Not for publication or presentation

A G E N D A
CIBMTR WORKING COMMITTEE FOR INFECTION AND IMMUNE RECONSTITUTION
Orlando, FL
Wednesday, February 15, 2023, 1:00 p.m. – 3:00 p.m. (EST)

Co-Chair:	**Christopher Dandoy, MD, MS, Cincinnati Children's Hospital Medical Center, Cincinnati, OH; Telephone: 513-803-7495; E-mail: christopher.dandoy@cchmc.org;**
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, MPH, UT MD Anderson Cancer Center, Houston, TX; Telephone: 713-792-0007; E-mail: rfchemaly@mdanderson.org;**
Scientific Director:	**Marcie Riches, MD, MS; CIBMTR Statistical Center, Milwaukee, WI; Telephone: 813-943-2800; E-mail: mlrichesmd@outlook.com**
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Statistician:	**Naya He, MS, CIBMTR Statistical Center, Milwaukee, WI; Telephone: 414-805-0685; E-mail: nhe@mcw.edu**

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1. **Introduction**
   a. **Welcome and introduction**
   b. **Minutes from February 2022 meeting** (Attachment 1)

2. **Accrual Summary** (Attachment 2)

3. **Presentations, Published or Submitted Papers**
   a. **CV20-04b** Bhatt NS, Sharma A, St Martin A, Abid MB, Brown VI, Diaz Perez MA, Frangoul H, Gadalla SM, Herr MM, Krem MM, Lazarus HM, Martens MJ, Mehta PA, Nishihori T, Prestidge T, Pulsipher MA, Rangarajan HG, Williams KM, Winestone LE, Yin DE, Riches ML, Dandoy CE, Auletta JJ. Clinical Characteristics and Outcomes of COVID-19 in Pediatric and Early Adolescent and Young Adult Hematopoietic Stem Cell Transplant Recipients: A Cohort Study. ***Transplant Cell Ther. 2022 Oct; 28(10):696.e1-696.e7. doi: 10.1016/j.jtct.2022.06.026. Epub 2022 Jul 4. PMID: 35798233; PMCID: PMC9251957.***
   b. **IN18-02** Muthalagu Ramanathan, Soyoung Kim, Naya He, Min Chen, Peiman Hematti, Muhammad Bilal Abid, Seth J. Rotz, Kirsten M. Williams, Hillard M. Lazarus, Baldeep Wirk, Dwight E. Yin, Christopher G. Kanakry, Miguel-Angel Perales, Roy F. Chemaly, Christopher E. Dandoy, Marcie Riches, Celalettin Ustun; The Incidence and Impact of Clostridioides Difficile Infection on Transplant Outcomes in Acute Leukemia and MDS after Allogeneic Hematopoietic Cell Transplant– A CIBMTR Study. ***Bone Marrow Transplant. 2022 Dec 21. doi: 10.1038/s41409-022-01896-z. Online ahead of print. PMID: 36543999.***

c. **IN19-01** Miguel-Angel Perales, Paul Szabolcs, Michael Martens, Naya He, Christopher Dandoy, Roy Chemaly, Marcie Riches. Delayed immune recovery after allogeneic hematopoietic cell transplantation is associated with decreased overall survival in adult but not pediatric recipients. ***Poster Presentation, 2023 Tandem Meetings.***

4. Studies in Progress (Attachment 3)

a. **IN18-01a** Comparison of early (by day 180) bacterial infections after haploidentical HSCT between patients receiving cyclophosphamide-based or other GVHD prophylaxis (Celalettin Ustun/Genovefa Papanicolaou): **Manuscript Preparation.**

b. **IN18-01b** Comparison of early (by day 180) fungal infections after haploidentical HSCT between patients receiving cyclophosphamide-based or other GVHD prophylaxis (Celalettin Ustun/Genovefa Papanicolaou): **Manuscript Preparation.**

c. **IN19-01** Immune recovery predicts post-transplant outcomes (Miguel-Angel Perales/ Paul Szabolcs): **Tandem 2023 Abstract, Manuscript Preparation.**

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.**

e. **IN20-01** Infectious complications in patients with B-Lymphoid hematologic malignancy treated with CD19 chimeric antigen receptor T cell therapy (Kitsada Wudhikarn/ Miranda McGhee/ Joshua A. Hill/ Megan Herr, etc): **Datafile Preparation.**

f. **CV20-04c** COVID-19 in Hematopoietic Cell Transplant Recipients-Race/Ethnicity (Abid, Gowda, Chemaly): **Protocol Development.**

h. **CV20-04d** COVID-19 in Hematopoietic Cell Transplant Recipients- Outcomes early v late (Chemaly,Infante): **Protocol Development.**

i. **CV20-04e** COVID-19 in CAR-T Recipients (G Shah, Politikos, Murthy, Hamandani, N Shah, Hossain, Stiff): **Protocol Development.**

5. Future/Proposed Studies

a. **PROP 2210-175** Influence of non-enterobacterales gram-negative bacilli bloodstream infections (BSIs) on hematopoietic cell transplantation (HCT) and cellular therapy outcomes (N Tran/ Z El Boghdadly) (Attachment 4)

b. **PROP 2210-36; 2210-57; 2210-163; 2210-241** Infectious complications in patients with relapsed/ refractory multiple myeloma receiving B-cell maturation antigen (BCMA) targeted chimeric antigen receptor (CAR) T cells (M B Abid/ Kitsada Wudhikarn/ M-A Perales/ S Mirza/ L Gowda/ S Devarakonda/ Y Efebera) (Attachment 5)

c. **PROP 2210-64** Epidemiology and risk factors associated with polyoma virus (BKV) viremia/viruria and/or BKV associated hemorrhagic cystitis (HC) in allogeneic Hematopoietic Cell Transplant (HCT) recipients (Z Shahid/ R Chemaly) (Attachment 6)

d. **PROP 2210-124** Impact of anti-fungal prophylaxis agent on the incidence of invasive fungal infections (IFI) among allogeneic transplant recipients (H Imlay/ S Patel) (Attachment 7)

e. **PROP 2210-188** The impact of donor source and graft-vs-host disease prophylaxis on the incidence of late viral infections after allogeneic hematopoietic cell transplantation (M B Abid/ Emily Baumrin/ Alison Loren) (Attachment 8)

f. **PROP 2210-244** Early Infectious Complications Associated with CART Cell Therapy Compared to Autologous Stem Cell Transplant in Lymphoma (F Khwaja/ S Ahmed) (Attachment 9)

Dropped Proposed Studies

a. **PROP 2208-01** Outcomes and Management of SARS-CoV2 Omicron Variant in Recipients of Hematopoietic Cell Transplantation (HCT) and CAR-T therapy. *Dropped due to overlap with current study/publication.*
b. **PROP 2209-11** Impact of Gastrointestinal Graft versus Host Disease on Infections occurring among patients with Steroid Sensitive, Steroid Dependent, and Steroid Resistant acute Graft versus Host Disease. *Dropped due to supplemental data needed.*
c. **PROP 2210-34** Impact of corticosteroid usage on the risk of infections in patients receiving CAR-T therapy. *Dropped due to supplemental data needed.*
d. **PROP 2210-37** Incidence of hypogammaglobulinemia following CD19-directed CAR-T therapy and its impact on CAR-T persistence and outcomes. *Dropped due to supplemental data needed.*
e. **PROP 2210-101** Reactivation of Chagas disease (CD) following autologous and allogeneic hematopoietic cell transplantation (HCT). A CIBMTR Analysis. *Dropped-small sample size.*
f. **PROP 2210-118** Characteristics of hypogammaglobulinemia after CAR T-cell therapy and effect of immunoglobulin replacement on infectious complications. *Dropped due to supplemental data needed.*
g. **PROP 2210-125** Incidence of CMV infection and disease in low-risk CMV serostatus (D+R-) allogeneic transplant recipients. *Dropped due to overlap with recent publications [IN1201, IN1701].*
h. **PROP 2210-154** Early platelet count recovery before white cell count recovery after allogeneic hematopoietic cell transplantation and effect on clinical outcome. *Dropped due to lower scientific priority.*
i. **PROP 2210-226** Impact of seasons and climates on outcomes of allogenic hematopoietic cell transplantation (HCT) in North America. *Dropped due to lower scientific priority.*
j. **PROP 2210-249** Incidence and Impact of Invasive Fungal Infection in Allogeneic Hematopoietic Stem Cell Transplant Recipients with FLT3-ITD-mutated Acute Myeloid Leukemia. *Dropped due to lower scientific priority.*

MINUTES AND OVERVIEW PLAN
CIBMTR WORKING COMMITTEE FOR INFECTION AND IMMUNE RECONSTITUTION
Salt Lake City, UT
Monday, April 25, 2022, 6:45 AM – 8:15 AM MDT

Co-Chair:	**Christopher Dandoy, M.D, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio; Telephone: 513-803-7495; E-mail: christopher.dandoy@cchmc.org;**
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; Telephone: 813-943-2800; E-mail: mlrichesmd@outlook.com**
Statistical Directors:	**Michael Martens, PhD, CIBMTR Statistical Center, Milwaukee, WI; Telephone: 414-955-8371; E-mail: mmartens@mcw.edu;**
Statistician:	**Naya He, MS, CIBMTR Statistical Center, Milwaukee, WI; Telephone: 414-805-0685; E-mail: nhe@mcw.edu**

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1. Introduction

a. *Welcome and introduction*
b. *Minutes from February 2021 meeting (Attachment 1)*

The meeting was called to order at 6:45am by Dr. Marcie Riches. She introduced the current working committee leadership and reviewed the CIBMTR COI policy and described Working Committees Membership, goals, expectations, guidelines for voting, and rules of authorship. The two sources of HCT data (TED vs. CRF level) were introduced as well as cellular therapy data.

2. Accrual summary (Attachment 2)

Due to the full agenda, the accrual summary of registration and research cases between 2008 and 2019 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 gave an update on study presentations, and manuscripts that were published or submitted within the last year.

a. **IN17-01a:** Goldsmith SR, Abid MB, Auletta JJ, Bashey A, Beitinjaneh A, Castillo P, Chemaly RF, Chen M, Ciurea S, Dandoy CE, Díaz MÁ, Fuchs E, Ganguly S, Kanakry CG, Kanakry JA, Kim S, Komanduri KV, Krem MM, Lazarus HM, Liu H, Ljungman P, Masiarz R, Mulroney C, Nathan S, Nishihori T, Page KM, Perales MA, Taplitz R, Romee R, Riches M. Posttransplant cyclophosphamide is associated with increased cytomegalovirus infection: a CIBMTR analysis. ***Blood. 2021 Jun 10;137(23):3291-3305. doi: 10.1182/blood.2020009362. PMID: 33657221; PMCID: PMC8351903. Published.***

b. **IN17-01b:** Singh A, Dandoy CE, Chen M, Kim S, Mulroney CM, Kharfan-Dabaja MA, Ganguly S, Maziarz RT, Kanakry CG, Kanakry JA, Patel SS, Hill JA, De Oliveir S, Taplitz R, Hematti P, Lazarus HM, Abid MB, Goldsmith SR, Romee R, Komanduri KV, Badawy SM, Friend BD, Beitinjaneh A, Politikos I, Perales MA, Riches M. Post-Transplantation Cyclophosphamide Is Associated with an Increase in Non-Cytomegalovirus Herpesvirus Infections in Patients with Acute Leukemia and Myelodysplastic Syndrome. ***Transplant Cell Ther. 2021 Sep 26:S2666-6367(21)01257-4. doi: 10.1016/j.jtct.2021.09.015. Epub ahead of print. PMID: 34587551. Published.***

c. **IN17-01c:** Mulroney CM, Abid MB, Bashey A, Chemaly RF, Ciurea SO, Chen M, Dandoy CE, Diaz Perez MA, Friend BD, Fuchs E, Ganguly S, Goldsmith SR, Kanakry CG, Kim S, Komanduri KV, Krem MM, Lazarus HM, Ljungman P, Maziarz R, Nishihori T, Patel SS, Perales MA, Romee R, Singh AK, Reid Wingard J, Yared J, Riches M, Taplitz R. Incidence and impact of community respiratory viral infections in post-transplant cyclophosphamide-based graft-versus-host disease prophylaxis and haploidentical stem cell transplantation. ***Br J Haematol. 2021 Jul;194(1):145-157. doi: 10.1111/bjh.17563. Epub 2021 Jun 14. PMID: 34124796. Published.***

d. **COV20-04a:** Sharma A, Bhatt NS, St. Martin A, Abid MB, Bloomquist J, Chemaly RF, Dandoy C, Gauthier J, Gowda L, Perales M-A, Seropian S, Shaw BE, Tuschl EE, Zeidan AM, Riches ML, Shah GL. Clinical characteristics and outcomes of COVID-19 in haematopoietic stem-cell transplantation recipients: an observational cohort study. ***The Lancet Haematology. doi:10.1016/S2352-3026(20)30429-4. Epub 2021 Jan 19. PMC7816949. Published.***

e. **COV20-04b:** Bhatt NS, Sharma A, St. Martin A, Martens M, Riches ML, Dandoy CE, Auletta JJ. COVID-19 in Pediatric Hematopoietic Cell Transplant Recipients: A CIBMTR Study, ***Blood 2021; 138 (Supplement 1):2868. doi: https://doi.org/10.1182/blood-2021-147924. Poster presentation, ASH 2021.***

f. **IN18-02:** Muthalagu Ramanathan, Bipin B. Savani, Naya He, Soyoung Kim, Min Chen, Roy Chemaly, Christopher E Dandoy, Miguel-Angel Perales, Marcie L. Riches, Celalettin Ustun; The Incidence and Impact of Clostridioides Difficile Infection (CDI) on Outcomes after Allogeneic Hematopoietic Cell Transplant (alloHCT) – a CIBMTR Study. *Blood* 2021; 138 (Supplement 1): 2894. Doi: https://doi.org/10.1182/blood-2021-145774. ***Poster presentation, TCT 2021.***

4. Studies in progress (Attachment 3)
Dr. Marcie Riches briefly listed all studies in progress.

a. **IN18-01a:** Comparison of early (by day 180) bacterial infections after haploidentical HSCT between patients receiving cyclophosphamide-based or other GVHD prophylaxis (Celalettin

Ustun/Genovefa Papanicolaou): ***Manuscript preparation.***

b. **IN18-01b:** Comparison of early (by day 180) fungal infections after haploidentical HSCT between patients receiving cyclophosphamide-based or other GVHD prophylaxis (Celalettin Ustun/Genovefa Papanicolaou): ***Manuscript preparation.***

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): ***Manuscript preparation.***

d. **IN19-01:** Immune recovery predicts post transplant outcomes (Miguel-Angel Perales/ Paul Szabolcs): ***Analysis.***

e. **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.***

f. **IN20-01:** Infectious complications in patients with B-Lymphoid hematologic malignancy treated with CD19 chimeric antigen receptor T cell therapy (Kitsada Wudhikarn/ Miranda McGhee/ Joshua A. Hill/ Megan Herr, etc): ***Datafile preparation.***

g. **COV20-04b:** Clinical Characteristics and Outcomes of COVID-19 in Pediatric Hematopoietic Stem Cell Transplant Recipients: A Cohort Study **(**Bhatt, Sharma, Auletta, Dandoy): ***Manuscript submitted.***

h. **COV20-04c:** COVID-19 in Hematopoietic Cell Transplant Recipients-Race/Ethnicity (Abid, Gowda, Chemaly): ***Protocol Development.***

i. **COV20-04d:** COVID-19 in Hematopoietic Cell Transplant Recipients- Outcomes early v late (Chemaly, Riches): ***Protocol Development.***

j. **COV20-04e:** COVID-19 in CAR-T Recipients (G Shah, Politikos, Murthy, Hamandani, N Shah, Hossain, Stiff): ***Protocol Development.***

5. Future/proposed studies

a. **PROP 2110-84:** Impact of Engraftment Syndrome on Immune Reconstitution and Clinical Outcomes with Predictive Modeling and Clinical Score Generation (S Goldsmith) (Attachment 4)

Dr. Goldsmith presented the proposal. The specific aims of this study are four-fold: 1. Characterize the incidence of reported ES in both Auto-HCT and Allo-HCT and draw comparisons between reported ES and probable ES (patients with a non-infectious fever occurring within the peri-engraftment period possibly associated with other syndromic symptoms). 2. Analyze, independently, the transplant-related outcomes among Auto-HCT and Allo-HCT recipients who do or do not experience ES to compare hospitalization/rehospitalization, non-relapse mortality, incidence of acute and chronic GVHD (in allo-HCT recipients), disease response (myeloma and lymphoma), relapse incidence, progression-free and overall survival. 3. Develop a scoring model to predict the likelihood of ES that could then be prospectively validated and guide management

on de-escalation of anti-infectious therapies or institution of immune suppression. 4. Leverage the immune-reconstitution data available through the CIBMTR to characterize the variances in immune cell reconstitution among patients with or without ES.

Discussion:

- *Is there a way to categorize the severity of engraftment symptoms? Need to limit to population after 2013.*
- *It is challenging to define and toss out engraftment symptoms for allogeneic population.*
- *It was noted that a similar ES study in autologous patients had previously been proposed to the RRT WC.*

b. **PROP 2110-180:** Influence of non-enterobacterales gram-negative bacilli bloodstream infections (BSIs) on hematopoietic cell transplantation (HCT) and cellular therapy outcomes (N Tran/ Z El Boghdadly) (Attachment 5)

Dr. Boghdadly presented the proposal. The specific aims of this study are four-fold: 1. Assess the cumulative incidence non-Enterobacterales gram-negative bacilli BSIs within the first 100 days post HCT and cellular therapy. 2. Identify risk factors for non-Enterobacterales gram-negative bacilli BSIs within the first 100 days post HCT and cellular therapy. 3. Assess influence of non-Enterobacterales gram-negative bacilli BSIs on relapse, GVHD, non-relapse mortality, time to engraftment post HCT. 4. Compare clinical characteristics, risk factors, and post-HCT outcomes between patients with no BSIs vs Enterobacterales BSIs (MBI-LCBI) vs non- Enterobacterales gram-negative bacilli BSIs cohort (if sample size allows).

Discussion:

- *Consider how the data is collected to design the study in order to have enough follow up for the patients.*
- *Will do a sub-analysis for patients after 2017 to compare different antibiotic prophylaxis.*
- *This study could make use of some of the cleaned data from other INWC studies that examined BSI.*

c. **PROP 2110-203:** Epidemiology and risk factors associated with polyoma virus (BKV) viremia/viruria and/or BKV associated hemorrhagic cystitis (HC) in allogeneic Hematopoietic Cell Transplant (HCT) recipients (Z Shahid/R Chemaly) (Attachment 6)

Dr. Shahid presented the proposal. The specific aims of this study are six-fold: 1. To assess the incidence of BKV associated HC, BK viremia and/or BK viuria in allogeneic HCT recipients including CBT. 2. To evaluate the differences in epidemiology of BKV associated disease based on underlying disease, conditioning regimens, graft source, intensity and GvHD prophylaxis and presence of GvHD. 3. To study risk factors associated with the development of BKV associated

HC, BK viremia and BK viuria including gender, laboratory parameters at time of diagnosis, and ethnic differences. 4. To study the impact of BK viremia and BK viruria on kidney function in the absence or presence of BKV associated HC. 5. To study the association of BKV associated HC with other viral reactivations in early and late post-transplant period. 6.To study the impact of BKV associated HC on clinical outcomes including overall survival and non-relapse mortality (adjusted for AKI, CKI).

Discussion:

- *Concerned that what is intended to study is not available in the dataset. Many centers are not routinely checking viremia or viuria and these are often tested in qualitive and not quantitative way.*
- *Questioned that if CIBMTR data could answer all the questions regarding symptoms.*
- *Reviewed that the 2150 form does capture information on symptoms, treatment, and viral loads for BK*

d. **PROP 2110-07**: Viral Hepatitis after allogeneic hematopoietic cell transplant using post-transplant cyclophosphamide for graft versus host disease prophylaxis (K Wudhikarn / M-A Perales) (Attachment 7)

Dr. Perales presented the proposal. The specific aims of this study are four-fold: 1. To assess the rate of viral hepatitis reactivation in patients who underwent allogeneic HCT with GVHD prophylaxis using post-transplant cyclophosphamide. 2. To compare the viral hepatitis reactivation rate in patients who underwent allogeneic HCT with GVHD prophylaxis using post-transplant cyclophosphamide with non-PTCy platform. 3. To assess the factors associated with viral hepatitis reactivation in patients who underwent allogeneic HCT with GVHD prophylaxis using PTCy. 4. To evaluate the impact of chronic viral hepatitis on hepatic complications and survival after alloHCT with PTCy.

Discussion:

- *Clarification that the study period is from 2007 to 2018, since viral forms stated from 2007 and CIBMTR already did Hepatitis B and C study looking at earlier years, prior to the commonality of PTCy use.*
- *CIBMTR viral hepatitis forms collect information on viral loads, prophylaxis, treatment, but these data have not been assessed for completeness.*
- *The committee is concerned about a potential low number of reactivation events.*
- *This study will have a global impact as not all regions have ready access to treatment and prophylaxis.*

e. **PROP 2110-107** Retrospective study of the impact of mammalian target of rapamycin inhibitors (mTORi) in the incidence of virus associated complications after allogeneic hematopoietic cell transplantation (HCT) (K Rechache / J Kanakry)(Attachment 8)

Dr. Kanakry presented the proposal. The specific aims of this study are three-fold: 1. Estimate the cumulative incidences of herpesvirus complications (human cytomegalovirus (CMV) infection, CMV disease, pre-emptive treatment for Epstein-Barr virus (EBV), EBV-post transplant lymphoproliferative disorder (PTLD), and human herpesvirus 6 (HHV6) encephalitis), and BK virus-associated hemorrhagic cystitis through 1-year post-HCT, comparing outcomes between mTORi-containing vs non-mTORi-containing GVHD regimens. 2. Compare NRM, OS, and GVHD rates at 1 year between mTORi-containing approaches and non-mTORi-containing approaches. 3. Evaluate cofactors related to differences in the incidence of viral complications, including conditioning intensity (NMA/RIC vs MAC), donor and recipient serostatus (for CMV and EBV), graft source (PBSC vs BM).

Discussion:

- *Suggested to exclude Letermovir prophylaxis. It was reviewed that the data on Letermovir use are incomplete due to how the question was asked prior to the recent 2100 revision. One option would be to examine by years (pre v post letermovir prophylaxis).*
- *The impact of the study is considered that sites could choose to use and mTORi if seen as beneficial, particularly in the PTCy population.*
- *Will consider comparing PTCY + mTORi to PTCY CNI.*
- *The committee would like to characterize patients who started with mTORi then switch to CNI or vice versa; however, this is not possible with the registry data*
- *It was noted that the EBV population was low and would be unable to be examined by use of pre-emptive therapy.*

f. **PROP 2110-123 & 2110-124** The impact of donor source and graft-vs-host disease prophylaxis on the incidence of late viral infections after allogeneic hematopoietic cell transplantation **(**M B Abid/ E L Baumrin/ A W Loren) (Attachment 9)

Dr. Abid presented the proposal. The specific aims of this study are three-fold: 1. To describe the types and incidence of late (>D+180) CMV and non-CMV viral infections in allogeneic hematopoietic cell transplantation (alloHCT) recipients. 2. To compare the types and incidence of late CMV and non-CMV viral infections in alloHCT recipients receiving matched related / unrelated vs haploidentical donor types, stratified by post-transplant cyclophosphamide (PTCy) vs non-PTCy GVHD prophylaxis. 3. To evaluate the impact of late viral infections on transplant outcomes, stratified by donor type and GVHD prophylaxis: a.Overall survival; b.Disease free survival; c.Relapse; d.Non relapse mortality.

Discussion:

- *This study will look at incidence and impact of late viral infections beyond 6 months. The Letermovir prophylaxis impact on late CMV will not be able to examined in this study as the data for Letermovir use are incomplete due to how the question was asked prior to the recent 2100 revision.*

GVHD is a confounder since a lot of CMV developed after GVHD treatment. CIBMTR using dynamic landmark analysis try to tease out the interaction of GVHD with these late infections.

g. **PROP 2110-176:** Impact of Public and Healthcare Infection Control Measures on Non-COVID-19 Community Respiratory Viral Infections in Transplant and Cellular Therapy Patients (S Patel/H Imlay) (Attachment 10)

Dr. Imlay presented the proposal. The specific aims of this study are two-fold: 1. Identify the impact of public and healthcare infection control measures on the incidence and severity of non-COVID- 19 CRVIs in transplant and cellular therapy patients during the COVID-19 pandemic in the United States. 2. Assess the impact of infection control measures on non-relapse mortality (NRM), treatment-related mortality (TRM), disease-free survival (DFS), and acute and chronic graft-versus-host disease (GVHD) severity and incidence.

Discussion:

- *Not all the centers were impacted by COVID at the same time so impact of COVID prevention measures are different across the country.*
- *CIBMTR cannot look the severity of respiratory virus infection and only can look at present or absent as it's reported.*
- *Recommended to censor patients at a diagnosis of COVID.*
- *Suggested to add pediatric patients to the study.*

h. **PROP 2110-201:** Incidence and Impact of Invasive Fungal Infection in Allogeneic Hematopoietic Stem Cell Transplant Recipients with FLT3-ITD-mutated Acute Myeloid Leukemia (P Vergidis/ S Chesdachai) (Attachment 11)

Dr. Chesdachai presented the proposal. The specific aims of this study are four-fold: 1. To compare the cumulative incidence and infection density of invasive fungal infection (candidiasis, cryptococcosis, aspergillosis, non-Aspergillus mold infection) occurring within 1 year after HSCT between patients with wild-type and mutated FLT3. 2. To determine fungal infection-related mortality in patients with wild-type and mutated FLT3. 3. To compare the impact of invasive fungal infection on 5-year transplant outcomes (relapse, non-relapse mortality, leukemia-free survival, overall survival, chronic GVHD) between patients with wild-type and mutated FLT3. 4. To identify pre-transplant risk factors for development of post-transplant fungal infection in FLT3-mutated AML.

Discussion:

- *From the prophylaxis perspective, based on how the data collected at the CIBMTR, will limit to the 2017 population.*

- *Suggested include acute and chronic GVHD as potential confounders for infection.*

Dropped proposed studies

a. **PROP 2109-03:** COVID-19 outcomes in chimeric antigen receptor T cell therapy (CART) recipients. ***Dropped due to overlap with current study/publication in process (CV20-04).***

b. **PROP 2109-12:** Epidemiology and management of invasive fungal infections after autologous hematopoietic stem cell transplantation for the treatment of lymphoma and solid tumors. ***Dropped due to small sample size.***

c. **PROP 2109-24:** Toxoplasmosis epidemiology in hematopoietic stem cell transplantation recipients across the United States. ***Dropped due to small sample size.***

d. **PROP 2110-04:** 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.***

e. **PROP 2110-33:** Infectious complications in patient with relapsed relapsed/refractory multiple myeloma receiving BCMA-targeted CAR-T therapy. ***Dropped-small sample size.***

f. **PROP 2110-103:** COVID-19 infection outcomes in patients receiving chimeric antigen receptor T-cell therapy (CAR-T). ***Dropped due to overlap with current study/publication (CV20-04).***

g. **PROP 2110-126:** Evaluating the extended use of letermovir as CMV prophylaxis beyond day 100 in allogeneic stem cell transplant. ***Dropped due to supplemental data needed.***

h. **PROP 2110-189:** CMV reactivation and role of pre-emptive therapy in patients undergoing commercial CAR T cell treatment for non-Hodgkin's lymphoma. ***Dropped due to supplemental data needed as the CAR-T patients do not report infections on the 2150 form.***

i. **PROP 2110-214:** Associations between COVID-19 infection, COVID-19 vaccination, and post-allogeneic hematopoietic cell transplantation (allo-HCT) complications. ***Dropped due to overlap with current study/publication (CV20-04).***

j. **PROP 2110-245:** An observational review of allogeneic hematopoietic cell transplantation in HIV infected patients with hematologic malignancy during the era of effective antiretroviral therapy and expanded unrelated and alternative donor sources. ***Dropped due to small sample size.***

k. **PROP 2110-312:** Impact of Letermovir prophylaxis on GVHD and relapse after allo-HCT. ***Dropped due to supplemental data needed.***

l. **PROP 2110-334:** Impact of Human Herpesvirus 6 infection on short- and long-term outcomes in hematopoietic stem cell transplant recipients. ***Dropped due to significant limitations based upon center practice for screening leading to low scientific impact.***

m. **PROP 2110-335:** Infectious complications post-CAR-T cell therapy for multiple myeloma. ***Dropped due to small sample size.***

6. Other Business

PROP 2110-338: Impact of HLA Genotype on CMV Reactivation Following Allogeneic Hematopoietic Stem Cell Transplant (Camacho-Bydume/Hsu) **P*resentation at Collaborative Study Proposals Session.***

Not for publication or presentation

Working Committee Overview Plan for 2022-2023

Study Number and Title	Current Status	Chairs Priority
IN18-01a: Comparison of early (by day+100) viral infections between post transplantation cyclophosphamide and other graft-vs-host disease prophylaxis	Manuscript Preparation	1
IN18-01b: Comparison of early (by day+100) bacterial infections between post transplantation cyclophosphamide and other graft-vs-host disease prophylaxis	Manuscript Preparation	4
IN18-02: Study the Incidence, and impact of C diff infection within 100 days on Transplant outcomes after allogeneic stem cell transplant	Submitted	7
IN19-01: Immune recovery predicts post-transplant outcomes	Analysis	3
IN19-02: Impact of antibacterial prophylaxis on outcomes after allogeneic hematopoietic stem cell transplant	Protocol development	6
IN20-01: Infectious complications after CAR.T Cell therapy	Data File Preparation	2
IN22-01 Viral Hepatitis after allogeneic hematopoietic cell transplant using post-transplant cyclophosphamide for graft versus host disease prophylaxis.	Protocol pending	5

Working Assignments for Working Committee Leadership (May 2022)

Miguel-Angel Perales	**IN18-01a:** Comparison of early (by day+100) viral infections between post transplantation cyclophosphamide and other graft-vs-host disease prophylaxis
	IN18-01b: Comparison of early (by day+100) bacterial infections between post transplantation cyclophosphamide and other graft-vs-host disease prophylaxis
	IN20-01: Infectious complications after CAR.T Cell therapy
Chris Dandoy	**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)
Roy Chemaly	**IN19-01:** Immune recovery predicts post-transplant outcomes (Miguel-Angel Perales)
	IN19-02: Impact of antibacterial prophylaxis on outcomes after allogeneic hematopoietic stem cell transplant (C Dandoy/ P Alonso/ Z El Boghdadly)

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

Variable	Allogeneic N(%)	Autologous N(%)
Number of Patients	32905	14843
Infection		
Donor/recipient CMV status		N/A
-/-	8332 (25)	
+/-	3217 (10)	
-/+	9879 (30)	
+/+	10793 (33)	
Missing/not tested	684 (2)	
Donor/recipient hepatitis B status		N/A
-/-	11169 (34)	
+/-	332 (1)	
-/+	3049 (9)	
+/+	281 (<1)	
-/?	221 (<1)	
+/?	7 (<1)	
?/-	13964 (42)	
?/+	3291 (10)	
Missing/not tested	591 (2)	
Donor/recipient hepatitis C status		N/A
-/-	18990 (58)	
+/-	95 (<1)	
-/+	200 (<1)	
+/+	9 (<1)	
-/?	120 (<1)	
+/?	1 (<1)	
?/-	11378 (35)	
?/+	135 (<1)	
Missing/not tested	1977 (6)	
Fungal Infection history		
No	30458 (93)	14699 (99)
Yes	2426 (7)	142 (<1)
Missing	21 (<1)	2 (<1)
Fungal Infection after starting of conditioning		
No	27472 (83)	14137 (95)
Yes	5429 (16)	706 (5)
Missing	4 (<1)	0
Infection prophylaxis after starting of conditioning		
No	397 (1)	248 (2)
Yes	32481 (99)	14584 (98)

Variable	Allogeneic N(%)	Autologous N(%)
Missing	27 (<1)	11 (<1)
Immune Reconstitution		
IgG at 100 day		
Data not available	11587 (35)	5501 (37)
Data available	21318 (65)	9342 (63)
IgM at 100 day		
Data not available	21831 (66)	6484 (44)
Data available	11074 (34)	8359 (56)
IgA at 100 day		
Data not available	21832 (66)	6417 (43)
Data available	11073 (34)	8426 (57)
CD3 at 100 day		
Lymphocyte analyses were not performed	18363 (56)	13370 (90)
Data not available	6100 (19)	706 (5)
Data available	8442 (26)	767 (5)
CD4 at 100 day		
Lymphocyte analyses were not performed	18363 (56)	13370 (90)
Data not available	6099 (19)	669 (5)
Data available	8443 (26)	804 (5)
CD8 at 100 day		
Lymphocyte analyses were not performed	18363 (56)	13370 (90)
Data not available	6329 (19)	730 (5)
Data available	8213 (25)	743 (5)
CD20 at 100 day		
Lymphocyte analyses were not performed	18363 (56)	13370 (90)
Data not available	12526 (38)	1343 (9)
Data available	2016 (6)	130 (<1)
CD56 at 100 day		
Lymphocyte analyses were not performed	18363 (56)	13370 (90)
Data not available	8898 (27)	1165 (8)
Data available	5644 (17)	308 (2)
Infection Prophylaxis		
Antibiotics		
No	8922 (27)	3609 (24)
Yes	23956 (73)	11223 (76)
Missing	27 (<1)	11 (<1)
Amoxicillin clavulanate oral (Augmentin)(after 2017)		
No	8605 (96)	4518 (96)
Yes	152 (2)	49 (1)
Missing	178 (2)	137 (3)
Cefdinir oral (Omnicef)(after 2017)		

Variable	Allogeneic N(%)	Autologous N(%)
No	8719 (98)	4515 (96)
Yes	38 (<1)	52 (1)
Missing	178 (2)	137 (3)
Cefpodoxime oral (Vantin)(after 2017)		
No	8719 (98)	4549 (97)
Yes	38 (<1)	18 (<1)
Missing	178 (2)	137 (3)
Ciprofloxacin IV or oral (Cipro)(after 2017)		
No	7236 (81)	3738 (79)
Yes	1521 (17)	829 (18)
Missing	178 (2)	137 (3)
Ertapenem IV(after 2017)		
No	8745 (98)	4560 (97)
Yes	12 (<1)	7 (<1)
Missing	178 (2)	137 (3)
Levofloxacin IV or oral (Levaquin)(after 2017)		
No	5419 (61)	1931 (41)
Yes	3338 (37)	2636 (56)
Missing	178 (2)	137 (3)
Moxifloxacin IV or oral (Avelox)(after 2017)		
No	8631 (97)	4508 (96)
Yes	126 (1)	59 (1)
Missing	178 (2)	137 (3)
Vancomycin IV(after 2017)		
No	8263 (92)	4386 (93)
Yes	494 (6)	181 (4)
Missing	178 (2)	137 (3)
Other antibacterial drug (after 2017)		
No	7120 (80)	3855 (82)
Yes	1637 (18)	712 (15)
Missing	178 (2)	137 (3)
Antifungal agent		
No	9525 (29)	6692 (45)
Yes	23353 (71)	8140 (55)
Missing	27 (<1)	11 (<1)
Amphotericin		
No	30780 (94)	14504 (98)
Yes	1785 (5)	89 (<1)
Missing	340 (1)	250 (2)
Caspofungin		
No	31041 (94)	14519 (98)

Variable	Allogeneic N(%)	Autologous N(%)
Yes	1524 (5)	74 (<1)
Missing	340 (1)	250 (2)
Fluconazole		
No	20070 (61)	6880 (46)
Yes	12495 (38)	7713 (52)
Missing	340 (1)	250 (2)
Itraconazole		
No	32102 (98)	14537 (98)
Yes	463 (1)	56 (<1)
Missing	340 (1)	250 (2)
Micafungin		
No	27739 (84)	14381 (97)
Yes	4826 (15)	212 (1)
Missing	340 (1)	250 (2)
Posaconazole		
No	28780 (87)	14543 (98)
Yes	3784 (11)	50 (<1)
Missing	341 (1)	250 (2)
Ravuconazole		
No	32542 (99)	14588 (98)
Yes	23 (<1)	5 (<1)
Missing	340 (1)	250 (2)
Voriconazole		
No	25629 (78)	14396 (97)
Yes	6936 (21)	197 (1)
Missing	340 (1)	250 (2)
Other systemic antifungal agent		
No	31826 (97)	14471 (97)
Yes	761 (2)	122 (<1)
Missing	318 (<1)	250 (2)
Antiviral agent		
No	4740 (14)	1598 (11)
Yes	28138 (86)	13234 (89)
Missing	27 (<1)	11 (<1)
Acyclovir		
No	9759 (30)	3512 (24)
Yes	22829 (69)	11081 (75)
Missing	317 (<1)	250 (2)
Foscarnet		
No	31878 (97)	14567 (98)
Yes	709 (2)	26 (<1)

Variable	Allogeneic N(%)	Autologous N(%)
Missing	318 (<1)	250 (2)
Ganciclovir		
No	30927 (94)	14554 (98)
Yes	1661 (5)	39 (<1)
Missing	317 (<1)	250 (2)
Valganciclovir		
No	30664 (93)	14475 (98)
Yes	1924 (6)	118 (<1)
Missing	317 (<1)	250 (2)
Valacyclovir		
No	25705 (78)	11655 (79)
Yes	6883 (21)	2938 (20)
Missing	317 (<1)	250 (2)
Other antiviral agent		
No	31722 (96)	14423 (97)
Yes	865 (3)	170 (1)
Missing	318 (<1)	250 (2)
Pneumocystis agent		
No	4331 (13)	5971 (40)
Yes	28547 (87)	8861 (60)
Missing	27 (<1)	11 (<1)
Other prophylaxis agent(Before 2017)		
No	19399 (81)	8281 (82)
Yes	2773 (12)	743 (7)
Missing	1798 (8)	1115 (11)
Disease		
Acute Leukemia/MDS	21570 (66)	183 (1)
Chronic Leukemia	924 (3)	0
Non-Hodgkin Lymphoma	1899 (6)	3377 (23)
Hodgkin Lymphoma	202 (<1)	1093 (7)
Solid tumors	24 (<1)	912 (6)
Myeloma/Plasma Cell Disorder	167 (<1)	9178 (62)
Non-malignant disorders	8119 (25)	100 (<1)
Year of transplant		
2008	3262 (10)	2195 (15)
2009	2998 (9)	931 (6)
2010	1860 (6)	414 (3)
2011	1345 (4)	497 (3)
2012	1436 (4)	537 (4)
2013	2669 (8)	1209 (8)
2014	3535 (11)	1296 (9)

Variable	Allogeneic N(%)	Autologous N(%)
2015	3536 (11)	1489 (10)
2016	3329 (10)	1571 (11)
2017	3121 (9)	1461 (10)
2018	3023 (9)	2069 (14)
2019	2791 (8)	1174 (8)

Footnote: Data reported later than April 2020 is not included in this table since data is not complete in the current retrieval.

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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

IN19-01 [Perales and Szabolcs]

Delayed CD4+ T cell recovery after allogeneic hematopoietic cell transplantation is associated with decreased overall survival in adult but not pediatric recipients

Background: AlloHCT can provide curative treatment for hematologic malignancies but is associated with prolonged lymphopenia that may contribute to increased risk of infection and relapse, resulting in decreased survival. We hypothesized that patients (pts) with rapid and robust immune recovery would have improved survival and decreased non-relapse mortality.

Methods: 2089 pts who underwent 1st alloHCT for AML/ALL/MDS from 2008 to 2019 reported to CIBMTR with available CD4 counts at days 100 and 180 were included. Optimal cut points for CD4 were obtained using likelihood test based upon a drop in OS. Cox proportional hazards regression was used for each outcome from d100 and d180 landmark separately. Logistic regression was used to identify risk factors associated with high CD4 at d100 by using stepwise variable selection method with significance level 0.01.

Results: Pts (median age 51, range 2-75) were categorized into 4 groups based on GVHD prophylaxis: TCD/CD34 = 207, PTCY = 304, CNI = 1203, CNI+ATG = 375. Pts with TCD/CD34 had more MA conditioning (80%) vs PTCY (44%), CNI (70%), and CNI+ATG (60%)($p<0.01$), whereas PTCY pts were more likely to receive bone marrow graft (31%) vs TCD/CD34 (1%), CNI (15%) and CNI+ATG (16%)($p<0.01$). More pts in the CNI group received systemic steroids in the 1st 100 days (48%) vs 27% in TCD/CD34, 34% in PTCY, and 39% in CNI+ATG ($p<0.01$). Median CD4 count ($x10^6$/L) at d100 and d180 were lowest in TCD/CD34 group (82, 140, respectively) vs PTCY (135, 184), CNI (201, 246) and CNI+ATG (106, 143)(Fig. 1, $p<0.01$). IgA levels (mg/dL) at d100 were highest in the CNI+ATG (74) vs TCD/CD34 (49), PTCY (59) and CNI (59) groups ($p<0.01$). There were no significant differences in IgA level or infections between the 4 groups at d180. We identified different cut points based on OS in adult ($\geq$ 20y) and pediatric (< 20y) pts: d100 CD4 (10^6/L): 104 and 248, respectively; d180 CD4 115 and 420, respectively; d180 IgA (mg/dL) 114 and 29, respectively. In a d100 landmark model, factors that impacted achieving the CD4 cut point in adults were graft source (PB vs BM OR 1.66 $p=0.003$), GVHD prophylaxis (vs CNI: CNI+ATG OR 0.19, TCD/CD34 OR 0.16, PTCY OR 0.33; all $p<0.001$) and steroid use (OR 0.60; $p<0.001$). The results of the COX regression model for OS are in Fig. 2. Several factors, including CD4 recovery, impacted OS in adult but not pediatric pts. In adults, d100 CD4 was associated with PFS, TRM but not relapse, infections, or cGVHD. Similarly, CD4 above the cut point at

day 180 was associated with improved OS, PFS, and TRM but no other outcomes in adults. No associations were identified in pediatric pts for d100 or 180 CD4.

Conclusions: Delayed immune recovery post alloHCT in adult pts is influenced by graft source and GVHD prophylaxis and is associated with decreased OS, PFS, TRM but not relapse. A non-involuted thymus and higher graft T cell dose/kg in children likely explain improved immune recovery and lesser impact on outcomes.

Figure 1: CD4 recovery at days 100 and 180.

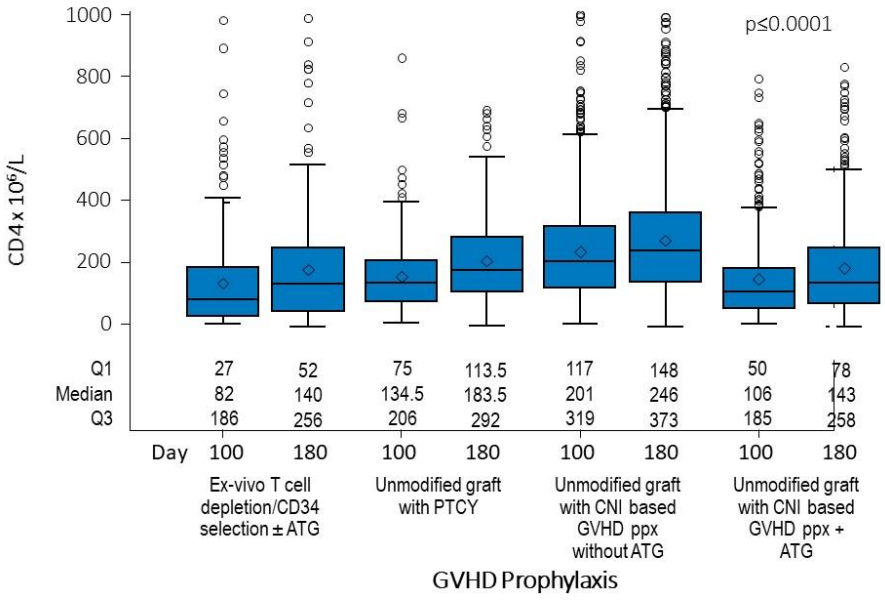

Figure 2. Cox Regression model for OS

Variable	Category	N	Events	Hazard Ratio	99% CI	p-value
Adult Patients						
CD4 Count at Day 100	< 104 x 10^6/L	529	205	1.000	-	0.001 (2 df)
	>= 104 x 10^6/L, within 12 months Post-TX	1101	386	0.595	(0.416, 0.853)	< 0.001
	>= 104 x 10^6/L, after 12 months Post-TX			1.031	(0.772, 1.376)	0.788
Patient Age (years)		1630		1.016	(1.008, 1.025)	< 0.001
Primary Disease	Acute Leukemia Early or Intermediate Stage	820	269	1.000	-	< 0.001 (3 df)
	Acute Leukemia Advanced Stage	170	79	1.697	(1.220, 2.362)	< 0.001
	Acute Leukemia Unknown Stage	26	14	1.552	(0.765, 3.151)	0.110
	MDS Any Stage	614	229	1.105	(0.865, 1.411)	0.295
Steroid Use	No	943	302	1.000	-	
	Yes	687	289	1.379	(1.114, 1.708)	< 0.001
Pediatric Patients						
CD4 Count at Day 100	< 248 x 10^6/L	316	61	1.000	-	
	>= 248 x 10^6/L	143	37	1.375	(0.802, 2.358)	0.128
Graft Source	Bone Marrow	131	25	1.000	-	< 0.001 (2 df)
	Peripheral Blood	70	27	2.400	(1.171, 4.919)	0.002
	Cord Blood	258	46	0.879	(0.462, 1.675)	0.608

Studies in Progress

IN18-01a Comparison of early (by day 180) bacterial infections after haploidentical HSCT between patients receiving cyclophosphamide-based or other GVHD prophylaxis (Celalettin Ustun/Genovefa Papanicolaou) This study is under manuscript preparation. The goal of this study is to have the manuscript submitted by June 2023.

IN18-01b Comparison of early (by day 180) fungal infections after haploidentical HSCT between patients receiving cyclophosphamide-based or other GVHD prophylaxis (Celalettin Ustun/Genovefa Papanicolaou) This study is under manuscript preparation. The goal of this study is to have the manuscript submitted by June 2023.

IN19-01 Immune recovery predicts post-transplant outcomes (Miguel-Angel Perales/ Paul Szabolcs) The study is under analysis. The goal of this study is to have the manuscript submitted by June 2023.

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.

IN20-01 Infectious complications in patients with B-Lymphoid hematologic malignancy treated with CD19 chimeric antigen receptor T cell therapy (Kitsada Wudhikarn/ Miranda McGhee/ Joshua A. Hill/ Megan Herr, etc). The study is in datafile preparation phase.

COV20-04(c) COVID-19 in Hematopoietic Cell Transplant Recipients-Race/Ethnicity (Abid, Gowda, Chemaly). The study protocol is under development.

COV20-04(d) COVID-19 in Hematopoietic Cell Transplant Recipients- Outcomes early v late (Chemaly, Infante). The study protocol is under development.

COV20-04 (e) COVID-19 in CAR-T Recipients (G Shah, Politikos, Murthy, Hamandani, N Shah, Hossain, Stiff): The study protocol is under development.

Response Summary:

This form is intended to be completed by a physician/researcher for the purpose of proposing a study. Content should not include Personal Identifiable Information (PII) or Protected Health Information (PHI). If you are a patient, do not complete this form. Patients: Contact your healthcare provider immediately for reports of problems with your treatment or problems with products received for your treatment. The CIBMTR uses de-identified data and is unable to associate reported treatment problems, adverse events, or corrections of information with a center, clinical trial, or healthcare provider.

Q1. Study Title

Influence of non-enterobacterales gram-negative bacilli bloodstream infections (BSIs) on hematopoietic cell transplantation (HCT) and cellular therapy outcomes

Q2. Key Words

Hematopoietic stem cell transplantation; cellular therapy; bacteremia; pseudomonas; acinetobacter; gram-negative bacilli

Q3. PRINCIPAL INVESTIGATOR

Provide the following information for each investigator:

Principal Investigator #1:

First and last name, degree(s):	Nikki Tran PharmD
Email address:	Nikki.Tran@osumc.edu
Institution name:	The Ohio State University Medical Center/James Cancer Hospital and Solove Research Institute
Academic rank:	N/A

Q4. Junior investigator status (defined as <40 years of age and/or ≤5 years from fellowship)

- Yes

Q5. Do you identify as an underrepresented/minority?

- Yes

Q6. Principal Investigator #2 (If applicable):

First and last name, degree(s):	Zeinab El Boghdadly, MD
Email address:	Zeinab.elboghdadly@osumc.edu
Institution name:	The Ohio State University Medical Center/James Cancer Hospital and Solove Research Institute
Academic rank:	Assistant professor of Internal medicine, division of infectious diseases

Q7. Junior investigator status (defined as <40 years of age and/or ≤5 years from fellowship)

- Yes

Q8. Do you identify as an underrepresented/minority?

- Yes

Q9. We encourage a maximum of two Principal Investigators per study. If more than one author is listed, please indicate who will be identified as the corresponding PI below:

Zeinab El Boghdadly

Q10. If you are a junior investigator and would like assistance identifying a senior mentor for your project please click below:

N/A

LETTER OF COMMITMENT:

Please note: *A letter of commitment will be signed by Lead and Last authors as it describes the expectations for filling that role. By signing the letter of commitment, the authors accept their responsibilities and will be held accountable for timely completion of all steps in the project. More details regarding author responsibilities can be found here:* *https://www.cibmtr.org/Studies/Observational/StudyManagement/p*

Q12. CURRENT ONGOING WORK WITH CIBMTR: Please list any ongoing CIBMTR projects that you are currently involved in and briefly describe your role.

Nikki Tran – No current ongoing work with CIBMTR
Zeinab El Boghdadly – Principal investigator on IN19-02 "Impact of antibiotic prophylaxis in patients undergoing allogeneic hematopoietic cell transplantation in the current era".

Q13. PROPOSED WORKING COMMITTEE:

- Infection and Immune Reconstitution

Q14. Please indicate if you have already spoken with a scientific director or working committee chair regarding this study.

- Yes

Q14a. If you have already spoken with a scientific director or working committee chair regarding this study, then please specify who:

Marcie Riches advised resubmission of this proposal

Q15. RESEARCH QUESTION:

What are the risk factors of bloodstream infections (BSIs) caused by non-enterobacterales gram-negative bacilli and its clinical impacts on relapse and non-relapse mortality within the first 100 days post HCT and cellular therapy?

Q16. RESEARCH HYPOTHESIS:

Patients with BSI caused by non-Enterobacterales Gram negative bacilli, including Pseudomonas aeruginosa, Acinetobacter, Stenotrophomonas, and Burkholderia have increased adverse clinical outcomes

Q17. SPECIFIC OBJECTIVES/OUTCOMES TO BE INVESTIGATED (Include Primary, Secondary, etc.)

Suggested word limit of 200 words:

Objectives:
Primary objective
- Assess the cumulative incidence non-Enterobacterales gram-negative bacilli BSIs within the first 100 days post HCT and cellular therapy
Secondary objectives:
- Identify risk factors for non-Enterobacterales gram-negative bacilli BSIs within the first 100 days post HCT and cellular therapy
- Assess influence of non-Enterobacterales gram-negative bacilli BSIs on relapse, GVHD, non-relapse mortality, time to engraftment post HCT
- Compare incidence, clinical characteristics, risk factors, and post-HCT outcomes between patients with no BSIs vs Enterobacterales BSIs vs non- Enterobacterales gram-negative bacilli BSIs cohort (if sample size allows)
Outcomes:
Primary:
Non-Enterobacterales BSI incidence and overall survival at 100 days and one year
Secondary:
1. Incidence of acute GVHD 2-4, relapse, graft rejection
2. Mortality (disease vs infection related), non-relapse mortality at 100 days and one year
3. Hospital length of stay

Q18. SCIENTIFIC IMPACT: Briefly state how the completion of the aims will impact participant care/outcomes and how it will advance science or clinical care.

Key Points:
1. Provide contemporary multicenter consortium-level data related to the impact of BSIs caused by non-Enterobacterales gram negative bacilli
2. Feasible to conduct using prior CIBMTR polymicrobial BSI studies
3. Inclusion of HCT (auto & allo) and CAR-T cell therapy
4. Revisit antibiotic prophylaxis and empiric treatment strategy
5. Implications on current clinical practice guidelines

Recipients of HCT and cellular therapy are at high risk for bacteremia due to impaired integrity of their mucosal barrier following conditioning or lymphodepleting regimen. Although the recommendations for antibacterial prophylaxis in this patient population have largely focused on coliforms (i.e. Escherichia coli, Klebsiella spp, Enterobacter spp) and Pseudomonas aeruginosa, empiric antibiotic regimen that would not be effective against some P. aeruginosa spp and non-enterobacterales gram-negative bacilli are still being used at centers. In addition, prolonged antibacterial exposure (prophylactic or therapeutic) significantly alters gut microbiome, increases abundance of certain bacteria and colonization with multidrug resistant organisms. Therefore, knowledge of the epidemiology, risk factors, and clinical impacts of bacteremia caused by specifically non-enterobacterales gram-negative bacilli may have implications on current prophylaxis and empiric treatment approaches in this population.

Q19. SCIENTIFIC JUSTIFICATION: Provide a background summary of previous related research and their strengths and weaknesses, justification of your research and why your research is still necessary.

Studies have demonstrated that HCT and cellular therapy recipients are at high risk for developing BSI due to damage to the integrity of mucosal barriers and presence of a central venous catheter (1,2). There are prior studies looking at bloodstream infections following HCT; however, these studies focused on both gram-positive and gram-negative or polymicrobial causes of BSI (4-7). A recent CIBMTR study conducted by Dandoy and colleague demonstrated that in patients with mucosal barrier injury, laboratory confirmed bloodstream infections were associated with significant morbidity and mortality in the first 100 days post-HCT. However, the study definition of BSI excluded non-enterobacterales organisms such as acinetobacter and stenotrophomonas (8). One study by Mikulska and colleagues looked at the BSI with gram negative bacilli and found that mortality rate at 7 days after BSI was 11% in general and as high as 39% for P. aeruginosa BSI (7). The study was conducted more than a decade ago in 2009 at a single center in Italy, these findings may not be representative of other centers. In addition, chimeric antigen receptor-modified T cell (CAR-T cell) therapy is increasingly being used for patients with B-cell malignancies. However, little is known about incidence and influence of BSI following cellular therapies (9).
There are no consortium-level data related to the impact of gram-negative bacilli BSI on HCT and/or cellular therapy outcomes. To the best of our knowledge, there is also no published analysis focused solely on non-enterobacterales gram-negative bacilli as cause of BSI following HCT and/or cellular therapy. Due to the virulence of non-enterobacterale gram negative pathogens and the difference in antibiotic coverage for these organisms, it is crucial to understand the incidence and impact of such infections post HCT and cellular therapy, especially compared to those post-HCT and cellular therapy without such infections. This may change empiric therapy and prophylactic practice. We aim to use CIBTMR database to assess this clinical question and provide clinicians with consortium-level data to guide institutional and national guidelines on empiric and prophylactic therapy targeting gram-negative pathogens.

Q19a. SCIENTIFIC JUSTIFICATION: If applicable, upload graphic as a single file (JPG, PNG, GIF)

N/A

Q20. PARTICIPANT SELECTION CRITERIA: State inclusion and exclusion criteria.

Inclusion criteria
Adults and pediatrics patients contained in the CIBMTR database between January 2017 and January 2023 who meet the following criteria:
- Patients with malignant and non-malignant hematological diseases
- Received autologous or allogeneic HCT with any type of graft sources
- Either matched related or unrelated donors for allogenic HCT
- Received CAR-T therapy regardless of prior HCT

Exclusion criteria
- Missing consent forms
- No 2100 form available
- Missing 30 and 100 day follow up forms

Q21. Does this study include pediatric patients?

- Yes

Q22. DATA REQUIREMENTS: After reviewing data on CIBMTR forms, list patient-, disease- and infusion-variables to be considered in the multivariate analyses. Data collection forms available at: http://www.cibmtr.org/DataManagement/DataCollectior Outline any supplementary data required. Additional data collection is extremely difficult and will make your proposal less feasible.

No supplemental data or additional data collection are required for this proposed study.
List of variables to be considered in the multivariate analyses:
HCT and hematologic malignancy characteristics:
• Age, sex
• Primary Diagnosis:
Type of Hematological disease (AML, ALL, CML etc.)
• Disease status at the time of transplant (Active, Remission, Unknown)
• Stem cell source (Cord, Marrow, Peripheral blood)
• Donor relation (Related, unrelated, Haploidentical)
• Match status (Mismatched, Matched)
• Cellular therapy related variables
• Type of conditioning/preparative regimen
• T cell depletion
• Total body radiation (TBR)
• Date of HCT
• Date of engraftment
• Date of admission
• Date of discharge
• Length of Hospital stay
• Use of antimicrobial prophylaxis (yes, no), name the drug, start date
Blood stream Infections in the first 30, 100 days:
• Date of infection
• Time from transplant to BSI (days)
• Name of organism
• Site of infection (blood with or without other sources)
• Septic shock
• ANC <500 mm3 when BSI occurred (yes, no)
• Platelet >20 × 109/L when BSI occurred (yes, no)
Clinical outcomes in the first 30 and 100 days:
• Acute gastrointestinal graft versus host disease (yes, no), date, degree
• Death (yes, no), date
• Cause of death (infection related vs disease)
• Relapse (yes, no), date
• Graft rejection (yes, no), date
• Secondary malignancy (yes, no), date of diagnosis

Q23. PATIENT REPORTED OUTCOME (PRO) REQUIREMENTS: If the study requires PRO data collected by CIBMTR, the proposal should include: 1) A detailed description of the PRO domains, timepoints, and proposed analysis of PROs; 2) A description of the hypothesis specific to PROS.

For additional information on what PRO measures have been collected and timepoints of collection, please reach out to the Late Effects and Quality of Life or Health Services Working Committee leadership: https://www.cibmtr.org/About/WhoWeAre/Com

No patient reported outcomes data are required for this proposed study.

Q24. SAMPLE REQUIREMENTS: If the study requires biologic samples from the CIBMTR Repository, the proposal should also include: 1) A detailed description of the proposed testing methodology and sample requirements; 2) A summary of the investigator's previous experience with the proposed assay systems. PIs should be encouraged to review the inventory details, sample types collected and reach out to research_repos@nmdp.org with any questions.

More information can be found at: https://www.cibmtr.org/Samples/Inventory/Pages/index

There is no sample requirements required for this proposed study.

Q25. NON-CIBMTR DATA SOURCE: If applicable, please provide: 1) A description of external data source to which the CIBMTR data will be linked; 2) The rationale for why the linkage is required, i.e., neither database contains all the data required to answer the study question.

N/A

Q26. REFERENCES:

REFERENCES:
1. Tomblyn M, Chiller T, Einsele H, Gress R, Sepkowitz K, Storek J et al. Guidelines for preventing infectious complications among hematopoietic cell transplant recipients: a global perspective. Preface. Bone Marrow Transplant 2009; 44(8): 453–455
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3. Engelhard D, Akova M, Boeckh MJ, Freifeld A, Sepkowitz K, Viscoli C et al. Bacterial infection prevention after hematopoietic cell transplantation. Bone Marrow Transplant 2009; 44(8): 467–470.
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5. Papanicolaou GA, Ustun C, Young JH, et al. Bloodstream Infection Due to Vancomycin-resistant Enterococcus Is Associated With Increased Mortality After Hematopoietic Cell Transplantation for Acute Leukemia and Myelodysplastic Syndrome: A Multicenter, Retrospective Cohort Study. Clin Infect Dis. 2019;69(10):1771-1779.
6. Ustun C, Young JH, Papanicolaou GA, et al. Bacterial blood stream infections (BSIs), particularly post-engraftment BSIs, are associated with increased mortality after allogeneic hematopoietic cell transplantation. Bone Marrow Transplant. 2019;54(8):1254-1265.
7. Mikulska M, Del Bono V, Raiola AM, Bruno B, Gualandi F, Occhini D et al. Blood stream infections in allogeneic hematopoietic stem cell transplant recipients: reemergence of Gram-negative rods and increasing antibiotic resistance. Biol Blood Marrow Transplant 2009; 15(1): 47–53.
8. Dandoy CE, Kim S, Chen M, et al. 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.
9. Cordeiro A, Bezerra ED, Hirayama AV, et al. Late Events after Treatment with CD19-Targeted Chimeric Antigen Receptor Modified T Cells. Biol Blood Marrow Transplant. 2020;26(1):26-33.

Q27. **CONFLICTS OF INTEREST: Do you have any conflicts of interest pertinent to this proposal concerning:**

1. Employment (such as an independent contractor, consultant or providing expert testimony)?
2. Relationships (such as executive and advisory committee positions, medical consultant, speaker's bureau)?
3. Ownership (such as equity, ownership or financial interests)?
4. Transactions (such as honoraria, patents, royalties and licenses)?
5. Legal (such as pending or current arbitration or legal proceedings)?

- No, I do not have any conflicts of interest pertinent to this proposal

Q27a. **If yes, provide detail on the nature of employment, name of organization, role, entity, ownership, type of financial transaction or legal proceeding and whether renumeration is >$5000 annually.**

N/A

BEFORE FINAL SUBMISSION, please review the PI checklist to ensure that you have completed all necessary steps. This will increase the likelihood of submitting a feasible and successful proposal.

Embedded Data:

N/A

Table 1. Characteristic of patients who received a first allogeneic[†] transplant then developed non-Enterobacterales gram negative bacilli blood stream infections within first 100 days post HCT between 2010 and 2020 reported to the CIBMTR

Characteristic	
No. of patients	722
No. of centers	137
Age of recipient, years - no. (%)	
Median (min-max)	53 (0-78)
0 - 9	102 (14)
10 - 19	55 (8)
20 - 29	53 (7)
30 - 39	63 (9)
40 - 49	64 (9)
50 - 59	125 (17)
60 - 69	203 (28)
70+	57 (8)
Gender - no. (%)	
Male	419 (58)
Female	303 (42)
Disease - no. (%)	
Acute myelogenous leukemia	248 (34)
Acute lymphoblastic leukemia	85 (12)
Other leukemia	13 (2)
Chronic myelogenous leukemia	12 (2)
Myelodysplastic/myeloproliferative disorders	159 (22)
Other acute leukemia	6 (1)
Non-Hodgkin lymphoma	35 (5)
Hodgkin lymphoma	3 (0)
Plasma cell disorder/Multiple Myeloma	1 (0)
Other Malignancies	1 (0)
Severe aplastic anemia	27 (4)
Inherited abnormalities erythrocyte differentiation or function	32 (4)
SCID and other immune system disorders	46 (6)
Inherited disorders of metabolism	7 (1)
Histiocytic disorders	2 (0)
Myeloproliferative Neoplasms	45 (6)
Donor type - no. (%)	
HLA-identical sibling	118 (16)
Twin	2 (0)
Mismatched related	
1 Ag/allele	9 (1)

Characteristic	
>=2 Ag/allele	104 (14)
Other related(matching TBD)	17 (2)
Well-matched unrelated (8/8)	248 (34)
Partially-matched unrelated (7/8)	57 (8)
Mis-matched unrelated (<=6/8)	4 (1)
Unrelated (matching TBD)	8 (1)
Cord blood	153 (21)
Missing	2 (0)
GVHD prophylaxis - no. (%)	
Ex-vivo T-cell depletion	17 (2)
CD34 selection	15 (2)
Post-CY + other(s)	139 (19)
Post-CY alone	4 (1)
CNI (TAC/CSA) + MMF +/- Other(except post-CY)	233 (32)
CNI (TAC/CSA) + MTX +/- Other(except MMF, post-CY)	241 (33)
CNI (TAC/CSA) +/- Other (except MMF, MTX, post-CY)	40 (6)
TAC alone	17 (2)
CSA alone	6 (1)
Others	7 (1)
Missing	3 (0)
Stem cell source - no. (%)	
Bone Marrow	164 (23)
Peripheral Blood	405 (56)
Cord Blood	153 (21)
Infections by 100 day	
Acinetobacter - no. (%)	
Yes	117 (16)
No	605 (84)
Pseudomonas or Burkholderia cepacia - no. (%)	
Yes	28 (4)
No	694 (96)
Flavobacterium - no. (%)	
Yes	1 (0)
No	721 (100)
Methylobacterium - no. (%)	
Yes	2 (0)
No	720 (100)
Pseudomonas aeruginosa - no. (%)	
Yes	108 (15)
No	614 (85)
Pseudomonas non-aeruginosa - no. (%)	

Characteristic	
Yes	11 (2)
No	711 (98)
Pseudomonas (all species except cepacia & maltophilia) - no. (%)	
Yes	342 (47)
No	380 (53)
Stenotrophomonas maltophilia - no. (%)	
Yes	150 (21)
No	572 (79)
Vibrio - no. (%)	
Yes	3 (0)
No	719 (100)
Year of transplant - no. (%)	
2010	93 (13)
2011	55 (8)
2012	45 (6)
2013	73 (10)
2014	90 (12)
2015	81 (11)
2016	91 (13)
2017	64 (9)
2018	81 (11)
2019	48 (7)
2020*	1 (0)

Footnote: *2020 cases are not complete in current retrieval

Table 2. Characteristic of patients who received a first autologous transplant then developed non-Enterobacterales gram negative bacilli blood stream infections within first 100 days post HCT between 2010 and 2019 reported to the CIBMTR

Characteristic	
No. of patients	95
No. of centers	52
Age of recipient - no. (%)	
Median (min-max)	58 (2-77)
0 - 9	6 (6)
10 - 19	2 (2)
20 - 29	5 (5)
30 - 39	2 (2)
40 - 49	13 (14)
50 - 59	26 (27)
60 - 69	36 (38)
70+	5 (5)
Gender - no. (%)	
Male	51 (54)
Female	44 (46)
Disease - no. (%)	
Non-Hodgkin lymphoma	21 (22)
Hodgkin lymphoma	7 (7)
Plasma cell disorder/Multiple Myeloma	57 (60)
Other Malignancies	10 (11)
Stem cell source - no. (%)	
Peripheral Blood	95 (100)
Infections by 100 day	
Acinetobacter (all species) - no. (%)	
Yes	14 (15)
No	81 (85)
Pseudomonas or Burkholderia cepacia - no. (%)	
Yes	2 (2)
No	93 (98)
Methylobacterium - no. (%)	
Yes	1 (1)
No	94 (99)
Pseudomonas aeruginosa - no. (%)	
Yes	22 (23)
No	73 (77)
Pseudomonas non-aeruginosa - no. (%)	
Yes	2 (2)

Characteristic	
No	93 (98)
Pseudomonas (all species except cepacia & maltophilia) - no. (%)	
Yes	44 (46)
No	51 (54)
Stenotrophomonas maltophilia - no. (%)	
Yes	14 (15)
No	81 (85)
Vibrio (all species) - no. (%)	
Yes	1 (1)
No	94 (99)
Year of transplant - no. (%)	
2010	1 (1)
2011	6 (6)
2012	6 (6)
2013	9 (9)
2014	14 (15)
2015	9 (9)
2016	14 (15)
2017	14 (15)
2018	13 (14)
2019	9 (9)

Table 3. Characteristic of patients who received a first commercial CAR-T therapy then developed non-Enterobacterales infections within first 100 days post HCT between 2017 and 2020 reported to the CIBMTR

Characteristic	
No. of patients	79
No. of centers	42
Age at infusion, by category - no. (%)	
Median (min-max)	56 (1-85)
< 10	7 (9)
10-19	9 (11)
20-29	6 (8)
30-39	4 (5)
40-49	7 (9)
50-59	12 (15)
60-69	17 (22)
>= 70	17 (22)
Gender - no. (%)	
Male	48 (61)
Female	31 (39)
Product - no. (%)	
Kymriah	19 (24)
Yescarta	42 (53)
Tecartus	3 (4)
Other	15 (19)
Recipient race - no. (%)	
White	55 (70)
African American	9 (11)
Asian	3 (4)
Native American	1 (1)
More than one race	2 (3)
Unknown	8 (10)
Missing	1 (1)
Recipient ethnicity - no. (%)	
Hispanic or Latino	11 (14)
Non-Hispanic or non-Latino	63 (80)
N/A - Not a resident of the U.S.	2 (3)
Unknown	3 (4)
Country - no. (%)	
US	79 (100)
Disease - no. (%)	
Acute myeloid leukemia (AML)	2 (3)

Characteristic	
Acute lymphoblastic leukemia (ALL)	17 (22)
Acute leukemia of ambiguous lineage and other myeloid neoplasms	1 (1)
Non-Hodgkin lymphoma (NHL)	57 (72)
Plasma cell disorder/multiple myeloma (PCD/MM)	1 (1)
Solid tumor	1 (1)
Karnofsky/Lansky performance score prior to CT - no. (%)	
90-100	25 (32)
80	18 (23)
< 80	27 (34)
Missing	9 (11)
Types of prior HCTs - no. (%)	
No prior HCT	51 (65)
Prior allo-HCT	10 (13)
Prior auto-HCT	17 (22)
Missing	1 (1)
Subsequent HCT since the CT infusion - no. (%)	
No	59 (75)
Yes	6 (8)
Missing	14 (18)
Infections by 100 day	
Acinetobacter (all species)- no. (%)	
Yes	6 (8)
No	73 (92)
Pseudomonas or Burkholderia cepacia - no. (%)	
Yes	5 (6)
No	74 (94)
Pseudomonas aeruginosa - no. (%)	
Yes	45 (57)
No	34 (43)
Pseudomonas non-aeruginosa - no. (%)	
Yes	5 (6)
No	74 (94)
Stenotrophomonas maltophilia - no. (%)	
Yes	20 (25)
No	59 (75)
Year of CT - no. (%)	
2017	4 (5)
2018	15 (19)
2019	35 (44)
2020	25 (32)

Characteristic	
Follow-up of survivors, months - median (range)	13 (5-43)

CIBMTR IN2210-xxx

(Combined draft of 2210-36, 2210-57, 2210-163, 2210-241)

Infectious complications in patients with relapsed/refractory multiple myeloma receiving B-cell maturation antigen (BCMA) targeted chimeric antigen receptor (CAR) T cells

Draft Protocol

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1. Hypothesis:

- Infectious complications following BCMA targeted CAR T-cell therapy are common but vary depending on the time from treatment with BCMA CAR T-cell therapy.
- Infections after BCMA targeted CAR T-cell therapy are associated with certain disease-, host- and CAR T-cell-related characteristics.
- The pattern of infections after BCMA targeted CAR T-cell therapy has evolved over time attributable to change in the supportive care.
- Infections after BCMA targeted CAR T-cell therapy are associated with inferior outcomes including overall survival and infection-related mortality.

2. Specific Aims:

a. Primary Aim: To describe the incidence, infection density, patterns and outcomes of infections in patients treated with BCMA CAR T-cell therapy.

b. Secondary Aims:

   i. To identify risk factors for infection in patients treated with BCMA CAR T-cell therapy.

   ii. To explore the impact of infectious complications on both short-term and long-term clinical outcomes following CAR T-cell therapy.

   iii. To assess longitudinal measures of hematologic reconstitution such as immune cell subsets following BCMA targeted CAR T-cell therapy and its potential implications for an immune-based antimicrobial prophylactic approach.

3. Scientific Impact:

Recently, BCMA CAR T-cell therapy has been approved as a standard treatment for patients with heavily treated relapsed/refractory multiple myeloma (RRMM) after 4 or more prior lines of treatment. BCMA CAR T-cell therapy provides an exceptionally high response rate and potentially durable disease control in these heavily treated refractory patients. Despite its excellent efficacy profile, like CD19 CAR T-cell product, BCMA CAR T-cell therapy could result in several side effects including immune-mediated toxicities, cytopenias and infections attributed to its off-target activities. The effect of BCMA CAR T-cell therapy on immune depletion could be profound and distinct from those treated with CD19 CAR T-cell therapy. Although there is increasing data about infections in patients treated with BCMA CAR T-cell therapy, most reports are from single centers, and there is limited real-world data and no high-quality evidence on appropriate infection

prophylactic measures in these patients. Therefore, it is of utmost importance to characterize the infectious complications for patients with R/R MM treated with BCMA CAR T-cell therapy using a large database such as CIBMTR. This study will provide us comprehensive information on the incidence, patterns, predisposing factors for infections in patients treated with BCMA CAR T-cell therapy. It also could provide a better insight into immune reconstitution and proper approaches of antimicrobial prophylaxis including IVIG replacement in R/R MM patients treated with BCMA CAR T-cell therapy.

4. Scientific Justification:

BCMA chimeric antigen receptor (CAR) T-cell therapy has become a standard of care for R/R MM (1, 2). Recently, BCMA CAR T-cell therapy was approved for treatment of R/R MM after 4 lines or more prior lines of therapy providing an exceptionally high response rate. Despite its outstanding activity, like CD19 CAR T-cell therapy, BCMA CAR T-cell therapy is also associated with considerable toxicites mainly cytokine release syndrome (CRS), Immune effector cell-associated neurotoxicity syndrome (ICANS), hypogammaglobulinemia, and cytopenias (3). Patients treated with CAR T-cell therapy have both innate and adaptive immunity impairment resulting in an increased risk of infectious complications. Although several single-center studies have explored the natural history of infectious complications after CD19 CAR-T cell therapy, data focusing on infection after BCMA CAR T-cell therapy is still lacking. Data from pivotal studies that lead to the approval of the BCMA CAR-T cell products indicated that infections were observed in 60-70% after treatment, with grade 3 or more severe infection seen in approximately 20% (1, 2). In the KarMMa study, the incidence of infection was 69% (16% bacterial, 15% viral, 7% fungal) including 22% grade ≥3. In the CARTITUDE-1 trial, 58% of patients developed infections which included 20% grade ≥3 infection and 4% sepsis.

Although there have been reports from single-center retrospective studies on infectious complications in patients treated with BCMA CAR T-cell therapy (4-7), real-world data from multi-center studies or registry based analysis on infectious complications after BCMA CAR T-cell therapy is lacking. Recently, Kambhampati and colleagues reported a high incidence of infections after BCMA CAR T-cell therapy including 40% bacterial, 53% viral and 6% fungal infection in 29 of 55 patients with R/R MM. Similar to CD19 CAR T-cell therapy, infectious complications mostly occurred within the first 100 days. However, unlike CD19 CAR T-cell therapy, in this study, viral infections were more commonly observed in patients treated with BCMA CAR T-cell than bacterial infections. Josyula *et al.* also reported the effect of BCMA CAR T-cell therapy on humoral

immunity and risk of infection in patients with R/R MM (5). In this study, the incidence of early infections (<30 days post-CAR T-cell therapy) appeared to be less common than for B lymphoid malignancies treated with CD19 CAR T-cells, whereas late infections were more frequent. In addition, viral infections were more frequent than bacterial infections.

Several risk factors including patient-, CAR T- and disease-related factors predispose patients treated with CAR T-cells to infectious complications. Besides the conventional risk factors of infection similar to patients treated with CD19 CAR T-cell therapy, cellular and immune kinetics both before and after BCMA CAR T-cell therapy are different from patients with B-cell lymphoid malignancies treated with CD19 CAR T-cell therapy. The different patterns of immune mediated complications (CRS and ICANS) especially those requiring anti-cytokine therapy (tocilizumab or steroid) may impact the incidence and patterns of infection compared to patients with lymphoma treated with CD19 CAR T-cells. Since BCMA plays a critical role in regulating the B cell maturation including the survival of plasma cells and antibody production, targeting BCMA could profoundly affect both humoral and cellular immunity which could potentially explain a predilection to viral infection observed in patients treated with BCMA CAR T-cells. In addition, most patients with R/R MM treated with BCMA CAR T-cells are heavily treated and almost all patients previously underwent ASCT indicating a very immunocompromised state. Studies have demonstrated that patients with plasma cell neoplasm had a higher incidence of hypogammaglobulinemia. Besides the quantitative effect on IgG level, CAR T-cells against different targets also result in differential impact on the diversity of IgG. Patients with R/R MM who were treated with BCMA CAR T-cells also lost the diversity of IgG against microorganisms (8). BCMA CAR T-cells may affect the pre-existing and reconstitution of new antibody-producing plasma cells and have a higher impact on organism specific Ig levels to several pathogens compared to CD19 CAR T-cells (9). Consequently, this single-center study showed a diminished vaccine response in patients with R/R MM.

Since BCMA CAR T-cell therapy is now an approved option for patients with R/R MM, it will be increasingly used in clinical practice. Therefore, there is a critical need to determine the characteristics of infectious complications in these patients and strategies to mitigate these adverse events. Protecting patients from subsequent complications after effective treatment of their underlying disease is fundamental to broader the use of CAR T-cell therapy in the management of MM. To address this need, we propose to determine the epidemiology of infectious complications after BCMA CAR T-cell therapy and to identify risk factors associated

with infection in the real-world setting. In addition, we also plan to explore the impact of infectious complications on survival outcomes in patients who received BCMA CAR T-cell products. The results of this study will help us to better understand the burden including risk factors of infectious complications and provide us insight on how to properly prevent infections in patients who receive BCMA CAR T-cell therapy for MM.

Study Population:

- **Inclusion Criteria**
    - Adult patients with R/R MM who underwent FDA-approved BCMA CAR T-cell therapy from March 2021 (time of approval of ide-cel) to December 2021 (include only the 1st CAR T-cell therapy)

- **Exclusion criteria:**
    - Patients who received BCMA CAR T-cell therapy under clinical trial

Outcomes:

- Infection density: Defined as the number of infections per patient days at risk. The densities of bacterial, viral, fungal, and all-cause infections will be studied separately over the time periods day 0-30, day 31-100, day 100-365 from the time of CAR T-cell infusion.
- Cumulative incidence of infection: This will be evaluated for bacterial, viral, fungal, and all-cause infections through 1 year after CAR T-cell infusion. This cumulative incidence will be analyzed and reported at day 30, day 100 and 1 year. Relapse/progressive disease, a new anti-myeloma treatment initiation (including hematopoietic cell transplantation) and death from non-infectious causes after BCMA CAR T-cell therapy are considered to be competing events for infection onset.
- Infection-free survival: Defined as survival after the first BCMA CAR T-cell therapy without infection. Surviving patients who are infection free will be censored at the time of last follow-up. Infection free survival will be reported at day 100 and 1 year.
- Infection-related mortality: Cumulative incidence of death caused by infection as a primary or contributory cause of death will be evaluated through 1 year (separately report at day +100 and 1 year). Relapse, re-initiation of anti-myeloma treatment, and death from non-infectious causes are considered competing events for this endpoint.

- Overall survival: Time from BCMA CAR T-cell infusion to death. Death from any cause will be considered an event. Surviving patients will be censored at the time of last follow-up. Median and 1-year overall survival will be reported.
- Cause of death: The primary cause of death will be described for expired patients. For patients with non-infectious causes of death, infection as a contributory cause will also be reported.

Variables to Be Described

- Number of Centers

Patient-Related factors

- Age at treatment with CAR T-cell therapy
- Gender: Male vs. Female
- Ethnicity: Caucasian, Hispanic, African American, Asian Pacific Islander
- Performance Status: Karnofsky score (≥90% vs. 80-80% vs. <80%) for adults
- CMV status pre-CAR T-cells
- IgG level before CAR T-cells (if available)
- Baseline ANC, ALC (pre-lymphodepletion) (or if require growth factor before LD chemo which may indirectly indicate baseline neutropenia – form 4000)
- Hematopoietic Cell Transplant Comorbidity Index: 0-2 vs. 3-4 vs. high risk group (≥ 5)
- History of prior infection as a part of HCT-CI.

Disease-Related factors

- Time from diagnosis to CAR T-cell infusion
- ISS-R staging at the time of diagnosis
- Presence of high risk cytogenetic/molecular abnormalities
- LDH level: Normal vs. Elevated
- Beta-2-microglobulin: Normal vs. Elevated
- Presence of plasmacytoma: Yes vs. No
- Presence of amyloidosis: Yes vs. No
- Free light chain subtype: Kappa vs. Lambda
- Disease status at CAR T-cell infusion: CR vs. non CR

- Number of prior lines of treatments
- Triple class refractory: Yes or No
- Transplant before CAR T-cell therapy
  - Type of transplant(s) if transplant(s) before CAR T-cell: Auto, Allo
- If transplant, time from transplant to CAR T-cell therapy
- Bridging therapy before CAR T-cell
- Time from last non-transplant therapy to CAR T-cell infusion
- Response to most recent therapy prior to CAR-T cell therapy (response classified as CR vs. non CR above, trying to get more granular information of the response for those not in CR – Stable disease (SD), progressive disease (PD), partial response (PR), very good partial response (VGPR) etc.)

<u>CAR T-cell Related factors</u>

- Lymphodepletion Regimen for CAR T-cells
- Time between start of Lymphodepletion and CAR.T infusion
- Dose of CAR T-cell (if available)
- Cytokines, Maximum level within the first 100 days and time to maximum level
  - CRP
  - Ferritin
- G-CSF: Yes/No (form 4100 – limitations include not capture all GCSF, plan vs. unplanned use and there is no duration)
- Exploratory variables:
    - Best response to CAR T-cell therapy by IMWG criteria: CR vs. Non-CR

<u>Infection Related (Within day 0-30, day 30-100, day 100-365 after CAR T-cell infusion)</u>

- Overall infection
- Bacterial infection: Yes/No
    - Bacterial infections (Descriptive data and if number allowed, stratification for comparison)
    - Site of bacterial infection
- Viral infection: Yes/No
    - Viral infections (Descriptive data: CMV, EBV, HZV, respiratory virus, etc)
    - Site of viral infection
- Fungal infection: Yes/No

  - Fungal infections (Descriptive data: Molds, Yeasts, Pneumocystis jiroveci)
  - Site of fungal infection
- IVIG replacement given: Yes/No
- Hypogammaglobulinemia after CAR T-cells (IgG level < 600): Yes or No

Time-dependent

- Neutrophil engraftment prior to infection: Yes/No
- Median time to neutrophil engraftment
- Absolute neutrophil count at day 100, 180, 365
- Absolute lymphocyte count at day 100, 180, 365
- Grade 4 organ toxicity prior to infection: Yes/No if yes what organ system
- Median time to grade 4 toxicity
- Graft Versus Host Disease (for patients with prior alloHCT receiving allo-T-cells) prior to infection (after CAR T infusion): Yes/No
- Median onset of GVHD after CAR T
- CRS prior to infection: Yes/No
- CRS ASTCT grade: (as a calculated variable)
- Median time to CRS
- Duration of CRS (Start and End dates)
- ICANS prior to infection: Yes/No
- ICANS ASTCT grade (as a calculated variable)
- Median time to ICANS
- Duration of ICANS (Start and End dates)
- Received steroids: Yes/No (if yes, for what indications)
- Received Tocilizumab: No vs. Yes
- Relapse/Progression prior to infection: Yes/No
- Alive Status: Live vs. Death

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

Study design:

Patient-, disease- and CAR T infusion-related factors will be described by the median and range for continuous variables and counts and percentages of total for categorical variables. Patient-,

disease- and CAR T infusion-related factors will be compared between groups using Pearson's chi-square test for categorical variables and Kruskal-Wallis/Wilcoxon tests for continuous variables. The probabilities of overall survival and infection free survival will be described using the Kaplan Meier estimator with the variance estimated by Greenwood's formula. Point estimates and 95% confidence intervals (CIs) will be provided for infection free survival at day 100, 1 year and for both overall survival at 1 year and median survival time. The cumulative incidences of infections and infection-related mortality will be described using the Aalen-Johansen estimator. Cumulative incidence estimates and 95% CIs will be provided for infection-related mortality at day 100, 1 year and infections at day 30, day 100 and 1 year. Infection densities (overall and by infection type) are defined for each patient as the number of infections per patient days-at-risk. Densities will be summarized separately during days 0-30, days 31-100 and days 100-365 using the sample mean, median, and range. Poisson regression models will be used to examine the association between baseline characteristics (including age, gender, prior lines of treatment, HCT-CI, performance status, history of transplantation, CAR T-cell product, etc.) and infection density during days 0-30, days 31-100 and days 100-365 after CAR T-cell infusion. Cox proportional hazards models will be used to evaluate potential risk factors impacting the cause-specific hazards of infections and infection-related mortality during days 0-30, days 31-100 and days 100-365. Cox models will also investigate associations of factors with overall and infection-free survival rates. A stepwise selection procedure will be used to identify variables for inclusion in the final models with a significant level with 0.05 used as the selection criterion. Interactions between significant variables will be tested. The proportional hazards assumptions for each variable will be tested. If the assumption is violated for any covariate(s), models will be constructed by breaking the post-transplant course into separate time periods within each of which proportionality holds, using maximization of the Cox partial likelihood to find the most appropriate cutpoint(s). The existence of center effects will be tested using the score test of Commenges and Anderson.

Non-CIBMTR Data Source: Not required

References:

1. Berdeja JG, Madduri D, Usmani SZ, Jakubowiak A, Agha M, Cohen AD, et al. Ciltacabtagene autoleucel, a B-cell maturation antigen-directed chimeric antigen receptor T-cell therapy in patients with relapsed or refractory multiple myeloma (CARTITUDE-1): a phase 1b/2 open-label study. Lancet. 2021;398(10297):314-24.
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Conflicts of Interest:

Do you have any conflicts of interest pertinent to this proposal concerning:

- *Employment (such as an independent contractor, consultant or providing expert testimony)?*
- *Relationships (such as executive and advisory committee positions, medical consultant, speaker's bureau)?*
- *Ownership (such as equity, ownership or financial interests)?*
- *Transactions (such as honoraria, patents, royalties and licenses)?*
- *Legal (such as pending or current arbitration or legal proceedings)?*

1. Kitsada Wudhikarn, MD: No conflict of interest to disclose
2. Abu-Sayeef Mirza, MD, MPH: No conflict of interest to disclose
3. Lohith Gowda, MD, MRCP: No conflict of interest to disclose
4. Muhammad Bilal Abid, MD, MRCP: No conflict of interest to disclose
5. Srinivas Devarakonda, MD: No conflict of interest to disclose
6. Yvonne Efebera, MD: No conflict of interest to disclose
7. Miguel Perales, MD: Yes as reported below

If yes, provide detail on the nature of employment, name of organization, role, entity, ownership, type of financial transaction or legal proceeding and whether renumeration is >$5000 annually.

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.

Characteristic of patients who received a first commercial CAR-T therapy for Plasma cell disorder between 2016 and 2021 reported to the CIBMTR

Characteristic	
No. of patients	250
No. of centers	40
Age at infusion, by category - no. (%)	
Median (min-max)	62 (18-81)
10-19	1 (0)
20-29	1 (0)
30-39	6 (2)
40-49	28 (11)
50-59	64 (26)
60-69	100 (40)
>= 70	50 (20)
Gender - no. (%)	
Male	147 (59)
Female	101 (40)
Missing	2 (1)
Product - no. (%)	
Other	250 (100)
Recipient race - no. (%)	
White	199 (80)
African American	32 (13)
Asian	9 (4)
Native American	1 (0)
Unknown	4 (2)
Missing	5 (2)
Recipient ethnicity - no. (%)	
Hispanic or Latino	14 (6)
Non-Hispanic or non-Latino	229 (92)
Unknown	7 (3)
Country - no. (%)	
US	250 (100)
Disease - no. (%)	
Plasma cell disorder/multiple myeloma (PCD/MM)	250 (100)
Karnofsky/Lansky performance score prior to CT - no. (%)	
90-100	117 (47)

Characteristic	
80	61 (24)
< 80	21 (8)
Missing	51 (20)
Types of prior HCTs - no. (%)	
No prior HCT	15 (6)
Prior auto-HCT	228 (91)
Prior auto and allo-HCT	3 (1)
Missing	4 (2)
Subsequent HCT since the CT infusion - no. (%)	
No	182 (73)
Yes	21 (8)
Missing	47 (19)
Bacterial infection by day 100 - no. (%)	
No	215 (86)
Yes	29 (12)
Missing	6 (2)
Fungal infection by day 100 - no. (%)	
No	243 (97)
Yes	1 (0)
Missing	6 (2)
Viral infection by day 100 - no. (%)	
No	217 (87)
Yes	27 (11)
Missing	6 (2)
Year of CT - no. (%)	
2016	4 (2)
2017	8 (3)
2018	59 (24)
2019	74 (30)
2020	78 (31)
2021	27 (11)
Follow-up of survivors, months - median (range)	25 (1-60)

Characteristic of patients who received a first commercial CAR-T therapy for Plasma cell disorder between 2016 and 2021 reported to the CIBMTR

Characteristic	
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2017	8 (3)
2018	59 (24)
2019	74 (30)
2020	78 (31)
2021	27 (11)
Follow-up of survivors, months - median (range)	25 (1-60)

Response Summary:

This form is intended to be completed by a physician/researcher for the purpose of proposing a study. Content should not include Personal Identifiable Information (PII) or Protected Health Information (PHI). If you are a patient, do not complete this form. Patients: Contact your healthcare provider immediately for reports of problems with your treatment or problems with products received for your treatment. The CIBMTR uses de-identified data and is unable to associate reported treatment problems, adverse events, or corrections of information with a center, clinical trial, or healthcare provider.

Q1. Study Title

Epidemiology and risk factors associated with polyoma virus (BKV) viremia/viruria and/or BKV associated hemorrhagic cystitis (HC) in allogeneic Hematopoietic Cell Transplant (HCT) recipients.

Q2. Key Words

polyoma virus (BKV) associated hemorrhagic cystitis, BK viremia/viuria, allogeneic hematopoietic cell transplant, infectious complications

Q3. PRINCIPAL INVESTIGATOR

Provide the following information for each investigator:

Principal Investigator #1:

First and last name, degree(s):	Zainab Shahid, MD, FACP, FIDSA
Email address:	shahidz@mskcc.org
Institution name:	Memorial Sloan Kettering Cancer Center
Academic rank:	Associate Attending

Q4. Junior investigator status (defined as <40 years of age and/or ≤5 years from fellowship)

- No

Q5. Do you identify as an underrepresented/minority?

- Yes

Q6. Principal Investigator #2 (If applicable):

First and last name, degree(s):	Roy F Chemaly, MD, MPH, FIDSA, FACP
Email address:	rfchemaly@mdanderson.org
Institution name:	MD Anderson Cancer Center
Academic rank:	Professor of Medicine

Q7. Junior investigator status (defined as <40 years of age and/or ≤5 years from fellowship)

- No

Q8. Do you identify as an underrepresented/minority?

- Yes

Q9. We encourage a maximum of two Principal Investigators per study. If more than one author is listed, please indicate who will be identified as the corresponding PI below:

N/A

Q10. If you are a junior investigator and would like assistance identifying a senior mentor for your project please click below:

N/A

LETTER OF COMMITMENT:

Please note: *A letter of commitment will be signed by Lead and Last authors as it describes the expectations for filling that role. By signing the letter of commitment, the authors accept their responsibilities and will be held accountable for timely completion of all steps in the project. More details regarding author responsibilities can be found here:* *https://www.cibmtr.org/Studies/Observational/StudyManagement/p*

Q12. CURRENT ONGOING WORK WITH CIBMTR: Please list any ongoing CIBMTR projects that you are currently involved in and briefly describe your role.

NA

Q13. PROPOSED WORKING COMMITTEE:

- Infection and Immune Reconstitution

Q14. Please indicate if you have already spoken with a scientific director or working committee chair regarding this study.

- Yes

Q14a. If you have already spoken with a scientific director or working committee chair regarding this study, then please specify who:

Miguel Perales and Roy Chemaly

Q15. RESEARCH QUESTION:

What is the disease burden associated with BKV associated HC, BK viremia and BK viuria? What are the risk factors and clinical outcomes associated with the development of BKV associated disease (HC, viremia and viuria) in different allogeneic HCT settings including cord blood transplant (CBT) ?

Q16. RESEARCH HYPOTHESIS:

HC is associated with significant morbidity and mortality after allogeneic HCT within 100 days of transplantation. BKV associated disease (BKV HC, BK viremia and/or BK viuria) is associated with the type and level of immunosuppression in the early post-transplant period. We hypothesize that the incidence of BK associated HC, BK viremia and/or BK viuria varies in different transplant settings. We aim to study its incidence in different transplant settings and identify predisposing risk factors associated with its development and understand its impact on clinical outcomes such as non-relapse mortality and overall survival.

Q17. SPECIFIC OBJECTIVES/OUTCOMES TO BE INVESTIGATED (Include Primary, Secondary, etc.)

Suggested word limit of 200 words:

- To assess the incidence of BKV associated HC, BK viremia and/or BK viuria in allogeneic HCT recipients including CBT
- To evaluate the differences in epidemiology of BKV associated disease based on underlying disease, conditioning regimens, graft source, intensity and GvHD prophylaxis and presence of GvHD
- To study risk factors associated with the development of BKV associated HC, BK viremia and BK viuria including gender, laboratory parameters at time of diagnosis, and ethnic differences
- To study the impact of BK viremia and BK viruria on kidney function in the absence or presence of BKV associated HC
- To study the association of BKV associated HC with other viral reactivations in early and late post-transplant period
- To study the impact of BKV associated HC on clinical outcomes including overall survival and non-relapse mortality (adjusted for AKI, CKI)

Q18. SCIENTIFIC IMPACT: Briefly state how the completion of the aims will impact participant care/outcomes and how it will advance science or clinical care.

BKV associated hemorrhagic cystitis causes high morbidity, prolonged length of stay, and mortality 1in allogeneic HCT recipients and is associated with increased cost 2. Human papilloma virus was first described as a cause of acute hemorrhagic cystitis in 1976 3. BK viuria was detected in the urine of pre- and post HCT recipients in allogeneic cell transplant recipients (1.8% vs 21.8%) 4 and later a prospective study of urinary excretion of polyomavirus in 53 alloHCT patients showed that 47% (21/53) of patients excreted the virus post HCT and 21 patients (71%) developed HC 5. Since the initial report more recent studies showed the incidence to be between 12%-16% in adults with slightly higher incidence in pediatric population (21%) 6,7,8. Most common risk factors associated with the development of BK HC are myeloablative regimens, unrelated donor transplants, cord blood transplantation, poor immune reconstitution and positive pretransplant BKV serology 9,10,11,12,13. Discrepant reports exist for other risk factors, including age, GvHD, CMV reactivation, HHV-6 viremia and HLA- mismatch 14,15,16.

Reports about the impact of BKV associated HC on clinical outcomes in HCT have variable results. LE Lunde et al reported that HC was more common in males and HLA-mismatch and cord blood graft recipients with increased treatment related mortality at 1 year and no effect on overall survival 17. Kerbauy et al reported younger age, male sex, grade 2-4 GvHD and cord blood source as risk factors for BK HV with decreased OS (hazard ratio [HR] 7.51, $P < 0.0001$), and an increased risk of TRM (HR 3.66, $P < 0.0001$) in a retrospective study of 133 adult allogeneic HCT recipients18. Abudayyeh et al reported BK viuria as a significant factor for kidney function decline in 2477 allogeneic HCT recipients ($p<0.001$) and poor overall survival in patients with BKV infection (HR 1.27, 95% CI 1.11–1.44)1.

This study will help better understand the epidemiology of BKV associated disease amongst a large cohort of allogeneic HCT recipients and it's true burden on clinical outcomes.This is further explained in scientific justification section.

Q19. SCIENTIFIC JUSTIFICATION: Provide a background summary of previous related research and their strengths and weaknesses, justification of your research and why your research is still necessary.

The proposed study will allow an opportunity to analyze a multicenter large cohort of allogeneic HCT recipients to better understand the epidemiology, risk factors associated with development of BK viremia/viruria and/or BKV HC and its impact on transplant outcomes. With the recent use of post-transplant cyclophosphamide for graft vs host disease (GvHD) prophylaxis which predisposes to uroepithelial injury, there may be changes in its epidemiology in recent years. The results generated from this study will help identify high risk settings for development of BKV HC, BK viuria/ viremia and provide insight about its true burden in modern day transplantation. In addition, there has been a first attempt to develop a risk assessment tool for symptomatic BKV infection at day 30 post SCT; however, did not evaluate risk of HC specifically (PMID: 32602954). The results of this work would be utilized to develop risk assessment tool that would help to develop risk mitigation and early intervention strategies in high-risk patients. Establishing further guidelines and screening for BKV infection would help improve SCT survivors' overall outcomes similarly to established screening for BKV nephropathy in kidney transplant recipients.

Q19a. SCIENTIFIC JUSTIFICATION: If applicable, upload graphic as a single file (JPG, PNG, GIF)

N/A

Q20. PARTICIPANT SELECTION CRITERIA: State inclusion and exclusion criteria.

Inclusion criteria:
All patients who have received an allogeneic hematopoietic cell transplantation including cord blood transplant, haploidentical HCT, matched unrelated and matched related transplants between 2017-2021 and have been reported to the CIBMTR as BK virus infection (HC, BK viremia and BK viruria). All diagnoses, donor choice, graft sources, and conditioning regimen will be included.

Q21. Does this study include pediatric patients?

- Yes

Q22. DATA REQUIREMENTS: After reviewing data on CIBMTR forms, list patient-, disease- and infusion-variables to be considered in the multivariate analyses. Data collection forms available at: http://www.cibmtr.org/DataManagement/DataCollectior Outline any supplementary data required. Additional data collection is extremely difficult and will make your proposal less feasible.

Patient-related:
• Age at transplant
• Gender: male vs. female
• Karnofsky performance status at transplant: ≥ 90 vs. < 90 vs. missing
• Race: Caucasian vs. others vs. missing
• Ethnicity
Transplant Course:
- BKV associated HC yes vs. no
- BK viremia yes vs no
- BK viuria yes vs no
- CMV reactivation: yes vs. no
- HHV-6 reactivation: yes vs. no
- AKI yes vs no
- CD4 count at day 40 and 100
- ALC at day 40 and 100
Disease-related:
- Underlying malignancy
- Time from diagnosis to transplantation
- Disease state at time of transplant: CR vs Cri vs PR vs SD
Transplant-related:
• Graft source: peripheral blood vs bone marrow vs cord blood
• Transplant donor type: Match related donor vs. match unrelated donor vs. mismatch unrelated donor vs. haploidentical
• Conditioning intensity: myeloablative vs. reduced intensity conditioning/ non-myeloablative
• Total Body Irradiation: TBI vs non-TBI based conditioning regimen.
• Graft manipulation (ex-vivo TCD, CD34 selection)- yes vs no
• GVHD prophylaxis: CNI + MTX ± others except MMF, post Cy vs. CNI + MMF ±others except post Cy vs. CNI + others except MMF, MTX vs. missing vs. other
• ATG/alemtuzumab use in conditioning: no vs. yes
• Donor-recipient sex match: male-male vs. male-female vs. female-male vs. female-female vs. missing
• CMV serostatus matching (+/-, +/+, -/-, -/+) between donor and recipient
• Year of transplant: continuous
• GvHD grade II-IV yes vs no

Q23. **PATIENT REPORTED OUTCOME (PRO) REQUIREMENTS: If the study requires PRO data collected by CIBMTR, the proposal should include: 1) A detailed description of the PRO domains, timepoints, and proposed analysis of PROs; 2) A description of the hypothesis specific to PROS.**

For additional information on what PRO measures have been collected and timepoints of collection, please reach out to the Late Effects and Quality of Life or Health Services Working Committee leadership: https://www.cibmtr.org/About/WhoWeAre/Com

NA

Q24. **SAMPLE REQUIREMENTS: If the study requires biologic samples from the CIBMTR Repository, the proposal should also include: 1) A detailed description of the proposed testing methodology and sample requirements; 2) A summary of the investigator's previous experience with the proposed assay systems. PIs should be encouraged to review the inventory details, sample types collected and reach out to research_repos@nmdp.org with any questions.**

More information can be found at: https://www.cibmtr.org/Samples/Inventory/Pages/index

NA

Q25. NON-CIBMTR DATA SOURCE: If applicable, please provide: 1) A description of external data source to which the CIBMTR data will be linked; 2) The rationale for why the linkage is required, i.e., neither database contains all the data required to answer the study question.

NA

Q26. REFERENCES:

1. A. Abudayyeh1, A. Hamdi1 , H. Lin , M. Abdelrahim , G. Rondon , B. S. Andersson , A. Afrough , C. S. Martinez , J. J. Tarrand , D. P. Kontoyiannis, D. Marin , A. O. Gaber, A. Salahudeen , B. Oran , R. F. Chemaly , A. Olson , R. Jones , U. Popat , R. E. Champlin, E. J. Shpall , W. C. Winkelmayer and K. Rezvani. Symptomatic BK Virus Infection Is Associated With Kidney Function Decline and Poor Overall Survival in Allogeneic Hematopoietic Stem Cell Recipients. American Journal of Transplantation 2016; 16: 1492–1502
2. Symptomatic BK Virus Infection Is Associated With
3. Kidney Function Decline and Poor Overall Survival in
4. Allogeneic Hematopoietic Stem Cell Recipients
2. L Gilis, S Morisset, G Billaud, S Ducastelle-Lepreˆtre, H Labussie`re-Wallet, F-E Nicolini, F Barraco, M Detrait, X Thomas, N Tedone, M Sobh, C Chidiac, T Ferry, G Salles, M Michallet and F Ader on behalf of the Lyon BK virus Study group. High burden of BK virus-associated hemorrhagic cystitis in patients undergoing allogeneic hematopoietic stem cell transplantation Bone Marrow Transplantation (2014) 49, 664–670;
3. Hashida et al. Acute hemorrhagic cystitis of childhood and papovavirus-like particles. Journal of Pediatrics 1976 Vol.89 No.1 pp.85-87
4. Ray R. Arthur,Anna Marie Beckmann,Chou Chi Li,Rein Saral,Keerti V. Shah, Direct detection of the human papovavirus BK in urine of bone marrow transplant recipients: Comparison of DNA hybridization with ELISA. Journal of Medical Virology. Volume 16, Issue 1 p. 29-36
5. Ray R. Arthur, Ph.D., Keerti V. Shah, M.D., Stephen J. Baust, P.A.-C., George W. Santos, M.D., and Rein Saral, M.D .Association of BK Viruria with Hemorrhagic Cystitis in Recipients of Bone Marrow Transplants .N Engl J Med 1986; 315:230–4
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13. Ala Abudayyeh, Amir Hamdi, Maen Abdelrahim, Heather Lin, Valda D. Page, Gabriela Rondon, Borje S. Andersson, Aimaz Afrough, Charles S. Martinez, Jeffrey J. Tarrand, Dimitrios P. Kontoyiannis, David Marin, A. Osama Gaber, Betul Oran, Roy F. Chemaly7 | Sairah Ahmed, Islam Abudayyeh, Amanda Olson, Roy Jones, Uday Popat, Richard E. Champlin, Elizabeth J. Shpall, Katayoun Rezvani. Poor immune reconstitution is associated with symptomatic BK polyomavirus viruria in allogeneic stem cell transplant recipientsTranspl Infect Dis. 2017;19:e12632
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Q27. **CONFLICTS OF INTEREST: Do you have any conflicts of interest pertinent to this proposal concerning:**

1. Employment (such as an independent contractor, consultant or providing expert testimony)?
2. Relationships (such as executive and advisory committee positions, medical consultant, speaker's bureau)?
3. Ownership (such as equity, ownership or financial interests)?
4. Transactions (such as honoraria, patents, royalties and licenses)?
5. Legal (such as pending or current arbitration or legal proceedings)?

- No, I do not have any conflicts of interest pertinent to this proposal

Q27a. **If yes, provide detail on the nature of employment, name of organization, role, entity, ownership, type of financial transaction or legal proceeding and whether renumeration is >$5000 annually.**

N/A

BEFORE FINAL SUBMISSION, please review the PI checklist to ensure that you have completed all necessary steps. This will increase the likelihood of submitting a feasible and successful proposal.

Embedded Data:

N/A

Characteristic of patients who received a first allogeneic transplant between 2017 and 2022 with BK virus infection post HCT reported to the CIBMTR

Characteristic	
No. of patients	1350
No. of centers	140
Age of recipient - no. (%)	
Median (min-max)	56 (0-81)
0 - 9	83 (6)
10 - 19	137 (10)
20 - 29	105 (8)
30 - 39	118 (9)
40 - 49	140 (10)
50 - 59	206 (15)
60 - 69	417 (31)
70+	144 (11)
Sex - no. (%)	
Male	801 (59)
Female	549 (41)
Disease - no. (%)	
Acute myelogenous leukemia	327 (24)
Acute lymphoblastic leukemia	207 (15)
Other leukemia	21 (2)
Chronic myelogenous leukemia	20 (1)
Myelodysplastic/myeloproliferative disorders	273 (20)
Other acute leukemia	13 (1)
Non-Hodgkin lymphoma	80 (6)
Hodgkin lymphoma	16 (1)
Plasma cell disorder/Multiple Myeloma	4 (0)
Severe aplastic anemia	86 (6)
Inherited bone marrow failure syndromes	30 (2)
Hemoglobinopathies	44 (3)
Paroxysmal nocturnal hemoglobinuria	2 (0)
SCID and other immune system disorders	25 (2)
Inherited disorders of metabolism	4 (0)
Histiocytic disorders	3 (0)
Myeloproliferative Neoplasms	195 (14)
Donor type - no. (%)	
HLA-identical sibling	168 (12)

Characteristic	
Mismatched related	
1 Ag/allele	10 (1)
>=2 Ag/allele	384 (28)
Other related(matching TBD)	92 (7)
Well-matched unrelated (8/8)	288 (21)
Partially-matched unrelated (7/8)	59 (4)
Mis-matched unrelated (<=6/8)	14 (1)
Unrelated (matching TBD)	216 (16)
Cord blood	106 (8)
Missing	13 (1)
GVHD prophylaxis - no. (%)	
Ex-vivo T-cell depletion	12 (1)
CD34 selection	51 (4)
Post-CY + other(s)	610 (45)
Post-CY alone	14 (1)
CNI (TAC/CSA) + MMF +/- Other(except post-CY)	219 (16)
CNI (TAC/CSA) + MTX +/- Other(except MMF, post-CY)	332 (25)
CNI (TAC/CSA) +/- Other (except MMF, MTX, post-CY)	43 (3)
TAC alone	19 (1)
CSA alone	5 (0)
Others	7 (1)
Missing	38 (3)
Stem cell source - no. (%)	
Bone Marrow	333 (25)
Peripheral Blood	911 (67)
Cord Blood	106 (8)
Year of transplant - no. (%)	
2017	362 (27)
2018	304 (23)
2019	322 (24)
2020	181 (13)
2021	153 (11)
2022	28 (2)
Follow-up - median (range)	35 (2-64)

Footnote: 948 patients have Form2150 completed.

Response Summary:

This form is intended to be completed by a physician/researcher for the purpose of proposing a study. Content should not include Personal Identifiable Information (PII) or Protected Health Information (PHI). If you are a patient, do not complete this form. Patients: Contact your healthcare provider immediately for reports of problems with your treatment or problems with products received for your treatment. The CIBMTR uses de-identified data and is unable to associate reported treatment problems, adverse events, or corrections of information with a center, clinical trial, or healthcare provider.

Q1. Study Title

Impact of anti-fungal prophylaxis agent on the incidence of invasive fungal infections (IFI) among allogeneic transplant recipients

Q2. Key Words

invasive fungal infection, antifungal, mold infection

Q3. PRINCIPAL INVESTIGATOR

Provide the following information for each investigator:

Principal Investigator #1:

First and last name, degree(s):	Hannah N. Imlay, MD, MS
Email address:	hannah.imlay@hsc.utah.edu
Institution name:	University of Utah
Academic rank:	Assistant Professor

Q4. Junior investigator status (defined as <40 years of age and/or ≤5 years from fellowship)

- Yes

Q5. Do you identify as an underrepresented/minority?

- No

Q6. Principal Investigator #2 (If applicable):

First and last name, degree(s):	Sagar S. Patel, MD
Email address:	sagar.patel@hci.utah.edu
Institution name:	University of Utah
Academic rank:	Assistant Professor

Q7. Junior investigator status (defined as <40 years of age and/or ≤5 years from fellowship)

- Yes

Q8. Do you identify as an underrepresented/minority?

- No

Q9. We encourage a maximum of two Principal Investigators per study. If more than one author is listed, please indicate who will be identified as the corresponding PI below:

Hannah Imlay

Q10. If you are a junior investigator and would like assistance identifying a senior mentor for your project please click below:

N/A

LETTER OF COMMITMENT:

Please note: *A letter of commitment will be signed by Lead and Last authors as it describes the expectations for filling that role. By signing the letter of commitment, the authors accept their responsibilities and will be held accountable for timely completion of all steps in the project. More details regarding author responsibilities can be found here:* *https://www.cibmtr.org/Studies/Observational/StudyManagement/p*

Q12. CURRENT ONGOING WORK WITH CIBMTR: Please list any ongoing CIBMTR projects that you are currently involved in and briefly describe your role.

Have submitted and presented previous proposals, but no currently ongoing CIBMTR projects.

Q13. PROPOSED WORKING COMMITTEE:

- Infection and Immune Reconstitution

Q14. Please indicate if you have already spoken with a scientific director or working committee chair regarding this study.

- No

Q15. RESEARCH QUESTION:

What is the association between choice of antifungal agent for primary prophylaxis and incidence of invasive fungal infection, invasive mold infection, and infection with non-Aspergillus molds among allogeneic transplant recipients?

Q16. RESEARCH HYPOTHESIS:

We hypothesize that the incidence of non-Aspergillus mold infection will be lowest among patients who receive isavuconazole or posaconazole for prophylaxis. In addition, we hypothesize that the incidence of IFI will be highest among patients with GVHD, mismatched and alternative donors, and those who received PTCy, alemtuzumab, or ATG.

Q17. SPECIFIC OBJECTIVES/OUTCOMES TO BE INVESTIGATED (Include Primary, Secondary, etc.)

Suggested word limit of 200 words:

Primary Aim:
1. Compare the efficacy of specific antifungal prophylaxis agents (fluconazole, posaconazole, isavuconazole, voriconazole, caspofungin) on diagnosis of IFI, invasive Aspergillosis, and invasive non-Aspergillosis mold infections among allogeneic HCT recipients.
Secondary Aims:
2. Determine risk factors associated with diagnosis of IFI, invasive Aspergillosis, and invasive non-Aspergillus mold infection.
3. Determine the impact of anti-mold prophylaxis on relapse, non-relapse mortality (NRM), acute and chronic graft-versus-host disease (GVHD), disease-free survival (DFS)

Q18. SCIENTIFIC IMPACT: Briefly state how the completion of the aims will impact participant care/outcomes and how it will advance science or clinical care.

There are no randomized controlled trials comparing agents with anti-mold activity among allogeneic HCT recipients, particularly in the neutropenic period. We aim to examine the association between choice of antifungal agent and risk of IFI, IA, and non-Aspergillus mold infection to inform clinical practice and design of future clinical trials.

Q19. SCIENTIFIC JUSTIFICATION: Provide a background summary of previous related research and their strengths and weaknesses, justification of your research and why your research is still necessary.

Invasive mold infections are associated with a high rate of mortality and morbidity among allogeneic HCT recipients; however, because non-Aspergillus mold infections are uncommon, they are difficult to study. Identification of at-risk subgroups will also optimize antifungal use in those populations.
The choice of antifungal agent as primary prophylaxis among patients undergoing allogeneic HCT is unclear, and currently varies by center practices and patient comorbidities. Although head to head comparisons of antifungal choice have been conducted between anti-mold and anti-Candida agents (e.g. fluconazole vs micafungin, fluconazole vs voriconazole), anti-mold agents have not been compared to one another in the context of allogeneic HCT. Furthermore, few studies have examined the effectiveness of a newer agent, isavuconazole, as primary prophylaxis
Given the large sample size of patients prospectively followed in the CIBMTR database, our study will be powered to examine invasive mold infections, including non-Aspergillus molds, and examine the impact of specific antifungal prophylaxis choices.

Q19a. SCIENTIFIC JUSTIFICATION: If applicable, upload graphic as a single file (JPG, PNG, GIF)

N/A

Q20. PARTICIPANT SELECTION CRITERIA: State inclusion and exclusion criteria.

Inclusion Criteria:
• First allogeneic HCTs
• All graft sources, donor relationships, conditioning regimens/intensities
• Patients of all ages
• Prophylaxis with fluconazole, echinocandin, voriconazole, posaconazole, isavuconazole (form 2100)
Exclusion Criteria:
• Absence of post-transplant infection data (Form 2100) and post-transplant CMV data (form 2150)
• Patients who were diagnosed with a fungal infection prior to transplant (Form 2400)

Q21. Does this study include pediatric patients?

- Yes

Q22. DATA REQUIREMENTS: After reviewing data on CIBMTR forms, list patient-, disease- and infusion-variables to be considered in the multivariate analyses. Data collection forms available at: http://www.cibmtr.org/DataManagement/DataCollectior Outline any supplementary data required. Additional data collection is extremely difficult and will make your proposal less feasible.

Data to be analyzed will be from data collected in the CIBMTR Report forms. No supplemental data will be required. Patient, disease and transplant variables to collect as below.

Required Forms:

- Infectious Disease Markers (Form 2004)
- Pre-Transplant Essential Data (Form 2400)
- Post-Transplant Essential Data (Form 2450)
- Pre-Cellular Therapy Essential Data (Form 4000)
- Post-HCT Follow-up Data (Form 2100)
- Cellular Therapy Product (Form 4003)
- Cellular Therapy Infusion (Form 4006)
- Cellular Therapy Essential Data Follow-Up (Form 4100)
- Fungal Infection Post-HSCT (Form 2146)

Patient characteristics:

- Age at transplant
- Gender
- Race
- Karnofsky performance status
- Co-morbidity index (HCT-CI)
- RFI risk category
- Transplant center

Disease characteristics:

- Disease
- Date of disease diagnosis
- Disease stage
- Pre-HCT splenectomy (yes vs. no)
- Cytogenetic studies
- Molecular studies
- Dates of pre-transplant chemotherapy
- Pre-transplant chemotherapy regimen
- Number of cycles of chemotherapy
- Total number of lines of chemotherapy
- PB blast count prior to HCT (≤1% vs. >1%)
- Remission status at transplant

Transplant characteristics:

- Donor relationship (related vs. unrelated)
- Graft source (bone marrow vs. peripheral blood)
- HLA matching status (HLA-identical, well-matched unrelated, partially-matched unrelated, haploidentical)
- Conditioning regimen including agents, dose (Flu/Bu, Flu/Mel, vs. others)
- Conditioning regimen intensity (MAC vs. RIC)
- TBI vs non-TBI based conditioning regimens
- Total nucleated cell dose
- CD34 cell dose (<5 x 106 vs. ≥5 x 106)
- T cell dose
- GVHD immunosuppressive regimen (TAC/MMF, TAC/MTX, CSA/MMF, CSA/MTX, Post-cy)
- Date of transplant
- Donor age
- Donor-recipient gender match
- Donor-recipient CMV status

Outcomes:

- Incidence and severity of acute and chronic GVHD
- Date of relapse
- Date of last follow up and status
- Date and cause of death
- Non-relapse mortality
- Invasive fungal infection
- Invasive mold infection
- Invasive non-Aspergillus molds infection

Q23. **PATIENT REPORTED OUTCOME (PRO) REQUIREMENTS: If the study requires PRO data collected by CIBMTR, the proposal should include: 1) A detailed description of the PRO domains, timepoints, and proposed analysis of PROs; 2) A description of the hypothesis specific to PROS.**

For additional information on what PRO measures have been collected and timepoints of collection, please reach out to the Late Effects and Quality of Life or Health Services Working Committee leadership: https://www.cibmtr.org/About/WhoWeAre/Com

NA

Q24. **SAMPLE REQUIREMENTS: If the study requires biologic samples from the CIBMTR Repository, the proposal should also include: 1) A detailed description of the proposed testing methodology and sample requirements; 2) A summary of the investigator's previous experience with the proposed assay systems. PIs should be encouraged to review the inventory details, sample types collected and reach out to research_repos@nmdp.org with any questions.**

More information can be found at: https://www.cibmtr.org/Samples/Inventory/Pages/index

NA

Q25. NON-CIBMTR DATA SOURCE: If applicable, please provide: 1) A description of external data source to which the CIBMTR data will be linked; 2) The rationale for why the linkage is required, i.e., neither database contains all the data required to answer the study question.

NA

Q26. REFERENCES:

References:
1. van Burik JA, Ratanatharathorn V, Stepan DE, et al. Micafungin versus fluconazole for prophylaxis against invasive fungal infections during neutropenia in patients undergoing hematopoietic stem cell transplantation. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2004;39(10):1407-1416.
2. Wingard JR, Carter SL, Walsh TJ, et al. Randomized, double-blind trial of fluconazole versus voriconazole for prevention of invasive fungal infection after allogeneic hematopoietic cell transplantation. Blood. 2010;116(24):5111-5118.
3. Fontana L, Perlin DS, Zhao Y, et al. Isavuconazole Prophylaxis in Patients With Hematologic Malignancies and Hematopoietic Cell Transplant Recipients. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2020;70(5):723-730.

Q27. CONFLICTS OF INTEREST: Do you have any conflicts of interest pertinent to this proposal concerning:

1. Employment (such as an independent contractor, consultant or providing expert testimony)?
2. Relationships (such as executive and advisory committee positions, medical consultant, speaker's bureau)?
3. Ownership (such as equity, ownership or financial interests)?
4. Transactions (such as honoraria, patents, royalties and licenses)?
5. Legal (such as pending or current arbitration or legal proceedings)?

- No, I do not have any conflicts of interest pertinent to this proposal

Q27a. If yes, provide detail on the nature of employment, name of organization, role, entity, ownership, type of financial transaction or legal proceeding and whether renumeration is >$5000 annually.

N/A

BEFORE FINAL SUBMISSION, please review the PI checklist to ensure that you have completed all necessary steps. This will increase the likelihood of submitting a feasible and successful proposal.

Embedded Data:

N/A

Characteristics of patients who underwent first allogeneic transplant and without prior invasive fungal infections (IFI) from 2017 to 2020 reported to CIBMTR

Characteristic	
No. of patients	7135
No. of centers	165
Age of recipient - no. (%)	
Median (min-max)	57 (0-88)
0 - 9	669 (9)
10 - 19	538 (8)
20 - 29	528 (7)
30 - 39	443 (6)
40 - 49	679 (10)
50 - 59	1157 (16)
60 - 69	2335 (33)
70+	786 (11)
Sex - no. (%)	
Male	4162 (58)
Female	2973 (42)
Disease - no. (%)	
AML	1818 (25)
ALL	864 (12)
Other leukemia	121 (2)
CML	105 (1)
MDS	1664 (23)
Other acute leukemia	59 (1)
NHL	340 (5)
HD	72 (1)
Plasma cell disorder	16 (0)
Other Malignancies	2 (0)
Severe aplastic anemia	447 (6)
Inherited abnormality of erythrocyte differentiation or function	380 (5)
SCID & other immune system disorders	260 (4)
Inherit.disord. of metabolism	27 (0)
Histiocytic disorders	1 (0)
Myeloproliferative Neoplasms	959 (13)
Conditioning regimen intensity - no. (%)	
MAC	3075 (43)
RIC	2555 (36)
NMA	1344 (19)
TBD	99 (1)

Characteristic	
Missing	62 (1)
Stem cell source - no. (%)	
Bone Marrow	1778 (25)
Peripheral Blood	4697 (66)
Cord Blood	660 (9)
Donor type - no. (%)	
HLA-identical sibling	1339 (19)
Mismatched related	
1 Ag/allele	60 (1)
>=2 Ag/allele	1411 (20)
Other related(matching TBD)	418 (6)
Well-matched unrelated (8/8)	2243 (31)
Partially-matched unrelated (7/8)	337 (5)
Mis-matched unrelated (<=6/8)	50 (1)
Unrelated (matching TBD)	548 (8)
Cord blood	660 (9)
Missing	69 (1)
Year of transplant - no. (%)	
2017	2306 (32)
2018	2184 (31)
2019	2010 (28)
2020	635 (9)
Antifungal prophylaxis	
Fluconazole - no. (%)	3142 (44)
Intraconazole - no. (%)	41 (1)
Posaconazole - no. (%)	945 (13)
Voriconazole - no. (%)	703 (10)
Isavuconazole - no. (%)	109 (2)
Caspofungin - no. (%)	305 (4)
Anidulafungin - no. (%)	16 (0)
Micafungin - no. (%)	1445 (20)
Other antifungal agent - no. (%)	193 (3)
No Antifungal agent reported – no (%)	281(4)
Fungal infection by day 100 - no. (%)	
No	6796 (95)
Yes	335 (5)
Missing	4 (0)

Response Summary:

This form is intended to be completed by a physician/researcher for the purpose of proposing a study. Content should not include Personal Identifiable Information (PII) or Protected Health Information (PHI). If you are a patient, do not complete this form. Patients: Contact your healthcare provider immediately for reports of problems with your treatment or problems with products received for your treatment. The CIBMTR uses de-identified data and is unable to associate reported treatment problems, adverse events, or corrections of information with a center, clinical trial, or healthcare provider.

Q1. Study Title

The impact of donor source and graft-vs-host disease prophylaxis on the incidence of late viral infections after allogeneic hematopoietic cell transplantation

Q2. Key Words

AlloHCT; Viral infections; GVHD; Conditioning intensity; CMV

Q3. PRINCIPAL INVESTIGATOR

Provide the following information for each investigator:

Principal Investigator #1:

First and last name, degree(s):	Muhammad Bilal Abid, MD
Email address:	mabid@mcw.edu
Institution name:	Medical College of Wisconsin
Academic rank:	Assistant Professor

Q4. Junior investigator status (defined as <40 years of age and/or ≤5 years from fellowship)

- Yes

Q5. Do you identify as an underrepresented/minority?

- Yes

Q6. Principal Investigator #2 (If applicable):

First and last name, degree(s):	Emily Lynde Baumrin, MD & Alison Wakoff Loren, MD, MSCE
Email address:	Alison.Loren@pennmedicine.upenn.edu
Institution name:	Professor of Medicine, Division of Hematology/Oncology.
Academic rank:	University of Pennsylvania

Q7. Junior investigator status (defined as <40 years of age and/or ≤5 years from fellowship)

- No

Q8. Do you identify as an underrepresented/minority?

- No

Q9. We encourage a maximum of two Principal Investigators per study. If more than one author is listed, please indicate who will be identified as the corresponding PI below:

N/A

Q10. If you are a junior investigator and would like assistance identifying a senior mentor for your project please click below:

N/A

LETTER OF COMMITMENT:

Please note: *A letter of commitment will be signed by Lead and Last authors as it describes the expectations for filling that role. By signing the letter of commitment, the authors accept their responsibilities and will be held accountable for timely completion of all steps in the project. More details regarding author responsibilities can be found here:* *https://www.cibmtr.org/Studies/Observational/StudyManagement/p*

Q12. CURRENT ONGOING WORK WITH CIBMTR: Please list any ongoing CIBMTR projects that you are currently involved in and briefly describe your role.

Our group participates in studies related to infections and immune reconstitution

Q13. PROPOSED WORKING COMMITTEE:

- Infection and Immune Reconstitution

Q14. Please indicate if you have already spoken with a scientific director or working committee chair regarding this study.

- Yes

Q14a. If you have already spoken with a scientific director or working committee chair regarding this study, then please specify who:

Dr. Marcie Riches

Q15. RESEARCH QUESTION:

What are the incidence and risk factors for the development of late viral infections after alloHCT and what is the impact on transplant outcomes?

Q16. RESEARCH HYPOTHESIS:

We hypothesize that:
1) The incidence and impact of late (> D+180) viral infections on alloHCT outcomes will differ between fully matched (related and unrelated) and haploHCT recipients with further differences associated with the use of post-transplant cyclophosphamide (PTCy).
2) Late (> D+180) CMV infections persist despite the introduction of letermovir prophylaxis, and have significant impact on transplant-related outcomes in recipients of PTCy.

Q17. SPECIFIC OBJECTIVES/OUTCOMES TO BE INVESTIGATED (Include Primary, Secondary, etc.)

Suggested word limit of 200 words:

1) To describe the types and incidence of late (>D+180) CMV and non-CMV viral infections in allogeneic hematopoietic cell transplantation (alloHCT) recipients.
a. Subaim 1: To describe the incidence of late CMV infections in alloHCT before (2012-2017) and after (2018-2020) the introduction of letermovir prophylaxis.
2) To compare the types and incidence of late CMV and non-CMV viral infections in alloHCT recipients receiving matched related / unrelated vs haploidentical donor types, stratified by post-transplant cyclophosphamide (PTCy) vs non-PTCy GVHD prophylaxis.
3) To evaluate the impact of late viral infections on transplant outcomes, stratified by donor type and GVHD prophylaxis:
a. Overall survival
b. Disease free survival
c. Relapse
d. Non relapse mortality
Viruses of interest will include:
CMV (viremia and disease)
HSV
VZV
HHV-6
EBV (viremia and disease / PTLD)
BK virus (urine and blood)
Community respiratory viruses (influenza, parainfluenza virus, rhinovirus, RSV, adenovirus, enterovirus, human metapneumovirus, coronavirus excluding SARS-CoV2)

Q18. SCIENTIFIC IMPACT: Briefly state how the completion of the aims will impact participant care/outcomes and how it will advance science or clinical care.

GVHD, infections and relapse are major causes of alloHCT failure. There is increasing use of haploidentical donors (haploHCT) and PTCy-based GVHD prophylaxis which facilitates engraftment and counters GVHD. In this setting, there is emerging evidence suggesting a higher incidence of early viral infections1-3. However, there are lack of data on late viral infectious complications. Additionally, the previous CIBMTR study (IN17-01) had data capped in 2017 and pre-dated the letermovir era. The landscape of CMV infections, in particular, has changed in recent years due to letermovir prophylaxis incorporated into transplant protocols, however, the impact on late CMV infections remains unclear. Hence, it is critical to study the impact of various GVHD prophylaxis regimens on late CMV and non-CMV viral infections in the current era.
This study will determine the incidence of late (> day+180) non-CMV and CMV viral infections, the risk factors associated with these infections, and the infections responsible for poor outcomes. Additionally, incidence and outcomes of delayed CMV viremia and infection will be analyzed in the years before and after the introduction of letermovir prophylaxis.

Q19. SCIENTIFIC JUSTIFICATION: Provide a background summary of previous related research and their strengths and weaknesses, justification of your research and why your research is still necessary.

Infections are a common complication of alloHCT and are associated with increased morbidity and mortality4. Incidence and type of infections are affected by the severity and duration of immunosuppression, which is determined by donor type, graft type, conditioning intensity, and GVHD prophylaxis1-3,5,6. The use of PTCy has become increasingly common and yet leads to delayed immune reconstitution7,8. Although PTCy was first used in recipients of haploHCT, its use has been extended to other graft types as well9. A recent CIBMTR study showed that haploHCT is the preferred donor source, after matched related donor (MRD) and matched unrelated donor (MUD), and will likely replace umbilical cord blood transplants10. Most respondents also predicted that calcineurin-based GVHD prophylaxis would be replaced by PTCy (55%). While a recently concluded large CIBMTR study examined early infections in patients receiving haploHCT, there are lack of data on late viral infections. It is therefore critical to examine the impact of haploHCT and PTCy on late infectious complications and outcomes in the context of donor source preferences of transplant physicians for the predicted future.

Several groups of investigators have identified an increased risk of infections and infection-related deaths in haploHCT recipients treated with PTCy (haploCy), particularly using peripheral blood stem cells (PBSC) as the graft source. Our study at the Medical College of Wisconsin evaluated a retrospective cohort of 78 consecutive haploCy recipients and showed that higher mortality was mediated by severe cytokine release syndrome (CRS). Viral and bacterial infections were particularly common and more frequently occurred in patients with higher-grade CRS on multivariable analysis (hazard ratio [HR], 3.05; P = .007). CRS grade was also a significant predictor for infection density, defined as number of infections per patient per days at risk. Severe CRS developing after haploCy was independently associated with viral infections and an increased risk of bacterial infections, likely through delayed neutrophil engraftment, and possibly due to corticosteroids and other immunomodulators (e.g., tocilizumab)5. In several other small retrospective studies evaluating haploCy recipients, infections are extremely common (80-95%), with a wide range of date of onset (range: 6 months – 23 months)11-13. While a CIBMTR study evaluating the incidence and impact of bacterial and fungal infections on haploHCT outcomes is underway (IN18-01) and another evaluating early viral infections just concluded (IN17-01), both of these studies were limited to infections within the first 180 days post-haploCy1-3. Hence, understanding the burden of late viral infections and their impact on outcomes of haploCy compared to other donor types and GVHD prophylaxis regimens remains a major knowledge gap.

As advances are made in viral prophylaxis strategies, the incidence and timing of viral infections are shifting from the early to the late period. A CIBMTR analysis including more than 10,000 adult alloHCT 2-year survivors showed that late infections contributed to one-third of all deaths14. There was also a continuous increase in the risk of deaths due to late infections. Older age, HCT from unrelated donors, male sex, and history of chronic GVHD with ongoing immunosuppression at 2 years post-HCT were associated with an increased risk of infection-related deaths. Prior single-center virus-specific studies also demonstrated increased risk of non-CMV herpes viruses and CMV viral infection in the late period15-17.

Recent data demonstrate that letermovir prophylaxis is associated with not just decreased CMV but also prolonged survival. A single-center study including 237 haploCy recipients showed decreased clinically significant CMV and reduced NRM at 1 year and superior OS and PFS at 2 years among letermovir prophylaxis recipients as compared to the control group18. A more recent single-center study including 333 alloHCT patients (CMV seropositive donors or recipients) showed an increased incidence of CMV reactivation and CMV-related mortality (HR 3.19, 95% CI, 1.29-7.92) after letermovir discontinuation at d+100. PTCy recipients particularly benefitted from letermovir prophylaxis19. Hence, it is critical to characterize late CMV infections in the era of letermovir prophylaxis in order to inform the extension of prophylactic and pre-emptive strategies for high-risk populations into the late period.

Q19a. SCIENTIFIC JUSTIFICATION: If applicable, upload graphic as a single file (JPG, PNG, GIF)

N/A

Q20. PARTICIPANT SELECTION CRITERIA: State inclusion and exclusion criteria.

Patient eligibility population:

Inclusion criteria:

• Patients receiving first alloHCT for AML, ALL, and MDS in CR1 between 2012 – 2021
• Age ≥ 2 years
• Donor types: MRD, MUD, haploHCT
• Stem cell source: BM, PB
• Conditioning: Myeloablative or Reduced intensity/non-myeloablative conditioning
• GVHD prophylaxis: All standard (CNI + MMF, CNI + MTX, CNI + sirolimus, PTCy +/- others)

Exclusion Criteria
• Syngeneic transplant
• Cord blood donor type
• Missing post-transplant infection information (no 2100 form).
• Patients receiving CD34 selection or ex vivo T-cell depletion.
• Patients receiving ATG and/or Alemtuzumab (CAMPATH)
• Center restriction: Patients transplanted at centers which have no reported haploHCT patients.
• Infection(s) reported during conditioning before Day+0.
• No consent

Main exposures of interest:
• HaploHCT with PTCy
• HaploHCT with other GVHD prophylaxis (may exclude if sample size too small)
• MRD/MUD with PTCy
• MRD/MUD with other GVHD prophylaxis (control)

Outcomes:
1) Aim 1: To describe the types and incidence of late CMV and non-CMV viral infections in allogeneic hematopoietic cell transplantation (alloHCT) recipients.
a. Sub aim 1: To describe the incidence of late CMV infections in alloHCT before (2012-2017) and after (2018-2021) the introduction of letermovir prophylaxis.
• Cumulative incidence of CMV viremia after D+180. Relapse, 2nd HCT, and death are competing risks.
• Cumulative incidence of CMV end-organ disease after D+180. Relapse, 2nd HCT, and death are competing risks.
• Cumulative incidence of non-CMV herpes viral infections after D+180. Relapse, 2nd HCT, and death are competing risks.
• Cumulative incidence of community respiratory viral infections after D+180. Relapse, 2nd HCT, and death are competing risks.
• Cumulative Incidence of other viral infections after D+180. Relapse, 2nd HCT, and death are competing risks.
• Density of viral infections after D+180, defined as the number of viral infections per patient per days at risk. Relapse, 2nd HCT, and death are competing risks.
2) Aim 2: To compare the types, incidence, and outcomes of late CMV and non-CMV viral infections in alloHCT recipients receiving matched related / unrelated vs haploidentical donor grafts, stratified by post-transplant cyclophosphamide (PTCy) vs non-PTCy GVHD prophylaxis.
• Cumulative incidence of CMV viremia after D+180. by Relapse, 2nd HCT, and death are competing risks.
• Cumulative incidence of CMV end-organ disease after D+180. . Relapse, 2nd HCT, and death are competing risks.
• Cumulative Incidence of non-CMV herpes viral infections after D+180. Relapse, 2nd HCT, and death are competing risks.
• Cumulative Incidence of community respiratory viral infections after D+180. Relapse, 2nd HCT, and death are competing risks.
• Cumulative Incidence of other viral infections after D+180. Relapse, 2nd HCT, and death are competing risks.
• Density of viral infections after D+180, defined as the number of viral infections per patient per days at risk. Relapse, 2nd HCT, and death are competing risks.
3) Aim 3: To evaluate the impact of late viral infections on transplant outcomes, stratified by donor type and GVHD prophylaxis.
• Relapse: non-relapse mortality is the competing risk.
• Overall survival: time to death. Death from any cause is an event. Surviving patients are censored at time of last follow-up.
• Disease Free survival: time to relapse or death from any cause.
• Non-relapse mortality: death without evidence of disease relapse. Relapse is the competing

Variables to be examined
Patient-related
• Age at transplant (by decade)
• Sex
• Race/ethnicity
• HCT-CI20
• KPS: >90% v <90%
• Disease: AML, ALL, or MDS
• DRI21
• Recipient CMV serostatus
• Recipient HSV, VZV, EBV serostatus

Donor Related
• Donor type22: matched related, matched unrelated, haploidentical (analysis defining group)
• Donor age (by decade)
• Donor CMV serostatus
• Donor sex
Transplant Related
• Donor/recipient sex match
• Date of transplant (analysis defining group)
• Time from hematologic diagnosis to HCT (0-6 mo vs 6 – 12 mo vs ≥ 12 mo)
• Conditioning intensity: myeloablative vs. reduced-intensity
• TBI-based conditioning: yes vs. no
• GVHD prophylaxis (analysis defining group): PTCy versus other (includes calcineurin inhibitor (CNI) +MMF, CNI +MTX, CNI +sirolimus, CNI alone)
• Graft source: peripheral blood vs. bone marrow
Time-Dependent variables 23
• Days to neutrophil engraftment
• If known: Absolute lymphocyte count, IgG level and CD4 count at various time points
• Maximum engraftment achieved
• Acute GVHD (time-dependent variable): Yes/No, grade
• Chronic GVHD (time-dependent variable): Yes/No, limited vs extensive
• Duration of immunosuppression
Cell counts infused
• Total nucleated cell dose (TNC)
• CD34 +/kg-bw
CMV Infection Related24
• CMV viremia between after D+180: Yes/No
• Time to CMV viremia from HCT
• CMV disease after D+180: Yes/No
• Time to CMV disease from HCT
• Site of organ involvement for CMV after D+180: GI vs Lung vs Liver vs Other
Other Infection Related
Non-CMV herpes viral infection (HSV, VZV, EBV, HHV6):
• Non-CMV herpes viremia after D+180: Yes/No
• Time to non-CMV herpes viremia
• Non-CMV herpes viral infection in non-blood sites after D+180: Yes/No
• Time to non-CMV herpes viral disease
Community respiratory virus infection (PIV, Influenza, RSV, Adenovirus, enterovirus, rhinovirus, human metapneumovirus, coronavirus excluding SARS-CoV2):
• Community respiratory viremia after D+180: Yes/No
• Time to community respiratory viremia
• Community respiratory virus in non-blood sites after D+180: Yes/No
• Time to community respiratory viral disease
Other viral infections (including BK viruria)
• Other viral infections in blood after D+180: Yes/No
• Time to other viral infections in blood
• Other viral infections in non-blood sites after D+180: Yes/No
• Time to other viral infections in non-blood sites
All viral infections:
• Co-infection (yeast/mold/bacteria): Presence/absence of co-infection of any type.
Study design:
This will be a retrospective registry study comprised of two major analyses. The first analysis will examine the four general cohorts (HaploCy, Haplo-CNI, MRD/MUD-Cy, and MRD/MUD-CNI) to determine the incidence and transplant-related outcomes of CMV viremia beyond day+180. We will also perform a stratified analysis comparing these same outcomes in patients transplanted before (2012-2017) and after (2018-2021) the introduction of letermovir, based on the recognition that there has been a practice change with the adoption of letermovir in the transplant protocols for the prevention of CMV reactivations in high-risk patients.
The second analysis will replicate the first with non-CMV viral infections overall and then stratified into non-CMV herpes viruses, community respiratory viruses, and other viruses including BK virus. The specific transplant outcomes of interest for both analyses will include OS, DFS, and cumulative incidences of relapse and TRM at 2 years.
Statistical analysis:
The variables, outcomes, and competing risks in the analyses will be described. Patient-, disease- and transplant-related factors will be compared between groups using the Pearson $\chi 2$ test for categorical variables and the Kruskal-Wallis test for continuous variables. In the analysis comparing the incidence of non-CMV viral infections and CMV viremia/disease across the four general cohorts, cumulative incidence estimates will be used accounting for competing risks. All tests will be performed with a two-sided alpha of 0.01 and reported with 99% confidence intervals.

The probabilities of disease-free and overall survival will be calculated using the Kaplan Meier estimator, with the variance estimated by Greenwood's formula. Values for other endpoints will be generated using cumulative incidence estimates to account for competing risks. The main effect variable in the non-CMV viral infection and CMV viremia/disease analysis will be time-dependent23. Therefore, dynamic landmark analysis will be employed, in which landmarks at the median and interquartile ranges for viral infection will be chosen, and serial cumulative incidence curves will be developed in order to visualize the univariate impact of the time-dependent main effect variable on time-dependent outcomes (RI, TRM).
Multivariable analyses using Cox proportional hazards regressions will be performed for each outcome. The variables considered in the multivariable regression models are listed above. The assumption of proportional hazards for each factor in the Cox model will be tested. Time-dependent variables will be added in the model in cases of violation of the proportional hazard assumption. The stepwise variable selection method will be used to identify significant risk factors that associate with the outcomes. The final model will retain factors significantly associated with the outcome variable at a 1% level. Acute and chronic GVHD will be incorporate in the model due to substantive knowledge and careful thought to underlying biologic mechanisms. Interactions between the main effect variables and other variables of interest will be tested. Each Cox model will be adjusted for center effect 25.

Q21. Does this study include pediatric patients?

- Yes

Q22. DATA REQUIREMENTS: After reviewing data on CIBMTR forms, list patient-, disease- and infusion-variables to be considered in the multivariate analyses. Data collection forms available at: http://www.cibmtr.org/DataManagement/DataCollectior Outline any supplementary data required. Additional data collection is extremely difficult and will make your proposal less feasible.

- Recipient baseline data (form 2000)
- Infectious disease markers (form 2004)
- Hematopoietic cellular transplant (HCT) infusion (form 2006)
- Post-HCT follow-up data (form 2100)
- Respiratory virus post-infusion form (form 2149)
- CMV/EBV/ADV/HHV6/BK Viral Infection Diagnostic and Treatment (form 2150)
- Pre-transplant essential data (form 2400)
- Post-transplant essential data (form 2450)
- Recipient death data (form 2900)

Q23. **PATIENT REPORTED OUTCOME (PRO) REQUIREMENTS: If the study requires PRO data collected by CIBMTR, the proposal should include: 1) A detailed description of the PRO domains, timepoints, and proposed analysis of PROs; 2) A description of the hypothesis specific to PROS.**

For additional information on what PRO measures have been collected and timepoints of collection, please reach out to the Late Effects and Quality of Life or Health Services Working Committee leadership: https://www.cibmtr.org/About/WhoWeAre/Com

N/A

Q24. **SAMPLE REQUIREMENTS: If the study requires biologic samples from the CIBMTR Repository, the proposal should also include: 1) A detailed description of the proposed testing methodology and sample requirements; 2) A summary of the investigator's previous experience with the proposed assay systems. PIs should be encouraged to review the inventory details, sample types collected and reach out to research_repos@nmdp.org with any questions.**

More information can be found at: https://www.cibmtr.org/Samples/Inventory/Pages/index

N/A

Q25. NON-CIBMTR DATA SOURCE: If applicable, please provide: 1) A description of external data source to which the CIBMTR data will be linked; 2) The rationale for why the linkage is required, i.e., neither database contains all the data required to answer the study question.

N/A

Q26. REFERENCES:

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Q27. CONFLICTS OF INTEREST: Do you have any conflicts of interest pertinent to this proposal concerning:

1. Employment (such as an independent contractor, consultant or providing expert testimony)?
2. Relationships (such as executive and advisory committee positions, medical consultant, speaker's bureau)?
3. Ownership (such as equity, ownership or financial interests)?
4. Transactions (such as honoraria, patents, royalties and licenses)?
5. Legal (such as pending or current arbitration or legal proceedings)?

- No, I do not have any conflicts of interest pertinent to this proposal

Q27a. If yes, provide detail on the nature of employment, name of organization, role, entity, ownership, type of financial transaction or legal proceeding and whether renumeration is >$5000 annually.

N/A

BEFORE FINAL SUBMISSION, please review the PI checklist to ensure that you have completed all necessary steps. This will increase the likelihood of submitting a feasible and successful proposal.

Embedded Data:

N/A

Characteristics of patients who underwent first allogeneic bone marrow or peripheral blood transplant for AML, ALL, MDS, MPN from 2012 to 2019 reported to CIBMTR

Characteristic	HLA-identical sibling	>=2 Ag/allele Mismatched related	Well-matched unrelated (8/8)	Partially-matched unrelated (7/8)	Mis-matched unrelated (<=6/8)
No. of patients	2605	1619	4735	760	48
No. of centers	144	127	149	111	26
Age of recipient, years- no. (%)					
Median (min-max)	59 (2-78)	57 (2-88)	62 (2-83)	56 (2-81)	54 (7-72)
0 - 9	67 (3)	52 (3)	94 (2)	37 (5)	1 (2)
10 - 19	113 (4)	109 (7)	139 (3)	69 (9)	5 (10)
20 - 29	142 (5)	148 (9)	235 (5)	31 (4)	5 (10)
30 - 39	173 (7)	123 (8)	260 (5)	65 (9)	4 (8)
40 - 49	275 (11)	191 (12)	431 (9)	85 (11)	7 (15)
50 - 59	647 (25)	314 (19)	900 (19)	166 (22)	8 (17)
60 - 69	1033 (40)	523 (32)	1999 (42)	233 (31)	13 (27)
70+	155 (6)	159 (10)	677 (14)	74 (10)	5 (10)
Gender - no. (%)					
Male	1535 (59)	958 (59)	2800 (59)	436 (57)	26 (54)
Female	1070 (41)	661 (41)	1935 (41)	324 (43)	22 (46)
Disease - no. (%)					
Acute myelogenous leukemia	998 (38)	789 (49)	1730 (37)	317 (42)	28 (58)
Acute lymphoblastic leukemia	399 (15)	344 (21)	554 (12)	138 (18)	8 (17)
Myelodysplastic/myeloproliferative disorders	912 (35)	387 (24)	1895 (40)	237 (31)	11 (23)
Myeloproliferative Neoplasms	296 (11)	99 (6)	556 (12)	68 (9)	1 (2)
GVHD prophylaxis - no. (%)					
Ex-vivo T-cell depletion	8 (0)	39 (2)	27 (1)	5 (1)	3 (6)

Characteristic	HLA-identical sibling	>=2 Ag/allele Mismatched related	Well-matched unrelated (8/8)	Partially-matched unrelated (7/8)	Mis-matched unrelated (<=6/8)
CD34 selection	44 (2)	54 (3)	101 (2)	17 (2)	2 (4)
Post-CY + other(s)	142 (5)	1423 (88)	273 (6)	114 (15)	25 (52)
Post-CY alone	22 (1)	1 (0)	43 (1)	1 (0)	1 (2)
CNI (TAC/CSA) + MMF +/- Other(except post-CY)	483 (19)	71 (4)	923 (19)	135 (18)	7 (15)
CNI (TAC/CSA) + MTX +/- Other(except MMF, post-CY)	1630 (63)	5 (0)	2806 (59)	405 (53)	7 (15)
CNI (TAC/CSA) +/- Other (except MMF, MTX, post-CY)	187 (7)	5 (0)	403 (9)	51 (7)	1 (2)
TAC alone	58 (2)	8 (0)	97 (2)	21 (3)	0 (0)
CSA alone	7 (0)	1 (0)	11 (0)	4 (1)	0 (0)
Others	22 (1)	4 (0)	47 (1)	7 (1)	2 (4)
Missing	2 (0)	8 (0)	4 (0)	0 (0)	0 (0)
Stem cell source - no. (%)					
Bone Marrow	308 (12)	548 (34)	810 (17)	188 (25)	25 (52)
Peripheral Blood	2297 (88)	1071 (66)	3925 (83)	572 (75)	23 (48)
Viral Infections occurring after 180 days post-HCT					
CMV - no. (%)					
No	2438 (94)	1506 (93)	4415 (93)	699 (92)	45 (94)
Yes	167 (6)	113 (7)	320 (7)	61 (8)	3 (6)
Non-CMV Herpes viruses - no. (%)					
No	2444 (94)	1477 (91)	4428 (94)	707 (93)	46 (96)
Yes	161 (6)	142 (9)	307 (6)	53 (7)	2 (4)
Community respiratory viruses - no. (%)					
No	2078 (80)	1290 (80)	3921 (83)	619 (81)	42 (88)

Characteristic	HLA-identical sibling	>=2 Ag/allele Mismatched related	Well-matched unrelated (8/8)	Partially-matched unrelated (7/8)	Mis-matched unrelated (<=6/8)
Yes	527 (20)	329 (20)	814 (17)	141 (19)	6 (13)
Other viral infections - no. (%)					
No	2483 (95)	1552 (96)	4550 (96)	724 (95)	48 (100)
Yes	122 (5)	67 (4)	185 (4)	36 (5)	0 (0)
Year of transplant - no. (%)					
2012	208 (8)	17 (1)	309 (7)	54 (7)	4 (8)
2013	364 (14)	97 (6)	638 (13)	128 (17)	3 (6)
2014	485 (19)	173 (11)	803 (17)	141 (19)	6 (13)
2015	419 (16)	213 (13)	766 (16)	131 (17)	4 (8)
2016	367 (14)	275 (17)	678 (14)	105 (14)	0 (0)
2017	309 (12)	290 (18)	638 (13)	86 (11)	10 (21)
2018	273 (10)	328 (20)	589 (12)	73 (10)	17 (35)
2019	180 (7)	226 (14)	314 (7)	42 (6)	4 (8)
Follow-up - median (range)	57 (3-101)	37 (2-98)	54 (3-101)	59 (3-98)	35 (12-87)

Response Summary:

This form is intended to be completed by a physician/researcher for the purpose of proposing a study. Content should not include Personal Identifiable Information (PII) or Protected Health Information (PHI). If you are a patient, do not complete this form. Patients: Contact your healthcare provider immediately for reports of problems with your treatment or problems with products received for your treatment. The CIBMTR uses de-identified data and is unable to associate reported treatment problems, adverse events, or corrections of information with a center, clinical trial, or healthcare provider.

Q1. Study Title

Early Infectious Complications Associated with CART Cell Therapy Compared to Autologous Stem Cell Transplant in Lymphoma

Q2. Key Words

viral, bacterial, CART, Transplant

Q3. PRINCIPAL INVESTIGATOR

Provide the following information for each investigator:

Principal Investigator #1:

First and last name, degree(s):	Fareed Khwaja MD
Email address:	FKhawaja@mdanderson.org
Institution name:	MD Anderson Cancer Center
Academic rank:	assistant professor

Q4. Junior investigator status (defined as <40 years of age and/or ≤5 years from fellowship)

- Yes

Q5. Do you identify as an underrepresented/minority?

- No

Q6. Principal Investigator #2 (If applicable):

First and last name, degree(s):	Sairah Ahmed MD
Email address:	sahmed3@mdanderson.org
Institution name:	MD Anderson Cancer Center
Academic rank:	associate professor

Q7. Junior investigator status (defined as <40 years of age and/or ≤5 years from fellowship)

- No

Q8. Do you identify as an underrepresented/minority?

- No

Q9. We encourage a maximum of two Principal Investigators per study. If more than one author is listed, please indicate who will be identified as the corresponding PI below:

FKhawaja@mdanderson.org

Q10. If you are a junior investigator and would like assistance identifying a senior mentor for your project please click below:

N/A

LETTER OF COMMITMENT:

Please note: *A letter of commitment will be signed by Lead and Last authors as it describes the expectations for filling that role. By signing the letter of commitment, the authors accept their responsibilities and will be held accountable for timely completion of all steps in the project. More details regarding author responsibilities can be found here:* *https://www.cibmtr.org/Studies/Observational/StudyManagement/p*

Q12. CURRENT ONGOING WORK WITH CIBMTR: Please list any ongoing CIBMTR projects that you are currently involved in and briefly describe your role.

Dr Ahmed - 2 projects ongoing

Q13. PROPOSED WORKING COMMITTEE:

- Infection and Immune Reconstitution

Q14. Please indicate if you have already spoken with a scientific director or working committee chair regarding this study.

- No

Q15. RESEARCH QUESTION:

To evaluate the difference in the rates of infections early after cellular therapy; CART vs autologous transplant; when the type of pharmacologic prevention modalities are similar

Q16. RESEARCH HYPOTHESIS:

Better understand the unique risks associated with development of infection within 6 months after cellular therapy

Q17. SPECIFIC OBJECTIVES/OUTCOMES TO BE INVESTIGATED (Include Primary, Secondary, etc.)

Suggested word limit of 200 words:

Primary: This study will primarily aim to compare the rates of infections between CAR T cell and autologous hematopoietic cell transplant (HCT) recipients within 6 months post-CART cell therapy.
Secondary:
1) We will compare rates of viral, bacterial and fungal infections.
2) We will identify unique host or therapy related characteristics that increase the risk of viral, bacterial or fungal infections.
3) We will compare clinical outcomes between patients with infections after CAR T cell therapy and after autologous HCT.

Q18. SCIENTIFIC IMPACT: Briefly state how the completion of the aims will impact participant care/outcomes and how it will advance science or clinical care.

Current strategies for infection prophylaxis post CART is generally taken from the approach after autologous transplant, however there is little data about the rates of infection in this population in comparison to auto transplant. This study will inform the practice patterns for future clinical scenarios

Q19. SCIENTIFIC JUSTIFICATION: Provide a background summary of previous related research and their strengths and weaknesses, justification of your research and why your research is still necessary.

The treatment of refractory or relapsed lymphoma has been undisputedly changed with the advent of anti CD19 CAR T cell therapy. Previous studies reported dismal response rates in refractory or relapsed B cell lymphoma (DLBCL), but results from the ZUMA-1 trial for CAR T cell therapy in the same population reported a complete response rate of 54% (1). As a result, CAR T cell therapy is slowly becoming the standard of care for treatment of refractory or relapsed B cell lymphoma; the use of CAR T therapy is also expanding to treat multiple myeloma and some solid tumors (2).
Due to the success seen in lymphoma patients, CAR T cell therapy is seen as an alternative to autologous stem cell transplantation (3, 4). Autologous transplantation is recommended in lymphoma patients in remission with high risk for relapse, as well as patients with relapsed/refractory lymphoma (5, 6). At our institution, CAR T cell therapy for DLBCL is being offered to patients who have failed 2 lines of previous therapy; this definition also includes patients who failed previous autologous stem cell transplant. Infections post-autologous transplant are typically bacterial, whereas cytomegalovirus (CMV) reactivation and invasive fungal infections are less commonly seen (7). This is thought to be due to the relatively lower degree of immunosuppression when compared to allogeneic stem cell transplantation. The degree of immunosuppression and risk of viral or fungal infections is not well known in CAR T cell recipients.
The infectious complications related to CAR T cell therapy are not well understood; subsequently, no standardized prophylaxis is recommended yet, leaving institutions to adopt local prophylaxis measures for these patients. Patients most often develop bacterial infections within the first 28 days, whereas viral infections, such as CMV reactivation, were not consistently reported (8). Yet, follow up period may be inadequate, as viral reactivation has been reported up to 7 months post CAR T therapy (9, 10) in some patients. Studies with longer follow up periods and higher number of patients are needed to better understand the unique risks associated with developing viral infections after CAR T cell therapy.

Q19a. SCIENTIFIC JUSTIFICATION: If applicable, upload graphic as a single file (JPG, PNG, GIF)

N/A

Q20. PARTICIPANT SELECTION CRITERIA: State inclusion and exclusion criteria.

1) Lymphoma patients who have received CAR T cell therapy for a diagnosis of lymphoma or autologous HCT regardless
2) Patients who are 18 years or older

Q21. Does this study include pediatric patients?

- No

Q21a. If this study does not include pediatric patients, please provide justification:

CART cell therapy is not approved for the treatment of lymphoma in the pediatric patient population

Q22. DATA REQUIREMENTS: After reviewing data on CIBMTR forms, list patient-, disease- and infusion-variables to be considered in the multivariate analyses. Data collection forms available at: http://www.cibmtr.org/DataManagement/DataCollectior Outline any supplementary data required. Additional data collection is extremely difficult and will make your proposal less feasible.

Patient-related:
- Age at CART infusion or HCT
- Gender: male or female
- Karnofsky performance status: < 80% vs. ≥ 80%
- HCT comorbidity index 0, 1, 2, and ≥ 3
- Additional markers
o LDH,
o baseline inflammatory markers (IL-6, IL-2, serum ferritin, interferon gamma, C reactive protein)
o thrombocytopenia
o neutropenia
o lymphopenia
o anemia
o history of CNS disease
o history of neurological disorder
Disease-related:
- Disease risk index (DRI)
- Prior autologous HCT (yes vs. no)
- Prior allogeneic HCT (yes vs no)
- Primary refractory vs. relapsed disease
- Number of prior therapy (before transplant): 2-3 vs. >3
- Disease status at the time of CART or HCT: chemoresponsive vs. non-responsive/refractory
- Bridging therapy prior to CART (yes/no)
- Extranodal involvement at the time of prior relapse or PD (yes / no)
- Length of prior CR1 (<= 12 vs. >12 months)
- B symptoms at the time of prior relapse or PD (yes / no)
- Volume of disease
- Stage
CART related:
- CART product
- time from LDC to infusion of cells
- CRS grade with toxicity variables
- ICANS grade with toxicity variables (seizure, papilledema, etc)
- Treatment for toxicity (IL6 antagonist, steroid use)
Infection related:
- antimicrobial prophylaxis
- etiology of infection
- duration of infection
- choice of therapy
- complications related to the infection (sepsis, multiorgan failure)
- Site of infection (upper respiratory tract infection or lower respiratory tract infection)
- rates of herpes simplex, varicella-zosters and human herpes 6 infections
- rate of candida infections, pneumocystis infections, invasive mold infections and endemic fungal infections
-rate of blood stream infections/bacteremia, bacterial pneumonia, and clostridium difficile infections

Q23. **PATIENT REPORTED OUTCOME (PRO) REQUIREMENTS: If the study requires PRO data collected by CIBMTR, the proposal should include: 1) A detailed description of the PRO domains, timepoints, and proposed analysis of PROs; 2) A description of the hypothesis specific to PROS.**

For additional information on what PRO measures have been collected and timepoints of collection, please reach out to the Late Effects and Quality of Life or Health Services Working Committee leadership: https://www.cibmtr.org/About/WhoWeAre/Com

NA

Q24. **SAMPLE REQUIREMENTS: If the study requires biologic samples from the CIBMTR Repository, the proposal should also include: 1) A detailed description of the proposed testing methodology and sample requirements; 2) A summary of the investigator's previous experience with the proposed assay systems. PIs should be encouraged to review the inventory details, sample types collected and reach out to research_repos@nmdp.org with any questions.**

More information can be found at: https://www.cibmtr.org/Samples/Inventory/Pages/index

NA

Q25. NON-CIBMTR DATA SOURCE: If applicable, please provide: 1) A description of external data source to which the CIBMTR data will be linked; 2) The rationale for why the linkage is required, i.e., neither database contains all the data required to answer the study question.

NA

Q26. REFERENCES:

References
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Q27. CONFLICTS OF INTEREST: Do you have any conflicts of interest pertinent to this proposal concerning:

1. Employment (such as an independent contractor, consultant or providing expert testimony)?
2. Relationships (such as executive and advisory committee positions, medical consultant, speaker's bureau)?
3. Ownership (such as equity, ownership or financial interests)?
4. Transactions (such as honoraria, patents, royalties and licenses)?
5. Legal (such as pending or current arbitration or legal proceedings)?

- No, I do not have any conflicts of interest pertinent to this proposal

Q27a. If yes, provide detail on the nature of employment, name of organization, role, entity, ownership, type of financial transaction or legal proceeding and whether renumeration is >$5000 annually.

N/A

BEFORE FINAL SUBMISSION, please review the PI checklist to ensure that you have completed all necessary steps. This will increase the likelihood of submitting a feasible and successful proposal.

Embedded Data:

N/A

Table1. Characteristic of patients who received a first commercial CAR-T therapy for Non-Hodgkin lymphoma (NHL) between 2015 and 2020 reported to the CIBMTR

Characteristic	
No. of patients	2685
No. of centers	113
Age at infusion, by category - no. (%)	
Median (min-max)	63 (18-91)
10-19	5 (0)
20-29	76 (3)
30-39	159 (6)
40-49	254 (9)
50-59	606 (23)
60-69	971 (36)
>= 70	614 (23)
Gender - no. (%)	
Male	1671 (62)
Female	1014 (38)
Product - no. (%)	
Kymriah	463 (17)
Yescarta	2222 (83)
Recipient race - no. (%)	
White	2157 (80)
African American	136 (5)
Asian	126 (5)
Pacific Islander	8 (0)
Native American	12 (0)
More than one race	13 (0)
Unknown	121 (5)
Missing	112 (4)
Recipient ethnicity - no. (%)	
Hispanic or Latino	262 (10)
Non-Hispanic or non-Latino	2230 (83)
N/A - Not a resident of the U.S.	96 (4)
Unknown	96 (4)
Missing	1 (0)
Country - no. (%)	
US	2626 (98)
Other	59 (2)

Characteristic	
Disease - no. (%)	
Non-Hodgkin lymphoma (NHL)	2685 (100)
Karnofsky/Lansky performance score prior to CT - no. (%)	
90-100	1059 (39)
80	807 (30)
< 80	513 (19)
Missing	306 (11)
Types of prior HCTs - no. (%)	
No prior HCT	1927 (72)
Prior allo-HCT	36 (1)
Prior auto-HCT	689 (26)
Prior auto and allo-HCT	6 (0)
Missing	27 (1)
Subsequent HCT since the CT infusion - no. (%)	
No	2402 (89)
Yes	159 (6)
Missing	124 (5)
Bacterial infection by day 100 - no. (%)	
No	2227 (83)
Yes	404 (15)
Missing	54 (2)
Fungal infection by day 100 - no. (%)	
No	2543 (95)
Yes	88 (3)
Missing	54 (2)
Viral infection by day 100 - no. (%)	
No	2355 (88)
Yes	276 (10)
Missing	54 (2)
Year of CT - no. (%)	
2017	5 (0)
2018	486 (18)
2019	945 (35)
2020	910 (34)
2021	339 (13)
Follow-up of survivors, months - median (range)	24 (1-50)

Table2. Characteristic of patients who received a first autologous transplant for Non-Hodgkin lymphoma (NHL) between 2015 and 2020 reported to the CIBMTR

Characteristic	
No. of patients	1481
No. of centers	114
Age of recipient - no. (%)	
Median (min-max)	59 (5-79)
0 - 9	4 (0)
10 - 19	19 (1)
20 - 29	50 (3)
30 - 39	86 (6)
40 - 49	199 (13)
50 - 59	434 (29)
60 - 69	538 (36)
70+	151 (10)
Sex - no. (%)	
Male	930 (63)
Female	551 (37)
Disease - no. (%)	
Non-Hodgkin lymphoma	1481 (100)
Stem cell source - no. (%)	
Bone Marrow	2 (0)
Peripheral Blood	1479 (100)
Bacterial infection by day 100 - no. (%)	
No	1151 (78)
Yes	330 (22)
Fungal infection by day 100 - no. (%)	
No	1448 (98)
Yes	33 (2)
Viral infection by day 100 - no. (%)	
No	1356 (92)
Yes	125 (8)
Year of transplant - no. (%)	
2015	296 (20)
2016	318 (21)
2017	293 (20)
2018	285 (19)
2019	227 (15)

Characteristic	
2020	62 (4)