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Risk Factors and Outcomes of Invasive Fungal Infections in Allogeneic Hematopoietic Cell Transplant Recipients

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Abstract Allogeneic hematopoietic cell transplant (HCT) recipients are at increased risk of invasive fungal infections (IFI), which are associated with a high mortality rate. We evaluated the impact of IFI in allogeneic HCT patients. In total, 541 consecutive allogeneic HCT recipients were included. The cumulative incidence of any IFI and mold infections at 1-year post-HCT was 10 and 7%, respectively. Median times to IFI and mold infection were 200 and 210 days, respectively. There was a trend toward fewer IFI and mold infections in the last several years. Both acute graft-versus-host disease (GVHD) (OR 1.83, $p = 0.05$) and corticosteroid duration (OR 1.0, $p = 0.026$) were significantly associated with increased risk of IFI, acute GVHD (OR 2.3, $p = 0.027$) emerged as the most important association with mold infections. Any IFI [HR 4.1 (2.79–6.07), $p < 0.0001$] and mold infections [HR 3.34 (2.1–5.1), $p < 0.0001$] were independently associated with non-relapse mortality (NRM). This association persisted in the setting of both acute and chronic GVHD. Corticosteroid treatment for >90 days was also significantly associated with higher NRM [HR 1.9 (1.3–2.6), $p < 0.0001$]. This study highlights the impact of IFI on NRM among HCT patients. The decrease in number of IFI and mold infections over the last several years may reflect the benefit of prophylaxis with mold-active antifungal agents.

Keywords Invasive fungal infections · Hematopoietic cell transplantation · Aspergillosis · Mold infections · Candidiasis

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Introduction

Patients undergoing allogeneic hematopoietic cell transplantation (HCT) are at high risk of invasive fungal infections (IFI), which are associated with a high mortality rate [1]. Over the last 3 decades, the use of fluconazole prophylaxis in this population has decreased the incidence of *Candida* infections, while invasive mold infections, such as invasive aspergillosis, mucormycosis and fusariosis have emerged as the major cause of IFI [2]. Newer generation antifungal agents active against *Aspergillus* and other molds have allowed more effective prophylactic and therapeutic strategies among HCT recipients [3]. However, universal anti-mold prophylaxis remains controversial and is not standardized [4, 5]. In 2008, the EORCT/MSG diagnostic criteria for IFI were updated to reflect advances in the field by introducing the nonculture-based test for galactomannan as a criterion for probable invasive aspergillosis [6]. In many institutions, non-culture-based tests have not been readily available until recently and they have not been routinely used.

We evaluated the incidence, risk factors and impact of IFI in a cohort of 541 patients who underwent allogeneic HCT from 2007 to 2012. During this time period, significant advances in the detection, prophylaxis and treatment of mold infections were introduced into clinical practice. In our institution, routine use of antifungal prophylaxis was codified and galactomannan assays were added to the algorithm for the diagnosis of invasive aspergillosis.

Methods

Patients

All adult patients ≥18 years-old who underwent allogeneic HCT with a peripheral blood stem cell or bone marrow graft at the University of Michigan Blood and Marrow Transplant (BMT) Program between January 2007 and December 2012 were included in this retrospective study and were followed for 2 years post-transplantation. This study was approved by the University of Michigan Institutional Review Board.

Transplantation

The majority of patients ($n = 398$, 74%) received a fludarabine-based preparative regimen, in most cases in combination with busulfan ($n = 365$, 67%). Other preparative regimens included busulfan with cyclophosphamide in 16 patients (3%), a combination of carmustine, etoposide, cytarabine, and melphalan in 10 (0.2%) and total body irradiation (1200 Gy) with cyclophosphamide in 40 (7.4%). All patients received antiviral prophylaxis with acyclovir from day 0 up to 1 year post-HCT and antibacterial prophylaxis with levofloxacin while neutropenic or on corticosteroids. There was no consistent, targeted antifungal prophylaxis until 2011. Before 2011, most patients received prophylaxis with either fluconazole or voriconazole, depending on transplant physician preference. Starting in 2011, patients undergoing fully matched HCT without graft-versus-host disease (GVHD) received fluconazole prophylaxis at a standard dose of 100 mg orally daily per institutional guidelines. HLA-mismatched patients and those who developed GVHD requiring systemic therapy received oral voriconazole or posaconazole (oral solution) prophylaxis until they were completely off immunosuppressive drugs.

Data Collection and Definitions

Demographic data were obtained from the University of Michigan BMT Database. Informatics assistance with data abstraction and the electronic medical record search engine (EMERSE) tool were provided by the University of Michigan Cancer Center's Biomedical Informatics Core with partial support from the National Institutes of Health (NIH) Support Grant (CA46592).

We reviewed clinical, microbiological, pathological and radiological data on all patients who had an IFI. Each documented IFI within the first 2 years post-HCT was recorded and classified as proven, probable or possible according to EORTC-MSG criteria [6], and only those categorized as proven or probable were included in this analysis. When available, galactomannan measurement in bronchoalveolar lavage fluid was included as part of the diagnostic criteria for invasive aspergillosis.

Nadir and duration of absolute neutrophil count in this patient population was very homogenous and predictable based on underlying disease and chemotherapy received during conditioning prior to receiving HCT. Therefore, neutropenia was not expected to impact the rate of occurrence of IFI in these patients, and nadir and duration of neutropenia were not included in the analysis.

Acute GVHD was defined and scored according to Glucksberg criteria [7], and chronic GVHD was defined and scored according to NIH Consensus Criteria for clinical trials [8].

Corticosteroid duration was measured as the total number of days the patient was on high-dose corticosteroids (≥0.3 mg/kg prednisolone or equivalent for >3 weeks) for any reason within the first 2 years after HCT. In patients with steroid-refractory acute GVHD, second line therapy was chosen at the discretion of the treating physician. Patients were divided into 2 groups according to the duration of steroid therapy (<90 or >90 days) for survival analysis.

Statistical Methods

Pairwise comparisons were performed, in which the χ^2 or Fisher's exact test was used for categorical variables and the Wilcoxon rank-sum test was used for continuous variables. Logistic regression was used to estimate associations of patient characteristics with development of IFI, while cumulative incidence methods were used to estimate associations of patient characteristics and infection with non-relapse mortality, for which relapse is a competing event. Statistical significance was defined as a p value less than 0.05. All computations were done with the statistical package R, version 3.0.1.

Results

Patient Characteristics

A total of 541 consecutive patients who underwent allogeneic HCT were included in the study (Table 1). The median age was 54 (range 18–73), and 322 (60%) were women. Fifty percent of the transplants were from related donors, and the source was peripheral blood stem cells in the vast majority of patients ($n = 507$, 94%). The underlying hematological diseases are summarized in Table 1.

Fungal Infections

Sixty-one patients (11.3%) had an IFI after allogeneic HCT, and 45 of those 61 patients had an invasive mold infection. The median time to occurrence of an IFI was 200 days (8–644 days). The median time to occurrence of an invasive mold infection was 210 days (9–644 days). The cumulative incidence of any IFI and mold infections at 1 year after HCT was 10 and 7%, respectively.

Two-thirds of the IFI (41 of 61 patients) occurred early in the study period between 2007 and 2010. We observed a decrease in the number of IFI after 2010 following the introduction of institutional guidelines for antifungal prophylaxis (Fig. 1). The occurrence of IFI due to Mucorales or other uncommon molds was sporadic throughout the 8 years of the study.

Among the 45 patients who had invasive mold infections, 5 had proven invasive infections. These included invasive rhinosinusitis caused by Mucorales in 3 patients and disseminated infection caused by *Scedosporium apiospermum* and *Alternaria* spp. in 1 patient each. The remaining 40 patients had probable mold infections, including invasive pulmonary aspergillosis in 29 (64%). Of these 29 patients, 18 had a diagnosis of probable invasive pulmonary aspergillosis established by EORTC/MSG criteria using BAL galactomannan. Other causes of probable invasive pulmonary mold infection included Mucorales in 3 patients and *Paecilomyces* spp. in 2 patients. One patient had probable rhinosinusitis caused by a Mucorales, and 4 patients had probable invasive pulmonary infection caused by molds that could not be identified.

Twelve patients were diagnosed with yeast infection, of which 6 were fungemias, 3 with *C. glabrata*, and 1 each with *C. albicans, C. parapsilosis*, and *Saccharomyces cerevisiae.* Six others had non-severe focal infections caused by *Candida* spp. One patient had pulmonary blastomycosis. Three patients, one of whom was receiving monthly pentamidine prophylaxis, developed *Pneumocystis jiroveci* pneumonia.

Forty of the 61 patients with IFI were receiving antifungal prophylaxis with azoles or micafungin at the time of diagnosis (Table 2). There were more breakthrough fungemias with yeasts in the micafungin group. Mold infections were scattered among patients receiving any of the 3 different prophylactic regimens.

Risk Factors for IFI and Invasive Mold Infections

On univariate analysis, acute GVHD (OR 2.04, $p = 0.019$) and a longer duration of corticosteroid therapy (OR 1.0, $p = 0.008$) were significantly associated with the development of any IFI.

Table 1 Characteristics of 541 HCT recipients and patients who had invasive fungal infections and invasive mold infections

	Total patients ($n = 541$)	Patients with IFI ($n = 61$)	Patients with mold infections ($n = 45$)
Median age at HCT, years (range)	54 (18–73)	56 (28–68)	56 (28–68)
Gender			
Male	219 (40%)	42 (69%)	32 (71%)
Female	322 (60%)	19 (31%)	13 (29%)
Disease			
AML	242 (45%)	28 (46%)	21 (47%)
NHL/HD	112 (21%)	13 (21%)	8 (18%)
MDS/MPD	65 (12%)	8 (13%)	7 (16%)
ALL	65 (12%)	6 (10%)	4 (9%)
MM/plasma cell	46 (9%)	6 (10%)	5 (11%)
Other*	11 (2%)	0 (0%)	0 (0%)
Graft source			
Bone marrow	34 (6%)	0 (0%)	0 (0%)
Peripheral blood	507 (94%)	61 (100%)	45 (100%)
HLA matching			
Matched	464 (86%)	49 (80%)	35 (78%)
Mismatched	78 (14%)	12 (20%)	10 (22%)
Donor type			
Related	270 (50%)	26 (43%)	18 (40%)
Unrelated	271 (50%)	35 (57%)	27 (60%)

ALL acute lymphoblastic leukemia, *AML* acute myeloid leukemia, *HD* Hodgkin's disease, *HCT* hematopoietic cell transplant, *IFI* invasive fungal infection, *MDS* myelodysplastic syndrome, *MM* multiple myeloma and plasma cell diseases, *MPD* myeloproliferative disease, *NHL* non-Hodgkin lymphoma

*Other: aplastic anemia (7), atypical chronic myeloid leukemia (1), congenital neutropenia (1), mycosis fungoide (1) and Sezary syndrome (1)

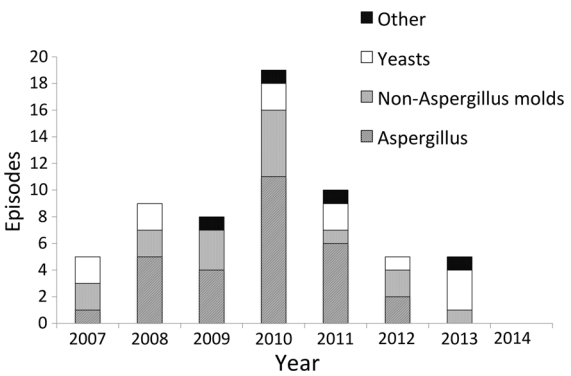

Fig. 1 Distribution of 61 invasive fungal infections over time among adult patients who underwent allogeneic HCT with a peripheral blood stem cell or bone marrow graft at the University of Michigan Blood and Marrow Transplant Program between January 2007 and December 2012. Patients were followed for 2 years post-transplantation*Other: *Blastomyces* spp. (1 episode), *Pneumocystis jiroveci* (3 episodes)

Transplantation of peripheral blood stem cells showed a significant association with IFI when compared with bone marrow grafts ($p = 0.029$). However, this finding is difficult to interpret as only 34 (6.2%) patients received bone marrow grafts (Table 3).

For mold infections, both acute GVHD (OR 2.5, $p = 0.012$) and duration of corticosteroid therapy (OR 1.0, $p = 0.03$) were significant risk factors. Peripheral blood stem cell transplantation was strongly associated with development of mold infection when compared with bone marrow grafts ($p < 0.0001$). Again, this finding is difficult to interpret because of the small number of patients who received a bone marrow graft (Table 4).

In order to assess the relative impact of GVHD and duration of corticosteroid therapy on the incidence of any IFI and on mold infections, in particular, we performed bivariate analysis. Both acute GVHD (OR 1.83, $p = 0.05$) and corticosteroid duration (OR 1.0,

Table 2 Invasive fungal infections in 40 patients receiving antifungal prophylaxis

Antifungal prophylaxis (number of patients)	Site of infection	Year of infection	
		2007–2010 Fungal organism (Total = 25)	2011–2014 Fungal organism (Total = 15)
Fluconazole (10)	Pulmonary	*Aspergillus* spp. (4)	*Pneumocystis jiroveci* (1)
		Mucorales (1)	*Aspergillus* spp. (3)
	Bloodstream		*Candida glabrata* (1)
Voriconazole (20)	Pulmonary	*Aspergillus* spp. (7)	*Aspergillus* spp. (5)
		Pneumocystis jiroveci (1)	*Paecilomyces* spp. (1)
	Rhinosinusitis	Mucorales (3)	Mucorales (1)
	Bloodstream	*Candida parapsilosis* (1)	
	Disseminated		*Alternaria* spp. (1)
Micafungin (10)	Pulmonary	*Aspergillus* spp. (3)	*Aspergillus* spp. (1)
	Rhinosinusitis	Mucorales (1)	
	Bloodstream	*Candida glabrata* (2)	*Saccharomyces cerevisiae* (1)
		Candida albicans (1)	
	Disseminated	*Scedosporium apiospermum* (1)	

$p = 0.026$) were significantly associated with increased risk of IFI. In the case of mold infections, acute GVHD (OR 2.3, $p = 0.027$) emerged as the most important association. Chronic GVHD was not significantly associated with a higher risk of IFI or mold infections (Table 5).

Risk Factors for Non-Relapse Mortality

The cumulative incidence of non-relapse mortality for all patients was 16 and 21% at 1 and 2 years, respectively. IFI were significantly associated with a higher 2-year mortality rate [62 vs. 21%, HR 3.2 (2.2–6), $p < 0.0001$], as were mold infections [58 vs. 23%, HR 2.6 (1.9–4.3), $p < 0.0001$] when compared with patients who did not have IFI or mold infections.

Corticosteroid treatment duration of more than 90 days was associated with significantly higher mortality [HR 1.9 (1.3–2.6), $p < 0.0001$]. This association was present in patients with and without acute or chronic GVHD. The mortality associated with IFI and mold infections, in particular, was significantly higher in patients receiving higher prednisone dose equivalent in mg/kg at the time of the infection [HR 2.1 (1.3–3.4) $p = 0.002$ and HR 2.05 (1.2–3.5), $p = 0.008$, respectively].

In patients with acute GVHD, having any IFI was associated with an increased 2-year mortality rate of 72% relative to 27% in patients with acute GVHD and no IFI [HR 2.9 (1.9–4.5), $p < 0.0001$]. Similarly, mold infections were associated with an increased 2-year mortality rate of 68% compared to 29% in patients with acute GVHD and no mold infection [HR 2.7 (1.7–4.2), $p = 0.0001$)] (Fig. 2). In patients with chronic GVHD, the presence of any IFI, but mold infections in particular, were associated with a significant increase in 2-year mortality ($p < 0.0001$) (Fig. 3).

Discussion

Invasive fungal infections and mold infections in particular are a major cause of morbidity and mortality not related to relapse in allogeneic HCT recipients [2, 9]. Classically, severe neutropenia secondary to aggressive conditioning regimens has been identified as a risk factor for fungal infections early after transplantation (<30 days). Immunosuppressive therapy for GVHD is typically identified as a major risk factor for fungal infections late after transplantation (>100 days) [10, 11].

Similar to prior reports, we found a rate of development of IFIs of 10% and of mold infections of 7% [12–15]. Previous studies reported the median time to development of an IFI or mold infection after allogeneic HCT to be about day +100 [11, 16–18]. We observed that most infections occurred later after HCT

Table 3 Univariate analysis of the impact of pre- and post-transplant characteristics of 541 HCT recipients on the development of invasive fungal infections

Variable	IFI		OR	*p* value
	No	Yes		
Source				
BM	34	0	N/A	0.029
PBSC	446	61		
Donor				
Related	244	26	1.40	0.230
Unrelated	236	35		
Match				
No	65	12	0.64	0.200
Yes	415	49		
Gender				
Male	280	42	0.63	0.117
Female	200	19		
Prior IFI				
No	458	56	1.85	0.230
Yes	22	5		
aGVHD				
No	202	16	2.04	0.019
Yes	278	45		
cGVHD				
No	219	22	1.48	0.159
Yes	261	39		
Age			1.02	0.075
Steroid duration			1.00	0.008

aGVHD acute graft-versus-host disease, *IFI* invasive fungal infections, *cGVHD* chronic graft-versus-host disease

Table 4 Univariate analysis of the impact of pre- and post-transplant characteristics of 541 HCT recipients on development of invasive mold infections

Variable	Invasive mold infection		OR	*p* value
	No	Yes		
Source				
BM	34	0		<0.0001
PBSC	462	45		
Donor				
Related	252	18	1.55	0.168
Unrelated	244	27		
Match				
No	67	10	0.55	0.114
Yes	429	35		
Gender				
Male	290	32	0.57	0.102
Female	206	13		
Prior IFI				
No	473	41	2.01	0.218
Yes	23	4		
aGVHD				
No	208	10	2.53	0.012
Yes	288	35		
cGVHD				
No	225	16	1.50	0.207
Yes	271	29		
Age			1.03	0.05
Steroid duration			1.0	0.03

BM bone marrow, *PBSC* peripheral blood stem cell, *aGVHD* acute graft-versus-host disease, *IFI* invasive fungal infections, *cGVHD* chronic graft-versus-host disease

at a median time of 200 and 210 days, for all IFI and for mold infections, respectively. This shift toward IFIs occurring later in the post-transplant course perhaps could be explained by the increasing use of antifungal prophylaxis typically until day +100.

In our study, 19 of 28 cases of probable invasive pulmonary aspergillosis had a positive BAL galactomannan. The number of allogeneic HCT remained steady during the study period. We suspect the peak number of cases of aspergillosis occurring in 2010 was likely related to the introduction of *Aspergillus* galactomannan testing on BAL samples as a microbiological criterion for IPA in the EORTC/MSG guidelines published in 2009 [6].

We also observed a decrease in the number of IFI after 2010 following the introduction of institutional guidelines for antifungal prophylaxis that recommended using voriconazole for all unrelated donor HCT through

Table 5 Bivariate analysis of the relative impact of GVHD and steroid duration on the incidence of invasive fungal and mold infections

Variable	Invasive fungal infection		Mold infection	
	OR	*p* value	OR	*p* value
aGVHD	1.83	0.052	2.30	0.027
Steroid duration	1.00	0.026	1.00	0.098
cGVHD	1.06	0.867	1.12	0.769
Steroid duration	1.00	0.029	1.00	0.094

aGVHD acute graft-versus-host disease, *cGVHD* chronic GVHD

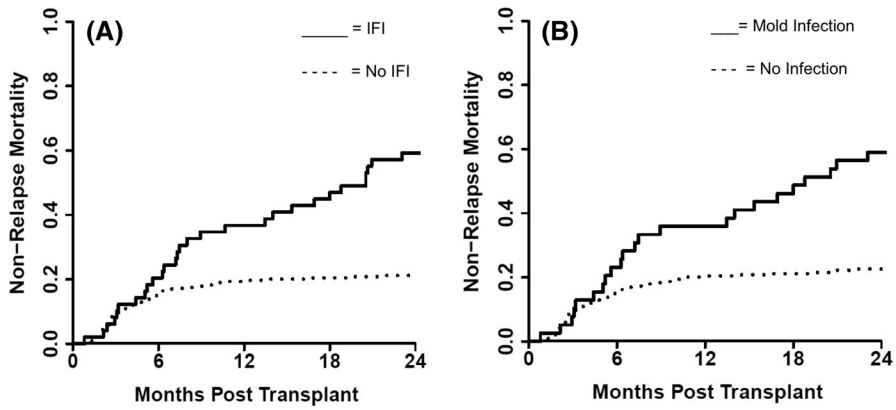

Fig. 2 Impact of any IFI and mold infections on non-relapse mortality in HCT recipients who had acute GVHD. **A** Impact of IFI on non-relapse mortality in patients with acute GVHD; **B** Impact of mold infections on non-relapse mortality in patients with acute GVHD

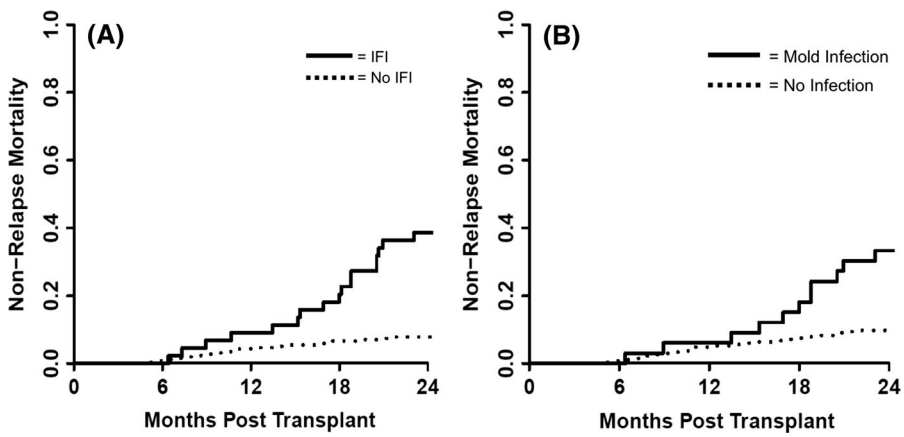

Fig. 3 Impact of any IFI and mold infections on non-relapse mortality in HCT recipients who had chronic GVHD. **A** Impact of IFI on non-relapse mortality in patients with chronic GVHD; **B** Impact of mold infections on non-relapse mortality in patients with chronic GVHD

day +100 and restarting this agent when steroids were given at total daily dose ≥0.3mg/kg.

In recent years, there has been an increased incidence of infections due to unusual fungi in HCT recipients [19, 20]. These changes have been attributed, in part, to the use of certain agents for antifungal prophylaxis, as well as more aggressive immunosuppression [1, 14]. In our HCT recipients, there were 7 patients who were infected with Mucorales, and 4 of them had been on voriconazole prophylaxis. These numbers, as in previous reports, are small, and it is difficult to assess causation, but these data add to the speculation of a voriconazole effect [21, 22]. We also noted disseminated infection with *Alternaria, Paecilomyces,* and *Scedosporium,* but there were no infections caused by *Fusarium* spp., which are increasingly reported in HCT recipients [2, 23].

The use of peripheral stem cells has been associated with a faster neutrophil recovery but more chronic GVHD when compared with bone marrow or cord blood transplantation [24]. In our study, transplantation of peripheral stem cells showed a significant association with IFI when compared with bone marrow transplants. This finding differs from prior published data, but might be explained by the small proportion of patients who received bone marrow grafts in our series.

Acute GVHD is a common clinical complication, occurring in up to 50% of patients early after allogeneic HCT. Corticosteroids remain the backbone in the management of patients with GVHD. Corticosteroids are widely recognized as a significant risk factor for development of IFI. On bivariate analysis, we found that acute GVHD and >90 day-exposure to high-dose corticosteroids were two independent variables that were associated with a significantly increased risk for IFI and for mold infections. Corticosteroids are known to suppress the phagocytic and killing activity of neutrophils and macrophages [25]. In vitro and in vivo studies have shown that corticosteroid exposure promotes mold and yeast

infection and also could enhance the virulence of these pathogens [26–28].

Acute GVHD is a known risk factor for IFI [29–31]. However, the question remains whether the role of GVHD may reflect the effect of corticosteroids and other immunosuppression used for the management of these patients. Our data confirm the findings of others that acute GVHD is an independent risk factor for late onset IFI [31, 32]. However, the exact mechanisms leading to a higher risk of IFIs in acute GVHD have not been elucidated. Acute GVHD is a complex process that encompasses mucosal damage, release of pro-inflammatory cytokines, and T cell differentiation followed by target tissue damage. There has been an increasing appreciation of the role of Th17 in the severity of GVHD [33]. Recent data suggest that Th17 is associated with extended inflammation and defective clearance of fungi [34]. In mice, a Th17 response driven by IL-23 was an important negative regulator of the Th1 immune response against fungi [35]. Moreover, the Th17 pathway was associated with an extended inflammatory response and impaired pathogen clearance in *Aspergillus* and *Candida* infections [36]. Further studies are needed to elucidate the association between acute GVHD and IFIs.

Chronic GVHD has a distinctive end-organ pathology causing fibrosis and has a strong association with T cell differentiation along the Th17 pathway [37, 38]. Chronic GVHD has been previously identified as an independent risk factor for IFI [31], but we did not find this association in our HCT recipients.

Significant advances in the management of some IFI, especially aspergillosis, have led to improved outcomes with overall mortality rates of 35–57% [1, 39–41]. In our study, IFIs and mold infections were independently associated with increased 2-year non-relapse mortality, particularly among those patients who were receiving high-dose corticosteroids at the time of development of IFI or mold infection. Two-year non-relapse mortality was higher in those patients who had acute or chronic GVHD associated with an IFI or mold infection.

This study has several limitations. Most importantly, it is a single center study reflecting the approach to HCT at only one transplant center. Additionally, the data were collected retrospectively. The role of antifungal prophylaxis in decreasing the number of mold infections was inferred, but not specifically studied.

In spite of the limitations, our study documents the epidemiology and impact of IFI on mortality among HCT patients. Most IFI and mold infections occurred late after transplantation (>200 days) and were associated with acute GVHD and prolonged use of corticosteroids. Development of an IFI or mold infection significantly increased non-relapse mortality among patients who had acute or chronic GVHD.

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Compliance with Ethical Standards

Conflict of interest Marisa H. Miceli, Tracey Churay, Thomas Braun, and Carol A. Kauffman have no conflicts to report. Daniel R. Couriel is an active member of Merck, Inc. Advisory Board.

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