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Relationship between clostridium difficile infection and gastrointestinal graft versus host disease in recipients of allogeneic stem cell transplantation

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Clostridium difficile infection (CDI) is a common infection in patients undergoing allogeneic stem cell transplantation (allo-SCT), with reported incidence ranging from 9 to 24% in the first 100 days, post transplantation [1–4]. The signs and symptoms of CDI bear resemblance to patients with acute gastrointestinal graft versus host disease (GI GVHD), making it difficult to differentiate between these two common complications of allo-SCT [5]. It has also been reported that the development of either CDI or GI GVHD can increase the risk of subsequent development of the other in the post-transplant period [1]. We examined the relationship between CDI and GI GVHD in the related and unrelated allo-SCT.

At our center, combination of tacrolimus, mycophenolate mofetil plus ATG (TM-thymo) at a total dose of 4.5 mg/kg as GVHD prophylaxis (IV infusion over 3 days: day –3, 0.5 mg/kg; day –2, 1.5 mg/kg; and day –1, 2.5 mg/kg) is used for all unrelated donor transplants since 2012; we previously reported excellent outcomes with relatively low rate of grade III–IV acute GVHD [6, 7]. For the matched related donor transplants and matched unrelated donor transplants done prior to 2012 we used a combination of tacrolimus and mycophenolate mofetil for GVHD prophylaxis. Mechanism of action of ATG in GVHD prevention is mediated through in vivo depletion of T cells, thus activation and expansion of effector cells are effectively attenuated [8]. The consequence of this action also can subject patients to increased risk of infections [7].

We retrospectively studied a total of 310 consecutive patients in 2 cohorts who underwent allo-SCT at our institution between 2009 and 2013. Two distinct cohorts were: 100 patients

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who received related donors (group 1, transplanted between 3/2010–12/2013), and 210 patients who received unrelated (group 2 transplanted between 12/2009–12/2013) allo-SCT. This study protocol was approved by Wayne State University Institutional Review Board. CDI was defined as infection in a patient with diarrhea and a positive result of a laboratory assay for toxigenic *clostridium difficile* qPCR in the stool.

Descriptive statistics were used to summarize demographic and baseline characteristics among study populations. Chi-square (or Fisher's exact) and Kruskal–Wallis tests were used to compare among groups for categorical and continuous variables, respectively. The Kaplan–Meier method was used to describe the distributions of CDI-free survival (CFS), acute GI GVHD-free survival (giGFS), acute GVHD-free survival (aGFS), and overall survival (OS) after treatment. CFS, giGFS, and aGFS were defined as the time from transplantation to development of *C. difficile*, acute GI GVHD, and acute GVHD, respectively, and to death from any cause; OS was defined as the time from transplantation to death from any cause. Univariate and multivariable Cox proportional hazards regression models were fitted to assess associations between patient characteristics and survival benefit (CFS, giGFS, aGFS, and OS).

Baseline characteristics of the two groups are outlined in Table 1. All patients received acyclovir/fluconazole/norfloxacin for prophylaxis against infections and received daily GCSF starting on day 6 post-transplant until neutrophil engraftment. The median follow-up of OS for the two groups was 2.43 years (95% CI, 2.22–2.87).

The cumulative incidence of CDI was 18% (95% CI, 11–26%) vs 26.7% (95% CI, 19–30%) in groups 1 and 2 respectively ($p = 0.24$). The median time to development of CDI was 12.5 days (range D-3 to D 113) in group 1 and 16 days (range D-3 to D209) in group 2. In a multivariable Cox regression analysis for risk factors for development of CDI, steroid use for GVHD was the only risk factor independently predictive of increased incidence of CDI (HR, 2.28; 95% CI, 1.29–4.05; $p < 0.001$) (Table 2). We decided not to include use of beta-lactam antibiotics in our analysis because most (>90%) patients received beta-lactam antibiotics in the post-transplant period.

The incidence of GI GVHD was higher in group 2 as compared to group 1 (33 vs 23%) and correspondingly the use of systemic steroids was higher in group 2 (45 vs 33%). The median time to development of GVHD was 39 days in group 1 and 28 days in group 2. Among the patients with CDI, 38% (7/18) in group 1 and 42% (24/57) also developed GI GVHD. In patients who developed both CDI and GI GVHD, CDI preceded GI GVHD in all patients (7/7) in group 1 and in 67% (16/24) of patients in group 2. Eight patients in group 2 developed CDI after development of GI GVHD. Majority of patients (95%) with a diagnosis of GI GVHD underwent GI biopsy to confirm the diagnosis including all patients who developed both CDI and GVHD. Rate of stage 3–4 GI GVHD was 35% (8/23) in group 1 and 30% (21/70) in group 2.

Development of CDI increased the subsequent risk of development of GI GVHD. Patients who developed CDI had a statistically significant higher probability of developing acute GI GVHD (HR, 1.92; 95% CI, 1.15–3.19; $p = 0.01$) (Fig. 1). In a multivariable Cox regression,

independent covariates associated with acute GI GVHD were CDI, diagnosis of lymphoma, unrelated donor transplant, use of ATG, and HLA mismatch. Development of acute GI GVHD was associated with increased mortality (HR 1.7; 95% CI, 1.15–2.5; $p = 0.01$) while development of CDI had no effect on OS.

To our knowledge this is the largest report of CDI among recipients of allo-SCT. We confirmed the high incidence of CDI in this patient population approaching 27% in recipients of unrelated donor transplants [1–4]. Similarly, our study confirms that the highest incidence of CDI is during pre-engraftment period within the first 2 weeks after transplantation, which correlates with the duration of neutropenia and antibiotic use. In addition, CDI can complicate therapy of GI GVHD with increased incidence with use of systemic steroids.

Our study confirms the earlier preliminary findings of increased risk of GI GVHD in patients who develop CDI in the post-transplant period [1]. One of the mechanisms of GVHD includes tissue inflammation leading to release of cytokines leading to activation of immune system [5]. We hypothesize that CDI causes worsening tissue injury and inflammation in the gut thus increasing the risk for GI GVHD. The other mechanism linking the two diagnoses may be decreased/altered microbial diversity, which is seen both in patients with CDI [9] and with GI GVHD [10]. Thus, reducing the incidence of CDI may help reduce the incidence of GI GVHD. Since colonization with *Clostridium difficile* prior to hematopoietic stem cell transplantation has been shown to be a significant risk factor for later development of CDI [11], further studies to identify the high risk patients and using prophylactic strategies to eliminate *Clostridium difficile* may help reduce the incidence of gastrointestinal graft-versus-host disease.

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Fig. 1.

Rates of development of subsequent GI GVHD in patients with and without prior CDI

Table 1

Baseline characteristics

	Matched related allogeneic (N = 100)	Unrelated allogeneic (N = 210)	P-value
Age at Transplant – median (range)	54 (19, 59.25)	56 (20, 62)	0.21
Gender – count (%)			0.57
Female	42 (42)	97 (46)	
Male	58 (58)	113 (54)	
Race – count (%)			0.01
African-American (AA)	13 (13)	8 (4)	
Caucasian (EA)	83 (83)	190 (90)	
Others	4 (4)	12 (6)	
Conditioning regimen – count (%)			0.04
MAC	68 (68)	116 (55)	
RIC	32 (32)	94 (45)	
Diagnosis – ?count (%)			0.20
Leukemia	48 (48)	120 (57)	
Lymphoma	29 (29)	39 (19)	
MDS	12 (12)	29 (14)	
Other	11 (11)	22 (10)	
Source of stem ?cells – count (%)			0.85
BM	9 (9)	16 (8)	
PBSC	91 (91)	194 (92)	
HLA match – ?count (%)			<0.001
10/10	93 (93)	138 (66)	
Others	6 (6)	68 (32)	
Missing	1 (1)	4 (2)	
GVHD prophylaxis – count (%)			<0.001
TACRO/MMF	97 (97)	100 (48)	
TACRO/MMF/THYMO	0 (0)	101 (48)	
Other	3 (3)	9 (4)	

TACRO tacrolimus, *MMF* mycophenolate mofetil, *THYMO* anti-thymocyte globulin

Table 2

Univariable and multivariable Cox regression analyses for development of CDI

	Unadjusted		Adjusted	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Age at transplant	1 (0.98, 1.02)	0.77	0.99 (0.96, 1.01)	0.28
Steroid use for GVHD				
No	Reference		Reference	
Yes	2.03 (1.27, 3.23)	<0.001	2.28 (1.29, 4.05)	<0.001
Race				
Caucasian	Reference		Reference	
African American	1.11 (0.45, 2.75)	0.83	1.58 (0.53, 4.7)	0.41
Others	1.63 (0.71, 3.77)	0.25	1.18 (0.44, 3.13)	0.75
Diagnosis				
Leukemia	Reference		Reference	
Lymphoma	1.11 (0.63, 1.96)	0.72	0.97 (0.5, 1.86)	0.92
MDS	1.59 (0.88, 2.88)	0.13	1.56 (0.8, 3.04)	0.19
Other	0.45 (0.16, 1.26)	0.13	0.47 (0.16, 1.4)	0.18
Regimen intensity				
MAC	Reference		Reference	
RIC	1.22 (0.78, 1.93)	0.38	1.51 (0.86, 2.66)	0.15
Group				
Matched related allogeneic	Reference		Reference	
Unrelated allogeneic	1.6 (0.94, 2.72)	0.08	1.41 (0.71, 2.8)	0.33
HLA match				
10/10	Reference		Reference	
9/10	1.59 (0.92, 2.73)	0.10	1.10 (0.56, 2.17)	0.79
<9/10	0.49 (0.15, 1.56)	0.23	0.40 (0.11, 1.39)	0.15
ATG use				
No	Reference		Reference	
Yes	1.17 (0.74, 1.87)	0.50	1.02 (0.55, 1.88)	0.95
Acute GI GVHD				
No	Reference		Reference	
Yes	1.69 (0.78, 3.69)	0.19	1.01 (0.43, 2.39)	0.98

GVHD Graft versus host disease; MDS Myelodysplastic syndrome; MAC Myeloablative conditioning; RIC reduced intensity conditioning; HLA Human leukocyte antigen; ATG Anti-thymocyte globulin; HR Hazard ratio.