Retrospective Analysis of *Clostridium Difficile*-Associated Disease at Oregon Health & Science University

By

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CERTIFICATE OF APPROVAL

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AIC	Akaike's Information Criteria
BAL	Bronchoalveolar lavage
BMT	Bone marrow transplant
CDAD	*Clostridium difficil*e associated disease
CIBMTR	Center for International Blood and Marrow Transplant Research
CMV	Cytomegalovirus
CNS	Central nervous system
DLI	Donor Lymphocyte Infusion
EIA	Enzyme immunoassay
ELFA	Enzyme linked fluorescent immunoassay
GI	Gastrointestinal
GVHD	Graft versus host disease
ID	Identifier
IgG	Immunoglobulin G
LRI	Lower respiratory tract infection
NAP1	North American pulsed field type 1, ribotype 027
OCTRI	Oregon Clinical and Translational Research Institute
OHSU	Oregon Health & Science University
R^2	Coefficient of determination
SAS	Statistical Analysis Software
WBC	White Blood Cell

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ABSTRACT

Background

*Clostridium difficil*e associated disease (CDAD) consists of severe diarrhea, fever, lower abdominal pain, anorexia, nausea, malaise and leukocytosis. Over the last few years, increasing incidence and severity of *Clostridium difficile* infections have been documented in hospitalized settings. The bone marrow transplant (BMT) population is one assumed to be at increased risk for *Clostridium difficile* infection due to the high levels of immunosuppression, in addition to prolonged and frequent hospitalizations. We undertook this study to see if incidence of CDAD has increased in our high risk BMT population and identify potential risk factors that may be modified to prevent disease in the future. The objectives of the current study are to analyze clinical data collected from OHSU's BMT population to 1) describe the burden and outcomes of CDAD in this BMT population; 2) to evaluate patient and epidemiologic factors associated with CDAD.

Methods

Using existing data from electronic medical records and various databases at Oregon Health and Science University from 2002-2008, we identified CDAD cases among BMT recipients along with controls matched for transplant year and time to infection. We used conditional logistic regression to identify risk factors for developing *Clostridium difficile* infection in the first year following bone marrow transplantation. Univariate and multivariate analyses were completed on subsets of the data, including early infections

(≤ 40 days after transplantation), late infections (> 40 days after transplantation) and allogeneic transplant recipients.

Results

Cases and controls were similar with regard to age, gender, race and ethnicity. The study population was predominantly white (96.1% cases, 98.0% controls). The median age was 53.3 years in controls and 54.6 years in cases, p=0.82. Cases included a greater number of allogeneic transplant recipients (73.5%) compared to the control group (50.0%). Approximately 14.7% of patients undergoing BMT experienced at least one episode of CDAD. A steady increase in the proportion of patients with CDAD was observed between 2002 and 2007.

Donor relation was the most prominent risk factor identified in multivariate analysis. Forty nine percent of cases (50) had unrelated donors compared to 22% (22) of the controls, matched OR 4.30, 95% confidence interval 2.04-9.07. There was no statistically significant difference between those with related donors and autologous transplant recipients (p=0.21). After controlling for donor relation, prednisone use and glycopeptide use, patients had an estimated 8.5% increased odds of CDAD for every additional day hospitalized (95% confidence interval: 1.6% increase to 15.8% increase, p=0.015). Glycopeptide exposure in the 30 days preceding the index date occurred in 60% (61) of cases and only 30% of controls (31), matched OR 3.82, 95% confident interval 1.357-10.771, p=0.01. The proportion of patients with active GI GVHD was much higher in the cases (20%, 20 patients) compared to the control group (2%, 2 patients). The odds of exposure to GI GVHD in cases is estimated to be 19 times the odds of

exposure to GI GVHD in the controls (95% CI 3-789, p<0.0001). In addition, a larger proportion (85%) of autologous transplant recipients experienced CDAD early after transplantation as opposed to late. Ninety two percent of late infections occurred in allogeneic transplant recipients.

Conclusion

The increasing trend in proportion of patients with CDAD after transplantation is an important one. Notable increases were observed between 2003-2004 and 2004-2005, which may be due to more sensitive methods of detection and the emergence of the NAP 1 strain in Oregon as opposed to increases in patient level risk factors.

The low power of this study limited the number of variables that could be examined using multivariate analysis. Many of the identified variables, specifically GVHD, use of immunosuppressive agents and length of hospitalization, are also strongly linked to transplant type (autologous vs. allogeneic). Transplant type, or the complications linked to transplant type, may be the underlying factors driving CDAD differences in this population. Utilizing a population of patients receiving only allogeneic transplants may lead to larger cell counts for some of these variables and the ability to perform the additional analyses required to identify pertinent associations. Differing risk factors between early and late infections indicate that time from transplantation is an important factor to consider in future studies. Late infections had a higher proportion of allogeneic transplant recipients (91.5% of cases) whereas early infections showed little difference between transplant types.

In addition, GI GVHD diagnosis around the time of CDAD diagnosis is important to consider in this population. Since grade 2 GI GVHD and CDAD have similar symptoms, it is reasonable to assume that GVHD may be the underlying cause of persistent CDAD symptoms in this population.

INTRODUCTION

Clostridium difficile

*Clostridium difficile w*as first isolated in 1935; the difficultly in isolating this bacteria gave rise to the name (Cookson, 2007). *Clostridium difficile* is an anaerobic, gram positive, spore forming bacteria that produces two exotoxins, toxin A and toxin B (Gerding et al., 1995). Resistance to low pH allows the bacteria to travel through the stomach and reside in the colon, causing symptomatic infection (McMaster-Baxter et al., 2007). *Clostridium difficil*e associated disease (CDAD) consists of severe diarrhea, fever, lower abdominal pain, anorexia, nausea, malaise and leukocytosis (Bartlett 2002; Bartlett et al., 2008; Centers for Disease Control and Prevention, 2004). Possible complications include pseudomembranous colitis, toxic megacolon, paralytic ileus, colon perforations, sepsis, and death (Centers for Disease Control and Prevention, 2004). During *Clostridium difficile* associated diarrhea, spores have been shown to disseminate in the hospital setting and survive in the environment for a long period of time (Roberts 2008). Spores are resistant to alcohol based cleansers and many antibiotics, resulting in high levels of environmental contamination around an affected patient (Hooker, 2007).

In addition to environmental exposure, severe co-morbidities (e.g. cancer, diabetes), age, immunodeficiency, extensive hospital stays, proton pump inhibitors, high serum creatinine levels, low IgG levels and prolonged antibiotic therapy have all been identified as risk factors for CDAD (Baxter et al., 2008; Centers for Disease Control and Prevention, 2004; Kyne et al., 2002; Owens et al., 2008). Antibiotic use, especially with fluoroquinolones, cephalosporins and clindamycin, is frequently identified as a risk

factor (Baxter et al., 2008; McMaster-Baxter et al., 2007). Current treatment for CDAD is limited. Only vancomycin has been approved by the FDA for treatment of *Clostridium difficile* infection, but metronidazole is widely used as the first line of therapy due to the lower cost and the reduced risk of vancomycin-resistant infections (Bartlett 2002; McMaster-Baxter et al., 2007; Nair et al., 1998; Owens et al., 2008; Warny et al., 1994).

Approximately 1% to 3% of healthy adults are asymptomatically colonized with *Clostridium difficile*. Higher levels of *Clostridium difficile* colonization have been observed in hospital employees and caregivers of patients at high risk for infection (Giannasca et al., 2004). Positive stool cultures have been documented for 16% to 21% of hospitalized patients (Clabots et al., 1992; McFarland et al., 1989). Patients with a history of hospitalization within the previous 30 days have been shown to be more likely to have a positive stool culture upon admission (Clabots et al., 1992). *Clostridium difficile* causes 15% to 25% of antibiotic-associated diarrhea (Bartlett et al., 2008). Active research is being done to evaluate why some patients develop CDAD and some remain colonized with no evidence of exotoxin production.

Bone Marrow Transplant Population

The bone marrow transplant population is assumed to have an increased risk for *Clostridium difficile* infection due to the high levels of immunosuppression and antibiotic use, in addition to prolonged and frequent hospitalizations. Chemotherapeutic agents significantly alter the bowel flora and potentially create an environment conducive to *Clostridium difficile* toxin production (Anand et al., 1993; Chakrabarti et al., 2000).

Clostridium difficile is a frequent cause of infectious diarrhea in patients undergoing high-dose chemotherapy for autologous peripheral blood stem cell transplantation (Bilgrami et al., 1999). In a prospective study on bone marrow transplant recipients in Hong Kong, *Clostridium difficile* was the most common microbe isolated in patients with diarrhea (Yuen et al., 1998). Higher non-relapse mortality in allogeneic (unrelated or related donors) stem cell transplant recipients has been reported in patients with a history of CDAD (Chakrabarti et al., 2000). Approximately 4% to 13% of patients develop CDAD following bone marrow transplantation (Chakrabarti et al., 2000; Hooker, 2007). Few studies have examined BMT-specific risk factors for CDAD in a large patient population.

Emergence of Drug Resistant *Clostridium difficile* Strains

Over the last few years, increasing incidence and severity of *Clostridium difficile* infections have been documented (McDonald et al., 2005). This increase occurred simultaneously in several countries using differing methods of diagnosis and spanned all age groups. A greater number of colectomies and an increase of CDAD in discharge diagnoses also occurred, suggesting that biases or changes in screening practices are not responsible for the observed number of infections (Cookson, 2007). NAP1 (North American pulsed field type 1, ribotype 027) was the strain identified to be associated with the increasing severity and incidence of CDAD (Blossom et al., 2007; McMaster-Baxter et al., 2007). Reports have suggested that patients with CDAD caused by NAP1 have increased mortality following diagnosis (Labbe et al., 2008; Pepin et al.,

2005). In addition, NAP1 is resistant to many antibiotics, including bacitracin, cefotaxime, ciprofloxacin, levofloxacin, ceftriaxone, clarithromycin, gatifloxacin, and moxifloxacin (Nair et al., 1998). NAP1 is also associated with metronidazole failure of 16% to 38%, resulting in greater need for vancomycin use and a longer duration of symptomatic shedding of spores (Pepin et al., 2005, Spigaglia et al., 2002). No studies have occurred in the BMT population since the emergence of NAP1.

Study Rationale and Objectives

We undertook this study to see if incidence of CDAD has increased in our high risk BMT population and identify potential risk factors that potentially could be modified to prevent disease in the future. The objectives of the current study are to analyze clinical data collected from OHSU's BMT population to 1) describe the burden and outcomes of CDAD in this BMT population; 2) to evaluate patient and epidemiologic factors associated with CDAD.

Clostridium difficile Testing at OHSU

Current testing for *Clostridium difficile* in health care settings does not typically differentiate between strains or include antibiotic susceptibility testing. Clinical testing is limited to the presence of *Clostridium difficile* toxins A and B. Currently, Kaiser Permanente Northwest Region, the clinical microbiology laboratory for OHSU, utilizes the Meridian Premier™ Toxins A and B assay. The Meridian enzyme immunoassay (EIA) has been shown to have 94.8% (95% confidence interval: 86.4% to 96.8%) sensitivity and

97% (95% confidence interval: 95.3% to 97.5%) specificity for detecting toxins A and B (Planche et al., 2008). Compared to five other methods currently used for CDAD diagnosis, the Meridian test was most likely to detect true positive samples (Planche et al., 2008). The Meridian EIA was implemented on May 9, 2005 for diagnostic use at Kaiser Permanente Northwest Region.

Between September 6, 2002 and May 8, 2005, the Vidas® *C. difficile* Toxin A ll, an enzyme linked fluorescent immunoassay (ELFA), was used for detection of *Clostridium difficile* toxin A in OHSU patients. The sensitivity and specificity for the Vidas® *C. difficile* Toxin A ll ELFA were 80.6% and 96.8%, respectively (Lipson et al., 2003). Enzyme immunoassays have been demonstrated to be reliable for detecting *Clostridium difficile* toxins, when positive (She et al., 2009).

In the OHSU bone marrow transplant population, all patients who develop diarrhea with greater than three loose stools per day have three stool specimens tested for *Clostridium difficile* toxins (OHSU Infection Prophylaxis Guidelines). If the first submitted specimen is positive for *Clostridium difficile* toxins, subsequent specimens are not collected. Due to risk of false negatives with both the Vidas® and Meridian Premier™ assays, submitting three different stool samples for testing maximizes the sensitivity of case detection.

METHODS

Case Identification

We identified a cohort of 676 adult patients (age ≥ 18) transplanted from September 1, 2002 to December 31, 2007 using the BMT registry that records all transplants at OHSU, along with transplanted related variables defined by the Center for International Blood and Marrow Transplant Research (CIBMTR) classification system. We obtained all *Clostridium difficile* Toxin Assay results from OHSU's infection control team between September 6, 2002 and December 31, 2008. These data were matched to the BMT database by medical record number to identify eligible cases.

Control Selection

For each identified case, an index date was given denoting the day of CDAD diagnosis (date of first positive specimen) and the time from transplant to this index date was calculated. SAS version 9.1 (SAS Institute Inc., Cary, NC, USA) was used to identify all possible controls with the same year of transplantation. We then randomly selected one control subject for each case, matched on the year of transplant, who was alive and at risk for infection at the same post-transplant time interval between transplant date and case CDAD diagnosis date. We then used this time interval to assign a corresponding "index date" for the matched controls. For example, if a case's first positive specimen was 72 days after transplantation, the matched control's index date was 72 days after the control's transplant date.

Data Collection

For cases and controls, we collected most covariate data for the 30 days preceding their respective index dates. Collected variables included, age at transplant, gender, race, ethnicity, diabetes, history of *Clostridium difficile* before transplant, transplant date, underlying disease, transplant type, donor relation, conditioning regimen (non-myeloablative vs. myeloablative), planned graft versus host disease (GVHD) prophylaxis, total number of transplants, gastrointestinal graft versus host disease (GI GVHD)*, mucositis*, graft failure/relapse*, other infections*, serum creatinine level*, neutrophil count*, lymphocyte count*, IgG serum level*, total number of days hospitalized*, antibiotic use*, glucocorticoids*, immunosuppressants*, proton pump inhibitors* and antidiarrheals*(Appendix A). [1]

For descriptive purposes, we collected further information about each CDAD case including length of follow-up post CDAD treatment, type of CDAD treatment, mortality (dead or alive at one year after transplantation and 12/31/2008), *Clostridium difficile* recurrence, and measures of *Clostridium difficile* severity(Appendix B).

Data received from the bone marrow transplant (BMT) database was transformed and imported directly into the *Clostridium difficile* Microsoft Access database. Data extracted from the Oregon Clinical and Translational Research Institute (OCTRI) research data warehouse and data received from the infection control team was also imported into the database. Variables collected during chart review were hand

[1] *Variables only evaluated the 30 days preceding the index date

entered directly into the database using a graphic user interface created by the data manager.

The BMT database is a registry housed at OHSU and maintained by BMT physicians whereby patient clinical information is collected prospectively prior to transplant, at day 100 post-transplant, then every 6 months following transplantation. Data were collected using standardized Center for International Blood and Marrow Transplant Research (CIBMTR) data collection forms. The BMT group monitors data on a regular basis, before data entry into a Microsoft Access database and then at 6 month intervals to verify accuracy. The BMT data manager pulled all transplant related variables for all transplants between September 1, 2002 and December 31, 2007.

The OCTRI research data warehouse serves as a repository that stores and maintains all clinical data for OHSU patients. Demographic, medication, admission/discharge and laboratory data for identified cases and controls were pulled by an OCTRI data analyst.

Infection control prospectively collects data on all (positive and negative) *Clostridium difficile* tests in the inpatient and outpatient setting. The infection control data manager provided data for all *Clostridium difficile* tests collected between September 6, 2002 and December 31, 2008.

After identifying cases and matched controls, OCTRI data were imported into the database and chart review was completed to identify the remaining variables of interest. Because of limited resources and time, all chart review was completed by the principal investigator.

Following data collection, we generated a new study identifier (ID) to replace the medical record number during analysis for the identified cases and controls. When we imported data into SAS version 9.1 (SAS Institute Inc., Cary, NC, USA), we utilized the study ID as the sole identifier.

We completed a 10% audit (20 records) to compare BMT data and OCTRI data to the electronic chart. We reviewed demographics, transplant data and laboratory data for discordance, and none was identified

Data Analysis

1) We used SAS version 9.1 (SAS Institute Inc., Cary, NC, USA) to examine the distribution of demographic and medical variables in cases and controls. Various frequency and mean procedures were used to evaluate the distribution of possible predictor variables.
2) Using SAS 9.1, we examined the crude relationship between covariates and *Clostridium difficile* infection using conditional univariate logistic regression. Wald's Chi^2 was used to determine p-values for variables with adequate cell counts ($\geq$5). For variables with limited cell counts (<5), we used exact statistics to evaluate the relationship between possible predictor variables and CDAD. Correlation between continuous variables was then evaluated using Spearman's correlation. We also categorized continuous variables to determine if this altered the level of significance.

Using SAS 9.1, we used a conditional multivariate logistic regression model to test which variables are associated with *Clostridium difficile* infection (yes/no) following bone marrow transplantation. We initially considered variables with adequate cell counts and an α level of 0.25 or less for the conditional univariate analysis for the conditional multivariate logistic regression model. Variables reaching a significance level of 0.25 or less with low cell counts are noted in Appendices E-H. We evaluated identified continuous variables for co-linearity. Co-linear variables were examined for clinical significance and determined if they needed to be removed. After eligible variable identification, we entered variables individually into the model in a stepwise procedure in the order of increasing p-values. Variables were removed based on a p-value greater than 0.05 at each step. We retained age and either transplant type or donor relation in the model due to potential confounding and associations with the outcome in previous research. In addition, the diagnostic test used to diagnose CDAD was initially included, but later removed when it did not confound the relationship between any of the variables and the outcome. We reviewed categorical variables for co-linearity at each step in the model selection process. After main effects models were identified, we evaluated interactions between identified factors and *Clostridium difficile* infection. We tested interactions with biologic plausibility for significance (α=0.05). Due to the limited power of the study, any interactions that resulted in improved Akaike's Information Criteria (AIC) or coefficient of determination (R^2) values were preserved in the final model, despite statistical significance. After selection of the final model, including variables with interactions, we evaluated the goodness of fit and discriminative ability of

the model using AIC and the R^2. We assessed potential outliers by looking at the residuals, however none were identified.

Secondary Analysis

After identification of the initial model (Model 1), additional conditional multivariate logistic regression models were built following the same procedure with subsets of the data. Based on the observed timing of CDAD onset following transplantation in our cohort, and the clinical significance of 40 days after transplantation for other infections, outcomes were divided into early and late infections (i.e. $\leq$40 days and > 40 days) to evaluate if risk factors differed for early versus late infection (Garcia-Vidal et al., 2008). Model 2 included case-control pairs with a first positive *Clostridium difficile* toxin assay less than or equal to 40 days after transplantation (early infections). Model 3 included case-control pairs with a first positive *Clostridium difficile* toxin assay greater than 40 days after transplantation (late infections).

Our initial analysis revealed allogeneic transplantation with unrelated donors and its complications to be strongly associated with CDAD, a finding likely due to prolonged immunosuppression in patients who receive transplant tissue from unrelated donors (versus those with self tissue or related donors such as siblings). Accordingly, since a number of our matched case-control pairs were discordant on this variable (e.g. case with unrelated donor matched with control with self/related donor) it was neither appropriate nor possible to analyze other potential risk factors in such discordant pairs. To control for the effect of donor relation upon the outcome of infection, we evaluated additional covariates using only those matched pairs with concordant allogeneic

transplants between cases and controls (e.g. case and matched controls both received unrelated or related tissue).

Power

PASS 2005 (NCSS, Kaysville, Utah, USA)) software was used to determine the ability of this study to detect a difference between cases and controls based on the sample size. For Model 1 or all infections, a sample size of 100 matched pairs, an α level of 0.05 and proportion of *Clostridium difficile* infection of 20%, was used to estimate power for the study. Eighty percent power was only achieved at an odds ratio of 3.0 or greater and if the percent of patients exposed to a given variable was between 25% and 75%.

For the early and late infections, power was greatly reduced. Based on a sample size of 50 matched pairs, an α level of 0.05 and 20% *Clostridium difficile* infection, we are only able to achieve power over 80% with an odds ratio of 4.0 or greater.

Human Subjects Protection

This research has been approved by the Oregon Health and Science University's Institutional Review Board with a waiver of consent. Data collection and chart review was completed by one individual to reduce access to identifiable information. After data collection, subject identifiers were removed and replaced by a de-identified patient identification number. All data are stored in a password protected form on Oregon Health and Science University's secure network.

RESULTS

Cases and controls were similar with regard to age, gender, race and ethnicity. The study population was predominantly white, non-Hispanic (96.1% cases, 98.0% controls). The median age was 53.3 years in controls and 54.6 years in cases. Cases were more likely to be allogeneic transplant recipients (73.5%) compared to the control group (50.0%) (Table 1)

Table 1: Demographics

Variable	Control, N=102 Frequency (Percent)	Case, N=102 Frequency (Percent)
Female	32 (31.37%)	44 (43.14%)
Race		
Asian	0 (0.00%)	2 (1.96%)
Black/African American	0 (0.00%)	1 (0.98%)
Native Hawaiian/Pacific Islander	1 (0.98%)	0 (0.00%)
White	100 (98.04%)	98 (96.08%)
Unknown/Not Reported	1 (0.98%)	1 (0.98%)
Ethnicity		
Not Hispanic or Latino	98 (96.08%)	98 (96.08%)
Hispanic or Latino	3 (2.94%)	3 (2.94%)
Unknown/Not Reported	1 (0.98%)	1 (0.98%)
Transplant Type		
Autologous	51 (50.00%)	27 (26.47%)
Allogeneic	51 (50.00%)	75 (73.53%)
Median Age (range)	53.28 (18.29-76.07)	54.58 (19.01-74.50)
Median days to Infection post-transplant (range)		35.5 (0-359)

Clostridium difficile Infections

Table 2 shows the proportion of patients transplanted each year that later developed at least one episode of CDAD. One hundred and two cases were identified with an increasing percentage each year.

Table 2: Percent of Transplants Each Year with at Least One CDAD Episode

Year	Total Number of Transplants	Number of Patients with at Least One CDAD Episode	Percent CDAD
2002*	36	2	5.56%
2003	107	9	8.41%
2004	132	19	14.39%
2005	148	26	17.57%
2006	132	24	18.18%
2007	137	22	16.06%
Total	**692**	**102**	**14.74%**

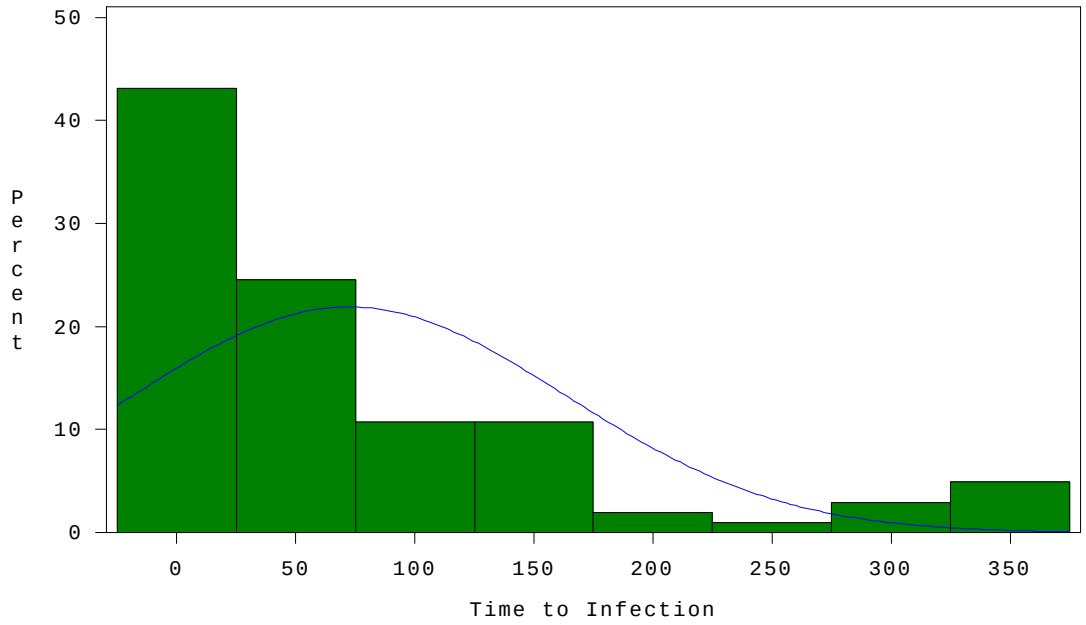
*2002 only includes transplants from September 1, 2002 to December 31, 2002

Table 3 (categorical variables) shows the distribution of CDAD outcomes, including treatment information, length of symptoms and status. Recurrence occurred in approximately 11% of cases. Unfortunately, measures of CDAD severity were not collected regularly by the clinical team. Fifty six percent of cases had unknown levels of infection severity. Most patients (78%) were hospitalized on the day the first positive specimen was collected.

Table 3: *Clostridium difficile* Infections, Categorical Variables

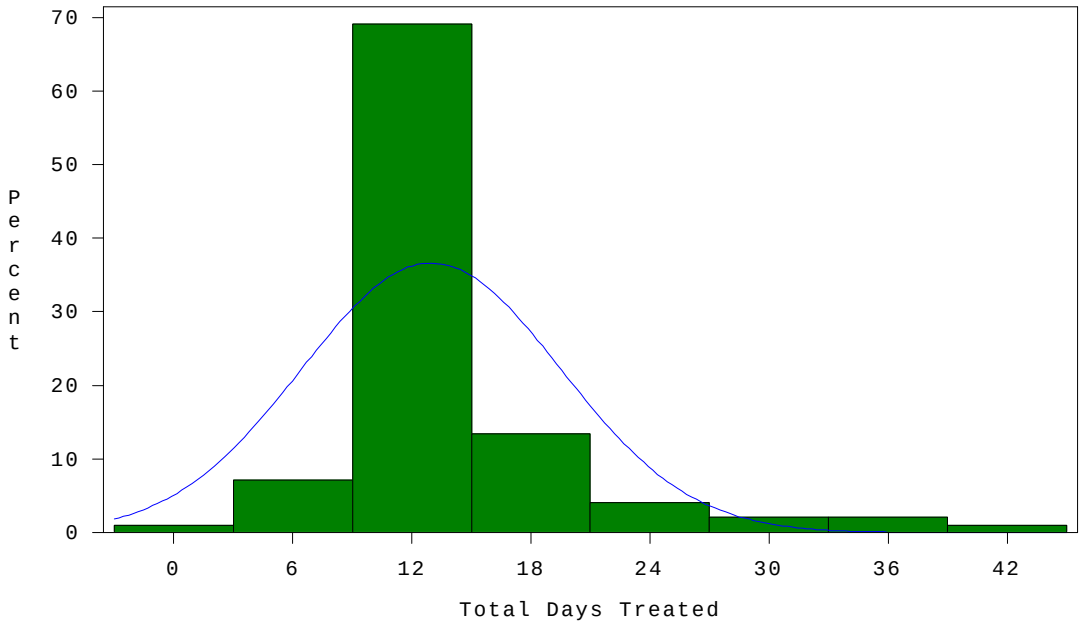
Variable	Frequency	Percent
Total	102	100.00
Hospitalized on Index Date	80	78.43
CDAD ≤ Day 40 After Transplantation	55	53.92
Received CDAD Treatment	101	99.02
Treatment Type		
None	1	0.98
Metronidazole	77	75.49
Metronidazole & Vancomycin	24	23.53
Symptoms Resolved	94	92.16
CDAD Recurrence	11	10.78
Number of Recurrences		
0	91	89.22
1	10	9.80
2	1	0.98
Alive at 1 Year	51	50.00
Alive on 12/31/2008	36	35.29

Figure 1: Time to first positive *Clostridium difficile* toxin assay following transplantation.



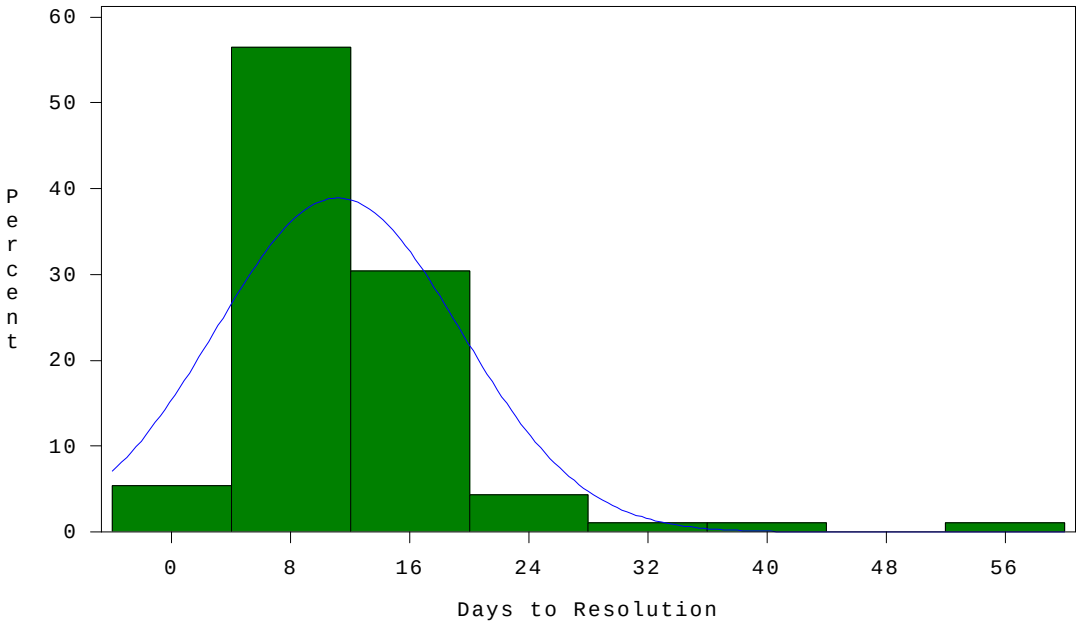
The median time to the first positive *Clostridium difficile* toxin assay following transplantation during the first year was 35.50 days (Minimum = 0 days, Maximum = 359 days), shown in Figure 1. CDAD developed within 40 days following transplantation in 53.92% of patients. However, 75% of infections occurred in the first 100 days following transplantation. Among patients who developed CDAD, 78.43% were hospitalized the full 24 hours on the day the first positive sample was collected.

Figure 2: Total number of days treated for CDAD with Metronidazole or Metronidazole & Vancomycin.



For those treated, the average time between sample collection and beginning treatment was 1.49 days (Minimum = 0 days, Maximum = 12 days). Only one patient, 0.98%, did not receive treatment with Metronidazole or Vancomycin following a positive toxin assay. The majority (75.49%) of patients received Metronidazole only. Twenty three percent of patients had clinical failures to Metronidazole, requiring both Metronidazole and Vancomycin. Average length of treatment, shown in Figure 2, was 12.97 days with a median of 11 days (Minimum = 1 day, Maximum = 42 days).

Figure 3: Total number of days CDAD symptoms persisted



Patients continued to have symptoms of CDAD for a mean of 11.16 days (Minimum = 0 days, Maximum = 56 days), shown in Figure 3. Persistent symptoms of CDAD may be attributable to other causes in this population and therefore are not reliable estimates of *Clostridium difficile* clearance.

Ten patients who did not have a history of GI GVHD received a diagnosis of grade 2 or greater GI GVHD within 14 days of their first positive *Clostridium difficile* toxin assay. In patients who received both Metronidazole and Vancomycin, clinical failures to Metronidazole, 20.83% were diagnosed with GI GVHD, biopsy or endoscopy proven, within 14 days of their first positive *Clostridium difficile* toxin assay compared to 6.48% of patients who were treated with Metronidazole only (exact p-value = 0.0546). Since grade 2 GI GVHD and CDAD have similar symptoms, it is reasonable to assume that

GVHD may be the underlying cause of symptoms in this group. To investigate this further, the duration of treatment and symptoms was evaluated excluding patients who had a GI GVHD diagnosis following CDAD diagnosis. There were no differences in mean or median length of treatment or symptom persistence between patients without a GI GVHD diagnosis or in the group including those with a subsequent GI GVHD diagnosis.

At one year following transplantation, only 50% of the patients with a previous CDAD diagnosis were alive compared to 77.5% of the control group.

Covariate Analysis

***Clostridium difficile* Infections**

The univariate analysis in all study patients, regardless of time to infection, demonstrated that underlying disease, transplant type, donor relation, planned GVHD prophylaxis and history of *Clostridium difficile* before transplantation were all significantly associated with CDAD. All these factors would be known at the time of transplantation and may provide useful information for assessing CDAD risk early in the transplant process. Donor relation was the most prominent risk factor in this group. Forty nine percent of cases (50) had unrelated donors compared to 22% (22) of the controls, matched OR 4.30, 95% confidence interval 2.04-9.07. There was no statistically significant difference between those with related donors and autologous transplant recipients (p=0.21). Factors associated with CDAD in the 30 days preceding the index date include active GI GVHD, CMV reactivation, disease relapse and use of any antibiotics, specifically carbapenems, glycopeptides, miscellaneous anti-infectives and penicillins. The proportion of patients with active GI GVHD was much higher in the cases (20%, 20 patients) compared to the control group (2%, 2 patients). The risk of exposure to GI GVHD in cases is estimated to be 19 times the risk of exposure to GI GVHD in the controls (95% CI 3-789, p<0.0001). Glycopeptide exposure in the 30 days preceding the index date occurred in 60% (61) of cases and only 30% of controls (31), matched OR 4.3, 95% confident interval 2.1-8.9, p<0.0001. Immunosuppressant and glucocorticoid use were highly associated with CDAD, indicating that allogeneic transplants with greater immunosuppression or the complications requiring immunosuppressive treatment may

be an important underlying risk factors. Specific immunosuppressive agents with a significant association include cellcept (p=0.03), tacrolimus (p=0.0005), methylprednisolone (p=0.0036) and prednisone (p=0.0001). Cases had a higher proportion of patients receiving all of these medications. Diagnosis with any infections or bacteremia in the 30 day period preceding the index date was also associated with CDAD development. The odds of bacteremia exposure in cases was 2.6 times the odds of bacteremia in controls, 95% confidence interval 1.3-5.3, p=0.006). Total number of days hospitalized and total number of antibiotics used in the 30 days preceding the index date were the only two significant continuous variables. For each additional day hospitalized, the odds of CDAD increased 1.1 times (95% confidence interval 1.05-1.2, p<0.0001). All continuous variables were categorized and evaluated for significance; however none were associated with CDAD after dividing the data into categories. Appendix I lists the odds ratios and 95% confidence intervals for significant variables identified during the univariate analysis.

Unfortunately, many variables significantly associated with CDAD, including underlying disease, planned GVHD prophylaxis, history of *Clostridium difficile* before transplantation, active GI GVHD, disease relapse and specific medications had limited cell counts restricting inclusion in further multivariate analysis.

In multivariate analysis, only donor relation, total number of days hospitalized, prednisone use and glycopeptide use remained significant after controlling for the effects of age (Table 5).

Patients with related donors did not have a risk that differed significantly from autologous transplant recipients in the main effects model, however those with unrelated donors had an odds of CDAD 3.1 times the odds of infection in autologous transplant recipients (95% confidence interval: 1.083-8.834, p=0.0098). After controlling for donor relation, prednisone use and glycopeptide use in the 30 days preceding the index date, patients had an estimated 8.5% increased odds of CDAD for every additional day hospitalized (95% confidence interval: 1.6% increase to 15.8% increase, p=0.015). Glycopeptide users had an estimated risk of CDAD 3.824 (95% confidence interval: 1.357-10.771, p=0.01) times the estimated risk of CDAD in those who did not use glycopeptides in the 30 days period preceding the index date.

Table 4: *Clostridium difficile* Infections Analysis

Variable	Controls Frequency Percent N=102	Cases Frequency Percent N=102	Crude Odds Ratio 95% Confidence Interval	Adjusted Odds Ratio 95% Confidence Interval
Donor Relation				
Auto/Syngeneic	51 50.00	27 26.47	Referent	Referent
Related	29 28.43	25 24.51	1.57 0.78-3.16	1.25 0.50-3.11
Unrelated	22 21.57	50 49.02	4.30* 2.04-9.07	3.09* 1.08-8.83
Underlying Disease†				
Acute Leukemia	24 23.53	49 48.04	Referent	
Chronic Leukemia	5 4.90	5 4.90	0.63 0.07-5.23	
Lymphoma	37 36.27	22 21.57	0.34* 0.14-0.74	
Myelodysplatic or Myeloproliferative diseases	4 3.92	10 9.80	1.25 0.31-6.03	
Other Leukemia	5 4.90	3 2.94	0.29 0.02-2.33	
Plasma Cell Disorders	23 22.55	12 11.76	0.17* 0.04-0.58	
Solid Tumor	4 3.92	1 0.98	0.15 0.003-1.70	
History of C.Diff before Transplant†	1 0.98	11 10.78	11.00* 1.60-473.48	
GI GVHD 30 Days Before Index Date†	2 1.96	20 19.61	19.000* 3.020-789.458	
GI GVHD 30 Days Before Index Date or 14 Days After Index Date†	2 1.96	30 29.41	29.00* 4.81->999.999	
CMV Reactivation 30 Days before Infection	11 10.78	21 20.59	2.67* 1.04-6.82	
Disease Relapse†	1 0.98	14 13.73	18.259* 3.05-Infinity	
Carbapenem	28 27.45	45 44.12	2.31* 1.20-4.42	
Cephalosporin - 3rd Generation	20 19.61	32 31.37	1.86 0.97-3.56	
Fluoroquinolone	61 59.80	58 56.86	0.88 0.49-1.57	
Glycopeptide	31 30.39	61 59.80	4.33* 2.10-8.95	2.88* 1.11-7.47
Misc Anti-Infective	9 8.82	22 21.57	2.86* 1.21-6.76	

Variable	Controls Frequency Percent N=102	Cases Frequency Percent N=102	Crude Odds Ratio 95% Confidence Interval	Adjusted Odds Ratio 95% Confidence Interval
Penicillin†	1 0.98	11 10.78	11.00* 1.60-473.48	
Immunosuppressants	74 72.55	90 88.24	2.78* 1.30-5.95	
Prednisone	23 22.55	52 50.98	4.22* 2.04-8.73	4.21* 1.54-11.49
Any Infections	22 21.57	46 45.10	2.85* 1.51-5.35	
Bacteremia	17 16.67	35 34.31	2.64* 1.32-5.28	
Total Number of Antibiotics	2.52	3.39	1.41* 1.15-1.72	
Patient Age at Transplant	50.43	50.84	1.00 0.98-1.03	1.08* 1.01-1.09
Total Number of Days Hospitalized 30 Days Before Index Date	8.16	14.20	1.10* 1.05-1.15	1.04* 1.02-1.14

*Statistically significant at $\alpha = 0.05$ Multivariate R^2=0.2342, AIC=98.958

†Cell count $\leq$ 5

Table 5: *Clostridium difficile* Infections, Model with Prednisone and Donor Relation Interaction

	Crude (Univariate Analysis)			Adjusted (Multivariate Analysis)		
Variable	**Odds Ratio**	**95% Confidence Interval**	**p-value**	**Odds Ratio**	**95% Confidence Interval**	**p-value**
Donor Relation			0.0006*			0.0055*
Auto/Syngeneic	Referent					
Related	1.569	0.778-3.162	0.2080			0.1897
Unrelated	4.303	2.042-9.069	0.0001*			0.0098*
Glycopeptide	4.333	2.099-8.945	<.0001*	3.824	1.357-10.771	0.0111*
Prednisone	4.222	2.042-8.732	0.0001*			0.8312
Patient Age at Transplant	1.003	0.981-1.025	0.8152	1.044	1.002-1.088	0.0381*
Total Number of Days Hospitalized 30 Days Before Index Date	1.099	1.051-1.150	<.0001*	1.085	1.016-1.158	0.0145*
Interaction: Prednisone & Donor Relation						0.0117*
Prednisone & Related				29.904	0.924-968.0	0.0555
Prednisone & Unrelated				1.130	0.037-34.436	0.9442

*Statistically significant at $\alpha = 0.05$ R^2=0.2745, AIC=91.953

The interaction between prednisone use and donor relation was also significant and significantly improved the model. The results for the model with this interaction term are displayed in Table 5. Despite the improved fit, only 27% of the variability in CDAD could be explained by the final model. The presence or absence of prednisone modifies the effect of donor relation. In the main effects model, patients with a related donor were not significantly different from those who received autologous transplants. After inclusion of the interaction, prednisone use in those with related donors had an estimated odds of CDAD 29.9 times the odds of those who did not use prednisone (95% confidence interval 0.924-968.0, p=0.06). The presence of prednisone did not alter the effects of patients with unrelated donors as drastically. Patients with an unrelated donor who used prednisone had an estimated risk of CDAD 1.13 times the risk in those

who did not use prednisone (95% confidence interval 0.037-34.436, p=0.9442). Prednisone use was no longer a statistically significant covariate in the model after adding the interaction term. The results of additional univariate analysis of prednisone use and donor relation are displayed in Table 6.

We also evaluated additional interactions between donor relation and glycopeptide use and donor relation and total number of days hospitalized in the multivariate model. These interactions were not statistically significant, nor did they improve the model fit.

Table 6: Donor Relation and Prednisone Use

Donor Relation and Prednisone	Control Frequency Percent	Case Frequency Percent	p-value	Odds Ratio 95% Confidence Interval	Total
Autologous/Syngeneic	47 46.08	25 24.51	Referent	Referent	72
Related	19 18.63	5 4.90	0.0616*	0.38 0.09-1.27	24
Unrelated	13 12.75	20 19.61	0.1353	3.14 0.96-11.82	33
Autologous/Syngeneic & Prednisone	4 3.92	2 1.96	1.0000	0.76 0.06-7.08	6
Related & Prednisone	10 9.80	20 19.61	0.0008*	6.27 1.93-24.89	30
Unrelated & Prednisone	9 8.82	30 29.41	<.0001*	6.89 2.45-23.59	39
Total	102	102			204

Patients with unrelated donors had the highest levels of prednisone use. In univariate analysis, patients had a higher risk for CDAD if they had an unrelated donor and used prednisone compared to those with autologous transplants and no prednisone use. There was not a statistically significant difference between autologous transplant recipients who used prednisone and those who did not, however the number of

patients in the group using prednisone were very small and do not provide a reliable estimate.

Glycopeptides were co-linear with 3rd Generation Cephalosporins, therefore an additional model (not shown) was built to examine the differences of these two antibiotic classes. The models are relatively similar, with a difference in AIC of 1.7. The model with glycopeptides, as opposed to 3rd generation cephalosporins, explained an additional 0.6% of the variability in CDAD. A large number of patients, 14.71% of controls and 23.53% of cases, took both glycopeptides and 3rd generation cephalosporins. Few patients took 3rd generation cephalosporins without glycopeptides. Table 7 shows the frequency of 3rd generation cephalosporin and glycopeptide use.

Table 7: Patients Taking Glycopeptides and 3rd Generation Cephalosporins

Antibiotic	Control Frequency Percent	Case Frequency Percent	Total
Neither	66 64.71	33 32.35	99
Glycopeptides & 3rd Generation Cephalosporins	15 14.71	24 23.53	39
Glycopeptides	16 15.69	37 36.27	53
3rd Generation Cephalosporins	5 4.90	8 7.84	13
Total	102	102	204

Early Infections

Appendix J shows the odds ratios for significant variables identified by univariate and multivariate analysis in the early infections subset. Female gender, unrelated donor, GI GVHD, glycopeptide use, prednisone use and total number of days hospitalized 30 days before index date were all associated with an increased risk of CDAD early after

transplantation. Gender, prednisone use and glycopeptides use were not significant in the multivariate model. Approximately 64% (35) of cases used glycopeptides compared to 40% (22) of controls (matched OR 3.2, 95% confidence interval 1.3-7.9, p=0.014). In addition, the proportion of patients with a GI GVHD diagnosis around the index date was significantly higher in the cases (10.9%, 6 patients) compared to the controls (0%, 0 patients).

Fluoroquinolone use and dexamethasone use in the early infections subset were the only two variables found to have an odds ratio less than one. Eighty five percent (47) of controls and 67% (37) of cases used fluoroquinolones (matched OR 0.33, 95% confidence interval 0.12-0.92, p=0.033) The distribution of dexamethasone use was similar between autologous and allogeneic transplant recipients in the control group, however only 40.62% (25) of allogeneic cases used dexamethasone compared to 52.17% (35) of autologous cases. Despite this difference, dexamethasone use was higher in the control group for both allogeneic and autologous transplant recipients. Twenty five patients (45%) in the case group compared to 35 (64%) patients in the control group took dexamethasone within 30 days of the index date (matched OR 0.41, 95% confidence interval 0.17-0.99, p=0.048).

Transplant type (autologous vs. allogeneic) was more evenly distributed between cases and controls in the early infections group compared to the late infections and all infections subsets, which were dominated by allogeneic transplant recipients. Fifty eight percent (32) of the cases had allogeneic transplants compared to 49% (27) of controls (matched OR 1.4, 95% confidence interval 0.7-2.7, p=0.39).

Gender was also significant early after transplantation. Females had an odds ratio of 2.833 (95% confidence interval: 1.117-7.186, p=0.028) for CDAD compared to males. Twenty five females (45.5%) were in the case group compared to only 14 females (25.5%) in the control group. Females had a slightly higher percentage of autologous transplants 53.9% (males: 46.2%). A higher proportion of female cases received autologous transplants (60.87%) compared to males (39.13%). We also evaluated underlying disease to further explain the relationship between CDAD and gender in the early infection phase. A greater number of female cases had lymphoma or plasma cell disorders as the underlying disease, whereas male controls had a higher proportion of lymphoma or plasma cell disorders as the underlying disease. Approximately 55.6% of females with a plasma cell disorder were cases compared to 28.6% of males with a plasma cell disorder. Similar findings were seen in patients with lymphoma (females: 58.3% were cases, males: 27.8% were cases). Both lymphoma and plasma cell disorders consistently had a reduced risk of CDAD across all data subsets.

Transplant type (p=0.446) and patient age (p=0.092) were not significant in the multivariate model. Total number of days hospitalized was the greatest risk factor identified in the multivariate analysis. After adjusting for transplant type, dexamethasone use and patient age, patients had an estimated 14% increased odds of CDAD for every additional day hospitalized (95% confidence interval: 4.3% increase to 24.8% increase, p=0.012). After adjusting for other variables, dexamethasone use was still protective in the first 40 days following transplantation with an odds of CDAD in the group with dexamethasone use 0.256 (95% confidence interval: 0.085-0.777, p=0.048)

times the odds of CDAD in the group not using dexamethasone. Allogeneic and autologous transplant recipients had similar patterns of dexamethasone use. Including interactions between dexamethasone and transplant type or dexamethasone and number of days hospitalized was not significant nor did it lead to an improved model.

To further evaluate the role of gender, interactions between gender and transplant type and gender and dexamethasone use were evaluated. Neither of these interactions were significant in the final model and both actually led to a higher AIC.

Late Infections

Results for the late infections analysis are displayed in Appendix K. The results for the late analysis were very similar to the results found in the all infections analysis. All cases, except four (91.5%), were allogeneic transplant recipients, compared to 51% (24) of controls (matched OR 20, 95% confidence interval 3.2-828.9, p=0.003). Many of the identified variables are strongly linked to the complications of allogeneic transplantation and increased disease severity, including GVHD and high levels of immunosuppression. Due to the large proportion of allogeneic transplant recipients in cases, further analysis of covariates was not possible when a large number of these patients were matched to autologous controls.

Sub-Analysis of Patients Receiving Allogeneic Transplants

History of *Clostridium difficile* before transplantation, active GI GVHD and total number of days hospitalized in the 30 days preceding infection were significantly

associated with CDAD in the allogeneic only group, shown in Table 8. Nineteen percent of cases (7) and no controls had a history of CDAD prior to transplantation (matched OR 9.6, 95% confidence interval 1.4-infinity, p=0.02). A larger proportion of cases (40.5% versus 5.4%) also had a GI GVHD diagnosis around the index date (matched OR 14.0, 95% confidence interval 2.1-592, p=0.001). Since a majority of patients (all except 3) were taking immunosuppressants, specific medications could be evaluated. Only prednisone and glucocorticoid use was significantly associated with CDAD in the allogeneic only group. Unrelated donor and glycopeptide use were not significantly associated with CDAD in patients receiving allogeneic transplants.

In the multivariate analysis of allogeneic patients, only prednisone use and total number of antibiotics used in the 30 days preceding diagnosis remained significant. This model was similar to the late infections model. After adjusting for donor relation, prednisone use and total number of antibiotics used in the 30 days preceding the index date, patient age at transplant was significantly associated with CDAD. A one year increase in age at transplantation is estimated to increase the odds of CDAD by 1.071 times (95% confidence interval: 1.012-1.135, p=0.02). Sixty five percent (24) of cases used prednisone compared to 40.5% (15) of controls (matched OR 8.5, 95% confidence interval 1.313 – 55.519, p=0.025). In addition, for every additional antibiotic used in the 30 days preceding the index date, the odds of CDAD are 1.84 (95% confidence interval: 1.084-3.122, p=0.024) times the odds of CDAD in the group taking one less antibiotic.

Table 8: Sub-Analysis of Patients Receiving Allogeneic Transplants

Variable	Controls Frequency Percent N=47	Cases Frequency Percent N=47	Crude Odds Ratio 95% Confidence Interval	Adjusted Odds Ratio 95% Confidence Interval
Unrelated Donor	17 45.95	25 67.57	2.33 0.90-6.07	2.81 0.86-9.17
History of C.Diff before Transplant†	0 0.00	7 18.92	9.61* 1.44-Infinity	
GI GVHD 30 Days Before Index Date†	2 5.41	11 29.73	10.00* 1.42-433.98	
GI GVHD 30 Days Before Index Date or 14 Days After Index Date†	2 5.41	15 40.54	14.00* 2.13-591.97	
Glycopeptide	13 35.14	22 59.46	2.29 0.94-5.56	
Glucocorticoids	25 67.57	33 89.19	3.67* 1.02-13.14	
Prednisone	15 40.54	24 64.86	5.50* 1.22-24.81	8.54* 1.31-55.52
Total Number of Days Hospitalized 30 Days Before Index Date	6.46	11.65	1.07* 1.01-1.13	
Total Number of Antibiotics	2.51	3.35	1.34 1.00-1.79	1.84* 1.08-3.12
Patient Age at Transplant	46.69	50.41	1.02 0.99-1.05	1.07* 1.01-1.14

*Statistically significant at $\alpha = 0.05$ Multivariate R^2=0.2214, AIC=40.518

†Cell count ≤ 5

DISCUSSION

The increasing trend in proportion of patients with CDAD after transplantation is an important one. The increase in CDAD over the years has been documented in other studies. A notable increase is seen in 2004 and again in 2005. The increase between 2004 and 2005 may be due to the more sensitive method of detection implemented in May 2005. In addition, emergence of the NAP 1 strain in Oregon was documented in 2005 and the increased proportions between 2003-2004 and 2004-2005 may represent this emergence. It is unlikely that an increase in patient level risk factors is responsible for the increasing number of infections. However, the consistent increase is disturbing and indicates that identification of modifiable patient-level risk factors may be important for future reduction in CDAD.

At one year following transplantation, only 50% of the patients with a previous CDAD diagnosis were alive compared to 77.5% of the control group. This could be a result of CDAD or increased mortality in allogeneic transplant recipients. Cases had a much higher proportion of allogeneic transplant recipients compared to controls. CDAD may also be indicative of a more severe underlying disease.

Many variables evaluated in this analysis were highly co-linear. Total number of days hospitalized was significantly correlated with total number of antibiotics used, (Spearman Correlation Coefficient=0.688). Total number of days hospitalized was also negatively correlated with white blood cell count, neutrophil count and lymphocyte count. Lower levels of immune function lead to greater length of hospitalization and antibiotic use, which is not unexpected. This high level of correlation limits the

conclusions we can make from this analysis. Patients are at an increased risk for CDAD as their length of hospitalization increases; however this may be due to increased immunosuppression, greater use of high-risk antibiotics or exposure to *Clostridium difficile* in the hospital setting.

Many of the identified variables are also strongly linked to transplant type (autologous vs. allogeneic), demonstrating that transplant type, or the complications linked to transplant type, may be the underlying factors driving CDAD differences in this population. Allogeneic transplant recipients also had a higher proportion of CDAD late after transplantation (67%). The consistent associations with glucocorticoid use, antibiotics and length of hospitalization indicate that prolonged immunosuppression may be the underlying risk factor. However, the strong correlation between these variables makes it very difficult to identify any one variable to modify and prevent CDAD in this population. Utilizing an allogeneic only population may lead to larger cell counts for some of these variables and the ability to perform the additional analysis required to identify pertinent associations.

The interaction between prednisone use and donor relation requires further evaluation. It is not clear why prednisone use increases the risk more in patients with related donors. We would expect prednisone to increase the risk in patients with related and unrelated donors equally. The indication for prednisone use, for example GVHD treatment compared to GVHD prophylaxis or treatment of an acute illness, may be important factors in assessing the risk for CDAD. Dose and duration of prednisone use

may also be important and depend on donor relation. We were unable to evaluate dose and length of therapy due to lack of data and time.

Differing risk factors between early and late infections indicate that time from transplantation is an important factor to consider. Further research needs to be completed to identify the reason for the gender discrepancy observed in the early infections analysis, which has not been seen in other studies of CDAD. The gender differences may be due to underlying disease or the conditioning regimens used in this group. Late infections had a higher proportion of allogeneic transplant recipients (91.5% of cases) whereas early infections showed little difference between transplant types. CDAD in the autologous population occurs early after transplantation (85%) and indicates that levels of immunosuppression or environmental exposure in the hospital setting may be associated with CDAD. These patients are less likely than allogeneic transplant recipients to have prolonged immunosuppression and complications requiring hospitalization late after transplantation, indicating that further evaluation of variables closer to the time of transplantation will be useful. More detailed evaluation of conditioning regimens in a larger group of autologous transplant recipients may identify more relevant results. The association between CDAD and dexamethasone use early after transplantation further supports this. Dexamethasone is commonly used in the conditioning regimen for multiple myeloma, a plasma cell disorder. This “protective” effect of dexamethasone may be a proxy for underlying disease or conditioning regimen. In addition, more autologous transplants are occurring in the outpatient setting. Monitoring the incidence of CDAD in this group as length of hospitalization

decreases may allow researchers to better separate hospitalization from immune suppression.

In addition, there might be more complicated outcomes after CDAD in this population which requires further investigation. The higher proportion of patients (50% versus 32.5%) who died within a year following transplantation in the cases may be indicative of these complications or of an underlying “sick” host, which may also put patients at higher risk for CDAD. The link between CDAD development around the time of GVHD development has been documented in previous research by Chakrabarti, et al. It is possible that CDAD may exacerbate GI GVHD, indicating that toxin mediated colitis may incite some local antigenicity. Further evaluation of this relationship may lead to greater understanding of the pathogenesis of CDAD or GVHD in this population.

LIMITATIONS AND STRENGTHS

Matched Study Design

Ideally, a prospective cohort would be the ideal study design to evaluate *Clostridium difficile* infection and outcomes following bone marrow transplantation. However, due to the low incidence and time restrictions of this study, the matched case-control design was more appropriate. The resources, logistics and patient involvement required to screen and monitor patients for *Clostridium difficile* infection for this length of time would provide a significant number of challenges, especially with losing patients during follow-up. Using clinical data, we are limited to the times of variable collection, but patients are more likely to continually be in contact with the clinic for a significant period of time following discharge from the hospital.

The high mortality of patients following bone marrow transplantation also prevented sampling a cohort and following patients until infection. To ensure controls were at risk for infection at the time cases were developing CDAD, time matching was implemented. Time-matching also allowed us to control for other time-related factors following transplantation. To control for changes in *Clostridium difficile* strains in addition to changes in transplantation practices, cases were matched to controls based on year of transplantation as well.

The primary limitation of this study was the inclusion of both allogeneic and autologous transplant recipients. We did not match on transplant type and this limited evaluation of some covariates. The principal risk factors were linked to allogeneic transplantation. Many of the variables included for evaluation, such as GVHD, are only

applicable to allogeneic transplantation. The mix of allogeneic and autologous transplant recipients diluted the results of this study. Matching on transplant type or evaluation of only one transplant type may have resulted in identification of more relevant risk factors. Despite this inadequacy, inclusion of both transplant types did allow for identification of differing proportions of early and late CDAD in allogeneic and autologous transplant recipients. This information is useful in determining important periods following transplantation to study CDAD in future studies.

Data Collection

Many limitations are present in this study; however these same limitations are present in any retrospective study design. Since data are evaluated retrospectively, the data collection depends on documentation by the treating clinical team. Specific variables, such as history of CDAD prior to transplantation, measurements of CDAD severity and resolution of CDAD symptoms may not be reliably documented in the chart. Because of the complex patient population with extensive follow-up, documentation was not an incapacitating problem for a majority of the variables collected. Standard criteria currently used by the bone marrow transplant group at OHSU were adopted to further ensure clinical documentation of variables of interest. For some variables, including GI GVHD, laboratory diagnoses were utilized to determine presence of GI GVHD. Since GI GVHD symptoms are similar to CDAD and medication related side effects, identifying GI GHVD attributable symptoms is difficult by clinical criteria only.

Chart review was completed by a single researcher with extensive experience in coordinating clinical research and data abstraction in the bone marrow transplant population, reducing error in capturing these variables. Using one individual improves consistency, but may reduce reproducibility. Utilizing very strict definitions during chart review controlled for chart abstraction errors.

Missing Values

Missing values were problematic for some of the laboratory measurements, including IgG levels and white blood cell counts. Controls were less likely to have these laboratory results available, especially as the length of time increases between the index date and date of transplantation. If these patients were healthier than their matched cases, with higher levels of IgG and white blood cell counts, this will weaken any association, if present, between CDAD and these laboratory values. Missing values were especially problematic in the autologous transplant population. Further analysis of only allogeneic transplant recipients may reduce the number of missing laboratory values.

Selection Bias

Since a cohort of all transplanted patients was identified and used to select the cases and controls, selection bias is highly unlikely. Controls were randomly matched to cases based on specific criteria, the only exclusion being death before the time of the case's infection, further limiting introduction of bias.

Medication Classification

Many variables, specifically medications, were only documented if the patient took the medication in the 30 day period preceding the index date (yes/no). No differentiation was made if the patient took the medication for 30 days or only one day. The cumulative dose for each medication may be an important factor to investigate, but was not available in this dataset. Excluding more detailed information from this analysis would dilute any association found between the differing doses and length of exposure to any medication and CDAD.

Environmental Exposures

This study was limited to examining patient level risk factors for CDAD. Environmental exposures, such as staff treating other patients with CDAD, adherence to hand washing guidelines or the presence of *Clostridium difficile* spores in patient rooms prior to infection, may also be important risk factors for infection. Unfortunately, many of these variables can only be collected in a prospective manner.

Sample Size

Power and sample size was another significant limitation. Due to the lack of data available for *Clostridium difficile* clinical testing prior to 2002 for OHSU patients, the study was limited to a very short time period. However, this also allowed for reduced variability in transplant practices. The small sample size allowed detection of only very large differences between the cases and controls with significant power. The low cell

counts for many variables, especially after sub-setting the data by early and late infections, restricted many variables from inclusion in the multivariate model. Variables such as GVHD, history of CDAD prior to transplantation and disease relapse may continue to be strongly associated with the development of symptomatic *Clostridium difficile* infections after controlling for other variables. Unfortunately, this study did not have the power to examine this further. Due to the limited sample size, the multivariate model is not useful in predicting who may or may not develop CDAD following bone marrow transplantation.

Strengths

This is the largest study evaluating risk factors for *Clostridium difficile* in the bone marrow transplant population. The results are not only important to the bone marrow transplant population, but all hospitalized patients with an increased risk of developing *Clostridium difficile* infection and its complications. The increased incidence, morbidity and mortality of *Clostridium difficile* infections require additional research to identify preventable risk factors and the subset of patients at higher risk. This has been the largest study completed in this population, which may have unique risk factors for developing CDAD.

PUBLIC HEALTH IMPLICATIONS AND FUTURE RESEARCH

Continued research investigating patient level risk factors for CDAD is important. The variability between autologous and allogeneic transplants limited further evaluation of specific variables. The next step is to re-evaluate these same variables within the allogeneic transplant population who are at substantially higher risk of CDAD. The low incidence of *Clostridium difficile* infections in specific hospitalized populations limits the sample size and power in a single facility. Future collaboration between institutions will be important to adequately determine significant associations.

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Appendix A

Variables evaluated for *Clostridium difficile* Infections (Descriptive & Analytic)

*indicates variables examined 30 days before infection

Variable	Variable Type	Response Type	Data Source	Additional Info
Clostridium difficile infection (CDAD)	Primary Outcome	Date Month of infection Year of infection Status Control (0) Case (1) Status – Early vs. Late Control (0) Case – early infection (≤ day 40) (1) Case – late infection (> day 40) (2)	Infection Control	One positive result from *Clostridium difficile* Toxin Assay following BMT: OHSU Service Code: 074-3525, CPT Codes: 87324
Medical Record Number	Unique patient identifier		BMT	
Study ID	De-identified unique patient identifier			New patient id that will be created following chart review and before data analysis
Number of days alive & at risk for infection	Matching Variable	Calculation: difference between date of day 0 (transplant) to infection (cases) or death (controls)	BMT (date of death) Infection control (infection date)	Number of days following transplantation that the patient is alive, at risk for *Clostridium difficile* infection, without a subsequent transplant
Year of transplant	Matching Variable	Year	BMT	For cases with multiple transplants, use the preceding transplant closest to *Clostridium difficile* infection

Variable	Variable Type	Response Type	Data Source	Additional Info
Index Date	Data Collection	Date	Infection Control BMT	Cases: date of specimen collection for the first positive *Clostridium difficile* assay Controls: transplant date + number of days between transplant and the case index date
Age at transplant	Covariate Demographic	Continuous	BMT: date of transplant OCTRI: birth date	
Gender	Covariate Demographic	Male (0) Female (1)	OCTRI	
Race	Covariate Demographic	American Indian/Alaska Native (1) Asian (2) Black/African American (3) More than 1 race (4) Native Hawaiian/Pacific Islander (5) White (6) Unknown/Not Reported (7)	OCTRI	
Ethnicity	Covariate Demographic	Not Hispanic or Latino (0) Hispanic or Latino (1) Unknown/Not Reported (2)	OCTRI	
Diabetes	Covariate Co-morbidity	No (0) Yes (1)	Chart review	

Variable	Variable Type	Response Type	Data Source	Additional Info
History of *Clostridium difficile* before transplant	Covariate Co-morbidity	No (0) Yes (1)	Chart review Infection Control	Positive *Clostridium difficile* result from infection control prior to transplant or mention of previous *Clostridium difficile* infection in the history and physical prior to transplant
Transplant Date	Covariate Transplant Related	Date	BMT	
Underlying Disease	Covariate Transplant Related	Acute Leukemia (0) Chronic Leukemia (1) Lymphoma (2) Myelodysplatic or Myeloproliferative diseases (3) Plasma Cell Disorders (4) Other Leukemia (5) Solid Tumor (6)	BMT	Uses CIBMTR classification
Transplant Type	Covariate Transplant Related	Autologous/Syngeneic (0) Allogeneic (1)	BMT	
Donor Relation	Covariate Transplant Related	Self/identical twin (0) Related (1) Unrelated (2)	BMT	
Conditioning Regimen	Covariate Transplant Related	Non-myeloablative (0) Myeloablative (1)	BMT	
GVHD Prophylaxis	Covariate Transplant Related	None (0) Cyclosporine (1) Cyclosporine, Methotrexate (2) Cyclosporine, Methotrexate, Prednisone (3) Cyclosporine, Mycophenolate Mofetil (4) Tacrolimus, Methotrexate, Prednisone (5)	BMT	

Variable	Variable Type	Response Type	Data Source	Additional Info
Total number of transplants	Covariate Transplant Related	Continuous	BMT	includes transplant of interest and all preceding transplants
Gastrointestinal Graft Versus Host Disease (GI GVHD)*	Covariate Transplant Complication	Any GI GVHD ≥grade 2 No (0) Yes (1) GI GVHD Grade None (0) Acute GI ≥grade 2 (1) Chronic extensive, GI (2) GI GVHD within 14 days following C.Diff diagnosis No (0) Yes (1)	Chart review	Diagnosed by endoscopy or biopsy
Mucositis, severity	Covariate Transplant Complication	No(0) Yes, PO (1) Yes, IV nutrition (2)	Chart review	
Graft failure/Relapse	Covariate Transplant Complication	No (0) Yes (1)	Chart review	
Other infections*	Covariate Transplant Complication	Bacteremia Fungemia Pneumonia Bacterial Fungal Viral Central Nervous System Bacterial Fungal Viral Viral Gastroenteritis VRE Colonization CMV Reactivation	OCTRI Chart review	Bacteremia/Fungemia – positive blood culture Pneumonia - positive BAL Gastroenteritis/VRE Colonization – positive stool Culture/Polymerase chain reaction/Antigen
Serum creatinine*	Covariate Laboratory Value	Continuous Closest result preceding infection	OCTRI	
Neutrophil count*	Covariate Laboratory Value	Continuous Closest result preceding infection	OCTRI	
Lymphocyte count*	Covariate Laboratory Value	Continuous Closest result preceding infection	OCTRI	

Variable	Variable Type	Response Type	Data Source	Additional Info
WBC*	Covariate Laboratory Value	Continuous Closest result preceding infection	OCTRI	
IGG serum*	Covariate Laboratory Value	Continuous Closest result preceding infection	OCTRI	
Hospitalizations*	Covariate Transplant Complication	Continuous Total number of days hospitalized 30 days before index date Patient hospitalized the day of diagnosis No (0) Yes (1)	OCTRI	
Antibiotic use*	Covariate Medications	Continuous Total # of antibiotics used Antibiotic Classes Aminoglycoside Aminopenicillin Antibacterial - Folate Antagonist Antileprotic - Sulfone Agent Antiprotozoal/Antibacterial Carbapenem Cephalosporin - 1st Generation Cephalosporin - 3rd Generation Cephalosporin - 4th Generation Cyclic Lipopeptide Fluoroquinolone Glycopeptide Lincosamide Macrolide Misc Anti-Infective Monobactam Penicillin Oxazolidinone	OCTRI Chart review	
Glucocorticoids*	Covariate Medications	Dexamethasone Hydrocortisone Methylprednisolone Prednisolone Prednisone	OCTRI Chart review	

Variable	Variable Type	Response Type	Data Source	Additional Info
Non-steroid Immunosuppressants*	Covariate Medications	Cellcept Cyclosporine Rituximab Sirolimus Tacrolimus	OCTRI Chart review	
Proton Pump Inhibitors*	Covariate Medications	Esomeprazole Lansoprazole Omeprazole Pantoprazole	OCTRI Chart review	
Antidiarrheals*	Covariate Medications	Kaopectate Imodium	OCTRI Chart review	

Appendix B

Variables evaluated for *Clostridium difficile* Outcomes (Descriptive)

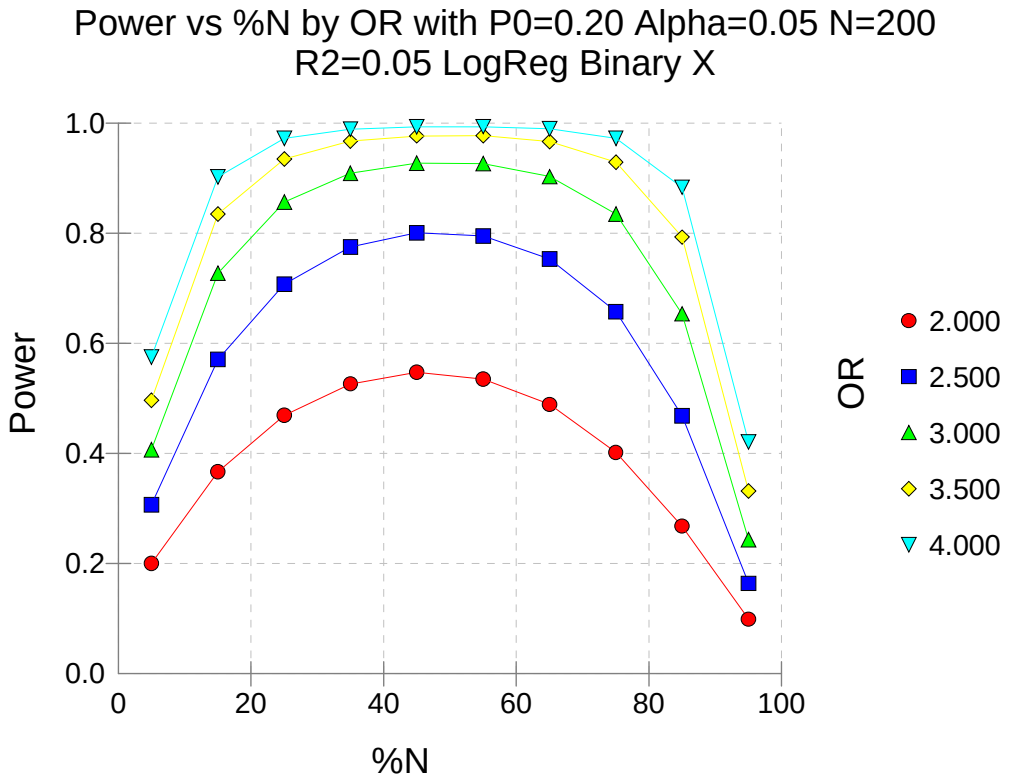
Variable	Variable Type	Response Type	Data Source	Additional Info
Follow-up	Covariate	Continuous Total number of days follow-up following infection (cases) or matched date (controls)	BMT Chart review	
Antibiotic – *Clostridium difficile* treatment	Covariate Infection Outcome	Total number of days treated Antibiotic type Metronidazole (0) Vancomycin (1) Both (2)	Chart review	
Status	Covariate Infection Outcome	Categorical Alive (0) Dead(1)	BMT Chart review	
Clostridium difficile recurrence	Covariate Infection Outcome	Categorical No (0) Yes (1) Number of times	OCTRI Chart review	Subsequent positive *Clostridium difficile* tests greater than 4 weeks following resolution of diarrhea and discontinuation of treatment (Hornbuckle 1998)
Clostridium difficile Severity	Covariate Infection Outcome	Mild (0) Diarrhea 500 mL or less per day and/or colitis Moderate (1) Diarrhea 501 – 1000 mL per day and/or colitis Severe (2) Diarrhea greater than 1000 mL per day and/or colitis, with a temperature of 35.6° C or less or temperature of 35.9° C or less for greater than 1 hour. Unknown (3)	Chart review	(Dubberke 2007)

Appendix C

Power for Model 1

Power	Percent of Exposure	Percent of *Clostridium difficile*	Odds Ratio
20%	5%	20%	2.0
47%	25%	20%	2.0
54%	55%	20%	2.0
40%	75%	20%	2.0
41%	5%	20%	3.0
86%	25%	20%	3.0
93%	55%	20%	3.0
83%	75%	20%	3.0
57%	5%	20%	4.0
97%	25%	20%	4.0
99%	55%	20%	4.0
97%	75%	20%	4.0

α level of 0.05, R^2 of 0.05 and a sample size of 200

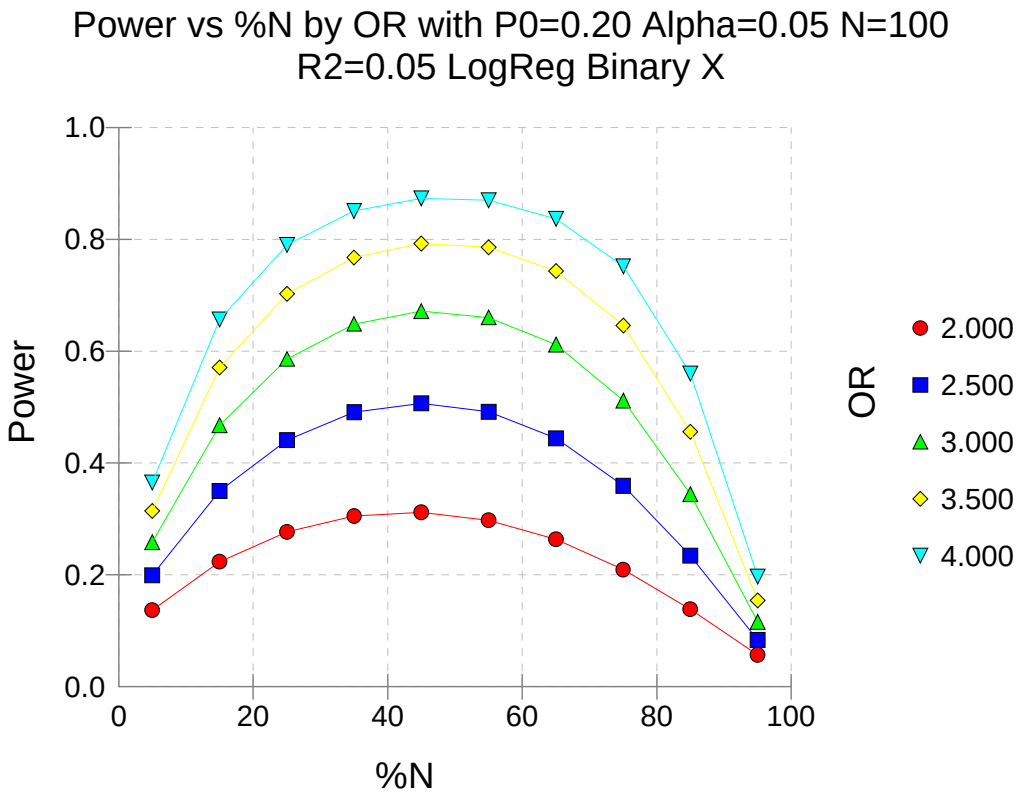


Appendix D

Power for Model 2 & Model 3

Power	Percent of Exposure	Percent of *Clostridium difficile*	Odds Ratio
14%	5%	20%	2.0
28%	25%	20%	2.0
30%	55%	20%	2.0
21%	75%	20%	2.0
26%	5%	20%	3.0
59%	25%	20%	3.0
66%	55%	20%	3.0
51%	75%	20%	3.0
36%	5%	20%	4.0
79%	25%	20%	4.0
87%	55%	20%	4.0
75%	75%	20%	4.0

α level of 0.05, R^2 of 0.05 and an estimated sample size of 100



Appendix E

Univariate Analysis: *Clostridium difficile* Infections

Demographics

Variable		Control Frequency Percent	Case Frequency Percent	p-value	Odds Ratio 95% Confidence Interval
Total		102	102		
Female		32 31.37	44 43.14	0.0866	1.667 0.929-2.990
Race†				0.7500	
	Asian	0 0.00	2 1.96	0.5000	2.414 0.188- Infinity
	Black/African American	0 0.00	1 0.98	1.0000	1.000 0.026- Infinity
	Native Hawaiian/Pacific Islander	1 0.98	0 0.00	1.0000	1.000 0-39.000
	White	100 98.04	98 96.08		Referent
	Unknown/Not Reported	1 0.98	1 0.98	1.0000	1.000 0.013-78.497
Ethnicity†				1.0000	
	Not Hispanic or Latino	98 96.08	98 96.08		Referent
	Hispanic or Latino	3 2.94	3 2.94	1.0000	1.000 0.072-13.796
	Unknown/Not Reported	1 0.98	1 0.98	1.0000	1.000 0.013-78.497

*Statistically significant at $\alpha = 0.05$

†Exact p-values, excluded from multivariate analysis due to low cell counts

Transplant Related Risk Factors

Variable	Control Frequency Percent	Case Frequency Percent	p-value	Odds Ratio 95% Confidence Interval
Total	102	102		
Underlying Disease†			0.0011*	
Acute Leukemia	24 23.53	49 48.04		Referent
Chronic Leukemia	5 4.90	5 4.90	0.9114	0.633 0.074-5.233
Lymphoma	37 36.27	22 21.57	0.0048*	0.335 0.141-0.740
Myelodysplatic or Myeloproliferative diseases	4 3.92	10 9.80	0.9864	1.251 0.309-6.032
Other Leukemia	5 4.90	3 2.94	0.3386	0.294 0.023-2.333
Plasma Cell Disorders	23 22.55	12 11.76	0.0023*	0.170 0.038-0.583
Solid Tumor	4 3.92	1 0.98	0.1704	0.152 0.003-1.695
Transplant Number†			0.7998	
1	87 85.29	88 86.27		Referent
2	11 10.78	12 11.76	1.0000	1.073 0.391-2.993
3	4 3.92	2 1.96	0.7039	0.509 0.046-3.551
Transplant Type			0.0012*	
Autologous	51 50.00	27 26.47		Referent
Allogeneic	51 50.00	75 73.53	0.0012*	2.667 1.473-4.827
Donor Relation			0.0006*	
Autologous/Syngeneic	51 50.00	27 26.47		Referent
Related	29 28.43	25 24.51	0.2080	1.569 0.778-3.162
Unrelated	22 21.57	50 49.02	0.0001*	4.303 2.042-9.069
Conditioning Regimen			0.8158	

Variable	Control Frequency Percent	Case Frequency Percent	p-value	Odds Ratio 95% Confidence Interval
Myeloablative	85 83.33	82 80.39		Referent
Non-myeloablative	11 10.78	12 11.76	0.7242	1.172 0.485-2.834
None/Unknown	6 5.88	8 7.84	0.5487	1.396 0.469-4.150
Planned GVHD Prophylaxis†			0.0459*	
None	55 53.92	34 33.33		Referent
Cyclosporine	1 0.98	0 0.00	1.0000	2.282 0-88.995
Cyclosporine, Mycophenolate Mofetil	11 10.78	11 10.78	0.5539	1.485 0.518-4.329
Cyclosporine, Methotrexate	5 4.90	9 8.82	0.1667	2.565 0.729-10.393
Cyclosporine, Methotrexate, Prednisone	30 29.41	47 46.08	0.0136*	2.208 1.161-4.365
Tacrolimus, Methotrexate, Prednisone	0 0.00	1 0.98	1.0000	1.000 0.026- Infinity

*Statistically significant at α = 0.05

†Exact p-values, excluded from multivariate analysis due to low cell counts

Co-morbidities

Variable	Control Frequency Percent	Case Frequency Percent	p-value	Odds Ratio 95% Confidence Interval
Total	102	102		
Diabetes	7 6.86	15 14.71	0.0959	2.143 0.874-5.256
History of C.Diff before Transplant†	1 0.98	11 10.78	0.0063*	11.000 1.599-473.475

*Statistically significant at α = 0.05

†Exact p-values, excluded from multivariate analysis due to low cell counts

Transplant Complications

Variable	Control Frequency Percent	Case Frequency Percent	p-value	Odds Ratio 95% Confidence Interval
Total	102	102		
GI GVHD 30 Days Before Index Date†	2 1.96	20 19.61	<.0001*	19.000 3.020-789.458
GVHD Grade†			<.0001*	
None	100 98.04	82 80.39		Referent
Acute GI GVHD	2 1.96	9 8.82	0.0215*	9.000 1.247-394.479
Chronic GI GVHD	0 0.00	11 10.78	0.0004*	19.930 3.104- Infinity
GI GVHD 30 Days Before Index Date or 14 Days After Index Date†	2 1.96	30 29.41	<.0001*	29.000 4.808->999.999
Mucositis 30 Days Before Index Date	30 29.41	35 34.31	0.2324	1.833 0.678-4.957
Mucositis Severity			0.3457	
None	72 70.59	67 65.69		Referent
Mucositis, PO Nutrition	19 18.63	18 17.65	0.7175	1.453 0.406-5.598
Mucositis, IV Nutrition	11 10.78	17 16.67	0.2522	2.135 0.656-7.837
CMV Reactivation 30 Days before Infection	11 10.78	21 20.59	0.0405*	2.667 1.043-6.815
Disease Relapse†	1 0.98	14 13.73	0.0002*	18.259 3.048- Infinity

*Statistically significant at $\alpha = 0.05$

†Exact p-values, excluded from multivariate analysis due to low cell counts

Antibiotic Classes

Class	Control Frequency Percent	Case Frequency Percent	p-value	Odds Ratio 95% Confidence Interval
Any Antibiotics	94 92.16	101 99.02	0.0156*	9.607 1.441-Infinity
Aminoglycoside†	2 1.96	3 2.94	1.0000	1.500 0.172-17.959
Aminopenicillin†	2 1.96	1 0.98	1.0000	0.500 0.008-9.605
Antibacterial - Folate Antagonist	62 60.78	60 58.82	0.7577	0.909 0.496-1.666
Antileprotic - Sulfone Agent	13 12.75	7 6.86	0.1867	0.538 0.215-1.350
Antiprotozoal/Antibacterial†	2 1.96	5 4.90	0.4531	2.500 0.409-26.253
Carbapenem	28 27.45	45 44.12	0.0118*	2.308 1.204-4.424
Cephalosporin - 1st Generation†	2 1.96	5 4.90	0.4531	2.500 0.409-26.253
Cephalosporin - 3rd Generation	20 19.61	32 31.37	0.0618	1.857 0.970-3.556
Cephalosporin - 4th Generation†	2 1.96	8 7.84	0.1094	4.000 0.798-38.666
Cyclic Lipopeptide†	3 2.94	4 3.92	1.0000	1.500 0.172-17.959
Fluoroquinolone	61 59.80	58 56.86	0.6550	0.875 0.487-1.572
Glycopeptide	31 30.39	61 59.80	<.0001*	4.333 2.099-8.945
Lincosamide†	2 1.96	2 1.96	1.0000	1.000 0.072-13.796
Macrolide†	1 0.98	4 3.92	0.3750	4.000 0.396-196.990
Misc Anti-Infective	9 8.82	22 21.57	0.0168*	2.857 1.208-6.757
Monobactam†	2 1.96	5 4.90	0.4531	2.500 0.409-26.253
Oxazolidinone	7 6.86	7 6.86	1.0000	1.000 0.323-3.101
Penicillin†	1 0.98	11 10.78	0.0063	11.000 1.599-473.475

Statistically significant at $\alpha = 0.05$

†Exact p-values, excluded from multivariate analysis due to low cell counts

Antidiarrheals

Medication	Control Frequency Percent	Case Frequency Percent	p-value	Odds Ratio 95% Confidence Interval
Antidiarrheals	50 49.02	56 54.90	0.3973	1.273 0.728-2.225
Imodium	50 49.02	55 53.92	0.4758	1.227 0.699-2.155

*Statistically significant at α = 0.05

†Exact p-values, excluded from multivariate analysis due to low cell counts

Only one patient took Kaopectate in the 30 day period preceding the index date, therefore this medication was excluded from the table and only analyzed within the Antidiarrheals variable.

Immunosuppressants/Glucocorticoids

Medication	Control Frequency Percent	Case Frequency Percent	p-value	Odds Ratio 95% Confidence Interval
Immunosuppressants	74 72.55	90 88.24	0.0086*	2.778 1.297-5.951
Non-steroid Immunosuppressants	46 45.10	70 68.63	0.0020*	2.500 1.400-4.464
Cellcept	8 7.84	19 18.63	0.0340*	2.571 1.074-6.156
Cyclosporine	44 43.14	55 53.92	0.1407	1.500 0.875-2.573
Sirolimus †	1 0.98	5 4.90	0.2188	5.000 0.559-236.488
Tacrolimus †	3 2.94	17 16.67	0.0005*	15.000 2.308-631.466
Glucocorticoids	63 61.76	85 83.33	0.0019*	2.833 1.467-5.472
Dexamethasone	37 36.27	32 31.37	0.3859	0.737 0.369-1.470
Hydrocortisone	30 29.41	28 27.45	0.7317	0.889 0.453-1.743
Methylprednisolone	10 9.80	28 27.45	0.0036*	3.250 1.471-7.178
Prednisolone†	1 0.98	2 1.96	1.0000	2.000 0.104-117.994
Prednisone	23 22.55	52 50.98	0.0001*	4.222 2.042-8.732

*Statistically significant at α = 0.05

†Exact p-values, excluded from multivariate analysis due to low cell counts

Only one patient took Rituximab in the 30 day period preceding the index date, therefore this medication was excluded from the table and only analyzed within the Immunosuppressants variable and the Immunosuppressants/Glucocorticoids variable.

Proton Pump Inhibitors

Medication	Control Frequency Percent	Case Frequency Percent	p-value	Odds Ratio 95% Confidence Interval
Proton Pump Inhibitors	86 84.31	87 85.29	0.8186	1.111 0.451-2.734
Esomeprazole†	1 0.98	3 2.94	0.6250	3.000 0.241-157.492
Lansoprazole	80 78.43	80 78.43	1.0000	1.000 0.477-2.098
Omeprazole	7 6.86	11 10.78	0.3226	1.667 0.606-4.586
Pantoprazole	6 5.88	8 7.84	0.7905	1.333 0.406-4.662

*Statistically significant at $\alpha = 0.05$

†Exact p-values, excluded from multivariate analysis due to low cell counts

Granulocyte Colony-stimulating Factors

Medication	Control Frequency Percent	Case Frequency Percent	p-value	Odds Ratio 95% Confidence Interval
Neupogen	37 36.27	47 46.08	0.1090	1.714 0.887-3.314

*Statistically significant at $\alpha = 0.05$

†Exact p-values, excluded from multivariate analysis due to low cell counts

Infections

Infection	Control Frequency Percent	Case Frequency Percent	p-value	Odds Ratio 95% Confidence Interval
Any Infections	22 21.57	46 45.10	0.001*	2.846 1.513-5.354
Bacteremia	17 16.67	35 34.31	0.006*	2.636 1.317-5.277
Bacterial Pneumonia	0 0.00	5 4.90	0.0625	6.725 0.916-Infinity
Fungal Pneumonia	0 0.00	4 3.92	0.1250	5.285 0.660-Infinity
Viral Pneumonia	2 1.96	2 1.96	1.0000	1.000 0.072-13.796
CNS - Bacterial	0 0.00	1 0.98	1.0000	1.000 0.026-Infinity
CNS - Fungal	0 0.00	1 0.98	1.0000	1.000 0.026-Infinity
Viral Gastroenteritis	1 0.98	1 0.98	1.0000	1.000 0.013-78.497
VRE Colonization	12 11.76	12 11.76	1.0000	1.000 0.449-2.226

*Statistically significant at $\alpha = 0.05$

†Exact p-values, excluded from multivariate analysis due to low cell counts

Univariate Analysis: Continuous Variables

	N	Mean	Med	Min	Max	Standard Deviation	p-value	Odds Ratio 95% Confidence Interval
Patient Age at Transplant							0.8152	1.003 0.981-1.025
Control	102	50.43	53.28	18.29	76.07	14.70		
Case	102	50.84	54.58	19.01	74.50	13.38		
Total Number of Days Hospitalized 30 Days Before Index Date							<.0001*	1.099 1.051-1.150
Control	102	8.16	5.50	0.00	30.00	8.99		
Case	102	14.20	14.00	0.00	30.00	9.10		
Total Number of Antibiotics							0.0008*	1.407 1.153-1.716
Control	102	2.52	2.00	0.00	8.00	1.82		
Case	102	3.39	3.00	0.00	9.00	1.51		
Plasma Creatinine, mg/dL							0.6645	1.115 0.682-1.824
Control	86	1.05	0.90	0.50	4.60	0.64		
Case	102	1.07	0.90	0.40	3.10	0.55		
White Blood Cell Count, K/cu mm							0.4256	1.032 0.955-1.116
Control	84	4.28	3.70	0.10	20.80	3.96		
Case	98	4.72	2.95	0.10	26.40	5.26		
Neutrophil Count, K/cu mm							0.4018	1.042 0.946-1.148
Control	86	3.04	1.95	0.00	18.50	3.17		
Case	100	3.34	2.00	0.00	19.50	3.91		
Lymphocyte Count, K/cu mm							0.1560	0.708 0.439-1.141
Control	86	0.64	0.45	0.00	5.00	0.78		
Case	100	0.44	0.30	0.00	5.20	0.66		
IgG Serum, mg/dL							0.1807	0.999 0.998-1.000
Control	50	682.00	612.00	163.00	2229.00	383.18		
Case	79	573.43	512.00	181.00	1540.00	279.02		

*Statistically significant at $\alpha = 0.05$

Appendix F

Univariate Analysis: Early Infections

Demographics

Variable	Control Frequency Percent	Case Frequency Percent	p-value	Odds Ratio 95% Confidence Interval
Total	55	55		
Female	14 25.45	25 45.45	0.0283*	2.833 1.117-7.186
Race†				
White	55 100.00	55 100.00		Referent
Ethnicity†			1.0000	
Not Hispanic or Latino	54 98.18	53 96.36		Referent
Hispanic or Latino	1 1.82	2 3.64	1.0000	2.000 0.104-117.994

*Statistically significant at $\alpha = 0.05$

†Exact p-values, excluded from multivariate analysis due to low cell counts

Transplant Related Risk Factors

Variable	Control Frequency Percent	Case Frequency Percent	p-value	Odds Ratio 95% Confidence Interval
Total	55	55		
Underlying Disease†			0.0494*	
Acute Leukemia	12 21.82	23 41.82		Referent
Chronic Leukemia	1 1.82	2 3.64	1.0000	1.462 0.070-91.900
Lymphoma	21 38.18	13 23.64	0.1606	0.466 0.155-1.287
Myelodysplatic or Myeloproliferative diseases	2 3.64	7 12.73	0.6118	2.128 0.342-23.084
Other Leukemia	3 5.45	1 1.82	0.5000	0.414 0-5.325
Plasma Cell Disorders	14 25.45	9 16.36	0.1667	0.362 0.076-1.389
Solid Tumor	2 3.64	0 0.00	0.3484	0.293 0-3.863
Transplant Number†			0.8154	
1	46 83.64	49 89.09		Referent
2	7 12.73	4 7.27	0.5078	0.500 0.081-2341
3	2 3.64	2 3.64	1.0000	0.843 0.050-11.920
Transplant Type			0.3859	
Autologous	28 50.91	23 41.82		Referent
Allogeneic	27 49.09	32 58.18	0.3859	1.357 0.680-2.707
Donor Relation			0.0726	
Autologous/Syngeneic	28 50.91	23 41.82		Referent
Related	15 27.27	9 16.36	0.4793	0.721 0.291-1.784
Unrelated	12 21.82	23 41.82	0.0487*	2.615 1.006-6.798
Conditioning Regimen†			0.3550	

Variable	Control Frequency Percent	Case Frequency Percent	p-value	Odds Ratio 95% Confidence Interval
Myeloablative	46 83.64	50 90.91		Referent
Non-myeloablative	4 7.27	1 1.82	0.1646	0.194 0.019-1.962
None/Unknown	5 9.09	4 7.27	0.4359	0.560 0.130-2.407
Planned GVHD Prophylaxis†			0.0962	
None	32 58.18	27 49.09		Referent
Cyclosporine, Mycophenolate Mofetil	4 7.27	1 1.82	0.4040	0.259 0.005-2.664
Cyclosporine, Methotrexate	1 1.82	7 12.73	0.0708	6.986 0.898-314.857
Cyclosporine, Methotrexate, Prednisone	18 32.73	19 34.55	1.0000	1.044 0.442-2.476
Tacrolimus, Methotrexate, Prednisone	0 0.00	1 1.82	1.0000	1.000 0.026-Infinity

*Statistically significant at $\alpha = 0.05$

†Exact p-values, excluded from multivariate analysis due to low cell counts

Co-morbidities

Variable	Control Frequency Percent	Case Frequency Percent	p-value	Odds Ratio 95% Confidence Interval
Total	55	55		
Diabetes†	5 9.09	5 9.09	1.0000	1.000 0.230-4.345
History of C.Diff before Transplant†	1 1.82	6 10.91	0.1250	6.000 0.728-275.986

*Statistically significant at $\alpha = 0.05$

†Exact p-values, excluded from multivariate analysis due to low cell counts

Transplant Complications

Variable	Control Frequency Percent	Case Frequency Percent	p-value	Odds Ratio 95% Confidence Interval
Total	55	55		
GI GVHD 30 Days Before Index Date (Acute GI) †	0 0.00	2 3.64	0.5000	2.414 0.188-Infinity
GI GVHD 30 Days Before Index Date or 14 Days After Index Date†	0 0.00	6 10.91	0.0312*	8.166 1.177-Infinity
Mucositis 30 Days Before Index Date	29 52.73	32 58.18	0.4097	1.600 0.523-4.891
Mucositis Severity			0.5897	
None	26 47.27	23 41.82		Referent
Mucositis, PO Nutrition	18 32.73	17 30.91	0.9004	1.332 0.314-6.096
Mucositis, IV Nutrition	11 20.00	15 27.27	0.5033	1.772 0.475-7.445
CMV Reactivation 30 Days before Infection†	2 3.64	5 9.09	0.2150	4.000 0.447-35.788
Disease Relapse†	0 0.00	1 1.82	1.0000	1.000 0.026-Infinity

*Statistically significant at $\alpha = 0.05$

†Exact p-values, excluded from multivariate analysis due to low cell counts

Antibiotic Classes

Class	Control Frequency Percent	Case Frequency Percent	p-value	Odds Ratio 95% Confidence Interval
Any Antibiotics	54 98.18	55 100.00	1.0000	1.000 0.026-Infinity
Aminoglycoside†	2 3.64	0 0.00	0.5000	0.414 0-5.325
Aminopenicillin†	2 3.64	0 0.00	0.5000	0.414 0-5.325
Antibacterial - Folate Antagonist	37 67.27	33 60.00	0.4164	0.714 0.317-1.608
Antileprotic - Sulfone Agent†	6 10.91	1 1.82	0.1250	0.167 0.004-1.374
Antiprotozoal/Antibacterial†	2 3.64	1 1.82	1.0000	0.500 0.008-9.605
Carbapenem	21 38.18	27 49.09	0.2067	1.750 0.734-4.172
Cephalosporin - 1st Generation†	1 1.82	1 1.82	1.0000	1.000 0.013-78.497
Cephalosporin - 3rd Generation	17 30.91	19 34.55	0.6834	1.182 2.638-0.529
Cephalosporin - 4th Generation†	0 0.00	5 9.09	0.0625	6.725 0.916-Infinity
Cyclic Lipopeptide†	1 1.82	2 3.64	1.0000	1.000 0.026-Infinity
Fluoroquinolone	47 85.45	37 67.27	0.0334*	0.333 0.121-0.917
Glycopeptide	22 40.00	35 63.64	0.0138*	3.167 1.265-7.929
Lincosamide†	1 1.82	1 1.82	1.0000	1.000 0.013-78.497
Misc Anti-Infective†	6 10.91	8 14.55	0.5655	1.400 0.444-4.411
Monobactam†	2 3.64	4 7.27	0.6875	2.000 0.287-22.110
Oxazolidinone†	5 9.09	4 7.27	1.0000	0.750 0.110-4.433
Penicillin†	0 0.00	3 5.45	0.2500	3.847 0.413-Infinity

*Statistically significant at $\alpha = 0.05$

†Exact p-values, excluded from multivariate analysis due to low cell counts

Antidiarrheals

Medication	Control Frequency Percent	Case Frequency Percent	p-value	Odds Ratio 95% Confidence Interval
Antidiarrheals	40 72.73	32 58.18	0.1361	0.556 0.256-1.203
Imodium	40 72.73	31 56.36	0.0895	0.500 0.225-1.113

*Statistically significant at α = 0.05

†Exact p-values, excluded from multivariate analysis due to low cell counts

Only one patient took Kaopectate in the 30 day period preceding the index date, therefore this medication was excluded from the table and only analyzed within the Antidiarrheals variable.

Immunosuppressants

Medication	Control Frequency Percent	Case Frequency Percent	p-value	Odds Ratio 95% Confidence Interval
Immunosuppressants	46 83.64	46 83.64	1.0000	1.000 0.351-2.851
Non-steroid Immunosuppressants	23 41.82	29 52.73	0.2917	1.462 0.722-2.959
Cellcept†	4 7.27	3 5.45	1.0000	0.750 0.110-4.433
Cyclosporine	23 41.82	27 49.09	0.4807	1.286 0.639-2.585
Tacrolimus†	0 0.00	4 7.27	0.1250	5.285 0.660-Infinity
Glucocorticoids	44 80.00	42 76.36	0.6180	0.778 0.290-2.088
Dexamethasone	35 63.64	25 45.45	0.0482*	0.412 0.171-0.993
Hydrocortisone	28 50.91	20 36.36	0.1094	0.500 0.214-1.168
Methylprednisolone	8 14.55	13 23.64	0.2324	1.833 0.678-4.957
Prednisone†	6 10.91	15 27.27	0.0393*	3.250 1.060-9.967

*Statistically significant at α = 0.05

†Exact p-values, excluded from multivariate analysis due to low cell counts

Only one patient took Prednisolone in the 30 day period preceding the index date, therefore this medication was excluded from the table and only analyzed within the Glucocorticoids variable and the Immunosuppressants/Glucocorticoids variable.

Proton Pump Inhibitors

Medication	Control Frequency Percent	Case Frequency Percent	p-value	Odds Ratio 95% Confidence Interval
Proton-Pump Inhibitors†	52 94.55	50 90.91	0.6875	0.500 0.045-3.489
Lansoprazole†	51 92.73	48 87.27	0.3270	0.500 0.125-1.999
Omeprazole†	3 5.45	4 7.27	1.0000	1.500 0.172-17.959
Pantoprazole†	3 5.45	4 7.27	1.0000	1.333 0.226-9.102

*Statistically significant at $\alpha = 0.05$

†Exact p-values, excluded from multivariate analysis due to low cell counts

Only one patient took Esomerprazole in the 30 day period preceding the index date, therefore this medication was excluded from the table and only analyzed within the Proton Pump Inhibitors variable.

Granulocyte Colony-stimulating Factors

Medication	Control Frequency Percent	Case Frequency Percent	p-value	Odds Ratio 95% Confidence Interval
Neupogen	32 58.18	37 67.27	0.3206	1.500 0.674-3.339

*Statistically significant at $\alpha = 0.05$

†Exact p-values, excluded from multivariate analysis due to low cell counts

Infections

Infection	Control Frequency Percent	Case Frequency Percent	p-value	Odds Ratio 95% Confidence Interval
Any Infections	16 29.09	24 43.64	0.1094	2.000 0.856-4.673
Bacteremia	12 21.82	18 32.73	0.1657	2.000 0.751-5.329
Bacterial Pneumonia†	0 0.00	1 1.82	1.0000	1.000 0.026-Infinity
Fungal Pneumonia†	0 0.00	1 1.82	1.0000	1.000 0.026-Infinity
Viral Pneumonia†	1 1.82	2 3.64	1.0000	2.000 0.104-117.994
Viral Gastroenteritis†	0 0.00	1 1.82	1.0000	1.000 0.026-Infinity
VRE Colonization	10 18.18	7 12.73	0.4692	0.700 0.266-1.839

*Statistically significant at $\alpha = 0.05$

†Exact p-values, excluded from multivariate analysis due to low cell counts

Univariate Analysis: Continuous Variables

	N	Mean	Med	Min	Max	Standard Deviation	p-value	Odds Ratio 95% Confidence Interval
Patient Age at Transplant							0.3546	1.015 0.983-1.049
Control	55	50.37	53.79	18.29	72.93	14.39		
Case	55	52.48	53.36	23.03	69.36	10.75		
Total Number of Days Hospitalized 30 Days Before Index Date							0.0106*	1.093 1.021-1.170
Control	55	12.76	13.00	0.00	30.00	7.62		
Case	55	17.33	17.00	0.00	30.00	8.09		
Total Number of Antibiotics							0.4962	1.111 0.820-1.504
Control	55	3.16	3.00	0.00	8.00	1.66		
Case	55	3.33	3.00	1.00	7.00	1.26		
Plasma Creatinine, mg/dL							0.8932	1.041 0.579-1.870
Control	53	1.01	0.90	0.50	4.60	0.70		
Case	55	1.01	0.80	0.40	3.10	0.60		
White Blood Cell Count, K/cu mm							0.6539	0.969 0.847-1.110
Control	51	3.16	2.20	0.10	20.80	3.88		
Case	51	2.80	1.20	0.10	19.90	3.67		
Neutrophil Count, K/cu mm							0.7279	0.973 0.836-1.133
Control	53	2.32	1.50	0.00	18.50	3.15		
Case	53	2.07	0.90	0.0	13.30	2.76		
Lymphocyte Count, K/cu mm							0.8204	0.901 0.368-2.207
Control	53	0.41	0.20	0.00	2.70	0.55		
Case	53	0.37	0.20	0.00	2.00	0.46		
IgG Serum, mg/dL							0.7158	1.000 0.998-1.002
Control	29	634.93	612.00	256.00	1298.00	237.40		
Case	38	694.61	702.50	274.00	1540.00	311.36		

*Statistically significant at $\alpha = 0.05$

Appendix G

Univariate Analysis: Late Infections

Demographics

Variable	Control Frequency Percent	Case Frequency Percent	p-value	Odds Ratio 95% Confidence Interval
Total	47	47		
Female	18 38.30	19 40.43	0.8415	1.083 0.494-2.374
Race†			0.7500	
Asian	0 0.00	2 4.26	0.5000	2.414 0.188-Infinity
Black/African American	0 0.00	1 2.13	1.0000	1.000 0.026-Infinity
Native Hawaiian/Pacific Islander	1 2.13	0 0.00	1.0000	1.000 0-39.000
White	45 95.74	43 91.49		Referent
Unknown/Not Reported	1 2.13	1 2.13	1.0000	1.000 .013-78.497
Ethnicity†			1.0000	
Not Hispanic or Latino	44 93.62	45 95.74		Referent
Hispanic or Latino	2 4.26	1 2.13	1.0000	1.0000 0-39.000
Unknown/Not Reported	1 2.13	1 2.13	1.0000	1.0000 0.013-78.497

*Statistically significant at $\alpha = 0.05$

†Exact p-values, excluded from multivariate analysis due to low cell counts

Transplant Related Risk Factors

Variable	Control Frequency Percent	Case Frequency Percent	p-value	Odds Ratio 95% Confidence Interval
Total	47	47		
Underlying Disease†			0.0097*	
Acute Leukemia	12 25.53	26 55.32		Referent
Chronic Leukemia	4 8.51	3 6.38	0.6706	0.273 0.004-6.480
Lymphoma	16 34.04	9 19.15	0.0145*	0.200 0.035-0.771
Myelodysplatic or Myeloproliferative diseases	2 4.26	3 6.38	0.8359	0.442 0.024-7.694
Other Leukemia	2 4.26	2 4.26	0.6706	0.273 0.004-6.480
Plasma Cell Disorders	9 19.15	3 6.38	0.0057*	0.062 0-0.488
Solid Tumor	2 4.26	1 2.13	0.6706	0.273 0.004-6.480
Transplant Number†			0.2266	
1	41 87.23	39 82.98		Referent
2	4 8.51	8 17.02	0.3438	2.333 0.533-13.984
3	2 4.26	0 0.00	0.5000	0.414 0-5.325
Transplant Type†			0.0029*	
Autologous	23 48.94	4 8.51		Referent
Allogeneic	24 51.06	43 91.49	<.0001*	20.000 3.199-828.956
Donor Relation†			<.0001*	
Autologous/Syngeneic	23 48.94	4 8.51		Referent
Related	14 29.79	16 34.04	0.0030*	13.044 1.851-571.966
Unrelated	10 21.28	27 57.45	<.0001*	25.845 3.746->999.999
Conditioning Regimen†			0.1718	

Variable	Control Frequency Percent	Case Frequency Percent	p-value	Odds Ratio 95% Confidence Interval
Myeloablative	39 82.98	32 68.09		Referent
Non-myeloablative	7 14.89	11 23.40	0.2773	2.058 0.640-7.685
None/Unknown	1 2.13	4 8.51	0.2500	5.275 0.489-275.559
Planned GVHD Prophylaxis†			0.0019*	
None	23 48.94	7 14.89		Referent
Cyclosporine	1 2.13	0 0.00	1.0000	7.894 0-307.858
Cyclosporine, Mycophenolate Mofetil	7 14.89	10 21.28	0.0399*	4.813 1.059-31.730
Cyclosporine, Methotrexate	4 8.51	2 4.26	0.7045	2.534 0.158-33.656
Cyclosporine, Methotrexate, Prednisone	12 25.53	28 59.57	0.0008*	7.286 1.970-41.450

*Statistically significant at α = 0.05

†Exact p-values, excluded from multivariate analysis due to low cell counts

Co-morbidities

Variable	Control Frequency Percent	Case Frequency Percent	p-value	Odds Ratio 95% Confidence Interval
Total	47	47		
Diabetes†	2 4.26	10 21.28	0.0377*	5.000 1.096-22.820
History of C.Diff before Transplant†	0 0.00	5 10.64	0.0625	6.725 0.916-Infinity

*Statistically significant at α = 0.05

†Exact p-values, excluded from multivariate analysis due to low cell counts

Transplant Complications

Variable	Control Frequency Percent	Case Frequency Percent	p-value	Odds Ratio 95% Confidence Interval
Total	47	47		
GI GVHD 30 Days Before Index Date†	2 4.26	18 38.30	0.0001*	17.000 2.664-710.462
GVHD Grade†			<.0001*	
None	45 95.74	29 61.70		Referent
Acute GI GVHD	2 4.26	7 14.89	0.0703	-0.1061-5.7541
Chronic GI GVHD	0 0.00	11 23.40	0.0004*	1.0859-Infinity
GI GVHD 30 Days Before Index Date or 14 Days After Index Date†	2 4.26	24 51.06	<.0001*	23.000 3.735-947.449
Mucositis 30 Days Before Index Date†	1 2.13	3 6.38	0.3414	3.000 0.312-28.841
Mucositis Severity†			0.7500	
None	46 97.87	44 93.62		Referent
Mucositis, PO Nutrition	1 2.13	1 2.13	1.0000	1.000 0.013-78.497
Mucositis, IV Nutrition	0 0.00	2 4.26	0.5000	2.414 0.188-Infinity
CMV Reactivation 30 Days before Infection	9 19.15	16 34.04	0.1000	2.400 0.846-6.812
Disease Relapse†	1 2.13	13 27.66	0.0005	16.817 2.779-Infinity

*Statistically significant at $\alpha = 0.05$

†Exact p-values, excluded from multivariate analysis due to low cell counts

Antibiotic Classes

Class	Control Frequency Percent	Case Frequency Percent	p-value	Odds Ratio 95% Confidence Interval
Any Antibiotics†	40 85.11	46 97.87	0.0313*	8.166 1.177-Infinity
Aminoglycoside†	0 0.00	3 6.38	0.2500	3.847 0.413-Infinity
Aminopenicillin†	0 0.00	1 2.13	1.0000	1.000 0.026-Infinity
Antibacterial – Folate Antagonist	25 53.19	27 57.45	0.6380	1.250 0.493-3.167
Antileprotic – Sulfone Agent	7 14.89	6 12.77	0.7817	0.857 0.288-2.550
Antiprotozoal/Antibacterial†	0 0.00	4 8.51	0.1250	5.285 0.660-Infinity
Carbapenem	7 14.89	18 38.30	0.0232*	3.200 1.172-8.735
Cephalosporin – 1st Generation†	1 2.13	4 8.51	0.3750	4.000 0.396-196.990
Cephalosporin – 3rd Generation†	3 6.38	13 27.66	0.0213*	4.333 1.191-23.707
Cephalosporin – 4th Generation†	2 4.26	3 6.38	1.0000	1.500 0.172-17.959
Cyclic Lipopeptide†	2 4.26	2 4.26	1.0000	1.000 0.072-13.796
Fluoroquinolones	14 29.79	21 44.68	0.1673	1.778 0.786-4.023
Glycopeptide	9 19.15	26 55.32	0.0022*	6.667 1.981-22.435
Lincosamides†	1 2.13	1 2.13	1.0000	1.000 0.013-78.497
Macrolide†	1 2.13	4 8.51	0.3750	4.000 0.396-196.990
Misc Anti-Infective†	3 6.38	14 29.79	0.0074*	6.500 1.472-59.329
Monobactam†	0 0.00	1 2.13	1.0000	1.000 0.026-Infinity
Oxazolidinone†	2 4.26	3 6.38	1.0000	1.500 0.172-17.959
Penicillin†	1 2.13	8 17.02	0.0391*	8.000 1.073-354.981

*Statistically significant at $\alpha = 0.05$

†Exact p-values, excluded from multivariate analysis due to low cell counts

Antidiarrheals

Medication	Control Frequency Percent	Case Frequency Percent	p-value	Odds Ratio 95% Confidence Interval
Antidiarrheals	10 21.28	24 51.06	0.0065*	4.500 1.523-13.296
Imodium	10 21.28	24 51.06	0.0065*	4.500 1.523-13.296

*Statistically significant at $\alpha = 0.05$

†Exact p-values, excluded from multivariate analysis due to low cell counts

Immunosuppressants

Medication	Control Frequency Percent	Case Frequency Percent	p-value	Odds Ratio 95% Confidence Interval
Immunosuppressants†	28 59.57	44 93.62	0.0004*	9.000 2.155-79.981
Non-steroid Immunosuppressants	23 48.94	41 87.23	0.0016*	7.000 2.088-23.468
Cellcept†	4 8.51	16 34.04	0.0109*	5.000 1.448-17.271
Cyclosporine	21 44.68	28 59.57	0.1510	1.875 0.795-4.422
Sirolimus†	1 2.13	5 10.64	0.2188	5.000 0.559-236.488
Tacrolimus†	3 6.38	13 27.66	0.0063*	11.000 1.599-473.475
Glucocorticoids	19 40.43	43 91.49	0.0003*	9.000 2.730-29.667
Dexamethasone†	2 4.26	7 14.89	0.1182	3.500 0.727-16.848
Hydrocortisone†	2 4.26	8 17.02	0.0795	4.000 0.849-18.836
Methylprednisolone†	2 4.26	15 31.91	0.0074*	7.500 1.715-32.796
Prednisolone†	1 2.13	1 2.13	1.0000	1.000 0.013-78.497
Prednisone	17 36.17	37 78.72	0.0010*	5.000 1.914-13.061

*Statistically significant at $\alpha = 0.05$

†Exact p-values, excluded from multivariate analysis due to low cell counts

Only one patient took Rituximab in the 30 day period preceding the index date, therefore this medication was excluded from the table and only analyzed within the Immunosuppressants variable and the Immunosuppressants/Glucocorticoids variable.

Proton Pump Inhibitors

Medication	Control Frequency Percent	Case Frequency Percent	p-value	Odds Ratio 95% Confidence Interval
Proton Pump Inhibitors	34 72.34	37 78.72	0.4097	1.600 0.523-4.891
Esomeprazole†	1 2.13	2 4.26	0.5488	1.750 0.445-8.152
Lansoprazole	29 61.70	32 68.09	0.4931	1.375 0.553-3.418
Omeprazole†	4 8.51	7 14.89	1.0000	2.000 0.104-117.994
Pantoprazole†	3 6.38	4 8.51	1.0000	1.333 0.226-9.102

*Statistically significant at $\alpha = 0.05$

†Exact p-values, excluded from multivariate analysis due to low cell counts

Granulocyte Colony-stimulating Factors

Medication	Control Frequency Percent	Case Frequency Percent	p-value	Odds Ratio 95% Confidence Interval
Neupogen	5 10.64	10 21.28	0.1772	2.250 0.693-7.306

*Statistically significant at $\alpha = 0.05$

†Exact p-values, excluded from multivariate analysis due to low cell counts

Infections

Infection	Control Frequency Percent	Case Frequency Percent	p-value	Odds Ratio 95% Confidence Interval
Any Infections	6 12.77	22 46.81	0.003*	4.200 1.584-11.138
Bacteremia†	5 10.64	17 36.17	0.016*	3.400 1.254-9.216
Bacterial Pneumonia†	0 0.00	4 8.51	0.1250	5.285 0.660-Infinity
Fungal Pneumonia†	0 0.00	3 6.38	0.2500	3.847 0.413-Infinity
Viral Pneumonia†	1 2.13	0 0.00	1.0000	1.000 0-39.000
CNS - Bacterial†	0 0.00	1 2.13	1.0000	1.000 0.026-Infinity
CNS - Fungal†	0 0.00	1 2.13	1.0000	1.000 0.026-Infinity
Viral Gastroenteritis†	1 2.13	0 0.00	1.0000	1.000 0-39.000
VRE Colonization†	2 4.26	5 10.64	0.2734	2.500 0.485-12.886

*Statistically significant at $\alpha = 0.05$

†Exact p-values, excluded from multivariate analysis due to low cell counts

Univariate Analysis: Continuous Variables

	N	Mean	Med	Min	Max	Standard Deviation	p-value	Odds Ratio 95% Confidence Interval
Patient Age at Transplant							0.5598	0.991 0.960-1.022
Control	47	50.49	52.18	20.72	76.07	15.20		
Case	47	48.91	55.20	19.01	74.50	15.83		
Total Number of Days Hospitalized 30 Days Before Index Date							0.0014*	1.104 1.039-1.173
Control	47	2.77	0.00	0.00	30.00	7.37		
Case	47	10.53	10.00	0.00	30.00	8.93		
Total Number of Antibiotics							0.0008*	1.653 1.233-2.216
Control	47	1.77	1.00	0.00	7.00	1.72		
Case	47	3.47	4.00	0.00	9.00	1.77		
Plasma Creatinine, mg/dL							0.5618	1.307 0.529-3.225
Control	33	1.12	1.00	0.60	3.10	0.51		
Case	47	1.13	1.10	0.40	2.70	0.48		
White Blood Cell Count, K/cu mm							0.2053	1.067 0.965-1.181
Control	33	6.02	5.20	1.30	14.60	3.46		
Case	47	6.80	5.30	0.10	26.40	5.92		
Neutrophil Count, K/cu mm							0.1843	1.095 0.958-1.252
Control	33	4.20	3.50	0.60	12.80	2.89		
Case	47	4.77	3.00	0.00	19.50	4.52		
Lymphocyte Count, K/cu mm							0.1526	0.641 0.349-1.179
Control	33	1.00	0.60	5.00	0.10	0.95		
Case	47	0.53	0.30	0.00	5.20	0.83		
IgG Serum, mg/dL							0.0881	0.998 0.995-1.000
Control	21	747.00	612.00	163.00	2229.00	522.66		
Case	41	461.12	437.00	181.00	931.00	187.77		

*Statistically significant at $\alpha = 0.05$

Appendix H

Univariate Analysis: Patients Receiving Allogeneic Transplants

Demographics

Variable		Control Frequency Percent	Case Frequency Percent	p-value	Odds Ratio 95% Confidence Interval
Total		37	37		
Female		11 29.73	12 32.43	0.8085	1.125 0.434-2.916
Race†				1.0000	
	Black/African American	0 0.00	1 2.70	1.0000	1.000 0.026-Infinity
	Native Hawaiian/Pacific Islander	1 2.70	0 0.00	1.0000	1.000 0-39.000
	White	36 97.30	36 97.30		Referent
Ethnicity†					
	Not Hispanic or Latino	2 5.41	1 2.70	1.0000	1.000 0-39.000
	Hispanic or Latino	35 94.59	36 97.30		Referent

*Statistically significant at $\alpha = 0.05$

†Exact p-values, excluded from multivariate analysis due to low cell counts

Transplant Related Risk Factors

Variable	Control Frequency Percent	Case Frequency Percent	p-value	Odds Ratio 95% Confidence Interval
Total	37	37		
Underlying Disease†			0.0189*	
Acute Leukemia	15 40.54	23 62.16		
Chronic Leukemia	4 10.81	5 13.51	1.0000	0.649 0.038-10.329
Lymphoma	9 24.32	3 8.11	0.0670	0.142 0.003-1.093
Myelodysplatic or Myeloproliferative diseases	2 5.41	5 13.51	0.8611	1.694 0.232-19.256
Other Leukemia	5 13.51	1 2.70	0.0554	0.120 0-1.046
Plasma Cell Disorders	2 5.41	0 0.00	0.5217	0.432 0-5.560
Transplant Number†			0.6309	
1	29 78.38	29 78.38		Referent
2	5 13.51	7 18.92	0.8770	1.366 0.318-6.665
3	3 8.11	1 2.70	0.7000	0.366 0.007-4.601
Donor Relation			0.0825	
Related	20 54.05	12 32.43		Referent
Unrelated	17 45.95	25 67.57	0.0825	2.333 0.897-6.072
Conditioning Regimen			0.1664	
Myeloablative	24 64.86	28 75.68		Referent
Non-myeloablative	11 29.73	4 10.81	0.1061	0.333 0.088-1.264
None/Unknown	2 5.41	5 13.51	0.5636	1.667 0.294-9.434
Planned GVHD Prophylaxis†			0.1847	
None	2 5.41	5 13.51		
Cyclosporine	1 2.70	0 0.00	0.9552	0.914 0-35.656
Cyclosporine, Mycophenolate Mofetil	11 29.73	4 10.81	0.1886	0.217 0.016-1.679
Cyclosporine, Methotrexate	4 10.81	2 5.41	0.7057	0.342 0.015-5.352
Cyclosporine, Methotrexate, Prednisone	19 51.35	26 70.27	0.8851	0.606 0.054-4.317

*Statistically significant at $\alpha = 0.05$

†Exact p-values, excluded from multivariate analysis due to low cell counts

Co-morbidities

Variable	Control Frequency Percent	Case Frequency Percent	p-value	Odds Ratio 95% Confidence Interval
Total	37	37		
Diabetes	4 10.81	8 21.62	0.2577	2.000 0.602-6.642
History of C.Diff before Transplant†	0 0.00	7 18.92	0.0156*	9.607 1.441-Infinity

*Statistically significant at α = 0.05

†Exact p-values, excluded from multivariate analysis due to low cell counts

Transplant Complications

Variable	Control Frequency Percent	Case Frequency Percent	p-value	Odds Ratio 95% Confidence Interval
Total	37	37		
GI GVHD 30 Days Before Index Date†	2 5.41	11 29.73	0.0117*	10.000 1.423-433.977
GVHD Grade†			0.0054*	
None	35 94.59	26 70.27		Referent
Acute GI GVHD	2 5.41	3 8.11	0.6250	3.000 0.241-157.492
Chronic GI GVHD	0 0.00	8 21.62	0.0063*	11.728 1.806-Infinity
GI GVHD 30 Days Before Index Date or 14 Days After Index Date†	2 5.41	15 40.54	0.0010*	14.000 2.130-591.968
Mucositis 30 Days Before Index Date	8 21.62	9 24.32	0.7064	1.333 0.298-5.957
Mucositis Severity			0.5000	
None	29 78.38	28 75.68		Referent
Mucositis, PO Nutrition	7 18.92	5 13.51	1.0000	0.721 0.060-6.338
Mucositis, IV Nutrition	1 2.70	4 10.81	0.5333	3.317 0.295-170.645
CMV Reactivation 30 Days before Infection	9 24.32	9 24.32	1.0000	1.000 0.290-3.454
Disease Relapse†	1 2.70	5 13.51	0.1250	5.285 0.660-Infinity

*Statistically significant at α = 0.05

†Exact p-values, excluded from multivariate analysis due to low cell counts

Antibiotic Classes

Class	Control Frequency Percent	Case Frequency Percent	p-value	Odds Ratio 95% Confidence Interval
Any Antibiotics	37 100.00	37 100.00		
Aminoglycoside†	1 2.70	1 2.70	1.0000	1.000 0.013-78.497
Aminopenicillin†	1 2.70	1 2.70	1.0000	1.000 0.013-78.497
Antibacterial - Folate Antagonist	25 67.57	24 64.86	0.7964	0.875 0.317-2.413
Antileprotic - Sulfone Agent	5 13.51	4 10.81	1.0000	0.800 0.159-3.717
Antiprotozoal/Antibacterial†	0 0.00	3 8.11	0.2500	3.847 0.413-Infinity
Carbapenem	10 27.03	14 37.84	0.2920	1.800 0.603-5.371
Cephalosporin - 1st Generation†	0 0.00	2 5.41	0.5000	2.414 0.188-Infinity
Cephalosporin - 3rd Generation†	4 10.81	5 13.51	1.0000	1.250 0.269-6.300
Cephalosporin - 4th Generation†	1 2.70	5 13.51	0.2188	5.000 0.559-236.488
Cyclic Lipopeptide†	0 0.00	2 5.41	0.5000	2.414 0.188-Infinity
Fluoroquinolone	18 48.65	17 45.95	0.8085	0.889 0.343-2.304
Glycopeptide	13 35.14	22 59.46	0.0681	2.286 0.940-5.556
Lincosamide†	2 5.41	1 2.70	1.0000	0.500 0.008-9.605
Macrolide†	1 2.70	3 8.11	0.6250	3.000 0.241-157.492
Misc Anti-Infective†	2 5.41	7 18.92	0.1250	6.000 0.728-275.986
Monobactam†	0 0.00	3 8.11	0.2500	3.847 0.413-Infinity
Oxazolidinone†	4 10.81	3 8.11	1.0000	0.750 0.110-4.433
Penicillin†	1 2.70	4 10.81	0.3750	4.000 0.396-196.990

*Statistically significant at $\alpha = 0.05$

†Exact p-values, excluded from multivariate analysis due to low cell counts

Antidiarrheals

Medication	Control Frequency Percent	Case Frequency Percent	p-value	Odds Ratio 95% Confidence Interval
Antidiarrheals	16 43.24	21 56.76	0.2571	1.714 0.675-4.354
Imodium	16 43.24	20 54.05	0.4807	1.571 0.556-4.781

*Statistically significant at α = 0.05

†Exact p-values, excluded from multivariate analysis due to low cell counts

Only one patient took Kaopectate in the 30 day period preceding the index date, therefore this medication was excluded from the table and only analyzed within the Antidiarrheals variable.

Immunosuppressants/Glucocorticoids

Medication	Control Frequency Percent	Case Frequency Percent	p-value	Odds Ratio 95% Confidence Interval
Immunosuppressants	35 94.59	36 97.30	1.0000	2.000 0.104-117.994
Non-steroid Immunosuppressants	33 89.19	33 89.19	1.000	1.000 0.186-5.369
Cellcept	7 18.92	11 29.73	0.3226	1.667 0.606-4.586
Cyclosporine	31 83.78	26 70.27	0.1474	0.375 0.099-1.414
Sirolimus †	1 2.70	1 2.70	1.0000	1.000 0.013-78.497
Tacrolimus †	3 8.11	7 18.92	0.2188	5.000 0.559-236.488
Glucocorticoids	25 67.57	33 89.19	0.0461*	3.667 1.023-13.143
Dexamethasone	9 24.32	10 27.03	0.7394	1.250 0.336-4.655
Hydrocortisone	7 18.92	9 24.32	0.5299	1.500 0.423-5.315
Methylprednisolone	6 16.22	13 35.14	0.0832	2.750 0.876-8.636
Prednisolone†	1 2.70	0 0.00	1.0000	1.000 0-39.000
Prednisone	15 40.54	24 64.86	0.0266*	5.500 1.219-24.813

*Statistically significant at α = 0.05

†Exact p-values, excluded from multivariate analysis due to low cell counts

Only one patient took Rituximab in the 30 day period preceding the index date, therefore this medication was excluded from the table and only analyzed within the Immunosuppressants and Immunosuppressants/Glucocorticoids variables.

Proton Pump Inhibitors

Medication	Control Frequency Percent	Case Frequency Percent	p-value	Odds Ratio 95% Confidence Interval
Proton Pump Inhibitors	29 78.38	27 72.97	0.5655	0.714 0.227-2.251
Esomeprazole†	1 2.70	0 0.00	1.0000	1.000 0-39.000
Lansoprazole	24 64.86	27 72.97	0.4417	1.500 0.534-4.214
Omeprazole	2 5.41	3 8.11	1.0000	1.500 0.172-17.959
Pantoprazole	2 5.41	3 8.11	1.0000	1.500 0.172-17.959

*Statistically significant at $\alpha = 0.05$

†Exact p-values, excluded from multivariate analysis due to low cell counts

Granulocyte Colony-stimulating Factors

Medication	Control Frequency Percent	Case Frequency Percent	p-value	Odds Ratio 95% Confidence Interval
Neupogen	8 21.62	13 35.14	0.1772	2.250 0.693-7.306

*Statistically significant at $\alpha = 0.05$

†Exact p-values, excluded from multivariate analysis due to low cell counts

Infections

Infection	Control Frequency Percent	Case Frequency Percent	p-value	Odds Ratio 95% Confidence Interval
Any Infections	12 32.43	16 43.24	0.5413	1.400 0.578-3.523
Bacteremia	10 27.03	10 27.03	1.0000	1.000 0.416-2.403
Bacterial Pneumonia†	0 0.00	3 8.11	0.2500	3.847 0.413-Infinity
Fungal Pneumonia†	0 0.00	2 5.41	0.5000	2.414 0.188-Infinity
Viral Pneumonia†	2 5.41	0 0.00	0.5000	0.414 0-5.325
CNS - Bacterial†	0 0.00	1 2.70	1.0000	1.000 0.026-Infinity
CNS - Fungal†	0 0.00	1 2.70	1.0000	1.000 0.026-Infinity
Viral Gastroenteritis†	1 2.70	1 2.70	1.0000	1.000 0.013-78.497
VRE Colonization	7 18.92	6 16.22	0.7817	0.857 0.288-2.550

*Statistically significant at $\alpha = 0.05$

†Exact p-values, excluded from multivariate analysis due to low cell counts

Univariate Analysis: Continuous Variables

	N	Mean	Med	Min	Max	Standard Deviation	p-value	Odds Ratio 95% Confidence Interval
Patient Age at Transplant							0.2876	1.017 0.985-1.051
Control	37	46.69	49.33	20.21	72.31	15.32		
Case	37	50.41	55.20	21.55	71.52	14.65		
Total Number of Days Hospitalized 30 Days Before Index Date							0.0331*	1.067 1.005-1.133
Control	37	6.46	0.00	0.00	30.00	9.20		
Case	37	11.65	10.00	0.00	30.00	8.93		
Total Number of Antibiotics							0.0533	1.335 0.996-1.789
Control	37	2.51	2.00	1.00	8.00	1.79		
Case	37	3.35	3.00	1.00	7.00	1.55		
Plasma Creatinine, mg/dL							0.7616	1.142 0.485-2.691
Control	34	1.16	1.00	0.60	3.10	0.55		
Case	37	1.16	1.00	0.40	3.10	0.54		
White Blood Cell Count, K/cu mm							0.2916	1.062 0.949-1.189
Control	34	5.09	4.65	0.10	14.60	3.78		
Case	37	5.98	4.50	0.10	23.50	5.91		
Neutrophil Count, K/cu mm							0.2582	1.085 0.942-1.251
Control	34	3.63	3.35	0.20	10.90	2.80		
Case	37	4.46	2.70	0.00	19.50	4.89		
Lymphocyte Count, K/cu mm							0.1298	0.477 0.183-1.243
Control	34	0.80	0.60	0.00	5.00	0.94		
Case	37	0.46	0.30	0.00	2.40	0.50		
IgG Serum, mg/dL							0.0572	0.997 0.994-1.000
Control	31	699.29	612.00	163.00	2229.00	426.27		
Case	33	505.58	492.00	181.00	1140.00	222.25		

*Statistically significant at $\alpha = 0.05$

Appendix I

Univariate Analysis Significant Results: Odds Ratios

Variable	All Infections N=102	Early Infections N=55	Late Infections N=47	Allogeneic Only N=37
Female	1.667 0.929-2.990	2.833 1.117-7.186	1.083 0.494-2.374	1.125 0.434-2.916
Underlying Disease	†	†	†	†
Acute Leukemia	Referent	Referent	Referent	Referent
Chronic Leukemia	0.633 0.074-5.233	1.462 0.070-91.900	0.273 0.004-6.480	0.649 0.038-10.329
Lymphoma	0.335 0.141-0.740	0.466 0.155-1.287	0.200 0.035-0.771	0.142 0.003-1.093
Myelodysplatic or Myeloproliferative diseases	1.251 0.309-6.032	2.128 0.342-23.084	0.442 0.024-7.694	1.694 0.232-19.256
Other Leukemia	0.294 0.023-2.333	0.414 0-5.325	0.273 0.004-6.480	0.120 0-1.046
Plasma Cell Disorders	0.170 0.038-0.583	0.362 0.076-1.389	0.062 0-0.488	0.432 0-5.560
Solid Tumor	0.152 0.003-1.695	0.293 0-3.863	0.273 0.004-6.480	0.649 0.038-10.329
Transplant Type				N/A
Autologous	Referent	Referent	Referent	N/A
Allogeneic	2.667 1.473-4.827	1.357 0.680-2.707	20.000 3.199-828.956	N/A
Donor Relation			†	

Variable	All Infections N=102	Early Infections N=55	Late Infections N=47	Allogeneic Only N=37
Autologous/Syngeneic	Referent	Referent	Referent	N/A
Related	1.569 0.778-3.162	0.721 0.291-1.784	13.044 1.851-571.966	Referent
Unrelated	4.303 2.042-9.069	2.615 1.006-6.798	25.845 3.746->999.999	2.333 0.897-6.072
Planned GVHD Prophylaxis	†	†	†	†
None	Referent	Referent	Referent	Referent
Cyclosporine	2.282 0-88.995	None	7.894 0-307.858	0.914 0-35.656
Cyclosporine, Mycophenolate Mofetil	1.485 0.518-4.329	0.259 0.005-2.664	4.813 1.059-31.730	0.217 0.016-1.679
Cyclosporine, Methotrexate	2.565 0.729-10.393	6.986 0.898-314.857	2.534 0.158-33.656	0.342 0.015-5.352
Cyclosporine, Methotrexate, Prednisone	2.208 1.161-4.365	1.044 0.442-2.476	7.286 1.970-41.450	0.606 0.054-4.317
Tacrolimus, Methotrexate, Prednisone	1.000 0.026-Infinity	1.000 0.026-Infinity	None	None

Variable	All Infections N=102	Early Infections N=55	Late Infections N=47	Allogeneic Only N=37
Diabetes	2.143 0.874-5.256	1.000† 0.230-4.345	5.000† 1.096-22.820	2.000 0.602-6.642
History of C.Diff before Transplant	11.000† 1.599-473.475	6.000† 0.728-275.986	6.725† 0.916-Infinity	9.607 1.441-Infinity
GI GVHD 30 Days Before Index Date	19.000† 3.020-789.458	2.414† 0.188-Infinity	17.000† 2.664-710.462	10.000 1.423-433.977
GVHD Grade	†	†	†	†
None	Referent	Referent	Referent	Referent
Acute GI GVHD	9.000 1.247-394.479	2.414† 0.188-Infinity	7.000 0.899-315.483	3.000 0.241-157.492
Chronic GI GVHD	19.930 3.104-Infinity	None	18.682 2.962-Infinity	11.728 1.806-Infinity
GI GVHD 30 Days Before Index Date or 14 Days After Index Date	29.000† 4.808->999.999	8.166† 1.177-Infinity	23.000† 3.735-947.449	14.000 2.130-591.968
CMV Reactivation 30 Days before Infection	2.667 1.043-6.815	4.000† 0.447-35.788	2.400 0.846-6.812	1.000 0.290-3.454
Disease Relapse	18.259† 3.048-Infinity	1.000† 0.026-Infinity	16.817† 2.779-Infinity	5.285 0.660-Infinity
Any Antibiotics	9.607 1.441-Infinity	1.000 0.026-Infinity	8.166 1.177-Infinity	N/A
Carbapenem	2.308 1.204-4.424	1.750 0.734-4.172	3.200 1.172-8.735	1.800 0.603-5.371
Fluoroquinolone	0.875 0.487-1.572	0.333 0.121-0.917	1.778 0.786-4.023	0.889 0.343-2.304
Glycopeptide	4.333 2.099-8.945	3.167 1.265-7.929	6.667 1.981-22.435	2.286 0.940-5.556
Misc Anti-Infective	2.857 1.208-6.757	1.400 0.444-4.411	6.500† 1.472-59.329	6.000† 0.728-275.986
Penicillin	11.000† 1.599-473.475	3.847† 0.413-Infinity	8.000† 1.073-354.981	4.000† 0.396-196.990
Immunosuppressants	2.778 1.297-5.951	1.000 0.351-2.851	9.000† 2.155-79.981	2.000† 0.104-117.994
Non-steroid Immunosuppressants	2.500 1.400-4.464	1.462 0.722-2.959	7.000† 2.088-23.468	1.000† 0.186-5.369
Cellcept	2.571 1.074-6.156	0.750 0.110-4.433	5.000† 1.448-17.271	1.667 0.606-4.586

Variable	All Infections N=102	Early Infections N=55	Late Infections N=47	Allogeneic Only N=37
Tacrolimus	15.000† 2.308-631.466	5.285† 0.660-Infinity	11.000† 1.599-473.475	5.000† 0.559-236.488
Glucocorticoids	2.833 1.467-5.472	0.778 0.290-2.088	9.000 2.730-29.667	3.667† 1.023-13.143
Dexamethasone	0.737 0.369-1.470	0.412 0.171-0.993	3.500 0.727-16.848	1.250 0.336-4.655
Methylprednisolone	3.250 1.471-7.178	1.833 0.678-4.957	7.500† 1.715-32.796	2.750 0.876-8.636
Prednisone	4.222 2.042-8.732	3.250 1.060-9.967	5.000 1.914-13.061	5.500 1.219-24.813
Any Infections	2.846 1.513-5.354	2.000 0.856-4.673	4.200 1.584-11.138	1.400 0.578-3.523
Bacteremia	2.636 1.317-5.277	2.000 0.751-5.329	3.400 1.254-9.216	1.000 0.416-2.403
Total Number of Days Hospitalized 30 Days Before Index Date (1 day increase)	1.099 1.051-1.150	1.093 1.021-1.170	1.104 1.039-1.173	1.067 1.005-1.133
Total Number of Antibiotics (1 antibiotic increase)	1.407 1.153-1.716	1.111 0.820-1.504	1.653 1.233-2.216	1.335 0.996-1.789

†Variables with cell counts $\leq$ 5.

Statistically significant at $\alpha = 0.05$

Appendix J

Multivariate Analysis: Early Infections

Variable	Controls Frequency Percent N=102	Cases Frequency Percent N=102	Crude Odds Ratio 95% Confidence Interval	Adjusted Odds Ratio 95% Confidence Interval
Female	14 25.45	25 45.45	2.83* 1.12-7.19	
GI GVHD 30 Days Before Index Date or 14 Days After Index Date†	0 0.00	6 10.91	8.17* 1.18-Infinity	
Transplant Type: Allogeneic	27 49.09	32 58.18	1.36 0.68-2.71	1.42 0.58-3.46
Donor Relation				
Autologous/Syngeneic	28 50.91	23 41.82	Referent	
Related	15 27.27	9 16.36	0.72 0.29-1.78	
Unrelated	12 21.82	23 41.82	2.62* 1.01-6.80	
Medications				
Fluoroquinolone	47 85.45	37 67.27	0.33* 0.12-0.92	
Glycopeptide	22 40.00	35 63.64	3.17* 1.27-7.93	
Dexamethasone	35 63.64	25 45.45	0.41* 0.17-0.99	0.26* 0.09-0.78
Prednisone†	6 10.91	15 27.27	3.250* 1.060-9.967	
Total Number of Days Hospitalized 30 Days Before Index Date	12.76	17.33	1.09* 1.02-1.17	1.14* 1.04-1.25
Patient Age at Transplant	50.37	52.48	1.02 0.98-1.05	0.99 0.99-1.10

*Statistically significant at $\alpha = 0.05$ Multivariate R^2=0.1760, AIC=62.948

†Cell count ≤ 5

Appendix K

Multivariate Analysis: Late Infections

Variable	Controls Frequency Percent N=47	Cases Frequency Percent N=47	Crude Odds Ratio 95% Confidence Interval	Adjusted Odds Ratio 95% Confidence Interval
Transplant Type†				
Autologous	23 48.94	4 8.51	Referent	
Allogeneic	24 51.06	43 91.49	20.00* 3.20-828.96	
Donor Relation†				
Autologous/Syngeneic	23 48.94	4 8.51	Referent	
Related	14 29.79	16 34.04	13.04* 1.85-571.97	
Unrelated	10 21.28	27 57.45	25.85* 3.75->999.999	
Diabetes†	2 4.26	10 21.28	5.00* 1.10-22.82	
History of C.Diff before Transplant†	0 0.00	5 10.64	6.725 0.916-Infinity	
GI GVHD 30 Days Before Index Date†	2 4.26	18 38.30	17.00* 2.66-710.46	
GI GVHD 30 Days Before Index Date or 14 Days After Index Date†	2 4.26	24 51.06	23.00* 3.74-947.45	
Disease Relapse†	1 2.13	13 27.66	16.82 2.78-Infinity	
Any Infections†	6 12.77	22 46.81	4.20* 1.58-11.14	
Bacteremia†	5 10.64	17 36.17	3.40* 1.25-9.22	
Any Antibiotics†	40 85.11	46 97.87	8.17* 1.18-Infinity	
Carbapenem	7 14.89	18 38.30	3.20* 1.17-8.74	
Cephalosporin – 3rd Generation†	3 6.38	13 27.66	4.333* 1.19-23.71	
Glycopeptide	9 19.15	26 55.32	6.67* 1.98-22.44	
Misc Anti-Infective†	3 6.38	14 29.79	6.50* 1.47-59.33	
Penicillin†	1 2.13	8 17.02	8.00* 1.07-354.98	
Immunosuppressants†	28 59.57	44 93.62	9.00* 2.16-79.98	

Variable	Controls Frequency Percent N=47	Cases Frequency Percent N=47	Crude Odds Ratio 95% Confidence Interval	Adjusted Odds Ratio 95% Confidence Interval
Non-steroid Immunosuppressants	23 48.94	41 87.23	7.00* 2.09-23.47	
Glucocorticoids	19 40.43	43 91.49	9.00* 2.73-29.67	8.49* 2.08-34.55
Prednisone	17 36.17	37 78.72	5.00* 1.91-13.06	
Patient Age at Transplant	50.49	48.91	0.99 0.96-1.02	1.04 0.98-1.10
Total Number of Antibiotics in the 30 Days Before Index Date	1.77	3.47	1.65* 1.23-2.22	1.86* 1.17-2.96
Total Number of Days Hospitalized 30 Days Before Index Date	2.77	10.53	1.10* 1.04-1.17	

*Statistically significant at $\alpha = 0.05$ Multivariate R^2=0.2918, AIC=38.724

†Cell count ≤ 5

Appendix L

Clostridium difficile Infections: Antibiotic Use and Donor Relation

3rd Generation Cephalosporin Use by Donor Relation

Donor Relation	3rd Generation Cephalosporins	Control		Case	
Autologous/Syngeneic	No	36	35.29%	9	8.82%
	Yes	15	14.71%	18	17.65%
Related	No	25	24.51%	23	22.55%
	Yes	4	3.92%	2	1.96%
Unrelated	No	21	20.59%	38	37.25%
	Yes	1	0.98%	12	11.76%

Glycopeptide Use by Donor Relation

Donor Relation	Glycopeptide	Control		Case	
Autologous/Syngeneic	No	36	35.29%	9	8.82%
	Yes	15	14.71%	18	17.65%
Related	No	18	17.65%	12	11.76%
	Yes	11	10.78%	13	12.75%
Unrelated	No	17	16.67%	20	19.61%
	Yes	5	4.90%	30	29.41%

Carbapenem Use by Donor Relation

Donor Relation	Carbapenem	Control		Case	
Autologous/Syngeneic	No	40	39.22%	18	17.65%
	Yes	11	10.78%	9	8.82%
Related	No	19	18.63%	14	13.73%
	Yes	10	9.80%	11	10.78%
Unrelated	No	15	14.71%	25	24.51%
	Yes	7	6.86%	25	24.51%

Misc. Anti-Infective Use by Donor Relation

Donor Relation	Misc. Anti-Infective	Control		Case	
Autologous/Syngeneic	No	49	48.04%	25	24.51%
	Yes	2	1.96%	2	1.96%
Related	No	25	24.51%	21	20.59%
	Yes	4	3.92%	4	3.92%
Unrelated	No	19	18.63%	34	33.33%
	Yes	3	2.94%	16	15.69%

Pre-Transplant Essential Data

CENTER IDENTIFICATION

CIBMTR Center # _____ EBMT Code (CIC) _____
Hospital: _____
Unit (circle)*: **A H O P** Other, specify: _____
*** Abbreviations, see pg 2**

Contact person: _____
Phone #: _____ Fax #: _____

Email: _____
Date of this Report: ___ ____ ___ - ____ - ____ ❑ changed
YYYY MM DD

CIBMTR USE ONLY
Report Form due? ❑Yes ❑No ❑Reg only
Date Received: _____ DE: _____

RECIPIENT IDENTIFICATION

Universal recipient ID#: _____
ID assigned by: ❑CIBMTR ❑EBMT ❑Other _____
Study ID #: _____ ❑BMT-CTN ❑NMDP ❑RCI-BMT ❑SCTOD
Consented for Research? ❑ Yes ❑ No
Consented for CIBMTR Related Specimen Repository? ❑Yes ❑No
Gender: ❑ Male ❑ Female
Date of Birth: ___ ____ ___ - ____ - ____
YYYY MM DD

Optional for non-US centers:
Ethnicity: ❑ Hispanic or Latino ❑ Not Hispanic or Latino
Race (*check all that apply*): ❑White ❑Black/African American ❑Asian
❑ American Indian/Alaska Native
❑ Native Hawaiian/Other Pacific Islander

DISEASE CLASSIFICATION

*Complete and attach **only** the relevant Disease Classification Sheet with date and status at transplantation:*

Date of diagnosis of primary disease for HSCT:
___ ____ ___ - ____ - ____
YYYY MM DD

HEMATOPOIETIC STEM CELL TRANSPLANT (HSCT)

Date of this HSCT: ___ ____ ___ - ____ - ____
YYYY MM DD

Chronological number of this HSCT: _____
If >1, most recent previous HSCT:
Date: ___ ____ ___ - ____ - ____
YYYY MM DD
Type: ❑ Auto ❑ Allo

Institution where previous HSCT was performed if different from current:
Name: _____
City: _____ State: _____
Country: _____

Cell source for this HSCT (check all that apply):
❑ BM ❑ PBSC ❑ UCB ❑ Other: _____

Allo HSCT (for multiple donors check all that apply):
donor gender: ❑ Male ❑ Female

Donor Type:
❑ Autologous (self) ❑ Multiple donors (skip HLA match only)
Allogeneic:
❑ Syngeneic (monozygotic twin)
❑ HLA-identical sibling (may include non-monozygotic twin)
❑ HLA-matched other relative
❑ HLA-mismatched relative
Degree of mismatch: ❑ 1 HLA antigen mismatch
❑ ≥ 2 HLA antigen mismatch (full Haploidentical)

❑ Unrelated donor (complete # of mismatches on HLA lines)
Registry or UCB Bank: Other, specify:
❑ __ __ __ __ _____
❑ __ __ __ __ _____

A	B	C	DRB1	DQB1	DPB1	
__	__	__	__	__	__	Antigenic (2 digits)
__	__	__	__	__	__	Allelic (4 digits)

0=matched; 1=one mismatch; 2=2 mismatches; ND=not done

HSCT *(continued)*

Was there **Ex vivo Graft Manipulation** other than for RBC removal or volume reduction? ❑ Yes ❑ No
(Check all that apply) Optional for non-U.S. Centers
❑ T-cell depletion
❑ Tumor purging
❑ Other negative selection, specify: _____
❑ CD34 selection
❑ ex vivo expansion
❑ Other, specify: _____

Performance Score pre-Preparative Regimen: ❑ Karnofsky ❑ Lansky
❑ 10 ❑ 20 ❑ 30 ❑ 40 ❑ 50 ❑ 60 ❑ 70 ❑ 80 ❑ 90 ❑ 100

CMV-antibodies (IgG or Total) (Multiple donors: report any positive CMV test as reactive)

	reactive	non-reactive	unknown	not done
Recipient:	❑	❑	❑	❑
Donor (allo only):	❑	❑	❑	❑

PREPARATIVE REGIMEN

Was a preparative regimen given? ❑ Yes ❑ No – *skip to page 2*
What was the total prescribed cumulative dose for the preparative regimen (per the protocol)?

(Check all that apply)	RAD unit cGy	Total Prescribed Dose Gy	mg/m²	mg/kg
❑ TBI	___ ___ ___ ___ ❑	❑		
❑ TLI, TNI, TAI	___ ___ ___ ___ ❑	❑		
❑ ALG, ALS, ATG, ATS (before d0)	___ ___ ___ ___		❑	❑
❑Horse ❑Rabbit ❑Other, specify: _____				
❑ anthracycline				
❑ daunorubicin	___ ___ ___ ___		❑	❑
❑ doxorubicin	___ ___ ___ ___		❑	❑
❑ idarubicin	___ ___ ___ ___		❑	❑
❑ bleomycin	___ ___ ___ ___		❑	❑
❑ busulfan	___ ___ ___ ___		❑	❑
❑Oral ❑IV ❑Both				
❑ carboplatin	___ ___ ___ ___		❑	❑
❑ carmustine (BCNU)	___ ___ ___ ___		❑	❑
❑ cisplatin	___ ___ ___ ___		❑	❑
❑ corticosteroids	___ ___ ___ ___		❑	❑
❑ cyclophosphamide	___ ___ ___ ___		❑	❑
❑ cytarabine (Ara-C)	___ ___ ___ ___		❑	❑
❑ etoposide (VP-16)	___ ___ ___ ___		❑	❑
❑ fludarabine	___ ___ ___ ___		❑	❑
❑ ifosfamide	___ ___ ___ ___		❑	❑
❑ imatinib mesylate (Gleevec, Glivec)	___ ___ ___ ___		❑	❑
❑ lomustine (CCNU)	___ ___ ___ ___		❑	❑
❑ melphalan (L-PAM)	___ ___ ___ ___		❑	❑
❑ mitoxantrone	___ ___ ___ ___		❑	❑
❑ monoclonal antibody (MAb)				
❑ Campath	___ ___ ___ ___		❑	❑
❑ Rituximab (Rituxan, anti-CD20)	___ ___ ___ ___		❑	❑
❑ Gemtuzumab (Mylotarg, anti-CD33)	___ ___ ___ ___		❑	❑
❑ Other MAb specify: _____	___ ___ ___ ___		❑	❑
❑ paclitaxel (Taxol, Xyotax)	___ ___ ___ ___		❑	❑
❑ teniposide (VM26)	___ ___ ___ ___		❑	❑
❑ thiotepa	___ ___ ___ ___		❑	❑
❑ other, specify: _____	___ ___ ___ ___		❑	❑
❑ radiolabeled MAb	units ❑mCi ❑mBq			
❑ Tositumomab (Bexxar)	___ ___ ___ . ___			
❑ Ibritumomab (Zevalin)	___ ___ ___ . ___			
❑ Other rMab specify: _____	___ ___ ___ . ___			

Is the INTENT of the preparative regimen MYELOABLATIVE (allo only)? ❑ Yes ❑ No, reason for NST/RIC (check all that apply):
❑ Age of recipient
❑ Comorbid conditions
❑ Prior HSCT
❑ Protocol-driven
❑ Other, specify: _____

Pre-Transplant Essential Data

CIBMTR Center #: ☐☐☐☐☐ CIBMTR Recipient ID#: ☐☐☐☐☐☐☐☐☐☐

This section is optional for non-U.S. Centers

COMORBID CONDITIONS

Is there a history of mechanical ventilation? ❑ Yes ❑ No
Is there a history of proven invasive fungal infection? ❑ Yes ❑ No

Were there ***clinically significant*** co-existing disease or organ impairment at time of patient assessment prior to preparative regimen?
❑ Yes ❑ No 'Allo' continue with ***Box A*** below, 'auto' continue with ***Box B*** below

Yes	No	NotDone	Comorbidity	Definitions
❑	❑	❑	Arrhythmia	Atrial fibrillation or flutter, sick sinus syndrome, or ventricular arrhythmias
❑	❑	❑	Cardiac	Coronary artery disease §, congestive heart failure, myocardial infarction, or EF ≤ 50%
❑	❑	❑	Cerebrovascular disease	Transient ischemic attack or cerebrovascular accident
❑	❑	❑	Diabetes	Requiring treatment with insulin or oral hypoglycemics but not diet alone
❑	❑	❑	Heart valve disease	Except mitral valve prolapse
❑	❑	❑	Hepatic, mild	Chronic hepatitis, bilirubin > ULN to 1.5 × ULN, or AST/ALT > ULN to 2.5 × ULN
❑	❑	❑	Hepatic, moderate/severe	Liver cirrhosis, bilirubin > 1.5 × ULN, or AST/ALT > 2.5 × ULN
❑	❑	❑	Infection	Requiring continuation of antimicrobial treatment after day 0
❑	❑	❑	Inflammatory bowel disease	Crohn's disease or ulcerative colitis
❑	❑	❑	Obesity	Patients with a body mass index > 35 kg/m^2
❑	❑	❑	Peptic ulcer	Requiring treatment
❑	❑	❑	Psychiatric disturbance	Depression or anxiety requiring psychiatric consult or treatment
❑	❑	❑	Pulmonary, moderate	DLco and/or FEV$_1$ 66-80% or dyspnea on slight activity
❑	❑	❑	Pulmonary, severe	DLco and/or FEV$_1$ ≤ 65% or dyspnea at rest or requiring oxygen
❑	❑	❑	Renal, moderate/severe	Serum creatinine > 2 mg/dL or >177 μmol/L, on dialysis, or prior renal transplantation
❑	❑	❑	Rheumatologic	SLE, RA, polymyositis, mixed CTD, or polymyalgia rheumatica
❑	❑	❑	Solid tumor, prior	Treated at any time point in the patient's past history, excluding nonmelanoma skin cancer
❑	❑	❑	Other	Specify:_____

§ One or more vessel-coronary artery stenosis requiring medical treatment, stent, or bypass graft.
EF indicates ejection fraction; ULN, upper limit of normal; SLE, systemic lupus erythmatosis; RA, rheumatoid arthritis; CTD, connective tissue disease; DLco, diffusion capacity of carbon monoxide.

Source: Blood, 2005 Oct 15;106(8):2912-2919

Box A **GVHD PROPHYLAXIS (ALLO ONLY)**

Was **GVHD** prophylaxis planned/given? ❑ Yes ❑ No
(Check all that apply)

- ❑ ALG, ALS, ATG, ATS (after d0)
- ❑ Corticosteroids
- ❑ Cyclosporine (CSA)
- ❑ ECP (extra-corporeal photopheresis)
- ❑ FK 506 (Tacrolimus, Prograf)
- ❑ Methotrexate (MTX)
- ❑ in vivo monoclonal antibody (MAb)
  - ❑ Anti CD25 (Zenapax, Daclizumab, AntiTAC)
  - ❑ Campath
  - ❑ Etanercept (Enbrel)
  - ❑ Infliximab (Remicade)
  - ❑ Other, specify:_____
- ❑ Mycophenolate (MMF, Cellcept)
- ❑ Sirolimus (Rapamycin, Rapamune)
- ❑ Other drug, specify:_____

Box B **POST-HSCT DISEASE THERAPY PLANNED AS OF DAY 0**

Is this HSCT part of a **planned multiple** (sequential) graft/HSCT protocol? ❑ Yes ❑ No

Is additional **post-HSCT therapy planned**?
❑ Yes ❑ No

(Check all that apply) Optional for non-U.S. centers

- ❑ bortezomib (Velcade)
- ❑ Cellular therapy (e.g. DCI, DLI)
- ❑ Intrathecal Chemotherapy
- ❑ imatinib mesylate (Gleevec, Glivec)
- ❑ lenalidomide (Revlimid)
- ❑ Local radiotherapy
- ❑ rituximab (Rituxan, Mabthera)
- ❑ thalidomide (Thalomid)
- ❑ Other, specify:_____

OTHER TOXICITY MODIFYING REGIMEN

Optional for non-U.S. Centers

Was KGF (palifermin, Kepivance) started or is there a plan to use it?
❑ Yes ❑ No ❑ Masked trial

Was FGF (velafermin) started or is there a plan to use it?
❑ Yes ❑ No ❑ Masked trial

* Abbreviations

YYYY = 4 digit year
MM = 2 digit month
DD = 2 digit day
AHOP = Adult, Hematology, Oncology or Pediatric Unit
ALLO = Allogeneic
ANC = Absolute Neutrophil Count
AUTO = Autologous
BM = Bone Marrow
BMT-CTN = Blood & Marrow Transplant Clinical Trials Network
CIBMTR = Center for International Blood & Marrow Transplant Research
CIC = Center Identification Code
CMV = Cytomegalovirus
CR = Complete Remission
DCI = Donor Cellular Infusion
DLI = Donor Lymphocyte Infusion
EBMT = European Group for Blood & Marrow Transplantation
EBV = Epstein Barr Virus
FACT = Foundation for the Accreditation of Cellular Therapy
FGF = Fibroblast Growth Factor
FISH = Fluorescent In-situ Hybridization
GVHD = Graft versus Host Disease
HSCT = Hematopoietic Stem Cell Transplant
KGF = Keratinocyte Growth Factor
NMDP = National Marrow Donor Program
NOS = Not Otherwise Specified
NST = Non-myeloablative Stem Cell Transplant
PBSC = Peripheral Blood Stem Cells
PTLD = Posttransplant lymphoproliferative disorder
RBC = Red Blood Cell
RCI-BMT = Resource for Clinical Investigations in Blood & Marrow Transplant
RIC = Reduced Intensity Conditioning
SCTOD = Stem Cell Therapeutic Outcomes Database
TBI, TLI, TNT = Total (Body, Lymphoid, Nodal) Irradiation
U = Unclassifiable
UCB = Umbilical Cord Blood
Unit = Adult, Hematology, Oncology, Pediatric (AHOP)
VOD = Veno-occlusive disease

Pre-Transplant Essential Data
Disease Classification Sheet

CIBMTR Center #: ☐☐☐☐☐ CIBMTR Recipient ID#: ☐☐☐☐☐☐☐☐☐☐

ACUTE LEUKEMIAS

Select most specific W.H.O. classification:

Acute Myelogenous Leukemia (AML)

AML with recurrent genetic abnormalities

- ❑ AML with t(8;21)(q22;q22), (AML1/ETO) (281)
- ❑ AML with abnormal BM eosinophils and inv(16)(p13q22) or t(16;16)(p13;q22), (CBFβ/MYH11) (282)
- ❑ APL with t(15;17)(q22;q12), (PML/RARα) and variants/{M3} (283)
- ❑ AML with 11q23 (MLL) abnormalities (284)
- ❑ AML with multilineage dysplasia (285)

AML, not otherwise categorized/{NOS}

- ❑ AML, minimally differentiated/{M0} (286)
- ❑ AML without maturation/{M1} (287)
- ❑ AML with maturation/{M2} (288)
- ❑ Acute Myelomonocytic Leukemia/{M4} (289)
- ❑ Acute Monoblastic/Acute Monocytic Leukemia/{M5} (290)
- ❑ Acute Erythroid Leukemia (erythroid/ myeloid and pure erythroleukemia)/{M6} (291)
- ❑ Acute Megakaryoblastic Leukemia/{M7} (292)
- ❑ Acute Basophilic Leukemia (293)
- ❑ Acute Panmyelosis with Myelofibrosis (294)
- ❑ Myeloid Sarcoma (295)
- ❑ AML, NOS (280)

Acute Lymphoblastic Leukemia (ALL)

- ❑ Precursor B-cell ALL {L1/L2} (191)

If known, indicate subtype:

- ❑ t(9;22)(q34;q11); BCR/ABL+ (192)
- ❑ t(v;11q23); MLL rearranged (193)
- ❑ t(1;19)(q23;p13) E2A/PBX1 (194)
- ❑ t(12;21)(p12;q22) ETV/CBF-α (195)

- ❑ Precursor T-cell ALL (196)
- ❑ ALL, NOS (190)

Acute Leukemias of ambiguous lineage

- ❑ Acute undifferentiated leukemia (31)
- ❑ Biphenotypic, bilineage or hybrid leukemia (32)
- ❑ Acute mast cell leukemia (33)
- ❑ Other acute leukemia, (89) specify:_____

Did AML transform from MDS or MPS? ❑Yes ❑No

Complete entire MDS Section on Disease Classification page 4 and entire AML Section

Was AML therapy related? ❑Yes ❑No ❑Unknown

AML, therapy related *(check all that apply)*

- ❑ Alkylating agent/radiation-related
- ❑ Topoisomerase II inhibitor-related
- ❑ Unknown

Was imatinib mesylate given for pretransplant therapy anytime prior to start of prep regimen? ❑Yes ❑No ❑Unknown

Status at Transplantation:

- ❑ Never treated
- ❑ Primary Induction Failure (PIF)
- ❑ Complete Remission (CR)
- ❑ Relapse

Number ❑1st ❑2nd ❑3rd or higher

For hematologic CR

Y	N	Unk	
❑	❑	❑	Cytogenetic remission
❑	❑	❑	Molecular remission

Pre-Transplant Essential Data
Disease Classification Sheet

CIBMTR Center #: ☐☐☐☐☐ CIBMTR Recipient ID#: ☐☐☐☐☐☐☐☐☐

CHRONIC MYELOGENOUS LEUKEMIA (CML)
Philadelphia chromosome+, Ph+, t(9;22)(q34;q11), or variant OR bcr/abl+

Did recipient receive treatment prior to this HSCT? ❑Yes ❑No

(check all that apply) ***Mandatory for CIBMTR Research Teams:***

- ❑ Ph+/bcr+ (41)
- ❑ Ph+/bcr- (42)
- ❑ Ph+/bcr unknown (43)
- ❑ Ph-/bcr+ (44)
- ❑ Ph unknown/bcr+ (47)

- ❑ Combination chemotherapy
- ❑ Dasatinib (Sprycel)
- ❑ Hydroxyurea (HU)
- ❑ Imatinib mesylate (Gleevec, Glivec)
- ❑ Interferon
- ❑ Nilotinib (Tasigna)
- ❑ Other, specify:_____

Status at Transplantation:

Phase
- ❑ Hematologic CR
  - *(Optional for non-U.S. centers)*
    CML disease status before treatment that achieved this CR:
    - ❑Chronic phase
    - ❑Accelerated phase
    - ❑Blast phase
- ❑ Chronic phase
- ❑ Accelerated phase
- ❑ Blast crisis

Number
- ❑ 1st
- ❑ 2nd
- ❑ 3rd or higher

For Chronic Phase and CR Only:

Cytogenetic remission:
- ❑Complete
- ❑No
- ❑Cytogenetics unknown

Molecular remission (bcr/abl):
- ❑Yes
- ❑No
- ❑bcr/abl unknown

CR=complete remission

MYELODYSPLASTIC OR MYELOPROLIFERATIVE DISEASES

Classification:

WHO: Myelodysplastic Syndromes (MDS)

At diagnosis	At transplantation
❑	❑ RA (51)
❑	❑ RARS (55)
❑	❑ RAEB-1 (61)
❑	❑ RAEB-2 (62)
❑	❑ RCMD (64)
❑	❑ RCMD/RS (65)
❑	❑ 5q-syndrome (66)
	❑ AML
❑	❑ MDS Unclassifiable/ {NOS} (50)

If transformed to AML, also complete Disease Classification page 3

Date of MDS Dx: ___ ____ ___ - ___ - ___ (YYYY MM DD)

WHO: Chronic Myeloproliferative Diseases {MPS}

At diagnosis	At transplantation
❑	❑ Chronic Neutrophilic Leukemia (165)
❑	❑ Chronic Eosinophilic Leukemia (hypereosinophilic syndrome) (166)
❑	❑ Chronic Idiopathic myelofibrosis (with extra-medullary hematopoiesis) {Myelofibrosis with myeloid metaplasia} {Acute myelofibrosis or myelosclerosis} (167)
❑	❑ Chronic Myeloproliferative Disease, unclassifiable {MPS, NOS} (60)
❑	❑ Essential thrombocythemia (ET) (58)
❑	❑ Polycythemia vera (PCV) (57)

Was Janus kinase 2 (jak2) gene mutation positive?
❑Yes ❑No ❑Not Done

Other

At diagnosis	At transplantation
❑	❑ Chronic myelomonocytic leukemia (CMMol, CMML) (54)
❑	❑ Juvenile myelomonocytic leukemia (JMML, JCML, JCMML) (36)

Was MDS/MPS therapy related? ❑Yes ❑No ❑Unknown

MDS, therapy related *(check all that apply)*
- ❑ Alkylating agent/radiation-related
- ❑ Topoisomerase II inhibitor-related
- ❑ Unknown

MDS/MPS/CMML

Status at Transplantation:
- ❑ Supportive care or treatment without chemotherapy
- ❑ Treated with chemotherapy
  - ❑ CR
  - ❑ Improvement, but no CR
  - ❑ NR – no response
  - ❑ Prog/worse
- ❑ Relapse after CR
  - Number: ❑ 1st ❑ 2nd ❑ 3rd or higher

JMML

Status at Transplantation:
- ❑ CCR – Continued Complete Response
- ❑ CR – Complete Response
- ❑ PR – Partial Response
- ❑ MR – Minimal Response
- ❑ SD – Stable Disease
- ❑ PD – Progressive Disease
- ❑ Not assessed

Pre-Transplant Essential Data
Disease Classification Sheet

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OTHER LEUKEMIAS

Classification:

Atypical chronic myeloid leukemia {CML, NOS}
- ❑ Ph-/bcr/abl- (45)
- ❑ Ph-/bcr unknown (46)
- ❑ Ph unknown/bcr- (48)
- ❑ Ph unknown/bcr unknown (49)

- ❑ Chronic Lymphocytic Leukemia (CLL), NOS (34)
- ❑ Chronic Lymphocytic Leukemia (CLL), B-cell/ Small Lymphocytic Lymphoma (SLL) (71)
- ❑ CLL, T-cell (72)
- ❑ Hairy Cell Leukemia (35)
- ❑ Prolymphocytic Leukemia (PLL), NOS (37)
  - ❑ PLL, B-cell (73)
  - ❑ PLL, T-cell (74)
- ❑ Other leukemia (39), specify:_____
- ❑ Other leukemia, NOS (30)

Status at Transplantation:
- ❑ Never treated
- ❑ Complete Remission (CR)
- ❑ nodular Partial Remission (nPR)
- ❑ Partial Remission (PR)
- ❑ No Response/Stable (NR/SD)
- ❑ Progression
- ❑ Relapse (untreated)

LYMPHOMAS

Classification:

Hodgkin Lymphoma
- ❑ Nodular lymphocyte predominant Hodgkin lymphoma (155)
- ❑ Lymphocyte-rich (151)
- ❑ Nodular sclerosis (152)
- ❑ Mixed cellularity (153)
- ❑ Lymphoma depleted (154)
- ❑ Hodgkin lymphoma, NOS (150)

Non-Hodgkin's Lymphoma

B-cell Neoplasms
- ❑ Burkitt's lymphoma/Burkitt cell leukemia {ALL L3} (111)
  - ❑ High-grade B-cell lymphoma, Burkitt-like (provisional entity) (135)
- ❑ Diffuse large B-cell lymphoma (107)
  If known, indicate subtype:
  - ❑ Intravascular large B-cell lymphoma (136)
  - ❑ Mediastinal large B cell lymphoma (125)
  - ❑ Primary effusion lymphoma (138)
- ❑ Extranodal marginal zone B-cell lymphoma of MALT type (122)
- ● Follicular lymphoma (includes variants)
  - ❑ Grade I (102)
  - ❑ Grade II (103)
  - ❑ Grade III (104)
  - ❑ Unknown (164)
- ❑ Lymphoplasmacytic lymphoma (121)
- ❑ Mantle cell lymphoma (115)
- ❑ Nodal marginal zone B-cell lymphoma (+/– monocytoid B cells) (123)
- ❑ Primary CNS lymphoma (118)
- ❑ Splenic marginal zone B-cell lymphoma (124)
- ❑ Waldenstrom macroglobulinemia (173)
- ❑ Other B-cell lymphoma (129), specify:_____

T-cell and NK-cell Neoplasms
- ❑ Adult T-cell lymphoma/leukemia (HTLV1+) (134)
- ❑ Aggressive NK-cell leukemia (27)
- ❑ Anaplastic large-cell lymphoma, T/null cell, primary cutaneous type (147)
- ❑ Anaplastic large-cell lymphoma, T/null cell, primary systemic type (148)
- ❑ Angioimmunoblastic T-cell lymphoma (AILD) (131)
- ❑ Enteropathy-type T-cell lymphoma (133)
- ❑ Extranodal NK/T-cell lymphoma, nasal type (137)
- ❑ Hepatosplenic gamma-delta T-cell lymphoma (145)
- ❑ Mycosis fungoides (141)
- ❑ Peripheral T-cell lymphoma {NOS} (130)
- ❑ Subcutaneous panniculitis-like T-cell lymphoma (146)
- ❑ Sezary syndrome (142)
- ❑ Large T-cell granular lymphocytic leukemia (126)
- ❑ Other T/NK cell lymphoma (139), specify:_____

Status at Transplantation:
- ❑ Never treated
- ❑ Primary refractory (less than PR to initial therapy)/PIF res
- ❑ Partial response (PR)
  - ❑ Without prior CR
  - ❑ with prior CR
- ❑ CR confirmed
- ❑ CR unconfirmed (CRU)*
- ❑ Rel

Number
- ❑ 1st
- ❑ 2nd
- ❑ 3rd or higher

Sensitivity to Chemotherapy:
- ❑ Sensitive
- ❑ Resistant
- ❑ Untreated
- ❑ Unknown

* CRU – complete response with persistent scan abnormalities of unknown significance

Pre-Transplant Essential Data
Disease Classification Sheet

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PLASMA CELL DISORDERS

Classification:

- ❑ Multiple myeloma-IgG (181)
- ❑ Multiple myeloma-IgA (182)
- ❑ Multiple myeloma-IgD (183)
- ❑ Multiple myeloma-IgE (184)
- ❑ Multiple myeloma-IgM (not Waldenstrom macroglobulinemia) (185)
- ❑ Multiple myeloma-light chain only (186)
- ❑ Multiple myeloma-non-secretory (187)
- ❑ Plasma cell leukemia (172)
- ❑ Solitary plasmacytoma (no evidence of myeloma) (175)
- ❑ Primary Amyloidosis (174)
- ❑ Other Plasma Cell Disorder (179), specify:_____

Light Chain
- ❑ Kappa
- ❑ Lambda

STAGE AT DIAGNOSIS

Salmon & Durie:
- ❑ 1 and ❑ A
- ❑ 2 ❑ B
- ❑ 3

OR

I.S.S.:

Serum β_2-microglobulin:

☐☐☐.☐☐☐ 1❑ µg/dL 2❑ mg/L 3❑ nmol/L

Serum albumin:

☐☐☐.☐ 1❑ g/dl 2❑ g/l

Status at Transplantation:

- ❑ Never treated
- ❑ Complete Remission (CR)
- ❑ Stringent Complete Remission (sCR)
- ❑ Very Good Partial Response (VGPR)
- ❑ Partial Response (PR)
- ❑ Stable Disease (SD)
- ❑ Progression
- ❑ Relapse from CR (untreated)

Number
- ❑ 1st
- ❑ 2nd
- ❑ 3rd or higher

	Stage	β_2-mic	S. albumin
❑	1	<3.5	>3.5
❑	2	<3.5 3.5-<5.5	<3.5 —
❑	3	≥5.5	—

BREAST CANCER

Classification:

Breast Cancer
- ❑ Inflammatory (251)
- ❑ Non-inflammatory (252)

Stage at Diagnosis
- ❑ 0
- ❑ I
- ❑ II
- ❑ III

Metastases
- ❑ No distant metastases
- ❑ Metastatic

Status at Transplantation:

- ❑ Adjuvant (Stage II, III only)
- ❑ Never treated
- ❑ Primary refractory
- Complete remission (CR)
  - ❑ CR confirmed
  - ❑ CR unconfirmed (CRU)
- ❑ 1st partial response (PR1)
- ❑ Relapse
  - ❑ Local
  - ❑ Metastatic

Number
- ❑ 1st
- ❑ 2nd
- ❑ 3rd or higher

Sensitivity to Chemotherapy
- ❑ Sensitive
- ❑ Resistant
- ❑ Untreated
- ❑ Unknown

* CRU – complete response with persistent scan abnormalities of unknown significance

"OTHER" DISEASE

Specify (900)***:***_____

Before using this category, check with transplant physician whether diagnosis can be classified among options on Disease Classification Pages 3-10.

For any "other" disease: Is a pathology report attached to this form?
- ❑ Yes
- ❑ No

Alternative HCT:
- ❑ Cardiac regeneration
- ❑ Neurologic regeneration
- ❑ Tolerance Induction Pre-solid Organ Transplant
- ❑ Other, specify:_____

Pre-Transplant Essential Data
Disease Classification Sheet

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OTHER MALIGNANCIES

Classification:

- ❑ Bone sarcoma (excluding Ewing family tumors) (273)
- ❑ Central nervous system tumors (include CNS PNET) (220)
- ❑ Colorectal (228)
- ❑ Ewing family tumors extra-osseous (includes PNET) (276)
- ❑ Ewing family tumors of bone (includes PNET) (275)
- ❑ Germ cell tumor, extragonadal only (225)
- ❑ Hepatobiliary (207)
- ❑ Lung cancer, non-small cell (203)
- ❑ Lung cancer, small cell (202)
- ❑ Medulloblastoma (226)
- ❑ Melanoma (219)
- ❑ Neuroblastoma (222)
- ❑ Ovary (214)
- ❑ Pancreas (206)
- ❑ Prostate (209)
- ❑ Renal cell (208)
- ❑ Retinoblastoma (223)
- ❑ Rhabdomyosarcoma (232)
- ❑ Soft tissue sarcoma (274)
- ❑ Testicular (210)
- ❑ Thymoma (231)
- ❑ Wilm tumor (221)
- ❑ Other solid tumor (269), specify:_____

Response Evaluation Criteria in Solid Tumors (RECIST) was used for this status evaluation: ❑ **Yes** ❑ **No**

1 Complete response (CR) – Disappearance of all target lesions for a period of at least one month

2 Complete response with persistent imaging abnormalities of unknown signficance (CRU)

3 Partial response (PR) – At least **30% decrease** in the sum of the longest diameter of measured lesions (target lesions) taking as reference the baseline sum of longest diameters

4 Stable disease (NR/SD) – Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as reference the smallest sum of the longest diameters since the treatment started

5 Progressive disease (PD) – At least a 20% increase in the sum of the longest diameter of measured lesions (target lesions), taking as reference the smallest sum of the longest diameters recorded since the treatment started of the appearance of one or more new lesions

Status at Transplantation:

- ❑ Adjuvant
- ❑ Never treated
- ❑ CR
- ❑ CRU
- ❑ PR — ❑ Without prior CR / ❑ with prior CR
- ❑ NR/SD
- ❑ PD
- ❑ Relapse (untreated)

Number
(complete for CR, CRU or relapse)

- ❑ 1st
- ❑ 2nd
- ❑ 3rd or higher

Sensitivity to Chemotherapy
(complete only for relapse)

- ❑ Sensitive (PR)
- ❑ Resistant (SD, PD)
- ❑ Untreated
- ❑ Unknown

ANEMIA/HEMOGLOBINOPATHY

Classification:

- ❑ Acquired Severe Aplastic Anemia (SAA), NOS (301)
- ❑ Acquired SAA, secondary to hepatitis (302)
- ❑ Acquired SAA, secondary to toxin/other drug (303)
- ❑ Acquired Amegakaryocytosis (not congenital) (304)
- ❑ Acquired Pure Red Cell Aplasia (PRCA) (not congenital) (306)
- ❑ Other acquired cytopenic syndrome (309), specify: _____
- ❑ Paroxysmal nocturnal hemoglobinuria (PNH) (56)
- ❑ Fanconi anemia (311)
- ❑ Diamond-Blackfan anemia (congenital PRCA) (312)
- ❑ Shwachman-Diamond (305)
- ❑ Other constitutional anemia (319), specify: _____
- ❑ Sickle cell disease (356)
- ❑ Sickle thalassemia (355)
- ❑ Thalassemia NOS (350)
- ❑ Other hemoglobinopathy (359), specify: _____

PLATELET DISORDERS

Classification:

- ❑ Congenital amegakaryocytosis/congenital thrombocytopenia (501)
- ❑ Glanzmann thrombasthenia (502)
- ❑ Other inherited platelet abnormalities (509), specify: _____

HISTIOCYTIC DISORDERS

Classification:

- ❑ Histiocytic disorders, NOS (570)
- ❑ Familial erythro/hemophagocytic lymphohistiocytosis (FELH) (571)
- ❑ Langerhans Cell Histiocytosis (Histiocytosis-X) (572)
- ❑ Hemophagocytosis (reactive or viral associated) (573)
- ❑ Malignant histiocytosis (574)
- ❑ Other histiocytic disorder (579), specify: _____

CR=complete remission

Pre-Transplant Essential Data
Disease Classification Sheet

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INHERITED DISORDERS OF METABOLISM/OSTEOPETROSIS

Classification:

- ❑ Adrenoleukodystrophy (ALD) (543)
- ❑ Aspartyl glucosaminuria (561)
- ❑ B-glucuronidase deficiency (VII) (537)
- ❑ Fucosidosis (562)
- ❑ Gaucher disease (541)
- ❑ Glucose storage disease (548)
- ❑ Hunter syndrome (II) (533)
- ❑ Hurler syndrome (IH) (531)
- ❑ I-cell disease (546)
- ❑ Krabbe disease (globoid leukodystrophy) (544)
- ❑ Lesch-Nyhan (HGPRT deficiency) (522)
- ❑ Mannosidosis (563)
- ❑ Maroteaux-Lamy (VI) (536)
- ❑ Metachromatic leukodystrophy (MLD) (542)
- ❑ Morquio (IV) (535)
- ❑ Mucolipidoses, NOS (540)
- ❑ Mucopolysaccharidosis (V) (538)
- ❑ Mucopolysaccharidosis, NOS (530)
- ❑ Neimann-Pick disease (545)
- ❑ Neuronal ceriod – lipofuscinosis (Batten disease) (523)
- ❑ Osteopetrosis (malignant infantile osteopetrosis) (521)
- ❑ Polysaccharide hydrolase abnormalities, NOS (560)
- ❑ Sanfilippo (III) (534)
- ❑ Scheie syndrome (IS) (532)
- ❑ Wolman disease (547)
- ❑ Other inherited disorder of metabolism (529), specify:_____
- ❑ Inherited Disorders of Metabolism, NOS (520)

IMMUNE DEFICIENCIES

Classification:

- ❑ Ataxia telangiectasia (451)
- ❑ Bare lymphocyte syndrome (406)
- ❑ DiGeorge anomaly (454)
- ❑ CD 40 Ligand deficiency (464)
- ❑ Cartilage hair hypoplasia (462)
- ❑ Chediak-Higashi syndrome (456)
- ❑ Chronic granulomatous disease (455)
- ❑ Common variable immunodeficiency (457)
- ❑ HIV infection (452)
- ❑ Immune Deficiencies, NOS (400)
- ❑ Leukocyte adhesion deficiencies (459)
- ❑ Kostmann syndrome-congenital neutropenia (460)
- ❑ Neutrophil actin deficiency (461)
- ❑ Omenn syndrome (404)
- ❑ Reticular dysgenesis (405)
- ❑ SCID, ADA deficiency severe combined immune deficiency (401)
- ❑ SCID, Absence of T and B cells (402)
- ❑ SCID, Absence of T, normal B cell (403)
- ❑ SCID, NOS (410)
- ❑ SCID other (419), specify: _____
- ❑ Wiskott Aldrich syndrome (453)
- ❑ X-linked lymphoproliferative syndrome (458)
- ❑ Other immune deficiency (479), specify: _____

Pre-Transplant Essential Data
Disease Classification Sheet

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AUTOIMMUNE DISORDERS

Classification	Involved Organs/Clinical Problem(s) *(Check all that apply)*	Yes	No	Primary Reason(s) for Transplant	Miscellaneous Labs @ Original Diagnosis	normal	elevated	not done
Connective Tissue Disease				**Antibodies:**				
❑ Systemic sclerosis (607)	❑ diffuse cutaneous	❑	❑	Scl 70 positive		❑	❑	❑
	❑ limited cutaneous	❑	❑	ACA positive		❑	❑	❑
	❑ lung parenchyma	❑	❑	ANA		❑	❑	❑
	❑ pulmonary hypertension	❑	❑					
	❑ systemic hypertension	❑	❑					
	❑ renal (biopsy type:_____)	❑	❑					
	❑ esophagus	❑	❑					
	❑ other GI Tract	❑	❑					
	❑ Raynaud	❑	❑					
	❑ CREST	❑	❑					
	❑ other, specify:_____	❑	❑					
❑ Systemic lupus erythematosus SLE (605)	❑ renal (biopsy type:_____)	❑	❑	ANA		❑	❑	❑
	❑ CNS (type:_____)	❑	❑	ds DNA		❑	❑	❑
	❑ PNS (type:_____)	❑	❑	C3		❑	❑ low	❑
	❑ lung	❑	❑	C4		❑	❑ low	❑
	❑ serositis	❑	❑	total complement		❑	❑ low	❑
	❑ arthritis	❑	❑	other,		❑	❑	❑
	❑ skin (type:_____)	❑	❑	specify:_____				
	❑ hematological (type:_____)	❑	❑					
	❑ vasculitis (type:_____)	❑	❑					
	❑ other, specify:_____	❑	❑					
❑ Sjögren syndrome (608)	❑ SICCA	❑	❑					
	❑ exocrine gland swelling	❑	❑					
	❑ other organ lymphocytic infiltration	❑	❑					
	❑ lymphoma, paraproteinemia	❑	❑					
	❑ vasculitis	❑	❑					
	❑ other, specify:_____	❑	❑					
❑ Polymyositis-dermatomyositis (606)	❑ proximal weakness	❑	❑	CPK		❑	❑	❑
	❑ generalized weakness (including bulbar)	❑	❑	typical biopsy		❑	❑	❑
	❑ pulmonary fibrosis	❑	❑	typical EMG		❑	❑	❑
	❑ vasculitis (type:_____)	❑	❑	typical rash (DM)		❑	❑	❑
	❑ malignancy (type:_____)	❑	❑					
	❑ other, specify:_____	❑	❑					
❑ Antiphospholipid syndrome (614)	❑ thrombosis (type:_____)	❑	❑	anticardiolipin IgG		❑	❑	❑
	❑ CNS (type:_____)	❑	❑	anticardiolipin IgM		❑	❑	❑
	❑ abortion	❑	❑	lab lupus inhibitor		❑	❑	❑
	❑ skin (livedo, vasculitis)	❑	❑	lupus anticoagulant		❑	❑	❑
	❑ hematological (type:_____)	❑	❑					
	❑ other, specify:_____	❑	❑					
❑ Other connective tissue disease, specify (634):_____		❑	❑					

Vasculitis		Yes	No	**Antibodies:**	normal	elevated	not done
❑ Wegener granulomatosis (610)	❑ upper respiratory tract	❑	❑	c-ANCA positive	❑	❑	❑
	❑ pulmonary	❑	❑	anti Pr3	❑	❑	❑
	❑ renal (biopsy type:_____)	❑	❑	anti MPO	❑	❑	❑
	❑ skin	❑	❑	c-ANCA IFA	❑	❑	❑
	❑ other, specify:_____	❑	❑	p-ANCA IFA	❑	❑	❑
Polyarteritis nodosa	❑ renal (type:_____)	❑	❑				
❑ Classical (631)	❑ mononeuritis multiplex	❑	❑	p-ANCA positive	❑	❑	❑
❑ Microscopic (632)	❑ pulmonary hemorrhage	❑	❑	c-ANCA positive	❑	❑	❑
	❑ skin	❑	❑	hepatitis serology	❑	❑	❑
	❑ GI Tract	❑	❑				
	❑ other, specify:_____	❑	❑				

NOTE: *Transplant Essential Data should be submitted at time of mobilization for all patients with autoimmune disease*

Pre-Transplant Essential Data
Disease Classification Sheet

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AUTOIMMUNE DISORDERS

Classification	Involved Organs/Clinical Problem(s) *(Check all that apply)*	Primary Reason(s) for Transplant	Miscellaneous Labs *(Check all that apply)*

Other vasculitis

- ❑ Churg-Strauss (635)
- ❑ Giant cell arteritis (636)
- ❑ Takayasu (637)
- ❑ Behçet's Syndrome (638)
- ❑ overlap necrotizing arteritis (639)
- ❑ other vasculitis, specify (611):_____

Arthritis

		Yes	No
❑ Rheumatoid arthritis (603)	❑ destructive arthritis	❑	❑
	❑ necrotizing vasculitis	❑	❑
	❑ eye (type:_____)	❑	❑
	❑ pulmonary	❑	❑
	❑ extra-articular (specify:_____)	❑	❑
	❑ other, specify:_____	❑	❑
❑ Psoriatic arthritis/psoriasis (604)	❑ destructive arthritis	❑	❑
	❑ psoriasis	❑	❑
	❑ other, specify:_____	❑	❑

- ❑ Juvenile idiopathic arthritis: systemic (Stills disease) (640)
- ❑ Juvenile idiopathic arthritis: Oligoarticular (641)
- ❑ Juvenile idiopathic arthritis: Polyarticular (642)
- ❑ Juvenile idiopathic arthritis: Other, specify (643):_____
- ❑ Other, arthritis, specify (633):_____

Multiple sclerosis

		Yes	No
❑ Multiple sclerosis (MS) (602)	❑ primary progressive	❑	❑
	❑ secondary progressive	❑	❑
	❑ relapsing/remitting	❑	❑
	❑ other specify:_____	❑	❑

Other Neurological Autoimmune Disease

- ❑ Myasthenia gravis (601)
- ❑ Other autoimmune neurological disorder, specify (644):_____

Hematological Autoimmune Disease

- ❑ Idiopathic thrombocytopenic purpura (ITP) (645)
- ❑ Hemolytic anemia (646)
- ❑ Evan syndrome (647)
- ❑ other autoimmune cytopenia, specify (648):_____

Bowel Disease

- ❑ Crohn's disease (649)
- ❑ Ulcerative colitis (650)
- ❑ Other autoimmune bowel disorder, specify (651):_____

Section 5 Infection Prophylaxis

**** Prophylaxis may be stipulated by patients' enrollment in clinical trials and should be followed as outlined in the clinical trial.****

A. HSV/VZV prophylaxis

1. HSV and VZV serologies should dictate therapy as outlined in the table below. If nausea or mucositis preclude oral intake, change to acyclovir 250mg/m² IV BID until patient is able to tolerate po intake.

	VZV - HSV -	VZV - HSV +	VZV + HSV -	VZV + HSV +
Autologous	no prophylaxis required	acyclovir 800 mg po daily through day +100	acyclovir 800 mg po daily through day +365	acyclovir 800 mg po daily through day +365
Allogeneic	no prophylaxis required	acyclovir 800 mg po BID until off all immune suppression	acyclovir 800 mg po BID through day +365 or off immune suppression	acyclovir 800 mg po BID through day +365 or off immune suppression

2. If patient develops overt signs of HSV infection on prophylactic (i.e., 250 mg/m^2) dosing, increase dose to 5 mg/kg IV q8hr. If symptoms persist or patient remains febrile despite therapeutic doses of acyclovir, send HSV culture.
3. Acyclovir doses may need adjustment during conditioning therapy if renal dysfunction exists.

	Normal Renal Function	Renal Impairment	
	≥ 50 mL/min	30-49 mL/min	< 30 mL/min
Acyclovir PO	800 mg PO daily	800 mg PO daily	400 mg PO daily
	800 mg PO BID	800 mg PO daily	400 mg PO daily
Acyclovir IV	250 mg/m2 IV q12h	500 mg IV Q24H	250 mg IV Q24H

4. For any patient or family member exposed to VZV, it is recommended they receive VZIG injection within 96 hours of the exposure. VZIG is available only through a study overseen by the ID service.
5. Family members and close contacts who receive the Varivax or Zostavax vaccine should not come in contact with the transplant or immune compromised patient for 1 month post vaccination as the live virus is shed in the stool.
6. If patients develop varicella zoster, they should be placed in contact/droplet precautions and moved to a negative air flow room. Consider placement off the oncology ward.

B. Gammaglobulin

1. Autologous patients will not receive routine gammaglobulin prophylaxis. IgG levels may be monitored at day +60 to +100 and at one year or more frequently if indicated. If IgG < 300 mg/dl, replacement with IVIG 200 mg/kg q 4 weeks may be given, but only at the transplant physician's discretion. Levels should be monitored and IVIG discontinued when levels are sustained above 300 mg/dl.
2. All allogeneic patients will have serum IgG levels checked on admission, then every other week until day +100. Patients should receive IVIG 200 mg/kg if IgG level < 300 mg/dl. Monitoring should continue past day +100 if GvHD is present.

C. CMV Monitoring and Treatment

Autologous patients: No CMV surveillance is required unless clinically indicated (ie patients with protracted fevers, GI symptoms). **If patient has documented CMV disease within one year of autologous transplant, weekly CMV PCRs should be followed through day +100.**

Allogeneic patients:

1. All allogeneic patients who are CMV (+) or have a CMV (+) donor will have weekly serum CMV PCRs beginning on admission through day +100, then continue every other week if steroid dose is > 10mg/day.
2. Patients who are CMV (-) with a CMV (-) donor should have monthly CMV PCRs through day +100.
3. Any patient that reactivates prior to or after day +100 should have prolonged surveillance
   a. If no GvHD is present, continue surveillance weekly for 3 months, then every other week for three months.
   b. If GvHD is present, continue surveillance weekly for 1 year
4. Triggers to begin pre-emptive therapy include a 2 consecutive weakly positive PCRs or a single PCR with a copy number > 400.
5. Valganciclovir should be use for any patient that meets the all of the following criteria:
   a. viral load < 5000 copies
   b. no history of medication non-compliance
   c. able to tolerate adequate oral intake
   d. no s/s or suspicion of end-organ disease
   e. no GI complaints (N/V/D), no evidence of gut GvHD
   f. afebrile
   g. negative CXR **CXR should be completed at documentation of reactivation**
6. Valganciclovir dosing of 900 mg po BID until PCRs are negative x 2 weeks, then 900 mg po daily x 14 days. If PCRs remain negative, d/c valganciclovir and restart prophylactic acyclovir.
7. If PCR viral load continues to rise after 10 – 14 days of therapy, change to IV ganciclovir or consider drug resistance.
8. If the patient does not meet the criteria outlined above, therapy should consist of ganciclovir 5 mg/kg IV BID until PCRs are negative x 2 weeks, then 5mg/kg IV daily x 14 days. If PCRs remain negative, d/c ganciclovir and restart prophylactic acyclovir.
9. If CMV reactivation occurs after day +100, begin either valganciclovir po or ganciclovir IV as directed above. Continue therapy until patient has negative PCRs on two consecutive weeks.
10. Patients with renal insufficiency whose CMV reactivates should receive ganciclovir 5mg/kg IV q12hr x 2 doses. The dose should then be adjusted for their renal function as below.

Ganciclovir Dosing in Renal Impairment

	Normal Renal Function	Renal Impairment			
	≥ 70 mL/min	50-69 mL/min	25-49 mL/min	10-24 mL/min	<10 mL/min (hemodyalysis)
Ganciclovir Induction	5 mg/kg IV q12hr	2.5-5 mg/kg IV q12hr	2.5 mg/kg IV q24hr	1.25 mg/kg IV q24hr	1.25-2.5 mg/kg IV 3x/week
Ganciclovir Maintenance	5 mg/kg IV q24hr	2.5 mg/kg IV q24hr	1.25 mg/kg IV q24hr	0.625 mg/kg IV q24hr	0.625 mg/kg IV 3x/week

Valganciclovir Dosing in Renal Impairment

	Normal Renal Function	Renal Impairment			
	≥ 60 mL/min	40-59 mL/min	25-39 mL/min	10-24 mL/min	<10 mL/min (hemodyalysis)
Valganciclovir Induction	900 mg po BID	450 mg po BID	450 mg po q24hr	450 mg po QOD	DO NOT USE
Valganciclovir Maintenance	900 mg po daily	450 mg po daily	450 mg po QOD	450 mg po twice weekly	DO NOT USE

D. Neutropenic Sepsis Prophylaxis

1. LGSH autologous patients will receive ciprofloxin 500 mg po BID from day-2 through neutrophil recovery or until first neutopenic temperature spike occurs and patients are placed on broad spectrum IV antibiotic therapy.
2. OHSU patients, both autologous and allogeneic, will receive ciprofloxin 500 mg po BID from day –1 until ANC > 500 on two consecutive days or until first neutopenic temperature spike occurs and patients are placed on broad spectrum IV antibiotic therapy. If patient is unable to tolerate po ciprofloxacin, change to 400 mg IV q12hr.

E. Clostridium Difficile Toxin Screen

1. In patients who develop diarrhea with >3 loose stools/day, three stool specimens will be sent for C. difficile toxin. If positive, metronidazole 500 mg po TID will be instituted.

F. Chronic Bacterial Prophylaxis

1. All patients with chronic graft-vs-host disease and asplenic patients should receive lifetime prophylaxis for encapsulated organisms with Pen VK 500 mg po daily.
   a. Alternatives for patients who are penicillin-allergic include:
      1. Erythromycin 400 mg po daily
      2. Bactrim SS 1 tablet po daily
   b. For patients with chronic bronchiolitis obliterans, consider Azithromycin 250 mg po daily or 500 mg po three times weekly.

G. Fungal Prophylaxis

1. All patients should have a pre-conditioning galactomannan EIA drawn with follow up CT chest to assess for lesions if result is positive (> 0.5 index).
2. Autologous patients will receive fluconazole 400 mg po/IV daily beginning day 0 and continuing through day +30.
3. Allogeneic patients, both ablative and non-nonablative, will receive fluconazole 400 mg po/IV daily beginning day 0 and continuing until day +75 for non-myeloablative transplants or day +100 for myeloablative transplants; or steroid dose is ≤ 0.5mg/kg/day, whichever comes later.
   a. Weekly galactomannan assays will be monitored and patients will be changed to voriconazole should an assay become positive.
   b. Voriconazole should be dosed at 6mg/kg IV q12hr x 2 doses, then 200 mg po/IV BID for prophylaxis.
   c. Alternatives should voriconazole be contraindicated (LFT abnormalities, drug interactions) is lipid amphotericin 3-5mg/kg IV or micafungin 100 mg IV daily.
   d. **NOTE: Due to high rate of drug interactions, please have pharmacist review drug:drug interactions prior to adding voriconazole.**
   e. Patients with a positive galactomannan assay should also have a CT chest without contrast to evaluate for fungal pneumonia.

4. Allogeneic patients who develop GvHD should be changed to posaconazole 200 mg po TID for fungal prophylaxis.
    a. If patients are unable to tolerate oral medications, change prophylaxis to voriconazole, as dosed above.
    b. Alternatives to voriconazole for prophylaxis include lipid amphotericin 1 mg/kg IV daily or 3 mg/kg three times weekly.
    c. If patients require steroids > 30 mg/day for chronic GvHD after day +100, antifungal prophylaxis should be restarted with posaconazole.

H. PCP Prophylaxis

1. All patients will receive Bactrim DS 1 tablet po BID beginning the first day of their conditioning regimen, continuing through day -2. If patient is sulfa allergic, no prophylaxis will be ordered at this time.
2. Both autologous and allogeneic patients should restart PCP prophylaxis between days +30 and +40. Standard treatment is Bactrim DS 1 tablet po BID on Mondays and Thursdays. This should continue for a total of 6 months for autologous patients. Allogeneic patients should continue PCP prophylaxis until they are off all immune suppression. Alternatives to Bactrim include:
    a. Dapsone 100 mg po daily (consider checking G6PD prior to initiation therapy in African-American and Hispanic patients)
    b. Pentamidine 300 mg IV once monthly
    c. Atovaquone 1500 mg po daily

    Keep in mind there is no toxoplasma prophylaxis with agents other than Bactrim