Emergence of Opportunistic Mould Infections in the Hematopoietic Stem Cell Transplant Patient

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Infection due to opportunistic moulds is an emerging problem in hematopoietic stem cell recipients. Through the 1990s, the incidence of invasive aspergillosis in allogenic graft recipients climbed steadily, peaking at 10% to 15%. In this decade, other opportunistic mould infections are emerging, including zygomycosis, fusariosis, and scedosporiosis. These epidemiologic changes are likely due to greater or different types of host immune suppression, medical interventions such as antifungal prophylaxis, and more successful treatment of aspergillosis, keeping immunosuppressed patients alive and at risk. The non-*Aspergillus* moulds generally exhibit variable susceptibility to antifungal agents, and outcomes continue to be disappointing. Thus, prevention of infection becomes a prominent concern in the care of these patients.

Introduction

The epidemiology of infection in hematopoietic stem cell transplant (HSCT) recipients continues to evolve in response to increasingly successful strategies for managing infectious and noninfectious complications. In earlier days of transplantation medicine, invasive candidiasis was a large contributor to infection-related mortality. In the 1990s, the introduction of fluconazole prophylaxis reduced the incidence of invasive candidiasis [1], which coincided with the second wave of fungal infections encountered in HSCT recipients: invasive aspergillosis (IA). As treatment strategies to combat IA improve and as more high-risk patients undergo increasingly complicated transplant procedures, the third wave of fungal infections, largely due to non-*Aspergillus* moulds and especially Zygomycetes, is being recognized. At the present time, specific antifungal prophylaxis directed at these organisms is not routine. This review discusses aspects of the epidemiology, clinical presentation, therapy, and outcomes of these emerging invasive mould infections (IMI).

Hyaline Moulds

The hyaline moulds are a diverse group of ubiquitous organisms that share a number of epidemiologic, clinical, and morphologic features. Infection due to hyaline moulds is referred to as hyalohyphomycosis, and it almost always occurs in immunocompromised individuals. Microscopically, the hyaline moulds have nonpigmented (hyaline) hyphae and conidia, and in tissue section appear as septate, branching hyphae. They have a predilection for angioinvasion, which can result in infarction and tissue necrosis. Distinguishing different species on histopathologic grounds is difficult; culture with sporulation is usually required for speciation. Some hyaline moulds, including *Fusarium* spp, *Paecilomyces* spp, and *Acremonium* spp, are capable of forming reproductive structures (phialides and conidia, or spores) in tissue, a process known as adventitious sporulation [2]. It is hypothesized that adventitious sporulation following hyphal invasion of vascular structures leads to sustained release of conidia into the bloodstream, resulting in fungemia and rapid dissemination of infection.

Invasive aspergillosis

The most frequently encountered invasive mould (and hyaline) infection among HSCT recipients is IA. *Aspergillus* spp are cosmopolitan in their distribution and can be isolated from soil, decaying vegetation, dust, building materials, plants, food, water, and the air. The conidia are small (2–5 μm) and are able to settle deep in the lungs following inhalation. In the healthy host, conidia are cleared by alveolar macrophages before infection is established. However, in the severely immunocompromised host, conidia can evade immune defense mechanisms and germinate into invasive hyphae. Most patients present with sinopulmonary infection, and dissemination via hematogenous spread to other sites is seen in up to a third of cases [3–5]. Risk factors for developing IA follow-

ing HSCT include the underlying hematologic disorder (acute leukemia, multiple myeloma, myelodysplastic syndromes, aplastic anemia), unrelated and T-cell depleted transplants, graft versus host disease (GVHD), high-dose and/or sustained corticosteroid administration, and cytomegalovirus (CMV) disease [6].

The incidence of IA markedly increased in the 1990s, coinciding with widespread use of fluconazole and a significant decline in the incidence of invasive candidiasis [1]. By 2000, rates as high as 15% to 20% were being reported in allogeneic HSCT recipients [7]. Since then, it appears that the incidence may be leveling off or even declining [8••].

This decline may be due in part to increased prescription of mould-active antifungal drugs such as the new triazoles and echinocandins, which are less cumbersome to administer as prophylaxis and empiric therapy than amphotericin B (AmB). They may prevent infection and/or treat early infection before fungal burden is sufficient to produce observable clinical and microbiological evidence of IA. Evidence supporting this hypothesis comes from a recently published study by Siwek et al. [9•]. They compared the incidence of IA among 92 HSCT recipients who received voriconazole as antifungal prophylaxis to that among 223 historical controls who received fluconazole, itraconazole, and/or AmB. The incidence of IA among control patients was 10%, but no voriconazole recipients were diagnosed with IA during the study period [9•]. Results of multicenter randomized trials comparing fluconazole with voriconazole and fluconazole with posaconazole for antifungal prophylaxis following HSCT may alter our approach to prophylaxis in this setting.

The timing of infection following HSCT has also evolved in the past decade. When IA was first identified as a problem, cases typically presented early (≤ 40 days) after HSCT, during the neutropenic period [6]. Advances in transplant medicine such as the use of peripheral blood cells as a stem cell source, nonmyeloablative conditioning regimens, and colony-stimulating growth factors have lead to shorter durations of neutropenia, coinciding with a shift to later presentation of IA. Presently, the majority of cases appear late (> 40 days) after HSCT, in the postengraftment period and are associated with risk factors such as GVHD and high-dose corticosteroids [6].

Aspergillus fumigatus continues to be the most frequently encountered species (up to 80%), followed by *Aspergillus flavus*, *Aspergillus terreus*, and *Aspergillus niger* [10]. However, *A. terreus* is emerging as a significant pathogen in some cancer centers. In a report of 300 cases of IA from their center in Houston, TX, Hachem et al. [11] identified *A. terreus* and *A. fumigatus* as the causative agents in 23% and 30% of cases, respectively. In Austria, Lass-Florl et al. [12] found that 48% of cases of proven IA were due to *A. terreus*. Though there is no clear explanation for the relatively high incidence seen at these centers, *A. terreus* infection has been associated with nosocomial outbreaks [11], and geographic factors may play a role.

The isolation of *A. terreus* (and *A. flavus*) is more likely to reflect invasive infection than other *Aspergillus* species [13]. In the Austrian case series, all patients had lung involvement and dissemination was common (63%) [12]. *A. terreus* has reduced susceptibility to AmB (minimum inhibitory concentration $[MIC]_{90}$ = 4 μg/ml) compared with other *Aspergillus* spp (MIC_{90} = 1 μg/ml) (Table 1) [11,14]. These in vitro susceptibility data correlate with in vivo results; poor response to therapy with AmB products has been reported in both human and animal studies [11,12,15]. Newer antifungal agents including voriconazole, posaconazole, and caspofungin are active against *A. terreus* in vitro [14,16], and accumulating clinical data indicate better outcomes when these agents are employed. In a study of 83 cases of IA due to *A. terreus*, receipt of voriconazole was protective against death in multivariable analysis (hazard ratio [HR] 0.29, 95% CI 0.15–0.56) [17]. Another series of 32 cases reported complete or partial response to conventional AmB (C-AmB), lipid formulation AmB (L-AmB), and voriconazole and/or caspofungin among 8%, 36%, and 62% of patients, respectively [12].

Another *Aspergillus* sp with reduced susceptibility in vitro to antifungal agents has recently been recognized and isolated from clinical specimens. This species, designated *Aspergillus lentulus*, has morphologic features similar to *A. fumigatus* but is a unique species when considering phylogenic and extrolite profiles [18–20]. It is not yet known whether the reduced susceptibility of this species to antifungal drugs translates into worse clinical outcomes.

IA following HSCT is associated with high mortality despite antifungal therapy [6,7,10]. A review of published literature found that HSCT recipients had the highest case-fatality rates (86.7%), whereas patients with lymphoma/leukemia had the lowest (49.3%) [21]. A recent large case series from a single center reported a significant reduction in the 90-day overall and attributable mortality from IA diagnosed between 1999 and 2004 to cases diagnosed between 1990 and 1998 [22]. Explanations for this apparent improvement in survival are likely multifactorial. Advances in diagnostic tests such as the galactomannan enzyme immunoassay and molecular formats, and widespread use of CT scanning may facilitate early diagnosis and treatment. Also, the newer antifungal drugs may impact response to therapy and survival. Although these agents are not without side effects, they are better tolerated than C-AmB and may be more efficacious [3,23].

The superiority of voriconazole for the treatment of IA compared with C-AmB has been demonstrated in a previously published randomized trial. Patients receiving voriconazole experienced better outcomes at week 12, with a successful outcome in 52.8% of patients in the voriconazole arm, compared with 31.6% of those in the C-AmB arm. In addition, voriconazole recipients

Table 1. In vitro susceptibility of opportunistic moulds to currently available antifungal agents

Study	Species	No. tested	Antifungal agent	MIC (μg/ml)		
				Range	50%	90%
Pfaller et al. [14]	*Aspergillus fumigatus*	114	Amphotericin B	0.5–4	1	1
		114	Itraconazole	0.25–2	1	2
		114	Posaconazole	0.03–1	0.25	0.5
		114	Voriconazole	0.12–4	0.25	0.5
Chan-Tack et al. [37]	*Aspergillus terreus*	101	Amphotericin B	1–16	4	4
		16	Itraconazole	0.25–1	0.5	0.5
		16	Posaconazole	0.06–0.25	0.12	0.25
		101	Voriconazole	0.06–0.12	0.25	0.25
		16	Caspofungin	0.015–0.12	0.03	0.06
	Fusarium spp	11	Amphotericin B	1–2	1	2
		11	Itraconazole	2–> 8	> 8	> 8
		11	Posaconazole	0.5–> 8	> 8	> 8
		11	Voriconazole	0.25–> 8	4	> 8
		11	Caspofungin	> 8	> 8	> 8
	Paecilomyces spp	6	Amphotericin B	0.06–> 8	0.5	ND
		6	Itraconazole	0.06–2	0.25	ND
		6	Posaconazole	0.03–0.5	0.12	ND
		6	Voriconazole	0.03–2	0.25	ND
		6	Caspofungin	0.03–8	0.06	ND
Pfaller et al. [14]	*Acremonium* spp	1	Amphotericin B	2	-	-
		1	Itraconazole	> 8	-	-
		1	Posaconazole	1	-	-
		1	Voriconazole	0.5	-	-
	Trichoderma spp	2	Amphotericin B	0.06–8	-	-
		2	Itraconazole	8–> 8	-	-
		2	Posaconazole	1–> 8	-	-
		2	Voriconazole	0.05–> 8	-	-
Chan-Tack et al. [37]	*Rhizopus* spp	15	Amphotericin B	0.06–1	0.5	1
		15	Itraconazole	0.25–32	0.5	4
		15	Posaconazole	0.12–1	0.25	0.5
		15	Voriconazole	4–64	8	16
		5	Caspofungin	> 8	> 8	ND
	Mucor spp	7	Amphotericin B	0.5–1	1	ND
		7	Itraconazole	0.5–> 16	> 16	ND
		6	Posaconazole	0.5–2	1	ND
		7	Voriconazole	16–> 16	> 16	ND
		3	Caspofungin	> 8	> 8	ND
	Absidia spp	10	Amphotericin B	0.06–0.12	0.12	0.12
		10	Itraconazole	0.03–0.25	0.06	0.25
		10	Posaconazole	0.06–0.25	0.06	0.12
		10	Voriconazole	2–16	16	16

MIC—minimum inhibitory concentration.

Table 1. In vitro susceptibility of opportunistic moulds to currently available antifungal agents *(continued)*

Study	Species	No. tested	Antifungal agent	MIC (μg/ml) Range	50%	90%
Chan-Trak et al. [37]	*Scedosporium apiospermum*	13	Amphotericin B	1–16	4	16
		13	Itraconazole	0.25–8	0.5	4
		13	Posaconazole	0.25–2	1	2
		13	Voriconazole	0.03–0.5	0.25	0.5
	Scedosporium prolificans	55	Amphotericin B	2–> 16	> 16	> 16
		55	Itraconazole	> 32	> 32	> 32
		55	Posaconazole	> 8	> 8	> 8
		55	Voriconazole	1–8	4	4
		55	Terbinafine	2–> 32	16	32

MIC—minimum inhibitory concentration.

had a significantly higher probability of 12-week survival (70.8% vs 57.9%, $P = 0.02$) [3]. Voriconazole was generally well tolerated, although transient visual disturbances occurred in 45% of patients. Other side effects included liver function abnormalities, hallucinations and confusion, and skin rash [3]. As a result of this study, voriconazole gained approval for first-line therapy for IA and is now considered a gold standard treatment for this infection.

The use of combination therapy to treat IA is controversial. A study comparing voriconazole plus caspofungin combination therapy with voriconazole alone (historical controls) for patients receiving salvage therapy for IA found combination therapy to be independently associated with better outcome [4]. Another study comparing any anti-*Aspergillus* agents in combination with monotherapy for IA in hematologic patients did not detect any difference in outcome [24]. In guinea pig models comparing voriconazole plus caspofungin combination with monotherapy, a survival advantage was not identified, although combination therapy did result in lower fungal burdens and greater tissue sterilization [25,26]. The interaction between voriconazole and caspofungin has been studied in vitro with variable results. Though synergistic effects have not been consistently observed, no antagonism has been identified [26,27]. Definitive proof of clinical utility will be gleaned only from results of randomized trials, which are currently in development.

Other hyaline moulds

After aspergillosis, invasive fusariosis represents the second most common invasive hyaline mould infection in HSCT recipients, and the incidence appears to be increasing [7,28,29,30•]. *Fusarium* spp are plant pathogens with a worldwide distribution. Acquisition of infection is often sinopulmonary, although broken skin (including vascular access sites) and pre-existing onychomycosis (due to *Fusarium* spp) are also important portals of entry. *Fusarium solani* is isolated most frequently, followed by *Fusarium moniliforme* and *Fusarium oxysporum* [30•,31]. Following HSCT, the incidence of infection is trimodal, with an early peak (< 40 days), a second peak between days 40 and 100, and a late peak after day 100. Neutropenia is an important risk factor, particularly for early disease, whereas chronic GVHD and corticosteroid exposure are associated with infection more than 40 days after HSCT [30•]. In a study of 31 patients, Marr et al. [7] identified multiple myeloma and receipt of mismatched or unrelated transplant as independently associated with fusariosis.

Fusarium spp are capable of adventitial sporulation, a feature that influences disease progression and clinical presentation. Nucci et al. [30•] described 61 cases of fusariosis following HSCT; the most frequent clinical presentation was disseminated infection with metastatic skin lesions (75%), followed by fungemia alone (11%), sinusitis (7%), and pneumonia (7%). Metastatic skin lesions associated with fusariosis include painful subcutaneous nodules and ecthyma grangrenosum–like lesions [32]. Blood cultures are often positive (50%–70%), especially during neutropenia [31], and prognosis is very poor. The authors reported a median survival after diagnosis of 13 days, and a 90-day survival rate of 13%, despite systemic antimould therapy in 73% of cases. Factors associated with increased risk of death include neutropenia, refractory/relapsed underlying disease, significant (≥ grade II) GVHD, and corticosteroid therapy [29,30•,31].

In a series of 84 patients with hematologic malignancy (including 33 HSCT recipients) diagnosed with fusariosis, patients with persistent neutropenia and those receiving corticosteroids were 5.4 and 2.2 times more likely to have a poor outcome, respectively. All patients with these two risk factors died, compared with 97% of those with neutropenia alone, and 33% of patients with neither persistent neutropenia nor receiving corticosteroids [29].

Relative resistance to antifungal agents complicates the treatment of fusariosis (Table 1). Caspofungin has limited or no activity, with MICs greater than 16 μg/ml [23]. *Fusarium* spp are not predictably susceptible to other mould-active agents; MICs of AmB, voriconazole, and posaconazole range from 2 μg/ml to more than

16 μg/ml, 0.25 μg/ml to greater than 16 μg/ml, and 1 μg/ml to greater than 16 μg/ml, respectively [14,33], and breakthrough fusariosis has been reported in patients receiving AmB and voriconazole [29,34]. Oral suspension posaconazole has been used as salvage therapy with some success. In a recent retrospective study of 21 patients with probable or proven fusariosis, complete or partial reported response to posaconazole was reported in 48% of patients; however, response was considerably lower (17%) in the six HSCT recipients [35]. Currently, recommended therapy for fusariosis includes a L-AmB preparation, voriconazole, or posaconazole, in addition to strenuous attempts at immune reconstitution.

Among the other hyaline moulds that occasionally cause invasive disease in HSCT recipients, *Acremonium* spp and *Paecilomyces* spp are most often encountered. They tend to be relatively resistant to antifungal agents. Many are capable of adventitious sporulation, facilitating hematogenous spread and resulting in metastatic skin lesions, high fungal burden, and positive blood cultures. Sites of infection include pulmonary, cutaneous, gastrointestinal, and disseminated [36,37]. Invasive infection is almost uniformly fatal in the absence of neutrophil recovery [38•]. Optimal therapy for these organisms has not been established, but successful outcomes with voriconazole and posaconazole have been reported [38•].

Scopulariopsis also deserves mention. This genus is unique in that it contains both hyaline and dematiaceous mould species. *Scopulariopsis brevicaulis* and *Microascus cirrosus* (teleomorph of *Scopulariopsis paisii*) are most frequently isolated from HSCT recipients [39]. *Scopulariopsis* spp typically cause onychomycosis but can cause invasive infection in the immunocompromised host. Routes of acquisition and clinical syndromes in this setting are similar to fusariosis. Limited susceptibility data are available, and optimal therapy has not been established.

Invasive Zygomycosis

Zygomycetes are ubiquitous, rapid-growing primitive moulds. Within the class Zygomycetes there are three orders: Mucorales, Mortierellales, Entomophthorales. Here our discussion will be limited to the order Mucorales. *Rhizopus* and *Mucor* spp are the most commonly encountered organisms from this order, followed by *Cunninghamella bertholletiae* and *Apophysomyces elegans* [40•]. Human infection with Zygomycetes is uncommon. In a single-center study of IMI among HSCT recipients from 1985 to 1999, invasive zygomycosis (IZ) made up 4.6% of all cases of IMI [7]. However, a number of recent publications highlight Zygomycetes infection in HSCT recipients, and suggest that the incidence of IZ in this population is increasing [8••,41–44].

Prolonged use of voriconazole in high-risk patients may select for Zygomycetes—moulds against which voriconazole has limited activity [14]. This hypothesis is supported by data from several recent reports. Kontoyiannis et al. [8••] compared cases of proven or probable IZ with proven or probable IA in cancer patients and with matched controls without fungal infection. In multivariate analysis comparing patients with IZ with IA, and with controls, the risk of developing IZ was 20.3 and 10.4 times greater, respectively, in patients receiving voriconazole [8••]. In a study of breakthrough fungal infections diagnosed in 13 of 139 patients receiving a median of 47 days (4–118) of voriconazole, almost half were due to Zygomycetes [41]. Several centers have published case series of IZ, reporting an apparent rise in incidence following the introduction of voriconazole to their units [9•,44].

Another factor that might have contributed to the emergence of IZ is increasingly successful management of IA and other complications of HSCT, helping patients live long enough to develop subsequent opportunistic invasive fungal infections in the setting of persistent, severe immunosuppression. In addition, heightened awareness of IZ and improved laboratory techniques for identifying these organisms may have led to an increase in the number of reported cases. Histopathologic identification and tissue culture are the mainstays of diagnosis. Blood cultures are seldom positive. In tissue, all Zygomycetes have similar morphology (ie, sparsely septate ribbon-like hyphae), thus differentiation into species is usually not possible without culture and sporulation. The organisms are easily damaged by tissue grinding, rendering the culture sterile. Molecular technologies such as polymerase chain reaction and in situ hybridization can be employed to speciate in this setting where hyphae are seen but cultures are sterile [45]. Currently, no serological markers of infection are in clinical use.

Studies mentioned earlier describe the association between voriconazole and IZ. Other risk factors identified among HSCT recipients include HLA-mismatched and unrelated donor, severe GVHD, and myelodysplastic syndrome as underlying disease [7]. Zygomycetes are generally transmitted via respiratory, percutaneous, and gastrointestinal routes, and among HSCT recipients, IZ typically presents with sinopulmonary, rhinocerebral, and disseminated infection [40•]. Concomitant infection is common, particularly with other fungal species such as *Aspergillus* and *Candida* spp. IZ is a rapidly progressive infection with a predilection for angioinvasion, and mortality is high [40•].

Current recommended first-line therapy includes L-AmB at high dose (5–10 mg/kg/d) and where possible, surgical excision of the infected area. In vitro and in vivo data indicate that posaconazole may have activity against Zygomycetes, although *Mucor* spp tend to be less susceptible in vitro (Table 1). A recent publication reports two posaconazole salvage studies for the treatment IZ [46]. Of 24 patients (including 11 HSCT recipients) receiving salvage posaconazole, 79% of all patients and 73% of HSCT

Table 2. Opportunistic moulds responsible for invasive infection among hematopoietic stem cell transplant recipients*

Hyaline moulds
Apergillus spp
Fusarium spp
Paecilomyces spp
Acremonium spp
Trichoderma spp
Scopulariopsis spp
Zygomycetes
Rhizopus spp
Mucor spp
Absidia spp
Cunninghamhella spp
Dematiaceous moulds
Scedosporium spp
Microascus spp
Alternaria spp
Exophilia spp
Ulocladium spp
Bipolaris spp

*Not a complete list.

recipients had complete or partial response to therapy. Hyperbaric oxygen has been used as an adjunctive therapy for IZ. Although some evidence suggests this therapy could benefit diabetic patients, its utility in patients with invasive disease in the setting of hematologic malignancies and following HSCT is doubtful [47].

Dematiaceous Fungi

The dematiaceous moulds are a diverse group of more than 100 species, characterized by darkly pigmented cell walls due to the presence of melanin. Infection caused by these organisms (phaeohyphomycosis) is infrequent, although it can occur in both immune-competent and immune-compromised individuals. Among HSCT recipients, the most frequently reported phaeohyphomycosis is scedosporiosis [48]. Two *Scedosporium* spp are known to cause human disease: *Scedosporium prolificans* and *Scedosporium apiospermum* (the anamorph or asexual form of *Pseudallescheria boydii*). Scedosporiosis in HSCT recipients is associated with neutropenia and GVHD, and it typically presents within 6 months of transplant [7,49•]. Common sites of infection are the lungs and central nervous system. Dissemination is frequent (> 50%), blood cultures are positive in up to a third of cases, and mortality is high [7,49•].

Both *Scedosporium* spp are considered resistant to AmB (Table 1) [14]. *S. apiospermum* is susceptible in vitro to the new triazoles, and successful treatment of disseminated infection in immunocompromised patients with voriconazole has been reported [49•,50]. *S. prolificans* is essentially pan-resistant. Synergy between triazoles and terbinafine has been demonstrated by the checkerboard method [38•]. This combination has led to a successful outcome in a HSCT recipient with disseminated *S. prolificans* infection [51].

Other species of dematiaceous moulds occasionally encountered among HSCT recipients include *Microascus* spp, *Alternaria* spp, *Exophiala* spp, *Bipolaris* spp, and *Ulocladium* spp (Table 2). Recommended treatment includes L-AmB and/or triazoles such as itraconazole, voriconazole, or posaconazole and surgical debridement where possible [48].

Conclusions

The epidemiology of IMI following HSCT has evolved in the past few decades. Although *Aspergillus* spp account for the majority of cases of IMI, we may be seeing a peak in the incidence of IA, coinciding with the emergence of non-*Aspergillus* moulds. The reasons for this changing epidemiology are not entirely clear, but it is likely due in large part to more widespread use of systemic antifungal agents, especially voriconazole, and changing transplant practices resulting in greater immune suppression. It is important to note, however, that the change in epidemiology is at least in part the result of successful prevention or treatment of other infections, such as IA, which may be analogous to the "emergence" of IA witnessed with successful fluconazole-induced prevention of invasive candidiasis. Many emerging mould species have reduced susceptibility to available antifungal drugs, and they have a tendency to disseminate rapidly. Thus, early diagnosis and identification of the causative organism is of the utmost importance. The new antimould agents may offer alternative strategies for prophylaxis and treatment; however, clinical outcomes data are lacking, highlighting the importance of ongoing collaborative prevention, surveillance, and treatment studies.

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