Epidemiology and Outcomes of *Clostridium difficile* Infection in Allogeneic Hematopoietic Cell and Lung Transplant Recipients

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Abstract

Background.—*Clostridium difficile* infection (CDI) is a common complication of lung and allogeneic hematopoietic cell (HCT) transplant, but the epidemiology and outcomes of CDI after transplant are poorly described.

Methods.—We performed a prospective, multicenter study of CDI within 365 days post-allogeneic HCT or lung transplantation. Data were collected via patient interviews and medical

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chart review. Participants were followed weekly in the 12 weeks post-transplant and while hospitalized and contacted monthly up to 18 months post-transplantation.

Results.—Six sites participated in the study with 614 total participants; 4 enrolled allogeneic HCT (385 participants) and 5 enrolled lung transplant recipients (229 participants). 150 CDI cases occurred within one year of transplantation; the incidence among lung transplant recipients was 13.1% and among allogeneic HCTs was 31.2%. Median time to CDI was significantly shorter among allogeneic HCT than lung transplant recipients (27 days vs. 90 days; p=0.037). CDI was associated with significantly higher mortality from 31–180 days post-index date among the allogeneic HCT recipients (Hazard ratio [HR]=1.80; p=0.007). There was a trend towards increased mortality among lung transplant recipients from 120–180 days post-index date (HR=4.7, p=0.09).

Conclusions.—The epidemiology and outcomes of CDI vary by transplant population; surveillance for CDI should continue beyond the immediate post-transplant period.

Keywords

Clostridium difficile; hematopoetic cell transplant; lung transplant; epidemiology; outcomes

Introduction

Clostridium difficile infection (CDI) is the most common infectious cause of healthcare-associated diarrhea, and risk factors for CDI include antibiotic use, high severity of illness, hospitalization, and immunosuppression.[1–4] Solid organ and hematopoetic cell transplant (HCT) recipients are particularly vulnerable to CDI[5]. The incidence of CDI among allogeneic HCT recipients is high, with an upper estimate of about 30%.[6–14] Among solid organ transplant recipients, those receiving a lung transplant are at increased risk of CDI, with incidence estimates up to 10.8%.[15,16] There are few data available on the association between transplantation, CDI, and morbidity and mortality. In one study lung transplant recipients had greater risk of fulminant colitis compared to non-transplant patients,[15] and CDI has been associated with increased mortality, particularly during the early post-transplant period.[16,17] In allogeneic HCT recipients, the impact of CDI on mortality is unclear. CDI was associated with significantly higher mortality within 180 days of infection in two studies,[8,18] but Willems at al. found no difference in overall survival between CDI cases and controls within two years of transplantation.[14] Additionally, variations in study design make it difficult to draw firm conclusions about the morbidity and mortality associated with CDI after allogeneic HCT and lung transplantation. A better understanding of the epidemiology and outcomes of CDI among allogeneic HCT and lung transplant recipients would help clinicians treat patients appropriately and help guide infection prevention priorities.

The purpose of this study was to describe and compare the incidence and outcomes of CDI after allogeneic HCT and lung transplantation, using a multicenter, prospective study design. This study was performed in conjunction with the Organ Transplant Infection Prevention and Detection Project (OTIP) of the Centers for Disease Control and Prevention (CDC). OTIP was a prospective cohort study of all proven and probable invasive fungal infections in

patients undergoing allogeneic HCT or lung transplantation (lung and allogeneic HCT transplants were selected for analysis because of the higher rates of invasive infections among these patients); however, data on other infections, including CDI, were collected as well, providing a prospective opportunity to study CDI after lung and allogeneic HCT transplant.

Patients and Methods

Six academic medical centers from across the United States participated in the OTIP study. Lung transplant recipients were enrolled at five sites, and allogeneic HCT recipients were enrolled at four sites, from April 2007 – March 2010. Study participants were enrolled during their transplant hospitalization. All participants provided written informed consent. Each institution's institutional review board (IRB) approved the study.

Data collection

Participants underwent clinical assessments at enrollment and weekly during their transplant hospitalization. After discharge, participants were contacted by phone weekly up to 12 weeks post-transplant. After 12 weeks, participants were contacted monthly. If readmitted to the hospital, participants were followed weekly until discharge. Participants were followed for 2.5 years post-transplant for readmissions, infections, and other outcomes.

Demographic data collected at enrollment included age, sex, race, underlying disease status, comorbid disease, type of transplant conditioning, prior chemotherapy/immunosuppressive therapies, and transplantation history. Other data collected at enrollment included transplant date, donor/recipient CMV status, immunosuppressive medications, and laboratory culture and/or test results, including *C. difficile* test results. The OTIP sites used a variety of CDI diagnostic methods during the study period: EIA for toxins A/B (sites B, D, and F), cytotoxicity assay (site A), antigen detection or PCR (site C), and GDH plus toxin A/B immunoassay (site E). The weekly inpatient and outpatient assessments included patient status (home, inpatient, ICU, deceased), mechanical ventilation, current medications, and symptoms of infection. All infections were reviewed by Infectious Diseases physicians at each site to determine whether the infection was probable, confirmed, or neither. Infections were defined according to National Nosocomial Infections Surveillance (NNIS) criteria.[19] In addition to patient interviews, clinical data were collected prospectively from medical records when participants were hospitalized and as available from outpatient clinic records. In order to be considered a CDI case, a patient was required to have a positive laboratory test for *C. difficile* and meet the NNIS criteria for gastroenteritis and/or GI tract infection in the clinical judgment of the Infectious Disease physician.

Data analyses

CDI cases were included if they occurred any time within 365 days post-transplant. The date of first positive laboratory test for *C. difficile* was used as the index date for analyses. For individuals without CDI, an analogous "index" date was randomly selected such that the distribution of time from transplant to index date was comparable between CDI cases and controls. For patients with >1 transplant during the study period, only the first transplant was

included, and patients were censored at the time of second transplant. For this analysis, patients were excluded if they were enrolled >7 days post-transplant; prospective data on these patients' pre- and peri-transplant medications were limited. Patients also were excluded if they had CDI at the time of transplant. There were 787 patients at the six sites enrolled in OTIP; 614 (86%) met all inclusion criteria for this study and were included in analyses (Figure 1).

Because the primary outcome of interest in the OTIP study was fungal infections, not CDI, limited data on antimicrobial use were available. Thus, analyses focused on demographics and outcomes among CDI cases and controls, as well as the general epidemiology of CDI among the lung and allogeneic HCT populations. Chi-square and logistic regression were used for univariate analyses of categorical variables, as appropriate. Kaplan-Meier plots and Cox proportional hazards models with heavy-side functions were used to compare survival between CDI cases and controls up to 180 days post-index date. A p-value of 0.05 was considered significant in all analyses. Analyses were performed with SPSS, version 23.0 (Armonk, NY), SAS version 9.2 (Cary, NC), and Stata MP11 (College Station, TX).

Results

A total of 614 patients met inclusion criteria for this study and were included in analyses. Lung transplant recipients accounted for 37% of the enrolled patients (N=229) and allogeneic HCT recipients accounted for 63% (N=385). 150 patients developed CDI within 365 days of transplant: 30 (20% of CDIs) among lung transplant recipients (incidence 13.1%) and 120 (80% of CDIs) among allogeneic HCT recipients (incidence 31.2%).

CDI incidence and time to infection in lung transplant recipients is shown in Table 1 and in allogeneic HCTs in Table 2. Site A enrolled 75% of the lung transplant patients. Two sites did not have any CDI cases; however, these sites accounted for only 7 transplants. Among the 3 sites with CDI cases among lung transplant recipients, site A had a median time to CDI of >100 days post-transplant, and time to the single CDI case at site C was 116 days. Site B had a much shorter median time to CDI onset of 17 days; at site B, 4 of the 7 CDI cases occurred within 20 days of transplant, one occurred at day 90, and 2 occurred >100 days post-transplantation. All four sites that enrolled allogeneic HCT patients reported CDI cases, with rates ranging from 12.1 – 37.8 CDI per 100 transplants. The median time from transplant to CDI ranged from 23–48 days at the 4 sites. Overall, the median time from transplant to CDI was shorter among allogeneic HCT recipients than among lung transplant recipients (mean = 27 days vs. 90 days; p=0.037; Figure 2).

Patient characteristics associated with CDI after lung transplantation are shown in Table 3 and after allogeneic HCT are shown in Table 4. Among lung transplant recipients only renal failure was significantly associated with CDI, but the numbers were very small. After allogeneic HCT, patients with CDI were more likely than uninfected patients to have received myeloablative conditioning (61% vs. 38%; p=0.003) and high dose dexamethasone (20% vs. 13%; p=0.053). Other cardiovascular disease was the only comorbidity that was more common among CDI cases than uninfected HCT recipients (29% vs. 18%; p=0.015), and lack of a preexisting comorbid disease was more common among uninfected persons

than CDI cases (46% vs. 31%; p=0.004). These relationships were primarily driven by site F, which enrolled 50% of the allogeneic HCTs. When site F was removed from analyses, those two comorbidity variables were no longer statistically significant (data not shown). By contrast, when site F was excluded, myeloablative conditioning remained associated with CDI: 86% of cases received myeloablative conditioning vs. 68% of controls (p=0.01). Any GVHD in the previous 30 days was more common among CDI cases than controls (23% vs. 12%; p=0.003). History of a symptomatic urinary tract infection (UTI) in the 30 days before the index date was more common among CDI cases than uninfected persons, although the difference was of borderline significance (6% vs. 2%, p=0.06).

Among lung transplant recipients, several outcomes (renal failure, BSI, and pneumonia) occurred significantly more often among CDI cases than controls in the 30 days post-index date (p<0.05 for all; Table 3). Notably, 27% of CDI cases experienced a BSI during the 30 days post-index date. Among the allogeneic HCT recipients, CDI cases were more likely than controls to have any GVHD during the 30 days post-index date (40% vs. 27%; p=0.009) (Table 4).

Survival within 180 days after CDI/index date is shown in Figure 3 for lung transplant recipients and Figure 4 for allogeneic HCT recipients. Among the lung transplants recipients, Cox regression was performed using a heavy-side function to compare mortality in the periods 0–30, 31–120, and 121–180 days post-index date. There was no significant difference in mortality between CDI cases and controls during the early periods (p=0.98 and p=0.23). There was a trend towards increased mortality during the late period among CDI cases (Hazard ratio [HR] = 4.7 [95% CI 0.8 – 28.1]; p=0.09) compared to controls. Among allogeneic HCT recipients, Cox regression was performed using a heavy-side function to determine mortality in the early time period 0–30 days compared to the later time period 31–180 days post-index date. There was no significant difference in mortality between CDI cases and controls during the early period (p=0.52), but mortality was significantly higher among CDI cases during the late period (HR=1.80 [95% CI 1.2 – 2.8]; p=0.007) compared to controls. Among patients who had died by 180 days post-index date, the underlying disease was the cause of death among 27% of allogeneic HCT recipients and 8% of lung transplant recipients (p=0.07), and any infection was the cause of death among 21% of the allogeneic HCT recipients and 32% of the lung transplant recipients (p=0.21).

Discussion

We compared the epidemiology of CDI in lung transplant and allogeneic HCT recipients. Overall, CDI is common in both populations, but the incidence among allogeneic HCT recipients is more than two times higher than the incidence of CDI in lung transplant recipients.

The epidemiology of CDI after lung transplantation is unclear, and the varying duration of follow-up periods in previous studies make it difficult to make comparisons among studies. CDI incidence has been estimated in the range of 7–31%,[20] and a recent meta-analysis reported the pooled prevalence of CDI at 10.8%, but the duration of follow-up varied by study.[21] Lee et al. and Dallal et al. retrospectively reviewed CDI in lung transplant recipients

and reported incidence estimates of >20%-31%, but their analyses covered >10 years.[15,16,22] Gunderson et al reported a lower CDI incidence of 4% within one year of lung transplantation compared with our estimate of 13.1%.[23] It may be that CDI incidence after lung transplantation varies by site due to practice variation, such as differing candidate selection, pre-transplant medications, and antimicrobial prophylaxis. Further multicenter studies with detailed analyses of risk factors for CDI are needed to address these questions.

We found the median time from transplant to CDI was significantly shorter among allogeneic HCT recipients than lung transplant recipients. This is likely due in part to the comparatively greater immunosuppression caused by allogeneic HCT conditioning regimens, with subsequent prolonged neutropenia, mucositis, and intense antimicrobial exposures. Notably, CDI cases among allogeneic HCT recipients were more likely than uninfected recipients to have received myeloablative conditioning or high dose dexamethasone. The relationship between myeloablative conditioning and CDI in HCT recipients has been noted previously.[7,11] The underlying biological mechanism behind this relationship may be two-fold: myeloablative conditioning increases neutropenia, damages the gut mucosa, and is associated with a higher risk of infection in the pre-engraftment period (and thus exposure to broad spectrum antimicrobials) versus non-ablative conditions; all of these may increase risk of CDI.[24] Alternatively, patients who receive myeloablative conditioning are more likely to develop diarrhea, and thus more likely to have concurrent asymptomatic *C. difficile* colonization detected. Notably, approximately half of the CDI cases in this study occurred >30 days after transplant, suggesting heightened suspicion of CDI after allogeneic HCT should continue beyond the immediate post-transplant period.

By comparison, CDI among lung transplant recipients appeared to occur more often in the later post-transplant period. The median time to CDI after lung transplant was 90 days, although this estimate was primarily driven by the 22 CDI cases at site A. Site B, which reported 7 CDI cases, had a median time to CDI of only 17 days. The time to CDI at site B appeared bi-modal, with 4 cases within 30 days of transplant and 3 cases from day 90 or later. This bi-modal distribution was not evident at site A. This discrepancy may be due to different transplant characteristics at the two sites or the small sample size at site B. Conversely, it is possible that the lung transplant recipients do have two distinct phases of increased risk for CDI: the first immediately following transplantation, and the second in the later post-transplant period, resulting from increased or renewed exposure to CDI risk factors.

Although antimicrobial usage data were not available for these analyses, we did have prospectively collected data on other infections among the transplant recipients, which can be used as a surrogate marker for antimicrobial use.[25] Additionally, transplant recipients, particularly allogeneic HCT, have almost universal exposure to antimicrobials. Among the allogeneic HCT recipients, symptomatic UTI was a borderline risk factor for CDI. UTIs are often treated with antimicrobials such as fluoroquinolones or cephalosporins, which in turn may increase the risk of CDI. An analysis using Medicare data found that UTIs were responsible for a greater population attributable risk fraction of CDI cases than any other type of infection,[25] and they may be a useful antimicrobial stewardship target.

We found mortality within 180 days of CDI/index date to be significantly higher in the allogeneic HCT population but not the lung transplant population. CDI was not associated with increased risk of mortality within the first 30 days, but mortality was significantly higher among CDI cases from 31–180 days post-index date after allogeneic HCT. This finding is different from that of Willems et al., who found no significant difference in survival between CDI cases and controls within two years.[14] Willems et al. measured survival post-HCT, whereas we measured survival in days from CDI or a random index date, selected to match the distribution of CDI case onset in the post-HCT period. Among the lung transplant recipients, while we did not detect a significant difference in survival at 180 days post-CDI/index date, we did find that mortality was marginally higher among CDI cases from 120 to 180 days post-index date. Lee et al found mortality among lung transplant recipients to be significantly higher after CDI, but their retrospective single-center cohort spanned 11 years.[16] It may be necessary to follow lung transplant recipients for a longer period of time to detect the effect of CDI on mortality. Notably, we found BSI and pneumonia to be significantly more frequent in the 30 days after CDI in the lung transplant population. It is unclear whether these infections truly result from CDI (or increased healthcare exposure caused by CDI), or whether CDI is merely a marker of increasing severity of illness. Alternatively, these infections may be a result of microbiome disruption associated with CDI; this relationship has been suggested previously with CDI and sepsis.[26] Overall, our data suggest that CDI likely increases mortality in allogeneic HCT recipients, while more data are needed on CDI and mortality after lung transplantation.

There are several limitations to this study. Because OTIP's original focus was on fungal infections, not CDI, data on antimicrobials were not collected. Stool samples were not collected, so we were unable to evaluate colonization with *C. difficile*. A variety of *C. difficile* diagnostic tests were used at the participating sites, and these may affect CDI rates.[27] Additionally, CDI epidemiology and *C. difficile* diagnosis have continued to change since this study was performed; for example, use of molecular diagnostics has increased.[27] Finally, this study was not designed for a detailed analysis of the relationship between CDI and GVHD. This relationship is complex, and previous research suggests GVHD, which is associated with loss of a healthy gut microbiome, may be both a risk factor and outcome of CDI.[6,7,24,28–30] This deserves additional study. Despite these limitations, this analysis has several strengths, including a prospective, multicenter, cohort study design. Patient assessments were performed throughout the study, regardless of whether the participants were inpatients or outpatients. The data collected were not limited to medical records and/or inpatient hospitalizations, and thus more accurately reflect patients' clinical status throughout the post-transplant period.

While no consensus exists on the exact burden among immunocompromised patients, CDI is clearly a problematic infection; the current analysis provides useful data on the epidemiology and outcomes of CDI in allogeneic HCT and lung transplant recipients. The epidemiology of CDI varies by transplant population, with CDI generally occurring earlier post-transplant among allogeneic HCT recipients than lung transplant recipients. Variations in CDI incidence among the 6 sites participating in the OTIP study suggest local practices may influence risk and outcomes of CDI; this is an important area for future study. CDI may be both a cause and indicator of increasing morbidity, particularly among lung transplant

recipients. Innovative strategies for CDI prevention and treatment among allogeneic HCT and lung transplant recipients are needed.

Acknowledgments

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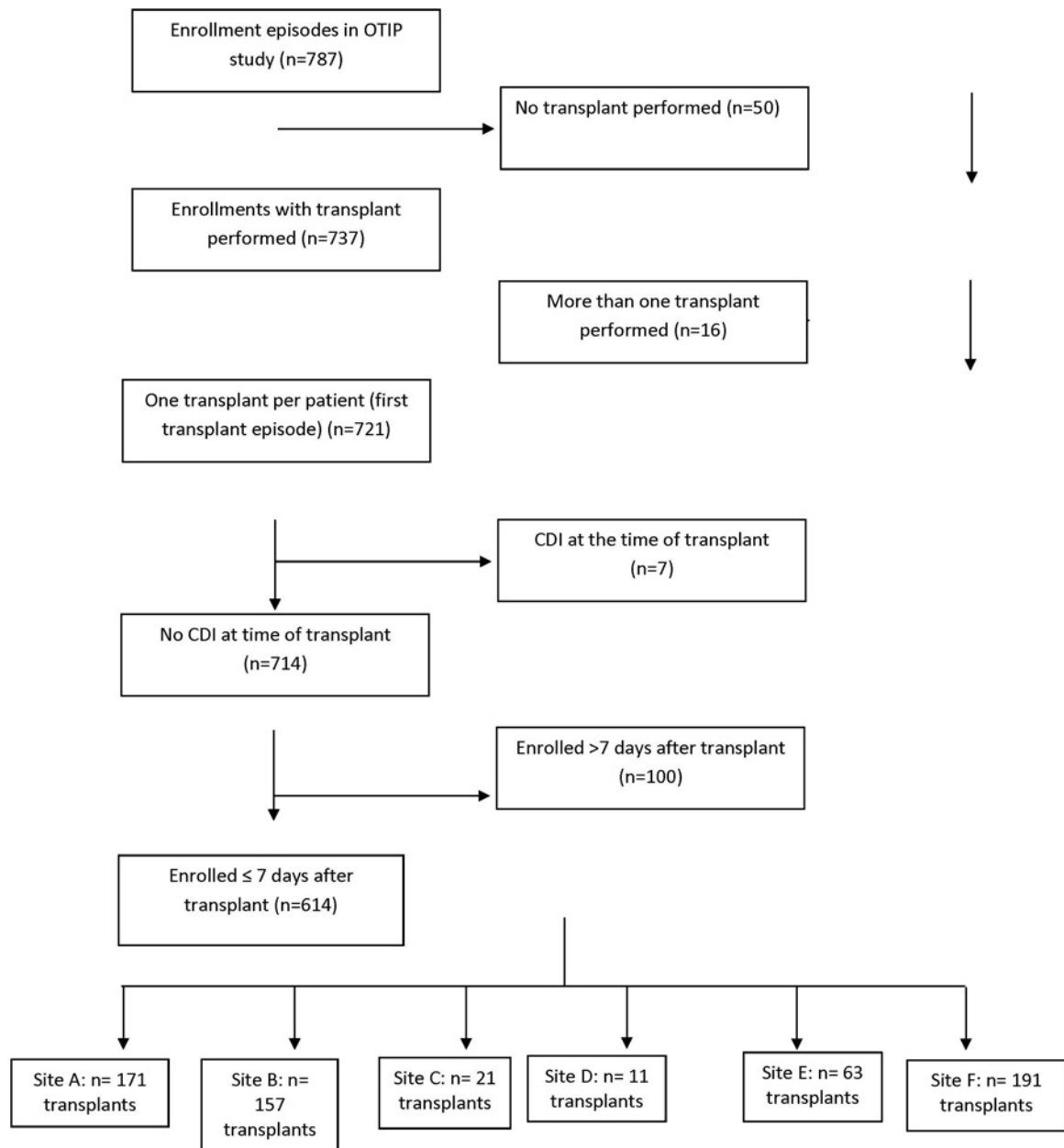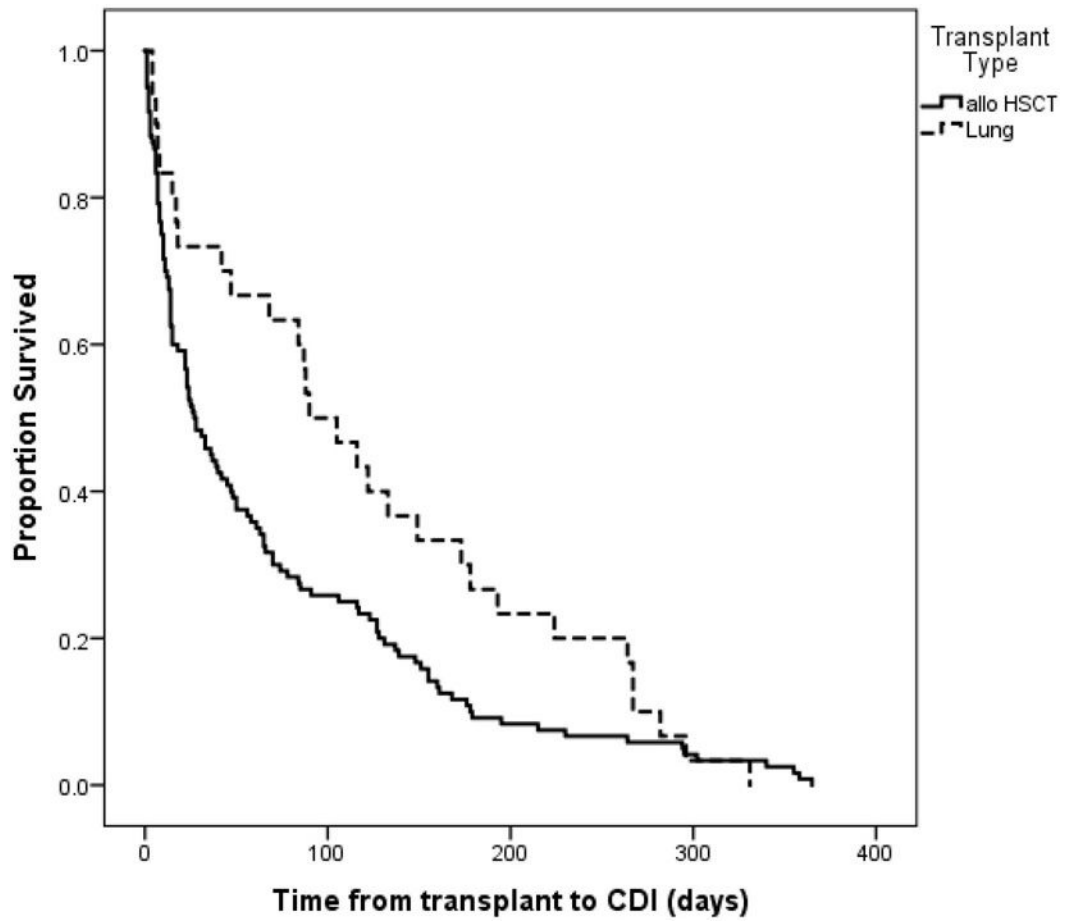
Figure 1.
STROBE diagram of study population.

Figure 2.
Comparison of time from transplant to CDI by transplant type. The median time from transplant to CDI was 27 days among allogeneic HCT patients and 90 days among lung transplant patients (log-rank p=0.037).
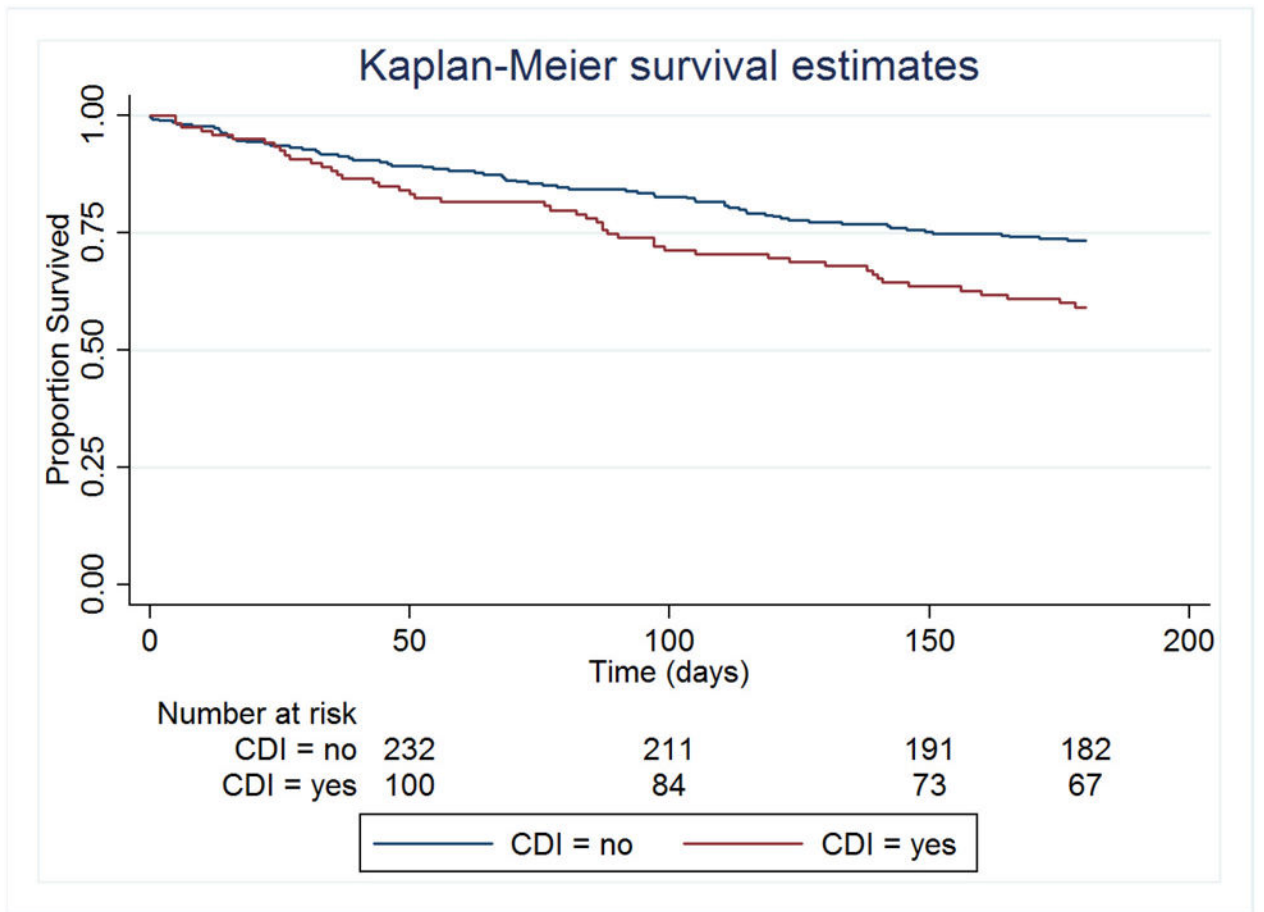
Figure 3.
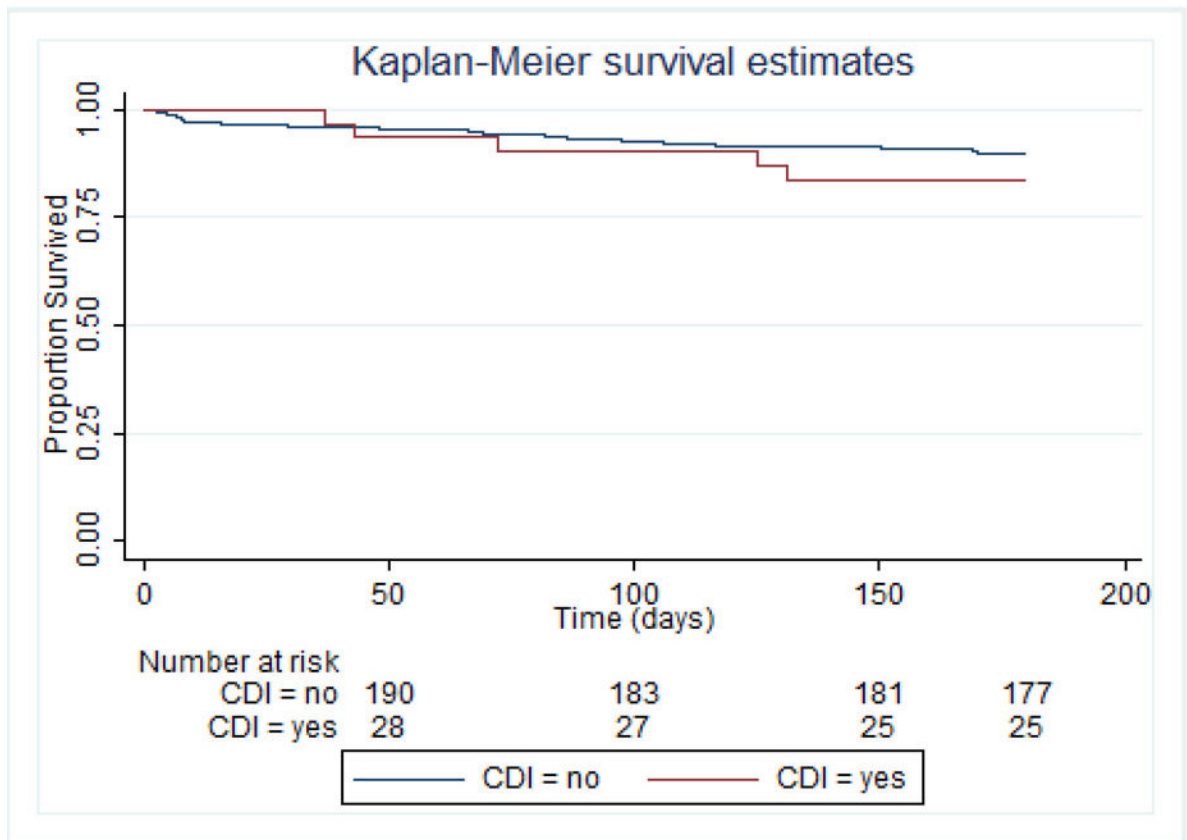Lung transplant recipients: Survival at 180 days after index date, stratified by CDI status.

Figure 4:
Allogeneic HCT recipients: Survival at 180 days after index date, stratified by CDI.

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Table 1.

Clostridium difficile **infections in 229 lung transplant recipients**

Site	Enrollment N (%)	CDI N (%)	CDI rate per 100 lung transplants	Time to CDI Median days (range)
A	171 (75)	22 (73)	12.9	105 (4 – 331)
B	30 (13)	7 (23)	23.3	17 (4 – 282)
C	21 (9)	1 (3)	4.8	[a](116)
D	2 (1)	0 (0)	0.0	-
E	5 (2)	0 (0)	0.0	-
F	NA	NA	NA	-
Total	229	30	13.1	90

[a]Median not calculated due to only 1 CDI case patient.

Table 2.

Clostridium difficile **infections in 385 allogeneic HCT transplant recipients**

Site	Enrollment N (%)	CDI N (%)	CDI rate per 100 allogeneic HCTs	Time to CDI Median days (range)
A	NA	NA	NA	NA
B	127 (33)	48 (40)	37.8	48 (1 – 340)
C	NA	NA	NA	-
D	9 (2)	2 (2)	22.2	^{a}(6, 50)
E	58 (15)	7 (6)	12.1	47 (1 – 230)
F	191 (50)	63 (53)	33.0	23 (1 – 365)
Total	385	120	31.2	27

^{a}Median not calculated due to 2 CDI case patients.

Table 3.

Variables associated with CDI after lung transplantation (N=229; p 0.20)[a]

Variable	CDI N (%)	No CDI N (%)	OR (95% CI)	p-value
Risk Factors				
Comorbidities				
Gastroesophageal reflux disease	12 (40)	52 (26)	1.9 (0.9 – 4.2)	0.12
Other GI disease	5 (17)	15 (8)	2.5 (0.8 – 7.3)	0.15[c]
Severity of illness in 30 days before index date				
ICU admission	11 (37)	48 (24)	1.8 (0.8 – 4.1)	0.14
Mechanical ventilation	11 (37)	48 (24)	1.8 (0.8 – 4.1)	0.14
Renal failure	3 (10)	3 (2)	7.3 (1.4 – 37.8)	0.031[c]
Symptomatic UTI	2 (7)	3 (2)	4.7 (0.7 – 29.2)	0.13[c]
Outcomes				
ICU admission[b]	3 (10)	8 (4)	2.7 (0.7 – 10.6)	0.16[c]
Mechanical ventilation	5 (17)	15 (8)	2.5 (0.8 – 7.3)	0.15[c]
Renal failure	3 (10)	4 (2)	5.4 (1.2 – 25.5)	0.050[c]
BSI	3 (10)	2 (1)	10.9 (1.7 – 68.5)	0.017[c]
Pneumonia	8 (27)	13 (7)	5.2 (1.9 – 13.9)	<0.001
Symptomatic UTI	2 (7)	3 (2)	4.7 (0.7 – 29.2)	0.13[c]

[a] Potential risk factors and outcomes with p>0.20 not included in the table: Age, sex, race, coronary artery disease, congestive heart failure, peripheral vascular disease, other cardiovascular disease, COPD, asthma, other pulmonary disease, cirrhosis, chronic renal insufficiency, end state renal disease, hemodialysis, peritoneal dialysis, splenectomy, diabetes, autoimmune disease, HIV, HCV, HBV, other comorbid disease, no comorbid disease, all pre-transplant medications; dialysis, bloodstream infection, pneumonia, febrile neutropenia, viremia, or respiratory tract infection in 30 days before index date; dialysis, viremia, and respiratory tract infection in 30 days after index date.

[b] ICU admissions at index date are excluded.

[c] Fisher's exact test.

Table 4.

Variables associated with CDI after allogeneic HCT (N=385; p 0.20)[a]

Variable	CDI N (%)	No CDI N (%)	OR (95% CI)	p-value
Risk Factors				
Comorbidities				
Other cardiovascular disease	35 (29)	48 (18)	1.9 (1.1 – 3.1)	0.015
Diabetes not requiring insulin	9 (8)	8 (3)	2.6 (1.0 – 6.9)	0.047
No comorbid disease	37 (31)	123 (46)	0.5 (0.3 – 0.8)	0.004
Pre-transplant medications				
Dexamethasone (high dose)	24 (20)	33 (13)	1.8 (1.0 – 3.1)	0.053
ATGAM	7 (6)	26 (10)	0.6 (0.2 – 1.4)	0.20
Other immunomodulator	32 (27)	53 (20)	1.5 (0.9 – 2.4)	0.14
Fludarabine	41 (34)	115 (43)	0.7 (0.4 – 1.1)	0.09
Busulfan	67 (56)	171 (65)	0.7 (0.4 – 1.1)	0.10
Campath	0 (0)	7 (3)	Undef	0.10[c]
Myeloablative conditioning	33 (61)	55 (38)	2.6 (1.4 – 4.9)	0.003
Severity of illness in 30 days before index date				
Symptomatic UTI	7 (6)	5 (2)	3.2 (1.0 – 10.4)	0.055[c]
Graft versus host disease (any)	28 (23)	31 (12)	2.3 (1.3 – 4.0)	0.003
Outcomes				
Pneumonia	7 (6)	8 (3)	2.0 (0.7 – 5.6)	0.19
Viremia	14 (12)	16 (6)	2.1 (1.0 – 4.4)	0.056
Respiratory tract infection	0 (0)	7 (3)	Undef	0.10[c]
Graft versus host disease (any)	48 (40)	71 (27)	1.8 (1.2 – 2.9)	0.009

[a]Potential risk factors and outcomes with p>0.20 not included in the table: Age, sex, race, coronary artery disease, congestive heart failure, peripheral vascular disease, COPD, asthma, other pulmonary disease, GERD, cirrhosis, other GI disease, chronic renal insufficiency, end stage renal disease, hemodialysis, peritoneal dialysis, splenectomy, diabetes requiring insuling, autoimmune disease, HIV, HCV, HBV, other disease, unmatched HCT donor, unrelated HCT donor, status of malignancy; other pre-transplant medications, ICU admission, mechanical ventilation, renal failure, dialysis, bloodstream infection, pneumonia, febrile neutropenia, viremia, or respiratory tract infection in 30 days before index date; ICU admission, mechanical ventilation, renal failure, dialysis, bloodstream infection, symptomatic UTI, febrile neutropenia, or respiratory tract infection in 30 days after index date.

[c]Fisher's exact test.