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A G E N D A
CIBMTR WORKING COMMITTEE FOR INFECTION AND IMMUNE RECONSTITUTION
Orlando, FL
Saturday, February 22, 2020, 12:15 – 2:15 PM

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;**
Co-Chair:	**Roy Chemaly, MD, UT MD Anderson Cancer Center, Houston, TX;** **Telephone: 713-792-0007; E-mail: rfchemaly@mdanderson.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**
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1. **Introduction**
   a. Welcome and introduction
   b. Introduction of incoming Co-Chair: Dr. Christopher Dandoy, M.D. Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio
   c. Minutes and Overview Plan from February 2019 meeting (Attachment 1)

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

3. **Studies published/submitted/Preliminary results**
   a. **IN13-01** Ustun C, Kim S, Chen M, Beitinjaneh AM, Brown VI, Dahi PB, Daly A, Diaz MA, Freytes CO, Ganguly S, Hashmi S, Hildebrandt GC, Lazarus HM, Nishihori T, Olsson RF, Page KM, Papanicolaou G, Saad A, Seo S, William BM, Wingard JR, Wirk B, Yared JA, Perales M-A, Auletta JJ, Komanduri KV, Lindemans CA, Riches ML. **Increased overall and bacterial infections following myeloablative allogeneic HCT for patients with AML in CR1.** *Blood Advances 3(17):2525-2536, 2019.* **Published.**
   b. **IN14-01** Naik S, Riches M, Soyoung K, Chen M, Bachier C, Shaughnessy P, Hill J, Ljungman P, Battiwalla M, Chhabra S, Daly A, Storek J, Ustun C, Diaz MA, Cerny J, Beitinjaneh A, Yared J, Brown V, Page K, Dahi PB, Ganguly S, Seo S, Chao N, Freytes CO, Saad A, Savani BN, Ahn KW, Boeckh M, Heslop HE, Lazarus HM, Auletta JJ, Kamble RT.**Survival Outcomes of Allogeneic Hematopoietic Cell Transplants with EBV positive or EBV negative Post Transplant Lymphoproliferative Disorder (PTLD), A CIBMTR Study.Submitted.** *Transpl Infect Dis. 2019 Oct;21(5):e13145. doi: 10.1111/tid.13145. Epub 2019 Jul 31.* **Published.**

c. **IN16-02** Christopher E. Dandoy, MD, MS; Soyoung Kim, PhD; Min Chen, MS; Kwang Woo Ahn, PhD; Monica I. Ardura, DO, MSCS; Valerie Brown, MD, PhD; Saurabh Chhabra, MD; Miguel Angel Diaz, MD, PhD; Christopher Dvorak, MD; Nosha Farhadfar, MD; Aron Flagg, MD; Siddartha Ganguly, MD; Gregory A. Hale, MD; Shahrukh K. Hashmi, MD; Peiman Hematti, MD; Rodrigo Martino, MD; Taiga Nishihori, MD; Roomi Nusrat, MD; Richard F. Olsson, MD; Seth J. Rotz, MD; Anthony D. Sung, MD; Miguel-Angel Perales, MD; Caroline A. Lindemans, MD, PhD; Krishna V. Komanduri, MD; Marcie L. Riches, MD, MS. **Incidence, Risk Factors, and Outcomes of Patients Who Develop Mucosal Barrier Injury–Laboratory Confirmed Bloodstream Infections in the First 100 Days After Allogeneic Hematopoietic Stem Cell Transplant,** *JAMA Netw Open. 2020;3(1):e1918668. doi:10.1001/jamanetworkopen.2019.18668.* **Published.**

d. **IN17-01 (a)** Incidence and Impact of Cytomegalovirus Infection in Haploidentical and Matched-Related Donors Receiving Post-Transplant Cyclophosphamide (PTCy): A CIBMTR Analysis (S Goldsmith/E Fuchs/A Bashey/S Ciurea/A Singh/ S Ganguly/R Taplitz/C Mulroney/R Maziarz/ R Romee) **2020 TCT Abstract (Oral); Manuscript preparation**

e. **IN17-01 (b)** Incidence and impact of Non-CMV herpes viral infection in Haploidentical and Matched Sibling Donors receiving Post-transplant Cyclophosphamide (PTCy): A CIBMTR Analysis. (A Singh/E Fuchs/A Bashey/S Ciurea/S Goldsmith/S Ganguly/Randy A Taplitz/C Mulroney/R Maziarz/R Romee)**2020 TCT Abstract (Poster); Manuscript preparation**

f. **IN17-01 (c)** Incidence and Impact of Community Respiratory Viral Infection (CRV) in Haploidentical and Matched Sibling Donors receiving post-transplant Cyclophosphamide (PTCy): A CIBMTR analysis (R Taplitz/R Maziarz/C Mulroney/R Romee, S Goldsmith/E Fuchs/A Bashey/S Ciurea/A Singh/S Ganguly) **2020 TCT Abstract (Oral); Manuscript preparation**

4. Studies in progress (Attachment 3)

a. **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) **Data file preparation** (Attachment 4)

b. **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) **Data file preparation** (Attachment 5)

c. **IN19-01** Immune recovery predicts post transplant outcomes (Miguel-Angel Perales/ Paul Szabolcs) **Protocol development** (Attachment 6)

d. **IN19-02** Impact of Antibiotic Prophylaxis in Patients Undergoing Allogeneic Hematopoietic Cell Transplantation in the Current Era (Zeinab El Boghdadly/ Christopher Eugene Dandoy/ Priscila Badia Alonso) **Protocol development** (Attachment 7)

5. Future/proposed studies

a. **PROP 1911-49** Risk for early post-transplant bacterial, viral and fungal infection in Hodgkin's lymphoma patients that receive pre-transplant therapy with checkpoint inhibitors (M McGhee/D P. Melendez/ J Holter-Chakrabarty/ S K. Vesely) (Attachment 8)

b. **PROP 1911-90** Changing epidemiology and outcomes of invasive candida infections in the current era of stem cell transplantation (J S. Green/ C Ustun) (Attachment 9)

c. **PROP 1911-197** Evaluating time from diagnosis to transplant as an important contributor for post-allogeneic stem cell transplant infections and infection/delayed immune-reconstitution associated mortality/morbidity (L Gowda/ C Ustin/ M de Lima/ J Boelens) (Attachment 10)

d. **PROP 1911-34** Infectious disease patterns, clinical impacts and treatment in aggressive B cell non-Hodgkin lymphoma and precursor B acute lymphoblastic leukemia patients treated with CD19 CAR T cell therapy (K Wudhikarn/ M-A Perales)
PROP 1911-50 Impact of early infection in chimeric antigen receptor T cell therapy outcomes in the first 100 days post-therapy (M McGhee/ D P. Melendez/ J Holter-Chakrabarty/ S K. Vesely)
PROP 1911-76 Infectious complications after CAR-T cell immunotherapy in patients with B-cell malignancies (J Maalouf/ J A. Hill/ C J. Turtle)
PROP 1911-155 Infections after CD19-targeted chimeric antigen receptor–modified T-cell therapy for non-Hodgkin lymphoma(M Herr/ T Hahn)
PROP 1911-158 Observational study of infectious complications among patients treated with anti-CD19 chimeric antigen receptor T cells (H Rangarajan/ P Satwani)
PROP 1911-209 Infectious complications and immune reconstitution following CD19-directed CAR-T cell therapy (J H. Baird/ S Sidana/ J Y. Spiegel/ D Epstein/ D B. Miklos)
PROP 1911-235 The role of intravenous immune globulins in patients after CAR-T therapy (E McGehee/ A Kansagra/ P Ramakrishnan/ F Awan)
PROP 1911-254 Patterns of infections post CD 19 directed CAR-T cells infusions (L Gowda)
PROP 1911-266 Risk factors for clinically significant infections following CD-19 CD19-targeted CAR-T cells therapy for hematological malignancies (A C Cordeiro/ G Fatobene/ M Bar/ V Rocha)(Attachment 11)

Dropped proposed studies

a. **PROP 1907-02** The effect of antibacterial prophylaxis on early post-transplant mortality in patients with multiple myeloma and lymphoma undergoing high-dose chemotherapy and autologous hematopoietic cell transplantation: A retrospective study on behalf of the infection and immune reconstitution working committee. *Dropped due to small sample size.*

b. **PROP 1911-86** Impact of Letermovir on rates of CMV reactivation and transplant outcomes. *Dropped due to supplemental /additional data needed.*

c. **PROP 1911-109** The impact of CMV serostatus on outcomes after haploidentical stem cell transplant. *Dropped due to overlap with current study/publication.*

d. **PROP 1911-226** Outcomes of allogeneic hematopoietic cell transplant recipients with serious viral infections including EBV, CMV, HHV6, BK and adenovirus post haploidentical transplants compared to cord transplants and matched donor allogeneic hematopoietic cell transplants (allo HCT). *Dropped due to low scientific impact.*

6. Other Business

MINUTES AND OVERVIEW PLAN
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**

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. Roy Chemaly as the new chair for INWC starting March 1st 2019, and thanked Dr. Caroline Lindemans for her excellent service to the INWC in the past 5 years. She also thanks Dr. Jan Styczynski, EBMT working party chair for his help.

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 to review the 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 3 minutes to allow for adequate time for 7 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.

She reminded the working committee members that the infection data are collected only on CRF level forms.

b. Minutes and Overview Plan from February 2018 meeting
The minutes and overview plan from the 2018 Tandem meeting held in Salt Lake City, Utah 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 published/submitted/Preliminary results

Dr. Marcie Riches note 3 papers have been published this year from INWC and a fourth submitted. She also reviewed that 2 studies the studies with results are in draft manuscript versions with expected circulation to the writing committee in the next several weeks.

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 Transplant*. 2018 Dec 13. doi: 10.1038/s41409-018-0401-4. [Epub ahead of print] PubMed PMID: 30546070. **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**, *Clin Infect Dis*. 2019 Jan 14. doi: 10.1093/cid/ciz031. [Epub ahead of print] PubMed PMID: 30649224. **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 Transplant*. 2019 Jan 29. doi: 10.1038/s41409-019-0457-9. [Epub ahead of print] PubMed PMID: 30696997. **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.**

4. Studies in progress

Dr. Miguel-Angel Perales introduced the ongoing studies.

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**

Dr. Anurag Singh updated the study.

Objectives of the study are: compare CMV and key viral infections in 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 for the development of non-CMV viral infections across these donor types

Patients inclusion criteria are First allo-HCT for AML, ALL and MDS, age ≥ 2 years, and HCT between 2008-2016. Excluded Ex-vivo T-cell depletion, CD34 selection, Non PTCy haplo-HCT, mismatched unrelated donor transplants, umbilical cord blood transplants, lack of donor/recipient CMV serostatus.

Dr. Perales pointed out the matched unrelated donor are also removed from the current population based upon discussions of overlap with GS1801.

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**

Dr. Celalettin Ustun updated the study.

Allogeneic hematopoietic cell transplant (HCT) outcomes differ between fully matched related donor transplants (MRD) and Haploidentical (HaploHCT) transplant with further differences associated with the use of post-transplant cyclophosphamide (PTCy). The study aims are: Determine the incidence and infection density of bacterial infections and fungal infections occurring within 100 days after HCT; Assess the impact of bacterial and fungal infections by day 100 on 1 year transplant outcomes(relapse, non-relapse mortality (NRM), disease free survival (DFS), overall Survival (OS) and Chronic GVHD.

Comments:

The population for IN18-01 will be the same population used for IN17-01

- Consider looking at infection and immune reconstitution events beyond day 100, consider subset analysis if there are too much missing
- Consider examining GVHD treatments at time of infection. The INWC leadership noted that these data are not fully available
- Consider examining the impact of multi-drug resistance. The INWC leadership noted that these data are not available except for VRE
- Examine center effects

Dr. Krishna Komanduri mentioned, the registry data has limitations. While we would like to see more details, this is a transplant rather than an infection registry.

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**
Dr. Muthalagu Ramanathan updated the study.
The study aims are: Determine Incidence of CDI (Clostridium Difficile infection) following Allogeneic HCT; Determine Impact of CDI on transplant outcomes (Acute GVHD, Chronic GVHD, TRM, Overall Survival); Identify pre-transplant risk factors for development of CDI after allogeneic HCT.
Eligible population: All patients age 2 years and older receiving first allogeneic HCT for AML, ALL, or MDS in 2010 to 2017. Fully HLA matched 8/8 related or unrelated donor. Cases will be patients reported with CDI by day 100 and controls will be all patients from the same centers with cases.
    - Dr. Ramanathan requested the addition of mismatched cord blood transplants to the study population and the working committee concurred.

There are 834 cases and 7253 controls identified in 148 transplant Centers (11.5%). Patient, donor and disease related characteristics seem comparable between cases and controls. Transplant related characteristics seem comparable in terms of time to transplant, HLA matching, GVHD prophylaxis, year of transplant, systemic antibacterial use etc.
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 based on Center's reporting
- Not all CDI causes clinical symptoms and definition of CDI is center specific
- Above center specific effects has been partially overcome by using controls from only centers that have cases;
- History of CDI prior to HCT, severity of CDI or the treatment administered is not captured in the CIBMTR database.

5. Future/proposed studies

Dr. Caroline Lindemans reported that 14 proposals were received this year and 8 will be presented.

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)

Dr. Jennifer Kanakry presented the proposal.
The Hypothesis of the proposal is: HCT approaches containing mTORi may be associated with lower incidence of herpesvirus-associated infection/diseases in the first year post-HCT.

Eligible population: Patients undergoing first allo HCT for any disease between January 2008 and December 2017 are included. Patients with UCB graft recipients, ex vivo T-cell depleted grafts, approaches that included planned post-HCT donor lymphocyte infusions are excluded.

The endpoints are comparing outcomes at mTORi-containing regimens vs non-mTORi containing regimens. The outcomes are: CMV infection, CMV disease, Pre-emptive treatment for EBV, EBV-PTLD, HHV6 encephalitis, NRM, OS and GVHD rates at 1 year.
Discussions:

- Limited to CMV at first year after transplant since the data stronger.
- There are no data on pre-emptive therapy for EBV
- Consider center effect, limit case and controls are from same centers may help.
- Sirolimus is associated with better control of CMV because it less the immunosuppression but will it affect GVHD as well. How to examine?
- Consider duration of sirolimus

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)

Dr. Alaa Ali presented the proposal.
The hypothesis are : High-risk MDS has a higher burden of infectious complications following allo-HCT compared to de-novo AML, due to older age, iron overload and pre-transplant neutropenia; engraftment and immune reconstitution (IR) follows a delayed and/or imbalanced course following allo-HCT compared to de-novo AML, due to longer time to neutrophils and platelets engraftment, competent microenvironment is required for both innate immunity and T cell reconstitution. It is an important topic since it will impact on surveillance and prophylactic programs.
The endpoints for the proposal will be Incidence rate of infections: viral, bacterial and fungal. Infection-related mortality; time to neutrophils and platelet engraftment; rate of graft failure; rate of delayed humoral IR (low immunoglobulin levels); rate of delayed adaptive immunity (T and B cells); rate of delayed innate immunity (monocytes, NK cells).
Discussion:

- Consider select patients from the same center, since different centers prefer different prophylaxis. Additionally, the choice of prophylaxis in individual patients may be altered by the prolonged neutropenia in MDS patients prior to HCT
- Consider add neutrophil counts at time of conditioning and time to engraftment as factors
- Consider adding HCT CI to analysis

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)
Dr. Caroline Lindemans mentioned this proposal was originally proposed in 2010 and only 22 cases at that time. If the study moving forward, the original group will be invited to join the study.
Dr. Paolo Melendez presented the proposal.
The hypothesis is 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.
The primary aim is to compare the transplant-related outcomes in patients that develop NTM infections vs. those who do not, in the first 2 years post-HSCT

Patient selection: Cases are patients with NTM infection in the first 2 years post-transplant. Controls are patients with no NTM infection within the same centers as cases. The plan proposed involves matching cases and controls by underlying disease and status, transplant intensity, graft source, and transplant date (within 3-5 years).
Outcomes are: overall survival, transplant related mortality and disease-free survival.
Discussion:

- The background data demonstrate more death in MTB group than in non-MTB group
- Why are the number of cases increasing every year since 2010? The reason maybe the PCR is widely used.
- Consider look at potential confounders such as lung problem, immune constitution issue.
- Methods of diagnosis is important however the forms do not collect. If we have to request additional data from the center that will be too much work.
- Consider a subset analysis of patients with and without bronchiolitis obliterans
- Consider a subset analysis of those with non-MTB reported as a bloodstream infection vs a pulmonary infection.

d. **PROP1811-59** Immune recovery predicts post-transplant outcomes (Miguel-Angel Perales)
Dr. Miguel-Angel Perales presented the proposal.
The study aims are: 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 III-IV), chronic GVHD, relapse/progression, PFS/DFS and OS; descriptive analysis of immune recovery post HCT including T, B and NK cells.
Scientific Impact of CIBMTR Immune Reconstitution study: this is the 1st multicenter analysis of immune reconstitution labs; largest dataset to date; confirm and expand single center studies results; proof of principle that CIBMTR can also analyze immune reconstitution
Discussions:

- Recommend examining other correlations (CD3, CD8) in addition to CD4 on HCT outcomes
- Consider examining the effect of ATG and/or alemtuzumab on immune recovery. This will need to include date/timing of ATG

- How to analyze? Would this be analyzed as a landmark analysis only for patients alive at day 100?
- Recommend examining dose of steroids. These data are unavailable.cluding pediatric population

*****After the meeting, leadership was reminded that a similar study was proposed several years ago by Dr. Paul Szsbolcs and Dr. Jan Storek.*

e. **PROP1811-77** Impact of seasons on outcomes of allogenic hematopoietic cell transplantation (HCT) in North America (P Teira)
Dr. Pierre Teira presented the proposal.
Dr. Caroline Lindemans mentioned a similar study was proposed in 2015 and if this proceeds that proposer would be invited as co-I.
Hypothesis: seasons may have an impact on outcomes of HCT due to seasonal epidemic infections and seasonal variations in the human circadian rhythms.
Specific aim is to assess the impact of the season where the HCT is done on cumulative incidence of Relapse, aGVHD, cGVHD, NRM, EFS and OS in HSCT in North America.
Patient eligibility population is all patients receiving a first HSCT, in USA (except Hawaii) and Canada, between 2005 and 2015, for any disease, from any donor, with any conditioning intensity and reported to the CIBMTR are included.
Discussions:
   - Consider analysis regionally due to different durations of season based upon location in N. America
   - Consider using the seasons for comparison as the flu season by each region
   - It is a complicated question. NIAID funded the TransNet Fungal Infection Consortia to examine fungal infections within 23 transplant centers. Looked at climate, precipitation etc., analyzed all factors however, could not find any trend and have not published.
   - Recommended that comparisons occur for specific pathogens (ex. Mold, respiratory viruses, etc)

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)
Dr. Zeinab Boghdadly presented the proposal.
Hypothesis: prophylactic antibiotic use is associated with decreased blood stream infection (BSI) prior to engraftment, but increased rates of acute GVHD, post-engraftment BSI, and non-relapse mortality in allogeneic transplant recipients
Specific aims are: compare incidence and timing of BSIs in patients who receive and do not receive antibiotic prophylaxis; determine the incidence of acute GVHD in patients who receive and do not receive antibiotic prophylaxis; compare OS (overall survival) and NRM (non-relapse mortality) between patients who receive antibacterial prophylaxis and those who do not; compare above outcomes between antibiotic sub-classifications.
Study Population/Design: all patients (pediatric and adult) undergoing first allogenic HCT reported (Form 2100,Q407) from January 2017 onward
Primary Outcomes: Pre-engraftment BSI, Acute GVHD 2-4, OS and NRM at 100 days and at 1 year
Secondary Outcomes: Acute GI GVHD 2-4 by day100, Infection type (BSI, CDI, septic shock, fungal, viral) by day100, Cause of Death (infection vs non-infectious)

Scientific Impact/Strengths: large global multicenter cohort; Contemporary; revisit the efficacy of antibiotic prophylaxis in the modern era; effects of early microbiota disruption on GVHD; address conflicting mortality benefits of prophylaxis; implications on current clinical practice guidelines.
Discussions:

- Unable to examine the microbiota data within CIBMTR. However, there is a prospective trial within the BMT CTN that will have detailed examination of antimicrobial administration and microbiota data
- Consider including anti-fungal and anti-viral prophylaxis
- Consider limiting the analysis to quinolones vs no antibacterial prophylaxis
- Consider subset cohorts, such as acute leukemia
- Consider reasons for no antibiotic prophylaxis, center effect or other reasons.

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)
Dr. Christopher D'Angelo presented the proposal.
Hypothesis is Melphalan requires gram positive gut bacteria to achieve optimal efficacy and infections requiring gram-positive antibiotics in the early post-transplant setting may disrupt required gut bacteria leading to reduced efficacy and increased risk of early relapse
The aims are: to test for an association between early infection and early relapse post-autologous transplant in adults with multiple myeloma 2009-2016; perform a multivariable regression analysis to control for potential confounders that may also increase risk of early relapse; to determine the impact of early-infection on the rate of complete response to autologous transplant.
The outcome is early infection (composite of gram-positive bacteremia and c. difficile colitis)
Discussions:

- Consider including all infections to see a clear reason for relapse
- Consider the alternate hypothesis that relapse may be due to poorer immune reconstitution leading to earlier relapse
- How is it that Melphalan at time of conditioning is related to infection later and impacted HCT outcomes? Is this due to altered immune stimulation/recovery or lower Melphalan exposure?
- Suggestion: limit patients to those proceeding to HCT within 6-12 months after myeloma diagnosis

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

Dr. Krishna Komanduri mentioned that besides the limitation of the data, there are always challenges on analyzing infection data.

Dr. Soyoung Kim presented Dynamic Landmark study.

Dr. Kim explained time-independent variable vs. time-dependent variable.
Examples of time-independent variables are: gender, KPS, race.
Examples of time-dependent variables are: Acute GVHD, infections.
An infection is a time-dependent variable and Infection status of a patient changes over time,
so, it is challenging to graphically display outcomes of interest such as KM/CIF.

To solve this problem, landmark study is commonly used.
The traditional landmark study is selecting one reasonable landmark time point. Infection status determined by using only infection information available up to the landmark time point, which makes infection time-independent.

The infection effect might depend on choosing landmark point. It is of interest to see the trend of infections across different landmark points. Dynamic landmark study allows to have several landmark time points, then, we can estimate survival probabilities or cumulative incidence rates for infections across several landmark time points.

Dr. Kim presented several graphical curves demonstrating the loss of patients based upon development of GVHD vs development of infection vs death. The impact over the first 3 months post-transplant are most pronounced in bacterial blood stream infections compared to viral or fungal infections. Dr. Kim and the statistical center are proceeding with a manuscript to highlight these limitations in the comparisons of our typical cumulative incidence curves following HCT when comparing across groups.

Not for publication or presentation ***Attachment 1***

Working Committee Overview Plan for 2019-2020							
Study number and title	**Current status**	**Goal with date**	**Total hours to complete**	**Total hours to goal**	**Hours allocated to 6/30/2019**	**Hours allocated 7/1/2019-6/30/2020**	**Total Hours allocated**
IN 13-01 Bacterial and fungal infections in patients undergoing allogeneic hematopoietic cell transplantation following nonmyeloablative and myeloablative regimens	Manuscript Preparation	Submission - May 2019	20	**20**	10	10	**20**
IN 14-01 Post allogeneic hematopoietic transplant Epstein Barr Virus related Lymphoproliferative disorder following conditioning with Antithymocyte globulin or Alemtuzumab	Submitted	Published – July 2019	0	**0**	0	0	**0**
IN16-02 Determination of the burden of mucosal barrier injury-laboratory confirmed bloodstream infections in the first 100 days after stem cell transplant	Manuscript Preparation	Published - June 2020	20	**20**	10	10	**20**
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	Data file Preparation	Published - June 2020	180	**180**	110	70	**180**
IN18-01 Comparison of Early (d100) Infections after Haplo HCT between patients receiving Cy-based vs other GVHD prophylaxis	Protocol development	Manuscript - June 2020	220	**150**	30	120	**150**
IN18-02 Study the Incidence, and impact of C diff infection within 100 days on Transplant outcomes after allogeneic stem cell transplant	Protocol Pending	Manuscript - June 2020	280	**210**	30	180	**210**
IN19-01 Immune recovery predicts post-transplant outcomes	Protocol Pending	Data file Preparation-June 2020	330	**100**	0	100	**100**
IN19-02 Impact of antibacterial prophylaxis on outcomes after allogeneic hematopoietic stem cell transplant	Protocol Pending	Data file Preparation-June 2020	330	**100**	0	100	**100**

Work Assignments for Working Committee Leadership (March 2019)	
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 lymphoproliferative disorder following conditioning with antithymocyte globulin or alemtuzumab (R Kamble/ P Hari/S Naik /C Bachier/P Shaughnessy)
Krishna Komanduri	**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)
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)
Roy Chemaly	**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)
Miguel Perales and Krishna Komanduri	**IN19-01** Immune recovery predicts post-transplant outcomes (Miguel-Angel Perales) (PROP1811-59)
Roy Chemaly	**IN19-0202** Impact of antibacterial prophylaxis on outcomes after allogeneic hematopoietic stem cell transplant (C Dandoy/ P Alonso/ Z El Boghdadly) (PROP1811-82 / PROP1811-150)

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	30445	13899
Infection		
Donor/recipient CMV status		
-/-	7830 (26)	N/A
+/-	2941 (10)	
-/+	9294 (31)	
+/+	9781 (32)	
Missing/not tested	599 (2)	
Donor/recipient hepatitis B status		
-/-	10157 (33)	12366 (89)
+/-	299 (<1)	N/A
-/+	2652 (9)	N/A
+/+	241 (<1)	1300 (9)
-/?	145 (<1)	N/A
+/?	5 (<1)	N/A
?/-	13489 (44)	N/A
?/+	3122 (10)	N/A
Missing/not tested	335 (1)	233 (2)
Donor/recipient hepatitis C status		
-/-	17434 (57)	13047 (94)
+/-	86 (<1)	N/A
-/+	184 (<1)	N/A
+/+	6 (<1)	211 (2)
-/?	43 (<1)	N/A
?/-	10999 (36)	N/A
?/+	125 (<1)	N/A
Missing/not tested	1568 (5)	641 (5)
Fungal Infection history		
No	28106 (92)	13762 (99)
Yes	2311 (8)	135 (<1)
Missing	28 (<1)	2 (<1)
Fungal Infection after starting of conditioning		
No	25094 (82)	12702 (91)
Yes	5018 (16)	621 (4)
Missing	333 (1)	576 (4)

Variable	Allogeneic N(%)	Autologous N(%)
Immune Reconstitution		
IgG at 100 day		
Data not available	10762 (35)	5134 (37)
Data available	19683 (65)	8765 (63)
IgM at 100 day		
Data not available	20144 (66)	6052 (44)
Data available	10301 (34)	7847 (56)
IgA at 100 day		
Data not available	20143 (66)	5987 (43)
Data available	10302 (34)	7912 (57)
CD3 at 100 day		
Lymphocyte analyses were not performed	17436 (57)	12631 (91)
Data not available	5283 (17)	568 (4)
Data available	7726 (25)	700 (5)
CD4 at 100 day		
Lymphocyte analyses were not performed	17436 (57)	12631 (91)
Data not available	5304 (17)	537 (4)
Data available	7705 (25)	731 (5)
CD8 at 100 day		
Lymphocyte analyses were not performed	17436 (57)	12631 (91)
Data not available	5505 (18)	592 (4)
Data available	7504 (25)	676 (5)
CD20 at 100 day		
Lymphocyte analyses were not performed	17436 (57)	12631 (91)
Data not available	11094 (36)	1141 (8)
Data available	1915 (6)	127 (<1)
CD56 at 100 day		
Lymphocyte analyses were not performed	17436 (57)	12631 (91)
Data not available	7886 (26)	980 (7)
Data available	5123 (17)	288 (2)
Infection Prophylaxis		
Infection prophylaxis after starting of conditioning		
No	393 (1)	243 (2)
Yes	30025 (99)	13645 (98)
Missing	27 (<1)	11 (<1)
Antibiotics		
No	8296 (27)	3464 (25)
Yes	22121 (73)	10424 (75)
Missing	28 (<1)	11 (<1)
Amoxicillin clavulanate oral (Augmentin)(after 2017)		
No	6231 (95)	3646 (95)

Variable	Allogeneic N(%)	Autologous N(%)
Yes	119 (2)	42 (1)
Missing	179 (3)	137 (4)
Cefdinir oral (Omnicef)(after 2017)		
No	6322 (97)	3641 (95)
Yes	28 (<1)	47 (1)
Missing	179 (3)	137 (4)
Cefpodoxime oral (Vantin)(after 2017)		
No	6328 (97)	3673 (96)
Yes	22 (<1)	15 (<1)
Missing	179 (3)	137 (4)
Ciprofloxacin IV or oral (Cipro)(after 2017)		
No	5187 (79)	3006 (79)
Yes	1163 (18)	682 (18)
Missing	179 (3)	137 (4)
Ertapenem IV(after 2017)		
No	6340 (97)	3682 (96)
Yes	10 (<1)	6 (<1)
Missing	179 (3)	137 (4)
Levofloxacin IV or oral (Levaquin)(after 2017)		
No	3981 (61)	1607 (42)
Yes	2369 (36)	2081 (54)
Missing	179 (3)	137 (4)
Moxifloxacin IV or oral (Avelox)(after 2017)		
No	6248 (96)	3635 (95)
Yes	102 (2)	53 (1)
Missing	179 (3)	137 (4)
Vancomycin IV(after 2017)		
No	5973 (91)	3538 (92)
Yes	377 (6)	150 (4)
Missing	179 (3)	137 (4)
Other antibacterial drug(after 2017)		
No	5159 (79)	3059 (80)
Yes	1191 (18)	629 (16)
Missing	179 (3)	137 (4)
Antifungal agent		
No	9441 (31)	6590 (47)
Yes	20977 (69)	7298 (53)
Missing	27 (<1)	11 (<1)
Amphotericin		
No	28349 (93)	13564 (98)
Yes	1753 (6)	85 (<1)
Missing	343 (1)	250 (2)
Caspofungin		

Variable	Allogeneic N(%)	Autologous N(%)
No	28702 (94)	13577 (98)
Yes	1400 (5)	72 (<1)
Missing	343 (1)	250 (2)
Fluconazole		
No	18801 (62)	6738 (48)
Yes	11301 (37)	6911 (50)
Missing	343 (1)	250 (2)
Itraconazole		
No	29656 (97)	13597 (98)
Yes	446 (1)	52 (<1)
Missing	343 (1)	250 (2)
Micafungin		
No	25706 (84)	13451 (97)
Yes	4396 (14)	198 (1)
Missing	343 (1)	250 (2)
Posaconazole		
No	26578 (87)	13600 (98)
Yes	3523 (12)	49 (<1)
Missing	344 (1)	250 (2)
Ravuconazole		
No	30079 (99)	13644 (98)
Yes	23 (<1)	5 (<1)
Missing	343 (1)	250 (2)
Voriconazole		
No	23381 (77)	13455 (97)
Yes	6721 (22)	194 (1)
Missing	343 (1)	250 (2)
Other systemic antifungal agent		
No	29428 (97)	13538 (97)
Yes	699 (2)	111 (<1)
Missing	318 (1)	250 (2)
Antiviral agent		
No	4671 (15)	1563 (11)
Yes	25747 (85)	12325 (89)
Missing	27 (<1)	11 (<1)
Acyclovir		
No	9187 (30)	3304 (24)
Yes	20941 (69)	10345 (74)
Missing	317 (1)	250 (2)
Foscarnet		
No	29419 (97)	13623 (98)
Yes	708 (2)	26 (<1)
Missing	318 (1)	250 (2)

Variable	Allogeneic N(%)	Autologous N(%)
Ganciclovir		
No	28507 (94)	13610 (98)
Yes	1621 (5)	39 (<1)
Missing	317 (1)	250 (2)
Valganciclovir		
No	28219 (93)	13532 (97)
Yes	1909 (6)	117 (<1)
Missing	317 (1)	250 (2)
Valacyclovir		
No	23641 (78)	10883 (78)
Yes	6487 (21)	2766 (20)
Missing	317 (1)	250 (2)
Other antiviral agent		
No	29274 (96)	13479 (97)
Yes	853 (3)	170 (1)
Missing	318 (1)	250 (2)
Pneumocystis agent		
No	3396 (11)	4436 (32)
Yes	26400 (87)	8314 (60)
Missing	649 (2)	1149 (8)
Other prophylaxis agent(Before 2017)		
No	19390 (81)	8270 (82)
Yes	2769 (12)	743 (7)
Missing	1757 (7)	1061 (11)
Disease		
Acute Leukemia/MDS	21878 (72)	180 (1)
Chronic Leukemia	891 (3)	0
Non-Hodgkin Lymphoma	1759 (6)	3165 (23)
Hodgkin Lymphoma	174 (<1)	1008 (7)
Solid tumors	24 (<1)	881 (6)
Myeloma/Plasma Cell Disorder	160 (<1)	8574 (62)
Non-malignant disorders	5559 (18)	91 (<1)
Year of transplant		
2008	3260 (11)	2195 (16)
2009	2997 (10)	931 (7)
2010	1859 (6)	414 (3)
2011	1344 (4)	495 (4)
2012	1434 (5)	537 (4)
2013	2666 (9)	1198 (9)
2014	3533 (12)	1285 (9)
2015	3525 (12)	1478 (11)
2016	3298 (11)	1541 (11)
2017	3051 (10)	1444 (10)

Variable	Allogeneic N(%)	Autologous N(%)
2018	2749 (9)	2018 (15)
2019	729 (2)	363 (3)

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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 with Preliminary Results

IN17-01(a): Incidence and Impact of Cytomegalovirus Infection in Haploidentical and Matched-Related Donors Receiving Post-Transplant Cyclophosphamide (PTCy): A CIBMTR Analysis. (S Goldsmith/E Fuchs/A Bashey/S Ciurea/A Singh/ S Ganguly/R Taplitz/C Mulroney/R Maziarz/ R Romee)

Manuscript preparation is underway. Plan to submit by July 2020.

Abstract:

Single-institution studies suggest increased incidence of CMV infection (DNAemia/organ disease) in recipients of haploidentical grafts with PTCy (HaploCy). It is unclear what factors confer the increased risk. Given increased use of PTCy in matched-sibling donor transplant (SibCy), we examined the impact of donor type and PTCy on transplant outcomes by donor(D)/recipient(R) CMV serostatus and reported CMV DNAemia by day 180.

Patients reported to the CIBMTR with AML/ALL/MDS receiving HaploCy (n = 757), SibCy (n=403), or Sib with calcineurin inhibitor and methotrexate/mycophenolate mofetil (SibCNI, n=1605) between 2012 and 2017 were examined (Table 1). Too few MUD with PTCy were reported to include MUD cohorts. Cumulative incidences of CMV DNAemia by d180 were 42% (99% CI, 37-46), 37% (31 - 43), and 23% (20 - 26) for HaploCy, SibCy, and SibCNI respectively [p<0.001]. CMV organ disease was similar [HaploCy, 4% (2-6); SibCy, 4% (2-7); SibCNI, 2% (1-3); p=0.115]. Median onset (days) of CMV infection differed [HaploCy: 38 (range, 2 – 176); SibCy, 32 (5 – 136); SibCNI: 42 (4 – 176), p<0.001]. Figures 1 and 2 show the multivariable analyses for survival, relapse, transplant related mortality, and chronic GVHD examining the effect of D/R CMV serostatus and by CMV DNAemia by day 180. Reference groups were D-/R- SibCNI and SibCNI without CMV DNAemia, respectively. The risk of CMV infection was greatest for CMV Seropositive recipients (R+) with the greatest risk in PTCy recipients regardless of donor [HaploCy: RR 50.3 (14.4 – 175.2); SibCy: RR 47.7 (13.3 – 171.4); SibCNI: RR 24.4 (7.2 – 83.1); p<0.001]. The D+/R- groups also have increased risk for CMV infection [HaploCy: RR 16.3 (4 – 70.5); SibCy: RR 10.1 (2.3 – 43.9); SibCNI: 8.4 (2.4 – 29.2)].

Our study shows that PTCy is associated with higher incidence of CMV infection among both Haplo and Sib transplants. Among seropositive and CMV-infected individuals, HaploCy had worse OS and TRM, whereas differences between SibCy and SibCNI were not significant. Neither CMV infection nor serostatus affect relapse. This study supports use of more aggressive prevention strategies in patients receiving PTCy and at risk for CMV infection.

Table 1.

	HaploCy n=757 (%)	SibCy n=403 (%)	SibTAC n=1605 (%)	P value
Gender, Female	298 (39)	160 (40)	672 (42)	0.450
R Age, median (range), y	58 (3 - 78)	46 (3 - 75)	57 (2 - 78)	<0.001
D age, median (range), y	36 (9 - 76)	45 (4 - 72)	54 (2 - 82)	<0.001
D/R CMV status				0.04
+/+	326 (43)	172 (43)	684(43)	
+/-	54 (7)	36 (9)	163 (10)	
-/+	217 (29)	101 (25)	282 (24)	
-/-	131 (17)	79 (20)	327 (20)	
Missing	29 (4)	15 (4)	48 (3)	
Disease				<0.001
AML	528 (70)	310 (77)	1025 (64)	
ALL	26 (3)	19 (5)	60 (4)	
MDS	203 (27)	74 (18)	520 (32)	
Graft, Marrow	308 (41)	131 (33)	200 (12)	<0.001
Conditioning Intensity, Myeloablative	314 (41)	222 (55)	935 (58)	<0.001
TBI, yes	531(70)	234 (58)	436 (27)	<0.001
Growth Factor, yes	620 (82)	319 (79)	379 (24)	<0.001
Time to HCT, median (range), mo	7 (1 - 165)	7 (<1 - 396)	5 (1 - 556)	<0.001

Figure 1

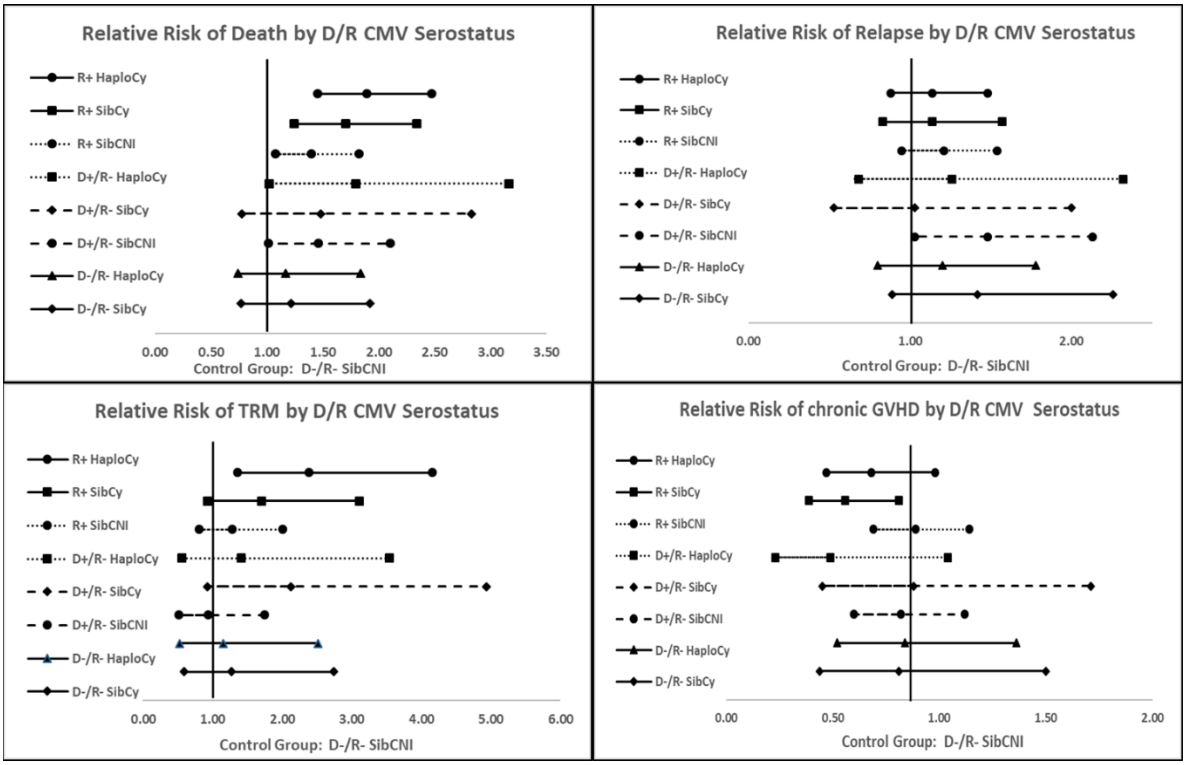
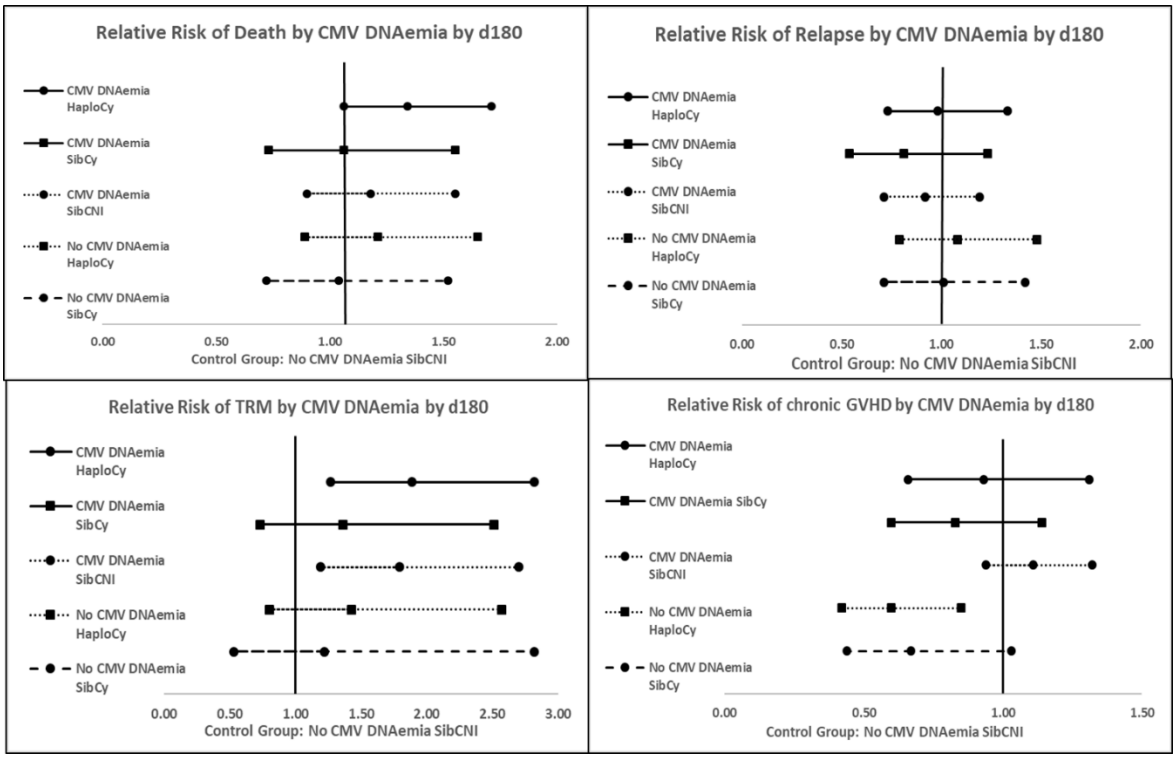


Figure 2



IN17-01(b): Incidence and impact of Non-CMV herpes viral infection in Haploidentical and Matched Sibling Donors receiving Post-transplant Cyclophosphamide (PTCy): A CIBMTR Analysis: (A Singh/E Fuchs/A Bashey/S Ciurea/S Goldsmith/S Ganguly/Randy A Taplitz/C Mulroney/R Maziarz/R Romee)

Manuscript preparation is underway. Plan to submit by July 2020.

Abstract:

Single-center studies have reported increased risk of CMV infection in patients undergoing allogeneic transplant using haploidentical graft with post-transplant cyclophosphamide (HaploCy), however limited data exists regarding the impact of this transplant platform on the incidence of non-CMV herpes viruses (NCHV) infection (viremia/disease). Furthermore, it is unclear if the donor type or altered immune reconstitution resulting from the use of PTCy contributes to this infection risk. To study this, patients reported to the CIBMTR with AML/ALL/MDS transplanted between 2012 and 2017 receiving HaploCy (n = 757), matched-sibling donors receiving PTCy (SibCy, n=403), or matched sibling with calcineurin inhibitor and methotrexate/mycophenolate mofetil (SibCNI, n=1605) with either marrow or peripheral blood grafts were examined (Table 1). Too few matched unrelated donors (MUD) receiving PTCY reported to CIBMTR resulted in exclusion of MUD transplants.

The cumulative incidence of NCHV in the HaploCy, SibCy and SibCNI were 6.9% (99% CI, 4.7-9.4), 3.2% (1.3-5.9), and 1.7% (1-2.6) respectively by day 30 [p<0.001] and increased to 13.9% (10.8 – 17.3), 10.7 % (7.1 – 15), and 5.7% (4.3 – 7.3) by 6 months after transplant [p<0.001] [Figure 1]. Notably, this is driven by a higher frequency of HHV-6 viremia [HaploCy = 9.3%; SibCy = 5.7%; SibCNI = 1.9%]. Figure 2 shows the multivariable models of survival, relapse, transplant related mortality, and chronic GVHD with a reference group of SibCNI without NCHV infection for the main effect variable of donor and infection. The model examines through the first 2 years after transplant and there was a center effect.

Our results suggest that HaploCY is associated with an increased incidence of NCHV infection and HHV-6 viremia predominates. The SibCy cohort experienced an increased incidence of NCHV infections as well. However, only in the HaploCy group is this independently associated with increased TRM and decreased survival. Improved surveillance and preemptive treatment may mitigate the mortality associated with NCHV infections in HaploCy recipients.

Table 1

Variable	HaploCy N=757 (%)	SibCy N=403 (%)	SibCNI N=1605 (%)	P value
Gender, Male	459 (61)	243 (60)	933 (58)	0.450
Age, median(range), y	58 (3 - 78)	46 (3 - 75)	57 (2 - 78)	<0.001
Disease				<0.001
AML	528 (70)	310 (77)	1025 (64)	
ALL	26 (3)	19 (5)	60 (4)	
MDS	203 (27)	74 (18)	520 (32)	

Variable	HaploCy N=757 (%)	SibCy N=403 (%)	SibCNI N=1605 (%)	P value
Graft, Marrow	308 (41)	131 (33)	200 (12)	<0.001
Conditioning intensity, RIC/NMA	443 (59)	181 (45)	670 (42)	<0.001
NCHV Viremia	92 (12)	38 (9)	60 (4)	<0.001
HHV-6	71 (77)	23 (61)	31 (52)	0.004
EBV	22 (24)	15 (39)	30 (50)	0.004
HSV	4 (4)	0	3 (5)	0.394
NCHV Organ disease	18 (2)	6 (1)	34 (2)	<0.001
HHV-6	4 (22)	0	6 (18)	0.457
EBV	0	0	1 (3)	0.698
HSV	11 (61)	4 (67)	16 (47)	0.496
VZV	3 (17)	2 (33)	11 (32)	0.458
Median follow-up of survivors, m	25 (3 - 74)	25 (3 - 69)	37 (2 - 75)	

Figure 1

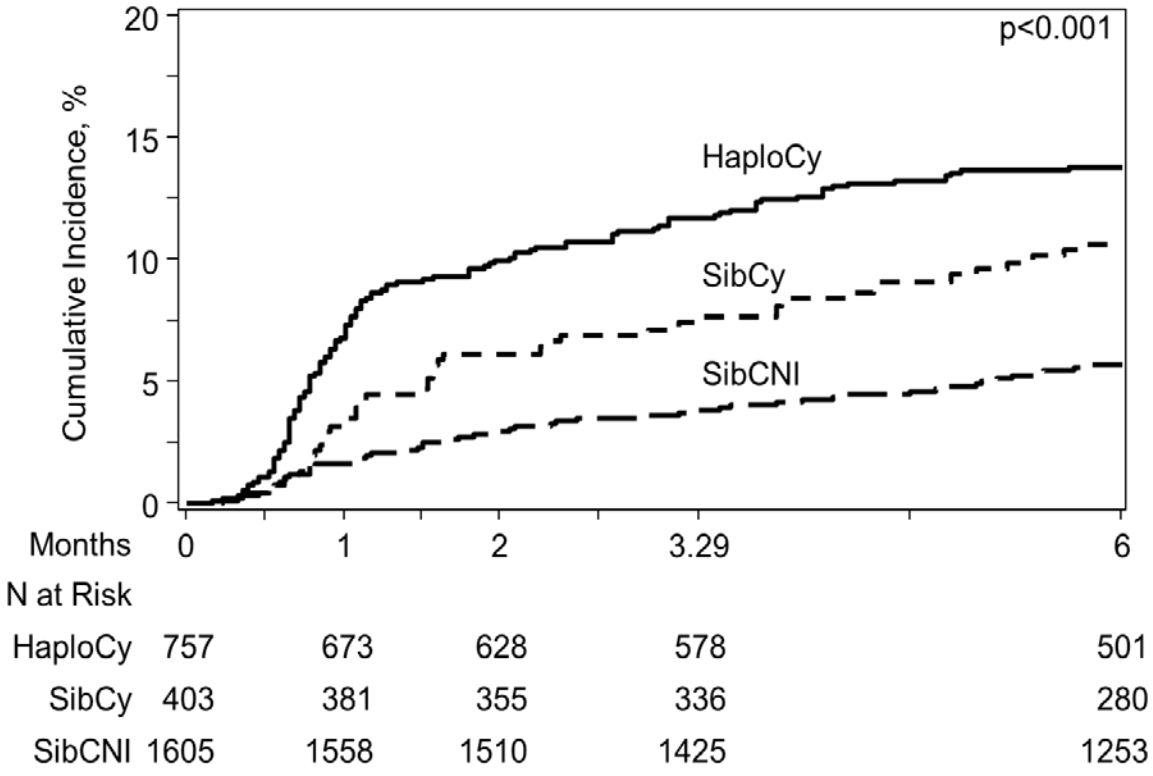
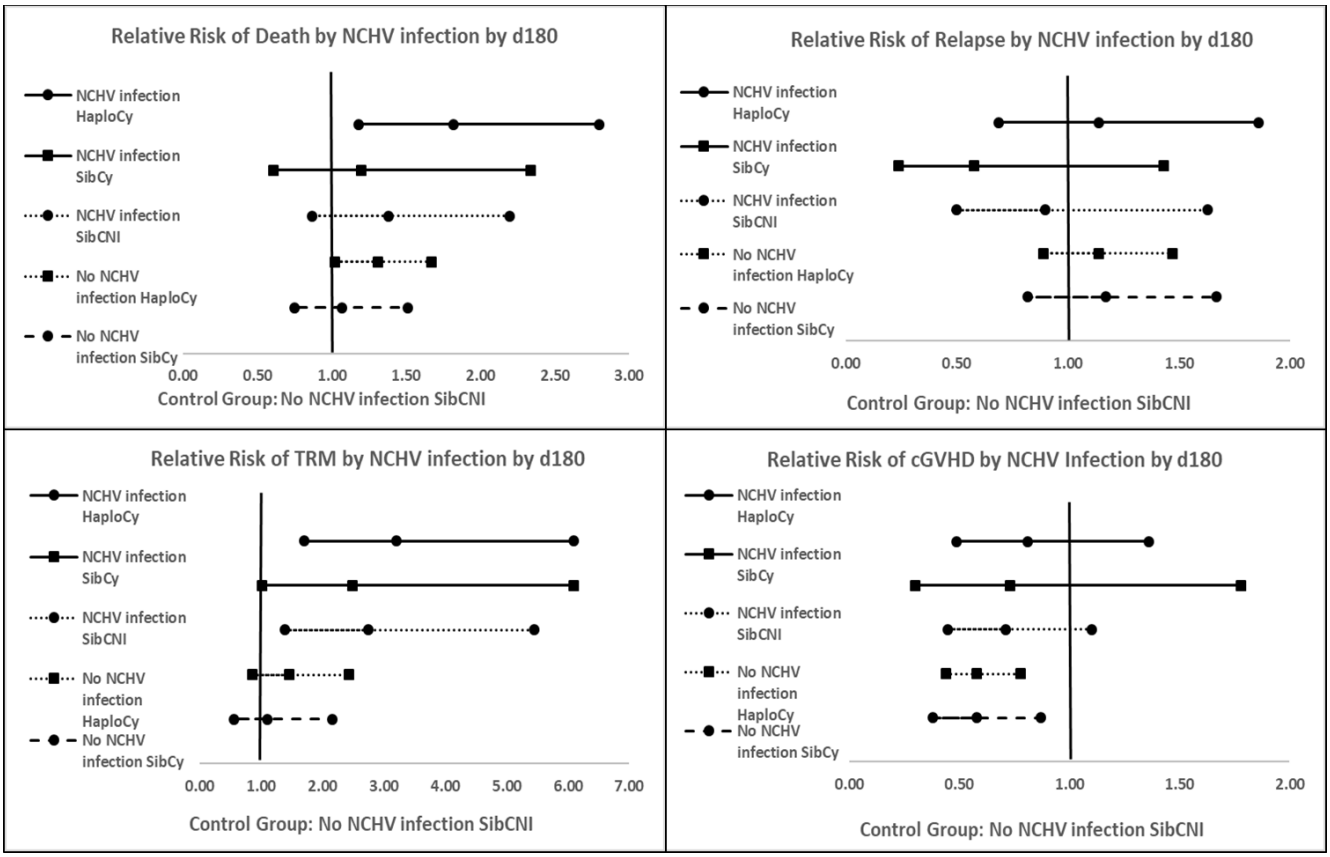


Figure 2


Relative Risk of Death by NCHV infection by d180
NCHV infection HaploCy
NCHV infection SibCy
NCHV infection SibCNI
No NCHV infection HaploCy
No NCHV infection SibCy
0.00 0.50 1.00 1.50 2.00 2.50 3.00
Control Group: No NCHV infection SibCNI
Relative Risk of Relapse by NCHV infection by d180
NCHV infection HaploCy
NCHV infection SibCy
NCHV infection SibCNI
No NCHV infection HaploCy
No NCHV infection SibCy
0.00 0.50 1.00 1.50 2.00
Control Group: No NCHV infection SibCNI
Relative Risk of TRM by NCHV infection by d180
NCHV infection HaploCy
NCHV infection SibCy
NCHV infection SibCNI
No NCHV infection HaploCy
No NCHV infection SibCy
0.00 1.00 2.00 3.00 4.00 5.00 6.00 7.00
Control Group: No NCHV infection SibCNI
Relative Risk of cGVHD by NCHV Infection by d180
NCHV infection HaploCy
NCHV infection SibCy
NCHV infection SibCNI
No NCHV infection HaploCy
No NCHV infection SibCy
0.00 0.50 1.00 1.50 2.00
Control Group: No NCHV infection SibCNI

IN1701(c): Incidence and Impact of Community Respiratory Viral Infection (CRV) in Haploidentical and Matched Sibling Donors receiving post-transplant Cyclophosphamide (PTCy): A CIBMTR analysis: (R Taplitz/R Maziarz/C Mulroney/R Romee, S Goldsmith/E Fuchs/A Bashey/S Ciurea/A Singh/S Ganguly)

Manuscript preparation is underway. Plan to submit by July 2020.

Abstract:

Introduction and Methods: There are reports of high rates of viral infections after haploidentical transplant, particularly in the setting of PTCy (HaploCy) although detailed data on incidence are lacking. We describe here the comparative incidence of community respiratory virus (CRV) infections occurring by day 180 post-transplant by donor source and their impact on outcomes including survival, relapse, chronic GVHD, and transplant related mortality (TRM) using CIBMTR registry data. The analysis included 2765 patients, all > 2 years of age, who underwent first allogeneic HCT for AML, ALL or MDS from 100 centers between 2012 and 2017 receiving either HaploCy (n=757), Matched related donor (MRD) transplant with PTCy (SibCy n= 403), and MRD transplant with calcineurin inhibitor and either methotrexate or mycophenolate mofetil (SibCNI n= 1605).

Results: The cumulative incidences of CRV in the HaploCy, SibCy and SibCNI were: 3% (99% CI, 1.6-4.8), 3% (1.3-5.5) and 2.4 %(1.5-3.5) respectively at day 30 (P =0.649, NS), but notably higher at 15.5% (12.3-19), 16.2% (11.7-21.2) and 9.4 %(7.6-11.4) at 6 months (P<.001) post-transplant [Figure 1]. Identified CRV included primarily Rhinovirus, Parainfluenza, and RSV accounting for approximately 70% of all CRV reported [Table 1]. Figure 2 shows the multivariable models through 2 years post-transplant for survival, relapse, TRM, and chronic GVHD with a reference group of SibCNI without CRV infection for the main effect variable of donor type and infection. Patients in the HaploCy cohort who developed a CRV by day 180 had a higher risk of TRM [p=0.002] and inferior survival [p = 0.001] compared to the reference group. Older age, more advanced disease, and higher HCT-CI were all associated with increased mortality.

Conclusions: The incidence of CRVs is higher for patients receiving PTCy, regardless of donor. This finding justifies further studies to understand long-term antiviral immune recovery in different donor sources and GVHD prophylaxis regimens. The higher overall mortality for HaploCy patients developing CRV infection warrants consideration for patient education and heightened awareness for clinicians, as well as long term follow up studies of such patients.

Figure 1: The cumulative incidence of CRV occurring by day 180 after transplant

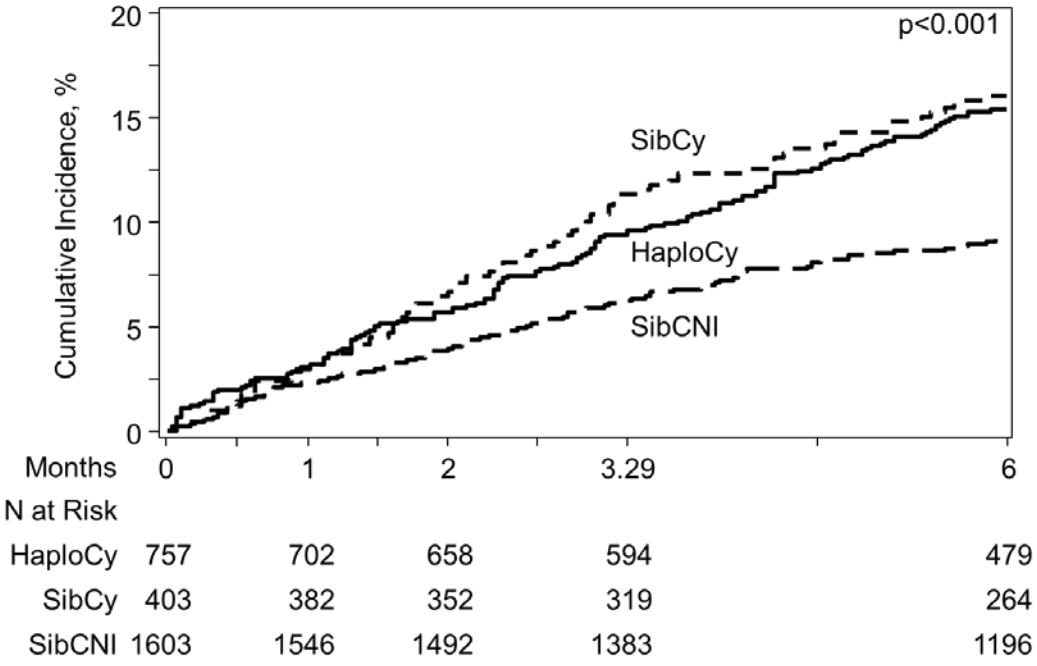
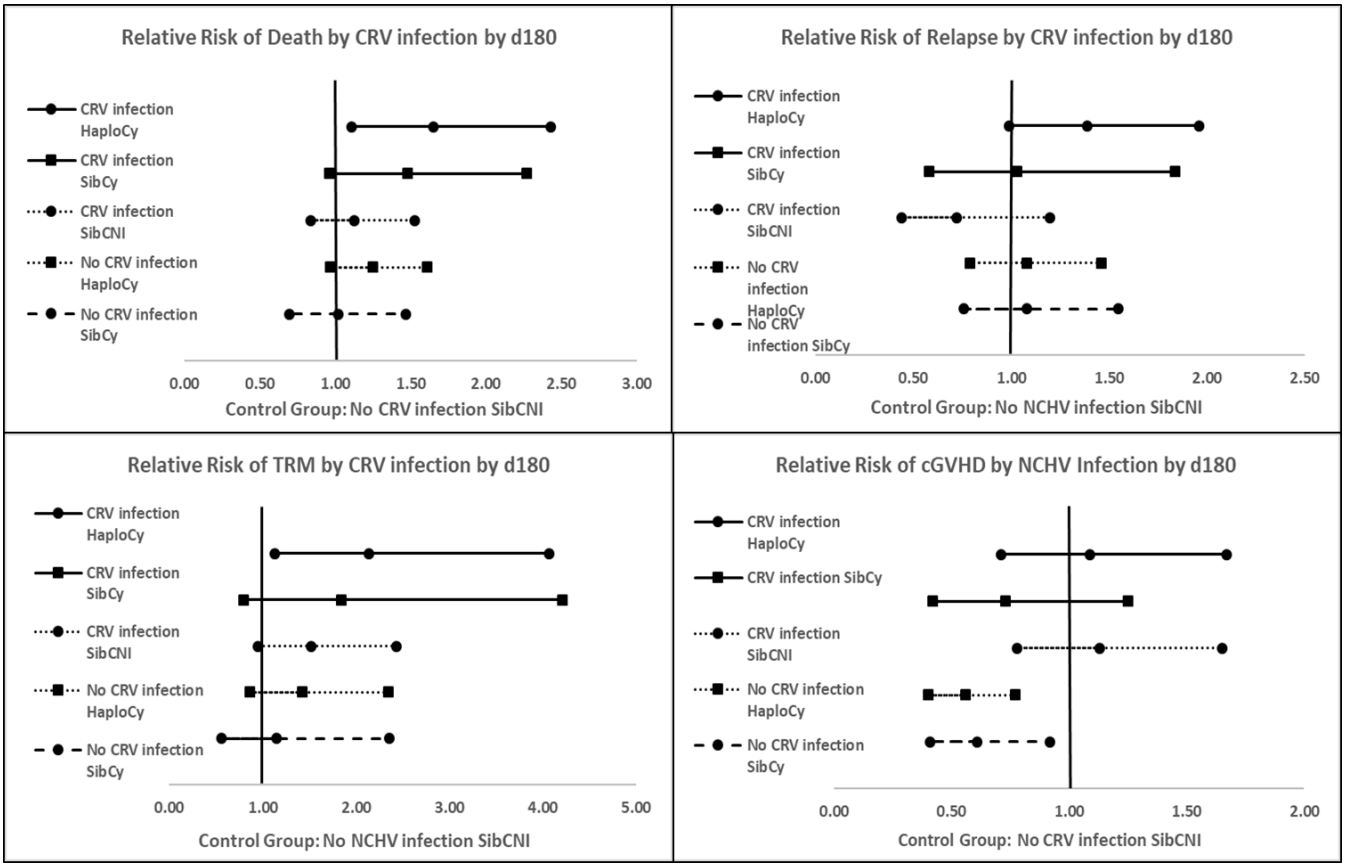


Table 1: Identified CRV by Transplant Type

	HaploCy N = 757 (%)	SibCy N= 403 (%)	SibCNI N=1605 (%)
Rhinovirus	27 (4)	30 (7)	53 (3)
Parainfluenza	24 (3)	15 (4)	41 (3)
RSV	32 (4)	10 (2)	45 (2)
Influenza	16 (2)	8 (2)	24 (1)
Adenovirus	20 (3)	12 (3)	15 (1)
Enterovirus	6 (1)	5 (1)	7 (<1)
Human metapneumovirus	2 (<1)	0	4 (<1)
Coronavirus	3 (<1)	0	3 (<1)

Figure 2: Multivariable models for transplant outcomes



Studies in Progress

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 analysis by June 2020.

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 is under data file preparation. The goal of this study is to finalize the analysis by June 2020.

IN19-01 Immune recovery predicts post transplant outcomes (Miguel-Angel Perales/ Paul Szabolcs) The study protocol is under development. The goal of this study is to finalize the protocol by June 2020.

IN19-02 Impact of Antibiotic Prophylaxis in Patients Undergoing Allogeneic Hematopoietic Cell Transplantation in the Current Era (Zeinab El Boghdadly/ Christopher Eugene Dandoy/ Priscila Badia Alonso) The study protocol is under development. The goal of this study is to finalize the protocol by June 2020.

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:

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 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.

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 PTCy and without PTCy conditioning regimen, reported to the CIBMTR, from 2012 to 2017

Variable	Haplo-identical (>=2MM) with Cy N(%)	HLA-identical sibs with Cy N(%)	HLA-identical sibs without Cy N(%)	P value
Patient related				
Number of patients	757	403	1605	
Number of centers	100	77	100	
Gender				0.450
Male	459 (61)	243 (60)	933 (58)	
Female	298 (39)	160 (40)	672 (42)	
Age, median(range), years	58 (3 - 78)	46 (3 - 75)	57 (2 - 78)	<0.001
Age at transplant, years				<0.001
<=10	35 (5)	4 (<1)	41 (3)	
11-20	51 (7)	23 (6)	85 (5)	
21-30	68 (9)	69 (17)	115 (7)	
31-40	44 (6)	62 (15)	137 (9)	
41-50	71 (9)	67 (17)	205 (13)	
51-60	152 (20)	82 (20)	392 (24)	
61-70	255 (34)	85 (21)	549 (34)	
>70	81 (11)	11 (3)	81 (5)	
Karnofsky/Lansky performance at HCT				<0.001
<80	119 (16)	65 (16)	200 (12)	
80-89	229 (30)	102 (25)	449 (28)	
>=90	390 (52)	233 (58)	946 (59)	
Missing	19 (3)	3 (<1)	10 (<1)	
Race/Ethnicity				<0.001
Caucasian, non-Hispanic	444 (59)	239 (59)	1109 (69)	
African-American, non-Hispanic	131 (17)	56 (14)	107 (7)	
Asian, non-Hispanic	52 (7)	29 (7)	97 (6)	
Pacific islander, non-Hispanic	2 (<1)	1 (<1)	11 (<1)	
Native American, non-Hispanic	3 (<1)	1 (<1)	9 (<1)	
Hispanic, Caucasian	72 (10)	45 (11)	134 (8)	
Hispanic, African-American	4 (<1)	4 (<1)	4 (<1)	
Hispanic, Asian	0	0	2 (<1)	
Hispanic, Parcific islander	0	0	1 (<1)	
Hispanic, Native American	1 (<1)	0	4 (<1)	
Missing	48 (6)	28 (7)	127 (8)	
Donor related				
Donor age, in decades				<0.001
0-17	28 (4)	22 (5)	103 (6)	

Variable	Haplo-identical (>=2MM) with Cy N(%)	HLA-identical sibs with Cy N(%)	HLA-identical sibs without Cy N(%)	P value
18-20	24 (3)	15 (4)	22 (1)	
21-30	172 (23)	64 (16)	115 (7)	
31-40	242 (32)	67 (17)	164 (10)	
41-50	186 (25)	73 (18)	240 (15)	
51-60	67 (9)	99 (25)	458 (29)	
61-70	27 (4)	58 (14)	427 (27)	
>70	5 (<1)	5 (1)	60 (4)	
Missing	6 (<1)	0	16 (<1)	
Donor age, median(range), years	36 (9 - 76)	45 (4 - 72)	54 (2 - 82)	<0.001
Donor/recipient gender match				0.001
Male-Male	289 (38)	156 (39)	507 (32)	
Male-Female	180 (24)	99 (25)	347 (22)	
Female-Male	170 (22)	87 (22)	426 (27)	
Female-Female	118 (16)	61 (15)	324 (20)	
Missing	0	0	1 (<1)	
Donor/Recipient CMV status				0.04
+/+	326 (43)	172 (43)	684 (43)	
+/-	54 (7)	36 (9)	163 (10)	
-/+	217 (29)	101 (25)	383 (24)	
-/-	131 (17)	79 (20)	327 (20)	
+/?	2 (<1)	1 (<1)	5 (<1)	
-/?	1 (<1)	1 (<1)	10 (<1)	
?/+	20 (3)	11 (3)	19 (1)	
?/-	6 (<1)	2 (<1)	14 (<1)	
Disease related				
Disease				<0.001
AML	528 (70)	310 (77)	1025 (64)	
ALL	26 (3)	19 (5)	60 (4)	
MDS	203 (27)	74 (18)	520 (32)	
HCT-CI				0.817
0	199 (26)	103 (26)	392 (24)	
1-2	209 (28)	124 (31)	447 (28)	
3-4	211 (28)	104 (26)	476 (30)	
5+	137 (18)	71 (18)	285 (18)	
Missing	1 (<1)	1 (<1)	5 (<1)	
Disease Status				<0.001
AML/ALL, early	308 (41)	189 (47)	719 (45)	
AML/ALL, intermediate	143 (19)	77 (19)	210 (13)	
AML/ALL, advanced	97 (13)	61 (15)	144 (9)	

Variable	Haplo-identical (>=2MM) with Cy N(%)	HLA-identical sibs with Cy N(%)	HLA-identical sibs without Cy N(%)	P value
AML/ALL, unknown	6 (<1)	2 (<1)	15 (<1)	
MDS, early	76 (10)	24 (6)	179 (11)	
MDS, advanced	127 (17)	50 (12)	338 (21)	
Cytogenetics for AML/ALL				<0.001
Normal	42 (6)	28 (7)	83 (5)	
Favorable	23 (3)	18 (4)	39 (2)	
Intermediate	256 (34)	140 (35)	518 (32)	
Poor	203 (27)	132 (33)	374 (23)	
Other	20 (3)	6 (1)	49 (3)	
Not tested/Missing	10 (1)	5 (1)	22 (1)	
MDS N/A	203 (27)	74 (18)	520 (32)	
IPSS-R prior to transplant (MDS only)				<0.001
Very low	19 (3)	14 (3)	60 (4)	
Low	67 (9)	22 (5)	133 (8)	
Intermediate	53 (7)	22 (5)	160 (10)	
High	30 (4)	10 (2)	73 (5)	
Very high	13 (2)	3 (<1)	38 (2)	
Missing	21 (3)	3 (<1)	56 (3)	
AML/ALL N/A	554 (73)	329 (82)	1085 (68)	
Transplant-related				
Graft type				<0.001
Bone Marrow	308 (41)	131 (33)	200 (12)	
Peripheral blood	449 (59)	272 (67)	1405 (88)	
Conditioning regimen intensity				<0.001
Myeloablative	314 (41)	222 (55)	935 (58)	
RIC/NMA	443 (59)	181 (45)	670 (42)	
GVHD prophylaxis				<0.001
Cyclophosphamide	757	403	0	
TAC/CSA + MMF +- others	0	0	362 (23)	
TAC/CSA + MTX +- others	0	0	1243 (77)	
TBI				<0.001
No	226 (30)	169 (42)	1169 (73)	
Yes	531 (70)	234 (58)	436 (27)	
G-CSF, GM-CSF				<0.001
No	133 (18)	84 (21)	1223 (76)	
Yes	620 (82)	319 (79)	379 (24)	
Missing	4 (<1)	0	3 (<1)	
Time from diagnosis to transplant				<0.001
<6 month	315 (42)	180 (45)	890 (55)	

Variable	Haplo-identical (>=2MM) with Cy N(%)	HLA-identical sibs with Cy N(%)	HLA-identical sibs without Cy N(%)	P value
6 month-1Y	195 (26)	117 (29)	348 (22)	
>1Y-2Y	135 (18)	49 (12)	181 (11)	
>=2Y	111 (15)	56 (14)	182 (11)	
Missing	1 (<1)	1 (<1)	4 (<1)	
Time from diagnosis to transplant, median(range), months	7 (1 - 165)	7 (<1 - 396)	5 (1 - 556)	<0.001
Cell counts				
Nucleated cell count, median(range), 10*8/kg, @infusion	4 (<1 - 37)	5 (<1 - 45)	9 (<1 - 42)	<0.001
Nucleated cell count, 10*8/kg				<0.001
<3	163 (22)	70 (17)	91 (6)	
3-9	235 (31)	118 (29)	474 (30)	
>9	101 (13)	67 (17)	521 (32)	
Missing but CD34 available	115 (15)	63 (16)	181 (11)	
Both Nucleated cell and CD34 Missing	143 (19)	85 (21)	338 (21)	
CD34+ cell count , median(range), 10*6/kg, @infusion	4 (<1 - 20)	5 (<1 - 17)	5 (<1 - 19)	<0.001
CD34 cell count, 10*6/kg				<0.001
0-5	360 (48)	179 (44)	576 (36)	
>5	247 (33)	133 (33)	665 (41)	
Missing but Nucleated available	7 (<1)	6 (1)	26 (2)	
Both Nucleated cell and CD34 Missing	143 (19)	85 (21)	338 (21)	
CD3+ cell count , median(range), 10*7/kg, @infusion	10 (<1 - 58)	13 (<1 - 59)	22 (<1 - 60)	<0.001
CD3 cell count, 10*7/kg				<0.001
<4	138 (18)	74 (18)	99 (6)	
4-8	43 (6)	17 (4)	47 (3)	
>8	228 (30)	126 (31)	755 (47)	
Missing	348 (46)	186 (46)	704 (44)	
Year of transplant				<0.001
2012	14 (2)	4 (<1)	130 (8)	
2013	49 (6)	35 (9)	279 (17)	
2014	107 (14)	48 (12)	397 (25)	
2015	154 (20)	112 (28)	349 (22)	
2016	200 (26)	106 (26)	265 (17)	
2017	233 (31)	98 (24)	185 (12)	
Median follow-up of survivors, months	25 (3 - 74)	25 (3 - 69)	37 (2 - 75)	

Table 1.2 Bacterial Infections by 180 days

Variable	Haplo-identical(>=2MM) with Cy N(%)	HLA-identical sibs with Cy N(%)	HLA-identical sibs without Cy N(%)	P value
Number of patients	**757**	**403**	**1605**	
Anaerobes by day180				0.017
Yes	33 (4)	12 (3)	36 (2)	
No	724 (96)	391 (97)	1569 (98)	
Time from transplant to Anaerobes, median(range), Days	11 (<1 - 164)	87 (<1 - 149)	45 (5 - 177)	0.001
Sites of Anaerobes				
In blood by day180				0.595
Yes	26 (79)	8 (67)	29 (81)	
No	7 (21)	4 (33)	7 (19)	
In GI by day 180				0.993
Yes	3 (9)	1 (8)	3 (8)	
No	30 (91)	11 (92)	33 (92)	
In lung by day 180				0.748
Yes	1 (3)	1 (8)	2 (6)	
No	32 (97)	11 (92)	34 (94)	
In Sinus by day 180				0.654
Yes	1 (3)	1 (8)	1 (3)	
No	32 (97)	11 (92)	35 (97)	
In upper GU by day 180				0.835
Yes	1 (3)	0	1 (3)	
No	32 (97)	12	35 (97)	
In other sites by day 180				0.270
Yes	2 (6)	1 (8)	0	
No	31 (94)	11 (92)	36	
Clostridium difficile by day180				0.004
Yes	119 (16)	51 (13)	175 (11)	
No	638 (84)	352 (87)	1430 (89)	
Time from transplant to Clostridium difficile, median(range), Days	9 (<1 - 180)	4 (1 - 177)	25 (<1 - 179)	<0.001
Sites of Clostridium difficile				
In GI by day 180				0.004
Yes	119	51	175	
Enterococcus Vanc Sensitive by day180				0.002
Yes	69 (9)	27 (7)	85 (5)	
No	688 (91)	376 (93)	1520 (95)	

Variable	Haplo-identical(>=2MM) with Cy N(%)	HLA-identical sibs with Cy N(%)	HLA-identical sibs without Cy N(%)	P value
Time from transplant to Enterococcus Vanc Sensitive, median(range), Days	29 (5 - 167)	22 (<1 - 171)	32 (<1 - 159)	0.785
Sites of Enterococcus Vanc Sensitive				
In blood by day180				0.456
Yes	30 (43)	8 (30)	33 (39)	
No	39 (57)	19 (70)	52 (61)	
In GI by day 180				0.784
Yes	3 (4)	1 (4)	2 (2)	
No	66 (96)	26 (96)	83 (98)	
In lung by day 180				0.419
Yes	4 (6)	2 (7)	2 (2)	
No	65 (94)	25 (93)	83 (98)	
In Sinus by day 180				0.691
Yes	3 (4)	1 (4)	6 (7)	
No	66 (96)	26 (96)	79 (93)	
In CNS by day 180				0.567
Yes	0	0	1 (1)	
No	69	27	84 (99)	
In upper GU by day 180				0.122
Yes	19 (28)	10 (37)	37 (44)	
No	50 (72)	17 (63)	48 (56)	
In Skin by day 180				0.827
Yes	1 (1)	0	1 (1)	
No	68 (99)	27	84 (99)	
In other sites by day 180				0.567
Yes	0	0	1 (1)	
No	69	27	84 (99)	
VRE by day180				<0.001
Yes	49 (6)	20 (5)	49 (3)	
No	708 (94)	383 (95)	1556 (97)	
Time from transplant to VRE, median(range), Days	17 (<1 - 179)	35 (<1 - 131)	31 (<1 - 175)	0.858
Sites of VRE				
In blood by day180				0.060
Yes	32 (65)	8 (40)	22 (45)	
No	17 (35)	12 (60)	27 (55)	
In GI by day 180				0.214
Yes	8 (16)	6 (30)	15 (31)	
No	41 (84)	14 (70)	34 (69)	

Variable	Haplo-identical(>=2MM) with Cy N(%)	HLA-identical sibs with Cy N(%)	HLA-identical sibs without Cy N(%)	P value
In lung by day 180				0.778
Yes	2 (4)	1 (5)	1 (2)	
No	47 (96)	19 (95)	48 (98)	
In Sinus by day 180				0.108
Yes	0	2 (10)	2 (4)	
No	49	18 (90)	47 (96)	
In CNS by day 180				0.492
Yes	0	0	1 (2)	
No	49	20	48 (98)	
In upper GU by day 180				0.511
Yes	7 (14)	2 (10)	10 (20)	
No	42 (86)	18 (90)	39 (80)	
In other sites by day 180				0.492
Yes	1 (2)	0	0	
No	48 (98)	20	49	
GNR, Enterobacteriaceae by day180				0.001
Yes	118 (16)	78 (19)	202 (13)	
No	639 (84)	325 (81)	1403 (87)	
Time from transplant to GNR, Enterobacteriaceae, median(range), Days	36 (<1 - 179)	13 (<1 - 171)	32 (<1 - 178)	0.329
Sites of GNR, Enterobacteriaceae				
In blood by day180				0.013
Yes	77 (65)	58 (74)	113 (56)	
No	41 (35)	20 (26)	89 (44)	
In GI by day 180				0.809
Yes	3 (3)	3 (4)	5 (2)	
No	115 (97)	75 (96)	197 (98)	
In lung by day 180				0.538
Yes	6 (5)	2 (3)	6 (3)	
No	112 (95)	76 (97)	196 (97)	
In Sinus by day 180				0.616
Yes	2 (2)	1 (1)	6 (3)	
No	116 (98)	77 (99)	196 (97)	
In upper GU by day 180				0.004
Yes	26 (22)	16 (21)	74 (37)	
No	92 (78)	62 (79)	128 (63)	
In Skin by day 180				0.826
Yes	2 (2)	2 (3)	3 (1)	

Variable	Haplo-identical(>=2MM) with Cy N(%)	HLA-identical sibs with Cy N(%)	HLA-identical sibs without Cy N(%)	P value
No	116 (98)	76 (97)	199 (99)	
In other sites by day 180				0.685
Yes	1 (<1)	0	2 (<1)	
No	117 (99)	78	200 (99)	
GNR, Non-Enterobacteriaceace by day180				0.003
Yes	47 (6)	27 (7)	58 (4)	
No	710 (94)	376 (93)	1547 (96)	
Time from transplant to GNR, Non-Enterobacteriaceace, median(range), Days	55 (2 - 148)	15 (<1 - 178)	62 (1 - 179)	0.034
Sites of GNR, Non-Enterobacteriaceace				
In blood by day180				0.640
Yes	31 (66)	20 (74)	37 (64)	
No	16 (34)	7 (26)	21 (36)	
In GI by day 180				0.274
Yes	0	0	2 (3)	
No	47	27	56 (97)	
In lung by day 180				0.295
Yes	6 (13)	1 (4)	9 (16)	
No	41 (87)	26 (96)	49 (84)	
In Sinus by day 180				0.210
Yes	2 (4)	4 (15)	8 (14)	
No	45 (96)	23 (85)	50 (86)	
In CNS by day 180				0.759
Yes	1 (2)	0	1 (2)	
No	46 (98)	27	57 (98)	
In upper GU by day 180				0.372
Yes	6 (13)	3 (11)	3 (5)	
No	41 (87)	24 (89)	55 (95)	
In Skin by day 180				0.985
Yes	3 (6)	2 (7)	4 (7)	
No	44 (94)	25 (93)	54 (93)	
Mycobacterium by day180				0.396
Yes	4 (<1)	4 (<1)	7 (<1)	
No	753 (99)	399 (99)		
Time from transplant to Mycobacterium, median(range), Days	52 (15 - 115)	90 (28 - 146)	41 (8 - 152)	0.726

Variable	Haplo-identical(>=2MM) with Cy N(%)	HLA-identical sibs with Cy N(%)	HLA-identical sibs without Cy N(%)	P value
Sites of Mycobacterium				
In blood by day180				0.765
Yes	1 (25)	1 (25)	3 (43)	
No	3 (75)	3 (75)	4 (57)	
In lung by day 180				0.706
Yes	2 (50)	1 (25)	2 (29)	
No	2 (50)	3 (75)	5 (71)	
In Sinus by day 180				0.183
Yes	0	2 (50)	1 (14)	
No	4	2 (50)	6 (86)	
In CNS by day 180				0.229
Yes	1 (25)	0	0	
No	3 (75)	4	7	
In other sites by day 180				0.542
Yes	0	0	1 (14)	
No	4	4	6 (86)	
Staphylococcus(aureus/NOS) by day180				0.009
Yes	70 (9)	26 (6)	94 (6)	
No	687 (91)	377 (94)	1511 (94)	
Time from transplant to Staphylococcus(aureus/NOS), median(range), Days	28 (<1 - 176)	44 (1 - 171)	45 (<1 - 174)	0.969
Sites of Staphylococcus(aureus/NOS)				
In blood by day180				0.355
Yes	56 (80)	21 (81)	67 (71)	
No	14 (20)	5 (19)	27 (29)	
In GI by day 180				0.422
Yes	1 (1)	0	0	
No	69 (99)	26	94	
In lung by day 180				0.028
Yes	2 (3)	0	11 (12)	
No	68 (97)	26	83 (88)	
In Sinus by day 180				0.502
Yes	2 (3)	2 (8)	3 (3)	
No	68 (97)	24 (92)	91 (97)	
In upper GU by day 180				0.388
Yes	5 (7)	0	6 (6)	
No	65 (93)	26	88 (94)	

Variable	Haplo-identical(>=2MM) with Cy N(%)	HLA-identical sibs with Cy N(%)	HLA-identical sibs without Cy N(%)	P value
In Skin by day 180				0.296
Yes	4 (6)	2 (8)	12 (13)	
No	66 (94)	24 (92)	82 (87)	
In other sites by day 180				0.124
Yes	0	0	4 (4)	
No	70	26	90 (96)	
Staphylococcus(coagulase negative) by day180				0.732
Yes	47 (6)	26 (6)	113 (7)	
No	710 (94)	377 (94)	1492 (93)	
Time from transplant to Staphylococcus(coagulase negative), median(range), Days	25 (1 - 176)	23 (<1 - 133)	35 (<1 - 177)	0.718
Site of Staphylococcus(coagulase negative)				
In blood by day180				0.614
Yes	34 (72)	21 (81)	89 (79)	
No	13 (28)	5 (19)	24 (21)	
In lung by day 180				0.625
Yes	2 (4)	1 (4)	2 (2)	
No	45 (96)	25 (96)	111 (98)	
In Sinus by day 180				0.226
Yes	1 (2)	0	0	
No	46 (98)	26	113	
In CNS by day 180				0.723
Yes	0	0	1 (<1)	
No	47	26	112 (99)	
In upper GU by day 180				0.692
Yes	10 (21)	4 (15)	18 (16)	
No	37 (79)	22 (85)	95 (84)	
In Skin by day 180				0.667
Yes	1 (2)	0	1 (<1)	
No	46 (98)	26	112 (99)	
In other sites by day 180				0.520
Yes	0	0	2 (2)	
No	47	26	111 (98)	
Streptococcus by day180				0.548
Yes	35 (5)	18 (4)	60 (4)	
No	722 (95)	385 (96)	1545 (96)	

Variable	Haplo-identical(>=2MM) with Cy N(%)	HLA-identical sibs with Cy N(%)	HLA-identical sibs without Cy N(%)	P value
Time from transplant to Streptococcus, median(range), Days	16 (4 - 179)	13 (1 - 164)	36 (4 - 180)	0.105
Sites of Streptococcus				
In blood by day180				0.221
Yes	26 (74)	16 (89)	41 (68)	
No	9 (26)	2 (11)	19 (32)	
In GI by day 180				0.407
Yes	0	0	2 (3)	
No	35	18	58 (97)	
In lung by day 180				0.157
Yes	7 (20)	1 (6)	5 (8)	
No	28 (80)	17 (94)	55 (92)	
In Sinus by day 180				0.217
Yes	0	1 (6)	5 (8)	
No	35	17 (94)	55 (92)	
In upper GU by day 180				0.433
Yes	2 (6)	0	5 (8)	
No	33 (94)	18	55 (92)	
In other sites by day 180				0.325
Yes	1 (3)	0	0	
No	34 (97)	18	60	
Other bacteria by day180				0.937
Yes	22 (3)	11 (3)	49 (3)	
No	735 (97)	392 (97)	1556 (97)	
Time from transplant to other bacteria, median(range), Days	15 (2 - 168)	48 (7 - 130)	58 (1 - 177)	0.028
Sites of other bacteria				
In blood by day180				0.720
Yes	14 (64)	6 (55)	33 (67)	
No	8 (36)	5 (45)	16 (33)	
In GI by day 180				0.152
Yes	3 (14)	1 (9)	1 (2)	
No	19 (86)	10 (91)	48 (98)	
In lung by day 180				0.744
Yes	3 (14)	2 (18)	5 (10)	
No	19 (86)	9 (82)	44 (90)	
In Sinus by day 180				0.170
Yes	0	2 (18)	5 (10)	
No	22	9 (82)	44 (90)	

Variable	Haplo-identical(>=2MM) with Cy N(%)	HLA-identical sibs with Cy N(%)	HLA-identical sibs without Cy N(%)	P value
In CNS by day 180				0.038
Yes	0	1 (9)	0	
No	22	10 (91)	49	
In upper GU by day 180				0.413
Yes	3 (14)	0	4 (8)	
No	19 (86)	11	45 (92)	

Notes:

Sites: **Blood**: Bone marrow, Blood-buffy coat, Central venous catheter,nos, Catheter insertion or exit site **Sinus/Upper RespiratoryL**:Upper airway & nasopharynx, Laryngitis-larynx, Sinuses, Sinus and/or Upper respiratory tract; **Lung/Lower Respiratory:** Respiratory nos, Lower respir.tract(lung); **GI**: Lips Tongue, oral cavity,oro-pharynx, Esophagus, Small intestine, Large intestine, Feces-stool, Gastrointestinal tract, not specified, Stomach, GI tract, Lower, GI tract, Upper; **Liver/Spleen**; Liver; **CNS**: Central nervious system nos, Spinal cord, Meninges and csf; **Lower GU**: Genito-urinary tract nos, Vagina, Urinary tract, Lower, Genital area; **Upper GU**: 41 Kidneys,renal pelvis,ureters,bladder, Urinary tract, Upper; **Skin:** Skin nos, Cellulitis, Rash, pustule,abscesses not from above; **Other site:** Diseminated-generalized, Eyes, Bone cortex(osteomyelitis)

Type of bacterial infections: **Anaerobes:** Listeria monocytogenes, Actinomyces, Bacillus, Bacteroides (gracillis, uniformis, vulgaris, other species), Capnocytophaga (all species), Clostridium (all species except difficile), Fusobacterium (all species), Lactobacillus (bulgaricus, acidophilus, other species), Leptotrichia buccalis, Propionibacterium (acnes, avidum, granulosum, other species), Stomatococcus mucilaginosis; **Clostridium difficile;** **Enterococcus Vanc Sensitive:** Enterococcus (all species); **VRE; GNR, Enterobacteriaceae:** Citrobacter (freundii, other species), Enterobacter (all species), Escherichia (also E. coli), Klebsiella (all species), Proteus (all species), Salmonella (all species), Serratia marcescens, Shigella (all species); **GNR, Non-Enterobacteriaceace:** Acinetobacter (all species), Flavobacterium, Methylobacterium, Pseudomonas (all , species except cepacia & maltophilia), Pseudomonas or Burkholderia cepacian, Stenotrophomonas maltophilia, Vibrio (all , species), Pseudomonas aeruginosa, Pseudomonas non-aeruginosa; **Mycobacterium**: Mycobacterium cheloneae, Mycobacterium fortuitum, Mycobacterium tuberculosis (tuberculosis, Koch bacillus), Mycobacterium avium - intracellulare (MAC, MAI), Mycobacterium haemophilum, Mycobacterium kansasii, Mycobacterium marinum, Mycobacterium mucogenicum, Mycobacterium abscessus, Mycobacterium species (cheloneae, fortuitum, haemophilum, kansasii, mucogenicum), Other mycobacterium, specify, Mycobacterium, NOS, Staphylococcus(aureus/NOS); **Staphylococcus(aureus/NOS):** Staphylococcus aureus, Staphylococcus, NOS, Staphylococcus (Methacillin Sensitive), Staphylococcus (Methacillin Resistant); **Staphylococcus(coagulase negative):** Staphylococcus, coagulase negative (not aureus); **Streptococcus:** Streptococcus (all species except Enterococcus), Streptococcus pneumoniae, Streptococcus, alpha-hemolytic, Streptococcus, Group B; **Other bacteria Leptospira (all species):** Mycoplasma (all species), Nocardia (all species), Rickettsia (all species), Bordetella pertussis (whooping cough), Branhamella or Moraxella catarrhalis (other species), Campylobacter (all species), Corynebacterium (all nondiptheria species), Haemophilus (all species,including influenzae), Leuconostoc (all species), Micrococcus, NOS, Neisseria (gonorrhoea, meningitidis, other species), Pasteurella multocida, Rhodococcus (all species), Treponema (syphillis), Chlamydia (pneumoniae), Corynebacterium jeikeium, Neisseria gonorrhoeae, Neisseria meningitidis, Haemophilus influenzae, Haemophilus non-influenzae, Legionella pneumophila, Legionella non-pneumophila

Table 1.3 Fungal Infections by 180 days

Variable	Haplo-identical(>=2MM) with Cy N(%)	HLA-identical sibs with Cy N(%)	HLA-identical sibs without Cy N(%)	P value
Number of patients	**757**	**403**	**1605**	
Aspergillus by day180				0.221
Yes	15 (2)	9 (2)	20 (1)	
No	742 (98)	394 (98)	1585 (99)	
Time from transplant to Aspergillus, median(range), Days	76 (2 - 179)	81 (6 - 110)	70 (3 - 175)	0.703
Sites of Aspergillus				
In blood by day180				0.482
Yes	8 (53)	3 (33)	7 (35)	
No	7 (47)	6 (67)	13 (65)	
In lung by day 180				0.646
Yes	4 (27)	4 (44)	6 (30)	
No	11 (73)	5 (56)	14 (70)	
In Sinus by day 180				0.507
Yes	3 (20)	1 (11)	6 (30)	
No	12 (80)	8 (89)	14 (70)	
In CNS by day 180				0.541
Yes	0	0	1 (5)	
No	15	9	19 (95)	
Candida by day180				<0.001
Yes	31 (4)	8 (2)	25 (2)	
No	726 (96)	395 (98)	1580 (98)	
Time from transplant to Candida, median(range), Days	56 (8 - 179)	29 (<1 - 141)	51 (3 - 171)	0.771
Sites of Candida				
In blood by day180				0.991
Yes	12 (39)	3 (38)	10 (40)	
No	19 (61)	5 (63)	15 (60)	
In GI by day 180				0.467
Yes	5 (16)	0	3 (12)	
No	26 (84)	8	22 (88)	
In lung by day 180				0.938
Yes	6 (19)	2 (25)	5 (20)	
No	25 (81)	6 (75)	20 (80)	
In Sinus by day 180				0.633
Yes	4 (13)	2 (25)	3 (12)	
No	27 (87)	6 (75)	22 (88)	

Variable	Haplo-identical(>=2MM) with Cy N(%)	HLA-identical sibs with Cy N(%)	HLA-identical sibs without Cy N(%)	P value
In CNS by day 180				0.029
Yes	0	1 (13)	0	
No	31	7 (88)	25	
In upper GU by day 180				0.297
Yes	1 (3)	0	3 (12)	
No	30 (97)	8	22 (88)	
In Skin by day 180				0.582
Yes	1 (3)	0	0	
No	30 (97)	8	25	
In other sites by day 180				0.297
Yes	1 (3)	0	3 (12)	
No	30 (97)	8	22 (88)	
Non-aspergillus mold by day180				0.009
Yes	7 (<1)	5 (1)	3 (<1)	
No	750 (99)	398 (99)	1602(99)	
Time from transplant to Non-aspergillus mold, median(range), Days	32 (13 - 153)	136 (59 - 156)	69 (41 - 135)	0.209
Sites of Non-aspergillus mold				
In blood by day180				0.719
Yes	1 (14)	1 (20)	0	
No	6 (86)	4 (80)	3	
In lung by day 180				0.404
Yes	1 (14)	0	1 (33)	
No	6 (86)	5	2 (67)	
In Sinus by day 180				0.585
Yes	1 (14)	2 (40)	1 (33)	
No	6 (86)	3 (60)	2 (67)	
In Skin by day 180				0.788
Yes	1 (14)	1 (20)	1 (33)	
No	6 (86)	4 (80)	2 (67)	
In other sites by day 180				0.585
Yes	2 (29)	1 (20)	0	
No	5 (71)	4 (80)	3	
Pneumocystis (PCP / PJP) by day180				0.035
Yes	0	2 (<1)	1 (<1)	
No	757	401(99)	1604(99)	

Variable	Haplo-identical(>=2MM) with Cy N(%)	HLA-identical sibs with Cy N(%)	HLA-identical sibs without Cy N(%)	P value
Time from transplant to Pneumocystis (PCP / PJP), median(range), Days		75 (31 - 119)	163 (163 - 163	0.221
Sites of Pneumocystis (PCP / PJP)				
In lung by day 180				0.035
Yes		2	1	

Notes:

Sites: **Blood**: Bone marrow, Blood-buffy coat, Central venous catheter,nos, Catheter insertion or exit site

Sinus/Upper RespiratoryL:Upper airway & nasopharynx, Laryngitis-larynx, Sinuses, Sinus and/or Upper respiratory tract; **Lung/Lower Respiratory:** Respiratory nos, Lower respir.tract(lung); **GI**: Lips Tongue, oral cavity,oro-pharynx, Esophagus, Small intestine, Large intestine, Feces-stool, Gastrointestinal tract, not specified, Stomach, GI tract, Lower, GI tract, Upper; **Liver/Spleen**; Liver; **CNS**: Central nervious system nos, Spinal cord, Meninges and csf; **Lower GU**: Genito-urinary tract nos, Vagina, Urinary tract, Lower, Genital area; **Upper GU**: 41 Kidneys,renal pelvis,ureters,bladder, Urinary tract, Upper; **Skin:** Skin nos, Cellulitis, Rash, pustule,abscesses not from above; **Other site:** Diseminated-generalized, Eyes, Bone cortex(osteomyelitis)

Type of fungal infections: ***Aspergillus***: Aspergillus, NOS, Aspergillus flavus, Aspergillus fumigatus, Aspergillus niger, Aspergillus ustus, Aspergillus terreus, Other Aspergillus, specify, **Candida:** Candida, NOS, Candida albicans, Candida krusei, Candida parapsilosis, Candida tropicalis, Candida (Torulopsis) glabrata, Candida guillermondi, Candida lusitaniae, Candida non-albicans, Other Candida, specify; **Non-aspergillus mold:** Fusarium (all species), Zygomycetes, NOS, Mucorales (all species), Rhizopus (all species), Scedosporium (all species); **Pneumocystis (PCP / PJP)**

Selection criteria

Selection Criteria (IN1801) Jun 2019	Removed	Remained
First allo transplant for AML, ALL and MDS 2012-2017		12145
Age>=2	181	11964
BM, PB only	1970	9994
Included if HLA identical Sib, mismatched related (mismatch>=2)	5615[a]	4379
Included only if GVHD prophylaxis in TAC/CSA+ MMF +/- others or GAC/CSA + MTX +/- others	715	3664
Included only if no ATG Campath	275	3389
Excluded if no 100-day follow-up	5	3384
Excluded if infection(s) reported before day 0	80	3304
Excluded if no consent	50	3254
Excluded quarantine centers from research studies	78	3176
Excluded if patients transplanted at centers which have no reported haploHCT patients[b]	411	2765

[a] twin, n=48; multiple donor, n=1; matched related, n=78; one mismatch related, n=40; mismatched related, HLA missing, n=92; matched unrelated donor, n=4249; mismatched unrelated donor, n=828; unrelated HLA missing , n=279

[b]92 centers have been removed

Completeness index as of 1/1/2019

Follow up	Mismatch related with Cy N(%)	HLA-identical sibs with Cy N(%)	HLA-identical sibs without Cy N(%)
Number of patients	757	403	1605
@6 month	100	100	100
@1 year	98	98	99
@2 year	91	93	95

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 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. We will limit to US centers.

Exclusion Criteria:

- Patients < 2 years old
- HLA-Mismatched marrow or peripheral blood stem cells from adult donor (i.e. mismatched UCB included)
- 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. Separate estimates for pediatric (2 – 18y) and adult (>18y) patients
b. Transplant related mortality (TRM) by 1 year: 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, 60 and 100.
c. Infection-Related mortality (IRM) by 1 year: 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, 60 and 100.
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 30, 60, and 100.
e. Incidence of chronic GVHD by 1 year: 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 by 1 year: Cumulative incidence of disease relapse/progression, with TRM as competing event. This will be examined as a dynamic landmark analysis for patients at day 30, 60 and 100.
g. Disease free survival by 1 year: will be defined as time to relapse or death from any cause. Patients are censored at last follow-up. This will be examined as a dynamic landmark analysis for patients at day 30, 60 and 100.
h. Overall survival (OS) by 1 year: time to death. Death from any cause will be considered an event. Surviving patients will be censored at time of last follow-up. This will be examined as a dynamic landmark analysis for patients at day 30, 60 and 100.
i. Cause of death by 1 year: descriptive only. This will include Primary cause of death and infection as a secondary COD
j. Frequency of recurrent CDI by 1 year: descriptive only
k. Frequency of Gram Negative BSI occurring ± 7 days of CDI: 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 status at transplant (AML/ALL)
- Cytogenetic Risk groups (AML/ALL)
- IPSS-R Categories (MDS)
- 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 vs cord blood – single vs cord blood - double
- GVHD prophylaxis
- ATG/Alemtuzumab (yes vs no)
- Year of HCT
- Systemic antibacterial use (yes vs no)

Time dependent variable

- Neutrophil engraftment (Yes vs No)
- Platelet engraftment (yes vs no)
- 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 by 1 year when compared to control cohort from the same center without documented CDI.

By using the dynamic landmark analysis, univariate analysis will be performed using Kaplan-Meier Method for OS and DFS, while acute / chronic GVHD, TRM, IRM and relapse will be calculated using the cumulative incidence method considering competing risks.

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.

Descriptive outcomes of TRM, IRM, OS, acute GVHD, chronic GVHD, and relapse will be examined separately for patients diagnosed with CDI between start of conditioning and day 0.

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 infection by 100 day, from 2013 to 2018

Variable	CDI by 100 day N(%)	No CDI by 100 day N(%)	CDI before conditioning N(%)
Patient related			
Number of patients	826	6725	77
Number of centers	127	127	42
Gender			
Male	485 (59)	3893 (58)	45 (58)
Female	341 (41)	2832 (42)	32 (42)
Age, median(range), years	54 (2 - 82)	59 (2 - 83)	44 (3 - 75)
Age at transplant, years			
<=10	67 (8)	296 (4)	3 (4)
11-20	77 (9)	337 (5)	9 (12)
21-30	66 (8)	447 (7)	8 (10)
31-40	56 (7)	511 (8)	13 (17)
41-50	91 (11)	710 (11)	14 (18)
51-60	153 (19)	1322 (20)	14 (18)
61-70	237 (29)	2419 (36)	13 (17)
>70	79 (10)	683 (10)	3 (4)
Race/Ethnicity			
Caucasian, non-Hispanic	605 (73)	5126 (76)	50 (65)
African-American, non-Hispanic	48 (6)	409 (6)	9 (12)
Asian, non-Hispanic	46 (6)	362 (5)	3 (4)
Pacific islander, non-Hispanic	5 (<1)	20 (<1)	0
Native American, non-Hispanic	7 (<1)	31 (<1)	0
Hispanic, Caucasian	80 (10)	511 (8)	10 (13)
Hispanic, African-American	5 (<1)	15 (<1)	0
Hispanic, Asian	0	5 (<1)	0
Hispanic, Parcific islander	0	2 (<1)	0
Hispanic, Native American	1 (<1)	7 (<1)	0
Missing	29 (4)	237 (4)	5 (6)
Karnofsky performance pre-Preparative Regimen			
<80	101 (12)	907 (13)	8 (10)
80-89	223 (27)	1935 (29)	21 (27)
>=90	497 (60)	3812 (57)	47 (61)
Missing	5 (<1)	71 (1)	1 (1)
HCT-CI			

Variable	CDI by 100 day N(%)	No CDI by 100 day N(%)	CDI before conditioning N(%)
0	190 (23)	1347 (20)	11 (14)
1-2	249 (30)	1971 (29)	28 (36)
3-4	239 (29)	2109 (31)	23 (30)
5+	147 (18)	1294 (19)	15 (19)
Missing	1 (<1)	4 (<1)	0
Donor related			
Donor/recipient gender match			
Male-Male	324 (39)	2540 (38)	26 (34)
Male-Female	206 (25)	1691 (25)	23 (30)
Female-Male	159 (19)	1338 (20)	19 (25)
Female-Female	131 (16)	1124 (17)	9 (12)
Missing	6 (<1)	32 (<1)	0
Donor/Recipient CMV status			
+/+	212 (26)	1792 (27)	22 (29)
+/-	77 (9)	600 (9)	5 (6)
-/+	294 (36)	2433 (36)	28 (36)
-/-	218 (26)	1726 (26)	21 (27)
+/?	5 (<1)	9 (<1)	0
-/?	5 (<1)	23 (<1)	0
?/+	9 (1)	87 (1)	1 (1)
?/-	6 (<1)	55 (<1)	0
Disease related			
Disease			
AML	422 (51)	3145 (47)	37 (48)
ALL	200 (24)	1188 (18)	28 (36)
MDS	204 (25)	2392 (36)	12 (16)
Disease status at HCT			
AML/ALL, early	383 (46)	2692 (40)	40 (52)
AML/ALL, intermediate	153 (19)	940 (14)	16 (21)
AML/ALL, advanced	81 (10)	669 (10)	9 (12)
AML/ALL, unknown	5 (<1)	32 (<1)	0
MDS, early	67 (8)	869 (13)	6 (8)
MDS, advanced	137 (17)	1518 (23)	6 (8)
Missing	0	5 (<1)	0
IPSS-R prior to transplant (MDS only)			
Very low	30 (4)	335 (5)	1 (1)

Variable	CDI by 100 day N(%)	No CDI by 100 day N(%)	CDI before conditioning N(%)
Low	54 (7)	647 (10)	2 (3)
Intermediate	54 (7)	657 (10)	3 (4)
High	33 (4)	322 (5)	3 (4)
Very high	9 (1)	122 (2)	0
Missing	24 (3)	309 (5)	3 (4)
AML/ALL N/A	622 (75)	4333 (64)	65 (84)
Cytogenetics for AML/ALL			
Normal	39 (5)	261 (4)	5 (6)
Favorable	24 (3)	178 (3)	4 (5)
Intermediate	238 (29)	1855 (28)	23 (30)
Poor	228 (28)	1557 (23)	25 (32)
Other	27 (3)	159 (2)	6 (8)
Not tested/missing	66 (8)	323 (5)	2 (3)
MDS, N/A	204 (25)	2392 (36)	12 (16)
Flow cytometry for MRD Analysis			
Yes	122 (15)	1221 (18)	10 (13)
No	589 (71)	4497 (67)	62 (81)
Missing	115 (14)	1007 (15)	5 (6)
Transplant-related			
Time from diagnosis to transplant			
<6 months	392 (47)	3154 (47)	34 (44)
6 month-1Y	212 (26)	1800 (27)	25 (32)
1Y-2Y	102 (12)	873 (13)	5 (6)
>=2Y	120 (15)	883 (13)	13 (17)
Missing	0	15 (<1)	0
Time from diagnosis to transplant, median(range), months	6 (2 - 277)	6 (<1 - 556)	6 (2 - 90)
Graft type			
Bone Marrow	134 (16)	1031 (15)	8 (10)
Peripheral blood	513 (62)	4638 (69)	47 (61)
Cord blood	179 (22)	1056 (16)	22 (29)
Donor/recipient HLA match			
Cord blood-double	99 (12)	707 (11)	15 (19)
Cord blood-single	80 (10)	349 (5)	7 (9)
HLA-identical siblings	251 (30)	2288 (34)	20 (26)
Other matched related	0	39 (<1)	0

Variable	CDI by 100 day N(%)	No CDI by 100 day N(%)	CDI before conditioning N(%)
8/8 unrelated	396 (48)	3342 (50)	35 (45)
Conditioning regimen intensity			
Myeloablative with TBI	238 (29)	1319 (20)	32 (42)
Myeloablative chemotherapy only	279 (34)	2172 (32)	28 (36)
RIC/NMA	309 (37)	3234 (48)	17 (22)
GVHD prophylaxis			
Ex vivo T-cell depletion	7 (<1)	32 (<1)	1 (1)
CD34 selection	13 (2)	132 (2)	4 (5)
Post-CY + other(s)	83 (10)	537 (8)	3 (4)
Post-CY alone	7 (<1)	62 (<1)	0
TAC/CSA + MMF +- others	260 (31)	2019 (30)	25 (32)
TAC/CSA + MTX +- others	365 (44)	3206 (48)	32 (42)
TAC/CSA + others (except MTX, MMF)	53 (6)	442 (7)	8 (10)
TAC/CSA alone	17 (2)	186 (3)	4 (5)
MMF +/- Other	5 (<1)	29 (<1)	0
MTX +/- Other	4 (<1)	30 (<1)	0
SIRO +/- others (Not TAC/CSA)	11 (1)	44 (<1)	0
Steroids alone	1 (<1)	6 (<1)	0
ATG/Alemtuzumab			
ATG alone	183 (22)	1461 (22)	28 (36)
CAMPATH alone	19 (2)	141 (2)	0
No ATG or CAMPATH	622 (75)	5110 (76)	49 (64)
Missing	2 (<1)	13 (<1)	0
Year of transplant			
2013	135 (16)	1212 (18)	14 (18)
2014	177 (21)	1406 (21)	23 (30)
2015	188 (23)	1339 (20)	16 (21)
2016	137 (17)	1205 (18)	15 (19)
2017	106 (13)	923 (14)	4 (5)
2018	83 (10)	640 (10)	5 (6)
Systemic antibacterial prophylaxis given			
Yes	631 (76)	5148 (77)	52 (68)
No	195 (24)	1550 (23)	25 (32)
Missing	0	27 (<1)	0
Median follow-up of survivors, months	36 (3 - 73)	36 (3 - 74)	37 (3 - 63)

Table 1.2 Infection and time dependent variables

Variable	CDI by 100 day N(%)	No CDI by 100 day N(%)	CDI before conditioning N(%)
Number of patients	**826**	**6725**	**77**
Infection and Time dependent variable			
Time from transplant to CDI, days	13 (<1 - 100)	N/A	-2 (-7 - -1)
Neutrophil engraftment			
Yes	808 (98)	6548 (97)	74 (96)
No	17 (2)	166 (2)	3 (4)
Missing	1 (<1)	11 (<1)	0
Time from transplant to ANC>500, days	15 (1 - 67)	15 (<1 - 113)	16 (10 - 63)
Platelet engraftment			
Yes	766 (93)	6199 (92)	67 (87)
No	60 (7)	519 (8)	10 (13)
Missing	0	7 (<1)	0
Time from transplant to platelet>=20K	21 (1 - 724)	18 (<1 - 510)	21 (1 - 115)
Acute GVHD grade II-IV			
No	442 (54)	4042 (60)	47 (61)
Yes	375 (45)	2611 (39)	29 (38)
Missing	9 (1)	72 (1)	1 (1)
Time from transplant to aGVHD, days	33 (7 - 168)	35 (7 - 178)	24 (9 - 69)
Acute GVHD grade II-IV occurring prior to CDI			
Yes	107 (13)	0	N/A
No	268 (32)	0	
No GVHD II-IV	442 (54)	4042 (60)	
Has GVHD II-IV no CDI	0	2611 (39)	
Missing	9 (1)	72 (1)	
Lower GI acute GVHD stage 2 - 4 occurring prior to CDI			
Yes	44 (5)	0	N/A
No	83 (10)	0	
No Lower GI GVHD2-4	690 (84)	5857 (87)	
Has lower GI, no CDI	0	796 (12)	
Missing	9 (1)	72 (1)	

Distribution of continuous variables

	group	n	Min	P5	P25	P50	P75	P95	Max
Patient age									
	CDI by 100 day	826	2.03	5.97	29.58	53.94	64.62	71.95	81.55
	No CDI by 100 day	6725	2.00	11.46	41.53	58.57	66.35	72.05	82.67
	CDI before conditioning	77	2.59	10.09	28.04	43.72	57.43	69.24	75.10
Time from diagnosis to HCT, months									
	CDI by 100 day	826	1.58	2.93	4.31	6.25	13.59	44.31	276.74
	No CDI by 100 day	6710	0.30	2.76	4.31	6.32	12.70	52.73	556.25
	CDI before conditioning	77	2.07	2.99	4.90	6.41	10.46	58.62	90.49
Time from HCT to ANC>500, days									
	CDI by 100 day	808	1.00	10.00	12.00	15.00	19.00	28.00	67.00
	No CDI by 100 day	6548	0.00	8.00	12.00	15.00	18.00	27.00	113.00
	CDI before conditioning	74	10.00	10.00	13.00	16.00	22.00	43.00	63.00
Time from HCT to platelet>=20K, days									
	CDI by 100 day	766	1.00	7.00	16.00	20.50	33.00	75.00	724.00
	No CDI by 100 day	6196	0.00	1.00	15.00	18.00	28.00	52.00	510.00
	CDI before conditioning	67	1.00	14.00	16.00	21.00	37.00	65.00	115.00
Time from HCT to aGVHD grade 2-4, days									
	CDI by 100 day	375	7.00	13.00	22.00	33.00	55.00	108.00	168.00
	No CDI by 100 day	2611	7.00	14.00	24.00	35.00	57.00	122.00	178.00
	CDI before conditioning	29	9.00	11.00	17.00	24.00	41.00	68.00	69.00
Time from HCT to last contact date, months									
	CDI by 100 day	826	0.33	2.14	5.99	12.86	36.22	53.36	73.06
	No CDI by 100 day	6724	0.03	1.91	6.18	13.55	36.05	59.87	73.85
	CDI before conditioning	77	0.23	1.28	4.77	18.26	36.68	59.90	63.03
Time from transplant to CDI, days									
	CDI by 100 day	826	0.00	1.00	3.00	13.00	41.00	84.00	100.00
	CDI before conditioning	75	-7.00	-6.00	-3.00	-2.00	-1.00	-1.00	-1.00

Note: extreme values are under review

Selection Criteria	**Removed**	**Remained**
First allo transplant for hematologic malignancy 2013-2018		15827
Age>=2	184	15643
AML, ALL and MDS only	3520	12123

BM, PB or Cords	192	11931
Matched related or matched unrelated or cords (any match)	2572*	9359
Excluded if no consent	131	9228
Excluded quarantine centers from research studies	282	8946
Excluded if no 100 day follow up form	155	8791
Excluded if conditioning regimen intensity missing	26	8765
Excluded if missing/no GVHD prophylaxis	95	8670
US only	803	7867
Excluded if patients transplanted at centers which have no reported CDI patients	239	7628

Note: *twin, n=46; mismatched related, n=1422; mismatched/missing unrelated, n=1103; multi donor,n=1.

1. **Completeness index as of 1/1/2019**

Follow up	C Difficile infection by 100 day N(%)	No C difficile infection by 100 day N(%)	C Difficile infection by day0 N(%)
Number of patients	826	6725	77
@6 month	100	100	100
@1 year	98	99	100

CIBMTR-IN19-01

Immune recovery predicts post-transplant outcomes
Draft Protocol

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1. Hypothesis:

Patients with rapid and robust immune recovery have improved survival and decreased non-relapse mortality.

2. Specific aims:

- Assess transplant outcomes in adult and pediatric patients who undergo allo-HCT based on day 100 CD4 count.
    - Survival
    - GVHD
    - Relapse/progression
    - Infections
- Assess transplant outcomes in adult and pediatric patients who undergo allo-HCT based on day 180 immune recovery of CD4 count and attaining IgA levels within normal range.
    - Survival
    - GVHD
    - Relapse/progression
    - Infections
- Descriptive analysis of immune recovery post HCT including T, B and NK cells, as well as Ig levels.
- Risk factors for poor immune recovery by day 100

3. 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.

4. Scientific justification:

Allogeneic hematopoietic stem cell transplantation (allo-HCT) 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.[1-11] 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-HCT is associated with improved overall survival (OS), decreased relapse and lower transplant-related mortality (TRM).[4-7] Investigators at MSKCC previously reported on immune reconstitution following *ex vivo* TCD allo-HCT, and showed an association between delayed immune recovery and worse HCT outcomes including rates of infection and survival.[1,8,12-15] There are, however, incomplete data regarding the effect of the quantitative and functional recovery of T cells on relapse and survival in most settings.[16-18] Furthermore, delayed recovery of IgA secretion (a surrogate marker of IVIG independent functional B cell recovery demonstrating the functional capacity of B lymphocytes for isotype switching) compared to IgG has been long recognized as a distinct pathological feature following allogeneic BMT;[19-22] and there is long standing evidence that those inflicted with either acute or chronic GVHD may have further delay in recovery of mucosal immunity and serum IgA levels.[23,24] Most of these studies, however, 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.

5. Patient eligibility population:

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

Inclusion criteria:

- Age ≥ 2 to ≤ 75 years
- first allo-HCT between 2008 and 2018
- Any donor
- GVHD prophylaxis (CNI/MTX, CNI/MMF, PTCY/CNI/MMF)
- Myeloablative or Reduced intensity/Non-myeloablative conditioning
- In vivo or Ex vivo T cell depletion allowed
- MDS, AML, ALL,

Exclusion Criteria

- Multiple donors (except cord)
- Syngeneic transplant
- If no 2100 form available
- If no lymphocyte subset analysis performed at day 100 and day 180 (R5, question 75)
- No consent

6. Outcomes: landmark analysis from day 100

a. Overall Survival (OS): time to death. Death from any cause is an event. Surviving patients are censored at the time of last follow-up.
b. Disease-Free Survival (DFS): time to relapse or death from any cause
c. Non-relapse mortality (NRM): death without evidence of disease relapse/progression. Relapse is the competing risk
d. Relapse: non-relapse mortality is the competing risk.
e. Chronic GVHD (cGVHD): Death is the competing risk.
f. Cumulative incidence of mycobacterial infections: death is the competing risk
g. Cumulative incidence of viral infections: death is the competing risk
h. Cumulative incidence of fungal infections: death is the competing risk
i. Cause of death: primary and infections as contributing cause

7. Variables to be examined

Recipient Related:

- Recipient Age at transplant
- Recipient Gender
- Race/ethnicity
- HCT-CI/ aHCT-CI
- Prior autologous transplant
- Recipient CMV Serostatus
- Karnofsky/Lansky Performance Score

Donor Related:

- Donor Age
- Donor gender
- Donor CMV Serostatus

Disease/Transplant Related:

- Disease
- Time from diagnosis to transplant
- Disease status at transplant (AML/ALL)
- Cytogenetic risk groups (AML/ALL)
- IPSS-R categories (MDS)
- Conditioning intensity: Myeloablative vs Reduced Intensity/Non-myeloablative
- Stem Cell Source: Bone Marrow vs Peripheral Blood vs Cord Blood
- GVHD Prophylaxis: Calcineurin inhibitor based (CSA/TAC) vs Sirolimus based vs PTCy based vs Other
- *Ex vivo* T-cell depletion: Yes vs No
- *In vivo* T-cell depletion: ATG (ATGAM) vs ATG (Thymoglobulin) vs Alemtuzumab
- IVIG given between day 0 – day 100: Yes vs No

Immune Recovery labs @ day 100

- CD4
- CD8
- CD4:CD8 ratio
- CD19/20
- CD56
- IgG
- IgA
- IgM

Time Dependent variable

- Neutrophil engraftment: yes vs no
- Days to neutrophil engraftment
- Acute GVHD grade II-IV: yes vs no
- Acute GVHD grade III-IV: yes vs no
- Days to onset of acute GVHD

Infections prior to day 100

- Bacterial infections: Median, range
- Viral infections: Median, range
- Fungal infections: Median, range
- Total infections: Median, range

8. Study design:

Patient-, disease- and transplant- related factors will be compared between groups using the Chi-square test for categorical variables and the Kruskal-Wallis test for continuous variables. All outcomes will be examined from day 100 post-transplant as a landmark analysis to account for the defining event creating the cohorts.

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 associate with the outcomes. Factors significantly associated with the outcome variable at a 1% level will be kept in the final model. Interactions between main effect and significant covariates will be tested. Center effects will be tested.

A Cox proportional hazards model will be used to determine the factors present at time of transplant and the events prior to day 100 that result in poor immune reconstitution.

9. 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

Paul Szabolcs:

No relevant COI.
Ad hoc consultant to REGENXBIO Inc.

10. 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. Storek J, Gooley T, Witherspoon RP, et al: Infectious morbidity in long-term survivors of allogeneic marrow transplantation is associated with low CD4 T cell counts. Am J Hematol 54:131-8, 1997

10. Storek J, Joseph A, Dawson MA, et al: Factors influencing T-lymphopoiesis after allogeneic hematopoietic cell transplantation. Transplantation 73:1154-8., 2002

11. Storek J, Viganego F, Dawson MA, et al: Factors affecting antibody levels after allogeneic hematopoietic cell transplantation. Blood 101:3319-24, 2003

12. 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

13. 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

14. 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

15. 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

16. 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

17. 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

18. 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

19. Brenner MK, Wimperis JZ, Reittie JE, et al: Recovery of immunoglobulin isotypes following T-cell depleted allogeneic bone marrow transplantation. Br J Haematol 64:125-32, 1986

20. Perreault C, Giasson M, Gyger M, et al: Serum immunoglobulin levels following allogeneic bone marrow transplantation. Blut 51:137-42, 1985

21. Velardi A, Cucciaioni S, Terenzi A, et al: Acquisition of Ig isotype diversity after bone marrow transplantation in adults. A recapitulation of normal B cell ontogeny. J Immunol 141:815-20, 1988

22. Witherspoon RP, Deeg HJ, Lum LG, et al: Immunologic recovery in human marrow graft recipients given cyclosporine or methotrexate for the prevention of graft-versus-host disease. Transplantation 37:456-61, 1984

23. Abedi MR, Hammarstrom L, Ringden O, et al: Development of IgA deficiency after bone marrow transplantation. The influence of acute and chronic graft-versus-host disease. Transplantation 50:415-21, 1990

24. Ringden O, Sundberg B, Markling L, et al: Polyclonal antibody secretion during acute graft-versus-host disease. Scand J Immunol 26:469-76, 1987

Characteristics of patients who underwent first ALLO transplants for AML/ALL/MDS from 2008 to 2018 in US reported to CIBMTR

Characteristic	
No. of patients	2236
No. of centers	110
Patient related	
Recipient age - no. (%)	
Median (min-max)	51.6 (2.1-74.6)
0-9	209 (9.3)
10-19	275 (12.3)
20-29	162 (7.2)
30-39	180 (8.1)
40-49	238 (10.6)
50-59	446 (19.9)
60-69	592 (26.5)
70+	134 (6)
Recipient Sex - no. (%)	
Male	1274 (57)
Female	962 (43)
Recipient race - no. (%)	
Caucasian	1802 (80.6)
African-American	244 (10.9)
Asian	108 (4.8)
Pacific islander	9 (0.4)
Native American	10 (0.4)
Unknown	63 (2.8)
Ethnicity - no. (%)	
Hispanic or Latino	247 (11)
Not Hispanic or Latino	1931 (86.4)
Missing	58 (2.6)
HCT-CI - no. (%)	
0	644 (28.8)
1	323 (14.4)
2	319 (14.3)
3+	942 (42.1)
TBD, review needed for history of malignancies	4 (0.2)
NA, f2400 (pre-TED) not completed	4 (0.2)
Prior autologous transplant - no. (%)	
No	2186 (97.8)
Yes	50 (2.2)
Karnofsky/Lansky Performance Score - no. (%)	

Characteristic	
<90	764 (34.2)
≥90	1459 (65.3)
Missing	13 (0.6)
Donor related	
Donor age - no. (%)	
Median (min-max)	32.4 (0.2-76.4)
0-9	162 (7.2)
10-19	107 (4.8)
20-29	548 (24.5)
30-39	339 (15.2)
40-49	271 (12.1)
50-59	211 (9.4)
60-69	146 (6.5)
70+	20 (0.9)
Missing	432 (19.3)
Donor sex - no. (%)	
Male	1332 (59.6)
Female	867 (38.8)
Missing	37 (1.7)
Donor/recipient CMV serostatus - no. (%)	
+/+	543 (24.3)
+/-	180 (8.1)
-/+	458 (20.5)
-/-	438 (19.6)
CB - recipient +	382 (17.1)
CB - recipient -	205 (9.2)
CB - recipient CMV unknown	8 (0.4)
Missing	22 (1)
Disease related	
Disease - no. (%)	
AML	1058 (47.3)
ALL	470 (21)
MDS	708 (31.7)
Time from diagnosis to transplant - median (min-max)	6.88 (0.66-549.34)
AML/ALL disease status - no. (%)	
CR1	935 (61.2)
CR2	380 (24.9)
CR3 +	53 (3.5)
PIF/Relapse	159 (10.4)
Missing	1 (0.1)
AML/ALL Cytogenetic score - no. (%)	

Characteristic	
Normal	98 (6.4)
Favorable	72 (4.7)
Intermediate	631 (41.3)
Poor	487 (31.9)
Other	68 (4.5)
TBD (needs rev.)	139 (9.1)
Not tested	14 (0.9)
Missing	19 (1.2)
IPSS-R cytogenetic score - no. (%)	
Very good	7 (1)
Good	296 (41.8)
Intermediate	134 (18.9)
Poor	107 (15.1)
Very poor	101 (14.3)
TBD (needs rev.)	39 (5.5)
Not tested	8 (1.1)
Missing	16 (2.3)
Conditioning regimen intensity - no. (%)	
MAC	1377 (61.6)
RIC	541 (24.2)
NMA	247 (11)
TBD	62 (2.8)
Missing	9 (0.4)
Graft type - no. (%)	
Bone Marrow	334 (14.9)
Peripheral Blood	1307 (58.5)
Cord Blood	595 (26.6)
Donor type - no. (%)	
HLA-identical sibling	444 (19.9)
Other related: Matched	14 (0.6)
Other related: Mismatched 1 antigen/allele	21 (0.9)
Other related: Mismatched ≥ 2 Ag/allele	247 (11)
Other related: matching missing	33 (1.5)
Well-matched unrelated (8/8)	737 (33)
Partially-matched unrelated (7/8)	125 (5.6)
Mis-matched unrelated (≤6/8)	15 (0.7)
Unrelated (matching TBD)	3 (0.1)
Cord blood	595 (26.6)
Missing	2 (0.1)
GVHD prophylaxis - no. (%)	
Ex-vivo T-cell depletion	66 (3)

Characteristic	
CD34 selection	195 (8.7)
Post-CY + other(s)	246 (11)
Post-CY alone	17 (0.8)
TAC + MMF ± other(s) (except post-CY)	272 (12.2)
TAC + MTX ± other(s) (except MMF, post-CY)	702 (31.4)
TAC + other(s) (except MMF, MTX, post-CY)	128 (5.7)
TAC alone	53 (2.4)
CSA + MMF ± other(s) (except post-CY)	416 (18.6)
CSA + MTX ± other(s) (except MMF, post-CY)	75 (3.4)
CSA + other(s) (except MMF, MTX, post-CY)	23 (1)
CSA alone	12 (0.5)
Other(s)	17 (0.8)
Missing	14 (0.6)
ATG/Campath - no. (%)	
ATG + CAMPATH	2 (0.1)
ATG alone	562 (25.1)
CAMPATH alone	90 (4)
No ATG or CAMPATH	1577 (70.5)
Missing	5 (0.2)
IVIG given* - no. (%)	
No	1133 (50.7)
Yes	1102 (49.3)
Missing	1 (0)
Year of transplant - no. (%)	
2008	155 (6.9)
2009	165 (7.4)
2010	143 (6.4)
2011	112 (5)
2012	112 (5)
2013	226 (10.1)
2014	305 (13.6)
2015	305 (13.6)
2016	279 (12.5)
2017	246 (11)
2018	188 (8.4)
Follow-up - median (min-max)	48.39 (4.61-127.37)

Footnote: Verification requires special retrieval to verify if occurred within 100 days and will be done after TCT.

Completeness of follow-up

Time (set date: 09/01/19)	**(N = 2236), %**
1-year	98
2-year	95
3-year	93
4-year	91

Selection Criteria (IN19-01) Nov 2019	**Removed**	**Remained**
First allo-HCT for AML/ALL/MDS between 2008 and 2018, 2<=age<=75 in US		20166
Excluded if no consent	515	19651
Excluded embargoed centers from research studies	709	18942
Excluded if no 100 day follow up form	721	18221
Exclude twin and multi-donor	Twin (n=**57**) Multi-donor (n=**62**)	18102
Only include patients who have lymphocyte subset analysis performed at day 100 and day 180	lymphocyte subset analysis performed, day 100(yes) & day 180(no) (n=1747) lymphocyte subset analysis performed, day 100(yes) & day 180(missing) (n=485) lymphocyte subset analysis performed, day 100(no) & day 180(yes) (n=1016) lymphocyte subset analysis performed, day 100(missing) & day 180(yes) (n=10) lymphocyte subset analysis performed, day 100(no) & day 180(no) (n=9591) lymphocyte subset analysis performed, day 100(no) & day 180(missing)(n=2992) lymphocyte subset analysis performed, day 100(missing) & day 180(no) (n=14) Missing (n= 11)	2236

CIBMTR-IN19-02

Impact of Antibiotic Prophylaxis in Patients Undergoing Allogeneic Hematopoietic Cell Transplantation in the Current Era

Draft Protocol

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1. **Hypothesis:**
   Pre-engraftment prophylactic antibiotic use is associated with decreased blood stream infections (BSI), but increased rates of acute graft versus host disease (GVHD), post-engraftment BSI, and non-relapse mortality (NRM) in allogeneic **hematopoietic stem cell transplant patients (HSCT).**

2. **Specific aims:**
   2.1 Compare incidence of BSI prior to engraftment and in the first 100 days in patients receiving and not receiving antibiotic prophylaxis
   2.2 Determine the incidence of acute GVHD in patients who received and did not receive antibiotic prophylaxis
   2.3 Compare overall survival (OS) and non-relapse mortality (NRM) between patients who received antibiotic prophylaxis vs those who did not
   2.4 Compare aforementioned outcomes between different antibiotic classes if sample size allows

3. **Scientific impact:**
   Antibiotic prophylaxis in patients undergoing allogenic HSCT has been the standard of practice for decades. However, there are some collateral consequences of this practice such as early microbiome disruption, acute GVHD, emergence of resistant bacterial infections and increased risk for *Clostridioides difficile* infection (CDI). This study will assess the efficacy of antibiotic prophylaxis in the modern era and results will have implications on current clinical practice.

4. Scientific justification:

Patients undergoing HSCT are at increased risk of infections, particularly BSI during the pre-engraftment period. [1] Current clinical practice guidelines recommend prophylactic antibiotics during neutropenia with fluoroquinolones (FQ) being the most commonly used drugs. [2] A number of studies and meta-analyses have shown the efficacy of this approach in reducing rates of neutropenic fever and BSI episodes with controversial benefit on overall mortality. [3]In a recent randomized open-label multicenter study, FQ prophylaxis did not reduce bacteremia incidence in children undergoing HSCT (11.0% vs 17.3%, P = 0.06) nor show a difference in bacterial infection related mortality in the primary analysis. However, the post-hoc analysis showed significant decrease in bacteremia rate per 1000 patient days in favor of FQ prophylaxis. 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 but the applicability to larger scale pediatric and adult HSCT patients remains unknown.

Emergence of antibiotic resistance is a concerning problem. In a large intercontinental study of gram-negative bacteremia in HSCT patients, half of isolates were resistant to FQ and non-carbapenem beta lactam which lead the authors to suggest revisiting FQ prophylaxis practices among HSCT patients. [5] Another detrimental effect of early antibiotic use is loss of gastrointestinal microbiome diversity and subsequent bacteremia from dominating colonizing gastrointestinal microrganisms.[6-8] Further, loss of microbiome diversity is associated with gastrointestinal graft versus host disease (GVHD)[9]. In other studies, early antibiotic use was an independent factor for GVHD-related NRM. [10]

In the modern era of multidrug-resistant bacteria and rapid microbiological molecular diagnostics, addressing these contemporary observations and examining the long-term effects of antibacterial prophylaxis in HSCT patients after decades of adopting prophylactic strategies require further data. Currently, there are no recent large-scale multi-center studies comparing clinical outcomes of HSCT patients who receive and do not receive pre-engraftment antibiotic prophylaxis.

In January 2017, the CIBMTR started capturing antibiotic prophylaxis data including start date and the type of prophylactic antibiotic used (questions #407-418, Form 2100 R5.0). In this study, we will compare the incidence of bloodstream infections, acute GVHD, NRM 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.

5. Patient eligibility population: Patients reported to the CIBMTR between January 2017 and June 2019 meeting the following:

<u>Inclusion Criteria</u>

- First allo transplant
- All ages
- All donor types
- Any disease
- Any stem cell source
- Any conditioning intensity

<u>Exclusion Criteria</u>

- Syngeneic or multiple donor (except cord) transplant
- Prior autologous transplant

- No consent
- No 2100 form available

Outcomes: Compared between those patients receiving and not receiving antibacterial prophylaxis

- Pre-engraftment BSI: Estimated as cumulative incidence with death as the competing risk
- Cumulative incidence of CDI by day 100: Estimated as cumulative incidence with death as the competing risk
- Cumulative incidence of MBI-LCBI in the first 100 days: Estimated as cumulative incidence with death as the competing risk
- Cumulative incidence on non-MBI-LCBI in the first 100 days: Estimated as cumulative incidence with death as the competing risk
- Neutrophil engraftment: Estimated as cumulative incidence with death as the competing risk
- Acute GVHD grade II – IV: Estimated as cumulative incidence with death as the competing risk
- Acute GVHD grade III – IV: Estimated as cumulative incidence with death as the competing risk
- Lower GI acute GVHD stage 3 – 4: Estimated as cumulative incidence with death as the competing risk
- Chronic GHVD: any severity. Estimated as cumulative incidence with death as the competing risk
- Non-relapse mortality (NRM): Defined as death without relapse/progression of hematological malignancy and estimated as cumulative incidence with relapse/progression as the competing risk. It will be assessed only for patients with malignant disease.
- Relapse: Estimated as cumulative incidence with death as the competing risk
- Overall survival (OS): time from HSCT to death from any cause. Patients are censored at time of last follow-up.
- Cause of death: Primary COD and infection as contributing COD

6. Variables to be described:

- Number of centers

<u>Patient related:</u>

- Recipient age
- Gender
- Race/Ethnicity
- Lansky/Karnofsky score at transplant
- HCT-CI

<u>Disease related:</u>

- Primary disease: malignant vs. non-malignant, specify disease type under each item
- Disease stage at the time of transplant (active, remission, unknown, NA if nonmalignant disease)

Transplant related:

- Stem cell source: cord, marrow, peripheral blood
- Donor/recipient HLA match
- Donor type: related vs. unrelated
- Conditioning regimen: Myeloablative vs. reduced intensity/non-ablative
- Total body irradiation: yes/no
- TBI dose
- GVHD prophylaxis: CNI +/- others vs. PTCY vs others
- *Ex vivo* T cell depletion: yes/no
- Use of ATG/alemtuzumab: yes/no
- Planned use of G-CSF/GM-CSF
- Year of transplant
- Duration of hospital days in the first 100 days

Infection related:

- Antibiotic received: FQ (levofloxacin, moxifloxacin, ciprofloxacin) vs non-FQ (specify name)
- Antibiotic prophylaxis start day relative to day 0
- Anti- pneumocystis (PJP) drug: Yes/No and agent
- Anti-pneumocystis prophylaxis start day relative to day 0
- Bacterial infections: Yes/No
- Bacterial infections: Anaerobes vs Enterococcus vs GNR-Enterobacteriaceae vs GNR-non-Enterocteriaceae vs Mycobacterium vs Staphylococcus vs Streptococcus vs Other
- Systemic inflammatory response syndrome (SIRS): Yes/No
- Septic shock: Yes/No
- Viral infections by day 100: Yes/No
- Viral infections by day 100: CMV vs non-CMV herpes viruses vs other
- Fungal infections by day 100: Yes/No
- Fungal infections by day100: Yeast vs Mold

7. Study design:

Patients will be categorized into two groups based on receipt of antibiotic prophylaxis (a) receiving antibiotic prophylaxis and (b) not receiving antibiotic prophylaxis. For patients receiving antibiotic prophylaxis, the type of prophylaxis will be used for subcategorization (FQ vs non-FQ) if sample size allows further analysis. We will do separate analysis for pediatric (<18 years) and adult patients (>18 years). We will use two-tailed tests at 0.01 significance to assess for any type of effect of antibiotic prophylaxis on clinical outcomes.

Descriptive patient-, disease-, transplant-, infection related variables will be compared using Chi-square test for categorical or Mann-Whitney U test for continuous variables. The Kaplan-Meier method will be used to estimate the probability of overall survival and the cumulative incidence of treatment related mortality at 100 days and one year. 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, CDI, all bacterial infections and BSI will be calculated according to the cumulative incidence. Cox proportional hazards will be performed to examine the impact

of the main effect variable on OS, NRM, any BSI, and acute GVHD. A center effect will be examined for all multivariable models.

8. 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. 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.
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. 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.
6. 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
7. 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.
8. 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.
9. 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.
10. Weber D, Jenq RR, Peled JU, et al. Microbiota Disruption Induced by Early Use of Broad-Spectrum Antibiotics Is an Independent Risk Factor of Outcome after Allogeneic Stem Cell Transplantation. *Biol Blood Marrow Transplant.* 2017;23(5):845-852.

Characteristic of patients who received first allogeneic transplants from January 2017 to June 2019 in US reported to the CIBMTR

Characteristic	No Antibacterial prophylaxis	With Antibacterial prophylaxis	Antibacterial prophylaxis N/A
No. of patients	856	3872	176
No. of centers	97	156	2
Recipient age - no. (%)			
Median (min-max)	46.7 (0.1-76.8)	57.3 (0.1-87.8)	61.1 (11.8-77.3)
0-9	174 (20.3)	319 (8.2)	0
10-19	125 (14.6)	236 (6.1)	6 (3.4)
20-29	48 (5.6)	290 (7.5)	10 (5.7)
30-39	43 (5)	265 (6.8)	15 (8.5)
40-49	66 (7.7)	392 (10.1)	25 (14.2)
50-59	120 (14)	666 (17.2)	28 (15.9)
60-69	222 (25.9)	1298 (33.5)	75 (42.6)
70+	58 (6.8)	406 (10.5)	17 (9.7)
Recipient Sex - no. (%)			
Male	500 (58)	2291 (59)	100 (57)
Female	356 (42)	1581 (41)	76 (43)
Recipient race - no. (%)			
Caucasian	635 (74)	2858 (74)	134 (76)
African-American	114 (13)	565 (15)	20 (11)
Asian	48 (6)	236 (6)	14 (8)
Pacific islander	1 (0)	16 (0)	0
Native American	4 (0)	38 (1)	3 (2)
Unknown	54 (6)	159 (4)	5 (3)
Recipient ethnicity - no. (%)			
Hispanic or Latino	108 (13)	437 (11)	15 (9)
Not Hispanic or Latino	692 (81)	3302 (85)	149 (85)
Missing	56 (7)	133 (3)	12 (7)
Karnofsky/Lansky Performance Score - no. (%)			
<90	332 (39)	1612 (42)	64 (36)
≥90	481 (56)	2170 (56)	97 (55)
Missing	43 (5)	90 (2)	15 (9)
HCT-CI - no. (%)			
0	267 (31)	921 (24)	37 (21)
1	143 (17)	580 (15)	37 (21)
2	113 (13)	535 (14)	26 (15)
3+	333 (39)	1834 (47)	76 (43)
TBD, review needed for history of malignancies	0	1 (0)	0
TBD, inconsistencies between parent and sub-questions	0	1 (0)	0

Characteristic	No Antibacterial prophylaxis	With Antibacterial prophylaxis	Antibacterial prophylaxis N/A
Disease - no. (%)			
Malignant disease			
AML	207 (24)	1008 (26)	41 (23)
ALL	118 (14)	465 (12)	12 (7)
Other leukemia	10 (1)	83 (2)	8 (5)
CML	13 (2)	54 (1)	2 (1)
MDS	262 (31)	1482 (38)	86 (49)
Other acute leukemia	7 (1)	26 (1)	0
NHL	34 (4)	149 (4)	19 (11)
HL	11 (1)	33 (1)	2 (1)
Multiple myeloma	0	11 (0)	2 (1)
Other Malignancies	0	2 (0)	0
Non-malignant disease			
Severe aplastic anemia	58 (7)	225 (6)	4 (2)
Inherited abnormality of erythrocyte differentiation of function	54 (6)	194 (5)	0
SCID & other immune system disorders	71 (8)	129 (3)	0
Inherited metabolism disorder	11 (1)	10 (0)	0
Histiocytic disorders	0	1 (0)	0
AML/ALL/OAL disease status - no. (%)			
CR1	217 (65)	989 (66)	28 (53)
CR2	64 (19)	305 (20)	4 (8)
CR3 +	10 (3)	37 (2)	0
PIF/Relapse	39 (12)	160 (11)	21 (40)
Missing	2 (1)	8 (1)	0
CLL/OL disease status - no. (%)			
CR	4 (40)	23 (28)	0
PR/Nodal PR	5 (50)	39 (47)	4 (50)
NR/SD	1 (10)	12 (14)	4 (50)
Progression	0	4 (5)	0
Missing	0	5 (6)	0
CML disease status - no. (%)			
Intermediate I	0	1 (2)	1 (50)
Advanced	5 (38)	14 (26)	1 (50)
Very advanced	2 (15)	4 (7)	0
Missing	6 (46)	35 (65)	0
MDS disease status - no. (%)			
Early	31 (12)	243 (16)	10 (12)
Advanced	111 (42)	642 (43)	18 (21)
Missing	120 (46)	597 (40)	58 (67)

Characteristic	No Antibacterial prophylaxis	With Antibacterial prophylaxis	Antibacterial prophylaxis N/A
NHL/HD disease status - no. (%)			
CR	19 (42)	86 (47)	9 (43)
Partial response	18 (40)	61 (34)	4 (19)
Resistant	8 (18)	29 (16)	8 (38)
Unknown	0	2 (1)	0
Missing	0	4 (2)	0
Plasma cell disorder disease status - no. (%)			
sCR/CR		4 (36)	0
near CR/Very good partial response		5 (45)	1 (50)
Partial response		2 (18)	1 (50)
Graft type - no. (%)			
Bone Marrow	287 (34)	953 (25)	44 (25)
Peripheral Blood	464 (54)	2511 (65)	119 (68)
Cord Blood	105 (12)	408 (11)	13 (7)
Donor type - no. (%)			
HLA-identical sibling	170 (20)	740 (19)	35 (20)
Other related: Matched	12 (1)	49 (1)	2 (1)
Other related: Mismatched 1 antigen/allele	11 (1)	25 (1)	0
Other related: Mismatched ≥ 2 Ag/allele	143 (17)	710 (18)	29 (16)
Other related: matching missing	42 (5)	208 (5)	3 (2)
Well-matched unrelated (8/8)	305 (36)	1402 (36)	86 (49)
Partially-matched unrelated (7/8)	48 (6)	220 (6)	7 (4)
Mis-matched unrelated (≤6/8)	7 (1)	35 (1)	0
Unrelated (matching TBD)	13 (2)	75 (2)	1 (1)
Cord blood	105 (12)	408 (11)	13 (7)
Conditioning regimen intensity - no. (%)			
MAC	462 (54)	1659 (43)	100 (57)
RIC	225 (26)	1365 (35)	57 (32)
NMA	138 (16)	766 (20)	6 (3)
TBD	12 (1)	49 (1)	13 (7)
Missing	19 (2)	33 (1)	0
TBI usage (internal, for review only) - no. (%)			
TBI (single dose > 500 cGy or fractionated > 800 cGy)	143 (17)	446 (12)	4 (2)
TBI (single dose ≤ 500 cGy or fractionated ≤ 800 cGy), other agents delivered at MA doses	10 (1)	114 (3)	6 (3)
TBI (single dose > 200 and ≤ 500 cGy, or fractionated > 200 and ≤ 800 cGy)	28 (3)	247 (6)	0
TBI = 200 cGy	109 (13)	646 (17)	4 (2)
TBI, dose unknown	0	1 (0)	0
Non-TBI regimen	547 (64)	2385 (62)	162 (92)

Characteristic	No Antibacterial prophylaxis	With Antibacterial prophylaxis	Antibacterial prophylaxis N/A
Missing	19 (2)	33 (1)	0
GVHD prophylaxis - no. (%)			
No GVHD prophylaxis	15 (2)	50 (1)	0
Ex-vivo T-cell depletion	14 (2)	63 (2)	0
CD34 selection	51 (6)	121 (3)	1 (1)
Post-CY + other(s)	223 (26)	1105 (29)	108 (61)
Post-CY alone	12 (1)	43 (1)	0
TAC + MMF ± other(s) (except post-CY)	74 (9)	527 (14)	16 (9)
TAC + MTX ± other(s) (except MMF, post-CY)	267 (31)	1218 (31)	49 (28)
TAC + other(s) (except MMF, MTX, post-CY)	39 (5)	171 (4)	0
TAC alone	9 (1)	61 (2)	2 (1)
CSA + MMF ± other(s) (except post-CY)	81 (9)	302 (8)	0
CSA + MTX ± other(s) (except MMF, post-CY)	49 (6)	132 (3)	0
CSA + other(s) (except MMF, MTX, post-CY)	7 (1)	10 (0)	0
CSA alone	6 (1)	12 (0)	0
Other(s)	9 (1)	57 (1)	0
ATG/Campath - no. (%)			
ATG + CAMPATH	0	3 (0)	0
ATG alone	220 (26)	926 (24)	45 (26)
CAMPATH alone	47 (5)	191 (5)	1 (1)
No ATG or CAMPATH	573 (67)	2728 (70)	130 (74)
Missing	16 (2)	24 (1)	0
Amoxicillin clavulanate oral (Augmentin) - no. (%)			
No	856	3771 (97)	0
Yes	0	93 (2)	0
Missing	0	8 (0)	176
Cefdinir oral (Omnicef) - no. (%)			
No	856	3838 (99)	0
Yes	0	27 (1)	0
Missing	0	7 (0)	176
Cefpodoxime oral (Vantin) - no. (%)			
No	856	3847 (99)	0
Yes	0	18 (0)	0
Missing	0	7 (0)	176
Ciprofloxacin IV or oral (Cipro) - no. (%)			
No	856	2933 (76)	0
Yes	0	932 (24)	0
Missing	0	7 (0)	176
Ertapenem IV - no. (%)			
No	856	3857 (100)	0

Characteristic	No Antibacterial prophylaxis	With Antibacterial prophylaxis	Antibacterial prophylaxis N/A
Yes	0	7 (0)	0
Missing	0	8 (0)	176
Levofloxacin IV or oral (Levaquin) - no. (%)			
No	856	1770 (46)	0
Yes	0	2095 (54)	0
Missing	0	7 (0)	176
Moxifloxacin IV or oral (Avelox) - no. (%)			
No	856	3777 (98)	0
Yes	0	88 (2)	0
Missing	0	7 (0)	176
Vancomycin IV - no. (%)			
No	856	3556 (92)	0
Yes	0	309 (8)	0
Missing	0	7 (0)	176
Other antibacterial drug - no. (%)			
No	856	3151 (81)	0
Yes	0	715 (18)	0
Missing	0	6 (0)	176
Year of transplant - no. (%)			
2017	418 (49)	1822 (47)	87 (49)
2018	355 (41)	1669 (43)	80 (45)
2019	83 (10)	381 (10)	9 (5)
Duration of hospital days in the first 100 days - median (min-max)	28 (2-130)	25 (0-119)	27 (10-114)
Follow-up - median (min-max)	12.04 (0.92-30.86)	12.14 (1.25-31.71)	12.3 (2.8-25.07)

Completeness of follow-up

Time (set date: 09/01/19)	No Antibacterial prophylaxis (N = 856), %	With Antibacterial prophylaxis (N = 3872), %	Antibacterial prophylaxis N/A (N = 176), %	Overall, %
1-year	87	89	89	88

Selection Criteria (IN19-02) Nov 2019	Removed	Remained
First allo-HCT between 2017 and 2019 in US		5836
Excluded if no consent	40	5796

Excluded embargoed centers from research studies	175	5621
Excluded if no 100 day follow up form	626	4995
Exclude twin and multi-donor	Twin (n=30) Multi-donor (n=61)	4904

Proposal: 1911-49

Title:
Risk for early post-transplant bacterial, viral and fungal infection in Hodgkin's lymphoma patients that receive pre-transplant therapy with checkpoint inhibitors

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Hypothesis:
Patients with Hodgkin's lymphoma (HL) that received checkpoint inhibitors (CPI) prior to hematopoietic cell transplant (HCT) will have a higher risk of bacterial, fungal and viral infection in the first 100 days post-transplant (allogeneic vs. autologous) than those that did not receive checkpoint inhibitors prior to HCT.

Specific aims:
Primary objective:
- To compare the occurrence of bacterial, viral and fungal infection in the first 100 days post-HCT between patients with HL that received CPI prior to (allogeneic vs. autologous) HCT vs. the ones that did not receive them.

Secondary objectives:
- To describe the incidence of bacterial, viral and fungal infections in the first 100 days post HCT in HL patients that do or do not receive CPI prior to transplant (allo vs. auto)
- To identify other risk factors besides prior CPI use for development of infection in patients that undergo HCT.
- To compare outcomes (disease-free survival and mortality) between those who did and did not receive CPI in each group

Scientific justification and impact:
Cancer immunotherapy using immune checkpoint inhibitors (CPI) has created a paradigm shift in oncology allowing treatment to focus on immunomodulation of the immune system rather than treatment targeted at the cancer cells. Within the tumor milieu, program cell death protein (PD-1) and its ligand, PDL-1, and cytotoxic T-lymphocyte associated antigen 4 (CTLA-4) are overexpressed. These immune checkpoint inhibitors are antagonistic antibodies that block these specific checkpoint molecules to induce reactivation of cytotoxic T-lymphocytes, that were previously quiescent due to T-cell exhaustion, and allow for tumor destruction. The use of these inhibitors has helped increased survival in patients with many malignancies including melanoma, non-small cell lung cancer, renal and bladder cancer, and Hodgkin's lymphoma where many conventional therapies have failed (1).
The imbalance created in the immune system by checkpoint inhibitors comes with consequence that include immune-related adverse events (IRAEs). Many of these events can be counteracted by decreasing lymphocyte activation with steroids or other immunomodulatory agents. These IRAEs can manifest in any organ of the body to create a wide host of clinical features similar to that seen in autoimmune diseases. These manifestations are typically treated with high dose steroids and if

refractory, other immunomodulating agents including TNF-alpha antagonists, azathioprine and mycophenolate mofetil (1, 2). Not only can IRAEs manifest similarly to infections and infection must be ruled out prior to starting immunosuppressant therapy, but the immunosuppressant therapy and concomitant lymphopenia can cause opportunistic infections (6). In case reports, these infections including CMV-induced hepatitis, Fournier's gangrene, pulmonary aspergillosis, and Pneumocystis pneumonia (3-6). A larger study using checkpoint inhibitors for melanoma showed a 13.5% risk of infection when using corticosteroids or infliximab versus 2% risk of infection of those who did not undergo management of IRAEs (7).

While the risk of infection associated with IRAEs is more widely reported, there have been case reports to suggest that immune checkpoint inhibitors independently increase the risk of infection without associated IRAEs. Two cases of development of acute pulmonary tuberculosis have been reported with checkpoint inhibitor therapy alone (8, 9). The mechanism for this increased risk is poorly understood. However, there are two suggested mechanisms. The first hypothesis being an immune reconstitution-like syndrome similar to that seen in HIV where rapid reestablishment of immune function is noted at the initiation of antiretroviral therapy and the second hypothesis is that the risk is secondary to drug-related lymphopenia (6, 10). A recent study performed in patients with non-small cell lung cancer receiving nivolumab showed an increased rate of infection, with the most prominent being bacterial infections, independent of the use of corticosteroids or immunomodulatory agents and may need to be considered as an IRAE in the future with more clinical evidence (11).

The increased risk of infection related to checkpoint inhibitors seems to be multifactorial and related to immunosuppressive therapies used for the treatment of IRAEs, immune reconstitution-like syndrome, and drug-related lymphopenia described above. Studies suggest that the use of these CPIs can have a prolonged effect. These therapies are currently being used as a treatment bridge to HCT, specifically for Hodgkin's lymphoma. However, to date, no study has been performed studying the effect that multiple checkpoint inhibitors have on the risk of infectious complications specifically in patients with Hodgkin's lymphoma who received CPI prior to HCT. Our proposal aims at looking into the potential relationship between the use of CPI prior to HCT and infection.

Patient eligibility population:

All patients (of all ages) that received HCT (both allogeneic and autologous) for the treatment of HL and were reported to CIBMTR from 2005 to present. These patients will be divided in 4 groups: patients that received checkpoint inhibitors (CPI group) prior to transplant (allo and auto cohorts) and patients that did not receive checkpoint inhibitors (control groups) prior to transplant.

Data requirements:

Patient-related:

- Age at transplant
- Gender
- Performance Status
- CMV status
- ABO
- Disease-stage at transplant: Early vs. Intermediate vs Advanced.
- Pre-transplant CMV status: positive vs. negative.
- lymphocyte count (absolute) prior to the start of the preparative regimen

Disease-related:

- Lymphoma histology at diagnosis
- Immunohistochemistry and cytogenetics of the lymphoma at diagnosis

- WBC, absolute lymphocyte count, lymphocytes percentage at diagnosis

CPI therapy-related (form 2018 R5.0):
- Date therapy started
- Date therapy stopped
- Number of cycles
- Drug given: Nivolumab, Pembrolizumab, Pidilizumab, Ipilimumab, Atezolizumab, Durvalumab or other.

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 vs haplo/mismatched >8/10
- 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, hydroxychloroquine, infliximab, methotrexate, mycophenolate, pentostatin, UV therapy, rituximab, sirolimus, tyrosine kinase inhibitors, JAK 2 inhibitors, other agents.
- 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

Infection-related:
- Did the patient develop infection?: yes vs. no
    - Date of infection diagnosis
    - Organism
    - Site of infection

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
- Infection free survival: Time to infection

Study design:
Our study will be directed to all patients with HL that undergo HCT. We will divide them in 4 groups by type of transplant (allo or auto) and their use of checkpoint inhibitors (Nivolumab, Pembrolizumab, Pidilizumab, Ipilimumab, Atezolizumab, durvalumab, etc) prior to transplantation: patients with prior CPI use (CPI group) and patients without CPI use (control group). The incidence of bacterial, fungal and viral infection in the post-transplant period will be described overall and compared between those with and without prior CPI use. We will describe patient characteristics and transplant-related outcomes for patients in both prior CPI use groups. To compare categorical variables chi-square tests (or Fisher's exact test) will be used and to compare continuous variables independent t-tests (or Wilcoxon rank-sum tests) will be used. We will compare the occurrence of infection at 100 days between those with and without prior CPI using logistic regression to adjust for type of transplant and other covariates and to evaluate other risk factors. Kaplan-Meier curves and the log-rank test will be used to compare time to infection (and other time to events such as time to death) between the CPI groups and controls. Cox proportional hazards models will be constructed to compare time to infection between those with and without prior CPI use while adjusting for other variables. Other risk factors can also be evaluated in this model. Transplant-related outcomes will be compared between those with and without prior CPI use using statistical techniques described above.

Conflicts of interest:
None

References:
1. Michot JM, Bigenwald C, Champiat S, Collins M, Carbonnel F, Postel-Vinay S, et al. Immune-related adverse events with immune checkpoint blockade: a comprehensive review. Eur J Cancer. 2016;54:139-48.
2. Postow MA. Managing immune checkpoint-blocking antibody side effects. Am Soc Clin Oncol Educ Book. 2015:76-83.
3. Kyi C, Hellmann MD, Wolchok JD, Chapman PB, Postow MA. Opportunistic infections in patients treated with immunotherapy for cancer. J Immunother Cancer. 2014;2:19.
4. Uslu U, Agaimy A, Hundorfean G, Harrer T, Schuler G, Heinzerling L. Autoimmune Colitis and Subsequent CMV-induced Hepatitis After Treatment With Ipilimumab. J Immunother. 2015;38(5):212-5.
5. Arriola E, Wheater M, Krishnan R, Smart J, Foria V, Ottensmeier C. Immunosuppression for ipilimumab-related toxicity can cause pneumocystis pneumonia but spare antitumor immune control. Oncoimmunology. 2015;4(10):e1040218.
6. Reungwetwattana T, Adjei AA. Anti-PD-1 Antibody Treatment and the Development of Acute Pulmonary Tuberculosis. J Thorac Oncol. 2016;11(12):2048-50.
7. Del Castillo M, Romero FA, Arguello E, Kyi C, Postow MA, Redelman-Sidi G. The Spectrum of Serious Infections Among Patients Receiving Immune Checkpoint Blockade for the Treatment of Melanoma. Clin Infect Dis. 2016;63(11):1490-3.
8. Lee JJ, Chan A, Tang T. Tuberculosis reactivation in a patient receiving anti-programmed death-1 (PD-1) inhibitor for relapsed Hodgkin's lymphoma. Acta Oncol. 2016;55(4):519-20.
9. Fujita K, Terashima T, Mio T. Anti-PD1 Antibody Treatment and the Development of Acute Pulmonary Tuberculosis. J Thorac Oncol. 2016;11(12):2238-40.
10. Chu YC, Fang KC, Chen HC, Yeh YC, Tseng CE, Chou TY, et al. Pericardial Tamponade Caused by a Hypersensitivity Response to Tuberculosis Reactivation after Anti-PD-1 Treatment in a Patient with Advanced Pulmonary Adenocarcinoma. J Thorac Oncol. 2017;12(8):e111-e4.

11. Fujita K, Kim YH, Kanai O, Yoshida H, Mio T, Hirai T. Emerging concerns of infectious diseases in lung cancer patients receiving immune checkpoint inhibitor therapy. Respir Med. 2019;146:66-70.

Table 1. Characteristics of patients who underwent first auto transplants for Hodgkin's lymphoma in US from 2013 to 2019 reported to the CIBMTR

Characteristic	**No CPI**	**CPI received**
No. of patients	495	16
No. of centers	110	13
Age of recipient - no. (%)		
Median (min-max)	33.1 (9-74.2)	29 (18.5-64)
0 - 9	2 (0.4)	0
10 - 19	57 (11.5)	1 (6.3)
20 - 29	143 (28.9)	8 (50)
30 - 39	103 (20.8)	3 (18.8)
40 - 49	87 (17.6)	3 (18.8)
50 - 59	50 (10.1)	0
60 - 69	46 (9.3)	1 (6.3)
70+	7 (1.4)	0
Disease status - no. (%)		
CR	284 (57.4)	9 (56.3)
PR	169 (34.1)	6 (37.5)
Resistant	37 (7.5)	1 (6.3)
Untreated	2 (0.4)	0
Unknown	3 (0.6)	0
Conditioning regimen - no. (%)		
BEAM	386 (78)	14 (87.5)
BEAM like	22 (4.4)	0
CBV	33 (6.7)	1 (6.3)
Others	53 (10.7)	1 (6.3)
Missing	1 (0.2)	0
Year of transplant - no. (%)		
2013	74 (14.9)	0
2014	73 (14.7)	0
2015	90 (18.2)	1 (6.3)
2016	85 (17.2)	2 (12.5)
2017	66 (13.3)	7 (43.8)
2018	79 (16)	6 (37.5)
2019	28 (5.7)	0
Infections by day 100		
Bacterial - no. (%)		
No	385 (77.8)	11 (68.8)
Yes	110 (22.2)	5 (31.3)

Characteristic	No CPI	CPI received
Viral - no. (%)		
No	453 (91.5)	14 (87.5)
Yes	42 (8.5)	2 (12.5)
Fungal - no. (%)		
No	486 (98.2)	16
Yes	9 (1.8)	0
Follow-up - median (min-max)	26.74 (0.36-76.97)	12.24 (3.26-52.3)

Table 2. Characteristics of patients who underwent first allogeneic transplants for Hodgkin's lymphoma in US from 2013 to 2019 reported to the CIBMTR

Characteristic	**No CPI**	**CPI received**
No. of patients	67	35
No. of centers	39	25
Age of recipient - no. (%)		
Median (min-max)	34.6 (5.8-70.2)	29.9 (15.7-72.1)
0 - 9	1 (1.5)	0
10 - 19	13 (19.4)	5 (14.3)
20 - 29	17 (25.4)	13 (37.1)
30 - 39	12 (17.9)	6 (17.1)
40 - 49	11 (16.4)	3 (8.6)
50 - 59	10 (14.9)	5 (14.3)
60 - 69	2 (3)	2 (5.7)
70+	1 (1.5)	1 (2.9)
Disease status - no. (%)		
CR	22 (32.8)	17 (48.6)
PR	29 (43.3)	11 (31.4)
Resistant	14 (20.9)	7 (20)
Unknown	2 (3)	0
Donor type - no. (%)		
HLA-identical sibling	10 (14.9)	9 (25.7)
Mismatched related		
≥2 Ag/allele	16 (23.9)	8 (22.9)
Other related (matching TBD)	1 (1.5)	2 (5.7)
Well-matched unrelated (8/8)	21 (31.3)	10 (28.6)
Partially-matched unrelated (7/8)	5 (7.5)	2 (5.7)
Mis-matched unrelated (≤6/8)	0	2 (5.7)
Unrelated (matching TBD)	2 (3)	1 (2.9)
Cord blood	12 (17.9)	1 (2.9)
Stem cell source - no. (%)		
Bone Marrow	20 (29.9)	10 (28.6)
Peripheral Blood	35 (52.2)	24 (68.6)
Cord Blood	12 (17.9)	1 (2.9)
Conditioning Intensity - no. (%)		
MAC	18 (26.9)	11 (31.4)
RIC/NMA	49 (73.1)	24 (68.6)
GVHD prophylaxis - no. (%)		
Ex-vivo T-cell depletion	3 (4.5)	0

CD34 selection	5 (7.5)	0
Post-CY + other(s)	15 (22.4)	18 (51.4)
CNI (TAC/CSA) + MMF +/- Other (except post-CY)	11 (16.4)	5 (14.3)
CNI (TAC/CSA) + MTX +/- Other (except MMF, post-CY)	19 (28.4)	11 (31.4)
CNI (TAC/CSA) +/- Other (except MMF, MTX, post-CY)	9 (13.4)	0
TAC alone	3 (4.5)	0
Others	1 (1.5)	0
Missing	1 (1.5)	1 (2.9)
Year of transplant - no. (%)		
2013	14 (20.9)	0
2014	16 (23.9)	0
2015	12 (17.9)	1 (2.9)
2016	6 (9)	3 (8.6)
2017	8 (11.9)	11 (31.4)
2018	7 (10.4)	17 (48.6)
2019	4 (6)	3 (8.6)
Infections by day 100		
Bacterial - no. (%)		
No	49 (73.1)	23 (65.7)
Yes	18 (26.9)	12 (34.3)
Viral - no. (%)		
No	42 (62.7)	22 (62.9)
Yes	25 (37.3)	13 (37.1)
Fungal - no. (%)		
No	64 (95.5)	35
Yes	3 (4.5)	0
Follow-up - median (min-max)	43.42 (3.26-69.24)	12.2 (2.7-36.74)

Proposal: 1911-90

Title:
Changing Epidemiology and Outcomes of Invasive Candida (IC) Infections in the Current Era of Stem Cell Transplantation.

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Research hypothesis:
- Incidence of Non-albicans candida and other breakthrough yeast infections has been increasing with fluconazole prophylaxis
- Non-albicans candida and other breakthrough yeast infections have a higher mortality compared to C. albicans infections.
- Early invasive Candida (IC) (before neutrophil engraftment) has a higher mortality compared to late IC (after neutrophil engraftment), and has a different set of risk factors associated with disease.

Specific aims:
- Characterize the epidemiology of breakthrough yeast infections in the modern era of antifungal prophylaxis, including Candida spp and other less common yeasts (example cryptosporidium, trichosporon, etc) and timing after transplant (early, before neutrophil engraftment, and late onset, after neutrophil engraftment).
- Identification of risk factors for breakthrough invasive yeast infections in the modern era of transplantation; assessment of expanded SCT platforms and donor sources.
- Mortality impact and incidence of Candida albicans versus Candida non-albicans spp.

Scientific impact:
There is limited data on breakthrough invasive *Candida* (IC) infections during the current era of hematopoietic stem cell transplantation (HCT) where antifungal prophylaxis with expanded fungal coverage is routinely used. With the global variation of Candida species distribution (1,2) and the ongoing concerns of the selection pressures of widely used antifungal prophylaxis for resistant candida isolates in breakthrough infections, it is essential to monitor epidemiologic trends and identify new risk factors for IC. This study aims to further characterize two aspects of IC. First, identify potential new risk factors for IC with expanded platforms of HCT including haploidentical transplant and increasingly complex patient populations receiving transplant. Second, reassess the changing epidemiology of *Candida* and non-*Candida* yeast species causing invasive disease with widespread use of newer generation azoles with expanded antifungal spectrum. These data will help the optimize early treatment interventions and preventative strategies to improve outcomes after HCT.

Scientific justification:
Invasive Candidiasis (IC), defined as Candida isolated from a normally sterile site, causes significant morbidity after HCT. Prior to the use of antifungal prophylaxis, the incidence of disseminated candidemia was approximately 11% after SCT, with mortality ranging from 39-73% (3,4). Risk factors for IC in those with hematologic malignancies include prolonged neutropenia (5,6,7), specifically neutropenia > 15 days (3), use of antibiotics (3,4), *Candida* colonization (5,8,9,10) and mucosal damage from cytotoxic chemotherapy (5).

Prevention of IC using universal fluconazole prophylaxis became standard of care when pivotal studies from the 1990s demonstrated reduced incidence of superficial and systemic invasive Candidiasis (11,12) with significantly improved survival after SCT (12). Data from the early 2000's showed the benefit of prophylaxis using azoles with expanded mold coverage (posaconazole) in preventing invasive aspergillosis in certain populations; ie MDS/ AML (13) and those with acute graft versus host disease after HCT (14). Currently, most SCT programs use a risk stratified approach for antifungal prophylaxis whereby subjects at high risk for aspergillosis or mucormycosis are receiving expanded antifungal prophylaxis (voriconazole or posaconazole) with fluconazole being used in subjects at lower risk of mold infections. While azoles are the most commonly used agents, echinocandins are also routinely used in clinical practice.

The epidemiology of IC have changed over time, and the impact of antifungal prophylaxis in transplant recipients is likely selecting for drug resistant fungal pathogens. Several registry studies of the general population demonstrated an increase in non-albicans *Candida*. Neutropenia, hematologic malignancy, stem cell transplantation, and use of prior antifungals were associated with higher incidence of *C. krusei* and *C. guillermondii* (17). In hematologic patients, data demonstrates an increase in *C. glabrata* (7,15), *C. krusei* (7,16,17), and *C. tropicalis* (17). These non-albicans *Candida* isolates have a higher propensity to be intrinsically resistant or less susceptible to antifungals (1) with increasing resistance noted over time (19). Additionally, there is increasing incidence of emerging candida spp such as *C. dubulinesis*, *C. kefyr* (17), and now worldwide concern for multidrug resistant *C. aureus* (18, 1*)*.

There is limited large scale systematic data on breakthrough *Candida* and yeast infections in SCT recipients. Recently Kuster et al reported data from the Swiss Transplant Cohort Study which identified a cumulative incidence of IC of 2.3% (n=10) among 479 HCT recipients over a four-year period. The incidence of breakthrough IC was 0.8%, and mortality of IC of 20% at 12 weeks (19). Cesaro et al. recently reported data from ESBMT on 28,500 subjects with acute leukemia receiving HCT, with a 1.2% incidence of candidemia by day 100 and significantly higher 100-day non-relapse mortality and lower 100-day overall survival. The case fatality rate was 22% in those with candidemia (20). Unfortunately, they were not able to report on the response rate to therapy or the epidemiology of the *Candida* species. With regional variation of *Candida* isolates, it is essential to continually monitor the regional epidemiologic trends and impact of breakthrough *Candida* infections, especially in the transplant population.

Patient eligibility population:

The study population will include all patients receiving first or second allogeneic HCT, from all donor types, for all diseases, between January 2005 and December 2019.

Data Requirements:

Variables to be analyzed:

Patient related:

Age, gender, performance status: ≥ 90% vs <90%

Disease related:

ASBMT RFI classification: low vs intermediate vs high, myeloid vs.
lymphoid, malignant vs. benign,time from diagnosis to transplant, disease status at HCT (CR1 vs.CR2 vs.>CR2 or active disease).

Transplant related:

Conditioning regimen: myeloablative vs reduced intensity/non-myeloablative, donor age (for unrelated recipients): ≤10y vs. 11-20y vs. 21-30y vs. 31-40y vs. 41-50y vs. >50y, donor-recipient sex: M-M vs. M-F vs. F-M vs. F-F, donor-recipient CMV serostatus: -/- vs +/- vs -/+ vs +/+, donor-recipient HLA-match: Related: Matched versus mismatched vs. haploidentical. Unrelated: Well-matched vs. mismatched. GVHD

prophylaxis: calcineurin inhibitor ± other vs. T-cell depletion vs. post cy vs. others. Source of stem cells: BM vs. PBSC vs. UCB Planned therapy with Growth factors (G-CSF or GM-CSF) post-transplant: yes vs. no (defined as day-3 to day+7). Year of transplant: 2005-2009 vs vs. 2010-2014 vs. 2015- 2019

Yeast infections related:
Cumulative incidence of yeast infection at day +360. Death and relapse are a competing risk, type of yeast, positive organ, blood, time from transplant to infection, antifungal prophylaxis.

Post-transplant time-dependent event variables:
Median time to neutrophil engraftment, median onset of grade II – IV acute GVHD, median onset of chronic GVHD.

Outcomes:
Overall survival:
Time to death from any cause. Patients are censored at time of last follow-up. There are no competing risks. Event will be summarized by a survival curve.

Transplant-related mortality:
Death without evidence of relapse or progression of underlying malignancy. This will be estimated using the cumulative incidence function with relapse/progression as the competing risk.

Causes of death:
In the event of relapse of disease for transplant, relapse is considered the primary cause of death.

Sample requirements:
none

Study design: retrospective descriptive case cohort study
Patient-, disease-, and transplant –related factors will be compared between groups using the Chi-square test for categorical variables and the Wilcoxon two-sample test for continuous variables. For time dependent variables (neutrophil engraftment and acute GVHD), the data are descriptive only as these events occur after transplant but may occur prior to day +42. The probabilities of 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.
A cox model for the entire population will be fit to assess the impact of yeast infection (on the outcomes of overall survival as a time dependent co-variate main effect variable. The proportional hazards assumption will be checked. If violated, it will be included as time-dependent covariate. An interaction between the main effect and significant covariates will be examined. Other infections, neutrophil engraftment, and acute GVHD grade II-IV will be considered as time-dependent covariates.

Data source: CIBMTR Research Database.
Data collection and forms:

Recipient baseline data form:
HCT type, product type, CMV R serostatus, age, gender, performance status, history of clinically significant fungal infection, more than 1, organism and site, active within two weeks.

Fungal infection pre-infusion data:

organism, date of infection, radiographic findings with specific sites, pathology and site, culture and source, KOH/Calcofluor/Giemsa stain, galactomannan assay and sample source, beta D glucan and sample source, PCR assay and sample source, antifungal therapy 7 days prior to infection and drug, date therapy started, status of infection.

Post HCT data form:
survival, neutrophil recovery and date, engraftment syndrome and date, aGHVD date and therapy, cGHVD date and therapy, T cell depletion. Infection prophylaxis antifungal drug and start date, mucositis requiring therapy, OMS grade, new malignancy diagnosis and site.

Fungal infection post-infusion data:
Organism, date of diagnosis, radiographic findings and image, pathology and source, culture and source, KOH/ Calcofluor/Giemsa stain and source, galactomannan assay and site, beta D glucan and site, PCR assay and site. WBC at time of infection, Neutrophils at time of infection, treatment of infection antifungal drug, date therapy started, duration of therapy administration still given at 30 days, status of infection.

Conflicts of interest:
none

References:
1. Schwartz, I.S. The Emerging Threat of Antifungal Resistance in Transplant Infectious Diseases. Curr infec dis reports. 2018.
2. Pfaller MA. Geographic variations in species distribution and echinocandin and azole antifungal resistance rates among Candida bloodstream infection isolates. J Clin Microbiol. 2011;49:396-9.
3. Meyers JD. Fungal infections in bone marrow transplant patients. Seminars in oncology. 1990; 17 (3 Suppl 6): 10-3.
4. Goodrich JM Clinical feature and analysis of risk factors for invasive candida infection after marrow transplantation. J Infect Dis. 1991; 164 (4): 731-40.
5. Bow EJ, Invasive fungal disease in adults undergoing remission-inductions therapy for acute myeloid leukemia: the pathogenic role of the antileukemic regimen. Clin Infect Dis. 1995; 21 (2): 361-9.
6. Lagunes L. Invasive candidiasis: from mycobiome to infection, therapy and prevention. Eur J Clin Microbiol Infect Dis. 2016;35(8):1221-6.
7. Hachem R. The changing epidemiology of invasive candidiasis: Candida glabrata and Candida krusei as the leading causes of candidemia in hematologic malignancy. Cancer 2008; 112(11): 2493-9.
8. Rossetti F. Fungal liver infection in marrow transplant recipients: prevalence at autopsy, predisposing factors and clinical features. Clin Infect Dis 1995; 20 (4): 801-11.
9. Schwartz RS. Multivariate analysis of factors associated with invasive fungal disease during remission induction therapy for acute myelogenous leukemia. Cancer. 1984;53(3):411-9.
10. Guiot HF. Risk factors for fungal infection in patients with malignant hematologic disorders: implications for empirical therapy and prophylaxis. Clin Infect Dis. 1994;18(4):525-32.
11. Goodman JL. A controlled trial of fluconazole to prevent fungal infections in patients undergoing bone marrow transplantation. NEJM. 1992. 326(13):845-51.
12. Slavin MA. Efficacy and safety of fluconazole prophylaxis for fungal infections after marrow transplantation--a prospective, randomized, double-blind study. J Infect Dis. 1995;171(6):1545-52
13. Cornely OA. Posaconazole vs. fluconazole or itraconazole prophylaxis in patients with neutropenia. NEJM 356(4):348-59
14. Ullmann AJ. Posaconazole or fluconazole for prophylaxis in severe graft-versus-host disease. NEJM. 356(4):335-47.

15. Pfaller MA. Results from the ARTEMIS DISK Global Antifungal Surveillance study, 1997 to 2005: an 8.5-year analysis of susceptibilities of Candida species and other yeast species to fluconazole and voriconazole determined by CLSI standardized disk diffusion testing. Journal of clinical microbiology. 2007;45(6):1735-45.
16. Pfaller MA. Results from the ARTEMIS DISK Global Antifungal Surveillance Study, 1997 to 2007: a 10.5-year analysis of susceptibilities of Candida Species to fluconazole and voriconazole as determined by CLSI standardized disk diffusion. Journal of clinical microbiology. 2010;48(4):1366-77.
17. Pfaller MA. Epidemiology and outcomes of invasive candidiasis due to non-albicans species of Candida in 2,496 patients: data from the Prospective Antifungal Therapy (PATH) registry 2004-2008. PloS one. 2014;9(7):e101510
18. Lockhart, SR. Emerging and reemerging fungal infections. Semin Diag path. 2019.
19. Kuster, S. Incidence and outcome of invasive fungal diseases after allogeneic hematopoietic stem cell transplantation: A Swiss transplant cohort study. TID. 2018.
20. Cesaro S. Incidence, Risk Factors, and Long-term Outcomes of Acute Leukemia Pateints with Early Candidemia After Allogeneic Stem Cell Transplantation. CID. 2019;67(4):564-72

Characteristics of patients who underwent first allogeneic transplants in US from 2007 to 2019 reported to the CIBMTR

Characteristic	
No. of patients	5148
No. of centers	160
Age of recipient - no. (%)	
Median (min-max)	56.3 (0.1-87.8)
0 - 9	515 (10)
10 - 19	384 (7.5)
20 - 29	363 (7.1)
30 - 39	333 (6.5)
40 - 49	509 (9.9)
50 - 59	860 (16.7)
60 - 69	1679 (32.6)
70+	505 (9.8)
Donor type - no. (%)	
HLA-identical sibling	984 (19.1)
Mismatched related	
1 Ag/allele	39 (0.8)
≥2 Ag/allele	909 (17.7)
Other related(matching TBD)	343 (6.7)
Well-matched unrelated (8/8)	1877 (36.5)
Partially-matched unrelated (7/8)	288 (5.6)
Mis-matched unrelated (≤6/8)	45 (0.9)
Unrelated (matching TBD)	110 (2.1)
Cord blood	553 (10.7)
Stem cell source - no. (%)	
Bone Marrow	1346 (26.1)
Peripheral Blood	3249 (63.1)
Cord Blood	553 (10.7)
Conditioning intensity - no. (%)	
MAC	2382 (46.3)
RIC/NMA	2765 (53.7)
Missing	1 (0)
GVHD prophylaxis - no. (%)	
Ex-vivo T-cell depletion	84 (1.6)
CD34 selection	186 (3.6)
Post-CY + other(s)	1502 (29.2)
Post-CY alone	57 (1.1)
CNI (TAC/CSA) + MMF +/- Other(except post-CY)	1051 (20.4)
CNI (TAC/CSA) + MTX +/- Other(except MMF, post-CY)	1804 (35)

Characteristic	
CNI (TAC/CSA) +/- Other (except MMF, MTX, post-CY)	233 (4.5)
TAC alone	73 (1.4)
CSA alone	18 (0.3)
Others	67 (1.3)
Missing	73 (1.4)
Fluconazole Prophylaxis - no. (%)	
No	2963 (57.6)
Yes	2185 (42.4)
Yeast Infections reported by day 100 (not mutually exclusive)	
Candida Albicans - no. (%)	37 (0.7)
Candida Non-Albicans - no. (%)	66 (1.3)
Other Yeast - no. (%)	1 (0)
No yeast infection reported - no. (%)	5047 (98)
Site of Infection Reported for Yeast infections (not mutually exclusive)	
Blood - no. (%)	39 (38.6)
Lung - no. (%)	17 (16.8)
Liver/Spleen - no. (%)	0
Other sites - no. (%)	44 (43.6)
Year of transplant - no. (%)	
2017	2405 (46.7)
2018	2215 (43)
2019	528 (10.3)
Follow-up - median (min-max)	12.11 (0.92-31.71)

Proposal: 1911-197

Title:
Evaluating time from diagnosis to transplant as an important contributor for post-allogeneic stem cell transplant infections and infection/delayed immune-reconstitution associated mortality/morbidity.

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Hypothesis:
We hypothesize that delay in transplant (or time to transplant) from the time of diagnosis is an important contributor for post-transplant infections and delayed immune-reconstitution, which contributes to non-relapse mortality (NRM).

Aims:
- Identify density and types of early and late infections (bacterial, viral and fungal) in patients that went to transplant a) within 3 months of diagnosis b) Between 3-6 months c) Between 6- 12 months and d) > 12 months from diagnosis with matched sibling donor (MSD), matched unrelated donor (MUD) and haplo-identical transplants (Haplo's).
- Identify T cell lymphocyte absolute numbers at days 100 and 180 and CD4/CD8 ratio for different timeline transplant recipients with individual donor types.
- Evaluate the impact of bacterial, viral or fungal infections by D 100 and day 180 on 1 year post-transplant outcomes- a) relapse b) Non-relapse Mortality (NRM), disease free survival (DFS) and acute and chronic graft versus host disease (GVHD).
- Evaluate quantitative immunoglobulin levels at D+ 100 and + 180 if available.

Rationale:
As a post remission strategy consolidation with allogenic stem cell transplant (ASCT) prolongs remission duration and is potentially curative in many cases. Of the different non-relapse mortality causes, infections are a major source of unmet need to improve overall success rates with ASCT(1). Appropriately, prior studies have identified the impact of conditioning regimens, graft versus host disease prophylaxis etc: on post-transplant risks. Continually, the field in general has understudied the impact of pre-transplant maneuvers on post-transplant infection risk. Irrespective of the reason for delay, in most cases patients with delayed transplants are likely exposed to higher burden of cytotoxic agents to maintain remission till they get to transplant(2). Repeat cytotoxic agents' exposure are well known to injure thymic epithelial compartment, an important reservoir for early lymphoneogenesis and immune reconstitution(2, 3). In addition, repeat chemo or radiation worsens mucosal injury, and helps microbes cross the barrier easily. So it is foreseeable that delay in transplant will likely lead to higher probability of post-transplant infections, a confirmation of which is not yet known. A few pediatric studies have confirmed a possible relation between time to transplant and post-transplant adverse events(4). To answer this question, we propose a pilot study using donor sources, GVHD prophylaxis and conditioning regimens that are commonly used in contemporary era.

Significance:
If our study shows that time is an important variable and reduced time to transplant is associated with lower rates of infections and infection related mortality, then programs will have to make a

commitment to work on expediting this process and set new benchmarks. With the introduction of haplos, which has now consistently shown equal efficacy to MSD/MUD, future studies can exploit this donor source judiciously to increase access to transplant expediently. Hopefully, this will lead to better overall transplant outcomes. Prior to that we need to characterize infections patterns and subtypes and their mortality risk, based on pre-transplant timelines

- Pre-emptively design tailored anti-microbial prophylaxis strategies to mitigate infection risk for different cohorts based on types of infections.
- Propel Immune-reconstitution pre-clinical work to expedite drugs that can be tested in trials or find appropriate drugs in induction phase that are less toxic to thymus and minimize mucosal breach.

Inclusion criteria:

- Patients receiving first T cell replete allogeneic HCT for AML, ALL, and MDS between 2012 – 2018. We will stratify them based on Complete Remission Status (CR1 vs CR2 and beyond)
- Patients receiving transplant within 1 year from diagnosis (4 groups to be included -< 3 months, 3-6months, 6- 12 months and > 12 months)
- HLA match related, matched unrelated donors and Haplo-identical donors with PTCY prophylaxis
- Adults > 18 years of age and less than or equal to 70 years.

Exclusion criteria:
Umbilical Cord Blood Transplant Recipients, Ex-vivo T cell depletion and ATG use as GVHD prophylaxis

Outcomes:
Incidence, frequency and type of bacterial/viral and fungal infections- cumulative incidence with death as competing risk. If any systemic or visceral involvement will also be characterized.
Infection associated mortality for different cohorts: Cumulative incidence of infection attributable to infection with death from non-infectious cause and relapse as competing events. Dynamic landmark analysis at days 30, 60 and 100 will be examined. Description of causes of death from different infections will also be given. Incidence of aGVHD (land mark analysis D 30) and cGVHD (landmark analysis D 100), with death as competing risk. Traditional definition of DFS, OS will be used.

Study variables:
Patient Related: Age at diagnosis (18-30 years and every decade till 70), Gender, Race, KPS < 70 or 70, HCTCI, Donor age (in decades), Donor/recipient ABO and CMV pairing, CD3,CD4 and CD 8 counts at 100 days and 6 months post-transplant. Quantitative B cell markers and immunoglobulin levels if available by D100 and D 180 post-transplant. CD3, Cd34 and Cd 19 quantitation in the graft if available.
Disease: AML, ALL, MDS. Time from diagnosis to transplant (<3 months, between 3-6 months, between 6- 12 months and > 12 months) , DRI (low vs high vs intermediate).
Treatment: Pre-transplant treatment (Number of lines, chemo vs hypomethylating agents), conditioning intensity (MAC vs RIC- Chemo vs RT), GVHD prophylaxis (Tacro/sirolimus, tacro/cellcept, Tacro/methotrexate, PTCY based, Cyclosporine based), growth factors peri-transplant (Y/N). If available data on bacterial, viral and fungal prophylaxis used.
Complication: Timing and types of infections (bacterial, viral and fungal) for different timelines for respective donor types. CMV reactivation by D180 (Y/N). GVHD- acute and chronic -Y/N- need for systemic immunosuppression -Y/N .
CIBMTR statistical team will be used for support. Patient, disease and transplant- related metrics 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 method. Cumulative incidence estimates to account for competing risks will be calculated. Cox proportional hazards regression will be used for outcome of interest. The variables to be considered in the multivariable regression models are listed above. The assumption of proportional hazards for each factor in the Cox model will be evaluated. When the proportional hazards assumption is violated, time-dependent variable will be added in the model. Interactions between main effect and significant covariates will be tested. Description of infections, B and T cell recovery will be presented.

References:

1. Yilmaz M, Chemaly RF, Han XY, Thall PF, Fox PS, Tarrand JJ, et al. Adenoviral infections in adult allogeneic hematopoietic SCT recipients: a single center experience. Bone Marrow Transplant. 2013;48(9):1218-23.
2. Perry GA, Jackson JD, Talmadge JE. Effects of a multidrug chemotherapy regimen on the thymus. Thymus. 1994;23(1):39-51.
3. Bejanyan N, Brunstein CG, Cao Q, Lazaryan A, Luo X, Curtsinger J, et al. Delayed immune reconstitution after allogeneic transplantation increases the risks of mortality and chronic GVHD. Blood Adv. 2018;2(8):909-22.
4. Boelens JJ, Rocha V, Aldenhoven M, Wynn R, O'Meara A, Michel G, et al. Risk factor analysis of outcomes after unrelated cord blood transplantation in patients with hurler syndrome. Biol Blood Marrow Transplant. 2009;15(5):618-25.

Characteristics of patients who underwent first allogeneic peripheral blood or bone marrow transplants for AML, ALL or MDS in US from 2012 to 2018 reported to the CIBMTR

Characteristic	<3 months	3-6 months	6-12 months	>12 months
No. of patients	448	2516	1741	1925
No. of centers	82	123	115	117
Age of recipient - no. (%)				
Median (min-max)	57.5 (19-70)	57.3 (18-70)	60.2 (18.1-70)	60.3 (18-70)
10 - 19	3 (0.7)	32 (1.3)	11 (0.6)	19 (1)
20 - 29	30 (6.7)	207 (8.2)	100 (5.7)	131 (6.8)
30 - 39	45 (10)	216 (8.6)	113 (6.5)	146 (7.6)
40 - 49	65 (14.5)	348 (13.8)	213 (12.2)	203 (10.5)
50 - 59	130 (29)	699 (27.8)	422 (24.2)	440 (22.9)
60 - 69	175 (39.1)	1014 (40.3)	882 (50.7)	986 (51.2)
Disease - no. (%)				
AML	316 (70.5)	1405 (55.8)	621 (35.7)	497 (25.8)
ALL	33 (7.4)	392 (15.6)	264 (15.2)	248 (12.9)
MDS	99 (22.1)	719 (28.6)	856 (49.2)	1180 (61.3)
Donor type - no. (%)				
HLA-identical sibling	232 (51.8)	796 (31.6)	472 (27.1)	564 (29.3)
Mismatched related				
1 Ag/allele	8 (1.8)	27 (1.1)	12 (0.7)	19 (1)
≥2 Ag/allele	73 (16.3)	439 (17.4)	347 (19.9)	370 (19.2)
Other related (matching TBD)	15 (3.3)	82 (3.3)	55 (3.2)	50 (2.6)
Well-matched unrelated (8/8)	105 (23.4)	1024 (40.7)	724 (41.6)	783 (40.7)
Partially-matched unrelated (7/8)	15 (3.3)	131 (5.2)	115 (6.6)	133 (6.9)
Mis-matched unrelated (≤6/8)	0	14 (0.6)	14 (0.8)	4 (0.2)
Unrelated (matching TBD)	0	3 (0.1)	2 (0.1)	2 (0.1)
Stem cell source - no. (%)				
Bone Marrow	74 (16.5)	515 (20.5)	324 (18.6)	321 (16.7)
Peripheral Blood	374 (83.5)	2001 (79.5)	1417 (81.4)	1604 (83.3)
Conditioning intensity - no. (%)				
MAC	258 (57.6)	1421 (56.5)	832 (47.8)	916 (47.6)
RIC/NMA	190 (42.4)	1095 (43.5)	909 (52.2)	1009 (52.4)
GVHD prophylaxis - no. (%)				
CD34 selection	2 (0.4)	19 (0.8)	15 (0.9)	19 (1)
Post-CY + other(s)	98 (21.9)	596 (23.7)	471 (27.1)	497 (25.8)
Post-CY alone	7 (1.6)	38 (1.5)	8 (0.5)	19 (1)
CNI (TAC/CSA) + MMF +/- Other (except post-CY)	46 (10.3)	336 (13.4)	272 (15.6)	283 (14.7)

Characteristic	<3 months	3-6 months	6-12 months	>12 months
CNI (TAC/CSA) + MTX +/- Other (except MMF, post-CY)	259 (57.8)	1300 (51.7)	799 (45.9)	903 (46.9)
CNI (TAC/CSA) +/- Other (except MMF, MTX, post-CY)	24 (5.4)	162 (6.4)	132 (7.6)	155 (8.1)
TAC alone	6 (1.3)	24 (1)	20 (1.1)	16 (0.8)
CSA alone	0	3 (0.1)	0	0
Others	3 (0.7)	22 (0.9)	9 (0.5)	14 (0.7)
Missing	3 (0.7)	16 (0.6)	15 (0.9)	19 (1)
Year of transplant - no. (%)				
2012	28 (6.3)	168 (6.7)	92 (5.3)	124 (6.4)
2013	65 (14.5)	343 (13.6)	224 (12.9)	216 (11.2)
2014	105 (23.4)	459 (18.2)	290 (16.7)	317 (16.5)
2015	70 (15.6)	443 (17.6)	300 (17.2)	299 (15.5)
2016	74 (16.5)	427 (17)	288 (16.5)	287 (14.9)
2017	59 (13.2)	336 (13.4)	294 (16.9)	335 (17.4)
2018	47 (10.5)	340 (13.5)	253 (14.5)	347 (18)
Infections by day 100				
Bacterial - no. (%)				
No	276 (61.6)	1521 (60.5)	1063 (61.1)	1178 (61.2)
Yes	172 (38.4)	995 (39.5)	678 (38.9)	747 (38.8)
Viral - no. (%)				
No	314 (70.1)	1606 (63.8)	1080 (62)	1204 (62.5)
Yes	134 (29.9)	910 (36.2)	661 (38)	721 (37.5)
Fungal - no. (%)				
No	421 (94)	2371 (94.2)	1645 (94.5)	1784 (92.7)
Yes	27 (6)	145 (5.8)	96 (5.5)	141 (7.3)
Follow-up - median (min-max)	36.81 (3.26-75.2)	36.55 (2.73-75.33)	35.89 (3.16-77.43)	35.66 (1.55-77.86)

Combined Proposal: 1911-34, 1911-50, 1911-76, 1911-155, 1911-158, 1911-209, 1911-235, 1911-254, 1911-266

Study Title:
Infectious complications in patients with B-lymphoid hematologic malignancy treated with CD19 CAR T cell therapy

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Research hypothesis:

- Infectious complications after CD19 CAR T cell treatment are common but vary upon the period post-CAR T cell therapy

- Infectious complications after CD19 CAR T cell treatment are associated with particular disease, host and CAR T cell related characteristics
- Infectious complication after CAR T cell therapy are associated with inferior outcomes in patients with B-lymphoid malignancy treated with CAR T cells
- Infection complications after CD19 CAR T cell treatment are preventable by antimicrobial prophylaxis and IVIG replacement

Specific aims:
- To describe the incidence and patterns of infections in patients treated with CAR T cells
- To describe risk factors of infection in patients treated with CAR T cells
- To explore the association between infectious complications and clinical outcomes following CAR T cell therapy
- To describe infection prophylactic strategies and their impact on the incidence and outcomes of infectious complication after CAR T cell therapy
- To assess longitudinal measures of hematologic and immune reconstitution following CAR19 therapy

Scientific impact:
Common side effects of CAR T cell therapy include cytokine release syndrome (CRS), immune effector cell associated neurotoxicity (ICANs) and B cell aplasia. Patients who are treated with CAR T cells are at risk of developing infectious complication from several factors including immune dysfunction from underlying diseases/prior treatment, cytopenia from lymphodepletion/CAR T cell therapy, and B cell aplasia. There are increasing data on infections after CAR T cell therapy. However, most data are from single centers and there is no high-level evidence on appropriate infection prophylactic measures in these patients. This study will provide us novel information about:
- The incidence, patterns and the predisposing factors of infections in patients treated with CAR T cells
- Impact of infectious complication on survival outcomes of patients treated with CAR T cells
- Proper approach of antimicrobial prophylaxis and IVIG replacement in patients treated with CAR T cells

Scientific justification:
CD19 directed chimeric antigen receptor (CAR) T cell has recently become the breakthrough therapy that changes the armamentarium of treatments for relapsed/refractory acute leukemia and lymphoma. Despite outstanding activity, CD19 CAR T cell possesses unique adverse event profiles, which notably include cytokine release syndromes (CRS), immune effector cells associated neurotoxicity (ICANS), and B cell aplasia. In addition, hypogammaglobulinemia and prolonged neutropenia are commonly encountered after CAR T cell therapy in these heavily treated patients. Based on the aforementioned reasons, patients treated with CAR T cells have both innate and adaptive immunity impairments resulting in increased risk of infectious complications. There are several single-center studies exploring infectious complications after administration of CAR-T cell therapy. Infectious complications most commonly included respiratory infections, bacterial site infections, and bacteremia with the most significant risk of infection occurring in the first 30 days post-infusion. The risk of infection after CAR T cell therapy is multifactorial and could be attributed to immunodeficiency states due to underlying malignancy or prior treatments, lymphodepletion chemotherapy, prolonged cytopenia and hypogammaglobulinemia after CAR T cell infusion. Data from retrospective single center studies identified severe cytokine release syndromes, heavily treated patients (>4 prior therapy), elevated baseline inflammatory cytokines as risk factors of infection. Several studies indicated that infection

events observed in patients treated with CAR T cell therapy were mostly mild to moderate in severity. Data from adult ALL observed increased mortality in patients who developed severe infections. Similar to the incidence, severity of infection and its impact on clinical outcomes could be influenced by several factors.

Although there have been some reported data on the incidence, pattern, risk factors and impact of infectious complications after CAR T cell therapy, most studies included patients from clinical trial settings or small number of heterogeneous patient populations and the results continue to be inconclusive. In addition, most studies have focused on the infection during the initial period after CAR T cell treatment. Data on delayed infection in CAR T cell treated patients is still limited. There is a lack of real-world data of infectious complications in patients treated with CD19 CAR T cell therapy.

Moreover, little is known about the proper prophylaxis and management strategy in this patient population. Although most centers implement CAR T cell therapy as a part of bone marrow transplant service and the post-treatment guidelines for these patients are adopted from bone marrow transplant patients, the impact of CAR T cell treatment on patients' immune status is likely different from allogeneic stem cell transplant. It is possible that the incidence and patterns of infection in CAR T cell treated patients are different from transplanted patients due to different immune status and immune reconstitution pattern. Data from JULIET trial demonstrated the median time of B cell recovery around 6.7 months. A single center analysis reported hypogammaglobulinemia in 67% of patients treated with CAR T cell. However, there was no association between hypogammaglobulinemia and late infection. Besides the effect of cytopenia and hypogammaglobulinemia, there are still lack of comprehensive data on immune reconstitution after CAR T cell treatment. Thus, antimicrobial and immunoglobulin replacement for infection prophylaxis in CAR T cell require further justification.

Given the rapid advancement and successful application of CAR-T cell immunotherapy for B cell malignancies, there is a critical need to determine the scope of infectious complications and strategies to mitigate these events. Protecting patients from subsequent complications after cure of their underlying disease is fundamental to the broader use of CAR-T cell immunotherapies. To address this need, we propose to determine the epidemiology of early and late infectious complications after CAR-T cell immunotherapy for B-cell malignancies, and to identify factors associated with higher infection risk in the real-world setting. In addition, we plan to explore the impact of infectious complications on outcomes and infection prophylactic strategy in B cell lymphoid malignancy patients who received two FDA approved CD19 specific CAR T cell product. The result of this study will guide us to better understand about the burden of infectious complication and properly manage infections in patients who receive CAR T cell therapy.

Patient eligibility population:

- Aggressive B cell NHL patients who underwent FDA-approved CD19 CAR T cell therapy from the inception to December 2019
- Precursor B cell acute lymphoblastic leukemia patients who underwent FDA-approved CD19 CAR T cell therapy from the inception to December 2019

Exclusion criteria:

- Patients who received CD19 CAR T cell therapy under clinical trial

Outcomes:

- Infection density: the number of infections per patient days at risk from time of infusion (Day 0; conditioning to Day 0 is excluded as these data are not currently collected)
- Cumulative incidence of infection by bacterial, viral, fungal, polymicrobial from Day 0 to Day +30, +100, and +180

- Infection specific survival, Infectious disease related mortality
- Overall survival, Event Free Survival
- Association (Hazard ratio) between pre/post CAR T cell factors and infectious complication occurrence

Data requirements:
We note that some of these data points will not be available in the registry and should be discussed in terms of feasibility

- Diagnosis
- Lymphoma: De novo vs Transformed
- ALL: Cytogenetic risks (Ph+ or Ph- ALL)
- Age at CAR T cell
- Gender: Male VS Female
- Ethnicity
- Disease status at CAR T cell
- Stage of disease at CAR T cell
- IPI at CAR T cell
- Number of prior lines of treatments including transplantation
- Transplant before CAR T cell therapy
    - Type of transplant if transplants before CAR T cell: Auto, Allo
- If allotransplant before CAR T cell
    - HLA compatibility: Matched, Mismatched, Haploidentical
    - Donor-Patient Relationship: Sibling, Unrelated, haploidentical, Cord blood
- Karnofsky Performance Status: <70 or >70
- Hematopoietic Cell Transplant Comorbidity Index: 0-2 VS >3
- CMV status
- Baseline LDH and platelet before lymphodepletion
- Infection (identified pathogen) or antimicrobial therapy prior to CAR T cell therapy (within the 30 days before CAR T cell)
- Bridging therapy before CAR T cell
    - Last date of treatment
    - Bridging therapy regimen
- Baseline CBC (WBC, ANC, ALC) before starting lymphodepletion
- Baseline IgG, IgA before starting lymphodepletion (if available)
- Baseline CRP, IL-6, Ferritin before lymphodepletion
- Lymphodepletion Regimens for CAR T cell
- Type of CAR T cell product ((Yescarta vs Kymriah)
- CAR T cell dose
- CAR-T cell persistence
- Time to Neutrophil Engraftment
- ANC and ALC at 14 days, 1 month, 3 months, 6 months, 1 year
- Peripheral blood count recovery data (lymphocyte subset) at 14 days, 1 month, 3 months, 6 months, 1 year
- IgG level at 1 month, 3 months, 6 months, 1 year
- CAR T Related Complication
    - CRS: Yes vs No. Grading per ASTCT consensus
    - ICANs: Yes vs No. Grading per ASTCT consensus

  - Graft Versus Host Disease
  - Grade 4 organ toxicity (yes/no)
- Peak Cytokine level: Peak IL-6 level, Peak Ferritin, Peak CRP (including date of peak level for all cytokines)
- Steroid: Type, date of first dose, dose, date of last dose (Calculate as prednisone equivalent dose density)
- Tocilizumab: date of first dose, number of doses, date of last dose
- Infection Data (Yes vs No) if Yes:
  - Bacterial: Severity, Organ, Type, Date, Treatment
  - Viral: Severity, Organ, Type, Date, Treatment
  - Fungal: Severity, Organ, Type, Date, Treatment
  - Others: Severity, Organ, Type, Date, Treatment
- Antimicrobial prophylaxis given (Antibiotic, antiviral, antifungal): Yes or No. (Duration if available)
- IVIG replacement given: Yes or No
- Growth factor given
- Best response to CAR T cell and date
- Disease relapse or progression and date
- CAR-T cell persistence
- Last contact
- Live/Death Status at last contact
- Cause of death

Sample requirements:
No biologic or serologic data are required with this proposal.

Study design:
The goal of this study is to describe the pattern and incidence of infectious complications during the 1-year post CAR T cell therapy and stratify into different timepoint (first 30 days, day 30-100, day 100 to 6 months, 6 to 12 months). Pattern of antimicrobial prophylaxis including IVIG replacement and their corresponding effect on treatment complication will be explored adjusting for significant patient-, disease-, and CAR T-related variables. The incidence will be displayed as cumulative incidence and infection density. Infection densities (overall and by infection type) is defined the mean number of infections per 100 patient days-at-risk. Clinical and laboratory parameters with potential association with infection will be explored. Prognostic implication of infectious complication on the non-relapse mortality and survival outcomes will be analyzed. Descriptive tables of patient-, disease-, and CAR T cell-related factors will be prepared. These tables will list median and range for continuous variables and percent of total for categorical variables. Comparison between groups will be done by Chi-square test for categorical variables and the Wilcoxon sample test for continuous variables. The probabilities of progression-free and overall survival stratified by the emergence of severe infection will be calculated using the Kaplan-Meier estimator with log rank test comparison. Cumulative incidence of non-relapse morality (NRM) will be estimated using Fine and Gray's test. Relapse, lymphoma treatment re-initiation, the last date of data capture by the CIBMTR registry and death from non-infectious cause are considered as competing events. Cox proportional hazards models will be used to determine the association between the clinical variables and the outcomes constructing for cumulative incidence of infection using a stepwise selection procedure. Variables considered in the model will be those significant at α=0.20 level from the univariable models. Variables remaining in the final models will be significant at α=0.05 level. Interactions between main effect and significant covariates will be tested.

Non-CIBMTR data source:
Not required

Conflicts of interest:
- Kitsada Wudhikarn, MD: No conflict of interest to disclose
- Miguel Perales, MD: Yes, as reported below
- Cameron J Turtle, MD, PhD: Yes, as reported below

Dr. Perales reports honoraria from Abbvie, Bellicum, Bristol-Myers Squibb, Incyte, Merck, Novartis, Nektar Therapeutics, Omeros, and Takeda. He serves on DSMBs for Servier and Medigene, and the scientific advisory boards of MolMed and NexImmune. He has received research support for clinical trials from Incyte, Kite/Gilead and Miltenyi Biotec. He serves in a volunteer capacity as a member of the Board of Directors of American Society for Transplantation and Cellular Therapy (ASTCT) and Be The Match (National Marrow Donor Program, NMDP), as well as on the CIBMTR Cellular Immunotherapy Data Resource (CIDR) Committee.

Dr. Cameron Turtle has the following conflicts of interest:
- Research funding: Juno/Celgene, Nektar Therapeutics
- Ad hoc consultancy/ad boards: Kite/Gilead, Novartis, Humanigen, PACT Pharma, Astra Zeneca, Myeloid Therapeutics, Allogene
- Scientific advisory boards: Precision Biosciences, Eureka Therapeutics, Caribou Biosciences, Arsenal, T-CURX
- Equity: Precision Biosciences, Eureka Therapeutics, Caribou Biosciences, Arsenal
- Patent/royalty: Juno/Celgene

References:
1. Kobe C, Dietlien M and Hellwig D. PET/CT for Lymphoma Post-therapy Response Assessment in Hodgkin Lymphoma and Diffuse Large B-cell Lymphoma. Semin Nucl Med. 2018 Jan;48(1):28-36
2. Minamimoto R, Fayad L, Advani R, et al. Diffuse Large B-Cell Lymphoma: Prospective Multicenter Comparison of Early Interim FLT PET/CT versus FDG PET/CT with IHP, EORTC, Deauville, and PERCIST Criteria for Early Therapeutic Monitoring. Radiology. 2016 Jul;280(1):220-9
3. Marcheselli R, Franceschetto A, Sacchi S et al. The prognostic role of end of treatment FDG-PET-CT in patients with diffuse large B cell lymphoma can be improved by considering it with absolute monocyte count at diagnosis. Leuk Lymphoma. 2019 Aug;60(8):1958-1964
4. Kostakoglu L and Nowakowski GS. End-of-Treatment PET/Computed Tomography Response in Diffuse Large B-Cell Lymphoma. PET Clin. 2019 Jul;14(3):307-315
5. Adams HJ, Nievelstein RA and Kwee TC Prognostic value of complete remission status at end-of-treatment FDG-PET in R-CHOP-treated diffuse large B-cell lymphoma: systematic review and meta-analysis. Br J Haematol. 2015 Jul;170(2):185-91
6. Mylam KJ, El-Galaly TC, Hutchings M, et al. Prognostic impact of clinician-based interpretation of 18F-fluorodeoxyglucose positron emission tomography/computed tomography reports obtained in patients with newly diagnosed diffuse large B-cell lymphoma. Leuk Lymphoma. 2014 Jul;55(7):1563-9.
7. Thomas A, Gingrich RD, Smith BJ, et al. 18-Fluoro-deoxyglucose positron emission tomography report interpretation as predictor of outcome in diffuse large B-cell lymphoma including analysis of 'indeterminate' reports. Leuk Lymphoma. 2010 Mar;51(3):439-46
8. Shah NR, Nagle SJ, Torigian DA, et al. Early positron emission tomography/computed tomography as a predictor of response after CTL019 chimeric antigen receptor -T-cell therapy in B-cell non-Hodgkin lymphomas. Cytotherapy. 2018 Dec;20(12):1415-1418

9. Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol. 2014 Sep 20;32(27):3059-68.
10. Younes A, Hilden P, Coiffier B, et al. International Working Group consensus response evaluation criteria in lymphoma (RECIL 2017). Ann Oncol. 2017 Jul 1;28(7):1436-1447
11. Ulaner GA, Lilienstein J, Gönen M, et al. False-Positive [18F] fluorodeoxyglucose-avid lymph nodes on positron emission tomography-computed tomography after allogeneic but not autologous stem-cell transplantation in patients with lymphoma. J Clin Oncol. 2014 Jan 1;32(1):51-6.
12. Adam HJK and Kwee TC. Proportion of false-positive lesions at interim and end-of-treatment FDG-PET in lymphoma as determined by histology: Systematic review and meta-analysis. Eur J Radiol. 2016 Nov;85(11):1963-1970

Baseline characteristics for patients undergoing 1st CAR-T for ALL/NHL with at least 100-days follow-up

Characteristic	ALL	NHL	Total
No. of patients	265	861	1126
No. of centers	54	72	101
Age at infusion, by category - no. (%)			
Median (min-max)	13.33 (0.41-73.49)	62.26 (15.02-88.99)	57.35 (0.41-88.99)
< 10	87 (32.8)	0	87 (7.7)
10-19	123 (46.4)	4 (0.5)	127 (11.3)
20-29	45 (17)	19 (2.2)	64 (5.7)
30-39	3 (1.1)	43 (5)	46 (4.1)
40-49	2 (0.8)	86 (10)	88 (7.8)
50-59	2 (0.8)	213 (24.7)	215 (19.1)
60-69	2 (0.8)	326 (37.9)	328 (29.1)
>= 70	1 (0.4)	170 (19.7)	171 (15.2)
Gender - no. (%)			
Male	156 (58.9)	551 (64)	707 (62.8)
Female	109 (41.1)	310 (36)	419 (37.2)
Recipient race - no. (%)			
White	181 (68.3)	736 (85.5)	917 (81.4)
African-American	18 (6.8)	40 (4.6)	58 (5.2)
Asian	10 (3.8)	38 (4.4)	48 (4.3)
Other	4 (1.5)	1 (0.1)	5 (0.4)
More than one race	37 (14)	20 (2.3)	57 (5.1)
Not reported	15 (5.7)	26 (3)	41 (3.6)
Recipient ethnicity - no. (%)			
Hispanic or Latino	103 (38.9)	89 (10.3)	192 (17.1)
Non Hispanic or non-Latino	137 (51.7)	723 (84)	860 (76.4)
Non-resident of the U.S.	9 (3.4)	16 (1.9)	25 (2.2)
Unknown	16 (6)	33 (3.8)	49 (4.4)
Karnofsky/Lansky performance score prior to CT - no. (%)			
90-100	178 (67.2)	331 (38.4)	509 (45.2)
80	43 (16.2)	258 (30)	301 (26.7)
< 80	31 (11.7)	157 (18.2)	188 (16.7)

Characteristic	ALL	NHL	Total
Not reported	13 (4.9)	115 (13.4)	128 (11.4)
Types of prior HCTs - no. (%)			
No	170 (64.2)	552 (64.1)	722 (64.1)
Yes	91 (34.3)	306 (35.5)	397 (35.3)
Prior allo-HCT(s)	81 (30.6)	21 (2.4)	102 (9.1)
Prior auto-HCT(s)	2 (0.8)	266 (30.9)	268 (23.8)
Prior auto and allo-HCT(s)	1 (0.4)	6 (0.7)	7 (0.6)
Not reported	7 (2.6)	13 (1.5)	20 (1.8)
Not reported	4 (1.5)	3 (0.3)	7 (0.6)
Year of CT - no. (%)			
2017	25 (9.4)	13 (1.5)	38 (3.4)
2018	158 (59.6)	537 (62.4)	695 (61.7)
2019	82 (30.9)	311 (36.1)	393 (34.9)
Commercial vs. noncommercial CAR-T product - no. (%)			
Commercial	208 (78.5)	816 (94.8)	1024 (90.9)
Noncommercial	57 (21.5)	45 (5.2)	102 (9.1)
Clinically significant infection within 100-days - no. (%)			
No	186 (70.2)	610 (70.8)	796 (70.7)
Yes	79 (29.8)	251 (29.2)	330 (29.3)
Bacterial	47 (17.7)	139 (16.1)	186 (16.5)
Fungal	6 (2.3)	35 (4.1)	41 (3.6)
Viral	39 (14.7)	104 (12.1)	143 (12.7)
Other	9 (3.4)	42 (4.9)	51 (4.5)
Clinically significant infection during the entire follow-up - no. (%)			
No	154 (58.1)	550 (63.9)	704 (62.5)
Yes	111 (41.9)	311 (36.1)	422 (37.5)
Bacterial	60 (22.6)	173 (20.1)	233 (20.7)
Fungal	9 (3.4)	43 (5)	52 (4.6)
Viral	64 (24.2)	144 (16.7)	208 (18.5)
Parasital	1 (0.4)	0	1 (0.1)
Other	22 (8.3)	59 (6.9)	81 (7.2)