23)	88 (28)	86 (26)	1146 (31)	
1	75 (15)	44 (14)	47 (14)	500 (14)	
2	65 (13)	39 (12)	51 (15)	514 (14)	
3+	236 (48)	133 (42)	144 (44)	1499 (41)	
Missing	2 (<1)	11 (3)	2 (<1)	26 (<1)	
DRI					
Low	17 (3)	18 (6)	12 (4)	136 (4)	
Intermediate	251 (51)	135 (43)	172 (52)	2075 (56)	
High	153 (31)	98 (31)	98 (30)	1027 (28)	
Very high	16 (3)	9 (3)	16 (5)	82 (2)	
TBD/Missing (need review)	51 (10)	55 (17)	32 (10)	365 (10)	
Transplant-related					
Graft type					<0.001
Bone Marrow	220 (45)	82 (26)	150 (45)	424 (12)	
Peripheral blood	268 (55)	233 (74)	180 (55)	3261 (88)	
Donor/recipient HLA match					<0.001
HLA-identical siblings	0	0	319 (97)	3642 (99)	
matched related	0	0	11 (3)	43 (1)	
Mismatched related, mismatch>=2	488	315	0	0	
Conditioning regimen intensity					<0.001
Myeloablative	195 (40)	145 (46)	182 (55)	2424 (66)	
RIC/NMA	293 (60)	170 (54)	148 (45)	1261 (34)	
GVHD prophylaxis					<0.001
Ex vivo T-cell depletion	0	54 (17)	0	40 (1)	
CD34 selection	0	40 (13)	0	75 (2)	
Post-CY + other(s)	487(99)	0	321 (97)	0	
Post-CY alone	1 (<1)	0	9 (3)	0	
TAC/CSA + MMF +- others	0	174 (55)	0	850 (23)	
TAC/CSA + MTX +- others	0	32 (10)	0	2280 (62)	
TAC/CSA + others (except MTX, MMF)	0	1 (<1)	0	282 (8)	
TAC/CSA alone	0	11 (3)	0	119 (3)	
Other GVHD prophylaxis	0	3 (<1)	0	39 (1)	
TBI					<0.001

Variable	Mismatch related with Cy N(%)	Mismatch related without Cy N(%)	Matched related with Cy N(%)	Matched related without Cy N(%)	P value
No	150 (31)	74 (23)	147 (45)	2441 (66)	
Yes	336 (69)	241 (77)	182 (55)	1235 (34)	
Missing	2 (<1)	0	1 (<1)	9 (<1)	
ATG /Alemtuzumab					<0.001
ATG alone	4 (<1)	63 (20)	6 (2)	389 (11)	
CAMPATH alone	0	16 (5)	0	39 (1)	
No ATG or CAMPATH	482 (99)	236 (75)	323 (98)	3250 (88)	
Missing	2 (<1)	0	1 (<1)	7 (<1)	
G-CSF, GM-CSF(day -3 to day +7)					<0.001
No	84 (17)	98 (31)	97 (29)	2657 (72)	
Yes	399 (82)	215 (68)	233 (71)	1024 (28)	
Missing	5 (1)	2 (<1)	0	4 (<1)	
Time from diagnosis to transplant					<0.001
<6 month	193 (40)	103 (33)	151 (46)	2003 (54)	
6 month-1Y	130 (27)	96 (30)	93 (28)	760 (21)	
1Y-2Y	88 (18)	60 (19)	43 (13)	448 (12)	
>=2Y	77 (16)	55 (17)	43 (13)	461 (13)	
Missing	0	1 (<1)	0	13 (<1)	
Time from diagnosis to transplant, median(range), months	8 (1 - 172)	9 (1 - 330)	6 (1 - 257)	5 (<1 - 497)	<0.001
Cell counts					
Nucleated cell count, median(range), 10*8/kg, @infusion	4 (<1 - 37)	3 (<1 - 59)	5 (<1 - 45)	8 (<1 - 52)	<0.001
Nucleated cell count, 10*8/kg					<0.001
<3	115 (24)	100 (32)	58 (18)	327 (9)	
3-9	149 (31)	65 (21)	107 (32)	1024 (28)	
>9	64 (13)	49 (16)	57 (17)	1014 (28)	
Missing	160 (33)	101 (32)	108 (33)	1320 (36)	
CD34+ cell count , median(range), 10*6/kg, @infusion	4 (<1 - 20)	4 (<1 - 19)	4 (<1 - 17)	5 (<1 - 20)	<0.001
CD34 cell count, 10*6/kg					<0.001
<4	177 (36)	118 (37)	101 (31)	854 (23)	
4-8	151 (31)	69 (22)	123 (37)	1239 (34)	
>8	54 (11)	47 (15)	27 (8)	491 (13)	
Missing	106 (22)	81 (26)	79 (24)	1101 (30)	

Variable	Mismatch related with Cy N(%)	Mismatch related without Cy N(%)	Matched related with Cy N(%)	Matched related without Cy N(%)	P value
CD3+ cell count , median(range), 10*7/kg, @infusion	7 (<1 - 58)	3 (<1 - 58)	8 (<1 - 59)	20 (<1 - 60)	<0.001
CD3 cell count, 10*7/kg					<0.001
<4	106 (22)	111 (35)	65 (20)	280 (8)	
4-8	29 (6)	13 (4)	21 (6)	120 (3)	
>8	128 (26)	68 (22)	93 (28)	1484 (40)	
Missing	225 (46)	123 (39)	151 (46)	1801 (49)	
Year of transplant					
2008	5 (1)	28 (9)	14 (4)	516 (14)	
2009	7 (1)	25 (8)	10 (3)	434 (12)	
2010	5 (1)	2 (<1)	4 (1)	340 (9)	
2011	1 (<1)	9 (3)	4 (1)	223 (6)	
2012	10 (2)	10 (3)	4 (1)	199 (5)	
2013	47 (10)	39 (12)	35 (11)	435 (12)	
2014	92 (19)	69 (22)	46 (14)	598 (16)	
2015	126 (26)	70 (22)	104 (32)	507 (14)	
2016	195 (40)	63 (20)	109 (33)	433 (12)	
Median follow-up of survivors, months	25 (3 - 119)	31 (3 - 125)	24 (3 - 120)	48 (2 - 122)	

Table 1.2 Infection and time dependent variables

Variable	Mismatch related with Cy N(%)	Mismatch related without Cy N(%)	Matched related with Cy N(%)	Matched related without Cy N(%)	P value
Number of patients	488	315	330	3685	
Cell counts at day 100					
White cell count , median(range), 10*9/L, @ day 180	5.0 (0.1 - 157.4)	4.6 (0.1 - 47.1)	4.7 (0.1 - 97.0)	5.0 (0.1 - 690.9)	
Missing	126 (26)	95 (30)	61 (18)	573 (16)	
Absolute lymphocyte count , median(range), 10*9/L, @day 180	1.1 (0.0 - 9.4)	1.0 (0.0 - 7.3)	1.0 (0.0 - 10.0)	1.0 (0.0 - 9.9)	
Missing	138 (28)	102 (32)	68 (21)	707 (19)	
CD3 , median(range), 10*9/L, @ day 100	0.2 (0.0 - 8.0)	0.3 (0.0 - 9.0)	0.2 (0.1 - 2.3)	0.6 (0.0 - 7.0)	
CD4 , median(range), 10*9/L, @ day 100	0.1 (0.0 - 0.5)	0.1 (0.0 - 8.0)	0.1 (0.0 - 9.0)	0.2 (0.0 - 8.0)	
CD8 , median(range), 10*9/L, @ day 100	0.1 (0.0 - 10.0)	0.2 (0.0 - 6.4)	0.1 (0.0 - 10.0)	0.3 (0.0 - 8.0)	
CD4:CD8 ratio , median(range), @ day 100	1.0 (0.0 - 16.7)	0.5 (0.1 - 14.4)	0.6 (0.1 - 9.1)	0.8 (0.0 - 1100.4)	
CD3 , median(range), 10*9/L, @ 6 month	0.6 (0.1 - 2.7)	0.6 (0.0 - 3.6)	0.5 (0.2 - 2.3)	0.7 (0.0 - 7.2)	
CD4 , median(range), 10*9/L, @ 6 month	0.2 (0.0 - 9.0)	0.2 (0.0 - 2.0)	0.2 (0.1 - 10.0)	0.3 (0.0 - 8.0)	
CD8 , median(range), 10*9/L, @ 6 month	0.4 (0.0 - 1.9)	0.4 (0.0 - 9.0)	0.5 (0.1 - 5.0)	0.3 (0.0 - 8.0)	
CD4:CD8 ratio , median(range), @ 6 month	0.5 (0.1 - 6.2)	0.4 (0.1 - 66.0)	0.5 (0.0 - 6.3)	0.7 (0.0 - 2142.9)	
CMV Infection					
Viremia (± organ disease) by day180					<0.001
Yes	219 (45)	104 (33)	125 (38)	805 (22)	
No	269 (55)	211 (67)	205 (62)	2880 (78)	
Time from transplant to viremia (± organ disease), median(range), days	39 (2 - 179)	32 (3 - 166)	32 (6 - 136)	41 (3 - 179)	<0.001
CMV organ disease (± viremia) by day180					<0.001
Yes	24 (5)	5 (2)	14 (4)	71 (2)	

Variable	Mismatch related with Cy N(%)	Mismatch related without Cy N(%)	Matched related with Cy N(%)	Matched related without Cy N(%)	P value
No	464 (95)	310 (98)	316 (96)	3614 (98)	
Time from transplant to CMV organ involvement (± viremia), median(range), days	56 (22 - 167)	41 (21 - 68)	48 (18 - 168)	58 (4 - 176)	0.363
CMV in GI					<0.001
Yes	2 (<1)	1 (<1)	1 (<1)	15 (<1)	
No	22 (5)	4 (1)	13 (4)	56 (2)	
No CMV reactivation other than viremia	464 (95)	310 (98)	316 (96)	3614 (98)	
CMV in lung					<0.001
Yes	11 (2)	1 (<1)	8 (2)	19 (<1)	
No	13 (3)	4 (1)	6 (2)	52 (1)	
No CMV reactivation other than viremia	464 (95)	310 (98)	316 (96)	3614 (98)	
CMV in liver					<0.001
Yes	0	0	1 (<1)	1 (<1)	
No	24 (5)	5 (2)	13 (4)	70 (2)	
No CMV reactivation other than viremia	464 (95)	310 (98)	316 (96)	3614 (98)	
CMV in other sites					<0.001
Yes	11 (2)	3 (<1)	4 (1)	41 (1)	
No	13 (3)	2 (<1)	10 (3)	30 (<1)	
No CMV reactivation other than viremia	464 (95)	310 (98)	316 (96)	3614 (98)	
Non-CMV viral Infection					
Non-CMV Viremia (± organ disease) by day180					<0.001
Yes	63 (13)	48 (15)	32 (10)	242 (7)	
No	425 (87)	267 (85)	298 (90)	3443 (93)	
Time from transplant to non-CMV Viremia (± organ disease), median(range), days	37 (2 - 166)	38 (5 - 166)	42 (10 - 175)	48 (2 - 173)	0.654
Non-CMV viral organ involvement (± viremia) by day180					<0.001
Yes	144 (30)	85 (27)	102 (31)	662 (18)	
No	344 (70)	230 (73)	228 (69)	3023 (82)	

Variable	Mismatch related with Cy N(%)	Mismatch related without Cy N(%)	Matched related with Cy N(%)	Matched related without Cy N(%)	P value
Time from transplant to non-CMV viral infection organ involvement (± viremia), median(range), days	43 (2 - 180)	39 (2 - 170)	44 (4 - 173)	52 (2 - 180)	0.007
Non-CMV viral infection in GI					<0.001
Yes	1 (<1)	0	1 (<1)	8 (<1)	
No	143 (29)	85 (27)	101 (31)	654 (18)	
No non-CMV viral infection other than viremia	344 (70)	230 (73)	228 (69)	3023 (82)	
Non-CMV viral infection in lung					<0.001
Yes	7 (1)	5 (2)	11 (3)	44 (1)	
No	137 (28)	80 (25)	91 (28)	618 (17)	
No non-CMV viral infection other than viremia	344 (70)	230 (73)	228 (69)	3023 (82)	
Non-CMV viral infection in liver					<0.001
Yes	0	2 (<1)	0	6 (<1)	
No	144 (30)	83 (26)	102 (31)	656 (18)	
No non-CMV viral infection other than viremia	344 (70)	230 (73)	228 (69)	3023 (82)	
Non-CMV viral infection in other sites					<0.001
Yes	140 (29)	84 (27)	96 (29)	620 (17)	
No	4 (<1)	1 (<1)	6 (2)	42 (1)	
No non-CMV viral infection other than viremia	344 (70)	230 (73)	228 (69)	3023 (82)	
Non-CMV Viral Infection in blood					
HSV					0.005
Yes	1 (<1)	4 (1)	0	8 (<1)	
No	487	311 (99)	330	3677	
Varicella					<0.001
Yes	0	2 (<1)	0	1 (<1)	
No	488	313 (99)	330	3684	
Adenovirus					<0.001
Yes	9 (2)	12 (4)	2 (<1)	11 (<1)	

Variable	Mismatch related with Cy N(%)	Mismatch related without Cy N(%)	Matched related with Cy N(%)	Matched related without Cy N(%)	P value
No	479 (98)	303 (96)	328 (99)	3674	
Enterovirus					0.003
Yes	0	0	1 (<1)	0	
No	488	315	329	3685	
HBV					0.551
Yes	0	0	1 (<1)	4 (<1)	
No	488	315	329	3681	
HCV					0.746
Yes	0	0	0	4 (<1)	
No	488	315	330	3681	
Influenza					0.820
Yes	0	0	0	3 (<1)	
No	488	315	330		
RSV					0.573
Yes	0	1 (<1)	0	5 (<1)	
No	488	314	330	3680	
Parainfluenza					0.565
Yes	1 (<1)	0	0	2 (<1)	
No	487	315	330	3683487	
HHV-6					<0.001
Yes	36 (7)	22 (7)	14 (4)	66 (2)	
No	452 (93)	293 (93)	316 (96)	3619 (98)	
EBV					0.490
Yes	15 (3)	13 (4)	11 (3)	100 (3)	
No	473 (97)	302 (96)	319 (97)	3585 (97)	
Polyoma virus					0.016
Yes	8 (2)	7 (2)	11 (3)	46 (1)	
No	480 (98)	308 (98)	319 (97)	3639 (99)	
Rotavirus					0.959
Yes	0	0	0	1 (<1)	
No	488	315	330	3684	
Rhinovirus					0.523
Yes	0	1 (<1)	0	4 (<1)	
No	488	314	330	3681	
Influenza A					
Yes	0	0	0	2 (<1)	

Variable	Mismatch related with Cy N(%)	Mismatch related without Cy N(%)	Matched related with Cy N(%)	Matched related without Cy N(%)	P value
No	488	315	330	3683 (>99)	
Other virus, specify					0.161
Yes	5 (1)	3 (<1)	2 (<1)	14 (<1)	
No	483 (99)	312 (99)	328 (99)	3671	
Non-CMV viral Infection in other sites					
HSV					0.106
Yes	6 (1)	10 (3)	8 (2)	58 (2)	
No	482 (99)	305 (97)	322 (98)	3627 (98)	
Varicella					0.078
Yes	0	5 (2)	2 (<1)	38 (1)	
No	488	310 (98)	328 (99)	3647 (99)	
Adenovirus					<0.001
Yes	11 (2)	11 (3)	7 (2)	36 (<1)	
No	477 (98)	304 (97)	323 (98)	3649 (99)	
Enterovirus					0.003
Yes	7 (1)	6 (2)	7 (2)	23 (<1)	
No	481 (99)	309 (98)	323 (98)	3662 (99)	
HCV					0.820
Yes	0	0	0	3 (<1)	
No	488	315	330		
Influenza					0.032
Yes	12 (2)	3 (<1)	9 (3)	46 (1)	
No	476 (98)	312 (99)	321 (97)	3639 (99)	
Parainfluenza					0.025
Yes	18 (4)	5 (2)	13 (4)	77 (2)	
No	470 (96)	310 (98)	317 (96)	3608 (98)	
HHV-6					0.006
Yes	1 (<1)	5 (2)	0	14 (<1)	
No	487	310 (98)	330	3671	
EBV					0.254
Yes	2 (<1)	0	0	4 (<1)	
No	486	315	330	3681	
Polyoma virus					<0.001
Yes	74 (15)	36 (11)	55 (17)	290 (8)	
No	414 (85)	279 (89)	275 (83)	3395 (92)	

Variable	Mismatch related with Cy N(%)	Mismatch related without Cy N(%)	Matched related with Cy N(%)	Matched related without Cy N(%)	P value
Rotavirus					0.923
Yes	3 (<1)	2 (<1)	1 (<1)	22 (<1)	
No	485 (99)	313 (99)	329	3663 (99)	
Rhinovirus					<0.001
Yes	20 (4)	16 (5)	24 (7)	99 (3)	
No	468 (96)	299 (95)	306 (93)	3586 (97)	
HPV					0.003
Yes	0	1 (<1)	0	0	
No	488	314	330	3685	
Influenza A					0.098
Yes	9 (2)	2 (<1)	7 (2)	31 (<1)	
No	479 (98)	313 (99)	323 (98)	3654 (99)	
Enterovirus NOS					0.517
Yes	1 (<1)	0	2 (<1)	0	
No	487 (>99)	315	328 (99)	3685	
Other virus, specify					0.183
Yes	1 (<1)	1 (<1)	0	7 (<1)	
No	487	314	330	3678	
Co-infection (fungal/bacteria infection within 30 days of viral infection)					<0.001
Yes	151 (31)	91 (29)	100 (30)	603 (16)	
No co-infection	152 (31)	76 (24)	81 (25)	750 (20)	
No viral infection	156 (32)	131 (42)	127 (38)	1876 (51)	
Missing	29 (6)	17 (5)	22 (7)	456 (12)	
Time dependent variable					
ANC500					<0.001
Yes	456 (93)	291 (92)	321 (97)	3623 (98)	
No	24 (5)	21 (7)	8 (2)	55 (1)	
Missing	8 (2)	3 (<1)	1 (<1)	7 (<1)	
Time from transplant to ANC>500, days	17 (1 - 125)	15 (1 - 149)	17 (<1 - 70)	15 (<1 - 96)	<0.001
Acute GVHD grade II-IV					0.517
No	309 (63)	206 (65)	202 (61)	2441 (66)	
Yes	174 (36)	105 (33)	123 (37)	1195 (32)	
Missing	5 (1)	4 (1)	5 (2)	49 (1)	

Variable	Mismatch related with Cy N(%)	Mismatch related without Cy N(%)	Matched related with Cy N(%)	Matched related without Cy N(%)	P value
Time from transplant to aGVHD, days	37 (13 - 166)	32 (9 - 147)	39 (13 - 175)	36 (7 - 178)	0.654
Chronic GVHD(any severity) at 1 year					<0.001
No	352 (72)	221 (70)	227 (69)	1895 (51)	
Yes	136 (28)	91 (29)	103 (31)	1786 (48)	
Missing	0	3 (<1)	0	4 (<1)	
Time from transplant to cGVHD, months	6 (2 - 34)	5 (1 - 18)	6 (3 - 34)	6 (2 - 67)	0.021
Median follow-up of survivors, months	25 (3 - 119)	31 (3 - 125)	24 (3 - 120)	48 (2 - 122)	

Table 1.3 Cause of death

Variable	Mismatch related with Cy N(%)	Mismatch related without Cy N(%)	MRD/MUD with Cy N(%)	MRD/MUD without Cy N(%)	P value
Number of Death	252	170	154	1886	
Cause of Death					<0.001
Primary disease	131 (52)	77 (45)	89 (58)	1061 (56)	
Infection as secondary cause of death	26	15	13	159	
Graft failure	4 (2)	0	2 (1)	12 (<1)	
Infection as secondary cause of death	1	0	0	6	
GVHD	19 (8)	8 (5)	10 (6)	255 (14)	
Infection as secondary cause of death	10	4	4	83	
Infection	35 (14)	31 (18)	12 (8)	183 (10)	
Infection as secondary cause of death	7	6	2	20	
IPn	10 (4)	3 (2)	3 (2)	40 (2)	
Infection as secondary cause of death	2	0	0	6	
ARDS	8 (3)	1 (<1)	3 (2)	25 (1)	
Infection as secondary cause of death	0	0	1	8	
Organ failure	22 (9)	23 (14)	18 (12)	161 (9)	
Infection as secondary cause of death	10	7	5	34	
Secondary malignancy	1 (<1)	3 (2)	2 (1)	36 (2)	
Infection as secondary cause of death	0	1	1	2	
Hemorrhage	9 (4)	3 (2)	5 (3)	19 (1)	
Infection as secondary cause of death	2	2	3	5	
Accident/suicide	0	0	1 (<1)	6 (<1)	
Vascular	2 (<1)	1 (<1)	0	7 (<1)	
Other	11 (4)	18 (11)	7 (5)	71 (4)	
Infection as secondary cause of death	1	5	0	1	
Unknown	0	2 (1)	2 (1)	10 (<1)	

Distribution of continuous variables

Variable	N	Min	1%	5%	25%	50%	75%	95%	99%	Max
Patient age										
Mismatched related with Cy	488	2.69	4.90	13.37	40.72	57.96	66.36	72.62	76.13	78.39
Mismatched related without Cy	315	2.08	3.68	7.17	28.29	57.09	64.96	71.87	74.39	77.02
MRD with Cy	330	2.77	6.01	19.13	32.55	49.16	60.31	68.29	73.23	75.36
MRD without Cy	3685	2.12	5.88	15.27	39.76	53.25	61.46	69.04	72.82	77.68
Time from HCT to death/last follow-up date, months										
Mismatched related with Cy	488	0.16	0.39	1.05	5.81	12.20	24.19	47.17	74.93	119.05
Mismatched related without Cy	315	0.20	0.33	1.12	4.51	12.01	25.16	59.41	97.40	124.70
MRD with Cy	330	0.20	0.59	2.04	6.97	12.57	24.74	55.56	89.18	119.51
MRD without Cy	3685	0.10	0.76	2.07	7.40	23.03	47.93	96.22	116.12	125.95
Time from diagnosis to transplant, median(range), months										
Mismatched related with Cy	488	0.63	1.61	2.66	4.82	7.58	16.48	57.53	147.07	171.91
Mismatched related without Cy	314	0.59	1.94	3.36	5.16	8.57	17.60	61.22	150.46	330.26
MRD with Cy	330	1.38	2.01	2.89	4.34	6.45	12.89	37.11	77.01	257.24
MRD without Cy	3672	0.43	1.68	2.37	3.75	5.49	11.88	55.16	143.16	497.24
Nucleated cell count, median(range), 10*8/kg										
Mismatched related with Cy	327	0.02	0.10	0.77	2.37	4.13	8.05	15.00	29.35	37.46
Mismatched related without Cy	214	0.00	0.00	0.02	0.16	3.40	8.34	20.69	38.99	58.59
MRD with Cy	222	0.04	0.56	1.34	2.90	4.90	9.10	18.44	31.90	45.44
MRD without Cy	2357	0.00	0.02	0.24	4.56	8.00	11.86	20.34	31.05	52.34
CD34+ cell count , median(range), 10*6/kg										
Mismatched related with Cy	378	0.04	0.06	0.75	2.51	4.23	5.96	11.81	16.92	19.91
Mismatched related without Cy	225	0.02	0.02	0.07	2.09	3.83	6.52	11.82	16.33	19.14
MRD with Cy	246	0.02	0.06	0.61	2.64	4.42	5.49	9.98	14.00	17.13
MRD without Cy	2541	0.01	0.04	0.90	3.26	5.03	7.14	11.21	16.01	20.00
CD3+ cell count , median(range), 10*7/kg										
Mismatched related with Cy	260	0.04	0.04	0.51	2.70	7.02	22.32	43.25	51.06	57.64
Mismatched related without Cy	187	0.00	0.00	0.00	0.00	2.65	18.12	40.42	58.27	58.38
MRD with Cy	173	0.01	0.27	0.81	2.78	8.05	23.48	41.50	54.92	58.71
MRD without Cy	1806	0.00	0.00	0.19	9.59	20.01	30.34	47.26	56.96	60.00
White cell count @180 day , median(range), 10*9/L										
Mismatched related with Cy	354	0.00	0.10	0.70	3.00	4.95	6.70	11.10	22.50	29.70
Mismatched related without Cy	218	0.00	0.10	0.40	2.90	4.50	6.80	10.40	14.50	21.50
MRD with Cy	263	0.10	0.10	0.60	2.90	4.60	6.20	11.70	26.20	27.70
MRD without Cy	3063	0.00	0.10	0.80	3.40	4.90	6.80	11.60	20.60	29.30

Variable	N	Min	1%	5%	25%	50%	75%	95%	99%	Max
Absolute lymphocyte count @180day, median(range), 10*9/L										
Mismatched related with Cy	349	0.00	0.00	0.15	0.60	1.08	1.89	4.16	8.09	9.44
Mismatched related without Cy	212	0.00	0.02	0.10	0.53	1.00	1.76	3.61	4.88	7.27
MRD with Cy	259	0.00	0.04	0.22	0.56	1.03	1.84	3.66	8.60	10.00
MRD without Cy	2958	0.00	0.00	0.16	0.60	1.00	1.57	3.11	5.75	9.85
Cd3 10*9/L, @ day 100*										
Mismatched related with Cy	52	0.00	0.00	0.01	0.09	0.24	0.54	1.31	8.00	8.00
Mismatched related without Cy	69	0.00	0.00	0.00	0.06	0.32	0.80	3.00	9.00	9.00
MRD with Cy	26	0.00	0.00	0.00	0.09	0.22	0.51	1.91	2.31	2.31
MRD without Cy	454	0.00	0.00	0.05	0.31	0.56	1.00	2.38	6.00	7.00
Cd4 10*9/L, @ day 100*										
Mismatched related with Cy	53	0.00	0.00	0.01	0.05	0.09	0.14	0.32	0.45	0.45
Mismatched related without Cy	67	0.00	0.00	0.00	0.02	0.08	0.21	0.44	8.00	8.00
MRD with Cy	30	0.00	0.00	0.00	0.04	0.09	0.24	8.00	9.00	9.00
MRD without Cy	465	0.00	0.00	0.00	0.12	0.23	0.36	0.67	1.40	8.00
Cd8 10*9/L, @ day 100*										
Mismatched related with Cy	56	0.00	0.00	0.00	0.03	0.09	0.38	4.00	10.00	10.00
Mismatched related without Cy	63	0.00	0.00	0.00	0.03	0.19	0.70	1.87	6.36	6.36
MRD with Cy	27	0.00	0.00	0.00	0.04	0.11	0.46	1.99	10.00	10.00
MRD without Cy	446	0.00	0.00	0.01	0.12	0.28	0.63	1.84	5.00	8.00
Cd310*9/L, @ 6 month*										
Mismatched related with Cy	30	0.05	0.05	0.09	0.29	0.60	1.26	1.80	2.70	2.70
Mismatched related without Cy	48	0.01	0.01	0.07	0.30	0.61	1.14	3.17	3.55	3.55
MRD with Cy	20	0.17	0.17	0.18	0.28	0.48	1.17	2.12	2.25	2.25
MRD without Cy	301	0.00	0.00	0.13	0.43	0.66	1.14	2.14	3.91	7.19
Cd4 10*9/L, @ 6 month*										
Mismatched related with Cy	41	0.02	0.02	0.03	0.11	0.18	0.25	0.50	9.00	9.00
Mismatched related without Cy	50	0.00	0.00	0.01	0.08	0.15	0.28	0.73	2.00	2.00
MRD with Cy	27	0.06	0.06	0.08	0.12	0.24	0.37	9.00	10.00	10.00
MRD without Cy	323	0.00	0.00	0.04	0.17	0.27	0.41	0.81	1.14	8.00
Cd8 10*9/L, @ 6 month*										
Mismatched related with Cy	37	0.02	0.02	0.03	0.10	0.44	0.88	1.60	1.90	1.90
Mismatched related without Cy	47	0.00	0.00	0.01	0.15	0.44	0.73	2.80	9.00	9.00
MRD with Cy	25	0.08	0.08	0.08	0.16	0.46	1.03	2.72	5.00	5.00
MRD without Cy	311	0.00	0.00	0.06	0.17	0.35	0.71	1.73	2.74	8.00

*High values are under review.

Variable	N	Min	1%	5%	25%	50%	75%	95%	99%	Max
Time from transplant to CMV Viremia (± organ disease) by 180 day, median(range), days										

Variable	N	Min	1%	5%	25%	50%	75%	95%	99%	Max
Mismatched related with Cy	217	2.00	3.00	9.00	29.00	39.00	47.00	87.00	176.00	179.00
Mismatched related without Cy	104	3.00	5.00	7.00	20.50	32.00	42.00	105.00	141.00	166.00
MRD with Cy	123	6.00	6.00	11.00	25.00	32.00	41.00	56.00	110.00	136.00
MRD without Cy	802	3.00	6.00	13.00	29.00	41.00	56.00	120.00	161.00	179.00

Variable	N	Min	1%	5%	25%	50%	75%	95%	99%	Max
Time from transplant to organ involvement (± viremia) by 180 day, median(range), days										
Mismatched related with Cy	24	22.00	22.00	29.00	38.00	56.00	76.50	151.00	167.00	167.00
Mismatched related without Cy	5	21.00	21.00	21.00	40.00	41.00	48.00	68.00	68.00	68.00
MRD with Cy	14	18.00	18.00	18.00	40.00	47.50	54.00	168.00	168.00	168.00
MRD without Cy	70	4.00	4.00	21.00	40.00	58.00	113.00	172.00	176.00	176.00

Variable	N	Min	1%	5%	25%	50%	75%	95%	99%	Max
Time from transplant to non-CMV Viremia (± organ disease) by 180 day, median(range), days										
Mismatched related with Cy	63	2.00	2.00	14.00	22.00	37.00	84.00	128.00	166.00	166.00
Mismatched related without Cy	48	5.00	5.00	11.00	22.00	37.50	72.50	137.00	166.00	166.00
MRD with Cy	32	10.00	10.00	16.00	23.00	42.00	108.00	171.00	175.00	175.00
MRD without Cy	240	2.00	3.00	11.50	25.00	47.50	79.50	156.50	173.00	173.00

Variable	N	Min	1%	5%	25%	50%	75%	95%	99%	Max
Time from transplant to non-CMV organ involvement (± viremia) by 180 day, median(range), days										
Mismatched related with Cy	143	2.00	2.00	8.00	17.00	43.00	76.00	152.00	179.00	180.00
Mismatched related without Cy	84	2.00	2.00	5.00	21.00	38.50	69.00	142.00	170.00	170.00
MRD with Cy	100	4.00	5.00	8.00	16.50	44.00	81.00	162.00	171.00	173.00
MRD without Cy	648	2.00	2.00	6.00	25.00	52.00	101.50	168.00	178.00	180.00

Distribution of continuous variables

GVHD_prophylaxis	gvhdlist	Mismatch related without Cy	MRD without Cy	total
Other GVHD prophylaxis	mtx	2 (20)	10 (31)	12
	mmf	3 (30)	6 (19)	9
	cor	1 (10)	2 (6)	3
	cor + mtx	0	3 (9)	3
	siro	0	3 (9)	3
	atg + mtx	0	2 (6)	2
	siro + oth	0	2 (6)	2
	atg	0	1 (3)	1
	cor + mab + siro	0	1 (3)	1
	cor + mmf	1 (10)	0	1
	cor + mtx + mmf	1 (10)	0	1
	mab	1 (10)	0	1
	mab + mmf	0	1 (3)	1
	mmf + siro	1 (10)	0	1
	mmf + siro + oth	0	1 (3)	1

Table 2.1 Characteristics of patients who underwent first ALLO transplants with Cy and without Cy conditioning regimen by Donor/Recipient CMV Serostatus, reported to the CIBMTR, from 2008 to 2016

Variable	+/+	+/-	-/+	-/-	P value
Patient related					
Number of patients	1958	518	1187	1035	
Number of centers	115	90	107	105	
Gender					<0.001
Male	1098 (56)	332 (64)	669 (56)	645 (62)	
Female	860 (44)	186 (36)	518 (44)	390 (38)	
Age, median(range), years	52 (2 - 78)	54 (2 - 76)	55 (3 - 78)	54 (2 - 77)	<0.001
Age at transplant, years					<0.001
<=10	59 (3)	16 (3)	25 (2)	41 (4)	
11-20	117 (6)	33 (6)	52 (4)	61 (6)	
21-30	177 (9)	43 (8)	90 (8)	82 (8)	
31-40	224 (11)	33 (6)	85 (7)	92 (9)	
41-50	298 (15)	76 (15)	175 (15)	149 (14)	
51-60	519 (27)	162 (31)	311 (26)	292 (28)	
61-70	482 (25)	139 (27)	378 (32)	274 (26)	
>70	82 (4)	16 (3)	71 (6)	44 (4)	
Karnofsky performance pre-Preparative Regimen					0.198
<80	241 (12)	55 (11)	168 (14)	137 (13)	
80-89	500 (26)	125 (24)	350 (29)	249 (24)	
>=90	1190 (61)	328 (63)	655 (55)	635 (61)	
Missing	27 (1)	10 (2)	14 (1)	14 (1)	
Race/Ethnicity					<0.001
Caucasian, non-Hispanic	1052 (54)	407 (79)	938 (79)	912 (88)	
African-American, non-Hispanic	234 (12)	40 (8)	80 (7)	27 (3)	
Asian, non-Hispanic	235 (12)	17 (3)	45 (4)	20 (2)	
Pacific islander, non-Hispanic	11 (<1)	2 (<1)	2 (<1)	3 (<1)	
Native American, non-Hispanic	10 (<1)	1 (<1)	2 (<1)	3 (<1)	
Hispanic, Caucasian	247 (13)	32 (6)	81 (7)	40 (4)	
Hispanic, African-American	3 (<1)	1 (<1)	3 (<1)	2 (<1)	
Hispanic, Asian	1 (<1)	0	1 (<1)	1 (<1)	
Hispanic, Parcific islander	2 (<1)	0	0	1 (<1)	
Hispanic, Native American	3 (<1)	2 (<1)	1 (<1)	0	
Missing	160 (8)	16 (3)	34 (3)	26 (3)	

Variable	+/+	+/-	-/+	-/-	P value
Donor related					
Donor age, years					<0.001
<=10	34 (2)	5 (<1)	33 (3)	28 (3)	
11-20	38 (2)	6 (1)	26 (2)	28 (3)	
21-30	235 (12)	49 (9)	120 (10)	113 (11)	
31-40	329 (17)	55 (11)	181 (15)	133 (13)	
41-50	378 (19)	91 (18)	252 (21)	204 (20)	
51-60	454 (23)	154 (30)	284 (24)	303 (29)	
61-70	369 (19)	118 (23)	218 (18)	164 (16)	
>70	51 (3)	23 (4)	23 (2)	19 (2)	
Missing	70 (4)	17 (3)	50 (4)	43 (4)	
Donor age, median(range), years	48 (2 - 85)	52 (5 - 82)	47 (1 - 76)	49 (2 - 80)	<0.001
Donor/recipient gender match					<0.001
Male-Male	593 (30)	148 (29)	412 (35)	384 (37)	
Male-Female	422 (22)	88 (17)	306 (26)	229 (22)	
Female-Male	505 (26)	184 (36)	257 (22)	261 (25)	
Female-Female	438 (22)	98 (19)	212 (18)	161 (16)	
Disease related					
Disease					0.007
AML	1008 (51)	255 (49)	632 (53)	502 (49)	
ALL	407 (21)	97 (19)	194 (16)	180 (17)	
MDS	543 (28)	166 (32)	361 (30)	353 (34)	
HCT-CI					<0.001
0	634 (32)	154 (30)	320 (27)	287 (28)	
1	278 (14)	63 (12)	156 (13)	148 (14)	
2	262 (13)	78 (15)	172 (14)	137 (13)	
3+	752 (38)	221 (43)	536 (45)	459 (44)	
Missing	32 (2)	2 (<1)	3 (<1)	4 (<1)	
DRI					
Low	78 (4)	23 (4)	44 (4)	34 (3)	
Intermediate	1053 (54)	307 (59)	638 (54)	567 (55)	
High	556 (28)	138 (27)	353 (30)	298 (29)	
Very high	57 (3)	9 (2)	33 (3)	23 (2)	
TBD/Missing (need review)	214 (11)	41 (8)	119 (10)	113 (11)	
Transplant-related					
Graft type					0.003
Bone Marrow	312 (16)	94 (18)	231 (19)	222 (21)	

Variable	+/+	+/-	-/+	-/-	P value
Peripheral blood	1646 (84)	424 (82)	956 (81)	813 (79)	
Donor/recipient HLA match					<0.001
HLA-identical siblings	1580 (81)	443 (86)	963 (81)	891 (86)	
matched related	26 (1)	3 (<1)	10 (<1)	8 (<1)	
Mismatched related, mismatch>=2	352 (18)	72 (14)	214 (18)	136 (13)	
Conditioning regimen intensity					0.019
Myeloablative	1220 (62)	316 (61)	678 (57)	657 (63)	
RIC/NMA	738 (38)	202 (39)	509 (43)	378 (37)	
GVHD prophylaxis					0.002
Ex vivo T-cell depletion	35 (2)	8 (2)	25 (2)	20 (2)	
CD34 selection	44 (2)	7 (1)	28 (2)	32 (3)	
Post-CY + other(s)	351 (18)	66 (13)	220 (19)	145 (14)	
Post-CY alone	2 (<1)	2 (<1)	1 (<1)	5 (<1)	
TAC/CSA + MMF +- others	381 (19)	129 (25)	271 (23)	221 (21)	
TAC/CSA + MTX +- others	945 (48)	255 (49)	538 (45)	523 (51)	
TAC/CSA + others (except MTX, MMF)	129 (7)	29 (6)	65 (5)	57 (6)	
TAC/CSA alone	54 (3)	14 (3)	32 (3)	24 (2)	
Other GVHD prophylaxis	17 (<1)	8 (2)	7 (<1)	8 (<1)	
TBI					<0.001
No	1154 (59)	319 (62)	655 (55)	608 (59)	
Yes	802 (41)	197 (38)	530 (45)	425 (41)	
Missing	2 (<1)	2 (<1)	2 (<1)	2 (<1)	
Time from diagnosis to transplant					0.272
<6 month	943 (48)	266 (51)	608 (51)	567 (55)	
6 month-1Y	471 (24)	111 (21)	267 (22)	212 (20)	
1Y-2Y	276 (14)	76 (15)	156 (13)	116 (11)	
>=2Y	265 (14)	62 (12)	151 (13)	137 (13)	
Missing	3 (<1)	3 (<1)	5 (<1)	3 (<1)	
Time from diagnosis to transplant, median(range), months	6 (<1 - 396)	6 (1 - 305)	6 (1 - 497)	6 (<1 - 343)	0.076
Cell counts					
Nucleated cell count, median(range), 10*8/kg, @infusion	8 (<1 - 59)	7 (<1 - 46)	7 (<1 - 52)	6 (<1 - 35)	<0.001
Nucleated cell count, 10*8/kg					<0.001
<3	201 (10)	48 (9)	184 (16)	156 (15)	
3-9	499 (25)	154 (30)	352 (30)	315 (30)	
>9	513 (26)	133 (26)	277 (23)	229 (22)	

Variable	+/+	+/-	-/+	-/-	P value
Missing	745 (38)	183 (35)	374 (32)	335 (32)	
CD34+ cell count , median(range), 10*6/kg, @infusion	5 (<1 - 20)	5 (<1 - 19)	5 (<1 - 19)	5 (<1 - 20)	0.233
CD34 cell count, 10*6/kg					0.002
<4	474 (24)	135 (26)	343 (29)	275 (27)	
4-8	641 (33)	176 (34)	389 (33)	342 (33)	
>8	278 (14)	47 (9)	149 (13)	127 (12)	
Missing	565 (29)	160 (31)	306 (26)	291 (28)	
CD3+ cell count , median(range), 10*7/kg, @infusion	19 (<1 - 60)	20 (<1 - 60)	15 (<1 - 59)	16 (<1 - 60)	0.005
CD3 cell count, 10*7/kg					0.001
<4	204 (10)	36 (7)	176 (15)	132 (13)	
4-8	65 (3)	27 (5)	47 (4)	42 (4)	
>8	741 (38)	200 (39)	424 (36)	371 (36)	
Missing	948 (48)	255 (49)	540 (45)	490 (47)	
Year of transplant					
2008	213 (11)	68 (13)	137 (12)	141 (14)	
2009	176 (9)	56 (11)	117 (10)	124 (12)	
2010	122 (6)	51 (10)	90 (8)	87 (8)	
2011	95 (5)	27 (5)	66 (6)	48 (5)	
2012	75 (4)	31 (6)	63 (5)	53 (5)	
2013	260 (13)	55 (11)	131 (11)	103 (10)	
2014	319 (16)	83 (16)	201 (17)	165 (16)	
2015	344 (18)	83 (16)	186 (16)	174 (17)	
2016	354 (18)	64 (12)	196 (17)	140 (14)	
Median follow-up of survivors, months	37 (2 - 122)	49 (3 - 120)	47 (3 - 125)	48 (3 - 122)	

Table 2.2 Infection and time dependent variables, by Donor/Recipient CMV Serostatus

Variable	+/+	+/-	-/+	-/-	P value
Number of patients	1958	518	1187	1035	
Cell dose					
White cell count , median(range), 10*9/L, @ day 180	5.1 (0.1 - 690.9)	4.8 (0.1 - 78.3)	4.7 (0.1 - 253.7)	4.9 (0.1 - 241.0)	
Missing	392 (20)	75 (14)	207 (17)	154 (15)	
Absolute lymphocyte count , median(range), 10*9/L, @day 180	1.3 (0.0 - 9.4)	0.9 (0.0 - 9.1)	1.1 (0.0 - 10.0)	0.8 (0.0 - 9.4)	
Missing	462 (24)	93 (18)	242 (20)	188 (18)	
CD3 , median(range), 10*9/L, @ day 100	0.7 (0.0 - 9.0)	0.5 (0.0 - 8.0)	0.5 (0.0 - 6.0)	0.3 (0.0 - 7.0)	
CD4 , median(range), 10*9/L, @ day 100	0.2 (0.0 - 9.0)	0.3 (0.0 - 8.0)	0.2 (0.0 - 3.9)	0.1 (0.0 - 0.7)	
CD8 , median(range), 10*9/L, @ day 100	0.4 (0.0 - 5.7)	0.2 (0.0 - 10.0)	0.3 (0.0 - 9.0)	0.1 (0.0 - 10.0)	
CD4:CD8 ratio , median(range), @ day 100	0.5 (0.0 - 1100.4)	1.2 (0.0 - 9.8)	0.7 (0.0 - 489.7)	1.2 (0.1 - 36.4)	
CD3 , median(range), 10*9/L, @ 6 month	0.9 (0.0 - 7.2)	0.6 (0.1 - 2.3)	0.6 (0.0 - 3.9)	0.4 (0.0 - 5.0)	
CD4 , median(range), 10*9/L, @ 6 month	0.3 (0.0 - 9.0)	0.3 (0.0 - 6.0)	0.2 (0.0 - 10.0)	0.2 (0.0 - 1.0)	
CD8 , median(range), 10*9/L, @ 6 month	0.6 (0.0 - 5.9)	0.3 (0.0 - 7.0)	0.4 (0.0 - 2.6)	0.2 (0.0 - 9.0)	
CD4:CD8 ratio , median(range), @ 6 month	0.5 (0.0 - 248.4)	0.8 (0.1 - 5.1)	0.5 (0.0 - 5.8)	1.2 (0.0 - 2142.9)	
CMV Infection					
CMV Viremia (± organ disease) by day180					<0.001
Yes	682 (35)	63 (12)	457 (39)	25 (2)	
No	1276 (65)	455 (88)	730 (61)	1010 (98)	
Time from transplant to CMV Viremia (± organ disease), median(range), days	38 (2 - 175)	46 (7 - 178)	39 (3 - 179)	70 (11 - 168)	<0.001
CMV organ disease (± viremia) by day180					<0.001
Yes	52 (3)	9 (2)	50 (4)	3 (<1)	

Variable	+/+	+/-	-/+	-/-	P value
No	1906 (97)	509 (98)	1137 (96)	1032	
Time from transplant to CMV organ disease (± viremia), median(range), days	56 (11 - 173)	73 (49 - 141)	45 (4 - 176)	36 (22 - 54)	0.077
CMV in GI					<0.001
Yes	12 (<1)	2 (<1)	5 (<1)	0	
No	40 (2)	7 (1)	45 (4)	3 (<1)	
No CMV infection other than viremia	1906 (97)	509 (98)	1137 (96)	1032	
CMV in lung					<0.001
Yes	21 (1)	0	17 (1)	0	
No	31 (2)	9 (2)	33 (3)	3 (<1)	
No CMV infection other than viremia	1906 (97)	509 (98)	1137 (96)	1032	
CMV in liver					<0.001
Yes	1 (<1)	1 (<1)	0	0	
No	51 (3)	8 (2)	50 (4)	3 (<1)	
No CMV infection other than viremia	1906 (97)	509 (98)	1137 (96)	1032	
CMV in other sites					<0.001
Yes	20 (1)	6 (1)	31 (3)	2 (<1)	
No	32 (2)	3 (<1)	19 (2)	1 (<1)	
No CMV infection other than viremia	1906 (97)	509 (98)	1137 (96)	1032	
Co-infection (fungal/bacteria infection within 30 days of viral infection)					<0.001
Yes	465 (24)	70 (14)	281 (24)	108 (10)	
No co-infection	479 (24)	88 (17)	320 (27)	145 (14)	
No viral infection	830 (42)	280 (54)	477 (40)	639 (62)	
Missing	184 (9)	80 (15)	109 (9)	143 (14)	
Time dependent variable					
ANC500					<0.001
Yes	1900 (97)	509 (98)	1154 (97)	1013 (98)	
No	51 (3)	8 (2)	28 (2)	20 (2)	
Missing	7 (<1)	1 (<1)	5 (<1)	2 (<1)	
Time from transplant to ANC>500, days	15 (<1 - 149)	15 (1 - 90)	15 (<1 - 96)	15 (1 - 67)	0.003

Variable	+/+	+/-	-/+	-/-	P value
Acute GVHD grade II-IV					0.148
No	1288 (66)	348 (67)	775 (65)	664 (64)	
Yes	639 (33)	165 (32)	403 (34)	356 (34)	
Missing	31 (2)	5 (<1)	9 (<1)	15 (1)	
Time from transplant to aGVHD, days	36 (7 - 177)	33 (9 - 171)	37 (7 - 178)	37 (9 - 176)	0.291
Chronic GVHD(any severity) at 1 year					0.031
No	1068 (55)	303 (58)	694 (58)	558 (54)	
Yes	886 (45)	214 (41)	492 (41)	477 (46)	
Missing	4 (<1)	1 (<1)	1 (<1)	0	
Time from transplant to cGVHD, months	6 (1 - 50)	6 (2 - 48)	6 (2 - 57)	6 (2 - 67)	0.222
Median follow-up of survivors, months	37 (2 - 122)	49 (3 - 120)	47 (3 - 125)	48 (3 - 122)	

Table 3.1 Characteristics of patients who underwent first ALLO transplants with Cy and without Cy conditioning regimen by CMV reactivation by 180 days, reported to the CIBMTR, from 2008 to 2016

Variable	CMV reactivation by 180 days	No CMV by 180	P value
Patient related			
Number of patients	1291	3527	
Number of centers	105	118	
Gender			0.004
Male	710 (55)	2102 (60)	
Female	581 (45)	1425 (40)	
Age, median(range), years	54 (2 - 78)	53 (2 - 78)	0.004
Age at transplant, years			0.004
<=10	26 (2)	123 (3)	
11-20	61 (5)	208 (6)	
21-30	95 (7)	311 (9)	
31-40	130 (10)	317 (9)	
41-50	197 (15)	515 (15)	
51-60	339 (26)	975 (28)	
61-70	369 (29)	936 (27)	
>70	74 (6)	142 (4)	
Karnofsky performance pre-Preparative Regimen			0.008
<80	152 (12)	464 (13)	
80-89	378 (29)	871 (25)	
>=90	740 (57)	2146 (61)	
Missing	21 (2)	46 (1)	
Race/Ethnicity			<0.001
Caucasian, non-Hispanic	802 (62)	2573 (73)	
African-American, non-Hispanic	163 (13)	230 (7)	
Asian, non-Hispanic	119 (9)	210 (6)	
Pacific islander, non-Hispanic	8 (<1)	12 (<1)	
Native American, non-Hispanic	6 (<1)	10 (<1)	
Hispanic, Caucasian	126 (10)	292 (8)	
Hispanic, African-American	5 (<1)	5 (<1)	
Hispanic, Asian	2 (<1)	1 (<1)	
Hispanic, Parcific islander	2 (<1)	1 (<1)	
Hispanic, Native American	2 (<1)	4 (<1)	
Missing	56 (4)	189 (5)	
Donor related			

Variable	CMV reactivation by 180 days	No CMV by 180	P value
Donor age, years			<0.001
<=10	13 (1)	88 (2)	
11-20	25 (2)	75 (2)	
21-30	155 (12)	368 (10)	
31-40	226 (18)	489 (14)	
41-50	276 (21)	670 (19)	
51-60	301 (23)	914 (26)	
61-70	204 (16)	677 (19)	
>70	34 (3)	85 (2)	
Missing	57 (4)	161 (5)	
Donor age, median(range), years	47 (2 - 80)	49 (1 - 85)	0.012
Donor/recipient gender match			0.031
Male-Male	405 (31)	1171 (33)	
Male-Female	316 (24)	757 (21)	
Female-Male	305 (24)	931 (26)	
Female-Female	265 (21)	668 (19)	
Donor/Recipient CMV status			<0.001
+/+	702 (54)	1256 (36)	
+/-	66 (5)	452 (13)	
-/+	472 (37)	715 (20)	
-/-	25 (2)	1010 (29)	
+/?	2 (<1)	12 (<1)	
-/?	0	19 (<1)	
?/+	22 (2)	41 (1)	
?/-	2 (<1)	22 (<1)	
Disease related			
Disease			0.565
AML	660 (51)	1797 (51)	
ALL	253 (20)	652 (18)	
MDS	378 (29)	1078 (31)	
HCT-CI			0.003
0	331 (26)	1099 (31)	
1	176 (14)	490 (14)	
2	183 (14)	486 (14)	
3+	590 (46)	1422 (40)	
Missing	11 (<1)	30 (<1)	

Variable	CMV reactivation by 180 days	No CMV by 180	P value
DRI			
Low	45 (3)	138 (4)	
Intermediate	658 (51)	1975 (56)	
High	416 (32)	960 (27)	
Very high	45 (3)	78 (2)	
TBD/Missing (need review)	127 (10)	376 (11)	
Transplant-related			
Graft type			0.041
Bone Marrow	259 (20)	617 (17)	
Peripheral blood	1032 (80)	2910 (83)	
Donor/recipient HLA match			<0.001
HLA-identical siblings	952 (74)	3009 (85)	
matched related	11 (<1)	43 (1)	
Mismatched related, mismatch>=2	328 (25)	475 (13)	
Conditioning regimen intensity			0.447
Myeloablative	778 (60)	2168 (61)	
RIC/NMA	513 (40)	1359 (39)	
GVHD prophylaxis			<0.001
Ex vivo T-cell depletion	32 (2)	62 (2)	
CD34 selection	37 (3)	78 (2)	
Post-CY + other(s)	347 (27)	461 (13)	
Post-CY alone	2 (<1)	8 (<1)	
TAC/CSA + MMF +- others	309 (24)	715 (20)	
TAC/CSA + MTX +- others	488 (38)	1824 (52)	
TAC/CSA + others (except MTX, MMF)	50 (4)	233 (7)	
TAC/CSA alone	21 (2)	109 (3)	
Other GVHD prophylaxis	5 (<1)	37 (1)	
TBI			<0.001
No	670 (52)	2142 (61)	
Yes	617 (48)	1377 (39)	
Missing	4 (<1)	8 (<1)	
Time from diagnosis to transplant			0.004
<6 month	608 (47)	1842 (52)	
6 month-1Y	328 (25)	751 (21)	
1Y-2Y	177 (14)	462 (13)	
>=2Y	177 (14)	459 (13)	

Variable	CMV reactivation by 180 days	No CMV by 180	P value
Missing	1 (<1)	13 (<1)	
Time from diagnosis to transplant, median(range), months	6 (1 - 370)	6 (<1 - 497)	0.002
Cell counts			
Nucleated cell count, median(range), 10*8/kg, @infusion	7 (<1 - 42)	7 (<1 - 59)	0.261
Nucleated cell count, 10*8/kg			0.032
<3	190 (15)	410 (12)	
3-9	354 (27)	991 (28)	
>9	316 (24)	868 (25)	
Missing	431 (33)	1258 (36)	
CD34+ cell count , median(range), 10*6/kg, @infusion	5 (<1 - 20)	5 (<1 - 20)	0.410
CD34 cell count, 10*6/kg			0.334
<4	356 (28)	894 (25)	
4-8	415 (32)	1167 (33)	
>8	171 (13)	448 (13)	
Missing	349 (27)	1018 (29)	
CD3+ cell count , median(range), 10*7/kg, @infusion	17 (<1 - 60)	17 (<1 - 60)	0.465
CD3 cell count, 10*7/kg			
<4	175 (14)	387 (11)	
4-8	44 (3)	139 (4)	
>8	517 (40)	1256 (36)	
Missing	555 (43)	1745 (49)	
Year of transplant			
2008	140 (11)	423 (12)	
2009	100 (8)	376 (11)	
2010	83 (6)	268 (8)	
2011	64 (5)	173 (5)	
2012	56 (4)	167 (5)	
2013	133 (10)	423 (12)	
2014	224 (17)	581 (16)	
2015	231 (18)	576 (16)	
2016	260 (20)	540 (15)	
Median follow-up of survivors, months	36 (3 - 125)	47 (2 - 122)	

Table 3.2 Infection and time dependent variables, by CMV Reactivation by 180

Variable	CMV reactivation by 180 days	No CMV by 180
Number of patients	1291	3527
Cell dose		
White cell count , median(range), 10*9/L, @ day 180	4.8 (0.1 - 210.2)	5.0 (0.1 - 690.9)
Missing	244 (19)	611 (17)
Absolute lymphocyte count , median(range), 10*9/L, @day 180	1.4 (0.0 - 9.9)	0.9 (0.0 - 10.0)
Missing	295 (23)	720 (20)
CD3 , median(range), 10*9/L, @ day 100	0.6 (0.0 - 9.0)	0.5 (0.0 - 8.0)
CD4 , median(range), 10*9/L, @ day 100	0.2 (0.0 - 8.0)	0.2 (0.0 - 9.0)
CD8 , median(range), 10*9/L, @ day 100	0.4 (0.0 - 9.0)	0.2 (0.0 - 10.0)
CD4:CD8 ratio , median(range), @ day 100	0.5 (0.0 - 489.7)	0.9 (0.0 - 1100.4)
CD3 , median(range), 10*9/L, @ 6 month	0.9 (0.0 - 4.3)	0.6 (0.0 - 7.2)
CD4 , median(range), 10*9/L, @ 6 month	0.2 (0.0 - 10.0)	0.2 (0.0 - 9.0)
CD8 , median(range), 10*9/L, @ 6 month	0.6 (0.0 - 7.0)	0.3 (0.0 - 9.0)
CD4:CD8 ratio , median(range), @ 6 month	0.4 (0.0 - 1832.5)	0.8 (0.0 - 2142.9)
CMV Infection		
CMV Viremia (± organ disease) by day180		
Yes	1253 (97)	0
No	38 (3)	3527
Time from transplant to Viremia (± organ disease), median(range), days	39 (2 - 179)	N/A
CMV organ involvement (± viremia) by day180		
Yes	114 (9)	0
No	1177 (91)	3527
Time from transplant to CMV organ involvement (± viremia), median(range), days	54 (4 - 176)	N/A
CMV in GI		
Yes	19 (1)	0
No	95 (7)	0
No CMV infection other than viremia	1177 (91)	3527
CMV in lung		
Yes	39 (3)	0
No	75 (6)	0
No CMV infection other than viremia	1177 (91)	3527
CMV in liver		

Variable	CMV reactivation by 180 days	No CMV by 180
Yes	2 (<1)	0
No	112 (9)	0
No CMV infection other than viremia	1177 (91)	3527
CMV in other sites		
Yes	59 (5)	0
No	55 (4)	0
No CMV infection other than viremia	1177 (91)	3527
Co-infection (fungal/bacterial infection within 30 days of viral infection)		
Yes	624 (48)	321 (9)
No co-infection	667 (52)	392 (11)
No viral infection	0	2290 (65)
Missing	0	524 (15)
Time dependent variable		
ANC500		
Yes	1283 (99)	3408 (97)
No	4 (<1)	104 (3)
Missing	4 (<1)	15 (<1)
Time from transplant to ANC>500, days	15 (<1 - 105)	15 (<1 - 149)
Acute GVHD grade II-IV		
No	704 (55)	2454 (70)
Yes	567 (44)	1030 (29)
Missing	20 (2)	43 (1)
Time from transplant to aGVHD, days	35 (7 - 177)	37 (7 - 178)
Chronic GVHD(any severity) at 1 year		
No	742 (57)	1953 (55)
Yes	546 (42)	1570 (45)
Missing	3 (<1)	4 (<1)
Time from transplant to cGVHD, months	6 (2 - 49)	6 (1 - 67)
Median follow-up of survivors, months	36 (3 - 125)	47 (2 - 122)

Table 4.1 Characteristics of patients who underwent first ALLO transplants with Cy and without Cy conditioning regimen by non-CMV viral infection by 180 days, reported to the CIBMTR, from 2008 to 2016

Variable	Other viral infections by 180 days	No other viral infections by 180
Patient related		
Number of patients	1210	3608
Number of centers	111	116
Gender		
Male	727 (60)	2085 (58)
Female	483 (40)	1523 (42)
Age, median(range), years	51 (2 - 76)	54 (2 - 78)
Age at transplant, years		
<=10	72 (6)	77 (2)
11-20	97 (8)	172 (5)
21-30	117 (10)	289 (8)
31-40	112 (9)	335 (9)
41-50	180 (15)	532 (15)
51-60	288 (24)	1026 (28)
61-70	300 (25)	1005 (28)
>70	44 (4)	172 (5)
Karnofsky performance pre-Preparative Regimen		
<80	148 (12)	468 (13)
80-89	335 (28)	914 (25)
>=90	714 (59)	2172 (60)
Missing	13 (1)	54 (1)
Race/Ethnicity		
Caucasian, non-Hispanic	773 (64)	2602 (72)
African-American, non-Hispanic	155 (13)	238 (7)
Asian, non-Hispanic	83 (7)	246 (7)
Pacific islander, non-Hispanic	3 (<1)	17 (<1)
Native American, non-Hispanic	2 (<1)	14 (<1)
Hispanic, Caucasian	125 (10)	293 (8)
Hispanic, African-American	5 (<1)	5 (<1)
Hispanic, Asian	1 (<1)	2 (<1)
Hispanic, Parcific islander	0	3 (<1)
Hispanic, Native American	2 (<1)	4 (<1)
Missing	61 (5)	184 (5)

Variable	Other viral infections by 180 days	No other viral infections by 180
Donor related		
Donor age, years		
<=10	35 (3)	66 (2)
11-20	32 (3)	68 (2)
21-30	137 (11)	386 (11)
31-40	208 (17)	507 (14)
41-50	243 (20)	703 (19)
51-60	276 (23)	939 (26)
61-70	192 (16)	689 (19)
>70	22 (2)	97 (3)
Missing	65 (5)	153 (4)
Donor age, median(range), years	46 (1 - 79)	49 (1 - 85)
Donor/recipient gender match		
Male-Male	388 (32)	1188 (33)
Male-Female	261 (22)	812 (23)
Female-Male	339 (28)	897 (25)
Female-Female	222 (18)	711 (20)
Donor/Recipient CMV status		
+/+	513 (42)	1445 (40)
+/-	112 (9)	406 (11)
-/+	313 (26)	874 (24)
-/-	239 (20)	796 (22)
+/?	3 (<1)	11 (<1)
-/?	6 (<1)	13 (<1)
?/+	17 (1)	46 (1)
?/-	7 (<1)	17 (<1)
Disease related		
Disease		
AML	564 (47)	1893 (52)
ALL	286 (24)	619 (17)
MDS	360 (30)	1096 (30)
HCT-CI		
0	320 (26)	1110 (31)
1	178 (15)	488 (14)
2	180 (15)	489 (14)
3+	521 (43)	1491 (41)

Variable	Other viral infections by 180 days	No other viral infections by 180
Missing	11 (<1)	30 (<1)
DRI		
Low	46 (4)	137 (4)
Intermediate	612 (51)	2021 (56)
High	373 (31)	1003 (28)
Very high	52 (4)	71 (2)
TBD/Missing (need review)	127 (10)	376 (10)
Transplant-related		
Graft type		
Bone Marrow	293 (24)	583 (16)
Peripheral blood	917 (76)	3025 (84)
Donor/recipient HLA match		
HLA-identical siblings	902 (75)	3059 (85)
matched related	21 (2)	33 (<1)
Mismatched related, mismatch>=2	287 (24)	516 (14)
Conditioning regimen intensity		
Myeloablative	785 (65)	2161 (60)
RIC/NMA	425 (35)	1447 (40)
GVHD prophylaxis		
Ex vivo T-cell depletion	24 (2)	70 (2)
CD34 selection	52 (4)	63 (2)
Post-CY + other(s)	290 (24)	518 (14)
Post-CY alone	2 (<1)	8 (<1)
TAC/CSA + MMF +- others	275 (23)	749 (21)
TAC/CSA + MTX +- others	475 (39)	1837 (51)
TAC/CSA + others (except MTX, MMF)	46 (4)	237 (7)
TAC/CSA alone	36 (3)	94 (3)
Other GVHD prophylaxis	10 (<1)	32 (<1)
TBI		
No	667 (55)	2145 (59)
Yes	543 (45)	1451 (40)
Missing	0	12 (<1)
Time from diagnosis to transplant		
<6 month	575 (48)	1875 (52)
6 month-1Y	269 (22)	810 (22)
1Y-2Y	179 (15)	460 (13)

Variable	Other viral infections by 180 days	No other viral infections by 180
>=2Y	184 (15)	452 (13)
Missing	3 (<1)	11 (<1)
Time from diagnosis to transplant, median(range), months	6 (1 - 370)	6 (<1 - 497)
Cell counts		
Nucleated cell count, median(range), 10*8/kg, @infusion	6 (<1 - 59)	7 (<1 - 52)
Nucleated cell count, 10*8/kg		
<3	194 (16)	406 (11)
3-9	357 (30)	988 (27)
>9	292 (24)	892 (25)
Missing	367 (30)	1322 (37)
CD34+ cell count , median(range), 10*6/kg, @infusion	5 (<1 - 20)	5 (<1 - 20)
CD34 cell count, 10*6/kg		
<4	339 (28)	911 (25)
4-8	381 (31)	1201 (33)
>8	161 (13)	458 (13)
Missing	329 (27)	1038 (29)
CD3+ cell count , median(range), 10*7/kg, @infusion	15 (<1 - 60)	18 (<1 - 60)
CD3 cell count, 10*7/kg		
<4	173 (14)	389 (11)
4-8	60 (5)	123 (3)
>8	433 (36)	1340 (37)
Missing	544 (45)	1756 (49)
Year of transplant		
2008	98 (8)	465 (13)
2009	110 (9)	366 (10)
2010	82 (7)	269 (7)
2011	53 (4)	184 (5)
2012	57 (5)	166 (5)
2013	141 (12)	415 (12)
2014	248 (20)	557 (15)
2015	215 (18)	592 (16)
2016	206 (17)	594 (16)
Median follow-up of survivors, months	37 (3 - 122)	47 (2 - 125)

Table 4.2 Infection and time dependent variables, by other infection by 180

Variable	Other infections by 180 days	No other infections by 180
Number of patients	1210	3608
Cell dose		
White cell count , median(range), 10*9/L, @ day 180	4.7 (0.1 - 690.9)	5.0 (0.1 - 343.1)
Missing	226 (19)	629 (17)
Absolute lymphocyte count , median(range), 10*9/L, @day 180	1.0 (0.0 - 8.6)	1.0 (0.0 - 10.0)
Missing	271 (22)	744 (21)
CD3 , median(range), 10*9/L, @ day 100	0.5 (0.0 - 9.0)	0.5 (0.0 - 8.0)
CD4 , median(range), 10*9/L, @ day 100	0.2 (0.0 - 8.0)	0.2 (0.0 - 9.0)
CD8 , median(range), 10*9/L, @ day 100	0.3 (0.0 - 9.0)	0.3 (0.0 - 10.0)
CD4:CD8 ratio , median(range), @ day 100	0.8 (0.1 - 36.4)	0.8 (0.0 - 1100.4)
CD3 , median(range), 10*9/L, @ 6 month	0.6 (0.0 - 2.7)	0.7 (0.0 - 7.2)
CD4 , median(range), 10*9/L, @ 6 month	0.2 (0.0 - 8.0)	0.3 (0.0 - 10.0)
CD8 , median(range), 10*9/L, @ 6 month	0.3 (0.0 - 9.0)	0.4 (0.0 - 7.0)
CD4:CD8 ratio , median(range), @ 6 month	0.6 (0.0 - 66.0)	0.6 (0.0 - 2142.9)
Non-CMV viral Infection		
Viremia (± organ disease) by day180		
Yes	385 (32)	0
No	825 (68)	3608
Time from transplant to Viremia (± organ disease), median(range), days	45 (2 - 175)	N/A
Virus organ involvement (± viremia) by day180		
Yes	993 (82)	0
No	217 (18)	3608
Time from transplant to Virus organ involvement (± viremia), median(range), days	48 (2 - 180)	N/A
Site of infection other than Viremia alone		
Non-CMV Viral infection in GI		
Yes	10 (<1)	0
No	983 (81)	0
No non-CMV viral infection other than viremia	217 (18)	3608
Non-CMV Viral infection in lung		
Yes	67 (6)	0
No	926 (77)	0
No non-CMV viral infection other than viremia	217 (18)	3608
Non-CMV viral infection in liver		
Yes	8 (<1)	0
No	985 (81)	0
No non-CMV viral infection other than viremia	217 (18)	3608

Variable	Other infections by 180 days	No other infections by 180
Non-CMV viral infection in other sites		
Yes	940 (78)	0
No	53 (4)	0
No non-CMV viral infection other than viremia	217 (18)	3608
Non-CMV viral Infection in blood		
HSV		
Yes	13 (1)	0
No	1197 (99)	3608
Varicella		
Yes	3 (<1)	0
No	1207	3608
Adenovirus		
Yes	34 (3)	0
No	1176 (97)	3608
Enterovirus		
Yes	1 (<1)	0
No	1209	3608
HBV		
Yes	5 (<1)	0
No	1205	3608
HCV		
Yes	4 (<1)	0
No	1206	3608
Influenza		
Yes	3 (<1)	0
No	1207	3608
RSV		
Yes	6 (<1)	0
No	1204	3608
Parainfluenza		
Yes	3 (<1)	0
No	1207	3608
HHV-6		
Yes	138 (11)	0
No	1072 (89)	3608
EBV		
Yes	139 (11)	0
No	1071 (89)	3608
Polyoma virus		
Yes	72 (6)	0

Variable	Other infections by 180 days	No other infections by 180
No	1138 (94)	3608
Rotavirus		
Yes	1 (<1)	0
No	1209	3608
Rhinovirus		
Yes	5 (<1)	0
No	1205	3608
Influenza A		
Yes	2 (<1)	0
No	1208 (>99)	3608
Other virus, specify		
Yes	24 (2)	0
No	1186 (98)	3608
Non-CMV viral Infection in other sites		
HSV		
Yes	82 (7)	0
No	1128 (93)	3608
Varicella		
Yes	45 (4)	0
No	1165 (96)	3608
Adenovirus		
Yes	65 (5)	0
No	1145 (95)	3608
Enterovirus		
Yes	30 (2)	0
No	1180 (98)	3608
HCV		
Yes	3 (<1)	0
No	1207	3608
Influenza		
Yes	70 (6)	0
No	1140 (94)	3608
Parainfluenza		
Yes	112 (9)	0
No	1098 (91)	3608
HHV-6		
Yes	20 (2)	0
No	1190 (98)	3608
EBV		
Yes	6 (<1)	0

Variable	Other infections by 180 days	No other infections by 180
No	1204	3608
Polyoma virus		
Yes	453 (37)	0
No	757 (63)	3608
Rotavirus		
Yes	22 (2)	0
No	1188 (98)	3608
Rhinovirus		
Yes	159 (13)	0
No	1051 (87)	3608
HPV		
Yes	1 (<1)	0
No	1209	3608
Influenza A		
Yes	49 (4)	0
No	1161 (96)	3608
Enterovirus NOS		
Yes	3 (<1)	0
No	1207 (>99)	3608
Other virus, specify		
Yes	9 (<1)	0
No	1201 (99)	3608
Co-infection (fungal/bacterial infection within 30 days of viral infection)		
Yes	634 (52)	311 (9)
No co-infection	576 (48)	483 (13)
No viral infection	0	2290 (63)
Time dependent variable		
ANC500		
Yes	1197 (99)	3494 (97)
No	8 (<1)	100 (3)
Missing	5 (<1)	14 (<1)
Time from transplant to ANC>500, days	15 (<1 - 149)	15 (<1 - 105)
Acute GVHD grade II-IV		
No	674 (56)	2484 (69)
Yes	521 (43)	1076 (30)
Missing	15 (1)	48 (1)
Time from transplant to aGVHD, days	35 (7 - 175)	37 (7 - 178)
Chronic GVHD(any severity) at 1 year		
No	691 (57)	2004 (56)

Variable	Other infections by 180 days	No other infections by 180
Yes	518 (43)	1598 (44)
Missing	1 (<1)	6 (<1)
Time from transplant to cGVHD, months	6 (1 - 49)	6 (2 - 67)
Median follow-up of survivors, months	37 (3 - 122)	47 (2 - 125)

CIBMTR STUDY IN18-01

COMPARISON OF EARLY (BY D+100) BACTERIAL AND FUNGAL INFECTIONS AFTER HAPLOIDENTICAL HSCT BETWEEN PATIENTS RECEIVING CYCLOPHOSPHAMIDE-BASED OR OTHER GVHD PROPHYLAXIS

Draft Protocol

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1.0 Hypothesis:

We hypothesize that the incidence of bacterial and fungal infections and the impact of these infections on allogeneic hematopoietic cell transplant (HCT) outcomes differ between fully matched related related donor transplants (MRD) and Haploidentical (HaploHCT) transplant with further differences associated with the use of post-transplant cyclophosphamide (PTCy).

2.0 Specific Aims

2.1 Determine the incidence and infection density of bacterial infections and fungal infections occurring within 100 days after HCT

2.2 Assess the impact of bacterial and fungal infections by day 100 on 1 year transplant outcomes

- 2.2.1 Relapse
- 2.2.2 Non-relapse mortality (NRM)
- 2.2.3 Disease free survival (DFS)
- 2.2.4 Overall Survival (OS)
- 2.2.5 Chronic GVHD

3.0 Scientific Impact/Justification:

Infections are a common complications of allogeneic hematopoietic cell transplantation (HCT) and are associated with increased morbidity and mortality. Incidence and type of infections are affected by severity and duration of immunosuppression that depends on graft type, content and intensity of conditioning regimens and GVHD prophylaxis or treatment. The use of post-transplantation cyclophosphamide (PostCy) has significantly increased over the last few years. Although postCy was first used in haploidentical donor HCT[1], its use has been extended to other graft types as well.[2] In this study, we like to evaluate the infectious complications of this approach and compare with others.

4.0 Study Population (*Same as IN1701)

Inclusion Criteria:

- Patients receiving first allogeneic HCT for AML, ALL, and MDS between 2008 – 2016
- Age ≥ 2 years

Exclusion Criteria:

- Patients who received UCBT
- Patients receiving an unrelated donor
- Patients with only a single mismatch related donor
- Patient information that lacks post-transplant infection information
- Center restriction: Patients transplanted at centers which have no reported haploHCT patients

- Patient cohorts for the general population are as follows:
  - HaploHCT with PTCy
  - HaploHCT with other GVHD prophylaxis
  - MRD with PTCy
  - MRD with other GVHD prophylaxis (Control)

5.0 OUTCOMES

5.1 Incidence of bacterial infections by day 100: This will be calculated as a cumulative incidence with death as the competing risk.

5.2 Incidence of fungal infections by day 100: This will be calculated as a cumulative incidence with death as the competing risk.

5.3 Infection density: This will calculated separately for bacterial and fungal infections

5.4 Transplant related mortality (TRM): Cumulative incidence defined as death without preceding disease relapse/progression. Relapse is competing event. This will be examined as a Dynamic landmark analysis at day 30, day 60 and day 100.

5.5 Infection-Related mortality (IRM): Cumulative incidence of death caused by infection. Relapse and death from non-infectious causes are competing events. This will be examined as a Dynamic landmark analysis at day 30, day 60, and day 100.

5.6 Incidence of acute GVHD: cumulative incidence of overall grade II – IV acute GVHD and lower GI stage 2 – 4 aGVHD. Death is the competing risk. This will be examined as a Dynamic landmark analysis at day 21 and day 42.

5.7 Incidence of chronic GVHD: cumulative incidence of overall chronic GVHD and GI cGVHD. Death is the competing risk. This will be examined as a landmark analysis for patients alive at day 100.

5.8 Relapse/Progression: Cumulative incidence of disease relapse/progression, with TRM as competing event.

5.9 Disease free survival: will be defined as time to relapse or death from any cause. Patients are censored at last follow-up.

5.10 Overall survival (OS): time to death. Death from any cause will be considered an event. Surviving patients will be censored at time of last follow-up.

5.11 Infection as cause of death: descriptive only.

6.0 VARIABLES TO BE ANALYZED (*Same as IN1701)

Patient related

- Patient age at transplant (in decades ≤ 10, 11-20, 21-30, 31-40, 41-50, 51-60, ≥ 60)
- Patient gender
- Patient race/ethnicity
- Karnofsky performance at transplant: <90% vs. ≥90%
- Recipient HCT-CI

Donor Related

- Donor age (in decades ≤ 10, 11-20, 21-30, 31-40, 41-50, 51-60, ≥ 60)
- Donor/recipient gender
- Donor/Recipient cmv serostatus

Disease/Transplant Related

- Disease
- Time from hematologic diagnosis to HCT
- Disease risk index (low vs intermediate vs high risk)
- Conditioning intensity (myeloablative vs. reduced-intensity/non-ablative)
- TBI-based conditioning (yes vs. no)
- GVHD prophylaxis
- Stem cell source (peripheral blood vs. marrow)
- Year of transplant
- Planned therapy with Growth factors (G-CSF or GM-CSF) post-transplant: yes vs. no (defined as day -3 to day +7)
- ATG/Alemtuzumab (yes vs no)

Cell counts

- Total nucleated cell dose (TNC)
- CD34 +/kg-bw
- CD3+/kg-bw cell doses
- Day 180 total white cell count
- Day 180 absolute lymphocyte count
- CD3 counts at day 100
- CD4 counts at day 100
- CD8 counts at day 100
- CD4:CD8 ratio at day 100
- CD3 counts at day 180
- CD4 counts at day 180
- CD8 counts at day 180
- CD4:CD8 ratio at day 180

Infection Related

- Type of bacterial infection
- Site of bacterial infection
- Time from transplant to bacterial infection
- Type of fungal infection
- Site of fungal infection
- Time from transplant to fungal infection

Time dependent

- Time to neutrophil engraftment
- aGVHD grade II-IV: Yes/No
- cGVHD: Yes/No

7.0 Study Design

Patient-, disease- and transplant- related factors will be compared between groups using the Chi-square test for categorical variables and the Wilcox on two sample test for continuous variables. The probabilities of progression-free and overall survival will be calculated using the Kaplan Meier estimator, with the variance estimated by Greenwood's formula. For values for other endpoints, cumulative incidence estimates to account for competing risks will be calculated. Cox proportional hazards regression will be used for outcomes of OS, DFS, NRM, IRM, chronic GVHD, and relapse. The variables to be considered in the multivariable regression models are listed. The assumption of proportional hazards for each factor in the Cox model will be tested. When the proportional hazards assumption is violated, time-dependent variable will be added in the model. The stepwise variable selection method will be used to identify significant risk factors which associated with the outcomes. Factors significantly associated with the outcome variable at a 5% level will be kept in the final model. Interactions between main effect and significant covariates will be tested. Center effects will be tested.

8.0 References:

1. Luznik L, O'Donnell PV, Symons HJ, et al. HLA-haploidentical bone marrow transplantation for hematologic malignancies using nonmyeloablative conditioning and high-dose, posttransplantation cyclophosphamide. *Biol Blood Marrow Transplant*. 2008;14(6):641-650.
2. Mielcarek M, Furlong T, O'Donnell PV, et al. Posttransplantation cyclophosphamide for prevention of graft-versus-host disease after HLA-matched mobilized blood cell transplantation. *Blood*. 2016;127(11):1502-1508.

Table 1.1 Characteristics of patients who underwent first ALLO transplants with Cy and without Cy conditioning regimen, reported to the CIBMTR, from 2008 to 2016

Variable	Mismatch related with Cy N(%)	Mismatch related without Cy N(%)	Matched related with Cy N(%)	Matched related without Cy N(%)	P value
Patient related					
Number of patients	488	315	330	3685	
Number of centers	88	82	68	117	
Gender					0.021
Male	299 (61)	202 (64)	204 (62)	2107 (57)	
Female	189 (39)	113 (36)	126 (38)	1578 (43)	
Age, median(range), years	58 (3 - 78)	57 (2 - 77)	49 (3 - 75)	53 (2 - 78)	<0.001
Age at transplant, years					<0.001
<=10	18 (4)	26 (8)	6 (2)	99 (3)	
11-20	26 (5)	32 (10)	15 (5)	196 (5)	
21-30	46 (9)	23 (7)	52 (16)	285 (8)	
31-40	28 (6)	18 (6)	47 (14)	354 (10)	
41-50	52 (11)	17 (5)	53 (16)	590 (16)	
51-60	97 (20)	67 (21)	70 (21)	1080 (29)	
61-70	167 (34)	103 (33)	78 (24)	957 (26)	
>70	54 (11)	29 (9)	9 (3)	124 (3)	
Karnofsky performance pre-Preparative Regimen					<0.001
<80	73 (15)	39 (12)	47 (14)	457 (12)	
80-89	155 (32)	72 (23)	88 (27)	934 (25)	
>=90	245 (50)	200 (63)	190 (58)	2251 (61)	
Missing	15 (3)	4 (1)	5 (2)	43 (1)	
Race/Ethnicity					<0.001
Caucasian, non-Hispanic	292 (60)	160 (51)	203 (62)	2720 (74)	
African-American, non-Hispanic	92 (19)	61 (19)	45 (14)	195 (5)	
Asian, non-Hispanic	33 (7)	44 (14)	17 (5)	235 (6)	
Pacific islander, non-Hispanic	5 (1)	1 (<1)	1 (<1)	13 (<1)	
Native American, non-Hispanic	2 (<1)	0	1 (<1)	13 (<1)	
Hispanic, Caucasian	37 (8)	27 (9)	37 (11)	317 (9)	
Hispanic, African-American	2 (<1)	1 (<1)	2 (<1)	5 (<1)	

Variable	Mismatch related with Cy N(%)	Mismatch related without Cy N(%)	Matched related with Cy N(%)	Matched related without Cy N(%)	P value
Hispanic, Asian	1 (<1)	0	0	2 (<1)	
Hispanic, Parcific islander	0	0	0	3 (<1)	
Hispanic, Native American	1 (<1)	1 (<1)	0	4 (<1)	
Missing	23 (5)	20 (6)	24 (7)	178 (5)	
Donor related					
Donor age, years					<0.001
<=10	1 (<1)	1 (<1)	5 (2)	94 (3)	
11-20	17 (3)	8 (3)	14 (4)	61 (2)	
21-30	115 (24)	72 (23)	46 (14)	290 (8)	
31-40	145 (30)	99 (31)	54 (16)	417 (11)	
41-50	126 (26)	82 (26)	63 (19)	675 (18)	
51-60	40 (8)	23 (7)	83 (25)	1069 (29)	
61-70	22 (5)	15 (5)	46 (14)	798 (22)	
>70	2 (<1)	1 (<1)	4 (1)	112 (3)	
Missing	20 (4)	14 (4)	15 (5)	169 (5)	
Donor age, median(range), years	36 (10 - 73)	37 (8 - 80)	45 (4 - 76)	52 (1 - 85)	<0.001
Donor/recipient gender match					<0.001
Male-Male	198 (41)	108 (34)	123 (37)	1147 (31)	
Male-Female	115 (24)	57 (18)	81 (25)	820 (22)	
Female-Male	101 (21)	94 (30)	81 (25)	960 (26)	
Female-Female	74 (15)	56 (18)	45 (14)	758 (21)	
Donor/Recipient CMV status					0.007
+/+	219 (45)	133 (42)	134 (41)	1472 (40)	
+/-	33 (7)	39 (12)	35 (11)	411 (11)	
-/+	136 (28)	78 (25)	85 (26)	888 (24)	
-/-	83 (17)	53 (17)	67 (20)	832 (23)	
+/?	1 (<1)	3 (<1)	0	10 (<1)	
-/?	1 (<1)	1 (<1)	1 (<1)	16 (<1)	
?/+	11 (2)	7 (2)	5 (2)	40 (1)	
?/-	4 (<1)	1 (<1)	3 (<1)	16 (<1)	
Disease related					
Disease					<0.001
AML	257 (53)	165 (52)	186 (56)	1849 (50)	
ALL	95 (19)	58 (18)	82 (25)	670 (18)	

Variable	Mismatch related with Cy N(%)	Mismatch related without Cy N(%)	Matched related with Cy N(%)	Matched related without Cy N(%)	P value
MDS	136 (28)	92 (29)	62 (19)	1166 (32)	
HCT-CI					<0.001
0	110 (23)	88 (28)	86 (26)	1146 (31)	
1	75 (15)	44 (14)	47 (14)	500 (14)	
2	65 (13)	39 (12)	51 (15)	514 (14)	
3+	236 (48)	133 (42)	144 (44)	1499 (41)	
Missing	2 (<1)	11 (3)	2 (<1)	26 (<1)	
DRI					
Low	17 (3)	18 (6)	12 (4)	136 (4)	
Intermediate	251 (51)	135 (43)	172 (52)	2075 (56)	
High	153 (31)	98 (31)	98 (30)	1027 (28)	
Very high	16 (3)	9 (3)	16 (5)	82 (2)	
TBD/Missing (need review)	51 (10)	55 (17)	32 (10)	365 (10)	
Transplant-related					
Graft type					<0.001
Bone Marrow	220 (45)	82 (26)	150 (45)	424 (12)	
Peripheral blood	268 (55)	233 (74)	180 (55)	3261 (88)	
Donor/recipient HLA match					<0.001
HLA-identical siblings	0	0	319 (97)	3642 (99)	
matched related	0	0	11 (3)	43 (1)	
Mismatched related, mismatch>=2	488	315	0	0	
Conditioning regimen intensity					<0.001
Myeloablative	195 (40)	145 (46)	182 (55)	2424 (66)	
RIC/NMA	293 (60)	170 (54)	148 (45)	1261 (34)	
GVHD prophylaxis					<0.001
Ex vivo T-cell depletion	0	54 (17)	0	40 (1)	
CD34 selection	0	40 (13)	0	75 (2)	
Post-CY + other(s)	487(99)	0	321 (97)	0	
Post-CY alone	1 (<1)	0	9 (3)	0	
TAC/CSA + MMF +- others	0	174 (55)	0	850 (23)	
TAC/CSA + MTX +- others	0	32 (10)	0	2280 (62)	
TAC/CSA + others (except MTX, MMF)	0	1 (<1)	0	282 (8)	
TAC/CSA alone	0	11 (3)	0	119 (3)	
Other GVHD prophylaxis	0	3 (<1)	0	39 (1)	

Variable	Mismatch related with Cy N(%)	Mismatch related without Cy N(%)	Matched related with Cy N(%)	Matched related without Cy N(%)	P value
TBI					<0.001
No	150 (31)	74 (23)	147 (45)	2441 (66)	
Yes	336 (69)	241 (77)	182 (55)	1235 (34)	
Missing	2 (<1)	0	1 (<1)	9 (<1)	
ATG /Alemtuzumab					<0.001
ATG alone	4 (<1)	63 (20)	6 (2)	389 (11)	
CAMPATH alone	0	16 (5)	0	39 (1)	
No ATG or CAMPATH	482 (99)	236 (75)	323 (98)	3250 (88)	
Missing	2 (<1)	0	1 (<1)	7 (<1)	
G-CSF, GM-CSF(day -3 to day +7)					<0.001
No	84 (17)	98 (31)	97 (29)	2657 (72)	
Yes	399 (82)	215 (68)	233 (71)	1024 (28)	
Missing	5 (1)	2 (<1)	0	4 (<1)	
Time from diagnosis to transplant					<0.001
<6 month	193 (40)	103 (33)	151 (46)	2003 (54)	
6 month-1Y	130 (27)	96 (30)	93 (28)	760 (21)	
1Y-2Y	88 (18)	60 (19)	43 (13)	448 (12)	
>=2Y	77 (16)	55 (17)	43 (13)	461 (13)	
Missing	0	1 (<1)	0	13 (<1)	
Time from diagnosis to transplant, median(range), months	8 (1 - 172)	9 (1 - 330)	6 (1 - 257)	5 (<1 - 497)	<0.001
Cell counts					
Nucleated cell count, median(range), 10*8/kg, @infusion	4 (<1 - 37)	3 (<1 - 59)	5 (<1 - 45)	8 (<1 - 52)	<0.001
Nucleated cell count, 10*8/kg					<0.001
<3	115 (24)	100 (32)	58 (18)	327 (9)	
3-9	149 (31)	65 (21)	107 (32)	1024 (28)	
>9	64 (13)	49 (16)	57 (17)	1014 (28)	
Missing	160 (33)	101 (32)	108 (33)	1320 (36)	
CD34+ cell count , median(range), 10*6/kg, @infusion	4 (<1 - 20)	4 (<1 - 19)	4 (<1 - 17)	5 (<1 - 20)	<0.001
CD34 cell count, 10*6/kg					<0.001
<4	177 (36)	118 (37)	101 (31)	854 (23)	
4-8	151 (31)	69 (22)	123 (37)	1239 (34)	
>8	54 (11)	47 (15)	27 (8)	491 (13)	

Variable	Mismatch related with Cy N(%)	Mismatch related without Cy N(%)	Matched related with Cy N(%)	Matched related without Cy N(%)	P value
Missing	106 (22)	81 (26)	79 (24)	1101 (30)	
CD3+ cell count , median(range), 10*7/kg, @infusion	7 (<1 - 58)	3 (<1 - 58)	8 (<1 - 59)	20 (<1 - 60)	<0.001
CD3 cell count, 10*7/kg					<0.001
<4	106 (22)	111 (35)	65 (20)	280 (8)	
4-8	29 (6)	13 (4)	21 (6)	120 (3)	
>8	128 (26)	68 (22)	93 (28)	1484 (40)	
Missing	225 (46)	123 (39)	151 (46)	1801 (49)	
Year of transplant					
2008	5 (1)	28 (9)	14 (4)	516 (14)	
2009	7 (1)	25 (8)	10 (3)	434 (12)	
2010	5 (1)	2 (<1)	4 (1)	340 (9)	
2011	1 (<1)	9 (3)	4 (1)	223 (6)	
2012	10 (2)	10 (3)	4 (1)	199 (5)	
2013	47 (10)	39 (12)	35 (11)	435 (12)	
2014	92 (19)	69 (22)	46 (14)	598 (16)	
2015	126 (26)	70 (22)	104 (32)	507 (14)	
2016	195 (40)	63 (20)	109 (33)	433 (12)	
Median follow-up of survivors, months	25 (3 - 119)	31 (3 - 125)	24 (3 - 120)	48 (2 - 122)	

Table 1.2 Infection and time dependent variables

Variable	Mismatch related with Cy N(%)	Mismatch related without Cy N(%)	Matched related with Cy N(%)	Matched related without Cy N(%)	P value
Number of patients	488	315	330	3685	
Cell counts at day 100					
White cell count , median(range), 10*9/L, @ day 100	3.6 (0.1 - 76.8)	4.1 (0.1 - 60.0)	4.0 (0.1 - 142.2)	4.4 (0.1 - 305.8)	
Missing	126 (26)	95 (30)	61 (18)	573 (16)	
Absolute lymphocyte count , median(range), 10*9/L, @day 100	0.7 (0.0 - 17.5)	0.7 (0.0 - 6.1)	0.7 (0.0 - 44.1)	0.9 (0.0 - 207.9)	
Missing	138 (28)	102 (32)	68 (21)	707 (19)	
CD3 , median(range), 10*9/L, @ day 100	0.9 (0.0 - 1677.0)	1.4 (0.0 - 3240.0)	55.5 (0.1 - 3442.0)	1.7 (0.0 - 7140.0)	
CD4 , median(range), 10*9/L, @ day 100	0.2 (0.0 - 900.0)	0.3 (0.0 - 979.0)	12.0 (0.0 - 299.0)	0.5 (0.0 - 1126.0)	
CD8 , median(range), 10*9/L, @ day 100	0.7 (0.0 - 1389.0)	1.4 (0.0 - 2613.0)	27.0 (0.0 - 2966.0)	1.1 (0.0 - 3312.0)	
CD4:CD8 ratio , median(range), @ day 100	1.0 (0.0 - 16.7)	0.5 (0.1 - 14.4)	0.6 (0.1 - 9.1)	0.8 (0.0 - 1100.4)	
Infections					
Bacterial infections by day100					<0.001
No	210 (43)	137 (43)	134 (41)	1964 (53)	
Yes	278 (57)	178 (57)	196 (59)	1721 (47)	
Fungal infections by day100					<0.001
No	419 (86)	278 (88)	283 (86)	3424 (93)	
Yes	69 (14)	37 (12)	47 (14)	261 (7)	
Time dependent variable					
ANC500					<0.001
Yes	456 (93)	291 (92)	321 (97)	3623 (98)	
No	24 (5)	21 (7)	8 (2)	55 (1)	
Missing	8 (2)	3 (<1)	1 (<1)	7 (<1)	
Time from transplant to ANC>500, days	17 (1 - 125)	15 (1 - 149)	17 (<1 - 70)	15 (<1 - 96)	<0.001
Acute GVHD grade II-IV					0.517
No	309 (63)	206 (65)	202 (61)	2441 (66)	
Yes	174 (36)	105 (33)	123 (37)	1195 (32)	
Missing	5 (1)	4 (1)	5 (2)	49 (1)	
Time from transplant to aGVHD, days	37 (13 - 166)	32 (9 - 147)	39 (13 - 175)	36 (7 - 178)	0.654

Variable	Mismatch related with Cy N(%)	Mismatch related without Cy N(%)	Matched related with Cy N(%)	Matched related without Cy N(%)	P value
Chronic GVHD(any severity) at 1 year					<0.001
No	352 (72)	221 (70)	227 (69)	1895 (51)	
Yes	136 (28)	91 (29)	103 (31)	1786 (48)	
Missing	0	3 (<1)	0	4 (<1)	
Time from transplant to cGVHD, months	6 (2 - 34)	5 (1 - 18)	6 (3 - 34)	6 (2 - 67)	0.021

CIBMTR-IN18-02

The Incidence, and impact of Clostridium difficile infection within 100 days on Transplant outcomes after allogeneic hematopoietic cell transplant

Draft Protocol

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1.0 HYPOTHESIS:

C Difficile infection (CDI) increases risk of acute and chronic graft versus host disease (GVHD) of gut and slows recovery from hematopoietic cell transplant (HCT) leading to increased transplant related mortality

2.0 SPECIFIC AIMS:

2.1 Determine Incidence of CDI following Allogeneic HCT

2.2 Determine Impact of CDI on transplant outcomes

- 2.2.1 Acute GVHD
- 2.2.2 Chronic GVHD
- 2.2.3 Transplant related mortality
- 2.2.4 Overall Survival

2.3 Identify pre-transplant risk factors for development of CDI after allogeneic HCT

3.0 SCIENTIFIC IMPACT/JUSTIFICATION:

CDI is common after HCT due to use of prophylactic antibiotics before and during allogeneic HCT. Although there are several reports of single institutional experience, the incidence, risk factors and impact CDI has on transplant outcomes has not been clearly defined. The determination of incidence and impact of CDI on HCT outcomes will further help develop strategies for prevention and treatment of CDI post HCT. Some of these could be how to translate evidence obtained from gut microbiota research[(1)], study the regular use of probiotics, prebiotics, fecal transplants etc.

Patients undergoing HCT appear to be one of the highest risk populations for this infection, with rates of CDI exceeding 25% in some studies. In a prospective cohort study of CDI in allogenic HCT recipients by Dubberke et al reported CDI up to 1 year after HCT the incidence was 34% with 60% of the CDI happening prior to day 30 and 78% occurred prior to day 100 [(2)]. CDI on the average is reported in 13- 18% of recipients after allogeneic HCT and 6-8% after autologous HCT, mainly in the first month post transplantation.

Risk factors that have been identified are allogeneic stem cell transplant, cord blood as the source of stem cells, acute graft-versus-host disease (GVHD), total body irradiation (TBI), elderly age, increased use of prophylactic antibiotics, steroids, PPI, prolonged hospitalizations, increased comorbidity index etc [(2-4)]. There was a strong relationship noted between early CDI and subsequent development of gastrointestinal tract GVHD in the year following allogeneic HSCT ($P < .001$)[(5)]. Other studies have reported no impact on transplant related mortality[(6)].

The determination of the risk factors for incidence of C Diff, incidence and impact of c diff on transplant outcomes such as GVHD, NRM, relapse and survival in a multi institutional study is the necessary first step to develop effective prevention, prophylaxis and treatment strategies for C Diff. Although several risk factors such as comorbidity index, disease status etc may be unmodifiable risk factors these patients can be targeted for preemptive monitoring and treatment of C Difficile.

4.0 STUDY POPULATION:

Inclusion criteria: All patients age 2 years and older receiving first allogeneic HCT for AML, ALL, or MDS with a fully HLA matched related or unrelated donor between 2010 and 2017. Stem cell sources include

marrow, peripheral blood, and umbilical cord blood. Cases will be patients reported with CDI by day 100 and controls will be all patients from the same centers with cases.

Exclusion Criteria:

- Patients < 2 years old
- HLA-Mismatched donors
- Lack of consent
- Lack of 2100 form

5.0 OUTCOMES*:*

a. Incidence of CDI within first 100 days: This will be calculated as a cumulative incidence with death as the competing risk.
b. Transplant related mortality (TRM): Cumulative incidence defined as death without preceding disease relapse/progression. Relapse is competing event. This will be examined as a Dynamic landmark analysis at day 21 and day 42.
c. Infection-Related mortality (IRM): Cumulative incidence of death caused by infection. Relapse and death from non-infectious causes are competing events. This will be examined as a Dynamic landmark analysis at day 21 and day 42.
d. Incidence of acute GVHD: cumulative incidence of overall grade II – IV acute GVHD and lower GI stage 2 – 4 aGVHD. Death is the competing risk. This will be examined as a Dynamic landmark analysis at day 21 and day 42.
e. Incidence of chronic GVHD: cumulative incidence of overall chronic GVHD and GI cGVHD. Death is the competing risk. This will be examined as a landmark analysis for patients alive at day 100.
f. Relapse/Progression: Cumulative incidence of disease relapse/progression, with TRM as competing event.
g. Disease free survival: will be defined as time to relapse or death from any cause. Patients are censored at last follow-up.
h. Overall survival (OS): time to death. Death from any cause will be considered an event. Surviving patients will be censored at time of last follow-up.
i. Primary cause of death: descriptive only.

6.0 VARIABLES TO BE DESCRIBED

Recipient/Donor related

- Patient age at transplant (≤ 10, 11-20, 21-30, 31-40, 41-50, 51-60, ≥ 60)
- Patient gender
- Karnofsky performance status
- HCT-CI
- Race
- Donor/Recipient gender match
- Donor/Recipient CMV serostatus

Disease Related

- Disease: AML, ALL or MDS

- Disease risk index (low vs intermediate vs high/very high)
- MRD present at time of HCT (yes vs no vs missing)

Transplant Related

- Time from diagnosis to HCT (0-6 mo vs 6 – 12 mo vs ≥ 12 mo)
- Conditioning intensity (Myeloablative with TBI vs Myeloablative chemotherapy only vs reduced intensity/non-myeloablative)
- Graft type (marrow vs peripheral blood vs cord blood)
- Donor type: HLA identical sib vs. matched related vs. matched unrelated
- GVHD prophylaxis
- ATG/Alemtuzumab (yes vs no)
- Year of HCT
- Systemic antibacterial use (yes vs no)

Time dependent variable

- Neutrophil engraftment (Yes vs No)
- Time to Neutrophil engraftment
- Platelet engraftment (yes vs no)
- Time to platelet engraftment (≥ 20K)
- Acute GVHD grade II-IV occurring prior to CDI (yes vs no)
- Lower GI acute GVHD stage 2 – 4 occurring prior to CDI (yes vs no)

7.0 STUDY DESIGN AND STATISTICAL CONSIDERATION:

A retrospective multicenter study will be conducted utilizing CIBMTR dataset. Patients will be eligible if they satisfied the criteria detailed in the "Study population" section. The objective of this analysis is to study the impact of CDI on transplant outcomes when compared to control cohort from the same center without documented CDI.

Univariate analysis will be performed using Kaplan-Meier Method and will be compared using log-rank test for OS and DFS, while acute / chronic GVHD, TRM, IRM and relapse will be calculated using the cumulative incidence method considering competing risks, with comparisons performed using Gray method. For acute GVHD, a dynamic landmark analysis will be examined at day 21 and day 42.

Multivariable analyses will be performed using Cox proportional hazard model for OS, DFS, TRM, IRM, acute GVHD, chronic GVHD and relapse. The main effect of CDI versus No CDI will be kept in all models as time-dependent variable. The proportional hazards (PH) assumption for each factor in the Cox model will be tested. If some covariates violate the PH assumptions, time-dependent covariates will be added. . A stepwise model selection procedure will be used to identify all significant risk factors. Potential interactions between main effect and significant covariates will be tested.

A Cox proportional Hazards model to assess risk factors for development of CDI will be performed. The time-dependent variables of neutrophil engraftment and preceding aGVHD (overall and lower GI) will be examined as potential post-transplant events affecting risk of CDI.

8.0: Limitations:

Prophylactic antibiotic use is not captured in CIBMTR database prior to March 2017. CIBMTR does not capture any diagnostic information for CDI, hence all data is reported based on Center's determination of C. Difficile Infection. History of CDI prior to HCT, severity of CDI or the treatment that was given is not captured in the CIBMTR database.

9.0 References:

1. Murphy S, Nguyen VH. Role of gut microbiota in graft-versus-host disease. Leuk Lymphoma. 2011;52(10):1844-56.
2. Dubberke ER, Reske KA, Olsen MA, Bommarito KM, Seiler S, Silveira FP, et al. Risk for Clostridium difficile Infection After Allogeneic Hematopoietic Cell Transplant Remains Elevated in the Postengraftment Period. Transplant Direct. 2017;3(4):e145.
3. Alonso CD, Marr KA. Clostridium difficile infection among hematopoietic stem cell transplant recipients: beyond colitis. Curr Opin Infect Dis. 2013;26(4):326-31.
4. Kamboj M, Xiao K, Kaltsas A, Huang YT, Sun J, Chung D, et al. Clostridium difficile infection after allogeneic hematopoietic stem cell transplant: strain diversity and outcomes associated with NAP1/027. Biol Blood Marrow Transplant. 2014;20(10):1626-33.
5. Alonso CD, Treadway SB, Hanna DB, Huff CA, Neofytos D, Carroll KC, et al. Epidemiology and outcomes of Clostridium difficile infections in hematopoietic stem cell transplant recipients. Clin Infect Dis. 2012;54(8):1053-63.
6. Scardina TL, Kang Martinez E, Balasubramanian N, Fox-Geiman M, Smith SE, Parada JP. Evaluation of Risk Factors for Clostridium difficile Infection in Hematopoietic Stem Cell Transplant Recipients. Pharmacotherapy. 2017;37(4):420-8.

Table 1. Characteristics of patients who underwent first ALLO transplants for AML, ALL or MDS with Clostridium difficile by 100 day, from 2010 to 2017

Variable	C Difficile infection by 100 day N(%)	No C difficile infection by 100 day N(%)
Patient related		
Number of patients	834	7253
Number of centers	148	148
Gender		
Male	480 (58)	4216 (58)
Female	354 (42)	3037 (42)
Age, median(range), years	54 (2 - 82)	58 (2 - 81)
Age at transplant, years		
2-10	46 (6)	235 (3)
11-20	51 (6)	299 (4)
21-30	78 (9)	495 (7)
31-40	71 (9)	555 (8)
41-50	104 (12)	875 (12)
51-60	175 (21)	1673 (23)
61-70	241 (29)	2502 (34)
>70	68 (8)	619 (9)
Karnofsky performance pre-Preparative Regimen		
<80	117 (14)	994 (14)
80-89	236 (28)	2043 (28)
>=90	479 (57)	4149 (57)
Missing	2 (<1)	67 (<1)
Race/Ethnicity		
Caucasian, non-Hispanic	645 (77)	5764 (79)
African-American, non-Hispanic	37 (4)	312 (4)
Asian, non-Hispanic	45 (5)	407 (6)
Pacific islander, non-Hispanic	5 (<1)	19 (<1)
Native American, non-Hispanic	6 (<1)	24 (<1)
Hispanic, Caucasian	61 (7)	457 (6)
Hispanic, African-American	4 (<1)	8 (<1)
Hispanic, Asian	0	5 (<1)
Hispanic, Pacific islander	0	3 (<1)
Hispanic, Native American	1 (<1)	6 (<1)
Missing	30 (4)	248 (3)
Donor related		

Variable	C Difficile infection by 100 day N(%)	No C difficile infection by 100 day N(%)
Donor/recipient gender match		
Male-Male	323 (39)	2836 (39)
Male-Female	219 (26)	1838 (25)
Female-Male	156 (19)	1371 (19)
Female-Female	134 (16)	1194 (16)
Missing	2 (<1)	14 (<1)
Donor/Recipient CMV status		
Cord Blood	29 (3)	139 (2)
+/+	277 (33)	2316 (32)
+/-	88 (11)	755 (10)
-/+	219 (26)	2161 (30)
-/-	196 (24)	1729 (24)
+/?	6 (<1)	9 (<1)
-/?	4 (<1)	26 (<1)
?/+	9 (1)	82 (1)
?/-	6 (<1)	36 (<1)
Disease related		
Disease		
AML	442 (53)	3464 (48)
ALL	165 (20)	1098 (15)
MDS	227 (27)	2691 (37)
HCT-CI		
0	190 (23)	1648 (23)
1	114 (14)	1013 (14)
2	129 (15)	1061 (15)
3+	396 (47)	3503 (48)
Missing	5 (<1)	28 (<1)
DRI		
Low	35 (4)	253 (3)
Intermediate	435 (52)	3384 (47)
High	259 (31)	2511 (35)
Very high	20 (2)	135 (2)
TBD/Missing (need review)	85 (10)	970 (13)
Minimal Residual Disease at HCT by Flow cytometry		
Yes	100 (12)	993 (14)
No	434 (52)	3641 (50)
Missing (not collected prior 2013)	300 (36)	2619 (36)

Variable	C Difficile infection by 100 day N(%)	No C difficile infection by 100 day N(%)
Transplant-related		
Time from diagnosis to transplant		
<6 month	424 (51)	3568 (49)
6 month-1Y	213 (26)	1845 (25)
1Y-2Y	109 (13)	906 (12)
>=2Y	88 (11)	913 (13)
Missing	0	21 (<1)
Time from diagnosis to transplant, median(range), months	6 (2 - 497)	6 (<1 - 556)
Graft type		
Bone Marrow	159 (19)	1219 (17)
Peripheral blood	646 (77)	5895 (81)
Cord blood	29 (3)	139 (2)
Donor/recipient HLA match		
Cord blood (fully matched)	29 (3)	139 (2)
HLA-identical siblings	329 (39)	3016 (42)
matched related	2 (<1)	47 (<1)
8/8 unrelated	474 (57)	4051 (56)
Conditioning regimen intensity		
Myeloablative with TBI	227 (27)	1387 (19)
Myeloablative chemotherapy only	319 (38)	2697 (37)
RIC/NMA	287 (34)	3158 (44)
Missing	1 (<1)	11 (<1)
GVHD prophylaxis		
Ex vivo T-cell depletion	6 (<1)	36 (<1)
CD34 selection	11 (1)	151 (2)
Post-CY + other(s)	68 (8)	431 (6)
Post-CY alone	4 (<1)	50 (<1)
TAC/CSA + MMF +- others	167 (20)	1545 (21)
TAC/CSA + MTX +- others	482 (58)	4212 (58)
TAC/CSA + others (except MTX, MMF)	61 (7)	514 (7)
TAC/CSA alone	23 (3)	236 (3)
Other GVHD prophylaxis	12 (1)	78 (1)
ATG/Alemtuzumab		
ATG + Alemtuzumab	0	1 (<1)
ATG alone	204 (24)	1672 (23)
Alemtuzumab alone	19 (2)	168 (2)

Variable	C Difficile infection by 100 day N(%)	No C difficile infection by 100 day N(%)
No ATG or Alemtuzumab	609 (73)	5394 (74)
Missing	2 (<1)	18 (<1)
Year of transplant		
2010	83 (10)	717 (10)
2011	66 (8)	496 (7)
2012	56 (7)	538 (7)
2013	115 (14)	1077 (15)
2014	153 (18)	1319 (18)
2015	157 (19)	1217 (17)
2016	123 (15)	1105 (15)
2017	81 (10)	784 (11)
Systemic antibacterial		
Yes	613 (74)	5334 (74)
No	221 (26)	1877 (26)
Missing	0	42 (<1)
Median follow-up of survivors, months	37 (3 - 97)	37 (3 - 102)

Selection Criteria (IN18-02)	**Removed**	**Remained**
First allo transplant for hematologic malignancy 2010-2017		18279
Age>=2	251	18028
AML, ALL and MDS only	3630	14398
Matched related or unrelated only	5138	9260
Excluded if no consent	172	9088
Excluded quarantine centers from research studies	214	8874
Excluded if no 100-day follow-up form	93	8781
Excluded if conditioning regimen intensity missing	3	8778
Excluded if missing/no GVHD prophylaxis	101	8677
Excluded if patients transplanted at centers which have no reported CDI patients	590	8087

Table 2 Infection and time dependent variables

Variable	C Difficile infection by 100 day N(%)	No C difficile infection by 100 day N(%)
Number of patients	834	7253
Time from transplant to CDI, months	14 (<1 - 99)	N/A
Neutrophil engraftment		
Yes	822 (99)	7108 (98)
No	11 (1)	128 (2)
Missing	1 (<1)	17 (<1)
Time from transplant to ANC>500, days	15 (1 - 47)	15 (<1 - 103)
Platelet engraftment		
Yes	784 (94)	6802 (94)
No	50 (6)	444 (6)
Missing	0	7 (<1)
Time from transplant to platelet>=20K	19 (7 - 724)	18 (<1 - 510)
Acute GVHD grade II-IV		
No	471 (56)	4445 (61)
Yes	351 (42)	2724 (38)
Missing	12 (1)	84 (1)
Time from transplant to aGVHD, days	31 (8 - 168)	34 (7 - 178)
Acute GVHD grade II-IV occurring prior to CDI		
Yes	113 (14)	0
No	238 (29)	0
No GVHD2-4 or no CDI	471 (56)	7253
Missing	12 (1)	0
Lower GI acute GVHD grade II-IV occur prior to CDI		
Yes	47 (6)	0
No	71 (9)	0
No Lower GI GVHD2-4 or no CDI	704 (84)	7253
Missing	12 (1)	0

Proposal: 1810-10

Title:
Retrospective study of the impact of mammalian target of rapamycin inhibitors (mTORi) in the incidence of herpesvirus-associated complications after allogeneic hematopoietic cell transplantation (HCT)

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Hypothesis:
Graft-versus-host disease (GVHD) prophylaxis regimens containing mTORi may be associated with lower incidence of diseases associated with human herpesviruses in the first year post-HCT.

Specific aims:
- Estimate the cumulative incidences of human cytomegalovirus (CMV) infection, CMV disease, pre-emptive treatment for Epstein-Barr virus (EBV), EBV-posttransplantation lymphoproliferative disorder (PTLD), and human herpesvirus 6 (HHV6) encephalitis through 1 year post-HCT, comparing outcomes between mTORi-containing vs non-mTORi-containing GVHD regimens
    - If numbers allow, perform additional sub-group analyses:
        - Evaluate these outcomes for mTORi-containing regimens vs non-mTORi-containing regimens among those HCTs that are post-transplantation cyclophosphamide (PTCy)-based
        - Evaluate these outcomes for mTORi-containing regimens vs non-mTORi-containing regimens among those HCTs that are proximal serotherapy-based
- Compare NRM, OS, and GVHD rates at 1 year between mTORi-containing approaches and non-mTORi-containing approaches
- Evaluate cofactors related to differences in the incidence of viral complications, including conditioning intensity (NMA/RIC vs MAC), donor and recipient serostatus (for CMV and EBV), graft source (PBSC vs BM)

Scientific impact:
The results from this study could help identify the relative impact of mTORi, increasingly included in GVHD prophylaxis strategies, in virus-associated complications post-HCT. This could provide registry-based clinical data to further evaluate the findings of smaller studies that indicate that mTORi may be associated with fewer CMV-related post-HCT complications and to then provide the impetus to better understand this finding on a pre-clinical, mechanistic level. In addition, there is an active question in the field of if PTCy may negate or modulate the protection seemingly afforded by mTORi.

Scientific justification:
In the solid organ transplant setting, mTORi-based regimens have been associated with lower rates of CMV infection and disease, although this effect does not seem to be related to inhibition of viral replication.[1-6] In renal transplant recipients, the addition of an mTORi to a reduced-dose of calcineurin inhibitor (CNI) was associated with lower rates of CMV infection compared to regular dose CNI-based approaches.[7-9] However, this has been less studied in HCT patients where CMV, as well as other herpesvirus complications, are of concern in the early period post-HCT. Thus, the effect, if real, is likely indirect and related to modulation of the cellular immune system. If due to this indirect effect, even viruses that cause diseases post-HCT through mechanisms unrelated to viral replication, such as EBV and the latent viral proliferation that gives rise to EBV-PTLD, may be lower in the setting of mTORi-containing approaches to GVHD prophylaxis. Indeed, there are pre-clinical data to suggest that mTORi

may have anti-tumor activity against gammaherpesviruses, EBV and HHV8.[10,11] However, there is a paucity of clinical data with regard to mTORi and EBV control and some reviews suggest that mTORi may not protect against EBV.[12] In prior CIBMTR analyses of CMV-associated complications post-HCT, the role of mTORi was not evaluated.[13,14]

We recently published the CMV-related infection and disease outcomes across a broad range of transplant approaches at the National Institutes of Health (NIH). In that study, we found that the cumulative incidence of CMV infection was significantly higher for HCT recipients whose GVHD prophylaxis was CNI-based, as compared to those with CNI+mTORi-based approaches. We acknowledge that there have been randomized trials that have shown no difference in CMV infection rates between CNI/methotrexate-based regimens and CNI/mTORi-based regimens.[15,16] Additionally, submitted as an abstract to the TCT 2019 conference, we have evaluated the rates of EBV-related issues post-HCT across the range of HCT approaches at the NIH. We have found that in the NIH cohort of 356 HCT recipients, mTORi-containing regimens were associated with lower incidence of EBV elevations in the blood and less EBV-directed pre-emptive therapy. Among PTCy-based approaches, EBV detection was higher for those receiving CNIs as adjunctive GVHD prophylaxis, as compared to mTORi adjunctive therapy. However, the numbers were overall small in these single-institution analyses, fueling interest in evaluating these same questions in a larger cohort.

Patient eligibility population:

Inclusion criteria:

- Patients undergoing first allo HCT for any disease between January, 2008, and December, 2017

Exclusion criteria:

- UCB graft recipients, ex vivo T-cell depleted grafts, approaches that included planned post-HCT donor lymphocyte infusions

Data requirements:

Collection forms:

2000 Recipient Baseline Data; 2006 HCT Infusion; 2004 Infectious Disease Markers; 2400 Pre-TED; 2402 Pre-TED – Disease Classification; 2450 Post-TED; 2100 Post-HSCT Data; 2900 Recipient Death Data; 2150 CMV/EBV/ADV/HHV6/BK

Variables:

- Patient/disease characteristic variables: sex (male/female); age at HCT; Karnofsky performance status (>90% vs <90%); HCT-CI; disease; malignant vs non-malignant
- Graft characteristic variables: donor age; donor-recipient sex (female into male vs other); degree of HLA match and relatedness (MUD vs MRD vs haplo); CMV IgG serostatus (donor, recipient); EBV IgG serostatus (donor, recipient); source of stem cells (bone marrow vs. peripheral blood)
- Transplantation regimen variables: year of transplant; conditioning: myeloablative vs. reduced intensity/nonmyeloablative; pre-HCT rituximab administration; GVHD prophylaxis (mTORi-containing vs non-mTORi-containing); post-HCT rituximab administration
- Viral Infection variables: time from transplant to infection, organ involved, type of infection
- Post-HCT event variables: time to graft failure, onset of grade 2-4 acute GVHD, onset of chronic GVHD, mortality, cause of death
- Desired outcome variables:
    - Cumulative incidence of CMV infection, CMV disease, pre-emptive treatment for EBV, EBV-PTLD, and HHV6-encephalitis with death as a competing risk, evaluated at

100-days post-HCT for CMV infection and HHV6 encephalitis and at 1 year post-HCT for CMV disease, pre-emptive EBV treatment, and EBV-PTLD
- OS at 100-days and 1 year: defined as the time to death; surviving patients censored at last follow-up
- NRM at 100-days and 1 year: defined as the time to death without evidence of disease presence; with relapse/progressive disease as a competing risk
- Cause of death
- Grades II-IV aGVHD incidence, grades III-IV aGVHD incidence, with graft failure, relapse, donor lymphocyte infusion, chronic GVHD, and death as competing risks
- cGVHD incidence (any, as well as limited vs. extensive and mild vs. moderate vs. severe), with graft failure, relapse, donor lymphocyte infusion, and death as competing risks

Study design (scientific plan):
Differences in outcomes as outlined in the specific aims section, by GVHD prophylaxis approach (mTORi-containing vs non-mTORi-containing) will be evaluated. The role of mTORi in the cumulative incidence of different herpesvirus-associated infectious complications will be evaluated, including the impact of co-factors such as degree of donor HLA match, conditioning intensity, and donor/recipient viral serostatus. Multivariate analysis will be performed considering variables that may be associated with differences in HCT outcomes, as listed in Sections IV and VIII.

Data source:
CIBMTR Research Database

References

1. Ritta M, Costa C, Solidoro P, et al. Everolimus-based immunosuppressive regimens in lung transplant recipients: impact on CMV infection. Antiviral Res 2015;113:19-26.
2. Radtke J, Dietze N, Spetzler VN, et al. Fewer cytomegalovirus complications after kidney transplantation by de novo use of mTOR inhibitors in comparison to mycophenolic acid. Transpl Infect Dis 2016;18:79-88.
3. Havenith SH, Yong SL, van Donselaar-van der Pant KA, van Lier RA, ten Berge IJ, Bemelman FJ. Everolimus-treated renal transplant recipients have a more robust CMV-specific CD8+ T-cell response compared with cyclosporine- or mycophenolate-treated patients. Transplantation 2013;95:184-91.
4. Nashan B, Gaston R, Emery V, et al. Review of cytomegalovirus infection findings with mammalian target of rapamycin inhibitor-based immunosuppressive therapy in de novo renal transplant recipients. Transplantation 2012;93:1075-85.
5. Jennings DL, Lange N, Shullo M, et al. Outcomes associated with mammalian target of rapamycin (mTOR) inhibitors in heart transplant recipients: A meta-analysis. Int J Cardiol 2018;265:71-6.
6. Devresse A, Leruez-Ville M, Scemla A, et al. Reduction in late onset cytomegalovirus primary disease after discontinuation of antiviral prophylaxis in kidney transplant recipients treated with de novo everolimus. Transpl Infect Dis 2018;20:e12846.
7. Mallat SG, Tanios BY, Itani HS, et al. CMV and BKPyV Infections in Renal Transplant Recipients Receiving an mTOR Inhibitor-Based Regimen Versus a CNI-Based Regimen: A Systematic Review and Meta-Analysis of Randomized, Controlled Trials. Clin J Am Soc Nephrol 2017;12:1321-36.
8. Hiramitsu T, Okada M, Futamura K, et al. 5-year follow-up of a randomized clinical study comparing everolimus plus reduced-dose cyclosporine with mycophenolate mofetil plus

standard-dose cyclosporine in de novo kidney transplantation: Retrospective single center assessment. Int Immunopharmacol 2016;39:192-8.
9. Hocker B, Zencke S, Pape L, et al. Impact of Everolimus and Low-Dose Cyclosporin on Cytomegalovirus Replication and Disease in Pediatric Renal Transplantation. Am J Transplant 2016;16:921-9.
10. Cen O, Longnecker R. Rapamycin reverses splenomegaly and inhibits tumor development in a transgenic model of Epstein-Barr virus-related Burkitt's lymphoma. Mol Cancer Ther 2011;10:679-86.
11. Holtan SG, Porrata LF, Colgan JP, Zent CS, Habermann TM, Markovic SN. mTOR inhibitor monotherapy is insufficient to suppress viremia and disease progression in Epstein-Barr virus-driven lymphoproliferative disorders (EBV-LPD). Am J Hematol 2008;83:688-9.
12. Pascual J, Royuela A, Fernandez AM, et al. Role of mTOR inhibitors for the control of viral infection in solid organ transplant recipients. Transpl Infect Dis 2016;18:819-31.
13. Teira P, Battiwalla M, Ramanathan M, et al. Early cytomegalovirus reactivation remains associated with increased transplant-related mortality in the current era: a CIBMTR analysis. Blood 2016;127:2427-38.
14. Ramanathan M, Teira P, Battiwalla M, et al. Impact of early CMV reactivation in cord blood stem cell recipients in the current era. Bone Marrow Transplant 2016;51:1113-20.
15. Torlen J, Ringden O, Garming-Legert K, et al. A prospective randomized trial comparing cyclosporine/methotrexate and tacrolimus/sirolimus as graft-versus-host disease prophylaxis after allogeneic hematopoietic stem cell transplantation. Haematologica 2016;101:1417-25.
16. Cutler C, Logan B, Nakamura R, et al. Tacrolimus/sirolimus vs tacrolimus/methotrexate as GVHD prophylaxis after matched, related donor allogeneic HCT. Blood 2014;124:1372-7.

Conflicts of interest
None

Table 1 Characteristics of patients who underwent first ALLO transplants for AML, ALL, MDS/MPS and NHL with and without Sirolimus as GVHD prophylaxis reported to the CIBMTR, from 2008 to 2016

Variable	GVHD Prophylaxis contains Sirolimus N(%)	GVHD Prophylaxis without Sirolimus N(%)
Number of patients	1380	9646
Number of centers	94	94
Gender		
Male	817 (59)	5635 (58)
Female	563 (41)	4011 (42)
Age, median(range), years	59 (2 - 82)	56 (<1 - 82)
Age at transplant, years		
<=10	7 (<1)	239 (2)
11-20	23 (2)	341 (4)
21-30	86 (6)	709 (7)
31-40	101 (7)	826 (9)
41-50	201 (15)	1418 (15)
51-60	322 (23)	2568 (27)
61-70	507 (37)	2943 (31)
>70	133 (10)	602 (6)
Disease		
AML	499 (36)	4486 (47)
ALL	187 (14)	1232 (13)
MDS/MPS	561 (41)	3157 (33)
NHL	133 (10)	771 (8)
Graft type		
Bone Marrow	82 (6)	1866 (19)
Peripheral blood	1298 (94)	7780 (81)
Donor/recipient HLA match		
HLA-identical siblings	393 (28)	3461 (36)
matched related	3 (<1)	38 (<1)
Mismatched related, 1 mismatch	1 (<1)	19 (<1)
Mismatched related,>=2 mismatch	26 (2)	503 (5)
Mismatched related, mismatch unknown	4 (<1)	111 (1)
8/8 unrelated	698 (51)	4378 (45)
7/8 unrelated	205 (15)	861 (9)
<=6/8 unrelated	11 (<1)	20 (<1)
Unrelated (HLA match information missing)	39 (3)	255 (3)
GVHD prophylaxis		

Variable	GVHD Prophylaxis contains Sirolimus N(%)	GVHD Prophylaxis without Sirolimus N(%)
No GVHD prophylaxis (forms under review)	0	71 (<1)
Cyclophosphamide	57 (4)	904 (9)
TAC/CSA + MMF +- others	243 (18)	2098 (22)
TAC/CSA + MTX +- others	314 (23)	6048 (63)
TAC/CSA + others (except MTX, MMF)	731 (53)	127 (1)
TAC/CSA alone	0	316 (3)
Other GVHD prophylaxis*	35 (3)	82 (<1)
Year of transplant		
2008	189 (14)	1350 (14)
2009	163 (12)	1173 (12)
2010	77 (6)	753 (8)
2011	97 (7)	480 (5)
2012	97 (7)	508 (5)
2013	152 (11)	1136 (12)
2014	206 (15)	1500 (16)
2015	198 (14)	1459 (15)
2016	201 (15)	1287 (13)
CMV infection		
Yes	265 (19)	2917 (30)
No	1115 (81)	6729 (70)
EBV infection		
Yes	76 (6)	545 (6)
No	1304 (94)	9101 (94)
HHV-6 infection		
Yes	64 (5)	288 (3)
No	1316 (95)	9358 (97)
Median follow-up of survivors, months	49 (3 - 122)	49 (3 - 126)

Footnote:

*Other GVHD prophylaxis	gvhdlist	GVHD Prophylaxis contains Sirolimus N(%)	GVHD Prophylaxis without Sirolimus N(%)
Other GVHD prophylaxis	mmf	0	28 (34)
	mtx	0	24 (29)
	mmf + siro	15 (43)	0
	mab + mmf	0	8 (10)
	siro	8 (23)	0
	cor	0	4 (5)
	cor + mtx	0	4 (5)
	cor + mmf	0	3 (4)
	mtx + siro	3 (9)	0
	atg	0	2 (2)
	cor + mmf + siro	2 (6)	0
	siro + oth	2 (6)	0
	atg + ecp + mmf	0	1 (1)
	atg + mmf + siro	1 (3)	0
	atg + mtx	0	1 (1)
	atg + mtx + mmf	0	1 (1)
	atg + oth	0	1 (1)
	atg + siro	1 (3)	0
	cor + mab	0	1 (1)
	cor + mab + siro	1 (3)	0
	cor + siro	1 (3)	0
	ecp + mtx	0	1 (1)
	mab	0	1 (1)
	mmf + siro + oth	1 (3)	0
	mtx + mmf + oth	0	1 (1)
	mtx + oth	0	1 (1)

Proposal: 1811-18

Title:
The burden of infectious complications and the kinetics of engraftment and immune reconstitution in high-risk MDS vs de-novo acute myeloid leukemia in adults.

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Hypothesis:
Myelodysplastic syndromes are clonal disorders of hematopoietic stem and progenitor cells with numerous chromosomal, genetic, and epigenetic aberrations. Nevertheless, there is also evidence that aberrant bone marrow microenvironment is another key contributor to disease initiation and progression. Allogeneic transplant normalizes the hematopoietic compartment but not the microenvironment. We hypothesize that engraftment and immune reconstitution (IR) after allo-HCT for MDS follows a delayed and/or unbalanced course compared to AML. Due to this altered IR and other factors such as prior immunosuppressive therapies and iron overload, MDS patients may be at particularly high risk of infections after allo-HCT, possibly justifying specific measures being taken in MDS patients.

Specific aims:
Primary objective of this study will be to compare the burden of infectious complications following allo-HCT for high-risk MDS compared to de-novo AML. Secondary objective is to characterize the kinetics of engraftment and IR up to day 100.

Scientific impact:
Establishing the slower or less efficient engraftment/IR and the high risk of infections after allo-HCT for MDS will lead to more vigilance monitoring for and preventing these complications, and justify reinforced surveillance and prophylactic programs in this patient population. It will also lead to a cautious approach when making decisions regarding other factors that influence IR such as conditioning, immunosuppression, graft manipulation etc and help develop strategies before, during and after transplant to enhance IR and decrease transplant related morbidity in MDS patients, particularly infections.

Scientific justification:
Infection following allo-HCT to treat MDS is a well-recognized cause of morbidity and mortality, accounting for 53% of overall mortality in a series of 109 patients[1]. However, available literature data do not indicate whether patients with MDS are at higher risk of severe infection than allogeneic HCT recipients transplanted for other diseases, and whether this justifies specific measures being taken in MDS patients. Nevertheless, MDS patients are on average among the oldest patients referred for HCT, and this may lead to a higher risk of post-HCT infection, especially of fungal origin, when compared to other patients with different underlying diseases. Moreover, iron overload, which is common in MDS due to chronic red cell transfusions and ineffective erythropoiesis, increases the risk of both bacterial[2] and fungal[3] infections after HCT. Notably, pre-transplant neutropenia (ANC<1.5×109/L) was associated with an increased infection-related mortality at three years post-transplant (26% *vs.* 12.3%) due to a more frequent occurrence of Gram positive bacterial and fungal infections[4]. Finally, it has been shown that the incidence and risk factors for bacterial, fungal and viral infections correlate with the kinetics of immune reconstitution[5][6], and serve as a guide for appropriate antimicrobial prophylaxis for transplant

patients. Whether the above factors, in addition to a delayed or unbalanced IR, contribute to a higher risk of infection in MDS patients after HCT is yet to be seen.
Alterations in the bone marrow microenvironment contribute to hematopoietic failure in MDS [7][8][9]. The stromal microenvironment following allo-HCT remains of host origin[10]. A significantly longer time to neutrophils and platelets engraftment following allo-HCT has been noted in MDS compared to AML in small studies[11] and was attributed to the altered microenvironment. The effect of the microenvironment on neutrophils, T-cell, B-cell or other immune cells numerical or functional reconstitution, however, has not been studied or compared to that seen in AML patients. A full T-cell immune reconstitution requires seeding of the thymus by lymphoid progenitors arising from donor hematopoietic stem cells[12]. The availability of competent bone marrow niches is required to provide a steady import of bone marrow-derived progenitors via the blood and maintain the de novo generation of T cells[13][14][15]. In addition, a competent microenvironment is also required for reconstitution of innate immunity and efficient differentiation of natural killer cells, monocytes, granulocytes and dendritic cells[16]. Therefore, a slow or unbalanced IR is expected following transplant for disorders with microenvironment aberrations such as MDS.

Patient eligibility population:
AML and MDS patients who underwent allo-HCT after 2012 (the year after which all the variables below can be collected). Only de-novo AML (no secondary or t-AML) and high-risk MDS (IPSS-R score>4.5) will be included. All ages, all conditioning regimens, all donors.

Data requirements:
Forms:

- AML pre-HCT data
- MDS pre-HCT data
- Pre-transplant essential data
- Post-transplant essential data
- Fungal infection post-HCT data

Variables:

- Age
- Donor type
- Donor age source
- Cell dose
- T-cell depletion (yes or no)
- Conditioning (MA vs RIC)
- GVHD prophylaxis
- Infection prophylaxis
- Growth factors or cytokines given (yes or no)
- CMV status
- ANC
- ALC
- Platelets
- Immunoglobulins levels
- Lymphocyte analysis (CD3, CD4, CD8, CD20, CD56, CD4/CD8 ratio)
- Number of clinical or culture-proven infections (bacterial, fungal, viral)
- aGVHD (yes or no)

- cGVHD (yes or no)
- High dose steroid therapy (yes or no)
- CMV reactivation (yes or no)

Study design:
Neutrophils and platelets recovery will be analyzed and compared in the immediate post-HCT period. The incidence of primary or secondary graft failure will be compared. Lymphocyte subsets and Immunoglobulins levels will be compared between the two groups at day 100 (later time points if available: 6 months, 1 year and 2 years). The 2-year cumulative incidences of infections will be compared and the pattern (bacterial, fungal and viral) and site of infection will be characterized.
Continuous variables will be compared using the Student's t-test. Categorical data will be analyzed using the Fisher exact test or a chi-square test. Multivariate analysis will be performed against conventional factors that affect outcome (conditioning, age, cell dose, HLA disparity, source, CMV status, cell dose). All P values are two-tailed. Significance will indicate a P value 0.05.

Data source: CIBMTR Research Database

References:
[1] H. J. Deeg, B. Storer, J. T. Slattery, C. Anasetti, K. C. Doney, J. A. Hansen, H.-P. Kiem, P. J. Martin, E. Petersdorf, J. P. Radich, J. E. Sanders, H. M. Shulman, E. H. Warren, R. P. Witherspoon, E. M. Bryant, T. R. Chauncey, L. Getzendaner, R. Storb, F. R. Appelbaum, D. N. Buell, R. M. Maher, W. E. Fitzsimmons, and J. R. Wingard, "Conditioning with targeted busulfan and cyclophosphamide for hemopoietic stem cell transplantation from related and unrelated donors in patients with myelodysplastic syndrome.," *Blood*, vol. 100, no. 4, pp. 1201–7, Aug. 2002.

[2] V. Pullarkat, S. Blanchard, B. Tegtmeier, A. Dagis, K. Patane, J. Ito, and S. J. Forman, "Iron overload adversely affects outcome of allogeneic hematopoietic cell transplantation," *Bone Marrow Transplant.*, vol. 42, no. 12, pp. 799–805, Dec. 2008.

[3] A. Altes, A. F. Remacha, P. Sarda, F. J. Sancho, A. Sureda, R. Martino, J. Briones, S. Brunet, C. Canals, and J. Sierra, "Frequent severe liver iron overload after stem cell transplantation and its possible association with invasive aspergillosis," *Bone Marrow Transplant.*, vol. 34, no. 6, pp. 505–509, Sep. 2004.

[4] B. L. Scott, J. Y. Park, H. J. Deeg, K. A. Marr, M. Boeckh, T. R. Chauncey, F. R. Appelbaum, R. Storb, and B. E. Storer, "Pretransplant neutropenia is associated with poor-risk cytogenetic features and increased infection-related mortality in patients with myelodysplastic syndromes.," *Biol. Blood Marrow Transplant.*, vol. 14, no. 7, pp. 799–806, Jul. 2008.

[5] S. Servais, E. Lengline, R. Porcher, M. Carmagnat, R. Peffault de Latour, M. Robin, F. Sicre de Fontebrune, E. Clave, G. Maki, C. Granier, A. Xhaard, N. Dhedin, J.-M. Molina, A. Toubert, H. Moins-Teisserenc, and G. Socie, "Long-Term Immune Reconstitution and Infection Burden after Mismatched Hematopoietic Stem Cell Transplantation," *Biol. Blood Marrow Transplant.*, vol. 20, no. 4, pp. 507–517, Apr. 2014.

[6] I. Heleen Bartelink, S. V Belitser, C. A. J. Knibbe, M. Danhof, A. J. De Pagter, T. C. G. Egberts, and J. J. Boelens, "Immune Reconstitution Kinetics as an Early Predictor for Mortality using Various Hematopoietic Stem Cell Sources in Children," *Biol. Blood Marrow Transplant.*, vol. 19, pp. 305–313, 2013.

[7] S. Geyh, S. Öz, R.-P. Cadeddu, J. Fröbel, B. Brückner, A. Kündgen, R. Fenk, I. Bruns, C. Zilkens, D. Hermsen, N. Gattermann, G. Kobbe, U. Germing, F. Lyko, R. Haas, and T. Schroeder, "Insufficient stromal support in MDS results from molecular and functional deficits of mesenchymal stromal cells," *Leukemia*, vol. 27, no. 9, pp. 1841–1851, Sep. 2013.

[8] R. A. Ferrer, M. Wobus, C. List, R. Wehner, C. Schönefeldt, B. Brocard, B. Mohr, M. Rauner, M. Schmitz, M. Stiehler, G. Ehninger, L. C. Hofbauer, M. Bornhäuser, and U. Platzbecker, "Mesenchymal stromal cells from patients with myelodyplastic syndrome display distinct functional alterations that are modulated by lenalidomide.," *Haematologica*, vol. 98, no. 11, pp. 1677–85, Nov. 2013.

[9] A. J. Li and L. M. Calvi, "The microenvironment in myelodysplastic syndromes: Niche-mediated disease initiation and progression," *Exp. Hematol.*, vol. 55, pp. 3–18, Nov. 2017.

[10] A. Spyridonidis, T. Küttler, R. Wäsch, E. Samek, M. Waterhouse, D. Behringer, H. Bertz, and J. Finke, "Reduced Intensity Conditioning Compared to Standard Conditioning Preserves the In Vitro Growth Capacity of Bone Marrow Stroma, Which Remains of Host Origin," *Stem Cells Dev.*, vol. 14, no. 2, pp. 213–222, Apr. 2005.

[11] M. Bitan, R. Or, M. Y. Shapira, I. B. Resnick, B. Gesundheit, A. Ackerstein, S. Samuel, S. Elad, and S. Slavin, "Time to engraftment following allogeneic stem cell transplantation is significantly longer in patients with myelodysplastic syndrome than with acute myeloid leukemia," *Bone Marrow Transplant.*, vol. 41, pp. 69–78, 2008.

[12] T. Serwold, L. I. R. Ehrlich, and I. L. Weissman, "Reductive isolation from bone marrow and blood implicates common lymphoid progenitors as the major source of thymopoiesis.," *Blood*, vol. 113, no. 4, pp. 807–15, Jan. 2009.

[13] W. Krenger, B. R. Blazar, and G. A. Hollander, "Thymic T-cell development in allogeneic stem cell transplantation," *Blood*, vol. 117, no. 25, pp. 6768–6776, Jun. 2011.

[14] I. Goldschneider, "Cyclical mobilization and gated importation of thymocyte progenitors in the adult mouse: evidence for a thymus-bone marrow feedback loop," *Immunol. Rev.*, vol. 209, no. 1, pp. 58–75, Feb. 2006.

[15] M. E. García-Ojeda, S. Dejbakhsh-Jones, I. L. Weissman, and S. Strober, "An alternate pathway for T cell development supported by the bone marrow microenvironment: recapitulation of thymic maturation.," *J. Exp. Med.*, vol. 187, no. 11, pp. 1813–23, Jun. 1998.

[16] J. Ogonek, M. Kralj Juric, S. Ghimire, P. R. Varanasi, E. Holler, H. Greinix, and E. Weissinger, "Immune Reconstitution after Allogeneic Hematopoietic Stem Cell Transplantation.," *Front. Immunol.*, vol. 7, p. 507, 2016.

Table 1 Characteristics of patients who underwent first ALLO transplants for AML, MDS reported to the CIBMTR, from 2013 to 2017

Variable	AML N(%)	MDS N(%)
Number of patients	3856	2788
Number of centers	216	165
Gender		
Male	2067 (54)	1806 (65)
Female	1789 (46)	982 (35)
Age, median(range), years	51 (<1 - 88)	65 (2 - 81)
Age at transplant, years		
<=10	282 (7)	15 (<1)
11-20	259 (7)	41 (1)
21-30	314 (8)	33 (1)
31-40	417 (11)	60 (2)
41-50	572 (15)	127 (5)
51-60	883 (23)	526 (19)
61-70	927 (24)	1476 (53)
>70	202 (5)	510 (18)
Disease/Disease status		
AML	3856	0
MDS-advanced	0	2038 (73)
MDS-early	0	750 (27)
Graft type		
Bone Marrow	742 (19)	336 (12)
Peripheral blood	2443 (63)	2309 (83)
Cord blood	671 (17)	143 (5)
Donor/recipient HLA match		
Cord blood	671 (17)	143 (5)
HLA-identical siblings	1100 (29)	780 (28)
matched related	27 (<1)	16 (<1)
Mismatched related, 1 mismatch	12 (<1)	4 (<1)
Mismatched related,>=2 mismatch	325 (8)	174 (6)
Mismatched related, mismatch unknown	134 (3)	74 (3)
8/8 unrelated	1220 (32)	1325 (48)
7/8 unrelated	230 (6)	201 (7)
<=6/8 unrelated	9 (<1)	2 (<1)
Unrelated (HLA match information missing)	128 (3)	69 (2)
Conditioning regimen intensity		

Variable	AML N(%)	MDS N(%)
Myeloablative	2166 (56)	830 (30)
RIC/NMA	1376 (36)	1647 (59)
Missing	314 (8)	311 (11)
GVHD prophylaxis		
No GVHD prophylaxis (forms under review)	37 (<1)	53 (2)
Ex vivo T-cell depletion	40 (1)	9 (<1)
CD34 selection	73 (2)	49 (2)
Cyclophosphamide	619 (16)	308 (11)
TAC/CSA + MMF +- others	1091 (28)	801 (29)
TAC/CSA + MTX +- others	1642 (43)	1256 (45)
TAC/CSA + others (except MTX, MMF)	191 (5)	183 (7)
TAC/CSA alone	113 (3)	78 (3)
Other GVHD prophylaxis	50 (1)	51 (2)
Year of transplant		
2013	756 (20)	565 (20)
2014	884 (23)	545 (20)
2015	846 (22)	585 (21)
2016	794 (21)	561 (20)
2017	576 (15)	532 (19)
Virial infections by 100 day		
Yes	1633 (42)	1094 (39)
With lymphocyte analyses performed at 100 day	442	308
No	2221 (58)	1694 (61)
With lymphocyte analyses performed at 100 day	564	367
Missing	2 (<1)	0
Bacterial infections by 100 day		
Yes	1596 (41)	1023 (37)
With lymphocyte analyses performed at 100 day	431	233
No	2258 (59)	1765 (63)
With lymphocyte analyses performed at 100 day	575	442
Missing	2 (<1)	0
Fungal infections by 100 day		
Yes	267 (7)	220 (8)
With lymphocyte analyses performed at 100 day	60	38
No	3587 (93)	2568 (92)
With lymphocyte analyses performed at 100 day	946	637
Missing	2 (<1)	0
IgG at 100 day		
Data not available	1359 (35)	939 (34)

Variable	AML N(%)	MDS N(%)
Data available	2497 (65)	1849 (66)
IgM at 100 day		
Data not available	2532 (66)	1937 (69)
Data available	1324 (34)	851 (31)
IgA at 100 day		
Data not available	2524 (65)	1938 (70)
Data available	1332 (35)	850 (30)
Were lymphocyte analyses performed at 100 day		
No	2842 (74)	2110 (76)
Yes	1006 (26)	675 (24)
Not tested/missing	8 (<1)	3 (<1)
Median follow-up of survivors, months	25 (3 - 65)	25 (3 - 63)

Proposal 1811-42

Title:
Infection with Atypical Nontuberculous Mycobacteria (NTM) after Hematopoietic Stem Cell Transplantation (HSCT)

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Hypothesis:
Patients that develop NTM infections have worse outcomes (decreased disease-free survival and higher mortality) than patients that do not develop NTM infections in the first 2 years post-HSCT

Specific aims:
Primary objective:

- To compare the transplant-related outcomes in patients that develop NTM infections vs. those who do not, in the first 2 years post-HSCT divided by time range groups: first 100 days post-HSCT, from day 100 to 1 year and from 1 year to 2 years post-HSCT

Secondary objectives:

- To determine the incidence of atypical non-tuberculous mycobacteria infections in the first 2 years post HSCT, divided by time range groups: first 100 days post-HSCT, from day 100 to 1 year and from 1 year to 2 years post-HSCT
- To describe the characteristics of patients that develop NTM infections in the first 2 years post-HSCT divided by time range groups: first 100 days post-HSCT, from day 100 to 1 year and from 1 year to 2 years post-HSCT
- To compare differences in patient characteristics and identify risk factors between post-transplant patients that did and did not develop NTM infections in the first 2 years post-HSCT divided by time range groups: first 100 days post-HSCT, from day 100 to 1 year and from 1 year to 2 years post-HSCT

Scientific justification and impact:
Nontuberculous mycobacterial disease in HSCT recipients has been increasingly recognized over the past years. Its incidence has been estimated in 0.37 to 3% [1-4], lower than populations such as HIV-infected patients or lung transplant recipients [5] but higher than the general population. However, most NTM cases reported in transplantation in the literature are isolated, with the two of the largest series of only 40 and 67 NTM-positive cultures/cases [1, 3]. NTM infection has been reported in multiple sites, including lungs, IV central lines, skin and soft tissue, blood stream, bone and joint, liver, bone marrow [6-9] and incorporating a number of species including *M. kansasii, Mycobacterium avium intracellulare, Mycobacterium tuberculosis,*

M. abscessus among others [2, 10, 11]. Most cases occur early in transplantation within the first 100 days [9].

Little is known with respect to risk factors for NTM infection in the post HSCT period. Allogeneic HSCT hosts seem to be at higher risk, compared to autologous transplantation patients in one case series [3]. Other suggested or theorized risk factors include the use of myeloablative conditioning therapy, use of T-cell depletion in allografts, use of alemtuzumab, steroids, diagnosis of GVHD, bronchiolitis obliterans, neutropenia, but none of these has been established given the paucity of cases found in the available studies [4, 6]. Outcomes of these infections seem overall favorable after appropriate treatment but, again, not well established. Treatment duration is not clear. In a series of 7 cases of NTM infection post-bone marrow transplant over a period of 5 years, 3 infections were localized in the lung and had a positive response to combination therapy with INH, rifampin and ETB but the duration of treatment was prolonged (2 years average). In contrast, among 23 patients with central venous catheter-related NTM infection, successful treatment with antibiotics for 2-4 weeks was reported [3]. Clearly, the impact of reduction of immunosuppression might also play a role in the treatment of these infections [12].

An area of recent increased interest is the possible relation between bronchiolitis obliterans (BO) and NTM infection. A compelling reason to link this population is found in lung transplant recipients, where NTM positive patients were more likely to develop BO than NTM negative patients (80% vs. 58%) at 5 years. In most cases (68%), NTM infection preceded the development of BO, with infection developing within 90 days of diagnosis of BO [5]. In HSCT recipients, there are reports of NTM lung infections in the setting of lung GVHD/BO [2, 13]. In some of these cases, NTMs were identified months after failed treatment for BO with therapy including the use of macrolide antibiotics, and radiological resolution has been reported after appropriate NTM treatment [13]. In a prospective study sponsored by the National Cancer Institute (NCT00656058) on the use of Montelukast in 25 patients with BO following stem cell transplantation, the general infection rate was high with mycobacterial infection constituting 2% of them [14]. While NTM infection in the lung is likely the result of initial colonization of bronchiectasis produced in the setting of BO as well as the T-cell dysfunction that results from its treatment, the overall course and response to treatment for BO could be also negatively affected if NTM infections are not identified and appropriately treated [5]. In addition, macrolide use for BO treatment could delay diagnosis of an NTM infection when present, and promote macrolide resistance [13]. All this is speculative at current time but could have real implications in the outcomes post HSCT.

Our knowledge on NTM infections in SCT recipients is very limited due to the low number of patients reported overall in the literature. As per the 2011 CIBMTR minutes, 64 NTM infections had been recorded which would encompass the largest number of patients in any retrospective study. We propose to evaluate these infections by identifying the incidence, risk factors, impact on and outcomes such as survival, and describe characteristics of NTM infections in this patient population. While we acknowledge that collected data is more readily available in the first 100 days post-HSCT , we think it is worth to look at the data after the first 100 days as that might allow an analysis of some of the late complications in HSCT, such as chronic GVHD and BO.

Patient eligibility population:
All patients (of all ages) that received a stem cell transplant (of all types) and were reported to CIBMTR from 2005 to present as having developed an NTM infection in the first 2 years post-transplant. The control group will be patients that are frequency matched for center, underlying disease and status, transplant intensity, graft source, and transplant date (within 3-5 years) and who did not develop an NTM infection during the first 2 years post transplant.

Data requirements:
Patient-related:

- Age at transplant
- Gender
- Performance Status
- CMV status
- ABO
- Disease: Acute Leukemia vs. Chronic Leukemia vs. Lymphoma vs. Aplastic Anemia vs. Immunodeficiency vs. Hemoglobinopathy/Metabolic
- Disease-stage at transplant: Early vs. Intermediate vs Advanced.
- Pre-transplant CMV status: positive vs. negative.

Infection-related:

- Infection with atypical mycobacteria
- Site of infection

Transplant-related:

- Donor type: autologous vs. allogeneic: related vs. unrelated vs. other related
- HLA match status: well matched vs. partially matched vs. mismatched vs. haplo/mismatched related donor
- Graft source: BM vs. PBSC vs. CB
- Conditioning therapy: Myeloablative vs. RIC/non-ablative
- GVHD prophylaxis: CsA +/- others vs. FK-506 +/- others vs. T-cell depletion vs. others
- ATG or alemtuzumab use at transplant: yes vs. no
- TBI use: yes vs. no.
- Supplemental IVIg given: yes vs. no,
- Acute GVHD grades II-IV by post-transplant day 100: yes vs. no
- Chronic GVHD, any severity, at any time post-transplant: yes vs. no
- Location of chronic GVHD: skin, mouth, eyes, GI tract, liver, lungs, joints and fascia, genital tract.
- Treatment for chronic GVHD: corticosteroids (systemic vs. topical), ALG, ALS, ATG, ATS, aldesleukin, alemtuzumab, anti-CD25, azathioprine, bortezomib, cyclosporine, interleukin inhibitors, extra corporeal photopheresis, etanercept, KF 506, hyrocychloroquine, infliximab, methotrexate, mycophenolate, pentostatin, UV therapy, rituximab, sirolimus, tyrosine kinase inhibitors, JAK 2 inhibitors, other agent.
- Antibacterial prophylaxis: amoxicillin, cefdinir, cefpodoxime, ciprofloxacin, ertapenem, levofloxacin, moxifloxacin, vancomycin, other.

- CD4 counts
- IgG level
- Presence of BOS: yes/no
- Engraftment: yes/no
- First or second transplant

Outcomes:

- Overall survival: time to death
- Transplant related mortality: time to death without evidence of disease relapse
- Disease free survival: time to death or relapse
- GVHD related mortality: time to GVHD related mortality
- Cause of death in NTM patients

Study design:

The incidence of NTM infections in the post-transplant period will be described. We will describe patient characteristics and transplant-related outcomes for patients with NTM infections. The control group will be patients that are frequency matched for center, underlying disease and status, transplant intensity, graft source, and transplant date (within 3-5 years) and who did not develop an NTM infection during the first 2 years post-transplant. To determine the risk factors for NTM infections, we will compare patient, disease and transplant characteristics between the patients without NTM and the patients with NTM infections. We will divide our patient sample by time range in: first 100 days post-HSCT, 100 days to 1 year post-HSCT, 1 to 2 years post-HSCT. Variables will be summarized in a table. To compare categorical variables chi-square (or Fisher's exact test) will be used and to compare continuous variables independent t-tests (or Wilcoxon rank-sum tests) will be used. Transplant-related outcomes will be compared between the controls and cases (patients with NTM infection). Kaplan-Meier curves and the log-rank test will also be used to compare time to death (and other time to events) between NTM and non-NTM patients. Cox proportional hazards models will be constructed to compare time to death between those with and without NTM infections while adjusting for other variables. To compare GVHD-related deaths (yes/no) between groups we will use logistic regression to allow adjustment for other covariates.

Conflicts of interest:

None

References:

1. Weinstock, D.M., et al., *High rates of infection and colonization by nontuberculous mycobacteria after allogeneic hematopoietic stem cell transplantation.* Bone Marrow Transplant, 2003. **31**(11): p. 1015-21.
2. Kang, J.Y., et al., *Clinical significance of nontuberculous mycobacteria from respiratory specimens in stem cell transplantation recipients.* Int J Hematol, 2015. **101**(5): p. 505-13.
3. Gaviria, J.M., et al., *Nontuberculous mycobacterial infections in hematopoietic stem cell transplant recipients: characteristics of respiratory and catheter-related infections.* Biol Blood Marrow Transplant, 2000. **6**(4): p. 361-9.
4. Au, W.Y., et al., *Nontuberculous mycobacterial infections in Chinese hematopoietic stem cell transplantation recipients.* Bone Marrow Transplant, 2003. **32**(7): p. 709-14.

5. Shah, S.K., et al., *Analysis of pulmonary non-tuberculous mycobacterial infections after lung transplantation.* Transpl Infect Dis, 2016. **18**(4): p. 585-91.
6. Al-Anazi, K.A., A.M. Al-Jasser, and W.K. Al-Anazi, *Infections caused by non-tuberculous mycobacteria in recipients of hematopoietic stem cell transplantation.* Front Oncol, 2014. **4**: p. 311.
7. Horwitz, M.E., et al., *Persistent Mycobacterium avium infection following nonmyeloablative allogeneic peripheral blood stem cell transplantation for interferon-gamma receptor-1 deficiency.* Blood, 2003. **102**(7): p. 2692-4.
8. Okano, A., et al., *Subcutaneous infection with Mycobacterium fortuitum after allogeneic bone marrow transplantation.* Bone Marrow Transplant, 2001. **28**(7): p. 709-11.
9. Roy, V. and D. Weisdorf, *Mycobacterial infections following bone marrow transplantation: a 20 year retrospective review.* Bone Marrow Transplant, 1997. **19**(5): p. 467-70.
10. *Clinicopathologic conference. Pulmonary and hepatic disease after chemotherapy and bone marrow transplantation for acute leukemia.* Am J Med, 1979. **66**(3): p. 484-94.
11. Kurzrock, R., et al., *Mycobacterial pulmonary infections after allogeneic bone marrow transplantation.* Am J Med, 1984. **77**(1): p. 35-40.
12. Navari, R.M., et al., *Mycobacterial infections in marrow transplant patients.* Transplantation, 1983. **36**(5): p. 509-13.
13. Miyake, N., et al., *Mycobacterium abscessus and massiliense lung infection during macrolide treatment for bronchiolitis obliterans after allogeneic hematopoietic stem cell transplantation.* J Infect Chemother, 2018. **24**(1): p. 78-81.
14. Williams, K.M., *How I treat bronchiolitis obliterans syndrome after hematopoietic stem cell transplantation.* Blood, 2017. **129**(4): p. 448-455.

Table1 Characteristic of patients who received an allo HCT, diagnosed with and without a non-MTB infection by 2 years, reported to the CIBMTR between 2005 and 2017

Variable	With non-MTB infection	Without non-MTB infection
Number of patients	309	22103
Number of centers	108	108
Gender		
Male	192 (62)	12875 (58)
Female	117 (38)	9228 (42)
Age, median(range), years	50 (<1 - 82)	49 (<1 - 82)
Age at transplant, years		
<10	38 (12)	2989 (14)
10-19	23 (7)	1847 (8)
20-30	28 (9)	1794 (8)
30-39	24 (8)	1886 (9)
40-49	43 (14)	2812 (13)
50-59	73 (24)	4703 (21)
60-69	69 (22)	5089 (23)
>=70	11 (4)	983 (4)
Disease		
AML-Acute myelogenous leukemia	116 (38)	7780 (35)
ALL-Acute lymphoblastic leukemia	44 (14)	2853 (13)
Other leukemia	13 (4)	698 (3)
CML-Chronic myelogenous leukemia	10 (3)	715 (3)
MDS-Myelodysplastic/myeloprolif.disorders	67 (22)	5141 (23)
Other acute leukemia	1 (<1)	249 (1)
Non-Hodgkin lymphoma	16 (5)	1343 (6)
Hodgkin lymphoma	1 (<1)	97 (<1)
Plasma cell disorder	2 (<1)	80 (<1)
Other Malignancies	0	16 (<1)
Severe aplastic anemia	6 (2)	993 (4)
Inherit.abnorm.erythrocyte diff/funct.	2 (<1)	772 (3)
SCID & oth immune system disorders	21 (7)	744 (3)
Inherit.abnorm. of platelets	0	19 (<1)
Inherit.disord. of metabolism	4 (1)	332 (2)
Histiocytic disorders	4 (1)	231 (1)
Autoimmune disease	0	13 (<1)
Other, specify	2 (<1)	27 (<1)

Variable	With non-MTB infection	Without non-MTB infection
Graft type		
Bone Marrow	68 (22)	4879 (22)
Peripheral blood	180 (58)	13128 (59)
Cord blood	61 (20)	4096 (19)
Donor/recipient HLA match		
Cord blood	61 (20)	4096 (19)
HLA-identical siblings	76 (25)	6293 (28)
matched related	2 (<1)	185 (<1)
Mismatched related, 1 mismatch	0	40 (<1)
Mismatched related,>=2 mismatch	9 (3)	971 (4)
Mismatched related, mismatch unknown	4 (1)	288 (1)
8/8 unrelated	114 (37)	7859 (36)
7/8 unrelated	31 (10)	1700 (8)
<=6/8 unrelated	3 (<1)	103 (<1)
Unrelated (HLA match information missing)	9 (3)	568 (3)
Year of transplants		
2007	32 (10)	2045 (9)
2008	32 (10)	2570 (12)
2009	38 (12)	2334 (11)
2010	30 (10)	1419 (6)
2011	16 (5)	1086 (5)
2012	21 (7)	1077 (5)
2013	30 (10)	2061 (9)
2014	46 (15)	2677 (12)
2015	28 (9)	2551 (12)
2016	18 (6)	2331 (11)
2017	18 (6)	1952 (9)

Proposal: 1811-59

Title:
Immune recovery predicts post transplant outcomes.

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Hypothesis:
Post transplant immune recovery predicts allogeneic HCT outcomes.

Specific aims:

- Assess outcomes in adult patients who undergo allo-HCT based on day 100 immune recovery of CD4 count.
- General Outcomes to be examined include:
    - NRM
    - acute GVHD (II-IV and II-IV)
    - chronic GVHD
    - relapse/progression
    - PFS/DFS
    - OS
- Descriptive analysis of immune recovery post HCT including T, B and NK cells.

Scientific impact:
Several centers have reported on the prognostic role of immune recovery parameters on HCT outcomes. Extending these findings to a large multicenter population will help validate these findings, promote additional studies within CIBMTR and potentially guide future intervention studies.

Scientific justification:
Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is an established treatment for hematologic malignancies. However, it is associated with significant adverse effects including infection, relapse, and graft versus host disease (GVHD). One variable that may affect these outcomes is the recovery of the immune system after transplantation.[1-8] Deficiencies in post-transplant T-cell reconstitution, and in particular of CD4+ T cells, correlate with an increased risk of infections.[1,2] Several groups have shown that early recovery of absolute lymphocyte count (ALC) after unmodified or partially T-cell depleted (TCD) allo-HSCT is associated with improved overall survival (OS), decreased relapse and lower transplant-related mortality (TRM).[4-7] We have previously reported on immune reconstitution following ex vivo TCD allo-HSCT, and also shown an association between delayed immune recovery and worse HCT outcomes including rates of infection and survival.[1,8-12] There are, however, incomplete data regarding the effect of the quantitative and functional recovery of T cells on relapse and survival in most settings.[13-15] Furthermore, most of these studies have reported results of single center experiences. Extending these findings to a large multicenter population will help validate these findings, promote additional studies within CIBMTR and potentially guide future intervention studies. The CIBMTR collects data on CD4 and CD8 recovery and as of February 2018, data was available on over 1400 patients from 29 centers that reported $\geq$ data collected.

Patient eligibility population:
This study will include adult patients who received a first allogeneic using a myeloablative or reduced intensity conditioning between 01/2008 and 12/2017.

Inclusion criteria:

- first allo-HCT between 2008 and 2017
- Age ≥ 18
- Donors include MSD, MUD and HLA-haploidentical
- GVHD prophylaxis (CNI/MTX, CNI/MMF, PTCY/CNI/MMF)
- Myeloablative or Reduced intensity conditioning
- In vivo or Ex vivo T cell depletion allowed
- All hematologic malignancies allowed

Data requirements:

Utilizing data collected by CIBMTR from pre and post HCT, which includes pre-transplant essential data form #2400, post-transplant essential data form #2450, chimerism studies form #2451, selective post-transplant selective data form #2455 and 100 day post-HSCT data form #2100. The parameters to be assessed are outlined in table 1 below.

Table 1 Data Requirements:

Type of data	Data point	Specific data
Patient Specific	Patient specific characteristics	• Age at transplant (Date of birth) • Gender • Race • Significant comorbidities • Prior autologous transplant • Remission status (CR1, CR2, etc) • HCT-CI • HCT-CI/age • CMV serostatus
Transplant Specific	Transplant date	• Transplant date
	Preparative regimen used	• Myeloablative • Reduced Intensity/ non-myeloablative
	GVHD prophylaxis	• Calcineurin inhibitor based (cyclosporin, tacrolimus) • Sirolimus • PTCY • Other
	Graft characteristic	• Donor-recipient HLA match • Donor gender • Donor Age • Donor CMV serostatus
Outcome Measures	Engraftment	• Time to absolute neutrophil count ≥500 cells/mm^3 for 3 consecutive laboratory readings • Time to unsupported platelets ≥20 x 10^9 cells/L and ≥50 x 10^9 cells/L • Donor-recipient chimerism • Graft failure (primary and secondary)
	Immune recovery	• CD4 and CD8 counts (ratio), CD3, CD19, CD20, NK
	GVHD	• Acute GVHD (aGVHD)

		○ Incidence of grade II-IV acute GVHD (aGVHD) (subset evaluating grade III-IV aGVHD) ○ Time to aGVHD • GVHD after day 100 ○ Incidence of chronic GVHD (cGVHD) ○ Severity of GVHD after day 100
	Mortality	• Time to mortality • Day 100, 6 months and 1 year mortality • Treatment related mortality at 6 months and 1 year • Cause of mortality
	Disease relapse	• Incidence of disease relapse • Time to disease relapse

Study design:
A retrospective study will be conducted utilizing CIBMTR data. Patients will be eligible for inclusion if they are ≥ 18 and who received a first allogeneic HCT using a MSD, MUD or haploidentical donor between 01/2008 and 12/2017. The objectives of this analysis are to determine immune recovery post transplant, indentify factors that affect immune recovery, and determine if CD4 recovery at day 100 predicts subsequent outcomes using a landmark analysis.

Conflicts of Interest:
Miguel Perales:

- Member, Scientific Advisory Board:
  - MolMed, NexImmune
- Ad hoc Advisory Board:
  - Abbvie, Bellicum, Incyte, Nektar Therapeutics, Novartis
- Consulting:
  - Merck
- Member, DSMB:
  - Medigene, Servier
- Research Funding (to institution):
  - Incyte (clinical trial), Miltenyi (clinical trial)
- Academic/Not-for-Profit:
  - Board Member: ASBMT, Be The Match (NMDP)
  - CIBMTR Advisory Committee
  - Tufts Cancer Center DSMB, University of Barcelona CAR T trial DSMB

References:

1. 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 93:467-80, 1999
2. Maury S, Mary JY, Rabian C, et al: Prolonged immune deficiency following allogeneic stem cell transplantation: risk factors and complications in adult patients. Br J Haematol 115:630-41, 2001
3. Maraninchi D, Gluckman E, Blaise D, et al: Impact of T-cell depletion on outcome of allogeneic bone-marrow transplantation for standard-risk leukaemias. Lancet 2:175-8, 1987

4. Savani BN, Mielke S, Rezvani K, et al: Absolute lymphocyte count on day 30 is a surrogate for robust hematopoietic recovery and strongly predicts outcome after T cell-depleted allogeneic stem cell transplantation. Biol Blood Marrow Transplant 13:1216-23, 2007
5. Powles R, Singhal S, Treleaven J, et al: Identification of patients who may benefit from prophylactic immunotherapy after bone marrow transplantation for acute myeloid leukemia on the basis of lymphocyte recovery early after transplantation. Blood 91:3481-6., 1998
6. Kim DH, Kim JG, Sohn SK, et al: Clinical impact of early absolute lymphocyte count after allogeneic stem cell transplantation. Br J Haematol 125:217-24, 2004
7. Chakrabarti S, Brown J, Guttridge M, et al: Early lymphocyte recovery is an important determinant of outcome following allogeneic transplantation with CD34+ selected graft and limited T-cell addback. Bone Marrow Transplant 32:23-30, 2003
8. Goldberg JD, Zheng J, Ratan R, et al: Early recovery of T-cell function predicts improved survival after T-cell depleted allogeneic transplant. Leuk Lymphoma 58:1859-1871, 2017
9. Small TN, Avigan D, Dupont B, et al: Immune reconstitution following T-cell depleted bone marrow transplantation: effect of age and posttransplant graft rejection prophylaxis. Biol Blood Marrow Transplant 3:65-75, 1997
10. Jakubowski AA, Small TN, Kernan NA, et al: T cell-depleted unrelated donor stem cell transplantation provides favorable disease-free survival for adults with hematologic malignancies. Biol Blood Marrow Transplant 17:1335-42, 2011
11. Jakubowski AA, Small TN, Young JW, et al: T cell depleted stem-cell transplantation for adults with hematologic malignancies: sustained engraftment of HLA-matched related donor grafts without the use of antithymocyte globulin. Blood 110:4552-9, 2007
12. van Heijst JW, Ceberio I, Lipuma LB, et al: Quantitative assessment of T cell repertoire recovery after hematopoietic stem cell transplantation. Nat Med 19:372-7, 2013
13. Kim DH, Sohn SK, Won DI, et al: Rapid helper T-cell recovery above 200 x 10 6/l at 3 months correlates to successful transplant outcomes after allogeneic stem cell transplantation. Bone Marrow Transplant 37:1119-28, 2006
14. Berger M, Figari O, Bruno B, et al: Lymphocyte subsets recovery following allogeneic bone marrow transplantation (BMT): CD4+ cell count and transplant-related mortality. Bone Marrow Transplant 41:55-62, 2008
15. Kanda J, Chiou LW, Szabolcs P, et al: Immune recovery in adult patients after myeloablative dual umbilical cord blood, matched sibling, and matched unrelated donor hematopoietic cell transplantation. Biol Blood Marrow Transplant 18:1664-1676 e1, 2012

Table 1 Characteristics of patients who underwent first ALLO transplants for AML, ALL and MDS/MPS with Lymphocyte analyses performed at 100 day, reported to the CIBMTR, from 2008 to 2017

Variable	N(%)
Number of patients	3622
Number of centers	152
Gender	
Male	2025 (56)
Female	1597 (44)
Age, median(range), years	57 (18 - 88)
Age at transplant, years	
11-20	64 (2)
21-30	329 (9)
31-40	348 (10)
41-50	522 (14)
51-60	927 (26)
61-70	1154 (32)
>70	278 (8)
Disease	
AML	1816 (50)
ALL	505 (14)
MDS/MPS	1301 (36)
Graft type	
Bone Marrow	448 (12)
Peripheral blood	2571 (71)
Cord blood	603 (17)
Donor/recipient HLA match	
Cord blood	603 (17)
HLA-identical siblings	1064 (29)
matched related	9 (<1)
Mismatched related, 1 mismatch	6 (<1)
Mismatched related,>=2 mismatch	200 (6)
Mismatched related, mismatch unknown	70 (2)
8/8 unrelated	1278 (35)
7/8 unrelated	253 (7)
<=6/8 unrelated	14 (<1)
Unrelated (HLA match information missing)	125 (3)

Variable	N(%)
Conditioning regimen intensity	
Myeloablative	1862 (51)
RIC/NMA	1565 (43)
Missing	195 (5)
GVHD prophylaxis	
No GVHD prophylaxis (forms under review)	50 (1)
Ex vivo T-cell depletion	59 (2)
CD34 selection	143 (4)
Cyclophosphamide	336 (9)
TAC/CSA + MMF +- others	1163 (32)
TAC/CSA + MTX +- others	1404 (39)
TAC/CSA + others (except MTX, MMF)	263 (7)
TAC/CSA alone	120 (3)
Other GVHD prophylaxis	84 (2)
Year of transplant	
2008	359 (10)
2009	342 (9)
2010	208 (6)
2011	197 (5)
2012	218 (6)
2013	419 (12)
2014	496 (14)
2015	477 (13)
2016	484 (13)
2017	422 (12)
CD3 @ 100 day	
No	415 (11)
Yes	3207 (89)
CD4 @ 100 day	
No	440 (12)
Yes	3182 (88)
CD8 @ 100 day	
No	566 (16)
Yes	3056 (84)
CD19 @ 100 day	
No	3265 (90)

Variable	N(%)
Yes	357 (10)
CD20 @ 100 day	
No	2978 (82)
Yes	644 (18)
CD56 @ 100 day	
No	1715 (47)
Yes	1907 (53)
Median follow-up of survivors, months	39 (3 - 126)

Both CD4 and CD8 are available at day 100, n=3005

Proposal: 1811-77

Title:
Impact of seasons on outcomes of allogenic hematopoietic cell transplantation (HCT) in North America

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Hypothesis:
Seasons may have an impact on outcomes of HCT due to seasonal epidemic infections and seasonal variations in the human circadian rhythms.

Specific aims:
To assess the impact of the season where the transplantation is done on disease relapse, incidence of acute and chronic graft versus host disease (GVHD), non-relapse mortality (NRM), event-free survival (EFS) and overall survival (OS) in patients receiving allogeneic hematopoietic cell transplantation (HCT) in North America.

Scientific justification:
While yearly seasonal incidence and outbreaks of many viruses are very well described and while the potential negative impact of those viruses for immunocompromised patients is very well known[1-5], there is a near complete lack of studies systematically analyzing the potential influence of seasons on HCT outcomes. Among viruses with life threatening potential in immunocompromised patients, the majority is epidemic in winter and springs (influenza and parainfluenza viruses, adenovirus, RSV, metapneumovirus, rotavirus, norovirus, coronavirus) and a minority is encountered in summer (enterovirus, West Nil virus). Moreover, bacterial infections of the upper and lower respiratory tract as well as digestive infection like Clostridium difficile, have also a seasonal distribution and may come as secondary complications of viral infections.
Besides seasonal infectious outbreaks, several physiologic circadian rhythms are modulated by seasonal changes such as external temperature or daily light exposure[6]. Notably, winter season is associated with immunologic and endocrine changes leading to a pro-inflammatory state[7]. Moreover, seasonal affective disorders, typically presenting as depressive mood in winter[8], may disturb adherence to medication and to appointment for follow-up after HCT.

Patient eligibility population:
All patients receiving a first allogeneic transplantation, in USA (except Hawai) and Canada, between 2005 and 2015, for any disease, from any donor, with any conditioning intensity and reported to the CIBMTR are included.

Data requirements:
Patient related:

- Age: < 16y vs 16 to 40 vs ≥40y.
- Gender: Male vs Female
- Race (White vs. Hispanic vs. Black vs. Other)
- Karnofsky performance score at transplant: < 90 vs. 90-100
- Disease: malignant vs non malignant disease
- CMV serostatus of donor and recipient

Transplant related:

- ASBMT RFI disease risk category: Low vs Intermediate vs High
- Year of transplant: 2005 – 2010 vs 2010 – 2015
- HCT type: autologous vs allogeneic
- Graft type: Bone marrow vs peripheral blood vs cord blood
- Donor Type: Related vs Unrelated
- Donor/Recipient HLA match: HLA-identical related vs non HLA-identical related vs HLA matched unrelated vs mismatched unrelated
- Conditioning intensity: Myeloablative (MA) vs RIC/Non MA
- TBI-based conditioning: Yes vs No
- T-cell depletion: Yes (in vivo/ex vivo) vs No
- GVHD prophylaxis: CSA/Tac + MMF ± Other (not MTX) vs CSA/Tac + MTX ± Other (Not MMF) vs CSA/Tac ± Other (not MTX/MMF) vs TCD vs Other
- Acute GVHD: grade 0-1 vs. 2-4 (as time-dependent variable)
- Chronic GVHD: limited vs extensive vs none (as a time-dependent variable)

Study design:

This study aims to determine whether the season of HCT impacts on the main outcomes of relapse, NRM, GVHD, EFS and OS.

Patients will be split in 4 seasons according to the dates of meteorological seasons: Winter (December 1 to February 28 or 29), Springs (March 1 to May 31), Summer (June 1 to August 31) and Fall (September 1 to November 30). Meteorological seasons appears more adequate than astronomical seasons based on dates of equinox and solstice to describe weather and environmental changes. If methodologically too complex, the 4 seasons could be merged in 2 seasons (Winter+Springs vs Summer+Fall).

Adults (16 years-old and more) and children (less than 16 years-old) will be analyzed separately. The age limit of 16 years-old which is usually the upper limit of age for the end of puberty appears more accurate than the legal definition of 18 years-old to differentiate adults and children on a biologic and physiologic basis. Moreover, in many studies looking at the age as a risk factors for outcomes, the turning point of poorer outcomes is about 14 to 16 years-old.

Median time from HCT to each outcome will also be analyzed for each season group and will be compared between groups in order to determine if complications occurs with the same timeframe depending on season of HCT. Causes of death will also be compared among seasons group.

A subset analysis will be conducted for nonmalignant diseases. A difference of outcome depending on seasons in these diseases may help to decide the best time to perform the transplantation. Indeed, for some nonmalignant diseases, such as hemoglobinopathies or bone marrow failure syndromes, HCT may not be an emergency treatment and patients could beneficiate to be transplanted in a more favorable season.

Outcomes:

Patients will be analyzed for:

- Overall survival: time to death. Death from any cause will be considered an event. Surviving patients will be censored at time of last follow-up.
- Disease Free survival: time to relapse or death from any cause.
- Non-relapse mortality: death without evidence of disease relapse. Relapse is the competing risk.
- Cause of death
- Relapse of malignant disease: NRM is the competing risk.

- aGVHD grade 2 – 4: Death is the competing risk. Patients are to be censored after relapse.
- cGVHD, any severity: Death is the competing risk. Patients are to be censored after relapse.

Statistical methodology:

- Patient-, disease-, and transplant – related factors will be compared between groups using the Pearson chi-square test for discrete variables and the Kruskal-Wallis test for continuous variables. Probabilities of disease-free and overall survival will be calculated using the Kaplan Meier estimator. Values for other endpoints will be generated using cumulative incidence estimates to account for competing risks.
- In multivariable analyses of seasons, the proportional hazard assumption will be examined. If violated, it will be included as a time-dependent covariate. A stepwise selection procedure will be used. Interactions between the main effect and significant covariates will be examined.

References:

1. Kmeid J, Vanichanan J, Shah DP, et al. Outcomes of Influenza Infections in Hematopoietic Cell Transplant Recipients: Application of an Immunodeficiency Scoring Index. Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation 2016;22:542-8.
2. Choi SM, Boudreault AA, Xie H, Englund JA, Corey L, Boeckh M. Differences in clinical outcomes after 2009 influenza A/H1N1 and seasonal influenza among hematopoietic cell transplant recipients. Blood 2011;117:5050-6.
3. Ogimi C, Waghmare AA, Kuypers JM, et al. Clinical Significance of Human Coronavirus in Bronchoalveolar Lavage Samples From Hematopoietic Cell Transplant Recipients and Patients With Hematologic Malignancies. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 2017;64:1532-9.
4. Seo S, Campbell AP, Xie H, et al. Outcome of respiratory syncytial virus lower respiratory tract disease in hematopoietic cell transplant recipients receiving aerosolized ribavirin: significance of stem cell source and oxygen requirement. Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation 2013;19:589-96.
5. Seo S, Xie H, Leisenring WM, et al. Risk Factors for Parainfluenza Virus Lower Respiratory Tract Disease after Hematopoietic Cell Transplantation. Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation 2018.
6. Grant WB, Bhattoa HP, Boucher BJ. Seasonal variations of U.S. mortality rates: Roles of solar ultraviolet-B doses, vitamin D, gene exp ression, and infections. The Journal of steroid biochemistry and molecular biology 2017;173:5-12.
7. Pierre K, Schlesinger N, Androulakis IP. The role of the hypothalamic-pituitary-adrenal axis in modulating seasonal changes in immunity. Physiological genomics 2016;48:719-38.
8. Menculini G, Verdolini N, Murru A, et al. Depressive mood and circadian rhythms disturbances as outcomes of seasonal affective disorder treatment: A systematic review. Journal of affective disorders 2018;241:608-26.

Conflicts of Interest:

None

Table 1 Characteristics of patients who underwent first ALLO transplants reported to the CIBMTR by seasons, from 2005 to 2017 in US and Canada

Variable	Winter N(%)	Spring N(%)	Summer N(%)	Fall N(%)
Number of patients	6781	7557	7472	7173
Number of centers	189	191	177	181
Country				
US	6614 (98)	7403 (98)	7311 (98)	7060 (98)
Canada	167 (2)	154 (2)	161 (2)	113 (2)
Age, median(range), years	49 (<1 - 79)	48 (<1 - 82)	47 (<1 - 81)	48 (<1 - 88)
Age at transplant, years				
<=16	1346 (20)	1471 (19)	1572 (21)	1431 (20)
16-40	1319 (19)	1529 (20)	1528 (20)	1453 (20)
>40	4116 (61)	4557 (60)	4372 (59)	4289 (60)
Disease				
AML	2388 (35)	2674 (35)	2509 (34)	2568 (36)
ALL	934 (14)	1044 (14)	990 (13)	956 (13)
Other leukemia	228 (3)	240 (3)	268 (4)	250 (3)
CML	253 (4)	275 (4)	274 (4)	227 (3)
MDS	1503 (22)	1636 (22)	1631 (22)	1579 (22)
Other acute leukemia	75 (1)	73 (<1)	77 (1)	67 (<1)
NHL	487 (7)	523 (7)	493 (7)	438 (6)
HL	22 (<1)	37 (<1)	39 (<1)	31 (<1)
Plasma cell disorder/Multiple Myeloma	20 (<1)	36 (<1)	23 (<1)	26 (<1)
Other Malignancies	10 (<1)	10 (<1)	6 (<1)	7 (<1)
Breast Cancer	0	0	1 (<1)	1 (<1)
Severe aplastic anemia	272 (4)	326 (4)	338 (5)	315 (4)
Inherited abnormalities erythrocyte differentiation or function	168 (2)	220 (3)	349 (5)	245 (3)
SCID and other immune system disorders	227 (3)	253 (3)	265 (4)	246 (3)
Inherited abnormalities of platelets	5 (<1)	11 (<1)	12 (<1)	10 (<1)
Inherited disorders of metabolism	110 (2)	115 (2)	104 (1)	113 (2)
Histiocytic disorders	63 (<1)	70 (<1)	75 (1)	82 (1)
Autoimmune Diseases	7 (<1)	3 (<1)	6 (<1)	4 (<1)
Other, specify	9 (<1)	11 (<1)	12 (<1)	8 (<1)
Graft type				
Bone Marrow	1434 (21)	1641 (22)	1841 (25)	1633 (23)
Peripheral blood	4110 (61)	4489 (59)	4340 (58)	4276 (60)
Cord blood	1237 (18)	1427 (19)	1291 (17)	1264 (18)

Variable	Winter N(%)	Spring N(%)	Summer N(%)	Fall N(%)
Donor/recipient HLA match				
Cord blood	1237 (18)	1427 (19)	1291 (17)	1264 (18)
HLA-identical siblings	1948 (29)	2231 (30)	2183 (29)	1935 (27)
matched related	32 (<1)	44 (<1)	47 (<1)	37 (<1)
Mismatched related, 1 mismatch	10 (<1)	11 (<1)	12 (<1)	14 (<1)
Mismatched related,>=2 mismatch	234 (3)	285 (4)	322 (4)	302 (4)
Mismatched related, mismatch unknown	84 (1)	84 (1)	96 (1)	87 (1)
8/8 unrelated	2409 (36)	2633 (35)	2701 (36)	2694 (38)
7/8 unrelated	596 (9)	605 (8)	589 (8)	644 (9)
<=6/8 unrelated	48 (<1)	42 (<1)	41 (<1)	52 (<1)
Unrelated (HLA match information missing)	183 (3)	195 (3)	190 (3)	144 (2)
Conditioning regimen intensity				
Myeloablative	3463 (51)	3898 (52)	3803 (51)	3673 (51)
RIC/NMA	2201 (32)	2396 (32)	2257 (30)	2227 (31)
Non Malignant disease	861 (13)	1009 (13)	1162 (16)	1024 (14)
Missing	256 (4)	254 (3)	250 (3)	249 (3)
GVHD prophylaxis				
No GVHD prophylaxis (forms under review)	97 (1)	93 (1)	96 (1)	90 (1)
Ex vivo T-cell depletion	129 (2)	142 (2)	122 (2)	125 (2)
CD34 selection	130 (2)	133 (2)	174 (2)	179 (2)
Cyclophosphamide	398 (6)	470 (6)	522 (7)	524 (7)
TAC/CSA + MMF +- others	2113 (31)	2333 (31)	2161 (29)	2135 (30)
TAC/CSA + MTX +- others	3014 (44)	3373 (45)	3345 (45)	3165 (44)
TAC/CSA + others (except MTX, MMF)	569 (8)	581 (8)	656 (9)	621 (9)
TAC/CSA alone	230 (3)	290 (4)	264 (4)	215 (3)
Other GVHD prophylaxis	86 (1)	117 (2)	101 (1)	91 (1)
Missing	15 (<1)	25 (<1)	31 (<1)	28 (<1)
Year of transplant				
2005	363 (5)	389 (5)	348 (5)	417 (6)
2006	426 (6)	468 (6)	492 (7)	504 (7)
2007	546 (8)	540 (7)	632 (8)	638 (9)
2008	734 (11)	742 (10)	790 (11)	697 (10)
2009	612 (9)	833 (11)	777 (10)	457 (6)
2010	393 (6)	477 (6)	441 (6)	372 (5)
2011	295 (4)	327 (4)	299 (4)	318 (4)
2012	309 (5)	329 (4)	290 (4)	334 (5)
2013	488 (7)	609 (8)	593 (8)	671 (9)
2014	743 (11)	705 (9)	732 (10)	825 (12)

Variable	Winter N(%)	Spring N(%)	Summer N(%)	Fall N(%)
2015	751 (11)	756 (10)	756 (10)	709 (10)
2016	607 (9)	735 (10)	697 (9)	648 (9)
2017	514 (8)	647 (9)	625 (8)	583 (8)
Virial infections by 100 day				
Yes	2737 (40)	2954 (39)	2892 (39)	2919 (41)
No	4034 (59)	4599 (61)	4572 (61)	4245 (59)
Missing	10 (<1)	4 (<1)	8 (<1)	9 (<1)
Bacterial infections by 100 day				
Yes	2908 (43)	3068 (41)	3234 (43)	2926 (41)
No	3863 (57)	4485 (59)	4230 (57)	4238 (59)
Missing	10 (<1)	4 (<1)	8 (<1)	9 (<1)
Fungal infections by 100 day				
Yes	427 (6)	557 (7)	585 (8)	548 (8)
No	6344 (94)	6996 (93)	6879 (92)	6616 (92)
Missing	10 (<1)	4 (<1)	8 (<1)	9 (<1)
Median follow-up of survivors, months	60 (3 - 165)	60 (3 - 157)	59 (3 - 156)	49 (3 - 151)

Proposal: 1811-82

Title:
Impact of antibacterial prophylaxis on outcomes after allogeneic hematopoietic stem cell transplant

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Hypothesis:
Antibacterial prophylaxis during allogeneic hematopoietic stem cell transplant (allo-HSCT) is associated with increased rates of acute graft versus host disease (GVHD), bloodstream infections (BSI), and transplant related mortality (TRM).

Specific aims:
- Examine the impact of antibacterial prophylaxis prior to engraftment on acute GVHD rates in allo-HSCT recipients
- Compare the incidence of BSI in the first 100 days post allo-HSCT between patients receiving and not receiving antibacterial prophylaxis
- Compare OS (overall survival) and NRM (non-relapse mortality) between pediatric patients who receive antibacterial prophylaxis and those who do not.

Scientific impact:
Many centers currently use antibacterial prophylaxis in patients undergoing allo-HSCT, however, there is emerging data that demonstrate increased BSI and acute GVHD in patients receiving antibiotics during transplant. The results of this study will directly influence clinical practice and have a large impact on the field.

Scientific justification:
Hematopoietic stem cell transplantation (HSCT) is the definitive therapy for many malignancies, marrow failure syndromes, and immune deficiencies in children, adolescents, and adults[1,2]. Transplant strategies and supportive care have evolved over the past few decades, resulting in improved overall survival (OS)[3]. Recently, evidence suggest broad spectrum antibiotic use is associated with loss of gastrointestinal microbiome diversity and bacteremia from gastrointestinal microrganisms.[4-6] Loss of microbiome diversity, that leads to domination of gastrointestinal pathogenic bacteria was associated with subsequent systemic infection with the corresponding pathogens in blood[6]. Further, loss of microbiome diversity is associated with recipients gastrointestinal graft versus host disease (GVHD)[7].
There are currently no recent multi-center studies comparing outcomes of HSCT patients who receive and do not receive antibacterial prophylactic medications during transplant. The CIBMTR currently captures patients who receive and do not receive antibacterial drugs for infection prophylaxis (question #407, Form 2100 R5.0). Additionally, it allows centers to input the type of prophylactic medications used: amoxicillin clavulanate, cefdinir, cefpodoxime, ciprofloxacin, ertapenem, levofloxacin, moxifloxacin, vancomycin, and other (list). The CIBMTR also requests the date the prophylactic antibiotic was started. In this study we will compare the incidence of acute GVHD, bloodstream infections, and OS between patients who receive prophylactic antibiotics and those who do not. Additionally, we will compare the outcomes between the various types of prophylactic medications.

Patient eligibility population:

- The study population will consist of all allogeneic patients (pediatric and adult) undergoing first hematopoietic stem cell transplant reported to the CIBMTR between 2009 and 2017
- Any stem cell source including bone marrow, peripheral or cord blood
- Any source including matched or mismatched related and unrelated donors
- Autologous hematopoietic stem cell transplant recipients and those who previously underwent transplant will be excluded

Data requirements:

Outcomes:

- Acute GVHD (aGVHD): Development of Grades II-IV and III-IV acute GVHD using the Glucksberg grading system. Event will be summarized by the cumulative incidence estimate. Death without aGVHD is a competing risk. Patients will be censored at second transplant.
- Bloodstream infection (BSI): Incidence of bloodstream infections (bacterial and fungal) in the first 100 days post- transplant. This will be assessed as the cumulative incidence function with death and relapse as competing risks.
- Non-relapse mortality (NRM): Defined as time to death without evidence of recurrence of hematological malignancy. Patients are censored at the date of last follow-up. The event will be summarized by the cumulative incidence estimate with relapse as a competing risk.
- Overall survival (OS): Time to death, patients will be censored at last follow-up.
- Cause of death: Infection as primary or secondary cause of death by day 100.

Patient-related variables:

- Age at transplant (continuous, <18 vs. >18 years)
- Gender: male vs. female

Transplant related:

- Antibacterial drug for infection prophylaxis: yes or no
- If antibacterial drug received, which drug(s) were used: amoxicillin clavulanate, cefdinir, cefpodoxime, ciprofloxacin, ertapenem, levofloxacin, moxifloxacin, vancomycin, and other (list)
- Disease: malignant vs. non-malignant
- Donor type: related vs. unrelated
- HLA match status: well matched vs. partially matched
- Graft type: BM vs. PBSC vs. CB
- Conditioning: Myeloablative vs. RIC/non-ablative; type of conditioning regimen
- GVHD prophylaxis: CSA +/- others vs. FK-506 +/- others vs. T cell depletion vs. others
- ATG use at transplant: yes vs. no
- Acute GVHD grades 2-4 post-transplant at day 100: yes or no
- Acute GVHD grades 3-4 post-transplant at day 100: yes or no
- Gastrointestinal acute GVHD (any) at day 100: yes or no
- Chronic GVHD at any time post-transplant: yes or no
- BSI in the first 100 days: yes or no
- Date of BSI in the first 100 days

Study design:
Using the criteria listed in section 5.3, patients will be categorized as (a) receiving antibacterial prophylaxis or (b) not receiving antibacterial prophylaxis. For patients receiving antibacterial prophylaxis, the type of prophylaxis will be used for subcategorization and analysis.
Descriptive tables of patient-, disease-, and transplant-related factors will be prepared. Patient-, disease-, and treatment-related factors will be compared by using Chi-square test if variables are categorical or by using Mann-Whitney U test if variables are continuous.
The Kaplan-Meier method will be used to estimate the probability of overall survival and the cumulative incidence of treatment related mortality and BSI in the first 100 days. The Log-Rank test will be used to assess differences in survival and Gray's test for competing risks will be used for differences in NRM (treating relapse and death from disease as competing risks) among the groups. Estimates of acute GVHD, chronic GVHD, NRM, and BSI will be calculated according to the cumulative incidence.

References:
1. Barriga F, Ramírez P, Wietstruck A, Rojas N. Hematopoietic stem cell transplantation: clinical use and perspectives. Biological Research. 2012;45:307-316.
2. Copelan EA. Hematopoietic stem-cell transplantation. N Engl J Med. 2006;354(17):1813-1826.
3. Remberger M, Ackefors M, Berglund S, et al. Improved survival after allogeneic hematopoietic stem cell transplantation in recent years. A single-center study. Biol Blood Marrow Transplant. 2011;17(11):1688-1697.
4. Galloway-Peña J, Smith D, Sahasrabhojane P, et al. The role of the gastrointestinal microbiome in infectious complications during induction chemotherapy for acute myeloid leukemia. Cancer. 2016
5. Holler E, Butzhammer P, Schmid K, et al. Metagenomic analysis of the stool microbiome in patients receiving allogeneic stem cell transplantation: loss of diversity is associated with use of systemic antibiotics and more pronounced in gastrointestinal graft-versus-host disease. Biol Blood Marrow Transplant. 2014;20(5):640-645.
6. Taur Y, Xavier JB, Lipuma L, et al. Intestinal domination and the risk of bacteremia in patients undergoing allogeneic hematopoietic stem cell transplantation. Clin Infect Dis. 2012;55(7):905-914.
7. Shono Y, Docampo MD, Peled JU, et al. Increased GVHD-related mortality with broad-spectrum antibiotic use after allogeneic hematopoietic stem cell transplantation in human patients and mice. Sci Transl Med. 2016;8(339):339ra371.

Proposal: 1811-150

Title:
Clinical Impact of Pre-Engraftment Antibacterial Prophylaxis in Adult Patients Undergoing Allogeneic Hematopoietic Cell Transplantation in the Current Era

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Hypothesis:
Pre-engraftment antibiotic prophylaxis might decrease the rate of infection episodes with questionable impact on early transplant related mortality.

Specific aims:
Primary:

- To compare infection rates and timing in the pre-engraftment period in allogenic transplant adult patients receiving antibacterial prophylaxis versus no prophylaxis

Secondary:

- Compare the effectiveness of different antibiotic prophylactic regimens
- Rate of blood stream infection including Central line-associated bloodstream infections (CLABSIs) and Mucosal Barrier Injury Laboratory-Confirmed Bloodstream Infection (MBI-LCBI)
- Clostridium difficile infection rate
- Rate of acute gastrointestinal graft versus host disease
- Overall survival
- Transplant related mortality

Scientific impact:
In the era of increasing antimicrobial resistance, the continued use of fluoroquinolones prophylaxis in n Neutropenic patients require further evaluation. Several reports have shown the negative impact of Fluoroquinolones including emergence of resistant isolates and increased risk for Clostridium difficile. Data is conflicting regarding antibacterial effects on mortality. There is no large contemporary data addressing these challenging clinical questions. Few institutions like ours don't use antibacterial prophylaxis prior to engraftment in allogenic patients. This study will provide insight regarding the risks and benefits of universal antibacterial prophylaxis in a large cohort of allogenic stem cell recipients. In addition, it will allow comparison between different prophylaxis approaches. This should lead to further identification of local bacterial susceptibility of implicated pathogens in neutropenic fever in future interventional comparative studies.

Scientific justification:
Patients with hematologic malignancies undergoing hematopoietic cell transplant (HCT) are at increased risk of infections during the pre-engraftment period. [1] The use of prophylactic antibiotics during neutropenia is the recommended common practice despite antimicrobial prophylaxis variability among institutions.[2] Multiple observational and randomized controlled studies have evaluated the efficacy of this approach in reducing rates of neutropenic fever episodes and blood stream infections. [7]However, a meta-analysis showed no mortality reduction with prophylactic antibiotics, in particular fluoroquinolones (FQ). In a cancer center survey of practices, six respondents (15 %) didn't use antibacterial prophylaxis prior to engraftment in allogenic transplant patients.[3] Furthermore, a recent

randomized open-label multicenter pediatric study showed that receiving FQ prophylaxis did not reduce bacteremia rates in children undergoing HCT (11.0% vs 17.3%, P = 0.06) and no infection related mortality was reported in either group. On the contrary, bacteremia rates were significantly lower in leukemia patients undergoing chemotherapy and receiving FQ prophylaxis (21.9% vs 43.4%, P = 0.001). [4] These findings are intriguing and whether they are applicable to adult patients undergoing HCT have yet to be fully elucidated. Other single center reports have shown that switching to FQ prophylaxis have not significantly changed their FQ-resistant gram negative bacteremia rates in adult HCT. [5] The ongoing concern is the promotion of multidrug resistance driven by selective antibiotic pressure. In addition, injudicious antibacterial l use can result in altered microbiome diversity which has been linked to deleterious effects on transplant outcomes including graft host disease. In an intercontinental study of gram negative bacteremia pattern of resistance in HCT patients, half of gram negative rods were resistant to FQ and non-carbapenem beta lactam which lead the authors to suggest revisiting FQ prophylaxis practices in HCT patients. [6] In the era of multidrug resistance, further data is needed to address these contemporary observations and examine the long term effects of antibacterial prophylaxis in HCT patients after more than a decade of adopting prophylactic practices. In this proposal, we aim to compare the rates of bacterial infection (bacteremia in particular) and clostridium difficile in adult patients undergoing HCT receiving antibacterial prophylaxis versus no prophylaxis.

Patient eligibility population:

As 2100 form was updated in Jan2017 and started to include the name of the antibacterial prophylaxis (Question 407), this will be the starting point of this study with plan for two years. All allogenic stem cell adult patients > 18 years old (including all donor and graft types) who have documentation of the type of antibacterial prophylaxis should be included. All allogenic stem cell patients who did not receive routine pre-engraftment antibacterial prophylaxis will also be included as the control arm. Infection questions section in form 2100 has to be filled to capture detailed infection related information as described below.

Data requirements:

Forms:

- Form 2000 R4: recipient baseline data
- Form 2100 : Post-HSCT Data
- For2006: Hematopoietic Stem Cell Transplant (HCT) Infusion
- Form 2900: Recipient Death Data
- Form 2400: Pre-Transplant Essential Data
- Form 2900: Recipient Death Data

Variables:

HCT and hematologic malignancy characteristics:

- Age, sex
- Primary Diagnosis:
  Type of Hematological malignancy (AML, ALL, CML etc.)
- Disease status at the time of transplant (Active, Remission, Unknown)
- Stem cell source (Cord, Marrow, Peripheral blood)
- Donor relation (Related, unrelated, Haploidentical)
- Match status (Mismatched, Matched)
- Type of Conditioning/preparative regimen
- T cell depletion

- TBI (total body radiation)
- Date of HCT
- Date of engraftment
- Date of admission
- Date of discharge
- Length of Hospital stay
- Use of antimicrobial prophylaxis (yes, no), name the drug, start date
- Use of IV immunoglobulin and growth factors (GM-CSF,G-CSF)

Infections in the first 30 days:

- Date of infection
- Name of organism
- Site of infection
- Further divide types of infections to Pneumonia, CLAMBI, CLABSI an
- Clostridium Difficile infection
- Septic shock

Clinical outcomes in the first 30 days:

- Acute gastrointestinal graft versus host disease (yes , No), date, degree
- Death (Yes, NO), Date
- Cause of death (infection related vs disease)

Study design:

Adult patients receiving allogeneic transplant from January 2017- January 2019 will classified into 2 groups based on receiving pre-engraftment antibacterial prophylaxis (prophylaxis group and no prophylaxis/control group). Demographics, hematological malignancies and transplant characteristics will be collected. Pre-engraftment Infection related data (date of infection, name of pathogen, site, and septic shock), 30 day overall survival and transplant-related mortality will be compared between the two groups. Subgroup comparative analysis of different types of antibacterial prophylaxis will be performed if sample number allow.

Proposed Statistics:

Demographics, hematological disease, HCT variables will be compared between the two groups using the Chi-square test for categorical variables and the Wilcoxon two-sample test for continuous variables. Will need to calculate incidence of pre-engraftment bacterial infection type, infection/ transplant related mortality disease free survival, overall survival with Kaplan-Meier probabilities. Risk factors for increased rates of infection to be identified in the model.

Multivariable models for OS , NRM, and the development of bacterial infections, clostridium difficile to be calculated using the Cox model with proportional hazards assumption.

Conflicts of interest:

None

References:

1. Freifeld AG, Bow EJ, Sepkowitz KA, et al. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the infectious diseases society of america. *Clin Infect Dis.* 2011;52(4):e56-93.

2. Baden LR, Swaminathan S, Angarone M, et al. Prevention and Treatment of Cancer-Related Infections, Version 2.2016, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw.* 2016;14(7):882-913.
3. Rashidi A, Wangjam T, Bhatt AS, Weisdorf DJ, Holtan SG. Antibiotic practice patterns in hematopoietic cell transplantation: A survey of blood and marrow transplant clinical trials network centers. *Am J Hematol.* 2018;93(11):E348-e350.
4. Alexander S, Fisher BT, Gaur AH, et al. Effect of Levofloxacin Prophylaxis on Bacteremia in Children With Acute Leukemia or Undergoing Hematopoietic Stem Cell Transplantation: A Randomized Clinical Trial. *Jama.* 2018;320(10):995-1004.
5. Miles-Jay A, Butler-Wu S, Rowhani-Rahbar A, Pergam SA. Incidence rate of fluoroquinolone-resistant gram-negative rod bacteremia among allogeneic hematopoietic cell transplantation patients during an era of levofloxacin prophylaxis. *Biol Blood Marrow Transplant.* 2015;21(3):539-545.
6. Averbuch D, Tridello G, Hoek J, et al. Antimicrobial Resistance in Gram-Negative Rods Causing Bacteremia in Hematopoietic Stem Cell Transplant Recipients: Intercontinental Prospective Study of the Infectious Diseases Working Party of the European Bone Marrow Transplantation Group. *Clin Infect Dis.* 2017;65(11):1819-1828.
7. Mikulska M, Averbuch D, Tissot F, et al. Fluoroquinolone prophylaxis in haematological cancer patients with neutropenia: ECIL critical appraisal of previous guidelines. *J Infect.* 2018;76(1):20-37.

Table 1 Characteristics of patients who underwent first ALLO transplants reported to the CIBMTR, from 2017 to June 2018

Variable	N(%)
Number of patients	3394
Number of centers	206
Age, median(range), years	52 (<1 - 88)
Age at transplant, years	
<=10	503 (15)
11-20	301 (9)
21-30	234 (7)
31-40	217 (6)
41-50	352 (10)
51-60	551 (16)
61-70	963 (28)
>70	273 (8)
Disease	
AML	865 (25)
ALL	378 (11)
Other leukemia	74 (2)
CML	44 (1)
MDS	1106 (33)
Other acute leukemia	26 (<1)
NHL	151 (4)
HL	37 (1)
Plasma cell disorder/Multiple Myeloma	8 (<1)
Severe aplastic anemia	245 (7)
Inherited abnormalities erythrocyte differentiation or function	244 (7)
SCID and other immune system disorders	150 (4)
Inherited abnormalities of platelets	3 (<1)
Inherited disorders of metabolism	38 (1)
Histiocytic disorders	19 (<1)
Other, specify	6 (<1)
Graft type	
Bone Marrow	985 (29)
Peripheral blood	2082 (61)
Cord blood	327 (10)
Donor/recipient HLA match	

Variable	N(%)
Cord blood	327 (10)
HLA-identical siblings	1041 (31)
matched related	81 (2)
Mismatched related, 1 mismatch	7 (<1)
Mismatched related,>=2 mismatch	344 (10)
Mismatched related, mismatch unknown	204 (6)
8/8 unrelated	1042 (31)
7/8 unrelated	139 (4)
<=6/8 unrelated	16 (<1)
Unrelated (HLA match information missing)	193 (6)
Conditioning regimen intensity	
Myeloablative	1187 (35)
RIC/NMA	1181 (35)
Non Malignancies	705 (21)
Missing	321 (9)
GVHD prophylaxis	
No GVHD prophylaxis (forms under review)	102 (3)
Ex vivo T-cell depletion	51 (2)
CD34 selection	76 (2)
Cyclophosphamide	938 (28)
TAC/CSA + MMF +- others	694 (20)
TAC/CSA + MTX +- others	1263 (37)
TAC/CSA + others (except MTX, MMF)	155 (5)
TAC/CSA alone	69 (2)
Other GVHD prophylaxis	46 (1)
Year of transplant	
2017	2792 (82)
2018	602 (18)

Footnote:

Variable	N(%)
Number of patients	3394
Antibacterial for infection prophylaxis	
No	753 (22)
Yes	2529 (75)
Missing	112 (3)
Amoxicillin clavulanate oral (Augmentin)	
No	3202 (94)
Yes	80 (2)
Missing	112 (3)
Cefdinir oral (Omnicef)	
No	3270 (96)
Yes	12 (<1)
Missing	112 (3)
Cefpodoxime oral (Vantin)	
No	3274 (96)
Yes	8 (<1)
Missing	112 (3)
Ciprofloxacin IV or oral (Cipro)	
No	2624 (77)
Yes	658 (19)
Missing	112 (3)
Ertapenem IV	
No	3277 (97)
Yes	5 (<1)
Missing	112 (3)
Levofloxacin IV or oral (Levaquin)	
No	2098 (62)
Yes	1184 (35)
Missing	112 (3)
Moxifloxacin IV or oral (Avelox) ?7¤0	
No	3214 (95)
Yes	68 (2)
Missing	112 (3)
Vancomycin IV	
No	3073 (91)
Yes	209 (6)
Missing	112 (3)
Other antibacterial drug	
No	2686 (79)
Yes	596 (18)
Missing	112 (3)
Median follow-up of survivors, months	6 (3 - 20)

Proposal: 1811-139

Title:
Impact of Early Post-transplant Infections on Relapse Risk Following Autologous Stem Cell Transplantation for Multiple Myeloma

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Hypothesis:
Early infections following autologous stem cell transplantation in multiple myeloma require antibiotic use that may promote gut dysbiosis and affect efficacy of high dose melphalan increasing risk for early relapse

Specific aims:

- To evaluate for an association between early post-transplant bacterial infections (within 30 days) and early disease relapse (within 2 years) post autologous transplant stratified by infection subgroup:
  - C difficile colitis
  - Gram negative bacteremia
  - Gram positive bacteremia
- To evaluate the impact of early infection on best response achieved following autologous transplant
- To perform a multi-variate analysis of demographic and disease contributors to early relapse including but not limited to:
  - Age
  - R-ISS Stage of multiple myeloma
  - High risk cytogenetics (t(4,14),t(14,16),del17p)
  - Immunochemical subtype (IgG, IgA, etc)
  - Lines of prior therapy
  - Planned maintenance therapy
- To investigate impact of antibiotic type (if available) on risk of early disease relapse according to:
  - PO vancomycin
  - IV vancomycin
  - IV cefepime
  - IV piperacillin/tazobactam

Scientific impact:
Approximately 38% of patients relapse within the first two years following autologous transplantation in multiple myeloma, which is associated with a poor prognosis and incompletely explained by disease biology.[1] The gut microbiome is required for the antineoplastic effects of alkylator therapy like

cyclophosphamide, and is subject to a variety of insults following hematopoietic stem cell transplantation including use of antibiotics for infection.[2] An association between the gut microbiome, antibiotics, and efficacy of melphalan has not been reported to date. Given the similarity in mechanism of action and toxicity profile to cyclophosphamide, we hypothesize that the gut microbiome is similarly required for the efficacy of melphalan therapy, where perturbations of the gut microbiome via infectious colitis or antibiotic administration may lead to a diminished treatment effect.
Identification of an adverse association between early infections and early relapse, mediated in part by antibiotic exposure, would prompt serious consideration in the use of antimicrobial agents in the post-transplant setting. Such a finding could be an *imminently modifiable risk factor* to improve disease responses following autologous stem cell transplantation using high dose melphalan in myeloma patients, which could be reasonably tested in a future study design.

Scientific justification:
Autologous stem cell transplantation using high dose melphalan is a cornerstone of therapy in multiple myeloma and often employed early after diagnosis.[3] Unfortunately, up to 38% of patients relapse early, within the first two years, which is associated with a poor prognosis and incompletely explained by disease biology or patient comorbidity.[1] The gut microbiome is increasingly being appreciated as an important mediator of both toxicity and efficacy of bone marrow transplantation, particularly in allogeneic transplantation but also with individual chemotherapeutic agents like cyclophosphamide, an alkylating agent with marked similarities to melphalan.[2, 4] A study by *Viaud et al* demonstrated that hematopoietic tumor-bearing mice with absent gut microbiota or those treated with gram-positive antibiotics had a markedly decreased response to cyclophosphamide compared to those raised in standard germ-replete conditions. The mechanism of action involved the translocation of gram positive gut bacteria across a weakened intestinal barrier to secondary lymphoid organs that stimulated the growth of a subset of T helper cells required for response to cyclophosphamide.[2] A separate retrospective study on patients with chronic lymphocytic leukemia treated with cyclophosphamide validated these findings by demonstrating that those who required treatment with gram-positive specific antibiotics like vancomycin demonstrated a meaningful reduction in disease response to cyclophosphamide-containing regimens even after controlling for dose intensity of treatment.[5] These studies demonstrate that antibiotic use impacts the gut microbiome and may impact the efficacy of alkylator therapy like cyclophosphamide. Given the similarity in drug class, mechanism of action, and toxicity, we hypothesize that melphalan may similarly require the presence of certain gut microbiota, such as gram positive organisms, to achieve optimal efficacy.
Infectious complications are relatively common following autologous transplantation including c. difficile colitis, which may occur in up to 10% of patients within a median time of 6 days post-transplant.[6, 7] Guidelines support the near universal use of oral vancomycin for treatment of c. difficile colitis, particularly in immune-suppressed patients such as those receiving stem cell transplantation.[8] The ubiquitous use of oral vancomycin for treatment of c. difficile colitis post-transplant indicates that the infection may reasonably be used as a surrogate for oral vancomycin exposure. Furthermore, development of c. difficile colitis likely produces a state of gut dysbiosis that may influence outcomes according to our hypothesis without antibiotic exposure. Although clear documentation of antibiotic exposure would be helpful, it would not be essential for our proposed analysis, which would certainly lead to future novel investigations to probe associations and potential mechanisms. In addition, initial management of neutropenic fever following bone marrow transplantation typically involves cefepime or piperacillin-tazobactam based on institutional preference, and these antibiotics may have a differing impact upon the gut microbiome with respect to differing anaerobic coverage.[9]
Here, we hypothesize that early infection with c. difficile colitis, which requires near universal treatment with anti-gram positive antibiotics like oral vancomycin will negatively alter the gut microbiome by

reducing populations of gram-positive bacteria required for the efficacy of melphalan therapy and lead to increased risk of early disease relapse. An additional effect on disease outcomes may be noted for early gram-positive and gram-negative bacteremia requiring antibiotic support.
The CIBMTR is the best candidate to perform this study by reducing potential confounders associated with single centers or limited patient populations. We would address potential confounders by performing a multivariate analysis including our endpoint as well as disease factors, patient comorbidity (ie age, performance status) and other potential contributors to examine for significance. This analysis, made possible through the large multi-center data set offered by the CIBMTR, would strengthen the applicability of the research findings to the population of myeloma patients undergoing autologous transplantation as a whole. Although specific data such as antibiotic use may not be available, most data reported to the CIMBTR capture early infections and early disease assessments rather well. Focusing on a specific, well-defined subset of patients (ie myeloma undergoing first auto transplant) treated with one specific antineoplastic agent (melphalan) reduces the heterogeneity in the population and limits confounding, allowing us to more directly associate findings to melphalan exposure rather than a regimen involving multiple agents.

Patient eligibility population:
Eligible patients would include adults aged 18+ with multiple myeloma undergoing their first autologous stem cell transplantation using high dose melphalan from 2009 onwards

Data requirements:
Demographic information:

- Patient age
- Performance status at transplant
- Sex
- Race/ethnicity

Disease factors:

- R-ISS stage at diagnosis
- Immunochemical subtype
- Number of prior lines of therapy
- High risk cytogenetics: (t(4,14),t(14,16),del17p)
- Planned maintenance therapy

Transplant factors:

- Melphalan dose
- Time from diagnosis to transplant
- Salvage versus consolidation transplantation

Peri-transplant antibiotics (if data available):

- TMP-SMX administration
- Fluroquinolone prophylaxis
- Oral Vancomycin post-transplant

Outcomes:

- Primary Outcome: Rate of relapse within 2 years post-transplant (early relapse) according to International Myeloma Working Group Guidelines stratified by development of c. difficile colitis or not within 30 days post-transplant[10]

- Secondary outcomes:
    - Rate of very good partial response or complete response post autologous transplant according to early infection or not
    - Impact of antibiotic use on early disease relapse
        - PO vancomycin
        - IV vancomycin
        - IV cefepime
        - IV piperacillin/tazobactam
    - Rate of gram negative and gram positive bacteremia in the first 100 days post-transplant and association of these infections with the outcome of early relapse defined above
    - Incidence of c. difficile colitis within 100 days post autologous transplantation
    - Investigate impact of disease and patient variables on outcome of early relapse in a multi-variate analysis

Study design:

Patients with multiple myeloma undergoing first autologous transplantation using high dose melphalan would be examined for early relapse according to those who did or did not develop an early infection post-transplantation, namely c. difficile colitis but also gram positive and gram-negative bacteremia. If an association was identified, we would perform a multivariate analysis to adjust for potential confounding by disease and patient risk factors known to be associated with an increased risk for early relapse (i.e. age, disease stage, high-risk genetic features). Secondary endpoints would be assessed including early infection incidences and antibiotic use if this data is available from the centers. We would also evaluate best response to autologous transplant according to development of early infection versus not.

References:

1. Kumar SK, Dispenzieri A, Fraser R, et al. Early relapse after autologous hematopoietic cell transplantation remains a poor prognostic factor in multiple myeloma but outcomes have improved over time. *Leukemia.* 2018;32:986-995.

2. Viaud S, Saccheri F, Mignot G, et al. The intestinal microbiota modulates the anticancer immune effects of cyclophosphamide. *Science.* 2013;342:971-976.

3. Attal M, Lauwers-Cances V, Hulin C, et al. Lenalidomide, Bortezomib, and Dexamethasone with Transplantation for Myeloma. *N Engl J Med.* 2017;376:1311-1320.

4. Andermann TM, Peled JU, Ho C, et al. The Microbiome and Hematopoietic Cell Transplantation: Past, Present, and Future. *Biol Blood Marrow Transplant.* 2018;24:1322-1340.

5. Pflug N, Kluth S, Vehreschild JJ, et al. Efficacy of antineoplastic treatment is associated with the use of antibiotics that modulate intestinal microbiota. *Oncoimmunology.* 2016;5:e1150399.

6. Kamboj M, Son C, Cantu S, et al. Hospital-onset Clostridium difficile infection rates in persons with cancer or hematopoietic stem cell transplant: a C3IC network report. *Infect Control Hosp Epidemiol.* 2012;33:1162-1165.

7. Alonso CD, Treadway SB, Hanna DB, et al. Epidemiology and outcomes of Clostridium difficile infections in hematopoietic stem cell transplant recipients. *Clin Infect Dis.* 2012;54:1053-1063.

8. McDonald LC, Gerding DN, Johnson S, et al. Clinical Practice Guidelines for Clostridium difficile Infection in Adults and Children: 2017 Update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA). *Clin Infect Dis.* 2018;66:987-994.

9. Freifeld AG, Bow EJ, Sepkowitz KA, et al. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the infectious diseases society of america. *Clin Infect Dis.* 2011;52:e56-93.

10. Kumar S, Paiva B, Anderson KC, et al. International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. *Lancet Oncol.* 2016;17:e328-e346.

Table 1 Characteristics of adult patients who underwent first AUTO transplants with Multiple Myeloma, reported to the CIBMTR, from 2009 to 2016

Variable	N(%)
Number of patients	4513
Number of centers	151
Age, median(range), years	60 (13 - 83)
Age at transplant, years	
11-20	1 (<1)
21-30	7 (<1)
31-40	127 (3)
41-50	578 (13)
51-60	1491 (33)
61-70	1884 (42)
>70	425 (9)
Karnofsky score at transplant	
<90	2031 (45)
>=90	2408 (53)
Missing	74 (2)
ISS at stage diagnosis	
Stage I	1281 (28)
Stage II	1204 (27)
Stage III	776 (17)
Missing	1252 (28)

Variable	N(%)
Year of transplant	
2009	317 (7)
2010	240 (5)
2011	334 (7)
2012	341 (8)
2013	628 (14)
2014	546 (12)
2015	700 (16)
2016	760 (17)
2017	647 (14)
C difficile colitis by 30 day	
Yes	165 (4)
No	4348 (96)
Gram Negative bacteremia by 30 day	
Yes	129 (3)
No	4384 (97)
Gram positive bacteremia by 30 day	
Yes	61 (1)
No	4452 (99)
Median follow-up of survivors, months	36 (3 - 114)

*There are 334 (7.5%) cases with at least one of the infections (Cdiff and/or GN BSI and/or GP BSI).