Not for publication or presentation

A G E N D A
CIBMTR WORKING COMMITTEE FOR INFECTION AND IMMUNE RECONSTITUTION
Salt Lake City, UT
Monday, April 25, 2022, 6:45 AM – 8:15 AM

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**

---

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

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

3. **Studies published/submitted/Preliminary results**
   a. **IN17-01 (a)** 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. **IN17-01 (b)** 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. **IN17-01 (c)** 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. **COV20-04(a)** 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. **COV20-04(b)** 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)

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

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

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

j. **COV20-04 (e)** 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)

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)

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)

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)

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)

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)

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)

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)

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.*

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.

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.*
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.*
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) [*presentation at Collaborative Study Proposals Session*]

MINUTES
CIBMTR WORKING COMMITTEE SESSION
Thursday, February 11, 2021, 1:00 - 4:00 pm
Co-Chair: Bronwen Shaw, MD, PhD; CIBMTR Statistical Center, Milwaukee, WI; E-mail: beshaw@mcw.edu
Co-Chair: John Wingard, MD; University of Florida, Gainesville, FL; E-mail: wingajr@ufl.edu

INTRODUCTION:

Dr. Wingard opened the virtual meeting at 1:00 pm by welcoming the working committee members and the presenters. He discussed the proposal selection and voting process. Though the pandemic amended the process for proposal selection, 368 working committee proposals were submitted and evaluated altogether by CIBMTR Working Committee Chairs and Scientific Directors. About 61% were screened out, 30% had less-relative scientific merit, and 3% were combined with overlapping proposals with relevant nature. 21 proposals (about 6%), were considered for advancing of further pro-development. The proposals were pre-recorded 5-minutes presentations of the 15 semi-finalists, which were presented by the principal investigators. Each presentation was followed by a 5-minute question and answer session, in which audience was invited to submit questions via live chat. For those not able to attend the live session, a link was posted with the session recording and voting was closed on Monday, February 15, 2021. Audience was also instructed on where to locate the scoring and voting links for the presentations. It was mentioned that over 1,000 Working Committee members voted on the first screening of these proposals. Dr. Shaw led the second part of the meeting starting with presentation #9.

GENERAL REMINDERS:

The following reminders were mentioned and posted via the chat option:

a. Thank you for participating in the CIBMTR Working Committee Session! Please cast your score here: https://mcwisc.co1.qualtrics.com/jfe/form/SV_7QwO1ZvzfPZV1NY to vote on the proposals that were presented during the session.
b. Several presenters provided their email addresses for any future communication.

PRESENTATIONS:

1. **Risk of subsequent neoplasms in patients with post-transplant cyclophosphamide use for graft-versus-host disease prophylaxis.** This proposal was presented by Dr. Ana Alarcon Tomas. The primary objective of this proposal is to describe the incidence rate, risk factors, characteristics, and outcomes of subsequent neoplasms in patients receiving post-transplant cyclophosphamide (PTCy) and compare it with calcineurin inhibitors-based graft-versus-host disease prophylaxis and the general population. The CIBMTR identified 64,935 patients ≥18 years of age who underwent a first allogeneic for a malignant disease between 2008-2017. 5,771 (9%) of these patients developed a subsequent neoplasm. Currently, there are no published studies on the incidence of subsequent neoplasms in patients who received post-transplant cyclophosphamide. The following questions were answered during the Q&A:
    a. How are we going to prove that these secondary neoplasms are related to post-transplant cyclophosphamide or cyclophosphamide in conditioning and not due to "by chance" itself- as in general population? This is a case-controlled study. For example, for each patient received with a post-transplant cyclophosphamide will be matched with at least three patients who didn't receive post-transplant cyclophosphamide. Characteristics including primary disease, HLA complexity, survival, follow up time etc. would be used for matching and reviewing survival will also allow us to see that this is because of PTCy and not by coincidence.

b. What is the median follow up time from transplant and subsequent malignancy in post-transplant cyclophosphamide group? I assume it is much shorter than other cohort? Information is not available for each median follow up time cohort. What is available is the median follow up for all patients and some numbers related to the type of diseases for each group. Dr. Rachel Phelan included in the chat that the median follow-up for the PT-Cy group is 38.2 months, and for the proposed control population is 60.3 months.
c. How is this in comparison with matched unrelated donor and cord transplants? Cord transplants will be excluded from the analysis because we don't think we can match those patients.
d. Do we have adequate follow up to answer this important question? We have follow-up for mantle hematological diseases but less time for solid tumors. However, when we saw the numbers that we have (around 5,000 - 5,700) subsequent neoplasms, the majority of cases occurred after the 1st - 5th year of post- transplant and have a 5-year median follow up. We think we have enough numbers to address this question now and we should not wait because it hasn't been published before. This is a noble study and if we wait for a longer median follow up, we might lose that opportunity to have it published first.

Additional questions and comments posted via the chat but were unanswered due to limited time can be found in Appendix A.

2. **Outcomes of chimeric antigen receptor-T cell therapy for patients with antecedent chronic lymphocytic leukemia (Richter's Syndrome)**. This proposal was presented by Dr. Farrukh Awan. The objective of this proposal is to assess outcomes in adult patients with chronic lymphocytic leukemia undergoing transformation to diffuse large B-cell lymphoma (Richter's Syndrome) and undergoing CAR-T therapy. The CIBMTR identified 36 patients underwent CAR-T for Richter's Syndrome from 2015-2019. The following questions were answered during the Q&A:
   a. I know that in the Ohio State paper have many patients that used concurrent Bruton Tyrosine Kinase (BTK) inhibitors. Will you be able to collect data on concurrent BTK inhibitors for these patients? Yes, this information is available through the CIBMTR dataset.
   b. Are you looking at diffuse large B-cell lymphoma derived Richter's Syndrome or chronic lymphocytic leukemia derived Richter's Syndrome? Yes, but it is difficult to determine a clonality between related and unrelated Richter's syndrome. Any studies that show similarities versus dissimilarities in the clone would be very helpful but unfortunately, previous studies have shown that this has been consistently difficult.
   c. You mentioned the opportunity of comparing to other treatment groups. Can you talk about that a little more? We can compare to patients with de novo diffuse large B-cell lymphoma. There are multiple approved and ongoing studies within CIBMTR of diffuse large B-cell lymphoma patients, who do undergo CAR-T therapy and look at toxicity outcomes and infectious outcomes, for example. There are efforts in place to look at outcomes of transplantation for patients with Richter's Syndrome, which can improve the impact of this project and be a competitor to those other ongoing studies.
   d. How many pts do we have? 36 patients
   e. How do you plan to deal with the very low patient numbers (n=36) to make meaningful conclusion? I agree that it is a small number, but it is substantial. Despite the small numbers, if the right competitors are used, such as those mentioned previously, this study can still provide an impactful dataset.

Additional questions and comments posted via the chat but were unanswered due to limited time can be found in Appendix B.

3. **Impact of graft versus host disease following allogeneic hematopoietic cell transplantation on leukemia free survival in hematologic malignancies**. This proposal was presented by Dr. Andrea Bauchat. The objectives of this proposal is to determine the impact of development of grade I-II acute graft versus host disease on relapse and leukemia-free survival, to assess the impact of development of grade III-IV acute graft versus host disease on relapse and leukemia-free survival, and to determine whether the impact of graft versus host disease on

relapse and leukemia-free survival is influenced by disease risk prior to HCT. The CIBMTR identified 1,345 children <18 years who received first HCT for acute lymphoblastic leukemia and acute myeloid leukemia receiving first allogeneic transplantation between 2008 - 2017. The following questions were answered during the Q&A:

a. What is the sample size of each sub-group: disease-risk index (DRI)-low, -intermediate, -high? Exact sample size not available but the high-risk group was less in comparison to others.
b. How will you factor in occurrence of chronic graft versus host disease in your analysis? Our main focus is on acute graft versus host disease because it will have more impact on our clinical practice. However, we will collect the data for the interactions of chronic graft versus host disease alone, and if the patient had a history of acute.
c. What is the biological basis for focusing this study on a pediatric population? The interest from our perspective is looking at the pediatric population compared to the adults. The literature on pediatric is severely lacking in comparison to adults and we need to expand on that for the patient population that we care for.
d. Are you going to separate acute myeloid leukemia and acute lymphoblastic leukemia numbers at DRI level? Yes, they are already divided from DRI protocol. Our acute lymphoblastic leukemia patients are about 1,300 and the acute myeloid leukemia are about 1,200.
e. Is the analysis going to be time dependent or landmark? Landmark
f. Do you have the date of this max acute graft versus host disease grade to take into account the time to event aspect of the effect? No
g. Do you have a plan to include/account for the various GVHD prophylaxis regimen "strengths?" We are taking into consideration of what GVHD prophylaxis regimen the patient uses. This data, which is already categorized, will show us the differences between trends.
h. What is the clinical benefit besides prognostic? This will help define a better foundation of which patients will benefit more from a little bit of graft versus host disease. If we can come up with a patient category that we see is beneficial to have exposure to a little bit of graft versus host disease, it can go forward with clinical trials and GVHD prophylaxis adjustment or manipulation to improve their Leukemia-free survival.

Additional questions and comments posted via the chat but were unanswered due to limited time can be found in Appendix C.

4. **Effect of HLA evolutionary divergence on survival and relapse following allogeneic hematopoietic cell transplant**. This proposal was presented by Dr. Christine Camacho-Bydume. The primary objective of this proposal is to determine if HLA evolutionary divergence (HED) of HLA class I alleles of HLA-A, -B, -C and HLA class II alleles of HLA-DR is associated with overall survival and relapse. The objective is to also evaluate association of HED with acute and chronic GVHD and treatment-related mortality (TRM). The CIBMTR identified pediatric and adult patients with acute myeloid leukemia, myelodysplastic syndromes, acute lymphoblastic leukemia, chronic myeloid leukemia, or lymphoma (non-Hodgkin or Hodgkin's lymphoma), who have received initial allogeneic 8/8 HLA-matched (HLA-A, -B, -C, -DR) transplant between 2008 - 2018. The following questions were answered during the Q&A:

   a. Could HLA diversity simply be a surrogate for race? How would you account for race in the study? Great question given there are particular HLA alleles that are more common in certain ethnic groups. We do think that evaluation of HED lows and highs within these different ethnicities can help to tease this out more, with potential to adjust for race more in this analysis. We think some of these differences in peptide binding grooves can help us to understand better the different peptides and how antigens are presented to T-cells.
   b. Extrapolating HLA data from solid tumors and checkpoint inhibitors and their antigen presentation is slightly challenging in context of allo donor T-cell interaction with antigen presented for bone marrow origin cancers. Yes, have to consider there could be some differences. Was a small previous study that

looked at this question, saw some signals there, larger population and different types of cancers, may be able to explore that more.

c. Leukemia (both lymphoblastic and myeloid) have low mutational burden as compared to melanoma and lung. Will the HED algorithm still work? Yes, we do expect to see differences in mutational burdens, and we do plan to look at the cohort at large to look at the disease subgroups to see more or less of this phenomenon in these groups. Do you have preliminary data in leukemias? There was a small study in Germany that looked at AML, to my knowledge only one that looked at leukemias. Mutational burden did see some differences, so we do expect it and also, besides the overall cohort, also plan to look at disease subgroups.
d. Given HED implications for infection surveillance, are you going to look at infectious sequelae differences? No, at the moment we have initially requested information in terms of tumor control, relapse, overall survival, graft versus host disease, and TRM. Not sure of availability of the other information but would be interesting to look at if available.
e. Would you please discuss the confounding effects of HLA mismatching for HLA-DRB3, 4, 5, DQ, and DP? Not known off the top of my head the percentages of mismatching differences in this cohort. For DR at least they will be matched, 8/8 matched, in terms of DP, don't have that info but if available it is something that can be looked at.

Additional questions and comments posted via the chat but were unanswered due to limited time can be found in Appendix D.

5. **Impact of IDH1 and IDH2 mutations on outcomes of acute myeloid leukemia patients undergoing allogeneic hematopoietic cell transplantation**. This proposal was presented by Dr. Evan C. Chen. The primary objective of this proposal is to identify differences in survival outcomes between mutIDH1/2 and wtIDH1/2 acute myeloid leukemia patients and to assess the prognostic significance of disease features in mutIDH1/2 and wtIDH1/2 acute myeloid leukemia patients. The CIBMTR identified patients ≥ 18 years old with a diagnosis of normal karyotype acute myeloid leukemia, receiving first allogeneic HCT during CR1 in 2013 - 2019. The following questions were answered during the Q&A:
   a. Is there any concern that patients with IDH1/2 mutated acute myeloid leukemia would have received more intensive conditioning / therapy than IDH1/2 wild-type? Yes, and it's important to look at how conditioning intensity can be an important covariant, which is a variable captured in CIBMTR.
   b. Will you have registry information on the type and duration of use of IDH inhibitors before/after HCT? It's currently not available with CIBMTR.
   c. IDH mutations are usually seen in older subjects. How will you a priori adjust for this known association? Age will certainly be a covariant in our multi-variant analysis.
   d. How reliable are the wild-type patients as some may just not be tested for IDH mutations? It is double checked. There is a datapoint in the forms that indicate whether or not testing has been done, versus if testing was done and IDH was found to be absent.
   e. Do you have information what the numbers will be like when you divide your patient groups with concomitant mutations such FLT3 or p53 that may have an impact on outcomes? Yes, the numbers are about 20-40 for co-mutated for ITD and NPM1 patients. p53 not provided.
   f. Is there data in CIBMTR forms that collect use of IDH inhibitors pre transplant? Will you be able to study their impact on the transplant? I'm not aware of this data point being available in the forms but it is something that we should follow up on.
   g. How do you analyze its (or ITS?) with multiple mutations? With regards to double-mutated patients, IDH1, and IDH2 patients, which are generally rarely reported, we would look at the CIBMTR forms to ensure accurate data entry. In regard to analyzing IDH with other co-mutations, we would include co-mutations as a co-variant in a multi-variant analysis, should the sample size permit.

h. What about other mutations in Wild type IDH? We focus on NPM1 and FLT3-ITD because they are prevalent in the cytogenetic risk population. We will look at the other mutations to see if they have any relevance at all.
i. Do the data forms reliably collect information on use of IDH inhibitors pretransplant? Data point is not available.

Additional questions and comments posted via the chat but were unanswered due to limited time can be found in Appendix E.

6. **Characteristics and outcomes of adolescent and young adults with multiple myeloma treated with autologous hematopoietic cell transplant**. This proposal was presented by Dr. Christin B. DeStefano. The primary objective of this proposal is to describe patient and disease related characteristics of adolescent and young adults (AYAs) with multiple myeloma treated with early high dose melphalan and AutoHCT and to characterize response to AutoHCT, survival outcomes, SPMs, and infections of AYA multiple myeloma patients and AutoHCT. The CIBMTR identified 1,142 AYA multiple myeloma patients who underwent autologous hematopoietic cell transplant) between 2008 -2018. The following questions were answered during the Q&A:
   a. What will differentiate this study from MM18-03 "To compare the outcomes in young patients with multiple myeloma at diagnosis undergoing upfront autologous hematopoietic stem cell transplant with older patients in the US: progression-free and overall survival"? There appears to be substantial population overlap. The Scientific Director clarified via the chat function that MM18-03 included the years 2013-2017 and excluded patients less than 40 years from the outcome analysis owing to small numbers.
   b. How do you plan to control for differences between your AYA group and older control group which would be attributable to age? In total, there are about 1,700 TED and CRF cases. We can adjust the critical variables of these cases, such as stage, treatment rendered, and cytogenetics, for example, to control for differences.
   c. Will results be stratified according to different induction regimens? Yes, we will adjust those critical variables amongst the CRF cases where this information is available.
   d. A cohort going back to 1995 seems too outdated. What was the N for a more recent group (since 2010)? There were 1,142 AYA cases between 2008-2018.
   e. This is a long cohort 1995-2019 with lots of changes in induction treatment, novel agents and time to bone marrow transplant. How will this be controlled for? We are going to study induction regimens, post-transplant treatment, use of tandem transplants in our analysis.
   f. Will you be also studying the effect of post-transplant maintenance therapy? Also, any effect of extramedullary plasmacytomas in this AYA group? We will for cases where this information is available. Extramedullary plasmacytomas are a good focus, as AYA patients may have a more aggressive presentation of myeloma.
   g. Are plasma cell leukemias included in this analysis? No

   Additional questions and comments posted via the chat but were unanswered due to limited time can be found in Appendix F.

7. **Impact of measurable residual disease status on outcomes of AML in patients 18-65 years old in CR1 undergoing Allo-HCT**. This proposal was presented by Dr. Firas El Chaer. The objectives of this proposal is to determine if acute myeloid leukemia measurable residual disease (MRD) analysis as currently performed has prognostic value when measured prior to AlloHCT, to explore factors that may modify the risk associated with detectable acute myeloid leukemia MRD pre-AlloHCT, and identification, using MRD combined with other clinical factors, of patients most at risk of post-AlloHCT relapse. The CIBMTR identified 753 MRD positive and 1986 MRD negative adult patients receiving first AlloHCT for de-novo AML in CR1 in 2007-2018. The following questions were answered during the Q&A:

a. What kind of MRD data is collected? Depending on the individual participating centers, the methodology uses molecular or immunotherapy? MRD
b. What is the rate of missing MRD status and are those patients different from those with MRD data available? The answer is not included in this study.
c. Are you going to also study the effect of post-transplant maintenance in AML FLT3, IHD mutations on relapse and overall survival? One of the aims of this study is to have future studies look at post-transplant maintenance from this study.
d. What do you mean by most "recent" pre-conditioning MRD assessment? Would testing need to be completed within a specific time frame before conditioning? All patients who will be receiving a stem cell transplant are required to get a bone marrow biopsy and peripheral blood aspiration before transplantation. Within a month before the transplant, we would look at data point.
e. What is your working definition of MRD? A combination of molecular testing as well as immunotherapy by NFC.
f. Are all mutations equivalent when thinking about MRD? Absolutely not.
g. How sure are you that the MRD patients are really MRD negative? We can never be absolutely sure.
h. How are you going to account for the different sensitivity of methods used to determine MRD? Are ELN risk available at CIBMTR, since when? The way that CIBMTR reports the acute myeloid leukemia data is by reporting their cytogenetics and mutation analysis so we can calculate the data for this population. The point of this study is to look at the commercial availability of these tests and we can rely on it or if we should standardize one testing at all centers.

Additional questions and comments posted via the chat but were unanswered due to limited time can be found in Appendix G.

8. **Racial, ethnicity and socioeconomic disparity in outcome of patients with chronic graft versus host disease.** This proposal was presented by Dr. Nosha Farhadfar. The objectives of this proposal are to determine whether clinical manifestations and severity of chronic GVHD differ based on racial/ethnic and socioeconomical status (SES) differences, to determine whether treatment patterns of chronic GVHD differ based on racial/ethnic and SES differences, and to evaluate whether chronic GVHD treatment outcomes differ based on racial/ethnic and SES differences. The CIBMTR identified 17,665 patients, age 18 years or older, who have received first allogeneic transplant for hematologic malignancy (acute myeloid leukemia, acute lymphoblastic leukemia, myelodysplastic syndrome) between 2008 - 2019. The following questions were answered during the Q&A:
   a. I like the idea for looking at outcomes based on race/ethnicity/SES but not sure if incidence should be a primary outcome because it will be dependent on donor type which is very different amongst the groups. The primary outcome of this study is to look at the outcome of patients who develop chronic graft versus host disease. We need to look at the whole cohort, report the incidence, and then focus on chronic graft versus host disease cohort as the primary endpoint of this study.
   b. How will you correct for the impact of race on HLA mismatch between recipients and donors due to the lower chance of identifying a fully matched donor in non-Hispanic white patients? For the same reason, should cord blood recipients be excluded? We are going to include both the donor type, graft source and degree of HLA matching as covariables in a multi-variable analysis. Cord blood recipients should not be excluded, as there was near 14% of Non-Hispanic black, 14% Hispanic, and 15% Asian who received cord transplant. Approximately 7-8% of cord transplants were received by Non-Hispanic whites. We do have the number to look into cords but if a statistician reviews and determines we don't have the power, then we can eliminate the cords.
   c. Is it possible to access constitutional DNA to look at ancestry information markers in this population? This information is not available for the population. The analysis will focus on self-reported race/ethnicity.
   d. All patients in your cohort from 2008 were not reported with NIH consensus criteria for chronic GVHD. Since you have large numbers, should you limit this to more recent time period? We do have all of the

information on graft versus host disease and whether it was limited or extensive. There is information on whether graft versus host disease is progressive, de-novo or interrupted. We have organ involvement and maximum grade of chronic graft versus host disease. NIH scoring is available for at least the past 4 years and maybe we can look at that group separately. Within the past 4 years, the population limited to NIH grading only in about 1,500 non-Hispanic white, 270 non-Hispanic black, and 200 Hispanic, who have developed chronic graft versus host disease.

Additional questions and comments posted via the chat but were unanswered due to limited time can be found in Appendix H.

9. **Time from diagnosis to transplant as an important contributor for post allogeneic stem cell transplant infections, immune reconstitution and its associated mortality/morbidity**. This proposal was presented by Dr. Lohith Gowda. The objectives of this proposal are to identify density and types of early and late infections (bacterial, viral and fungal) in patients that went to transplant a) <6 months b) between 6- 12 months and c) > 12 months from diagnosis; to identify T cell lymphocyte absolute numbers at days 100 and 180 and CD4/CD8 ratio for the timeline cohorts examining individual donor types; to evaluate the impact of bacterial, viral or fungal infections by day 100 and day 180 on 1-year post-transplant outcomes (relapse, non-relapse mortality, disease free survival, acute and chronic graft versus host disease); and to evaluate quantitative immunoglobulin levels at D+ 100 and + 180 if available. The CIBMTR identified 6,877 ≥ 18 years old patients who underwent first allogeneic transplants for AML in CR1, ALL in CR1 or MDS in the United States from 2012 to 2019. The following questions were answered during the Q&A:
    a. How many patients in the registry have the immune parameters you wish to assess? >2100
    b. How will you account for the type of treatment used prior to transplant? For example, treatments such as hypomethylating agents may require months of treatment before transplant versus induction chemo that works more quickly. We do have some variables that are available, such as types of therapy, and we can analyze levels of intensity of therapy (low to high) and post-transplantation outcomes. The exact number of how many patients who have had different intensities of therapies is not available.

    Additional questions and comments posted via the chat but were unanswered due to limited time can be found in Appendix I.

10. **Efficacy and safety of CD19 directed CAR T-cell therapy for non-Hodgkin B-cell lymphomas with secondary central nervous system involvement**. This proposal was presented by Dr. Hamza Hashmi. The primary objective of this proposal. The CIBMTR identified 55 adult patients (age ≥ 18) who received CD19 CAR T-cell therapy for B-cell NHL with secondary central nervous system (CNS) involvement. The following questions were answered during the Q&A:
    a. How will you differentiate between immune effector cell-associated neurotoxicity syndrome (ICANS) and CNS relapse? ICANS will be documented as a neurotoxicity and CNS relapse will be when the form is filled out.
    b. Is this active CNS disease or previously treated CNS disease? The data received from CIBMTR looks at CNS disease at the time of diagnosis and the CNS disease that is present at the time of cellular therapy.
    c. Do you have any registry information on concomitant CNS therapy (chemo/radiation) pre, peri and post transplantation? Answer was not available at this time.
    d. How many patients are in your study? How will you define whether the patients have cleared their CNS involvement? There are currently 60 patients in the history of this data. Of the 60, 40 had this disease at the time of diagnosis and 20 had this disease at the time of cellular therapy. Whether the patients have cleared their CNS involvement, this information is not available at the time.
    e. Since this is your primary endpoint, how will you account for the differences of frequency of CRS and ICANS across different products (e.g. high in Yescarta, lower in Kymriah, low in Breyanzi)? If you look at the toxicity profile of CD19 therapy, they seem to be relatively similar.

f. Could you please include other agents such as anakinra, siltuximab, and other agents? Dasatinib for this populations for ICANS? Also, was CNS disease under control at CAR-T therapy? As for Anakinra, siltuximab, and other agents, I'm not sure if CIBMTR is capturing this data. As for dasatinib, I'm not sure if this information is available as well. Per Dr. Pasquini of CIBMTR in the live chat, he commented "we capture treatment of ICANS, like siltuximab, dasatinib has been reported as other treatment."
g. Will you have detail on the nature and extender features of secondary CNS involvement to associate with the toxicity and outcome? I only have the essential data with me but am hopeful that this comprehensive research will have further detail.
h. Will all the patients included have active CNS disease at the time of CAR-T or, are treated CNS disease are also included? They are both included, and we are able to tell who has had active disease with a prior history at the time they got the CAR-T therapy.

Additional questions and comments posted via the chat but were unanswered due to limited time can be found in Appendix J.

11. **Haploidentical donor versus matched donor allogeneic hematopoietic cell transplantation in patients with myelofibrosis**. This proposal was presented by Dr. Tania Jain. The primary objective of this proposal is to explore the impact of donor type on overall survival of patients undergoing HCT for myelofibrosis. The CIBMTR identified 1,640 patients ≥18 years old diagnosed with primary, post-ET or post-PV myelofibrosis and undergoing first HCT between 2013 and 2019. The following questions were answered during the Q&A:
    a. Are you also going to compare the effect of pretransplant Ruxo in haplo vs MUD/MRD? Also, are you going to look for graft failures as well in these patient populations? Yes, this will be included. We also do look at graft failures in these populations.
    b. Is there a difference in time from diagnosis to HCT across the groups? The median time from diagnosis to transplant for haploidentical patients was 38 months, while for HLA- identical sibling and URD 8/8 was 21 and 24 months, respectively.
    c. Are you including all conditioning regimens types: MAC, RIC and NMA? Yes, and they will be looked at for comparison in the univariable and may be taken to the multivariable analysis as well.
    d. For the graft failure or rejection analysis are you going to include spleen size? Ideally it should be included but the spleen size measurement has many variables and it may not be a clean assessment. We don't collect precise spleen size in our forms, but it can be analyzed as spleen size as splenomegaly, no splenomegaly or splenectomy.
    e. Can you comment on the bone marrow vs peripheral blood in the three groups? Peripheral blood is more common in the donor source (about 80%).

    Additional questions and comments posted via the chat but were unanswered due to limited time can be found in Appendix K.

12. **Assessing utilization and clinical outcome differences by sex and race in CAR-T for relapsed/refractory NHL**. This proposal was presented by Dr. Arushi Khurana. The objective of this proposal is to enhance our understanding of sex- and race-based differences in utilization of CAR-T vs AutoHCT and outcomes after CAR-T. The CIBMTR identified 1,133 patients to compare sex and race/ethnicity rates for first cellular infusion (AutoHCT vs. CAR-T) for relapsed/refractory non-hodgkins lymphoma patients from 2017 – 2019 (aim 1a). The CIBMTR identified 619 non-hodgkins lymphoma patients who relapse after first AutoHCT to describe subsequent treatment patterns (e.g. CAR-T, second AutoHCT, AlloHCT, other treatment, no treatment) by sex and race/ethnicity (aim 1b). The CIBMTR identified 1,253 patients to identify sex-and race-based differences in response to CD19 CAR-T in aggressive lymphomas (aim 2). The following questions were answered during the Q&A:
    a. Is there gender and race-based difference in SEER data with or without treatment for diffuse large B-cell lymphoma even before CAR T? Yes, that data does exist.

b. Can this be stratified by center/geography (private/public, large urban/rural)? Yes, it will be shown based on zip code (of patient and of recorded center), which will allow us to differentiate from urban/rural as well.
c. We saw almost no neurotoxicity in women so would you be plotting CRS and ICANS based on gender and race? Yes, and we believe CIBMTR is the best resource for this because of the larger numbers
d. How do you differentiate between larger trial centers vs less resourced centers? The information is reported based on the center type. Basing on academic or zip code, or city versus rural center, that will also be a way to differentiate the centers.
e. Would disease response status prior to cellular therapy be taken into account for analysis? Yes, that is one of the co-variants that will be included.
f. How reliable is the data you will get to study "access", as there are many factors, depending on patient specific factors (education, resource, finances, mobility, support, performance, etc.), center specific (criteria), and also access depends on the hematologist/oncologist who sees these patients in the community? Access to a center is not one of the main issues in this study. It is more about why some of these minorities receiving other treatments when they should be receiving cellular therapy at the time of indication.
g. Is there any way to take into account insurance issues? We do look at the insurance statuses as one of the co-variants.
h. Would it be possible to look at differences in access based on commercial CAR T vs. clinical trials? The majority of the patients from the forms received are from commercial CAR T.

Additional questions and comments posted via the chat but were unanswered due to limited time can be found in Appendix L.

13. **Optimal GVHD prevention strategy in older, robust patients with acute leukemias and myeloid malignancies undergoing myeloablative, matched donor hematopoietic cell transplantation**. This proposal was presented by Dr. Richard J. Lin. The primary objective of this proposal is to compare CRFS among patients ≥ 60 years old undergoing myeloablative conditioned, allogeneic hematopoietic cell transplantation with following graft versus host disease prophylaxis in 2 matched-pair analysis and to compare other transplant outcomes in the above 2 matched-pair analysis. The CIBMTR identified 1,301 patients at ≥ 60 years old at the time of first allo-HCT between 2010 and 2019, with any myeloablative conditioning defined by CIBMTR, 8/8 matched related or unrelated donor only, graft versus host disease prophylaxis (ex-vivo TCD/CD34+ selection versus PTCy-based versus Tac/MTX). The following questions were answered during the Q&A:
    a. What do you mean by "robust?" Is it based on KPS, HCT-CI, or just the fact that someone got MA. regimen? We use the definition of a patient getting a myelo-conditioning as a way of saying that they are robust by their transplant centers.
    b. Are patients with In-vivo T cell depletion (Campath or ATG) excluded from this analysis? T cell depletion and CD34 selection does include ATG and does not include Campath.
    c. Why do you pool post-CY and ex vivoCD34+ selection? Can we still consider ex vivoCD34 selection to be a promising transplant modality in 2021? We wanted to compare a 2-match pair analysis and not a direct comparison between CD34 selection and post-CY. We do know which will be better for an older patient.
    d. Why exclude TBI? For older patients, we don't consider TBI to be a conditioning regimen.
    e. How many patients with Tac/methotrexate prophylaxis had ATG? Answer was not available at the time of Q&A.
    f. Do we know GFR (creatinine) coming into allo in these groups? In this study, we didn't include the GFR (creatinine) as a variable but we have some evidence in older patients that does play a major role. I can discuss with our statistician on whether we can include this as a variable.

    Additional questions and comments posted via the chat but were unanswered due to limited time can be found in Appendix M.

14. **Outcomes of elderly patients receiving CD-19 directed CAR-T therapy for B-cell lymphomas**. This proposal was presented by Dr. Sayeef Mirza. The primary objectives of this proposal to evaluate cumulative incidence grades, duration and median time to onset of CRS and CRES/ICANS in patients > 65 years of age receiving CD-19 directed CAR-T therapy, describe post CAR-T clinical outcomes and resource utilization in elderly, and identify disease biology, comorbidities and other clinical predictive markers of toxicity, response, and survival in elderly patients. The CIBMTR identified 1,036 patients (<65y,n=612; 65-74y, n=348; >75y, n=76) with the diagnosis of any B-cell lymphoid malignancy (indolent or aggressive lymphoma) receiving CAR-T cell product (CD19 target). The following questions were answered during the Q&A:
    a. Would you please also look at Incidence of pancytopenia, hypogammaglobulinemia and HLH in elderly versus younger in 3 cohorts <60, 60-75 ,>75? I think it's very important to look at this as the data becomes available to us. We are primarily looking at different age groups. We have 81 patients over the age of 75 and five patients over the age of 85. Overall, there are 435 (40 %) of the group are over 65 years old.
    b. How does this defer from the data presented by Dr. Pasquini last year in older patients? This data will be more helpful in including both CAR-T products.
    c. In case of CAR T was used for post-alloHCT relapse, would the donor age of the CART source be analyzed? This is something that we should include in our analysis.
    d. Are data on baseline geriatric scores or HCT-CI available for all? The answer was not available at the time of the Q&A.
    e. Do we have registry information on whether CAR-T production succeeded or not, when attempted? The answer was not available at the time of the Q&A but the moderator did state that on behalf of CIBMTR, this information is not captured.

    Additional questions and comments posted via the chat but were unanswered due to limited time can be found in Appendix N.

15. **Determinants of successful discontinuation of immune suppression following allogeneic hematopoietic cell transplantation**. This proposal was presented by Dr. Joseph Pidala. The primary objective of this proposal is to validate prediction models for immune suppression discontinuation (ISD) and ISD failure developed in prior DISCIS-defined population, explore ISD and ISD failure in a new population inclusive of full range of diversity in current HCT practices, construct and validate dynamic prediction models of ISD and ISD failure in the expanded population. The CIBMTR identified 20,031 patients with a hematologic malignancy who received an allogeneic HCT from matched sibling donor, matched or mismatched unrelated donor, umbilical cord blood or haploidentical donor between 2009-2018. The following questions were answered during the Q&A:
    a. Can you explain how the ISD data information was made feasible? We used CIBMTR follow up data in the previous analysis that led to the development of the prediction model for ISD that we intend to validate in this study.
    b. Can you provide more granularity on how the time of discontinuation of immune suppression will be defined? In the CIBMTR data, there is a hard stop date for a complete discontinuation of immune suppression. That granular data is available, and it was the data we used for the prior project. We used that hard stop of all systemic immune suppression because that's an unambiguous measure of success.
    c. Many with PTCY may be discontinuing by days 100 or 60- likely based on center practice rather than patient response, how will this be addressed? Our prior project was successfully addressed this issue, specifically within that study population. The first step in this project is to validate those findings. We will definitely be studying how immune suppression was performed and what are the subsequent outcomes.
    d. Do you plan to use age as one of the variables regarding likelihood to discontinue IST, or will you have a separate pediatric specific model? Yes, we will consider age as a variable and evaluate the need for a pediatric specific model.

Additional questions and comments posted via the chat but were unanswered due to limited time can be found in Appendix O.

CLOSING:

Dr. Shaw, on behalf of herself and co-chair, Dr. John Wingard, did thank presenters, conference organizers, and the CIBMTR staff for having coordinated this virtual session. She did mention that this session was recorded and encouraged attendees to take survey, as access would be available until Monday, February 15, 2021.

APPENDICES:

A. Risk of subsequent neoplasms in patients with post-transplant cyclophosphamide use for graft-versus-host disease prophylaxis.

1. How will authorship work for these studies? The same as usual, there are fewer studies being accepted but the process otherwise is the same
2. What if a higher risk of cancer is related to the almost uniform use of 2GyTBI in these patients rather than PTCY?
3. What is the breakdown of haploidentical versus matched sib/MUD in the post-transplant cyclophosphamide group?
4. How can we r/o genetic predisposition on samples and variables of TBI based conditioning therapies?
5. What is your sample size and follow-up period?
6. How long post BMT you will follow up? From where will you receive the SN data?
7. Will you be adjusting for chronic GVHD when looking at your outcome of SN?
8. Is this study statistically powered to detect a difference between PTCY and above a certain threshold? What is the threshold?
9. Will analysis be conducted separately for TBI/non-TBI and MAC/RIC conditioning? Are you evaluating all malignancies?
10. Since the total CY exposure is likely not that different in PTCY vs. BU/CY or CY/TBI, is your hypothesis that the timing of exposure to CY may lead to a difference in risk? And if so, why?
11. Information on skin cancers - ssc, bcc available?
12. Matching for HLA matching could be a limitation because the PTCY patients are more likely to receive haploidentical grafts.

B. Outcomes of chimeric antigen receptor-T cell (CAR-T) therapy for patients with antecedent chronic lymphocytic leukemia (Richter's Syndrome).

1. If patients had failed an auto or allo, how do you plan to compare to the results of auto? Isn't it a different group?
2. Can you please provide your thoughts if the small n will be able to generate meaningful results at this time?
3. Would you include both transformed lymphoma from other low-grade lymphoma and Richter's transformation?
4. Are there concerns about underreporting Richter's?
5. Since the numbers are small, can we go back to centers to establish clonality?

C. Impact of graft versus host disease following allogeneic hematopoietic cell transplantation on leukemia free survival in hematologic malignancies. *No additional questions*

D. Effect of HLA evolutionary divergence on survival and relapse following allogeneic hematopoietic cell transplant.

1. Does the HED algorithm take into account variations outside the peptide binding groove?

2. What is the size of the cohort you are looking at?

E. Impact of IDH1 and IDH2 mutations on outcomes of acute myeloid leukemia patients undergoing allogeneic hematopoietic cell transplantation. *No additional questions*

F. Characteristics and outcomes of adolescent and young adults with multiple myeloma treated with autologous hematopoietic cell transplant.

1. How do you plan to control for differences between your AYA group and older control group?

G. Impact of MRD status on outcomes of AML in patients 18-65 years old in CR1 undergoing Allo-HCT.

1. How are you going to account for the different sensitivity of methods used to determine MRD? Are ELN risk available at CIBMTR, since when?
2. Hi Firas, How are defining the MRD?
3. The methods for MRD assessment may be quite heterogeneous, including the threshold of detection. How will you deal with the high likelihood of false MRD negative assessments from using inadequately sensitive quantification?
4. MRD test is different from different centers. How can you control for this?
5. How do you account for different MRD- cut-offs?
6. To clarify, if AML-MRD is to become a "precision medicine tool", does that mean is will be used to guide treatment decisions in addition to being prognostic?
7. How will control for the various methods for detecting MRD as different techniques have different sensitivities/accuracy?
8. if both multiparameter flow and NGS are available and are discordant on the same patient, how will that be analyzed?
9. is the MRD before alloSCT is the one to be analyzed?
10. Will this require more data from centers to answer some of the questions above?

H. Racial, ethnicity and socioeconomic disparity in outcome of patients with chronic graft versus host disease.

1. Is age significantly different in your Hispanic cohort? How do you adjust for it?
2. Was the MMUD recipient cohort limited to single antigen mismatch? Or all mismatches (understanding most MMUD will likely be single antigen MM)?
3. Do you have information on health insurance? Why not to study this question in a more homogeneous patient population to avoid the complexity and interactions in different factors?
4. Are there any other sociodemographic variables available that could be used to adjust for socioeconomic status, or is median income in the patient's ZIP code the only one?
5. Baker et al 2009 demonstrated no impact of household income on GVHD (acute or chronic) and only minimal impact of race on Grade III-IV aGVHD (none of cGVHD). Why do you think this null relationship should be pursued again?
6. Is there a plan to study as per continent distribution?
7. Is there a better index to gauge SES or poverty level?
8. Are Native American/Hawaiian/Pacific islanders being grouped elsewhere?

I. Time from diagnosis to transplant as an important contributor for post allogeneic stem cell transplant infections, immune reconstitution and its associated mortality/morbidity.

1. Do you plan to address the confounding influence of different factors leading to delay in transplant timing?
2. How are you going to account for number of cycles of chemotherapy versus no

chemotherapy as a confounder in the time delay?

J. Efficacy and safety of CD19 directed CAR T-cell therapy for non-Hodgkin B-cell lymphomas with secondary central nervous system involvement.

1. Is site-specific response (CNS vs. other lesions) and pattern of relapse/progression (CNS vs. systemic) available?
2. Why not to consider a comparative group?
3. Will you stratify patients according if they received IT chemo vs radiation therapy?

K. Haploidentical donor versus matched donor allogeneic hematopoietic cell transplantation in patients with myelofibrosis.

1. Availability of somatic mutations?
2. Is pretransplant Splenectomy data available? Are you going to factor this in the outcomes?
3. At least look at splenectomies?
4. What risk stratification is being used? DIPSS or DIPSS+?

L. Assessing utilization and clinical outcome differences by sex and race in CAR-T for relapsed/refractory NHL. *No additional questions*

M. Optimal GVHD prevention strategy in older, robust patients with acute leukemias and myeloid malignancies undergoing myeloablative, matched donor hematopoietic cell transplantation. *No additional questions*

N. Outcomes of elderly patients receiving CD-19 directed CAR-T therapy for B-cell lymphomas. *No additional questions*

O. Determinants of successful discontinuation of immune suppression following allogeneic hematopoietic cell transplantation.

1. How is immune suppression stop defined in the CIBMTR database?
2. How long after HCT do you expect data regarding ongoing IST usage to be reliable since many patients leave the transplant center and are managed elsewhere long-term?
3. How long will you deal with restart IST?

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: 2020 data was not included in this table since it's not complete in our current retrieval.

CIBMTR®
CENTER FOR INTERNATIONAL BLOOD & MARROW TRANSPLANT RESEARCH

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
IN18-02

The Incidence and Impact of Clostridioides Difficile Infection (CDI) on Transplant Outcomes after Allogeneic Hematopoietic Cell Transplant (alloHCT) – A CIBMTR Study

Introduction: CDI is common after alloHCT mainly due to the frequent use of antibiotics before and during transplant. CDI is reported in 13 to 18% of recipients after alloHCT and in 6 to 8% after autologous HCT, mainly in the first-month post HCT. The determination of incidence and impact of CDI on HCT outcomes will help further our understanding towards the prevention and management of CDI post HCT.

Methods: Using the CIBMTR dataset, we examined all patients aged two years and older who received first alloHCT for acute myeloid leukemia (AML), Acute Lymphocytic leukemia (ALL), or myelodysplastic syndrome (MDS) from related or unrelated donors between 2013 and 2018 at US centers. Stem cell sources included HLA-matched marrow, peripheral blood (PBSC), and umbilical cord blood (UCB) (4/6 or higher). The objective was to study the impact of CDI by day 100 on transplant outcomes by one year compared to the control cohort (without documented CDI from the same centers). Multivariable analyses were performed using Cox proportional hazard model for overall survival (OS), disease-free survival (DFS), Transplant related mortality (TRM), Infection-related mortality (IRM), chronic GVHD, and relapse. Both aGVHD preceding CDI and CDI preceding aGVHD were analyzed. Due to overlap in the onset of CDI and aGVHD, an interaction of these time-dependent events in some models were noted necessitating incorporation of a composite variable (CV - CDI+aGVHD) for OS, TRM, IRM, and cGVHD models.

Results: A total of 826 patients with CDI and 6723 controls from 127 centers were analyzed. The cumulative incidence of CDI by day 100 following alloHCT was 18.7% (99% CI: 15% – 22.7%) and 10.2% (99% CI: 9.2% – 11.1%) in pediatric and adult patients, respectively [Figure 1]. The median time to diagnosis of CDI was 13 days (0 – 100). Recurrent CDI by 1 year occurred in 15% of patients. Myeloablative conditioning with total body irradiation (compared to Reduced-intensity/non-myeloablative (RIC/NMA) conditioning) and lower gastrointestinal GVHD preceding the diagnosis of CDI were risk factors for CDI. A diagnosis of MDS was associated with a lower risk of CDI. There was

significant overlap in the onset of aGVHD and CDI [Figure 2] such that for patients with both CDI and aGVHD [n=378], 115 (30%) had aGVHD prior to CDI, and 70% were diagnosed with CDI first.
CV - CDI + aGVHD was associated with a statistically significant increase in IRM and TRM and a decrease in OS. Specifically, CDI was associated with a 2.58-fold [99% CI: 1.43 – 4.66; p<0.001] increase in IRM which increased to >4 fold when CV-CDI + aGVHD was considered, irrespective of whether aGVHD preceded CDI or vice versa [CDI first: 4.88 (99% CI: 2.38 – 9.97), p<0.001; aGVHD first 4.15 (99% CI: 1.46 – 11.80), p = 0.0005]. CDI alone was not associated with increased risk of cGVHD [0.85 (99%CI: 0.66-1.09), p=0.0921], and the CV - CDI+aGVHD had similar risk of cGVHD as aGVHD without CDI. CDI had no impact on relapse or DFS.

Conclusion: CDI tightly overlaps with aGVHD. Not surprisingly, the combination of CDI and aGVHD is associated with decreased overall survival and increased TRM. More concerning is that patients having both aGVHD and CDI had a >4-fold increased risk of death due to any infection. Our results highlight the burden and impact of CDI after alloHCT and the critical need to develop new/improved strategies for prevention in alloHCT recipients.

Figure 1. Cumulative Incidence of CDI within 100 days post allo SCT based on age

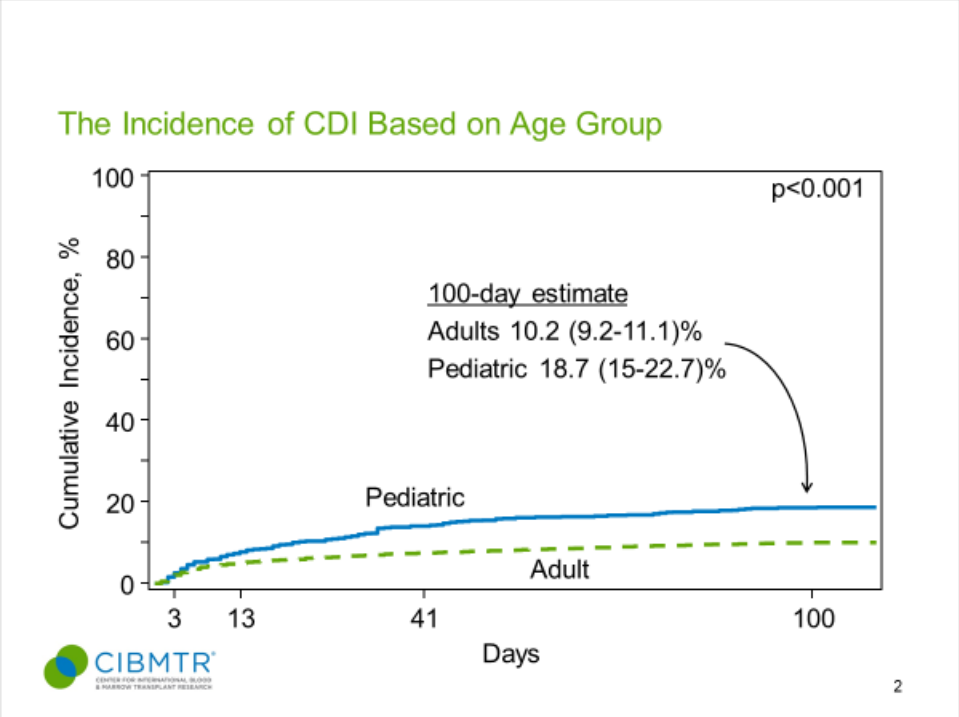
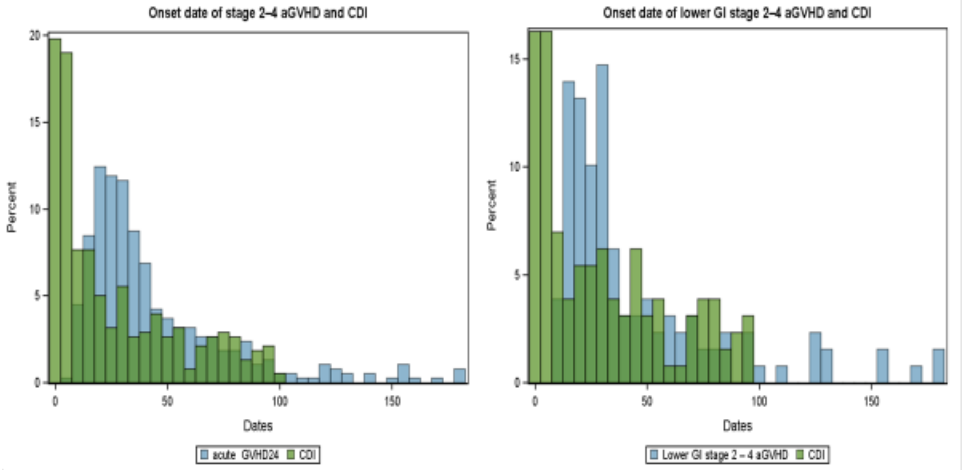


Figure 2. Overlap in onset of CDI and stage 2-4 aGVHD/lower GI aGVHD post allo SCT.



CIBMTR®
CENTER FOR INTERNATIONAL BLOOD & MARROW TRANSPLANT RESEARCH

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 2022.

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 2022.

IN18-02 The Incidence, and impact of Clostridium difficile infection within 100 days on Transplant outcomes after allogeneic stem cell transplant (Muthalagu Ramanathan/ Bipin Savani/ Celalettin Ustun) The study is in manuscript preparation phase. The goal of this study is to have the manuscript submitted by June 2022.

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. The goal of this study is to have the manuscript submitted by June 2023.

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. The goal of this study is to have the manuscript submitted by June 2023.

COV20-04(b) Clinical Characteristics and Outcomes of COVID-19 in Paediatric Haematopoietic Stem Cell Transplant Recipients: A Cohort Study (Bhatt, Sharma, Auletta, Dandoy). The manuscript is submitted. The goal of this study is to have the manuscript submitted by June 2022.

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, Riches). 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

Impact of Engraftment Syndrome on Immune Reconstitution and Clinical Outcomes with Predictive Modeling and Clinical Score Generation

Q2. Key Words

engraftment syndrome, outcomes, immune reconstitution, antibiotic stewardship

Q3. PRINCIPAL INVESTIGATOR

Provide the following information for each investigator:

Principal Investigator #1:

First and last name, degree(s):	Scott Goldsmith, MD
Email address:	sgoldsmith@coh.org
Institution name:	City of Hope National Medical 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):	N/A
Email address:	N/A
Institution name:	N/A
Academic rank:	N/A

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:

Scott Goldsmith

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

- Yes, I am a junior investigator and would like assistance identifying a senior mentor for my project

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.

I was the lead PI for the CMV outcomes research in Post-transplant Cyclophosphamide haploidentical and matched related donor patients and was first author on the Blood publication this year

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

Q15. RESEARCH QUESTION:

What are the incidence of and factors that correlate with engraftment syndrome among Auto-HCT and Allo-HCT recipients reported to the CIBMTR? Can a predictive risk model be generated to identify likelihood of engraftment syndrome compared to other etiologies that could be validated and employed clinically?

Q16. RESEARCH HYPOTHESIS:

1. Engraftment syndrome in Auto-HCT and Allo-HCT may be associated with prolonged hospitalization (if transplantation was inpatient) or increased requirement for hospitalization (if transplantation was outpatient). Management may be heterogenous, and outcomes such as non-relapse mortality may be worse in patients who develop engraftment syndrome.
2. Data from a large CIBMTR dataset on engraftment syndrome in Auto-HCT and Allo-HCT may allow for development of a clinical predictive model for assessing the likelihood of engraftment syndrome which may provide evidence-based guidance for resource management.
3. Among patients who experience engraftment syndrome or suspected engraftment syndrome, differences in the early reconstitution of immune cells may differ as compared to those who engraft without ES.

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

Suggested word limit of 200 words:

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, in order 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

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.

Engraftment syndrome (ES) has a heterogenous presentation and one that overlaps with several, potentially life-threatening entities including infection and acute GHVD. ES, while often self-limited, can progress to multi-organ system failure and death. Given the overlapping time-frame and nature of these entities, they often require empiric therapy for all of them including broad-spectrum antibiotics, immunosuppressants, and hospitalization, which strains resources, promotes poor antibiotic stewardship, and leads occasionally to counterintuitive practices (eg. additional immunosuppression in the setting of possible sepsis and needed immune-reconstitution). The incidence of ES has not been well-characterized in large cohorts derived from registry data. Such characterization could provide more insight into the incidence and features of ES in both the Auto-HCT and Allo-HCT setting, and allow for evidence-based guidance of management. The data may allow for predictive scoring to support the diagnosis of ES or an alternative, that may be validated either internally or externally. Additionally, this study would leverage the immune reconstitution data available through the CIBMTR registry in order to delineate the patterns of immune cell reconstitution in those with or without ES, and serve as the platform for future prospective study of ES. Such data may also be able to be correlated with transplant-related outcomes to determine if there is a correlation between the development of ES and GVHD or an improvement in the incidence of relapse and progression-free survival due to a robust immune reconstitution.

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.

Numerous institutional reports have qualitatively described the occurrence of ES in the Auto-HCT and Allo-HCT platforms. A lack of consensus in criteria and nomenclature has led to a heterogenous report of descriptions and incidences ranging from 6-80% in the Allo-HCT setting. In one of the largest retrospective studies reported, Chang and colleagues (2014) conducted a systematic review of 18 manuscripts pertaining to ES in Allo-HCT, identifying 119/927 patients (13%) experiencing ES. This was lower relative to the incidences that had previously been reported, and was justified by the fact that they used stricter criteria for eligibility. Engraftment syndrome was associated with a significantly higher incidence of acute GVHD and non-relapse mortality, which translated to lower overall survival at 2 years and no impact on relapse. These findings are both interesting and hypothesis-generating. However, the sample size of patients who developed ES was relatively small even with a large systematic review. Additionally, while they conducted some biomarker assays focused on the cytokines of ST2, IL2R, and TNFR1, they and other have not conducted a robust analysis on the constitutional makeup of the immune system upon engraftment among those who do or do not develop ES.

An analysis of the CIBMTR database pertaining to engraftment syndrome would provide the largest dataset to comprehensively analyze the incidence of ES among both Allo-HCT and Auto-HCT recipients. It would provide, essentially, the true incidence of the syndrome in both cohorts. Beyond defining the incidence of the syndrome, it would allow for accurate correlation of the occurrence of ES with key transplant-related outcomes which could inform prospective studies. An aspect of this project that would provide immediate clinical relevance is the development of predictive scores that support clinical decision pathways in favor of ES management or an alternative. At a scientific level, this would be the first and largest study to characterize the immune reconstitution in patients who experience ES as compared to those that do not.

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:

1. Adult and pediatric patients receiving either Allo-HCT for hematologic malignancy or Auto-HCT for hematologic malignancy
   a. For data analysis purposes would be divided into separate cohorts
2. Patients receiving their first transplant
3. Patients with baseline data, HCT infusion data, post-HSCT data (form 2100), and post-transplant essential data

Exclusion Criteria:

1. Patients with documented active infection within 1 day of engraftment
2. Patients receiving cellular therapies/products that are not a hematopoietic cell transplant
3. Umbilical cord blood transplantation

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.

Baseline data: Sex, age, history of infection (viral, fungal), Conditioning regimen (MA vs. RIC, TBI y/n, thymo), DSAs
Infusion data: Auto/allo, donor sex, mobilization drugs used, TNCs and diff, CD34+,graft manipulation, positive cultures in graft
Post-HSCT: Hematpoeitic recovery (inclusion criterium), growth factor (type/planned), immune reconstitution data at time points reported, Engraftment syndrome reported (data, symptoms, biopsy, therapy, resolution), GVHD ppx in conditioning and afterward, acute and chronic GVHD incidence, organ, grade, treatment, status), clinically significant infections, Functional status (intent to complete as outpatient +/- unplanned admission), inpatient days

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/Comı

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:

1. Edenfield WJ, Moores LK, Goodwin G, Lee N. An engraftment syndrome in autologous stem cell transplantation related to mononuclear cell dose. Bone Marrow Transplant. 2000 Feb;25(4):405-9. doi: 10.1038/sj.bmt.1702155. PMID: 10723584.
2. Cornell RF, Hari P, Drobyski WR. Engraftment Syndrome after Autologous Stem Cell Transplantation: An Update Unifying the Definition and Management Approach. Biol Blood Marrow Transplant. 2015;21(12):2061-2068. doi:10.1016/j.bbmt.2015.08.030
3. Kollimuttathuliamc S, McKiernan P, Siegel DS et al; Engraftment Syndrome in the Setting of Autologous Stem Cell Transplantation for Multiple Myeloma-a Single Institution Review of over 600 Patients. Blood 2019; 134 (Supplement_1): 4576. doi: https://doi.org/10.1182/blood-2019-132052
4. Spitzer TR. Engraftment syndrome following hematopoietic stem cell transplantation. Bone Marrow Transplant. 2001 May;27(9):893-8. doi: 10.1038/sj.bmt.1703015. PMID: 11436099.
5. Chang L., Frame D., Braun T. et al. Engraftment Syndrome after Allogeneic Hematopoietic Cell Transplantation Predicts Poor Outcomes. 2014 May; 20(9):1407-17. https://doi.org/10.1016/j.bbmt.2014.05.022
6. Liu, Z, Zhang, S, Horn, B, Moreb, JS. Postautologous stem cell transplantation engraftment syndrome: Improved treatment and outcomes. Clin Transplant. 2020; 34:e13797. https://doi.org/10.1111/ctr.13797
7. Dhakal B, Thapa B, Dong H, et al. Budesonide Prophylaxis Reduces the Risk of Engraftment Syndrome After Autologous Hematopoietic Cell Transplantation in Multiple Myeloma. Clin Lymphoma Myeloma Leuk. 2021; 21(10), 775-81

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. Characteristics of patients who underwent first allogeneic transplant for AML, ALL, MDS, MPN, HL, NHL and MM from 2013 to 2020 with engraftment syndrome reported to CIBMTR

Characteristic	
No. of patients	615
No. of centers	113
No. of patients with immune reconstitution data available	406
Age of recipient - no. (%)	
Median (min-max)	56 (1-83)
0 - 9	58 (9)
10 - 19	65 (11)
20 - 29	42 (7)
30 - 39	40 (7)
40 - 49	52 (8)
50 - 59	114 (19)
60 - 69	183 (30)
70+	61 (10)
Sex - no. (%)	
Male	406 (66)
Female	209 (34)
Disease - no. (%)	
Acute myelogenous leukemia	192 (31)
Acute lymphoblastic leukemia	129 (21)
Myelodysplastic/myeloproliferative disorders	173 (28)
Non-Hodgkin lymphoma	45 (7)
Hodgkin lymphoma	11 (2)
Plasma cell disorder/Multiple Myeloma	9 (1)
Myeloproliferative Neoplasms	56 (9)
Donor type - no. (%)	
HLA-identical sibling	79 (13)
Twin	16 (3)
Mismatched related	
1 Ag/allele mismatched	5 (1)
>=2 Ag/allele mismatched	101 (16)
Other related (matching TBD)	19 (3)
Well-matched unrelated (8/8)	280 (46)
Partially-matched unrelated (7/8)	79 (13)

Characteristic	
Mis-matched unrelated (<=6/8)	3 (0)
Unrelated (matching TBD)	32 (5)
Missing	1 (0)
Stem cell source - no. (%)	
Bone Marrow	143 (23)
Peripheral Blood	472 (77)
Conditioning regimen intensity - no. (%)	
MAC	325 (53)
RIC	231 (38)
NMA	37 (6)
TBD	16 (3)
Missing	6 (1)
GVHD prophylaxis - no. (%)	
Ex-vivo T-cell depletion	13 (2)
CD34 selection	14 (2)
Post-CY + other(s)	138 (22)
Post-CY alone	1 (0)
TAC/CSA + MMF +- other(s) (except post-CY)	96 (16)
TAC/CSA + MTX +- other(s) (except MMF, post-CY)	257 (41)
TAC/CSA + other(s) (except MMF, MTX, post-CY)	64 (15)
TAC/CSA alone	8 (1)
Other(s)	5 (1)
Missing	19 (3)
Year of transplant - no. (%)	
2013	79 (13)
2014	80 (13)
2015	105 (17)
2016	84 (14)
2017	88 (14)
2018	70 (11)
2019	68 (11)
2020*	41 (7)

Footnote: 2020 cases are not completed in current retrieval.

Table 2. Characteristics of patients who underwent first autologous transplant for HL, NHL and MM from 2013 to 2020 with engraftment syndrome reported to CIBMTR

Characteristic	
No. of patients	459
No. of centers	69
No. of patients with immune reconstitution data available	357
Age of recipient - no. (%)	
Median (min-max)	61 (15-79)
10 - 19	3 (1)
20 - 29	6 (1)
30 - 39	10 (2)
40 - 49	56 (12)
50 - 59	143 (31)
60 - 69	190 (41)
70+	51 (11)
Sex - no. (%)	
Male	245 (53)
Female	214 (47)
Disease - no. (%)	
Non-Hodgkin lymphoma	84 (18)
Hodgkin lymphoma	14 (3)
Plasma cell disorder/Multiple Myeloma	361 (79)
Stem cell source - no. (%)	
Peripheral Blood	459 (100)
Conditioning regimen intensity - no. (%)	
MAC	17 (4)
RIC	66 (14)
TBD	19 (4)
Missing	357 (78)
Year of transplant - no. (%)	
2013	31 (7)
2014	33 (7)
2015	45 (10)
2016	79 (17)
2017	69 (15)
2018	121 (26)
2019	62 (14)
2020*	19 (4)

Footnote: 2020 cases are not completed in current retrieval.

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, BCIDP
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:

Nikki Tran

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.

- No

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 bloodstream infections caused by non-enterobacterales gram-negative bacilli, including pseudomonas aeruginosa, acinetobacter, and stenotrophomonas, have increased relapse and mortality.

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

Suggested word limit of 200 words:

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 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)

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.

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 P. aeruginosa 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 immunocompromised patients, including those who have undergone HCT are at high risk for developing BSI due to damage to the integrity of mucosal barriers, impaired phagocytes, 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. Given the study was conducted also almost 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 in the past decade have emerged over the past decade as promising therapy for patients with B-cell malignancies. However, little is known about incidence and influence of BSI following cellular therapy9.
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-enterobacterales 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 as 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
Patients contained in the CIBMTR database between January 2017 and January 2022 who meets the following criteria:
- Received first autologous or allogeneic HCT with any type of graft sources
- Either matched related or unrelated donors for allogenic HCT
- Received first CAR-T therapy
- Adults 18-79 years of age

Exclusion criteria
- Prior HCT before CAR-T therapy
- Prior CAR-T therapy before HCT
- Missing consent forms
- Missing data
- No 2100 form available

Q21. Does this study include pediatric patients?

- No

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

Inclusion of pediatric patients may skew the infection data results as pediatric and adult patients immune defense to infections especially the degree of mucosal barrier injury and immune reconstitution may affect response to infection.

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 malignancy (AML, ALL, CML etc.)
• Disease status at the time of transplant (Active, Remission, Unknown)
• Stem cell source (Cord, Marrow, Peripheral blood)
• Donor relation (Related, unrelated, Haploidentical)
• Match status (Mismatched, Matched)
• 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:

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
2. See I, Iwamoto M, Allen-Bridson K, Horan T, Magill SS, Thompson ND. Mucosal barrier injury laboratory-confirmed bloodstream infection: results from a field test of a new National Healthcare Safety Network definition. Infect Control Hosp Epidemiol 2013; 34(8): 769–776.
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.
4. Poutsiaka DD, Price LL, Ucuzian A, Chan GW, Miller KB, Snydman DR. Blood stream infection after hematopoietic stem cell transplantation is associated with increased mortality. Bone Marrow Transplant 2007; 40(1): 63–70.
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)

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
Email address:	zainab.shahid@atriumhealth.org
Institution name:	Levine Cancer Institute, Atrium Health, Charlotte, NC
Academic rank:	Associate Professor of Medicine

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
Email address:	rfchemaly@mdanderson.org
Institution name:	UT 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.

N/A

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 MD, Marcie Riches MD

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.

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

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.

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.
Similarly, 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.

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.

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?

- No

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

Reports on epidemiology and natural history of BKV associated HC, BK viremia and BK viuria suggest differences among adult and pediatric populations with higher incidence in pediatric population. Including pediatric patients will not allows us to understand BKV disease in adults, its risk factors associated and impact on clinical outcome. Pediatric population will need to be studied separately.

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

- Overall incidence of BKv associated HC, BK viruria and BK Viremia in the absence or presence of HC at day 100 and 1 year post HCT
- Median time to Bk viruria and BK viremia
- Transplant details: graft source, intensity, conditioning regimen
- GvHD prophylaxis (of interest is post-transplant cyclophosphamide, ATG)
- Cumulative incidence of GvHD grade II-IV
- Decline in kidney function post HCT (constant decline in GFR of equal or greater than 25% over the study period)
- Presence of CMV and HHV-6 infections
- Time to neutrophils and platelets engraftment
- Overall survival at 1 year
- Non-relapse mortality at year 1

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
6. Silva Lde P, Patah PA, Saliba RM, et al. Hemorrhagic cystitis after allogeneic hematopoietic stem cell transplants is the complex result of BK virus infection, preparative regimen intensity and donor type. Haematologica 2010; 95: 1183–1190.
7. Gargiulo G, Orlando L, Alberani F, et al. Haemorrhagic cystitis in haematopoietic stem cell transplantation (HSCT): a prospective observational study of incidence and management in HSCTcentres within the GITMO network (Gruppo Italiano Trapianto Midollo Osseo). Ecancer Medical Sci 2014; 8: 420.
8. Kondo M, Kojima S, Kato K, Matsuyama T. Late-onset hemorrhagic cystitis after hematopoietic stem cell transplantation in children. Bone Marrow Transplant 1998; 22: 995–998.
9. Giraud G, Bogdanovic G, Priftakis P, Remberger M, Svahn B-M, Barkholt L et al. The incidence of hemorrhagic cystitis and BK-viruria in allogeneic hematopoietic stem cell recipients according to intensity of the conditioning regimen. Haematologica 2006; 91: 401–404.
10. Bogdanovic G, Priftakis P, Giraud G, Dalianis T. A related donor and reduced intensity conditioning reduces the risk of development of BK virus-positive haemorrhagic cystitis in allogeneic haematopoetic stem cell-transplanted patients. Anticancer Res 2006; 26: 1311–1318.
11. Megged O, Stein J, Ben-Meir D, Shulman LM, Yaniv I, Shalit I et al. BK-virusassociate hemorrhagic cystitis in children after hematopoietic stem cell transplantation. J Pediatr Hematol Oncol 2011; 33: 190–193.
12. Wong ASY, Chan K-H, Cheng VCC, Yuen K-Y, Kwong Y-L, Leung AYH. Relationship of pre-transplantation polyoma BK virus serologic findings and BK viral reactivation after hematopoietic stem cell transplantation. Clin Infect Dis 2007; 44: 830–837.
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
14. Han TT, Xu LP, Liu DH et al. Cytomegalovirus is a potential risk factor for late-onset hemorrhagic cystitis following allogeneic hematopoietic stem cell transplantation.AmJ Hematol 2014; 89: 55–61
15. Laskin BL, Denburg M, Furth S et al. BK viremia precedes hemorrhagic cystitis in children undergoing allogeneic hematopoietic stem cell transplantation. Biol Blood Marrow Transplant 2013; 19: 1175–82
16. Laila Schneidewind , Thomas Neumann, Florian Knoll, Kathrin Zimmermann, Sigrun Smola, Christian Andreas Schmidt, William Krüger. Are the Polyomaviruses BK and JC Associated with Opportunistic Infections, Graft-versus-Host Disease, or Worse Outcomes in Adult Patients Receiving Their First Allogeneic Stem Cell Transplantation with Low-Dose Alemtuzumab Acta Haematol 2017;138:3–9
17. LE Lunde, S Dasaraju, Q Cao, CS Cohn, M Reding, N Bejanyan, B Trottier, J Rogosheske, C Brunstein, E Warlick, JAH Young,DJ Weisdorf and C Ustun. Hemorrhagic cystitis after allogeneic hematopoietic cell transplantation: risk factors, graft source and survival. Bone Marrow Transplantation (2015), 1–6
18. Eduardo Cerello Chapchap, Vinicius Renan Pinto de Mattos, Juliana Dall' Agnol da Rocha, Iracema Esteves, Jose Mauro Kutner, Fabio Rodrigues Kerbauy, Andreza Alice Feitosa Ribeiro, Clarisse Martins Machado, Nelson Hamerschlak, Fabio Pires de Souza Santos. Severe hemorrhagic cystitis caused by the BK polyomavirus is associated with decreased survival post-allogeneic hematopoietic stem cell transplantation. Transpl Infect Dis. 2019;21:e13101.

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 2020 with BK virus infection post HCT reported to the CIBMTR

Characteristic	
No. of patients	886
No. of centers	129
Age of recipient, years - no. (%)	
Median (min-max)	54 (0-79)
0 - 9	47 (5)
10 - 19	89 (10)
20 - 29	76 (9)
30 - 39	84 (9)
40 - 49	107 (12)
50 - 59	144 (16)
60 - 69	259 (29)
70+	80 (9)
Sex - no. (%)	
Male	511 (58)
Female	375 (42)
Disease - no. (%)	
Acute myelogenous leukemia	226 (26)
Acute lymphoblastic leukemia	153 (17)
Other leukemia	19 (2)
Chronic myelogenous leukemia	14 (2)
Myelodysplastic/myeloproliferative disorders	192 (22)
Other acute leukemia	10 (1)
Non-Hodgkin lymphoma	54 (6)
Hodgkin lymphoma	13 (1)
Plasma cell disorder/Multiple Myeloma	3 (0)
Severe aplastic anemia	43 (5)
Inherited abnormalities erythrocyte differentiation or function	37 (4)
SCID and other immune system disorders	16 (2)
Inherited disorders of metabolism	2 (0)
Myeloproliferative Neoplasms	104 (12)
Donor type - no. (%)	
HLA-identical sibling	119 (13)
Twin	2 (0)
Mismatched related	
1 Ag/allele	8 (1)
>=2 Ag/allele	261 (29)
Other related(matching TBD)	62 (7)
Well-matched unrelated (8/8)	261 (29)

Characteristic	
Partially-matched unrelated (7/8)	49 (6)
Mis-matched unrelated (<=6/8)	13 (1)
Unrelated (matching TBD)	12 (1)
Cord blood	93 (10)
Missing	6 (1)
GVHD prophylaxis - no. (%)	
Ex-vivo T-cell depletion	10 (1)
CD34 selection	32 (4)
Post-CY + other(s)	409 (46)
Post-CY alone	10 (1)
CNI (TAC/CSA) + MMF +/- Other(except post-CY)	171 (19)
CNI (TAC/CSA) + MTX +/- Other(except MMF, post-CY)	211 (24)
CNI (TAC/CSA) +/- Other (except MMF, MTX, post-CY)	23 (3)
TAC/CSA alone	11 (1)
Others	2 (0)
Missing	7 (1)
Stem cell source - no. (%)	
Bone Marrow	229 (26)
Peripheral Blood	564 (64)
Cord Blood	93 (10)
Year of transplant - no. (%)	
2017	347 (39)
2018	288 (33)
2019	246 (28)
2020*	5 (1)
Follow-up - median (range)	25 (3-51)

Footnote: 2020 cases are not complete in current retrieval.

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

Viral Hepatitis after allogeneic hematopoietic cell transplant using post-transplant cyclophosphamide for graft versus host disease prophylaxis

Q2. Key Words

Viral hepatitis, hepatitis B, hepatitis C, Post-transplant cyclophosphamide

Q3. PRINCIPAL INVESTIGATOR

Provide the following information for each investigator:

Principal Investigator #1:

First and last name, degree(s):	Kitsada Wudhikarn, MD
Email address:	kwudhikarn@gmail.com
Institution name:	Chulalongkorn University
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):	Miguel-Angel Perales, MD
Email address:	peralesm@mskcc.org
Institution name:	Memorial Sloan Kettering 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:

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.

Infection in patients with lymphoma treated with CD19 Chimeric Antigen Receptor T cell, Lead Junior Investigator

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 rate/incidence and outcomes of viral hepatitis reactivation/infection after alloHCT using post-transplant cyclophosphamide as acute GVHD prophylaxis?

Q16. RESEARCH HYPOTHESIS:

1. Patients who underwent allogeneic HCT with post-transplant cyclophosphamide have increased incidence of post-transplant viral hepatitis reactivation compared to non-PTCy platforms
2. Patients with hepatitis reactivation post-alloHCT with PTCy have increased incidence of liver associated complication

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

Suggested word limit of 200 words:

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

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.

As PTCy has been increasingly used for acute GVHD prophylaxis and it has been more than a decade since the last CIBMTR report on viral hepatitis-associated outcomes in transplant patients, it is not known if PTCy would alter the risk of hepatitis reactivation. This proposal will describe the incidence including risk factors of hepatitis reactivation, the liver-related complications (SOS, liver GVHD), and survival outcomes of patients after alloHCT using PTCy for acute GVHD prophylaxis. This study would provide us more insight into the incidence, effect of viral hepatitis reactivation on post-transplant outcomes in patients receiving PTCy in the era of novel viral hepatitis treatment. It will guide us on the appropriate duration and choice of viral hepatitis prophylaxis in these patients.

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.

Chronic viral hepatitis infection is a common public health problem worldwide. Although hepatitis viral infection is not a contraindication to allogeneic HCT, adequate prophylactic anti-hepatitis viral therapy is required to prevent reactivation and potential adverse hepatic consequences. In a CIBMTR study published almost a decade ago, investigators reported outcomes of patients who underwent HLA identical matched related donor alloHCT and found no increased mortality from donor or recipient hepatitis B- and/or hepatitis C-positive serostatus. With universal highly effective hepatitis B viral prophylaxis, the incidence of hepatitis B reactivation after alloHCT was low, approximately 1-2% among the high-risk patient-donor category. In addition to hepatitis B infection, chronic hepatitis C infection is more prevalent in the US affecting up to approximately 1.3% of the total population. Ramos et al. conducted a single-center case-control study and showed that hepatitis C seropositivity was a significant risk factor for non-relapse mortality after alloHCT. Another retrospective study from the same center reported a high incidence of acute HCV exacerbation (27%), and HCV reactivation after alloHCT (12%), respectively. Although the authors reported no difference in liver-related mortality, need for changes in conditioning regimens or post-HCT immunosuppressive agents attributed to an effective direct antiviral therapy, 12% and 13% of patients developed VOD and cirrhosis, respectively. Risk factors for hepatitis reactivation in most studies included active hepatitis infection, the intensity of conditioning regimens, degree of immunosuppression, CMV serostatus, and graft versus host disease (4). Most available studies described the incidence and impact on outcomes of viral hepatitis in the setting of matched allogeneic transplantation with calcineurin inhibitor-based GVHD prophylaxis. There is, however, a paucity of evidence in transplanted patients undergoing PTCy GVHD prophylaxis. PTCy is an effective T cell depleting approach and could therefore result in an increased risk of infection after alloHCT. On the other hand, PTCy may offer better GVHD prophylaxis and results in a lower incidence of GVHD, which in turn could lower the risk of post-transplant hepatitis reactivation. Interestingly, recent data showed that the incidence of CMV and non-CMV herpes infection have increased after PTCy, therefore, it could affect the incidence of viral hepatitis reactivation as well. In conclusion, it is not known if PTCy would alter the risk of hepatitis reactivation. This proposal will describe the incidence including risk factors of hepatitis reactivation, liver-related complications (SOS, liver GVHD), and survival outcomes of patients after alloHCT using PTCy for acute GVHD prophylaxis.

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

[Click here]

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

All patients undergoing allogeneic hematopoietic cell transplantation with GVHD prophylaxis using post-transplant cyclophosphamide between 1999 and 2018 with recipient or donor viral hepatitis seropositivity (1999 was used when the first patient was accrued to the original PTCy clinical trial published by Luznik L et al.)

Q21. Does this study include pediatric patients?

- No

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

Allogeneic Hematopoietic Cell Transplants using PTCy for acute GVHD prophylaxis were mostly performed in adult patients.

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.

1. Diagnosis
2. Age at allogeneic HCT
3. Gender: Male VS Female
4. Year of HCT
5. HCT-CI score
6. Liver function category in HCT CI before transplant
7. Prior treatment lines before alloHCT
8. Rituximab exposure pre-alloHCT
9. Conditioning regimen (MA, RIC, NMA)
10. TBI conditioning regimen (Gy)
11. Total dose of cyclophosphamide: in milligram/kg
12. Donor/Recipient relationship (Related, Unrelated, Cord)
13. Donor pre-transplant CMV status
14. Recipient pre-transplant CMV status
15. Donor pre-transplant hepatitis B status: HBsAg, HBcAb, HBsAb, HBV DNA PCR
16. Recipient pre-transplant hepatitis B status: HBsAg, HBcAb, HBsAb, HBV DNA PCR
17. Donor pre-transplant hepatitis C status: HCV RNA, Anti-HCV
18. Recipient pre-transplant hepatitis C status: HCV RNA, Anti-HCV
19. Previous hepatitis C treatment of donor and/or recipient
20. HBV prophylactic regimen before alloHCT
21. HIV status of patients
22. If HIV seropositive, anti-HIV treatment regimen and CD4 prior to alloHCT
23. HLA match degree: Match, mismatch, haploidentical
24. Acute GVHD at any time after HCT
25. Organ involvement and grade of acute GVHD
26. Maximal severity of acute GVHD
27. Chronic GVHD at any time after HCT

a. Date of first diagnosis
b. Chronic GVHD requiring systemic IST
c. Date of systemic IST initiation
d. Severity of achronic GVHD

28. Liver complication post-transplant:

a. Acute GVHD of liver: Stage
b. Chronic GVHD of liver: Severity
c. SOS
d. Cirrhosis
e. Other liver toxicity

29. Relapse after HCT
30. Date of relapse: Time from HCT to relapse
31. Treatment for relapse
32. Date of treatment for relapse post-alloHCT
33. Sinusoidal obstructive syndrome: Yes vs No, Grade
34. Date of SOS diagnosis
35. Maximal Grade of SOS and outcomes
36. Post-alloHCT hepatitis B reactivation/exacerbation
37. Date of post- alloHCT hepatitis B reactivation/exacerbation
38. Post-transplant hepatitis C reactivation/exacerbation
39. Date of post- alloHCT hepatitis C reactivation/exacerbation
40. Post-alloHCT HBV treatment
41. Post-alloHCT HCV treatment
42. Rituximab exposure post-alloHCT
43. Alive or death after HCT
44. Date of death or last follow up
45. Cause of death

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

Not required

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

Not required

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.

Not required

Q26. REFERENCES:

1. Tomblyn M, Chen M, Kukreja M, Aljurf MD, Al Mohareb F, Bolwell BJ, et al. No increased mortality from donor or recipient hepatitis B- and/or hepatitis C-positive serostatus after related-donor allogeneic hematopoietic cell transplantation. Transpl Infect Dis. 2012;14(5):468-78.
2. Ramos CA, Saliba RM, de Padua L, Khorshid O, Shpall EJ, Giralt S, et al. Impact of hepatitis C virus seropositivity on survival after allogeneic hematopoietic stem cell transplantation for hematologic malignancies. Haematologica. 2009;94(2):249-57.
3. Kyvernitakis A, Mahale P, Popat UR, Jiang Y, Hosry J, Champlin RE, et al. Hepatitis C Virus Infection in Patients Undergoing Hematopoietic Cell Transplantation in the Era of Direct-Acting Antiviral Agents. Biol Blood Marrow Transplant. 2016;22(4):717-22.
4. Siyahian A, Malik SU, Mushtaq A, Howe CL, Majeed A, Zangeneh T, et al. Prophylaxis for Hepatitis B Virus Reactivation after Allogeneic Stem Cell Transplantation in the Era of Drug Resistance and Newer Antivirals: A Systematic Review and Meta-Analysis. Biol Blood Marrow Transplant. 2018;24(7):1483-9.
5. Oltolini C, Greco R, Galli L, Clerici D, Lorentino F, Xue E, et al. Infections after Allogenic Transplant with Post-Transplant Cyclophosphamide: Impact of Donor HLA Matching. Biol Blood Marrow Transplant. 2020;26(6):1179-88.
6. Retiere C, Willem C, Guillaume T, Vie H, Gautreau-Rolland L, Scotet E, et al. Impact on early outcomes and immune reconstitution of high-dose post-transplant cyclophosphamide vs anti-thymocyte globulin after reduced intensity conditioning peripheral blood stem cell allogeneic transplantation. Oncotarget. 2018;9(14):11451-64.
7. Goldsmith SR, Abid MB, Auletta JJ, Bashey A, Beitinjaneh A, et al. Posttransplant cyclophosphamide is associated with increased cytomegalovirus infection: a CIBMTR analysis. Blood. 2021 Jun 10;137(23):3291-3305.
8. Singh A, Dandoy CE, Chen M, Kim S, Mulroney CM, Kharfan-Dabaja MA, et al. Post-Transplant cyclophosphamide is associated with increase in Non-CMV Herpesvirus infections in Acute leukemia and MDS patients. Transplant Cell Ther. 2021 Sep 26:S2666-6367(21)01257-4

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)?

- Yes, I have 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.

1. Kitsada Wudhikarn, MD: No conflict of interest to disclose
2. Miguel Perales, MD: Yes as reported below

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

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 from July 2007 to December 2018 with either HBV or HCV positive serology prior to transplant reported to CIBMTR

Characteristic	PTCy	Non-PTCy
No. of patients	158	1050
No. of centers	63	136
Age of recipient - no. (%)		
Median (min-max)	60 (1-88)	55 (0-79)
0 - 9	2 (1)	129 (12)
10 - 19	1 (1)	45 (4)
20 - 29	5 (3)	38 (4)
30 - 39	14 (9)	63 (6)
40 - 49	25 (16)	140 (13)
50 - 59	34 (22)	290 (28)
60 - 69	59 (37)	292 (28)
70+	18 (11)	53 (5)
Sex - no. (%)		
Male	107 (68)	665 (63)
Female	51 (32)	385 (37)
HBV positive - no. (%)		
No	29 (18)	169 (16)
Yes	129 (82)	881 (84)
HCV positive - no. (%)		
No	120 (76)	810 (77)
Yes	38 (24)	240 (23)
Disease - no. (%)		
Acute myelogenous leukemia	65 (41)	339 (32)
Acute lymphoblastic leukemia	12 (8)	111 (11)
Other leukemia	6 (4)	54 (5)
Chronic myelogenous leukemia	4 (3)	32 (3)
Myelodysplastic/myeloproliferative disorders	34 (22)	231 (22)
Other acute leukemia	1 (1)	9 (1)
Non-Hodgkin lymphoma	7 (4)	62 (6)
Hodgkin lymphoma	1 (1)	2 (0)
Plasma cell disorder/Multiple Myeloma	0 (0)	1 (0)
Severe aplastic anemia	7 (4)	32 (3)
Inherited abnormalities erythrocyte differentiation or function	2 (1)	14 (1)
SCID and other immune system disorders	4 (3)	100 (10)
Inherited disorders of metabolism	0 (0)	2 (0)
Histiocytic disorders	0 (0)	2 (0)
Myeloproliferative Neoplasms	15 (9)	59 (6)
Donor type - no. (%)		

Characteristic	PTCy	Non-PTCy
HLA-identical sibling	15 (9)	290 (28)
Mismatched related		
1 Ag/allele	4 (3)	9 (1)
>=2 Ag/allele	113 (72)	26 (2)
Other related(matching TBD)	7 (4)	12 (1)
Well-matched unrelated (8/8)	9 (6)	385 (37)
Partially-matched unrelated (7/8)	8 (5)	90 (9)
Mis-matched unrelated (<=6/8)	2 (1)	8 (1)
Unrelated (matching TBD)	0 (0)	6 (1)
Cord blood	0 (0)	220 (21)
Missing	0 (0)	4 (0)
Stem cell source - no. (%)		
Bone Marrow	60 (38)	156 (15)
Peripheral Blood	98 (62)	674 (64)
Cord Blood	0 (0)	220 (21)
Conditioning regimen intensity - no. (%)		
MAC	48 (30)	496 (47)
RIC	35 (22)	377 (36)
NMA	74 (47)	148 (14)
TBD	0 (0)	23 (2)
Missing	1 (1)	6 (1)
GVHD prophylaxis - no. (%)		
Ex-vivo T-cell depletion	0 (0)	17 (2)
CD34 selection	0 (0)	50 (5)
Post-CY + other(s)	157 (99)	0 (0)
Post-CY alone	1 (1)	0 (0)
CNI (TAC/CSA) + MMF +/- Other(except post-CY)	0 (0)	353 (34)
CNI (TAC/CSA) + MTX +/- Other(except MMF, post-CY)	0 (0)	477 (45)
CNI (TAC/CSA) +/- Other (except MMF, MTX, post-CY)	0 (0)	101 (10)
CNI (TAC/CSA) alone	0 (0)	33 (4)
Others	0 (0)	19 (2)
2047/2147 form received - no. (%)		
Only 2047 form	0 (0)	62 (6)
Only 2147 form	4 (3)	12 (1)
Both 2047 and 2147 form	154 (97)	976 (93)

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

: 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)

Q2. Key Words

mTOR inhibitor, herpesvirus, CMV

Q3. PRINCIPAL INVESTIGATOR

Provide the following information for each investigator:

Principal Investigator #1:

First and last name, degree(s):	Kamil Rechache, MD
Email address:	kamil.rechache@nih.gov
Institution name:	National Institutes of Health
Academic rank:	Clinical Fellow, Hematology-Oncology

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):	Jennifer Kanakry, MD
Email address:	jennifer.kanakry@nih.gov
Institution name:	National Institutes of Health
Academic rank:	Associate Research Physician

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:

Kamil Rechache

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.

Routine, consistent involvement in the Infection and Immune Reconstitution WC and the Lymphoma WC, more intermittent involvement in the GVH, graft sources, and non-malignant disease WCs, as sometimes their meetings overlap with other WCs. Co-author on 2 publications from the Infection and IR WC in 2020, prior PI role in the Lymphoma WC with publication on outcomes of patients with HL, comparing RIC with haplo-PTCy to RIC with MSD CNI-based regimen.

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

Q15. RESEARCH QUESTION:

Are there different incidences of clinically significant viral infections and disease events when comparing mTOR inhibitor-containing GVHD prophylaxis regimens with non-mTOR inhibitor pharmacologic GVHD prophylaxis regimens? In subgroup analyses of PTCy-treated patients, is the recently published increased risk of CMV infection modulated by the use of mTORi with PTCy, compared to non-mTORi PTCy regimens?

Q16. RESEARCH HYPOTHESIS:

Graft-versus-host disease (GVHD) prophylaxis regimens containing mTORi may be associated with lower incidence of viral infection, reactivation, and disease in the first year post-HCT. While PTCy may be associated with increased risk of viral events, such as CMV infection, choice of adjunct agents in PTCy-based regimens (mTORi vs CNI) may modulate this risk.

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

Suggested word limit of 200 words:

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

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.

The results from this study could help identify the relative impact of mTORi, increasingly included in GVHD prophylaxis strategies, in virus-associated complications post-HCT. This could provide registry-based clinical data to further evaluate the findings of smaller studies that indicate that mTORi may be associated with fewer CMV-related post-HCT complications and to then provide the impetus to better understand this finding on a pre-clinical, mechanistic level. In addition, there is an active question in the field of if PTCy may negate or modulate the protection seemingly afforded by mTORi. Given CIBMTR working committee project that demonstrated that PTCy-based approaches are associated with higher rates of CMV infection, higher rates of non-CMV herpesvirus infection (namely HHV6 reactivation), and CRVIs,1-3 a better understanding the roles that the adjunct immunosuppressants have in viral control will help the field further understand how to optimize PTCy-based platforms and ameliorate the potential for control and prevention of virus-associated HCT complications. While these 3 recent CIBMTR studies showing higher viral infectious complications with PTCy might suggest that PTCy is an inferior approach to HCT, the benefits and superior HCT outcomes that PTCy affords cannot be disregarded. Thus, these recent CIBMTR data motivate further evaluation of these virus-associated complications as they relate to HCT platform approaches to continue to improve upon HCT platforms and associated outcomes. With regard to CMV, this study could provide pre-letermovir data to then compare at a later date to post-letermovir data. In discussions with the WC, the letermovir data are not robust to date and the form will not be updated until late 2021. Thus, letermovir-related questions will likely need to be addressed as a future question when the data are sufficient.
This proposal was first presented as a herpesvirus-specific proposal 2019 (1810-10) and there was significant interest. On assessment of patient numbers, this was feasible with regard to the number of patients receiving GVHD prophylaxis with sirolimus and those receiving pharmacologic GVHD prophylaxis without sirolimus. There were data on CMV infection, EBV infection, HHV6 infection. However, while the proposal scored well, only one proposal could move forward and this was not selected. We were encouraged at that time to re-submit the proposal in 1-2 years, which we did in 2020 (PROP 2010-71), but the prioritization at that time was COVID19, with limited resources in the Working Committee for non-COVID19 related questions – so the proposal was not accepted for consideration due to relative scientific impact compared to other proposals. In the last year, there have been 3 major publications related to viral infectious complications by CIBMTR, all showing increased infections with PTCy-based approaches (IN17-01a-c).1-3

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.

In the solid organ transplant setting, mTORi-based regimens have been associated with lower rates of CMV infection and disease, although this effect does not seem to be related to inhibition of viral replication.4-9 In renal transplant recipients, the addition of an mTORi to a reduced-dose of calcineurin inhibitor (CNI) was associated with lower rates of CMV infection compared to regular dose CNI-based approaches.10-12 However, this has been less studied in HCT patients where CMV, as well as other herpesvirus complications, are of concern in the early period post-HCT. Thus, the effect, if real, is likely indirect and related to modulation of the cellular immune system. If due to this indirect effect, even viruses that cause diseases post-HCT through mechanisms unrelated to viral replication, such as EBV and the latent viral proliferation that gives rise to EBV-PTLD, may be lower in the setting of mTORi-containing approaches to GVHD prophylaxis. Indeed, there are pre-clinical data to suggest that mTORi may have anti-tumor activity against gammaherpesviruses, EBV and HHV8.13,14 However, there is a paucity of clinical data with regard to mTORi and EBV control and some reviews suggest that mTORi may not protect against EBV.15 In prior CIBMTR analyses of CMV-associated complications post-HCT, the role of mTORi was not evaluated.3,16,17

We recently published the CMV-related infection and disease outcomes across a broad range of transplant approaches at the National Institutes of Health (NIH).18 In that study, we found that the cumulative incidence of CMV infection was significantly higher for HCT recipients whose GVHD prophylaxis was CNI-based, as compared to those with CNI+mTORi-based approaches. We acknowledge that there have been randomized trials that have shown no difference in CMV infection rates between CNI/methotrexate-based regimens and CNI/mTORi-based regimens.19,20 Additionally, submitted as an abstract to the TCT 2019 conference, we have evaluated the rates of EBV-related issues post-HCT across the range of HCT approaches at the NIH.21 We have found that in the NIH cohort of 356 HCT recipients, mTORi-containing regimens were associated with lower incidence of EBV elevations in the blood and less EBV-directed pre-emptive therapy. Among PTCy-based approaches, EBV detection was higher for those receiving CNIs as adjunctive GVHD prophylaxis, as compared to mTORi adjunctive therapy. However, the numbers were overall small in these single-institution analyses, fueling interest in evaluating these same questions in a larger cohort.

Since this proposal has been submitted previously, we have benefited from review, feedback, and recommendations. Herein, we submit our justification for the proposed study objectives and inclusion criteria. One recommendation was to focus on CMV only, as the data are most robust there. While this is certainly a reasonable suggestion, we would like to still propose that CMV, EBV, BKV, and HHV6 are examined here, as details of all of these infections are available since July 2017 and, before that time, there are data on organism and site of infection. Thus, the specific disease entities that we aim to evaluate (CMV infection, CMV disease, EBV disease, EBV-PTLD, BK virus-associated hemorrhagic cystitis, HHV6 encephalitis) are entities that should be captured and are different/distinct from data related to virus detection in blood of no clinical significance. Given the rarity of events and the limitation in data, as well as the potential for both primary and reactivation events post-HCT, we do propose to not look at adenovirus-related disease events. For the proposed viruses, the data should be present both in form 2150 after July 2017 and before. While BK virus-associated hemorrhagic cystitis was not captured as an entity until July 2017 on 2150, in our pre-submission discussion with Dr. Riches and the WC, it is felt that the incidence of BK virus-associated hemorrhagic cystitis could be extracted to cover the entire proposed study period, using data on form 2100 for events prior to July 2017. Another recommendation was to limit the transplant indications to AML/ALL/MDS. However, in delving further into this recommendation, this is primarily (understandably) recommended if outcomes of interest are relapse and TRM. We do not propose to focus on outcomes such as relapse that would be tied more specifically to underlying disease. Rather, virus-associated events and outcomes should largely not be tied to HCT indication. While our initial proposal did aim to include patients transplanted for any indication, to study a more homogeneous population, we have revised this submission to include only patients transplanted for a hematologic malignancy, as patients transplanted for non-malignant diseases may truly have a different baseline risk of viral complications of HCT inherent to their underlying disease process and pre-HCT state (such as in primary immunodeficiency diseases). It was recommended that the study timeframe be moved to more recent times, so we have shifted the proposed dates of study from 2008-2017 to 2014-2020.

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: Patients undergoing first allo HCT for any hematologic malignancy between January, 2014 and December 2020.
Exclusion criteria: UCB graft recipients, ex vivo T-cell depleted grafts, approaches that included planned post-HCT donor lymphocyte infusions, patients receiving letermovir as CMV prophylaxis

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.

• Supplemental data collection will not be required
• CIBMTR data will not need to be combined with data from another group
• Collection forms: 2000 Recipient Baseline Data; 2006 HCT Infusion; 2004 Infectious Disease Markers; 2400 Pre-TED; 2402 Pre-TED – Disease Classification; 2450 Post-TED; 2100 Post-HSCT Data; 2900 Recipient Death Data; 2150 CMV/EBV/ADV/HHV6/BK
• Variables
o Patient/disease characteristic variables: sex (male/female); age at HCT; Karnofsky performance status (>90% vs <90%); HCT-CI; disease; malignancy
o Graft characteristic variables: donor age; donor-recipient sex (female into male vs other); degree of HLA match and relatedness (MUD vs MRD vs haplo); CMV IgG serostatus (donor, recipient); EBV IgG serostatus (donor, recipient); source of stem cells (bone marrow vs. peripheral blood)
o Transplantation regimen variables: year of transplant; conditioning: myeloablative vs. reduced intensity/nonmyeloablative; pre-HCT rituximab administration; GVHD prophylaxis (mTORi-containing vs non-mTORi-containing); post-HCT rituximab administration
o Viral Infection variables: time from transplant to infection, organ involved, type of infection
o Post-HCT event variables: time to graft failure, onset of grade 2-4 acute GVHD, onset of chronic GVHD, mortality, cause of death
o Desired outcome variables:
o Cumulative incidence of CMV infection, CMV disease, pre-emptive treatment for EBV, EBV-PTLD, BK virus-associated hemorrhagic cystitis, and HHV6-encephalitis with death as a competing risk, evaluated at 100-days post-HCT for CMV infection, BK virus-associated HC, and HHV6 encephalitis and at 1 year post-HCT for CMV disease, pre-emptive EBV treatment, and EBV-PTLD
o OS at 100-days and 1 year: defined as the time to death; surviving patients censored at last follow-up
o NRM at 100-days and 1 year: defined as the time to death without evidence of disease presence; with relapse/progressive disease as a competing risk
o Cause of death
o Grades II-IV aGVHD incidence, grades III-IV aGVHD incidence, with graft failure, relapse, donor lymphocyte infusion, chronic GVHD, and death as competing risks
o cGVHD incidence (any, as well as limited vs. extensive and mild vs. moderate vs. severe), with graft failure, relapse, donor lymphocyte infusion, and death as competing risks

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

none

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

none

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.

none

Q26. REFERENCES:

1. Singh A, Dandoy CE, Chen M, et al. Post-Transplant cyclophosphamide is associated with increase in Non-CMV Herpesvirus infections in Acute leukemia and MDS patients. Transplant Cell Ther 2021. DOI: 10.1016/j.jtct.2021.09.015.
2. Taplitz R, Maziarz RT, Mulroney C, et al. Incidence and Impact of Community Respiratory Viral Infection (CRV) in Haploidentical and Matched Sibling Donors Receiving Post-Transplant Cyclophosphamide (PTCy): A CIBMTR Analysis. Biol Blood Marrow Tr 2020;26(3):S71-S72. (In English) (<Go to ISI>://WOS:000516887900095).
3. Goldsmith SR, Abid MB, Auletta JJ, et al. Posttransplant cyclophosphamide is associated with increased cytomegalovirus infection: a CIBMTR analysis. Blood 2021;137(23):3291-3305. (In English). DOI: 10.1182/blood.2020009362.
4. Ritta M, Costa C, Solidoro P, et al. Everolimus-based immunosuppressive regimens in lung transplant recipients: impact on CMV infection. Antiviral Res 2015;113:19-26. DOI: 10.1016/j.antiviral.2014.10.016.
5. Radtke J, Dietze N, Spetzler VN, et al. Fewer cytomegalovirus complications after kidney transplantation by de novo use of mTOR inhibitors in comparison to mycophenolic acid. Transpl Infect Dis 2016;18(1):79-88. DOI: 10.1111/tid.12494.
6. Havenith SH, Yong SL, van Donselaar-van der Pant KA, van Lier RA, ten Berge IJ, Bemelman FJ. Everolimus-treated renal transplant recipients have a more robust CMV-specific CD8+ T-cell response compared with cyclosporine- or mycophenolate-treated patients. Transplantation 2013;95(1):184-91. DOI: 10.1097/TP.0b013e318276a1ef.
7. Nashan B, Gaston R, Emery V, et al. Review of cytomegalovirus infection findings with mammalian target of rapamycin inhibitor-based immunosuppressive therapy in de novo renal transplant recipients. Transplantation 2012;93(11):1075-85. DOI: 10.1097/TP.0b013e31824810e6.
8. Jennings DL, Lange N, Shullo M, et al. Outcomes associated with mammalian target of rapamycin (mTOR) inhibitors in heart transplant recipients: A meta-analysis. Int J Cardiol 2018;265:71-76. DOI: 10.1016/j.ijcard.2018.03.111.
9. Devresse A, Leruez-Ville M, Scemla A, et al. Reduction in late onset cytomegalovirus primary disease after discontinuation of antiviral prophylaxis in kidney transplant recipients treated with de novo everolimus. Transpl Infect Dis 2018;20(2):e12846. DOI: 10.1111/tid.12846.
10. Mallat SG, Tanios BY, Itani HS, et al. CMV and BKPyV Infections in Renal Transplant Recipients Receiving an mTOR Inhibitor-Based Regimen Versus a CNI-Based Regimen: A Systematic Review and Meta-Analysis of Randomized, Controlled Trials. Clin J Am Soc Nephrol 2017;12(8):1321-1336. DOI: 10.2215/CJN.13221216.
11. Hiramitsu T, Okada M, Futamura K, et al. 5-year follow-up of a randomized clinical study comparing everolimus plus reduced-dose cyclosporine with mycophenolate mofetil plus standard-dose cyclosporine in de novo kidney transplantation: Retrospective single center assessment. Int Immunopharmacol 2016;39:192-198. DOI: 10.1016/j.intimp.2016.07.019.
12. Hocker B, Zencke S, Pape L, et al. Impact of Everolimus and Low-Dose Cyclosporin on Cytomegalovirus Replication and Disease in Pediatric Renal Transplantation. Am J Transplant 2016;16(3):921-9. DOI: 10.1111/ajt.13649.
13. Cen O, Longnecker R. Rapamycin reverses splenomegaly and inhibits tumor development in a transgenic model of Epstein-Barr virus-related Burkitt's lymphoma. Mol Cancer Ther 2011;10(4):679-86. DOI: 10.1158/1535-7163.MCT-10-0833.
14. Holtan SG, Porrata LF, Colgan JP, Zent CS, Habermann TM, Markovic SN. mTOR inhibitor monotherapy is insufficient to suppress viremia and disease progression in Epstein-Barr virus-driven lymphoproliferative disorders (EBV-LPD). Am J Hematol 2008;83(8):688-9. DOI: 10.1002/ajh.21216.
15. Pascual J, Royuela A, Fernandez AM, et al. Role of mTOR inhibitors for the control of viral infection in solid organ transplant recipients. Transpl Infect Dis 2016;18(6):819-831. DOI: 10.1111/tid.12601.
16. Teira P, Battiwalla M, Ramanathan M, et al. Early cytomegalovirus reactivation remains associated with increased transplant-related mortality in the current era: a CIBMTR analysis. Blood 2016;127(20):2427-38. DOI: 10.1182/blood-2015-11-679639.
17. Ramanathan M, Teira P, Battiwalla M, et al. Impact of early CMV reactivation in cord blood stem cell recipients in the current era. Bone Marrow Transplant 2016;51(8):1113-20. DOI: 10.1038/bmt.2016.89.
18. Melendez-Munoz R, Marchalik R, Jerussi T, et al. Cytomegalovirus Infection Incidence and Risk Factors Across Diverse Hematopoietic Cell Transplantation Platforms Using a Standardized Monitoring and Treatment Approach: A Comprehensive Evaluation from a Single Institution. Biol Blood Marrow Transplant 2019;25(3):577-586. DOI: 10.1016/j.bbmt.2018.10.011.
19. Torlen J, Ringden O, Garming-Legert K, et al. A prospective randomized trial comparing cyclosporine/methotrexate and tacrolimus/sirolimus as graft-versus-host disease prophylaxis after allogeneic hematopoietic stem cell transplantation. Haematologica 2016;101(11):1417-1425. DOI: 10.3324/haematol.2016.149294.
20. Cutler C, Logan B, Nakamura R, et al. Tacrolimus/sirolimus vs tacrolimus/methotrexate as GVHD prophylaxis after matched, related donor allogeneic HCT. Blood 2014;124(8):1372-7. DOI: 10.1182/blood-2014-04-567164.
21. Hellewell EM, Skeffington LR, Kenyon MI, et al. Incidence of Epstein-Barr Virus (EBV) Detection in the Blood, Pre-Emptive Therapy, and EBV-Posttransplantation Lymphoproliferative Disorder (EBV-PTLD) after Allogeneic Hematopoietic Cell Transplantation (HCT) across a Broad Range of HCT Approaches and All Graft Sources. Biol Blood Marrow Tr 2019;25(3) (In English) (<Go to ISI>://WOS:000540655500537).

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 2014 and 2020 for AML, ALL, MDS, MPN, HL, NHL and MM reported to the CIBMTR

Characteristic	GVHD Prophylaxis contains Sirolimus	GVHD Prophylaxis without Sirolimus
No. of patients	1342	9672
No. of centers	78	164
Age of recipient, years - no. (%)		
Median (min-max)	64 (3-88)	60 (1-83)
0 - 9	3 (0)	268 (3)
10 - 19	12 (1)	424 (4)
20 - 29	53 (4)	564 (6)
30 - 39	69 (5)	599 (6)
40 - 49	115 (9)	999 (10)
50 - 59	237 (18)	2022 (21)
60 - 69	579 (43)	3742 (39)
70+	274 (20)	1054 (11)
Sex - no. (%)		
Male	793 (59)	5702 (59)
Female	549 (41)	3970 (41)
Disease - no. (%)		
Acute myelogenous leukemia	383 (29)	3592 (37)
Acute lymphoblastic leukemia	133 (10)	1363 (14)
Myelodysplastic/myeloproliferative disorders	490 (37)	2864 (30)
Non-Hodgkin lymphoma	106 (8)	594 (6)
Hodgkin lymphoma	15 (1)	85 (1)
Plasma cell disorder/Multiple Myeloma	4 (0)	30 (0)
Myeloproliferative Neoplasms	211 (16)	1144 (12)
Donor type - no. (%)		
HLA-identical sibling	247 (18)	2290 (24)
Mismatched related		
1 Ag/allele mismatched	5 (0)	99 (1)
>=2 Ag/allele mismatched	130 (10)	1871 (19)
Other related(matching TBD)	42 (3)	419 (4)
Well-matched unrelated (8/8)	689 (51)	3940 (41)
Partially-matched unrelated (7/8)	133 (10)	625 (6)

Characteristic	GVHD Prophylaxis contains Sirolimus	GVHD Prophylaxis without Sirolimus
Mis-matched unrelated (<=6/8)	31 (2)	22 (0)
Unrelated (matching TBD)	65 (5)	406 (4)
GVHD prophylaxis - no. (%)		
Post-CY + other(s)	316 (24)	2677 (28)
Post-CY alone	0 (0)	81 (1)
CNI (TAC/CSA) + MMF +/- Other(except post-CY)	246 (18)	1499 (15)
CNI (TAC/CSA) + MTX +/- Other(except MMF, post-CY)	194 (14)	4940 (51)
CNI (TAC/CSA) +/- Other (except MMF, MTX, post-CY)	564 (42)	97 (1)
CNI (TAC/CAS) alone	0 (0)	241 (2)
Others	22 (2)	65 (1)
Missing	0 (0)	72 (1)
Stem cell source - no. (%)		
Bone Marrow	139 (10)	2004 (21)
Peripheral Blood	1203 (90)	7668 (79)
Transplant year - no. (%)		
2014	210 (16)	1769 (18)
2015	194 (14)	1717 (18)
2016	204 (15)	1579 (16)
2017	231 (17)	1429 (15)
2018	234 (17)	1415 (15)
2019	190 (14)	1330 (14)
2020*	79 (6)	433 (4)
Infection by 1 year		
CMV - no. (%)		
Yes	288 (21)	2749 (28)
No	1054 (79)	6923 (72)
EBV - no. (%)		
Yes	74 (6)	670 (7)
No	1268 (94)	9002 (93)
HHV-6 - no. (%)		
Yes	148 (11)	493 (5)
No	1194 (89)	9179 (95)
BK- no. (%)		

Characteristic	GVHD Prophylaxis contains Sirolimus	GVHD Prophylaxis without Sirolimus
Yes	159 (12)	1335 (14)
No	1183 (88)	8337 (86)

Footnote: 2020 cases are not completed in current retrieval.

CIBMTR STUDY PROPOSAL # P2110-123 and P2110-124

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

Principal Investigators:

1. Muhammad Bilal Abid, MD
Email: mabid@mcw.edu
Assistant Professor of Medicine,
Hematology/Oncology, BMT & Cellular Therapy & Infectious Diseases.
Medical College of Wisconsin.

2. Emily Lynde Baumrin, MD
Email: Emily.Baumrin@pennmedicine.upenn.edu
Instructor of Medicine and Dermatology
Department of Dermatology
University of Pennsylvania.

3. Alison Wakoff Loren, MD, MSCE
Email: Alison.Loren@pennmedicine.upenn.edu
Professor of Medicine,
Division of Hematology/Oncology.
University of Pennsylvania.

Statistical Directors:
Soyoung Kim, PhD,
8701 Watertown Plank Road
Milwaukee, WI 53226
Telephone: 414-955-8271
E-mail: skim@mcw.edu

Study Statistician:
Naya He, MS, MPH,
CIBMTR Statistical Center
9200 W. Wisconsin Ave.
CLCC, Suite C5500
Telephone: 414-805-0685
Email: nhe@mcw.edu

Scientific Director:

Marcie Riches, MD, MS
University of North Carolina at Chapel Hill
Division of Hematology/Oncology
170 Manning Drive, POB 3, #7305
Chapel Hill, NC 27599
Telephone: 919-966-3048
Fax: 919-966-7748
E-mail: marcie_riches@med.unc.edu

Working Committee Chairs:

Christopher Dandoy, MD
Cincinnati Children's Hospital Medical Center
3333 Burnet Ave, MLC 7015
Cincinnati, OH 45229-3549
Telephone: (801) 209-3843
E-mail: christopher.dandoy@cchmc.org

Miguel-Angel Perales, MD
Memorial Sloan Kettering Cancer Center
1275 York Avenue
New York, NY 10065
Telephone: 212.639.8682
E-mail: peralesm@mskcc.org

Roy Chemaly, MD
MD Anderson Cancer Center
1515 Holcombe Blvd., Box 402
Houston, TX 77030
Telephone: (713) 792-0007
E-mail: rfchemaly@mdanderson.org

1. 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?

2. 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.

3. Specific aims:

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)

4. Scientific impact:

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 infections[1-3]. However, there is 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.

5. Scientific justification:

Infections are a common complication of alloHCT and are associated with increased morbidity and mortality[4]. Incidence and type of infections are affected by severity and duration of immunosuppression, which is determined by donor type, graft type, conditioning intensity, and GVHD prophylaxis[1-3,5,6]. The use of PTCy has become increasingly common and yet leads to delayed immune reconstitution[7,8]. Although PTCy was first used in recipients of haploHCT, its use has been extended to other graft types as well[9]. 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 transplants[10]. 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-haploCy[1-3]. **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 deaths[14]. 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 period[15-17]. **It is critical to characterize late CMV infections in the era of letermovir prophylaxis in order to inform extension of prophylactic and pre-emptive strategies for high-risk populations into the late period.**

6. Patient eligibility population:

Inclusion criteria:

- Patients receiving first alloHCT for AML, ALL, and MDS in CR1 between 2012 – 2020
- 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)

7. 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 (2018-2020) 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

8. Variables to be examined

Patient related

- Age at transplant (by decade)
- Sex
- Race/ethnicity
- HCT-CI[18]
- KPS: >90% v <90%
- Disease: AML, ALL, or MDS
- DRI[19]
- Recipient CMV serostatus
- Recipient HSV, VZV, EBV serostatus

Donor Related

- Donor type[20]: 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[21]

- 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 Related[22]

- 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.

9. 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 (2018-2020) 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-dependent[21]. 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[23].

10. Data requirements:

- 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)

11. Conflicts of Interest: none

12. PRO Requirements: none

13. Sample requirements: none

14. Non-CIBMTR data source: N/A

15. References:

1. Goldsmith SR, Abid MB, Auletta JJet al. Posttransplant cyclophosphamide is associated with increased cytomegalovirus infection: a CIBMTR analysis. Blood 2021; 137:3291-3305.
2. Mulroney CM, Abid MB, Bashey Aet al. 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; 194:145-157.
3. Singh A, Dandoy CE, Chen Met al. 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.
4. Cordonnier C, Ljungman P, Cesaro Set al. The EHA Research Roadmap: Infections in Hematology. Hemasphere 2021; 5:e662.
5. Abid MB, Hamadani M, Szabo Aet al. Severity of Cytokine Release Syndrome and Its Association with Infections after T Cell-Replete Haploidentical Related Donor Transplantation. Biol Blood Marrow Transplant 2020; 26:1670-1678.
6. Abboud R, Keller J, Slade Met al. Severe Cytokine-Release Syndrome after T Cell-Replete Peripheral Blood Haploidentical Donor Transplantation Is Associated with Poor Survival and Anti-IL-6 Therapy Is Safe and Well Tolerated. Biol Blood Marrow Transplant 2016; 22:1851-1860.
7. Rambaldi B, Kim HT, Reynolds Cet al. Impaired T- and NK-cell reconstitution after haploidentical HCT with posttransplant cyclophosphamide. Blood advances 2021; 5:352-364.
8. Ciurea SO, Zhang MJ, Bacigalupo AAet al. Haploidentical transplant with posttransplant cyclophosphamide vs matched unrelated donor transplant for acute myeloid leukemia. Blood 2015; 126:1033-1040.
9. Marks DI, Abid MB. A Stem Cell Donor for Every Adult Requiring an Allograft for Acute Lymphoblastic Leukemia? Biol Blood Marrow Transplant 2017; 23:182-183.
10. Farhadfar N, Burns LJ, Mupfudze Tet al. Hematopoietic Cell Transplantation: Practice Predictions for the Year 2023. Biol Blood Marrow Transplant 2020.
11. Crocchiolo R, Bramanti S, Vai Aet al. Infections after T-replete haploidentical transplantation and high-dose cyclophosphamide as graft-versus-host disease prophylaxis. Transpl Infect Dis 2015; 17:242-249.
12. Slade M, Goldsmith S, Romee Ret al. Epidemiology of infections following haploidentical peripheral blood hematopoietic cell transplantation. Transpl Infect Dis 2017; 19.
13. Fayard A, Daguenet E, Blaise Det al. Evaluation of infectious complications after haploidentical hematopoietic stem cell transplantation with post-transplant cyclophosphamide following reduced-intensity and myeloablative conditioning: a study on behalf of the Francophone Society of Stem Cell Transplantation and Cellular Therapy (SFGM-TC). Bone Marrow Transplant 2019.

14. Norkin M, Shaw BE, Brazauskas Ret al. Characteristics of Late Fatal Infections after Allogeneic Hematopoietic Cell Transplantation. Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation 2019; 25:362-368.
15. Boeckh M, Leisenring W, Riddell SRet al. Late cytomegalovirus disease and mortality in recipients of allogeneic hematopoietic stem cell transplants: importance of viral load and T-cell immunity. Blood 2003; 101:407-414.
16. Baumrin E, Cheng MP, Kanjilal S, Ho VT, Issa NC, Baden LR. Severe Herpes Zoster Requiring Intravenous Antiviral Treatment in Allogeneic Hematopoietic Cell Transplantation Recipients on Standard Acyclovir Prophylaxis. Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation 2019; 25:1642-1647.
17. Koc Y, Miller KB, Schenkein DPet al. Varicella zoster virus infections following allogeneic bone marrow transplantation: frequency, risk factors, and clinical outcome. Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation 2000; 6:44-49.
18. Sorror ML, Maris MB, Storb Ret al. Hematopoietic cell transplantation (HCT)-specific comorbidity index: a new tool for risk assessment before allogeneic HCT. Blood 2005; 106:2912-2919.
19. Armand P, Kim HT, Logan BRet al. Validation and refinement of the Disease Risk Index for allogeneic stem cell transplantation. Blood 2014; 123:3664-3671.
20. Weisdorf D, Spellman S, Haagenson Met al. Classification of HLA-matching for retrospective analysis of unrelated donor transplantation: revised definitions to predict survival. Biol Blood Marrow Transplant 2008; 14:748-758.
21. Kim S, Logan B, Riches M, Chen M, Ahn KW. Statistical Methods for Time-Dependent Variables in Hematopoietic Cell Transplantation Studies. Transplant Cell Ther 2021; 27:125-132.
22. Ljungman P, Boeckh M, Hirsch HHet al. Definitions of Cytomegalovirus Infection and Disease in Transplant Patients for Use in Clinical Trials. Clin Infect Dis 2017; 64:87-91.
23. Commenges D, Andersen PK. Score test of homogeneity for survival data. Lifetime Data Anal 1995; 1:145-156; discussion 157-149.

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

Impact of Public and Healthcare Infection Control Measures on Non-COVID-19 Community Respiratory Viral Infections in Transplant and Cellular Therapy Patients

Q2. Key Words

infection, COVID, hematopoietic cell transplantation, chimeric antigen receptor therapy, respiratory viral infection

Q3. PRINCIPAL INVESTIGATOR

Provide the following information for each investigator:

Principal Investigator #1:

First and last name, degree(s):	Sagar Patel, MD
Email address:	sagar.patel@hci.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):	Hannah Imlay
Email address:	Hannah.Imlay@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:

Sagar Patel

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.

RT18-03: Principal Investigator

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:

Did the implementation of public and healthcare-institution infection control measures as part of the COVID-19 pandemic reduce community respiratory viral infections in transplant and cellular therapy patients?

Q16. RESEARCH HYPOTHESIS:

We hypothesize that broad implementation of public and healthcare-institution infection control measures (personal protective equipment (PPE), universal masking, and physical distancing) in response to the COVID-19 pandemic has also reduced the incidence and severity of other community respiratory viral infections (CRVIs) in transplant and cellular therapy patients.

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

Suggested word limit of 200 words:

Primary Aim:
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
Secondary Aims:
1. 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

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.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), causing coronavirus disease 2019 (COVID-19), emerged in December 2019 leading to an ongoing global pandemic with a death toll of at least 4.55 million people. Globally, countries and cities have rapidly had to establish new personal protective equipment guidelines to protect healthcare workers and patients, establish universal masking mandates to reduce viral transmission, and enforce physical distancing via stay-at-home orders and limits on public gatherings.1-3 The Centers for Disease Control (CDC) and other public health authorities recommend community mitigation strategies to reduce transmission.4 Moreover, intensive cleaning protocols of private and public buildings and spaces coupled with individual hand washing and sanitization have also been dramatic new practices.5 A transmission model of COVID-19 stratified by disease status and awareness revealed that individual adoption of handwashing, masking, and physical distancing can be an effective strategy to mitigate and delay the epidemic.6

Historically, infection control practices at transplant and cellular therapy centers vary widely making the study of a universal approach difficult. The current COVID-19 pandemic provides us a unique opportunity to study the epidemiological impact of these simple, but widely used infection control practices on other respiratory viruses that still pose serious risks to the immunocompromised host. While the intention of these interventions is to reduce the risk of COVID-19, they may have an additional benefit on CRVIs. The findings of this study may have substantive impacts on inpatient and outpatient infection control practices, post-treatment home care recommendations, and provide data on activity restrictions in this population. Identifying which transplant and cellular therapy patients are at greatest risk would allow targeting of specific infection control measures. Finally, these results consequently can help provide the foundation for future prospective, randomized studies.

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.

CRVIs represent a broad group of organisms that pose a significant threat to immunocompromised patients, such as those who have received an autologous or allogeneic hematopoietic cell transplant or received a cellular therapy product. CRVIs include respiratory syncytial virus (RSV), human parainfluenza viruses I-IV (HPIV), human metapneumovirus (HMPV), influenza, human rhinovirus/enterovirus (HRV), respiratory adenoviruses (ADV), and human coronavirus. Several risk factors have been previously identified for the development of CRVIs. CMV seropositivity is a risk factor for CRVI following transplant and is associated with increased mortality. Moreover, CMV viremia is an independent predictor for progression of CRVI to a lower respiratory tract infection.8 Conversion from upper tract infections to lower tract infection is associated with high-dose steroid use, GVHD, cord blood graft source, and antigen mismatch allogeneic HCTs.9,10 Early CRVIs occurring the first 100 days after HCT are associated with airflow decline in pulmonary function testing as well as the development of alloimmune lung syndromes, which include idiopathic pneumonia syndrome (IPS), bronchiolitis obliterans syndrome (BOS), and bronchiolitis obliterans and organizing pneumonia (BOOP).11,12 A recent single center study of autologous and allogeneic HCTs showed 76% of CRVIs occurred after the first 100 days of transplant with 46% developing lower tract infections. Ultimately, 10% developed CRVIs with significant late morbidity and potential mortality.8 Efforts such as a prospective interventional clinical surveillance program using multiplex PCR diagnostic studies as compared to a historical cohort not using such showed greater anti-viral therapy use, fewer lower respiratory tract infections, reduced hospital admissions, and lower mortality.13

Potentially, viral load may impact severity and recovery in those who contract COVID-19.14 Relatively simple, low-cost infection control measures such as masking and distancing may have dramatic impacts on respiratory infection spread. A case control study of symptomatic COVID-19 outpatients from 11 U.S. health care facilities identified that close contact with persons with known COVID-19 or going to restaurants offering on-site eating and drinking options were associated with COVID-19 positivity. Adults with COVID-19 were twice as likely to have gone to a restaurant in the previous two weeks then those with negative COVID-19 results.4 This study uses a novel approach to see the impact of large-scale, population-level infection control measures on CRVIs that remain a significant source of morbidity and mortality in our transplant and cellular therapy patients.

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

[Click here]

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

Inclusion Criteria:

• First or second autologous HCT, allogeneic HCT, or CAR-T therapy during 3/1/2020 to 2/28/2021
• Positive nasal swab, bronchoalveolar lavage, or biopsy for influenza, respiratory syncytial virus, parainfluenza, human metapneumovirus, human rhinovirus, or adenovirus
• All diseases
• All graft sources
• All donor relationships, conditioning regimens/intensities
• Patients ≥ 12 years of age
• Centers in the United States only

Exclusion Criteria:

• Patients who have a diagnosis of COVID-19

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.**

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)
• Respiratory Virus Post-Infusion (Form 2149)
Patient characteristics:
• Age/Gender
• Karnofsky performance status
• Co-morbidity index (HCT-CI)
• RFI risk category
• Transplant center
• Total number of patients surveyed yearly
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)
• Conditioning regimen including agents
• Conditioning regimen intensity
• TBI vs non-TBI based conditioning regimens
• 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/gender
• Donor-recipient CMV status

This is a retrospective, cohort analysis examining the impact of public and healthcare institution-level infection control methods on non-COVID-19 CRVIs (RSV, HPIV, HMPV, HRV, ADV, and influenza). We will identify the incidence and severity of non-COVID-19 CRVIs in transplant and cellular therapy patients, normalized by total number of patients who reported data for each calendar year. We will also assess the impact of this intervention (heightened infection control measures, mask-wearing, physical distancing) on relapse, NRM, TRM, DFS, acute and chronic GVHD severity and incidence. The exposed cohort will be the population meeting inclusion criteria from 3/1/2020 to 2/28/2021. This will be compared to historical unexposed cohorts from 3/1/2019 to 2/28/2019 and 3/1/2018 to 2/28/2018. These selected time periods would reflect otherwise consistent transplant practices and supportive care measures. Univariate probabilities of survival outcomes will be calculated using the Kaplan-Meier estimator; the log-rank test will be used for univariate comparisons. Probabilities of infection, TRM, NRM, and GVHD will be calculated using cumulative incidence curves accommodating competing risks. Potential prognostic factors include patient-, disease-, and transplant-related characteristics. Assessment of risk factors for outcomes of interest will be evaluated in multivariate analyses using Cox proportional hazards regression or logistic regression where applicable. If the proportional hazards assumption is violated, it will be added as time-dependent covariate. A step-wise selection procedure will be used to identify significant covariates.

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:

1. Escandon K, Martin GP, Kuppalli K, Escandon K. Appropriate usage of face masks to prevent SARS-CoV-2: sharpening the messaging amid the COVID-19 pandemic. Disaster Med Public Health Prep. 2020:1-8.
2. Khalil MM, Alam MM, Arefin MK, et al. Role of Personal Protective Measures in Prevention of COVID-19 Spread Among Physicians in Bangladesh: a Multicenter Cross-Sectional Comparative Study. SN Compr Clin Med. 2020:1-7.
3. Ippolito M, Vitale F, Accurso G, et al. Medical masks and Respirators for the Protection of Healthcare Workers from SARS-CoV-2 and other viruses. Pulmonology. 2020;26(4):204-212.
4. Fisher KA TM, Feldstein LR, et al. Community and Close Contact Exposures Associated with COVID-19 Among Symptomatic Adults ≥18 Years in 11 Outpatient Health Care Facilities — United States, July 2020. MMWR Morb Mortal Wkly Rep. 2020(69):1258–1264.
5. Tabish HB, Basch CH. Back to the basics: Hand washing is public health 101 and it works to slow down the spread of viruses. Infect Dis Health. 2020.
6. Teslya A, Pham TM, Godijk NG, Kretzschmar ME, Bootsma MCJ, Rozhnova G. Impact of self-imposed prevention measures and short-term government-imposed social distancing on mitigating and delaying a COVID-19 epidemic: A modelling study. PLoS Med. 2020;17(7):e1003166.
7. Centers for Disease C, Prevention, Infectious Disease Society of A, American Society of B, Marrow T. Guidelines for preventing opportunistic infections among hematopoietic stem cell transplant recipients. MMWR Recomm Rep. 2000;49(RR-10):1-125, CE121-127.
8. Marinelli T, Wee LYA, Rowe E, et al. Respiratory Viruses Cause Late Morbidity in Recipients of Hematopoietic Stem Cell Transplantation. Biol Blood Marrow Transplant. 2020;26(4):782-788.
9. Chemaly RF, Hanmod SS, Rathod DB, et al. The characteristics and outcomes of parainfluenza virus infections in 200 patients with leukemia or recipients of hematopoietic stem cell transplantation. Blood. 2012;119(12):2738-2745; quiz 2969.
10. Nichols WG, Corey L, Gooley T, Davis C, Boeckh M. Parainfluenza virus infections after hematopoietic stem cell transplantation: risk factors, response to antiviral therapy, and effect on transplant outcome. Blood. 2001;98(3):573-578.
11. Erard V, Chien JW, Kim HW, et al. Airflow decline after myeloablative allogeneic hematopoietic cell transplantation: the role of community respiratory viruses. J Infect Dis. 2006;193(12):1619-1625.
12. Versluys AB, Rossen JW, van Ewijk B, Schuurman R, Bierings MB, Boelens JJ. Strong association between respiratory viral infection early after hematopoietic stem cell transplantation and the development of life-threatening acute and chronic alloimmune lung syndromes. Biol Blood Marrow Transplant. 2010;16(6):782-791.
13. Pinana J, Montoro J, Aznar C, et al. The clinical benefit of instituting a prospective clinical community-acquired respiratory virus surveillance program in allogeneic hematopoietic stem cell transplantation. J Infect. 2020;80(3):333-341.
14. Pujadas E, Chaudhry F, McBride R, et al. SARS-CoV-2 viral load predicts COVID-19 mortality. Lancet Respir Med. 2020;8(9):e70.

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 community respiratory viral infections post HCT between 2017 and 2021 reported to the CIBMTR

Characteristic	1/1/17 - 2/29/20	3/1/20 - present
No. of patients	3819	124
No. of centers	152	57
Age of recipient - no. (%)		
Median (min-max)	49 (0-81)	45 (0-75)
0 - 9	591 (15)	28 (23)
10 - 19	323 (8)	11 (9)
20 - 29	330 (9)	11 (9)
30 - 39	319 (8)	6 (5)
40 - 49	399 (10)	10 (8)
50 - 59	600 (16)	14 (11)
60 - 69	959 (25)	35 (28)
70+	298 (8)	9 (7)
Sex - no. (%)		
Male	2199 (58)	78 (63)
Female	1620 (42)	46 (37)
Disease - no. (%)		
Acute myelogenous leukemia	965 (25)	25 (20)
Acute lymphoblastic leukemia	578 (15)	24 (19)
Other leukemia	115 (3)	0 (0)
Chronic myelogenous leukemia	69 (2)	0 (0)
Myelodysplastic/myeloproliferative disorders	701 (18)	15 (12)
Other acute leukemia	40 (1)	0 (0)
Non-Hodgkin lymphoma	204 (5)	2 (2)
Hodgkin lymphoma	39 (1)	1 (1)
Plasma cell disorder/Multiple Myeloma	14 (0)	1 (1)
Other Malignancies	4 (0)	0 (0)
Severe aplastic anemia	240 (6)	14 (11)
Inherited abnormalities erythrocyte differentiation or function	105 (3)	0 (0)
Inherited bone marrow failure syndromes	39 (1)	9 (7)
Hemoglobinopathies	100 (3)	8 (6)
Paroxysmal nocturnal hemoglobinuria	2 (0)	0 (0)
SCID and other immune system disorders	211 (6)	12 (10)
Inherited disorders of metabolism	36 (1)	0 (0)
Histiocytic disorders	12 (0)	0 (0)
Autoimmune Diseases	2 (0)	0 (0)
Other diseases	2 (0)	0 (0)
Myeloproliferative Neoplasms	341 (9)	13 (10)

Characteristic	1/1/17 - 2/29/20	3/1/20 - present
Donor type - no. (%)		
HLA-identical sibling	186 (5)	9 (7)
Twin	1 (0)	0 (0)
Mismatched related		
1 Ag/allele	4 (0)	2 (2)
>=2 Ag/allele	120 (3)	29 (23)
Other related(matching TBD)	128 (3)	2 (2)
Well-matched unrelated (8/8)	144 (4)	0 (0)
Partially-matched unrelated (7/8)	35 (1)	0 (0)
Mis-matched unrelated (<=6/8)	1 (0)	0 (0)
Unrelated (matching TBD)	78 (2)	73 (59)
Cord blood	565 (15)	9 (7)
Missing	2557 (67)	0 (0)
GVHD prophylaxis - no. (%)		
Ex-vivo T-cell depletion	29 (1)	0 (0)
CD34 selection	88 (2)	0 (0)
Post-CY + other(s)	1231 (32)	49 (40)
Post-CY alone	36 (1)	0 (0)
CNI (TAC/CSA) + MMF +/- Other(except post-CY)	876 (23)	17 (14)
CNI (TAC/CSA) + MTX +/- Other(except MMF, post-CY)	1184 (31)	37 (30)
CNI (TAC/CSA) +/- Other (except MMF, MTX, post-CY)	155 (4)	5 (4)
CNI (TAC/CSA) alone	110 (3)	9 (7)
Others	28 (1)	1 (1)
Missing	82 (2)	6 (5)
Stem cell source - no. (%)		
Bone Marrow	1024 (27)	33 (27)
Peripheral Blood	2227 (58)	82 (66)
Cord Blood	565 (15)	9 (7)
Missing	3 (0)	0 (0)
Infections post HCT		
Adenovirus - no. (%)		
Yes	712 (19)	46 (37)
No	3107 (81)	78 (63)
Enterovirus (coxsackie, echo, polio) - no. (%)		
Yes	2 (0)	0 (0)
No	3817 (100)	124 (100)
Influenza, NOS - no. (%)		
Yes	79 (2)	2 (2)
No	3740 (98)	122 (98)
Respiratory Syncytial Virus - no. (%)		

Characteristic	1/1/17 - 2/29/20	3/1/20 - present
Yes	774 (20)	8 (6)
No	3045 (80)	116 (94)
Human Parainfluenza Virus (all species) - no. (%)		
Yes	684 (18)	13 (10)
No	3135 (82)	111 (90)
Rhinovirus (all species) - no. (%)		
Yes	1390 (36)	47 (38)
No	2429 (64)	77 (62)
Influenza A Virus - no. (%)		
Yes	563 (15)	1 (1)
No	3256 (85)	123 (99)
Influenza B Virus - no. (%)		
Yes	227 (6)	1 (1)
No	3592 (94)	123 (99)
Enterovirus (ECHO, Coxsackie, EV-D68 and others) - no. (%)		
Yes	275 (7)	12 (10)
No	3544 (93)	112 (90)
Human metapneumovirus - no. (%)		
Yes	199 (5)	4 (3)
No	3620 (95)	120 (97)
Coronavirus (not SARS-CoV-2) - no. (%)		
Yes	585 (15)	15 (12)
No	3234 (85)	109 (88)
Year of transplant - no. (%)		
2017	1456 (38)	0 (0)
2018	1330 (35)	0 (0)
2019	977 (26)	0 (0)
2020	56 (1)	76 (61)
2021	0 (0)	48 (39)
Follow-up - median (range)	26 (3-54)	6 (3-16)

Table 2. Characteristic of patients who received a first autologous transplant then developed community respiratory viral infections post HCT between 2017 and 2021 reported to the CIBMTR

Characteristic	1/1/17 - 2/29/20	3/1/20 - present
No. of patients	982	2
No. of centers	105	2
Age of recipient - no. (%)		
Median (min-max)	58 (0-79)	49 (24-73)
0 - 9	45 (5)	0 (0)
10 - 19	23 (2)	0 (0)
20 - 29	33 (3)	1 (50)
30 - 39	52 (5)	0 (0)
40 - 49	126 (13)	0 (0)
50 - 59	268 (27)	0 (0)
60 - 69	338 (34)	0 (0)
70+	97 (10)	1 (50)
Sex - no. (%)		
Male	512 (52)	1 (50)
Female	470 (48)	1 (50)
Disease - no. (%)		
Acute myelogenous leukemia	3 (0)	0 (0)
Non-Hodgkin lymphoma	194 (20)	1 (50)
Hodgkin lymphoma	50 (5)	1 (50)
Plasma cell disorder/Multiple Myeloma	675 (69)	0 (0)
Other Malignancies	50 (5)	0 (0)
Inherited abnormalities erythrocyte differentiation or function	1 (0)	0 (0)
Hemoglobinopathies	4 (0)	0 (0)
SCID and other immune system disorders	4 (0)	0 (0)
Autoimmune Diseases	1 (0)	0 (0)
Stem cell source - no. (%)		
Bone Marrow	6 (1)	0 (0)
Peripheral Blood	976 (99)	2 (100)
Infections post HCT		
Adenovirus - no. (%)		
Yes	20 (2)	0 (0)
No	962 (98)	2 (100)
Influenza, NOS - no. (%)		
Yes	29 (3)	0 (0)
No	953 (97)	2 (100)
Respiratory Syncytial Virus - no. (%)		
Yes	173 (18)	0 (0)

Characteristic	1/1/17 - 2/29/20	3/1/20 - present
No	809 (82)	2 (100)
Human Parainfluenza Virus (all species) - no. (%)		
Yes	170 (17)	0 (0)
No	812 (83)	2 (100)
Rhinovirus (all species) - no. (%)		
Yes	334 (34)	1 (50)
No	648 (66)	1 (50)
Influenza A Virus - no. (%)		
Yes	192 (20)	0 (0)
No	790 (80)	2 (100)
Influenza B Virus - no. (%)		
Yes	72 (7)	0 (0)
No	910 (93)	2 (100)
Enterovirus NOS - no. (%)		
Yes	64 (7)	0 (0)
No	918 (93)	2 (100)
Human metapneumovirus - no. (%)		
Yes	63 (6)	0 (0)
No	919 (94)	2 (100)
Coronavirus (not SARS-CoV-2) - no. (%)		
Yes	86 (9)	1 (50)
No	896 (91)	1 (50)
Year of transplant - no. (%)		
2017	377 (38)	0 (0)
2018	414 (42)	0 (0)
2019	177 (18)	0 (0)
2020	14 (1)	2 (100)
Follow-up - median (range)	26 (1-56)	12 (12-12)

Table 3. Characteristic of patients who undergoing 1st CAR-T then developed community respiratory viral infections between 2017 and 2021 reported to the CIBMTR

Characteristic	1/1/17 - 2/29/20	3/1/20 - present
No. of patients	263	25
No. of centers	64	15
Age at infusion, by category - no. (%)		
Median (min-max)	55 (1-87)	61 (40-82)
< 10	23 (9)	0 (0)
10-19	35 (13)	0 (0)
20-29	20 (8)	0 (0)
30-39	13 (5)	0 (0)
40-49	20 (8)	4 (16)
50-59	46 (17)	8 (32)
60-69	67 (25)	9 (36)
>= 70	39 (15)	4 (16)
Gender - no. (%)		
Male	161 (61)	16 (64)
Female	101 (38)	9 (36)
Missing	1 (0)	0 (0)
Product - no. (%)		
Kymriah	99 (38)	0 (0)
Yescarta	164 (62)	21 (84)
Tecartus	0 (0)	4 (16)
Recipient race - no. (%)		
White	202 (77)	18 (72)
African American	17 (6)	1 (4)
Asian	10 (4)	0 (0)
Pacific Islander	2 (1)	1 (4)
Native American	1 (0)	1 (4)
More than one race	4 (2)	1 (4)
Unknown	18 (7)	2 (8)
Missing	9 (3)	1 (4)
Recipient ethnicity - no. (%)		
Hispanic or Latino	65 (25)	4 (16)
Non-Hispanic or non-Latino	182 (69)	21 (84)
N/A - Not a resident of the U.S.	8 (3)	0 (0)
Unknown	8 (3)	0 (0)
Disease - no. (%)		
Acute lymphoblastic leukemia (ALL)	73 (28)	0 (0)
Non-Hodgkin lymphoma (NHL)	190 (72)	25 (100)

Characteristic	1/1/17 - 2/29/20	3/1/20 - present
Karnofsky/Lansky performance score prior to CT - no. (%)		
90-100	123 (47)	11 (44)
80	75 (29)	3 (12)
< 80	51 (19)	7 (28)
Missing	14 (5)	4 (16)
Types of prior HCTs - no. (%)		
No prior HCT	171 (65)	19 (76)
Prior allo-HCT	28 (11)	0 (0)
Prior auto-HCT	59 (22)	6 (24)
Prior auto and allo-HCT	2 (1)	0 (0)
Missing	3 (1)	0 (0)
Subsequent HCT since the CT infusion - no. (%)		
No	197 (75)	24 (96)
Yes	41 (16)	0 (0)
Missing	25 (10)	1 (4)
Infections post HCT		
Adenovirus - no. (%)		
Yes	25 (10)	5 (20)
No	238 (90)	20 (80)
Influenza, NOS - no. (%)		
Yes	6 (2)	0 (0)
No	257 (98)	25 (100)
Respiratory Syncytial Virus - no. (%)		
Yes	38 (14)	1 (4)
No	225 (86)	24 (96)
Human Parainfluenza Virus (all species) - no. (%)		
Yes	38 (14)	5 (20)
No	225 (86)	20 (80)
Rhinovirus (all species) - no. (%)		
Yes	125 (48)	12 (48)
No	138 (52)	13 (52)
Influenza A Virus - no. (%)		
Yes	31 (12)	0 (0)
No	232 (88)	25 (100)
Influenza B Virus - no. (%)		
Yes	16 (6)	0 (0)
No	247 (94)	25 (100)
Enterovirus (ECHO, Coxsackie and others) - no. (%)		
Yes	30 (11)	2 (8)
No	233 (89)	23 (92)

Characteristic	1/1/17 - 2/29/20	3/1/20 - present
Human metapneumovirus - no. (%)		
Yes	19 (7)	1 (4)
No	244 (93)	24 (96)
Coronavirus (not SARS-CoV-2) - no. (%)		
Yes	32 (12)	1 (4)
No	231 (88)	24 (96)
Year of CT - no. (%)		
2017	2 (1)	0 (0)
2018	116 (44)	0 (0)
2019	132 (50)	0 (0)
2020	13 (5)	18 (72)
2021	0 (0)	7 (28)
Follow-up of survivors, months - median (range)	25 (3-41)	6 (4-13)

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

Incidence and Impact of Invasive Fungal Infection in Allogeneic Hematopoietic Stem Cell Transplant Recipients with FLT3-ITD-mutated Acute Myeloid Leukemia

Q2. Key Words

Acute myeloid leukemia, FLT3 mutation, candidiasis, cryptococcosis, aspergillosis, mucormycosis, fusariosis, scedosporiosis

Q3. PRINCIPAL INVESTIGATOR

Provide the following information for each investigator:

Principal Investigator #1:

First and last name, degree(s):	Paschalis Vergidis, MD MSc
Email address:	Vergidis.Paschalis@mayo.edu
Institution name:	Mayo Clinic
Academic rank:	Assistant Professor of Medicine, Division of Infectious Diseases

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?

- No

Q6. Principal Investigator #2 (If applicable):

First and last name, degree(s):	Supavit Chesdachai
Email address:	Chesdachai.Supavit@mayo.edu
Institution name:	Mayo Clinic
Academic rank:	Assistant Professor of 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?

- 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.

N/A

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:

Are patients with FLT3-ITD-mutated acute myeloid leukemia undergoing hematopoietic stem cell transplantation (HSCT) at increased risk for invasive fungal infection and associated mortality?

Q16. RESEARCH HYPOTHESIS:

We hypothesize that the incidence of invasive fungal infection in HSCT recipients with FLT-3-ITD mutated leukemia is higher compared to those with wild-type FLT3.

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

Suggested word limit of 200 words:

Primary Objective

• 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.

Secondary Objectives

• To determine fungal infection-related mortality in patients with wild-type and mutated FLT3

• 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

• To identify pre-transplant risk factors for development of post-transplant fungal infection in FLT3-mutated AML.

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.

The mortality of invasive fungal infections in patients with hematologic malignancies and HSCT recipients remains high despite advances in antifungal therapy. FLT3-mutated AML is associated with high relapse rate that further increases the risk of infection. Moreover, patients treated with FLT3 inhibitors may not receive appropriate antifungal prophylaxis due to the significant drug-drug interactions with triazoles. The proposed project will provide insight into the incidence and outcomes of fungal infection in a specific group of HSCT recipients for which we have limited evidence. Our project will also inform clinicians on preventive strategies based on the pre-transplant history of infection in FLT3-mutated AML.

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.

Hematopoietic stem cell transplantation (HSCT) is the most effective post-remission treatment for acute myeloid leukemia (AML). FMS-like tyrosine kinase 3 (FLT3) mutations occur in approximately 30% of patients. FLT3-internal tandem duplication (ITD) mutations are associated with an unfavorable risk profile characterized by short-lived remissions and poor prognosis. Inhibitors of mutated FLT3 have revolutionized the treatment of AML. In clinical trials, the addition of midostaurin or sorafenib to 7+3 chemotherapy was associated with improved survival.
Patients with AML have disease-associated neutrophil dysfunction and oftentimes prolonged chemotherapy-associated neutropenia that places them at risk for invasive fungal infection. Antifungal prophylaxis has become the standard of care for patients with AML, allogeneic HSCT and graft-versus-host disease (GVHD). Posaconazole has anti-mold activity and is typically used in this setting. Drug-drug interactions challenge the approach to antifungal prophylaxis. Midostaurin is metabolized via the cytochrome P450 3A4 (CYP3A4). Posaconazole is a strong CYP3A4 inhibitor. Given this significant interaction antifungal prophylaxis with fluconazole or an echinocandin is preferred in many centers.
FLT3 (and its ligand) is an immune-enhancing molecule that plays a significant role in dendritic cell development and renders dendritic cells competent to activate natural killer cells. FLT3-primed dendritic cells were protective against Aspergillus infection in an experimental murine HSCT model. The incidence of invasive fungal infections in FLT3-mutated AML has not been well characterized. In a small single-center study, FLT3 mutation status was associated with increased risk of invasive mold infection after induction chemotherapy. Midostaurin or salvage gilteritinib did not significantly increase the risk of mold infection in this population. This finding is consistent with in vitro data showing that midostaurin at therapeutic concentrations does not impair T-cell function. A strength of the clinical study was that the incidence of fungal infection was determined in a center that does not provide routine anti-mold triazole prophylaxis. The study was limited by the small sample size (n=108).
Little is known about the incidence of fungal infection post allogeneic HSCT in FLT3-mutated AML. In a previous CIBMTR study, 511 adults with de novo AML who underwent HCST from 2008 through 2011 were evaluated. More patients with the FLT3 mutation died of relapsed leukemia. However, FLT3 mutation status was not associated with increased non-relapse mortality or decreased overall survival. A major strength of this study was analysis of data from a large multicenter cohort. However, rates of infection (bacterial or fungal) were not determined.
In another CIBMTR study, pre-transplant invasive fungal infections were associated with inferior progression-free survival and decreased overall survival after HSCT. However, significant survivorship was observed which justified the decision to pursue transplant. The investigators concluded that factors affecting mortality and post-transplant antifungal therapies should be further investigated.
In the proposed work, we will determine fungal infection density, cumulative incidence and associated mortality in a group of HSCT recipients that are at high risk for relapsed disease and prolonged neutropenia. We will also study the impact of pre-transplant fungal infection on post-transplant outcomes. The study will span over a 14-year period. We will perform separate analysis for the periods before and after the introduction of FLT3 inhibitors. The work will inform clinicians on the significance of pre-transplant fungal infection in a cohort of AML patients that may not receive mold-active prophylaxis and their subsequent risk of post-transplant fungal infection.

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 aged ≥2 years receiving first allogeneic HSCT for AML between January 2007 and December 2020 (Data on FLT3 mutation not consistently recorded before 2007). Stem cell sources include bone marrow, peripheral blood, umbilical cord blood.
Exclusion Criteria:
No consent. No form 2100 available.

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
• Patient age at transplant
• Patient sex
• Patient race/ethnicity
• Patient CMV serostatus
• Recipient HCT-comorbidity index
• Karnofsky performance at transplant
Donor Related
• Donor age
• Donor sex
• Donor CMV serostatus
• Donor/recipient HLA match status
Disease/Transplant Related
• Time from AML diagnosis to HSCT
• Cytogenetic risk groups
• ASBMT RFI Classification
• Disease status at transplant
• Conditioning intensity (myeloablative, reduced intensity)
• TBI-based conditioning
• Ex vivo T-cell depletion
• GVHD prophylaxis
• Stem cell source (peripheral, bone marrow, umbilical cord)
• Year of transplant
• Treatment ATG/Alemtuzumab
Post-transplant time-dependent variables
• Time to neutrophil engraftment
• Time to acute GVHD (grade II-IV)
• Time to chronic GVHD
Labs at day 100
• Total white cell count
• Absolute lymphocyte count
• CD4 counts
• CD8 counts
• CD4:CD8 ratio
• CD19/20
• CD56
• IgG, IgM, IgA
Infection Related
We propose to study invasive fungal infections. Skin/mucosal infections will not be analyzed.
• Fungal infection before conditioning (type, site)
• Antifungal prophylaxis
• Type of post-transplant fungal infection
• Organism(s)
• Site of post-transplant fungal infection
• Time from transplant to fungal infection
• CMV reactivation
Outcome Related
• AML relapse
• Non-relapse mortality
• Leukemia-free survival
• Overall survival
• Cause of death

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

Not required

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

This is a retrospective cohort study that does not require biologic samples from the CIBMTR biorepository.

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.

Not applicable

Q26. REFERENCES:

Stone RM et al. Midostaurin plus chemotherapy for acute myeloid leukemia with a FLT3 mutation. N Engl J Med. 2017;377(5):454

Röllig C et al. Addition of sorafenib versus placebo to standard therapy in patients aged 60 years or younger with newly diagnosed acute myeloid leukaemia (SORAML): a multicentre, phase 2, randomised controlled trial. Lancet Oncol. 2015 Dec;16(16):1691-9

Stemler J et al. Antifungal prophylaxis and novel drugs in acute myeloid leukemia: The midostaurin and posaconazole dilemma. Ann Hematol. 2020 Jul;99(7):1429-1440

Phoompoung P et al. Invasive mold infections in FLT3 mutated acute myeloid leukemia. Clin Lymphoma Myeloma Leuk. 2021 May;21(5):e477-e482

Montagnoli C et al. Provision of antifungal immunity and concomitant alloantigen tolerization by conditioned dendritic cells in experimental hematopoietic transplantation. Blood Cells Mol Dis. 2008 Jan-Feb;40(1):55-62

Eidenschenk C, Crozat K, Krebs P, et al. FLT3 permits survival during infection by rendering dendritic cells competent to activate NK cells. Proc Natl Acad Sci U S A 2010; 107:9759-64.

Deol A et al. Does FLT3 mutation impact survival after hematopoietic stem cell transplantation for acute myeloid leukemia? A Center for International Bone and Marrow Transplant Research (CIBMTR) analysis. Cancer. 2016 Oct;122(19):3005-3014

Maziarz RT et al. Pre-existing invasive fungal infection is not a contraindication to allogeneic HSCT for patients with hematologic malignancies: a CIBMTR study. Bone Marrow Transplant. 2017 Feb;52(2):270-278

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.

Vergidis
Site principal investigator: Cidara (ReSTORE), Scynexis (FURI)
DSMB member: AbbVie (BELLINI, CANOVA)
Fees paid to Mayo Clinic
Chesdachai: None

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 2007 and 2020 for AML reported to the CIBMTR

Characteristic	Without FLT-3 mutation	With FLT-3 mutation
No. of patients	8782	1007
No. of centers	176	125
Age of recipient – no. (%)		
Median (min-max)	52 (2-88)	53 (3-76)
2 – 9	450 (5)	24 (2)
10 – 19	582 (7)	61 (6)
20 – 29	739 (8)	80 (8)
30 – 39	884 (10)	105 (10)
40 – 49	1362 (16)	163 (16)
50 – 59	2178 (25)	247 (25)
60 – 69	2147 (24)	272 (27)
70+	440 (5)	55 (5)
Gender – no. (%)		
Male	4693 (53)	487 (48)
Female	4089 (47)	520 (52)
Donor type – no. (%)		
HLA-identical sibling	1924 (22)	193 (19)
Twin	21 (0)	3 (0)
Mismatched related		
1 Ag/allele mismatched	71 (1)	13 (1)
>=2 Ag/allele mismatched	787 (9)	180 (18)
Other related(matching TBD)	187 (2)	42 (4)
Well-matched unrelated (8/8)	3188 (36)	329 (33)
Partially-matched unrelated (7/8)	798 (9)	67 (7)
Mis-matched unrelated (<=6/8)	60 (1)	8 (1)
Unrelated (matching TBD)	43 (0)	7 (1)
Cord blood	1680 (19)	161 (16)
Missing	23 (0)	4 (0)
GVHD prophylaxis - no. (%)		
Ex-vivo T-cell depletion	128 (1)	13 (1)
CD34 selection	259 (3)	37 (4)
Post-CY + other(s)	977 (11)	244 (24)
Post-CY alone	40 (0)	7 (1)
CNI (TAC/CSA) + MMF +/- Other(except post-CY)	2580 (29)	233 (23)
CNI (TAC/CSA) + MTX +/- Other(except MMF, post-CY)	3833 (44)	391 (39)
CNI (TAC/CSA) +/- Other (except MMF, MTX, post-CY)	553 (6)	50 (5)
TAC/CSA alone	275 (4)	20 (2)

Characteristic	Without FLT-3 mutation	With FLT-3 mutation
Others	87 (1)	9 (1)
Missing	50 (1)	3 (0)
Stem cell source - no. (%)		
Bone Marrow	1533 (17)	194 (19)
Peripheral Blood	5569 (63)	652 (65)
Cord Blood	1680 (19)	161 (16)
Yeast infection by 1 year - no. (%)		
No	7933 (90)	961 (95)
Yes	728 (8)	46 (5)
Missing	121 (1)	0 (0)
Mold infection by 1 year - no. (%)		
No	7907 (90)	927 (92)
Yes	754 (9)	80 (8)
Missing	121 (1)	0 (0)
Year of transplant - no. (%)		
2007 - 2010	3812 (43)	0 (0)
2011 - 2014	2320 (26)	268 (27)
2015 - 2018	2327 (26)	655 (65)
2019 – 2020*	323 (4)	84 (8)

Footnote: 2020 cases are not complete in current retrieval.