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Evaluating Risk Factors for Clostridium difficile Infection (CDI) In Stem Cell Transplant (SCT) Recipients: A National Study

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2011

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An abstract of

A thesis submitted to the Faculty of the

Rollins School of Public Health of Emory University

in partial fulfillment of the requirements for the degree of

Master of Public Health

in Epidemiology

2014

Abstract

Evaluating Risk Factors for Clostridium difficile Infection (CDI) In Stem Cell Transplant (SCT) Recipients: A National Study

By: Nishi Shah

Introduction: Clostridium difficile infections (CDI) are the leading cause of infectious diarrhea among patients undergoing stem cell transplantation (SCT). Autologous and allogeneic SCTs differ in terms of indications, preparatory regimen, length of stay and their rationale for efficacy. We have therefore analyzed National Inpatient Sample (NIS) database provided by Healthcare Cost and Utilization Project (HCUP) separately for autologous and allogeneic SCT recipients to evaluate risk factors for CDI.

Methods: We used the NIS database to study adult patients admitted for primary procedures of autologous and allogeneic SCT between 01/2001 until 12/2010. We performed separate multivariate logistic regression analyses to evaluate risk factors of CDI in auto and allo-SCT pts. Comorbidities and clinical variables were identified using comorbidity and clinical classification software (CCS) by HCUP. SAS 9.3 was used for analyses.

Results: Autologous SCTs constituted 61.5% of SCTs performed. Out of the 53072 auto-SCTs performed, 6% reported CDI while 8.5% of allo-SCTs reported CDI. Univariate analyses identified age, gender, indication for transplant, radiation, respiratory failure, septicemia, lengthy hospital stay and multiple comorbidities as risk factors for CDI in both subsets. On multivariate analyses, there was significant

interaction between age and the indication for transplant (p=0.003) No particular indication for auto and allo-SCT was associated with CDI on multivariate analyses. Septicemia was associated with higher CDI in both auto (OR=1.64 [1.35-2]) and allo-SCTs (OR=1.69 [1.36-2.1]). Males were at a higher risk for CDI (auto-SCT OR=1.29 [1.09-1.53] and allo-SCT OR=1.36 [1.18-1.57]). Patients who stayed longer had a higher risk of developing CDI (auto-SCT OR= 2.81 [2.29-3.45] and allo-SCT OR=2.63 [2.15-3.22]). There was an association between CDI and the presence of multiple co-morbidities among autologous SCTs (OR=1.32 [1.11-1.57]), and allogeneic SCTs (OR=1.18 [1.0-1.4]).

Conclusions: The incidence of CDI is higher among allogeneic SCTs. CDI was associated with longer hospital stay, septicemia and male gender for auto and allo-SCTs. While this analysis does not permit us to directly ascribe the associations to be causative for CDI, it helps us identify the more vulnerable population for CDI, and provides a rationale for development of effective approaches for preventing CDI in this population.

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Professional Acknowledgement

I want to thank Dr. Nooka for being such an amazing mentor, advisor and employer. I wouldn't have made it so far in the journey without you. I am grateful to Dr. Langston and Dr. McClellan for their support and patience while I was working on my thesis. All three of you have been great sources of encouragement.

I also want to thank RSPH faculty for being such amazing teachers. All I had to do was ask and everyone has helped me throughout. Lastly, thank you Dana for your guidance. It helped me understand the correct methodologies.

Personal Acknowledgment

Thank you Tanvi didi and Siva. If it weren't for you, I would have not thought of coming to Emory. Everything falls short to describe the support given by my parents and family. Milan Uncle: Thank you! I would have been lost without you. To all my friends here who form such a strong support system, thank you!

Table of Contents

Introduction:

Clostridium difficile, gram-positive spore-forming bacteria is a normal component of gut flora. When the competing gut flora are eliminated by the use of antibiotics, clostridium difficile may proliferate and result in clostridium difficile infection (CDI) with disease symptoms ranging from clostridium difficile associated diarrhea (CDAD) to pseudomembranous colitis and toxic megacolon in 3% to 8% of patients(McFarland *et al.*, 1989, Jawa & Mercer, 2012). CDI is the most common cause of infectious diarrhea in hospitalized patients. Among the 300000 patients diagnosed in the US with CDI every year, about 14000 patients die due to CDI related complications(Lucado *et al.*, 2006, *Vital signs: preventing Clostridium difficile infections*, 2012, Hall *et al.*, 2012, McDonald *et al.*, 2005).

Epidemiological studies evaluating the incidence of CDI and the related morbidity and mortality in hematopoietic stem cell transplant (SCT) recipients are limited. This question gains more relevance in the context of the results of a multi-institutional survey of eleven cancer centers in the United States demonstrating increased pooled rates of hospital acquired CDI in cancer patients. Patients with known malignancy were twice likely to acquire CDI compared to the control non-cancer patient population (15.8 vs. 7.4 per 10,000 patient-days, respectively)(Kamboj *et al.*, 2012). SCT patients are more prone to acquire CDI and its related complications, due to a myriad of causes. Both by the virtue of their disease and the treatment of their disease with chemotherapy, they are at increased risk for CDI and its related complications. Chemotherapy related neutropenia, susceptibility to other infectious complications necessitating use of broad-spectrum

antibiotics, prolonged hospitalizations, altered integrity of the intestinal mucosa due to chemotherapy induced gastroenteritis, graft versus host disease (GVHD) and inability to mount a humoral response to C. difficile-specific toxins make SCT patients more susceptible for CDI (Aronsson *et al.*, 1985, Kyne *et al.*, 2000). To date, varying incidence rates of CDI have been reported in the SCT patients, ranging from 3.5 to 27 % in allogeneic SCT (allo-SCT) patients and 6.5 to 9% among autologous SCT (auto-SCT) patients(Alonso & Marr, 2013). Allo-SCT remains the only curative modality for patients with hematological malignancies. Transplant-related mortality (TRM) from SCT, has decreased substantially over the past three decades due to better matching of donor recipient care and better supportive care. However, TRM remains a major obstacle, with TRM rates ranging from 15%–20%. Since infectious complications comprise a major portion of this mortality, identifying the most common infectious causes of death and attempting to decrease them with appropriate interventions can further decrease the TRM. The opportunity to reduce CDI related mortality is one such option. A recent retrospective analysis by Morris et al, demonstrated that the incidence of CDI has increased by about 30%, compared with the data from previous 10 years. During the same period, the CDI related overall mortality increased from 3.5 to 15.3% suggesting the need for interventions both to decrease the incidence of CDI and also interventions to reduce its devastating consequences.

Contrary to allo-SCT, auto-SCT utilizes the efficacy of high-dose myeloablative therapy for disease control. The causes for acquiring CDI in auto-SCT patients are almost similar to allo-SCT, but the lower incidence of CDI in auto-SCT reported in

earlier series may be related to the shorter hospital stays, less interruption of the intestinal mucosa and the lack of GVHD.

Prior studies evaluating CDI in SCT patients identified risk factors for acquiring CDI. Elderly patients> 60 years; myeloablative conditioning regimen; use of total body irradiation (TBI) ≥ 12 Gy as a part of conditioning regimen, duration of neutropenia, duration of hospitalization, developing acute lower gastrointestinal (GI) GVHD; administration of antibiotics such as fluoroquinolones, acylaminopenicillin+ß-lactamase inhibitors, carbapenems, and glycopeptides, overall number of antibiotics, and usage of proton pump inhibitors (PPI) have also been identified as risk factors across various single institutional trials(Slimings & Riley, 2014, Trifilio *et al.*, 2013, Willems *et al.*, 2012, Alonso *et al.*, 2012, Paul *et al.*, 2006). Due to the limitations of previous trials, evaluating CDI in SCT patients among a selected group of patients at the institutional level, the differing risk factors for acquiring CDIs across institutions based on their sample sizes, we have used a large national database to address the questions regarding the true incidence rates of CDI among SCT patients. We have evaluated the differences in their incidence and mortality among auto-SCT and allo-SCT patients separately and examined the factors that might contribute to the differences. We also attempted to identify risk factors for acquiring CDI among each group separately.

Methodology: Description of Dataset (*<07 matching basics - ESR - 9_04_2013a.pdf>*):The Nationwide Inpatient Sample (NIS) contains all-payer data on hospital inpatient stays from States participating in the Healthcare Cost and

Utilization Project (HCUP). Each year of the NIS provides information on approximately 8 million inpatient stays from about 1,000 hospitals. All discharges from sampled hospitals are included in the NIS database. The NIS is designed to approximate a 20-percent sample of U.S. community hospitals, defined by the AHA to be "all non-Federal, short-term, general, and other specialty hospitals, excluding hospital units of institutions." NIS is a stratified single-stage cluster design. To take the sample design into account in all of our analysis, we used the strata and cluster on hospital. The target universe is all discharges from community, non-rehabilitation hospitals in the United States. The sample frame is all discharges from community, non-rehabilitation hospitals in the participating HCUP Partner States. This universe of U.S. community hospitals is divided into strata (variable name NIS_Stratum) using five hospital characteristics: ownership/control, bed size, teaching status, urban/rural location, and U.S. region. The sampling clusters are hospitals (variable name HOSPID). DISCWT (variable name) is the weight used for getting national estimates. For running logistic regression, we normalized weights to actual sample size to avoid amplification of the association. To normalize weights to the actual sample size, we divided each weight by the raw mean of all weights.

Our study: For our study, we used 10 years of data from 2001 to 2010. Our study consisted of adult patients who had a stem cell transplant procedure done during their hospital stay. Stem cell transplant recipients were identified using ICD-9 codes for Principal procedure (PR1). The ICD-9 codes for autologous stem cell transplant recipients are 4101, 4104, 4107 and 4109. The ICD-9 codes for allogeneic stem cell

transplant recipients are 4102, 4103, 4105 and 4108. CDI was identified using ICD-9 codes (00845) for diagnoses. If a diagnosis of '00845' was listed in any of the 15 diagnoses listed, the patient was coded as having CDI. SAS 9.3 was used for analyses. For the demographic characteristics, proc surveyfreq and proc surveymeans were used taking the sample design into account. For logistic regression, we used proc surveylogistic. We added year as another stratum as we are taking multiple years into account for analyses. The demographic variables that we used for our analyses are gender (Female a reference group), race (Whites [Ref], Blacks and others), age (<40 years, 40-65 years [Ref], >65 years), length of stay [LOS] (LOS ≤ Median is the reference group) and in-hospital mortality (IHM). Clinical variables used were indication for transplant (multiple myeloma, hodgkin's disease, non-hodgkin's disease, leukemia and others), septicemia, radiation, respiratory failure, diabetes and comorbidities. We used the comorbidity software that assigned variables to identify comorbidities in hospital discharge records using the diagnosis coding of ICD-9-CM. The software created the comorbidity measures reported by Elixhauser et al (Elixhauser et al., 1998). Comorbidity was divided into two groups: zero or one co-morbidity was put in one group and multiple (two or more comorbidities) were put in another group. Comorbidity software also helped to identify patients of diabetes. We used the clinical classification software (CCS) developed by HCUP to identify the clinical variables for our analyses(Elixhauser A, 2014). The CCS for ICD-9-CM is a diagnosis and procedure categorization scheme that can be employed in many types of projects analyzing data on diagnoses and procedures. Indication for transplant was divided into 5 groups: multiple myeloma

(MM), Hodgkin's lymphoma (HL), non-Hodgkin's lymphoma (NHL), leukemia and others. The above mentioned diseases were identified using CCS codes for diagnosis. The CCS codes for multiple myeloma, Hodgkin's disease, non-Hodgkin's disease and leukemia were 40, 37, 38 and 39 respectively. Similarly, patients of septicemia, radiation and respiratory failure were identified using CCS codes 2, 211 and 131 respectively.

Since the patients of autologous and allogeneic transplant receive different regimens during pre-transplant period and are used for different indications (Table 1), we ran separate analyses for the two groups.

We assessed for confounding and interaction from a pre-specified set of potential confounding factors, such as age, gender, race, length of stay, co-morbidities, radiation, diabetes, respiratory failure, and septicemia by adding all of these covariates in our model. We assessed interaction by doing a Breslow Day test for interaction of each covariate with indication for transplant. Secondly, we assessed interaction effects of all of these covariates by adding interaction terms with exposure variable in the model, and then performing likelihood ratio test to assess the statistical significance of these interaction terms. Since the likelihood ratio test was found to be significant, we dropped one interaction term at a time, to end up with a final model with significant interaction terms and relevant confounders. All statistical analyses were conducted using SAS version 9.3 for Windows (SAS, Cary North Carolina). A p value of less than 0.05 was considered statistically significant.

Results:

Group and subject characteristics:

An estimated 98,684 admissions for stem cell transplant took place in the time period of January 2001 to December 2010. Of 98,684 admissions, 86,261 (87%) had no missing data on age, race, gender, discharge status and presence of comorbidities. We included these 86,261 patients for our analyses (Fig.1). As shown in Table 1 and Fig. 1, of the 86,261 SCT recipients, 53072 (61%) were autologous SCT recipients, whereas the remaining 33189 (39%) were allogeneic SCT recipients.

Among autologous SCT patients, multiple myeloma was the most common indication (43%). The proportion of patients with HL, NHL and leukemia were 11%, 30% and 7% respectively in autologous SCT group (Table 2). As shown in Table 3, 64% of allogeneic SCT recipients had a diagnosis of leukemia. 15% of allogeneic SCT recipients had a diagnosis of NHL. Multiple myeloma and Hodgkin's lymphoma formed a small portion (4% and 3% respectively).

Table 1 further elaborates the characteristics of SCT patients and helps to understand the difference in descriptive characteristics of autologous and allogeneic SCT patients. Among the 53,072 autologous SCT recipients, 59% were males. Majority (65%) fell in the age group of 40-65 years. The proportion of whites in auto-SCT group was 75% while blacks constituted 10% of the auto-SCTs. 4% of auto-SCTs underwent radiation during their hospital stay for SCT. 16% developed septicemia during their hospital stay while 3% developed respiratory failure during their hospital stay. 10% of SCT recipients were diabetics. The median length of

hospital stay was 18 days for an autologous SCT. 1146 (2%) auto-SCT recipients died during their hospital stay.

Similar to auto-SCTs, majority (58%) of allo-SCTs were males. 65% of the recipients fell in the age group of 40-65 years whereas 29% of patients were 18-39 years old. 78% of the allo-SCT recipients were whites. Allo-SCT recipients stayed longer and their median length of stay was 26 days. 22% of allo-SCT recipients underwent radiation during their hospital stay for SCT. 20% had septicemia during their hospital stay and 9% developed respiratory failure during their stay. 8% of allo-SCTs had a history of diabetes. There was a higher proportion of in-hospital mortality among allo-SCT recipients (9% vs 2%).

As seen in table 3 and table 4, the age distribution among the different types of patients was different. The majority of multiple myeloma patients fell in the age group of 40-65 years among both autologous (75%) and allogeneic (90%) SCT recipients. Among Hodgkin's' lymphoma patients, most of the patients were in the 18-39 years group (63% in auto-SCTs and 71% in allo-SCTs) reflecting the peak incidence of the disease. Patients with a diagnosis of NHL and leukemia who underwent SCT fell in the age group of 40-65 years group. In both autologous and allogeneic SCT patients, males and whites formed the majority for all the different indications. Allogeneic SCT recipients had a higher proportion of patients who underwent radiation. Leukemia patients underwent radiation more often than others in both autologous and allogeneic SCT recipients. Leukemia patients were also more likely to develop septicemia as compared to others in both autologous and allogeneic SCT recipients. Allogeneic SCT recipients were more likely to develop

respiratory failure during their hospital stay for all different indications of SCT. In both autologous and allogeneic SCT patients, diabetes as a comorbidity was present most often in multiple myeloma patients. In both autologous and allogeneic SCT recipients, multiple myeloma patients had shorter hospital stays whereas leukemia patients stayed longer than the median in both autologous and allogeneic SCT groups.

The incidence of CDI among SCT recipients overall was 7% (n=6049). Autologous and allogeneic SCT recipients differed in the incidence of CDI (Table 1) with a higher incidence of CDI among allo SCTs (9%) vs. 6% for auto SCTs (p-value<0.05).

Table 4 shows CDI incidence among autologous SCT recipients were we see that leukemia patients were more likely to develop CDI than MM patients and Hodgkin's lymphoma and patients with other diseases were less likely to develop CDI. Older patients were more likely to develop CDI (OR 40-65 vs. 18-39 year old 1.37 (1.08-1.74), OR >65 vs. 18-39 year old 1.67 (1.3-2.16)). CDI had a higher association with males in auto-SCT patient population (OR 1.25 (1.08-1.37)). No particular race was associated with the development of CDI in auto-SCT patients. Auto-SCT recipients with two or more comorbidities were more likely to develop CDI than those with 1 or none (OR 2 or more comorbidities vs. 0 or 1 comorbidity 1.39 (1.16-1.67)). A significantly greater percentage of those auto-SCT patients who developed CDI stayed longer in the hospital (76%) versus those who did not develop CDI (54%). Auto-SCT patients who underwent radiation, developed septicemia or respiratory failure were more likely to develop CDI as compared to

those without. (ORs Radiation vs. none 1.48 (1.08-2.01), Septicemia vs. none 2.16 (1.77-2.63), Respiratory failure vs. none 2.33 (1.61-3.38))

Fig. 6 shows CDI rates among allo SCTs and we find that NHL patients were less likely to develop CDI as compared to leukemia patients among allogeneic SCT recipients. No other indications had a statistically significant difference as compared to leukemia patients. Unlike autologous SCT recipients, older allo-SCT patients were less likely to develop CDI (ORs 18-39 vs. 40-65 yr. olds 1.02 [0.8-1.3], >65 vs. 40-65 yr. olds 0.53 [0.32-0.87]). Males were more likely to develop CDI as compared to females (OR 1.33(1.14-1.55)). Similar to autologous SCTs, race was not associated with the development of CDI among allogeneic SCT recipients. The presence of two or more comorbidities was not a statistically significant risk factor for development of CDI (OR two or more vs. one or no comorbidities= 1.18 (0.97-1.44)). The presence of diabetes was not a risk factor for development of CDI among allogeneic SCT recipients (OR Diabetes vs. none 0.85(0.58-1.24)). Like autologous SCT recipients, patients who had radiation during their hospital stay; those who developed septicemia or respiratory failure were more likely to develop CDI when compared to those who did not. (ORs Radiation vs. none 1.36 (1.09-1.69), Septicemia vs. none 2.16 (1.76-2.66), Respiratory failure vs. none 1.61 (1.29-2.0)). Patients who stayed longer in the hospital were more likely to develop CDI as compared those who stayed less than 26 days (median) (OR LOS >26 vs. less 3.06 (2.44-3.84)).

We conducted a multivariate analysis where adjustment was made for age, race, gender, comorbidities, diabetes, radiation, septicemia, respiratory failure and length of stay. Among auto-SCTs, there was significant interaction between age and

diagnostic indication. Patients in the age group of 18 to 39 years were at a lower risk for developing CDI as compared to the reference group of 40 to 65 years old multiple myeloma patients who underwent auto-SCT (Table 5). Among the age group of 40 to 65 years, patients of Hodgkin's lymphoma, non-Hodgkin's lymphoma and other diseases were at lower risk of developing CDI as compared to multiple myeloma patients in the same age group. 40 to 65 year old leukemia patients were at higher risk of developing CDI as compared to the reference group although the difference was not statistically significant. Older patients in any age group were at similar risk of developing CDI as compared to the reference group. After adjusting for other covariates, males were still at a higher risk of developing CDI (OR 1.29 (1.09-1.53)). Patients with two or more comorbidities had a higher likelihood of developing CDI (OR 2 or more vs. 0 or 1:-1.32 (1.11-1.57)). Auto-SCT patients who had developed septicemia were at a higher risk of developing CDI as compared to those without even after adjusting for other factors (OR 1.64 (1.35-2)). Patients who stayed longer were at higher likelihood of developing CDI (OR 2.81 (2.29-3.45)).

Multivariate analyses for allogeneic SCT patients showed no significant interaction (Table 6). Hodgkin's lymphoma and NHL patients were at a lower risk of developing CDI as compared to Leukemia patients although the decrease is not statistically significant. Older allo-SCT patients were at a lower risk of developing CDI as compared to younger Allo-SCT patients. Male gender (OR 1.36 (1.18-1.57)), presence of two or more co-morbidities (OR 1.18 (1-1.4)), septicemia (OR 1.69 (1.36-2.1)) and increased length of stay (OR 2.63 (2.15-3.22)) were the other risk factors for CDI that stayed statistically significant on multivariate analyses.

Discussion:

This study helps to understand the clinical profile of autologous and allogeneic stem cell transplant patients. As seen in Table 1, the two groups are different substantially in terms of clinical indication, the type of treatment they receive, the length of stay etc. Since allogeneic stem cell transplantation is a more rigorous process, it was probably recommended less often to older patients and patients with multiple co-morbidities. Multiple myeloma is the most common indication for autologous stem cell transplant whereas leukemia is the most common indication for allogeneic stem cell transplant. Accordingly, the age distribution among auto and allo-SCT patients aligns with the most common indication.

Although previous studies have looked at the epidemiology of Clostridium difficile infection among stem cell transplant patients, this study is novel in that it looks at a national dataset of in-hospital admissions for Stem Cell transplant. Due to the large sample size, it was possible to look at the association of different clinical factors for stem cell transplant like septicemia, radiation and respiratory failure as well as different indications for stem cell transplant.

To our knowledge this is the first of its study using a national database like NIS. The analysis showed that longer length of stay in the hospital is associated with increased likelihood of CDI. It would be difficult to assess whether longer length of stay is responsible for higher CDI or the presence of CDI led to longer stay in the hospital. Our study corroborates with previous studies that show allogeneic SCT have higher CDI rate than autologous SCT patients(Trifilio *et al.*, 2013, Kamboj *et al.*, 2012, Chopra *et al.*, 2011, Alonso *et al.*, 2012). The other potential risk factors that

were looked at included diabetes, radiation, and septicemia. Although it may be intuitive to think that diabetic patients are more likely to develop Clostridium difficile infection as they are at increased risk of immunosuppression and as previously shown by Hassan et al (Hassan *et al.*, 2013), our results did not show difference in CDI among diabetics and non-diabetics. Previous studies have shown that total body irradiation (TBI) is a risk factor for development of CDI (Willems *et al.*, 2012). While this dataset does not allow us to identify patients who received TBI, we identified SCT patients who received radiation during their hospital stay and assumed this represents TBI in most cases. As consistent with previous literature, radiation was more commonly given to allogeneic SCT patients. Among all allogeneic SCT patients, radiation was found to be strongly associated with development of CDI, when we adjusted for other variables like comorbidities, indication for transplant, diabetes, septicemia, etc; radiation was not found to be significantly associated with CDI.

Septicemia patients are given more antibiotics and for longer duration placing them at increased risk of developing CDI. Sepsis has been identified as a risk factor for CDI among hospitalized patients (Halabi *et al.*, 2013). While this dataset does not allow us to identify specific antibiotics or the timeframe of administration, it was clear that the presence of septicemia was a risk factor for CDI infection on uni-variate as well as multi-variate analyses.

The most common indication for auto-SCT was multiple myeloma whereas the most common indication for allogeneic SCT was leukemia. Hence we used multiple myeloma patients in the age group of 40 to 65 years age group as the reference

group when conducting multivariate analyses for auto-SCT patients. Similarly, for allo-SCT patients, leukemia patients in the age group of 18 to 39 years were considered as the reference group.

Among auto-SCT patients, leukemia patients were found to be at increased risk for CDI infection. This could have been due to increased length of stay for leukemia patients, type of myelo-ablative regimen, administration of radiation or increased prevalence of septicemia among leukemic patients. Hence when we adjusted for all the different covariates, there was no statistically significant difference in the risk of CDI among different diseases. There was significant interaction between age and type of disease. On multivariate analyses, younger patients with any of the different diagnostic indications were at lower risk of developing CDI as compared to the reference group. In the age group of 40 to 65 years, leukemia patients had a stronger association with CDI than MM patients. Hodgkin's lymphoma patients were at a lower risk of developing CDI as compared to myeloma patients in the age group of 40 to 65 years. This difference exists even after adjusting for the other risk factors. Older patients with different diagnostic indications were at the same risk of developing CDI as the reference group. When adjusted for the different factors, age > 65 years as such was not found to be a risk factor for developing CDI in auto-SCT patients. Nevertheless this lack of association could be due to the limited numbers in this category for each indication.

Among allogeneic SCT patients, leukemia patients were at the highest risk of developing CDI. Unlike auto-SCT patients, older allo-SCT patients were at a lower risk of developing CDI. Allo-SCT being a more toxic procedure is offered only

selectively to older patients. Also, older patients are typically given reduced intensity conditioning regimens that could affect their CDI risk. This could possibly explain the lower risk of developing CDI in older Allo-SCT patients.

Patients with respiratory failure represent a cohort of critically ill patients. They require ICU admission and almost certainly longer hospital stay. CDI has been found to be relatively common among mechanically ventilated patients (Micek *et al.*, 2013, Halabi *et al.*, 2013). While our dataset does not allow us to identify ICU patients, we used respiratory failure as one of the surrogate markers for ICU stay. On univariate analyses, respiratory failure was found to be risk factor for CDI in both autologous and allogeneic SCT patients. But when we adjusted for other factors and ran multivariate analyses, respiratory failure was not associated with CDI. This could possibly mean that respiratory failure by itself is not a risk factor but patients of respiratory failure have a higher length of stay. Hence the effect was not seen on multivariate analyses.

Due to the nature of the dataset, we were able to look at different risk factors for CDI. Also, it is a nationally representative sample. A hospital-based study would not be able to identify these different risk factors.

However, our study has several limitations. One weakness in the NIS and other large, national databases of this type is the inability to follow individual patients over time. Like any administrative dataset, the dataset does not provide detailed clinical information to explore certain specific aspects of treatment. Details regarding treatment like Graft Versus Host disease, type of induction regimen, presence of neutropenic fever, disease status (advanced vs early), time to

engraftment and type of anti-biotic prophylaxis are not available. Previous studies have shown them as risk factors for the development of CDI (Trifilio *et al.*, 2013, Alonso *et al.*, 2012). We used broad categories for indications of Stem cell transplant. Leukemia as a category included acute myelogenous leukemia, acute lymphocytic leukemia, chronic lymphocytic leukemia, hairy cell leukemia, chronic myelogenous leukemia etc. Each of these might have different conditioning regimens and varying patient characteristics. Similarly the category of others would include all the other indications for stem cell transplant such as myelodysplastic syndrome, aplastic anemia, breast cancer and other solid tumors. With our study, we would not be able to find the association of CDI with each of the different diseases individually.

IDSA guidelines recommend measuring CDI rate as number of cases per 10,000 patient days (Cohen *et al.*, 2010). With discharge level data, it is not possible to measure CDI rate in this way. Another weakness in the NIS is the inability to follow CDI patients over time. We cannot measure the time to onset of CDI. The data is present only till discharge. If a patient develops CDI after discharge, it would not be recorded in this dataset. But 50% of CDI occur during the first month after SCT. The rate of recurrence of CDI and the associated readmission would not be recorded either. Since its discharge data, it may not be as accurate as data obtained from reviewing medical charts. The data lacks information on laboratory values, radiographic findings, vital signs, and other details of any single patient's course. The results of toxin assays and other tests used to diagnose CDI are unavailable in the NIS dataset; therefore, we relied on the ICD-9 coding system to identify patients.

ICD diagnostic codes for specific pathogens have been known to underestimate mortality because they are typically used only when there is laboratory confirmation of a specific etiology. But studies have found a good correlation between ICD-9 codes and toxin assays. Therefore it has been demonstrated as an acceptable method for CDI in multiple studies. (Scheurer *et al.*, 2007, Dubberke *et al.*, 2006). However, sensitivities for most commonly used diagnostic assays to detect CDI range from only 75% to 95%. If particular subgroups of patients with comorbidities like diabetes and sepsis had higher mortality rates than non-CDI patients depending on the strain and toxin type that their CDI manifests, our study would not be able to discern these risk factors. CDI has various manifestations from asymptomatic carriage to toxic megacolon. Our study would not be able to identify these different manifestations and the specific risk factors for these manifestations. Many hospitals may not use strict criteria for diagnosing various infectious diseases, which is referred to as up-coding. This aggressive coding allows the hospitals to increase charges, and thus reimbursement and we have no way to identify this practice.

Nevertheless, this is a large study evaluating the trends of CDI in Stem Cell transplant patients at the national level. These results attempt to accurately estimate risk factors of CDI in stem cell transplant population. We were able to identify gender, septicemia, length of stay, presence of two or more co-morbidities as risk factors for development of CDI among allogeneic SCT patients. Older age appears to be associated with lower risk of developing CDI in allo-SCT group. Although not statistically significant, patients who underwent allo-SCT for diagnosis

other than Leukemia were found to be at a lesser risk for developing CDI. For auto-SCT, gender, septicemia, presence of two or more comorbidities and length of stay were risk factors for development of CDI. Younger auto-SCT patients, irrespective of their diagnostic indications were at a lower risk of developing CDI than myeloma patients who are 40-65 year old. Older auto-SCT patients were not at particularly at higher risk for CDI. The association between CDI and length of stay and CDI and septicemia is potentially bi-directional. As can be seen, Clostridium difficile is not uncommon in this patient population. Our study helps understand some of the risk factors in the stem cell transplant population. Currently, the mainstays of CDI prevention include antimicrobial stewardship and infection control practices such as barrier precautions and environmental cleaning. Despite the implementation of these measures in SCT patients, rates continue to remain high and therefore alternative strategies for prevention, including prophylactic agents against C.difficile should be considered. This study could help in identifying higher risk groups in this patient population.

Table 1 Characteristics of Stem Cell Patients

Covariates	Total (n=86261)	Auto-SCT (n=53072)	Allo-SCT (n=33189)	p-value
Agecat				<0.0001
*18-39**	19717 (22.9%)	10028 (18.9%)	9689 (29.2%)	
40-65	55659 (64.5%)	34226 (64.5%)	21433 (64.6%)	
>65	10885 (12.6%)	8818 (16.6%)	2067 (6.2%)	
Gender**				0.39
Male	50295 (58.3%)	31089 (58.6%)	19206 (57.9%)	
*Race**				<0.0001
White	65419 (75.8%)	39538 (74.5%)	25881 (78%)	
Black	6996 (8.1%)	5448 (10.3%)	1584 (4.8%)	
Others	13811 (16%)	8087 (15.2%)	5724 (17.2%)	
*CDI**	5891 (6.8%)	3060 (5.8%)	2831 (8.5%)	<0.0001
*In-Hospital mortality**	4168 (4.8%)	1146 (2.2%)	3022 (9.1%)	<0.0001
*Indication**				<0.0001
Multiple Myeloma	24279 (28.1%)	22826 (43%)	1453 (4.4%)	
Hodgkin's Lymphoma	7013 (8.1%)	5911 (11.1%)	1102 (3.3%)	
Non-Hodgkin's Lymphoma	20674 (24%)	15768 (29.7%)	4906 (14.8%)	
Leukemia	24810 (28.8%)	3652 (6.9%)	21158 (63.8%)	
Others	9484 (11%)	4914 (9.3%)	4570 (13.8%)	
*Comorbidities**				0.0007
0 or 1	42692 (49.5%)	28958 (54.6%)	13734 (41.4%)	
2 or more	43659 (50.5%)	24114 (45.4%)	19455 (58.6%)	
*Radiation**	9628 (11.2%)	2356 (4.4%)	7272 (21.9%)	<0.0001
*Septicemia**	15083 (17.5%)	8326 (15.7%)	6757 (20.4%)	<0.0001
*Respiratory Failure**	4679 (5.4%)	1572 (3%)	3107 (9.4%)	<0.0001
*Diabetes**	8121 (9.4%)	5436 (10.2%)	2685 (8.1%)	0.0002
Length of Stay				
LOS (Median)	21	18	26	

Table 2 Characteristics of patients by disease for Autologous SCT patients

Covariates	Multiple Myeloma n=22826	NHL n=15768	Hodgkin's disease n=5911	Leukemia n=3652	Others n=4914
Age in categories					
18-39	622 (2.7%)	2395 (15.2%)	3736 (63.2%)	879 (24.1%)	2396 (48.8%)
40-65	17124 (75%)	10426 (66.1%)	1969 (33.3%)	2453 (67.2%)	2254 (45.9%)
>65	5081 (22.3%)	2947 (18.7%)	206 (3.5%)	321 (8.8%)	265 (5.4%)
Gender					
Male	13089 (57.3%)	9779 (62%)	3258 (55.1%)	1937 (53%)	3026 (61.6%)
Race					
White	16052 (70.3%)	12674 (80.4%)	4158 (70.3%)	2676 (73.3%)	3977 (80.9%)
Black	3468 (15.2%)	799 (5.1%)	566 (9.6%)	318 (8.7%)	297 (6%)
Others	3306 (14.5%)	2294 (14.5%)	1187 (20.1%)	659 (18%)	641 (13%)
Comorbidities					
0 or 1	11420 (50%)	8985 (57%)	3955 (66.9%)	2286 (62.6%)	2312 (47%)
2 or more	11406 (50%)	6782 (43%)	1957 (33.1%)	1366 (37.4%)	2603 (53%)
Radiation	229 (1%)	1177 (7.5%)	259 (4.4%)	652 (17.9%)	39 (0.8%)
Septicemia	3524 (15.4%)	2541 (16.1%)	943 (16%)	624 (17.1%)	694 (14.1%)
Resp Failure	559 (2.4%)	483 (3.1%)	169 (2.9%)	144 (3.9%)	217 (4.4%)
Diabetes	2790 (12.2%)	1751 (11.1%)	343 (5.8%)	310 (8.5%)	242 (4.9%)
Length of Stay					
LOS ≤ 18	15132 (66.3%)	3760 (23.8%)	1634 (27.6%)	686 (18.8%)	2673 (54.4%)
LOS > 18	7694 (33.7%)	12008 (76.2%)	4277 (72.4%)	2966 (81.2%)	2241 (45.6%)
CDI	1305 (5.7%)	996 (6.3%)	254 (4.3%)	281 (7.7%)	224 (4.6%)
IHM	412 (1.8%)	359 (2.3%)	102 (1.7%)	107 (2.9%)	168 (3.4%)

Table 3 Characteristics of Allogeneic SCT patients by disease

	Multiple Myeloma n=1453	NHL n=4906	Hodgkin's disease n=1102	Leukemia n=21158	Others n=4570
Age in categories					
18-39	112 (7.7%)	963 (19.6%)	783 (71.1%)	6565 (31%)	1265 (27.7%)
40-65	1301 (89.5%)	3711 (75.6%)	318 (28.9%)	13111 (62%)	2992 (65.5%)
>65	40 (2.8%)	232 (4.7%)	-	1482 (7%)	313 (6.8%)
Gender					
Male	895 (61.6%)	3147 (64.1%)	631 (57.3%)	11947 (56.5%)	2587 (56.6%)
Race					
White	1122 (77.2%)	3935 (80.2%)	881 (79.9%)	16535 (78.2%)	3409 (74.6%)
Black	122 (8.4%)	202 (4.1%)	69 (6.3%)	977 (4.6%)	214 (4.7%)
Others	209 (14.4%)	769 (15.7%)	152 (13.8%)	3646 (17.2%)	948 (20.7%)
Comorbidities					
0 or 1	878 (60.4%)	2788 (56.8%)	426 (38.7%)	12592 (59.5%)	2521 (55.2%)
2 or more	575 (39.6%)	2118 (43.2%)	675 (61.3%)	8567 (40.5%)	2049 (44.8%)
Radiation	187 (12.9%)	943 (19.2%)	113 (10.3%)	5401 (25.5%)	628 (13.7%)
Septicemia	252 (17.3%)	779 (15.9%)	137 (12.4%)	4549 (21.5%)	1040 (22.8%)
Resp Failure	77 (5.3%)	414 (8.4%)	106 (9.6%)	1971 (9.3%)	539 (11.8%)
Diabetes	172 (11.8%)	353 (7.2%)	62 (5.6%)	1607 (7.6%)	490 (10.7%)
Length of Stay					
LOS ≤ 26	1049 (72.2%)	2917 (59.5%)	690 (62.6%)	9259 (43.8%)	2091 (45.8%)
LOS > 26	404 (27.8%)	1989 (40.5%)	412 (37.4%)	11899 (56.2%)	2479 (54.2%)
CDI	96 (6.6%)	315 (6.4%)	72 (6.5%)	1970 (9.3%)	379 (8.3%)
IHM	77 (5.3%)	413 (8.4%)	77 (7%)	1945 (9.2%)	483 (10.6%)

Table 4. Analyses for different covariates and the risk of developing Clostridium difficile infection among Autologous SCT patients

Total=53072	CDI=Yes (5.8%) n=3060	CDI=No (94.2%) n=50012	Univariate Odds Ratio (95% CI)	Multivariate Odds Ratio (95% CI)
Indication				
Multiple Myeloma	1305 (42.6%)	21522 (43%)	1.00 (Ref)	
Hodgkin's Lymphoma	254 (8.3%)	5658 (11.3%)	0.79 (0.58-1.07)	
Non-Hodgkin's Lymphoma	996 (32.5%)	14771 (29.5%)	1.15 (0.97-1.37)	
Leukemia	281 (9.2%)	3371 (6.7%)	1.45 (1.1-1.92)	
Others	224 (7.3%)	4690(9.4%)	0.77 (0.56-1.05)	
*Agecat***				
18-39	426 (13.9%)	9602 (19.2%)	0.73 (0.57-0.93)	
40-65	1991 (65.1%)	32236 (64.5%)	1.00 (Ref)	
>65	644 (21%)	8175 (16.3%)	1.22 (1.02-1.46)	
*Gender**				
Male	1946 (63.6%)	29143 (58.3%)	1.25 (1.05-1.48)	1.29 (1.09-1.53)
*Race**				
White	2369 (77.4%)	37169 (74.3%)	1.00 (Ref)	1.00 (Ref)
Black	274 (9%)	5173 (10.3%)	0.83 (0.65-1.06)	0.89 (0.7-1.14)
Others	417(13.6%)	7670 (15.3%)	0.85 (0.66-1.11)	0.89 (0.69-1.15)
*Comorbidities**				
0 or 1	1432 (46.8%)	27526 (55%)	1.00 (Ref)	1.00 (Ref)
2 or more	1628 (53.2%)	22486 (45%)	1.39 (1.16-1.67)	1.32 (1.11-1.57)
Diabetes*	289 (9.4%)	5146 (10.3%)	0.91 (0.68-1.22)	0.77 (0.58-1.01)
Radiation*	192 (6.3%)	2165 (4.3%)	1.48 (1.08-2.01)	1.27 (0.93-1.75)
Septicemia*	842 (27.5%)	7484(15%)	2.16 (1.77-2.63)	1.64 (1.35-2)
Respiratory Failure*	190 (6.2%)	1382 (2.8%)	2.33 (1.61-3.38)	1.35 (0.95-1.91)
*Length of Stay**				
LOS≤18	729 (23.8%)	23157 (46.3%)	1.00 (Ref)	1.00 (Ref)
LOS>18	2331 (76.2%)	26855 (53.7%)	2.76 (2.23-3.41)	2.81 (2.29-3.45)
* p-value for interaction >0.05				
** p-value for interaction <0.05				

Table 5 Stratified Odds Ratio estimates for different indications among Autologous SCT patients

Covariates	Multiple Myeloma	Hodgkin's disease	NHL	Leukemia	Others
18-39	0.39 (0.2-0.78)	0.44 (0.28-0.69)	0.55 (0.32-0.95)	0.49 (0.22-1.12)	0.67 (0.37-1.19)
40-65	1.00 (Ref)	0.54 (0.33-0.88)	0.66 (0.53-0.83)	1.35 (0.83-2.18)	0.5 (0.28-0.91)
>65	0.93 (0.69-1.24)	1.20 (0.57-2.52)	1.0 (0.71-1.41)	0.86 (0.31-2.35)	1 (0.39-2.58)

Table 6 Analyses for different covariates and the risk of developing Clostridium difficile infection among Allogeneic SCT patients

Total=33189	CDI =Yes(8.5%) n=2831	CDI=No (91.5%) n=30358	Univariate Odds Ratio (95% CI)	Multivariate Odds Ratio (95% CI)
Indication				
Leukemia	1970 (69.6%)	19189 (63.2%)	1.00 (Ref)	1.00 (Ref)
Hodgkin's Lymphoma	72 (2.5%)	1030 (3.4%)	0.65 (0.42-1.01)	0.81 (0.49-1.34)
Non-Hodgkin's Lymphoma	315 (11.1%)	4591 (15.1%)	0.64 (0.5-0.82)	0.78 (0.60-1.02)
Multiple Myeloma	96 (3.4%)	1357 (4.5%)	0.73 (0.49 -1.09)	0.96 (0.61-1.51)
Others	379 (13.4%)	4191 (13.8%)	0.80 (0.63-1.03)	0.92 (0.7-1.21)
Agecat#				
18-39	968 (34.2%)	8721 (28.7%)	1.27 (1.08-1.5)	1.02 (0.8-1.3)
40-65	1746 (61.7%)	19687 (64.8%)	1.00 (Ref)	1.00 (Ref)
>65	118 (4.2%)	1949 (6.4%)	0.81 (0.55-1.18)	0.53 (0.32-0.87)
*Gender**				
Male	1815 (64.1%)	17391 (57.3%)	1.33 (1.14-1.55)	1.36 (1.18-1.57)
Race#				
White	2199 (77.7%)	23682 (78%)	1.00 (Ref)	1.00 (Ref)
Black	142 (5%)	1441 (4.7%)	1.06 (0.76-1.49)	1.03 (0.74-1.44)
Others	490 (17.3%)	5234 (17.2%)	1.01 (0.81-1.26)	0.86 (0.68-1.07)
*Comorbidities**				
0 or 1	1555 (54.9%)	17900 (59.0%)	1.00 (Ref)	1.00 (Ref)
2 or more	1276 (45.1%)	12457 (41.0%)	1.18 (0.97-1.44)	1.18 (1.0-1.4)
Diabetes*	199 (7%)	2486 (8.2%)	0.85 (0.58-1.24)	0.84 (0.61-1.16)
Radiation*	767 (27.1%)	6507 (21.4%)	1.36 (1.09-1.69)	1.19 (0.96-1.48)
Septicemia*	957 (33.8%)	5800 (19.1%)	2.16 (1.76-2.66)	1.69 (1.36-2.1)
Respiratory Failure*	386 (13.6%)	2721 (9%)	1.61 (1.29-2.0)	0.96 (0.76-1.2)
*Length of Stay**				
LOS≤26	705 (24.9%)	15300 (50.4%)	1.00 (Ref)	1.00 (Ref)
LOS>26	2126 (75.1%)	15057 (49.6%)	3.06 (2.44-3.84)	2.63 (2.15-3.22)
* p-value for interaction >0.05				
** p-value for interaction <0.05				

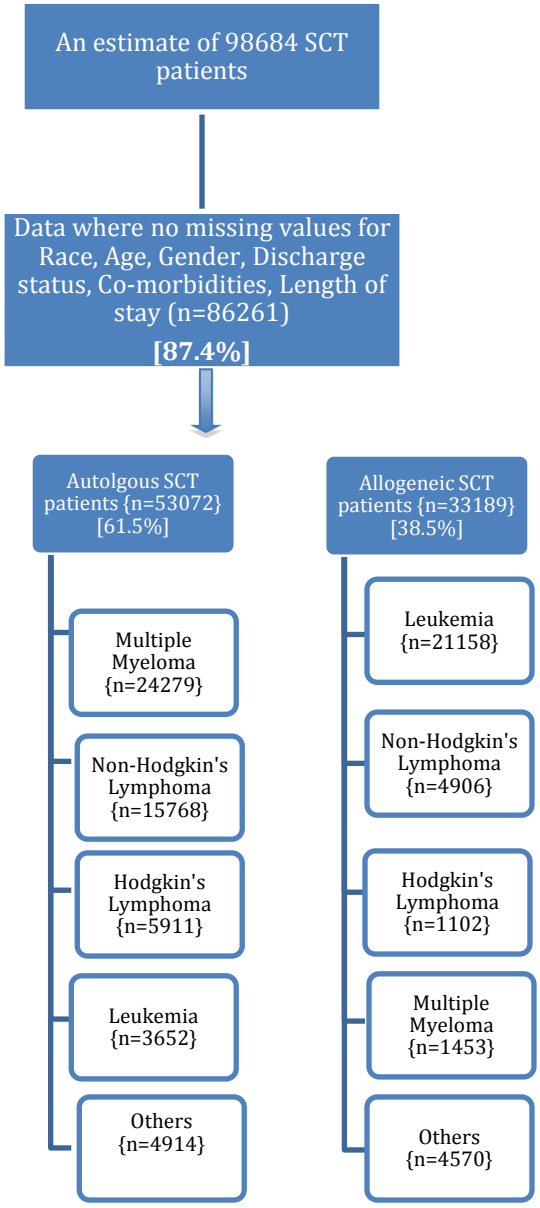
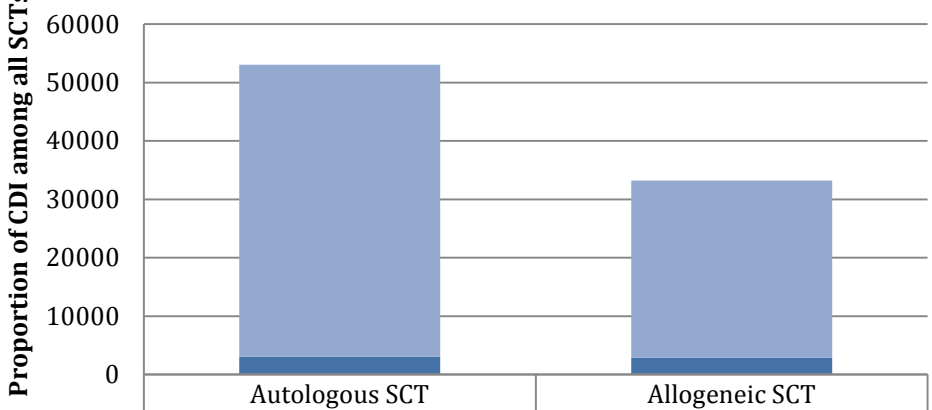


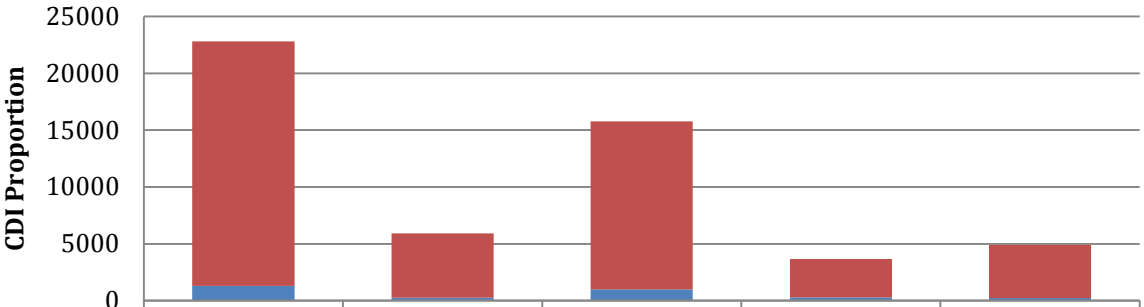
Fig. 1 Distribution of patients for analyses

Fig. 2 Clostridium difficile infection rate among Autologous and Allogeneic SCT patients



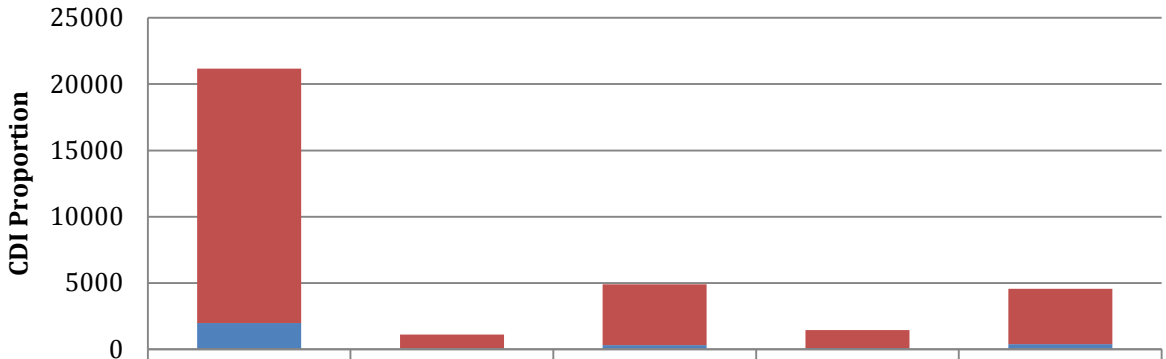
	Autologous SCT	Allogeneic SCT
Non-CDI	50012	30358
CDI	3060	2831

Fig. 3 Clostridium difficile by Disease in Autologous SCT patients



	Multiple Myeloma	Hodgkin's Disease	Non-Hodgkin's disease	Leukemia	Others
Non-CDI	21522	5658	14771	3371	4690
CDI	1305	254	996	281	224

Fig. 4 Clostridium difficile by Disease in Allogeneic SCT patients



	Leukemia	Hodgkin's Disease	Non-Hodgkin's disease	Multiple Myeloma	Others
Non-CDI	19189	1030	4591	1357	4191
CDI	1970	72	315	96	379

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