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Breakthrough Invasive Mold Infections in the Hematology Patient: Current Concepts and Future Directions

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Although the widespread use of mold-active agents (especially the new generation of triazoles) has resulted in reductions of documented invasive mold infections (IMIs) in patients with hematological malignancies and allogeneic hematopoietic stem cell transplantation (HSCT), a subset of such patients still develop breakthrough IMIs (bIMIs). There are no data from prospective randomized clinical trials to guide therapeutic decisions in the different scenarios of bIMIs. In this viewpoint, we present the current status of our understanding of the clinical, diagnostic, and treatment challenges of bIMIs in high-risk adult patients with hematological cancer and/or HSCT receiving mold-active antifungals and outline common clinical scenarios. As a rule, managing bIMIs demands an individualized treatment plan that takes into account the host, including comorbidities, certainty of diagnosis and site of bIMIs, local epidemiology, considerations for fungal resistance, and antifungal pharmacological properties. Finally, we highlight areas that require future investigation in this complex area of clinical mycology.

Keywords. breakthrough mold infection; posaconazole; voriconazole; isavuconazole; prophylaxis.

The epidemiology of invasive fungal infections (IFIs) in patients with hematological malignancies and allogeneic hematopoietic stem cell transplantation (HSCT) has evolved in the last 3 decades, partly due to the selection pressure of antifungal practices [1]. Historically, fluconazole prophylaxis has resulted in dramatic decreases of cases of invasive candidiasis, at the expense of an increase in invasive mold infections (IMIs), especially invasive aspergillosis (IA), against which fluconazole has no activity. Several oncology and transplant centers have increasingly introduced antifungal agents with anti-mold activity such as the newer triazoles (voriconazole, posaconazole, isavuconazole), the echinocandins (caspofungin, micafungin, anidulafungin) or even the lipid formulations of amphotericin B (AMB) as prophylaxis with a goal to prevent IMIs (primary prophylaxis) or, increasingly, as secondary prophylaxis in patients with prior IMI undergoing chemotherapy or HSCT [2–5].

Although this strategy has resulted in a decline in the incidence of IMIs in high-risk hematology patients, a subset of such patients still develop breakthrough IMIs (bIMIs) [4–9]. These patients typically have relapsed or refractory hematological cancer, significant comorbidities, and, not surprisingly, crude and bIMI-attributable mortality is substantial [10–13]. Importantly, there is no consensus on the definition of what constitutes a bIMI, and there is significant heterogeneity of such definition among studies [4–10, 12, 14]. For practical purposes and for the scope of this viewpoint, we define bIMIs as new cases of proven, probable, or possible IMIs (by EORTC/MSG criteria) developing in the setting of receiving at least 7 days of a mold-active antifungal as primary or secondary prophylaxis, as steady-state drug levels are expected by that time [15]. Notably, there is absence of controlled data from prospective randomized clinical trials to guide diagnostic and therapeutic decisions in the scenario of bIMIs, as the modern pivotal trials were conducted in patients with documented (proven or probable) IA who were not on mold-active prophylaxis and were subject to significant selection of enrolling patients with no significant comorbidities and a low/modest risk of death.

The incidence and spectrum of bIMIs vary significantly depending on the specific mold-active antifungal used for prophylaxis, local epidemiology, and patient characteristics (Table 1). Importantly, the causes of bIMIs might be different in different stages of the underlying hematological cancer. For example, the frequency and type of bIMIs differ in the scenario of primary prophylaxis during remission-induction chemotherapy in newly diagnosed leukemia or during the pre-engraftment period post-HSCT versus late bIMIs that occur during prophylaxis for long-standing refractory/relapsed leukemia or corticosteroid-resistant chronic graft-versus-host disease (GvHD). In the former setting, IMIs are less frequent, most IMIs consist of IA

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Table 1. Representative Studies Describing Proven or Probable Breakthrough Invasive Mold Infections in Adult Patients with Hematologic Cancer or Hematopoietic Stem Cell Transplantation Receiving Mold-active Antifungals for Primary or Secondary Prophylaxis[a]

Patient Population, Indication of Antifungal Use and Study Design	Type of bIMIs	Frequency of bIMIs[b]	Reference
Posaconazole-associated bIMIs			
Primary prophylaxis in AML/MDS patients with prolonged neutropenia; prospective, randomized, multicenter clinical trial	IA most common, unspeciated mold infection	1% (3/304)	[4]
Primary prophylaxis in HSCT recipients with GvHD; prospective, double-blind, randomized, multicenter clinical trial	IA most common, scedosporiosis, unspeciated mold infections	3.7% (11/301)	[5]
Primary prophylaxis during neutropenia after chemotherapy or HSCT; retrospective, single-center observational study	Mucormycosis most common proven bIMI	10.9% (22/202)	[6]
Primary prophylaxis for AML or GvHD; retrospective, single-center observational study	IA most common, mucormycosis, fusariosis	2.5% (7/279)	[13]
Primary prophylaxis in AML/MDS patients with neutropenia or HSCT recipients with GvHD; prospective, single-center observational study	IA most common, *Geosmithia argillacea* infection	9.7% (3/31)	[14]
Primary prophylaxis in AML patients during induction chemotherapy; prospective, multicenter observational study	All IA cases	2.7% (7/260)	[16]
Primary prophylaxis in leukemia (including HSCT) patients; retrospective, single-center observational study	IA most common, fusariosis, penicilliosis	1.7% (6/343)	[17]
Primary prophylaxis in AML/MDS patients with neutropenia during remission-induction chemotherapy; retrospective, single-center observational study	No bIMIs	0% (0/67)	[18]
Primary prophylaxis in AML/MDS patients with neutropenia during remission-induction chemotherapy; retrospective, single-center observational study	IA	1.7% (3/179)	[19]
Primary prophylaxis in AML/MDS patients with neutropenia during remission-induction chemotherapy; retrospective, single-center observational study	Probable bIMI, mucormycosis	2.9% (4/140)	[20]
Primary prophylaxis in hematology and HSCT patients; retrospective, single-center observational study	No bIMIs	0% (0/100)	[21]
Isavuconazole-associated bIMIs			
Primary or secondary prophylaxis or primary treatment for IA; retrospective, single-center observational study	Mucormycosis most common, IA, fusariosis	6% (6/100)	[22]
Primary or secondary prophylaxis or treatment of fungal pneumonia; retrospective, single-center observational study	IA caused by non-*fumigatus* or *fumigatus* species most common, mucormycosis, scedosporiosis	N/A	[23]
Voriconazole-associated bIMIs			
Primary prophylaxis or empirical therapy in HSCT recipients with GvHD; retrospective, single-center observational study	Mucormycosis	3.2% (4/124)	[9]
Primary treatment for IA in hematology (including HSCT) patients; retrospective, single-center observational study	Mucormycosis most common, penicilliosis, *Scopulariopsis* infection, IA, fusariosis	1.9% (7/368)	[10]
Primary treatment for IMI or primary prophylaxis or empirical therapy in HSCT recipients; retrospective, single-center observational study	Mucormycosis most common, IA, scedosporiosis, *Acremonium* infection	7.2% (10/139)	[12]
Primary or secondary prophylaxis in HSCT recipients; retrospective, single-center observational study	Mucormycosis	7.4% (4/54)	[24]
Primary prophylaxis in HSCT recipients; prospective, double-blind, randomized, multicenter clinical trial	IA most common, mucormycosis	7.9% (24/305)	[25]
Primary prophylaxis in AML/MDS patients with neutropenia during remission-induction chemotherapy; retrospective, single-center observational study	Mucormycosis	1.7% (1/58)	[18]
Primary prophylaxis in HSCT recipients; prospective, randomized, open-label, multicenter clinical trial	IA	0.4% (1/224)	[26]
Itraconazole-associated bIMIs			
Primary prophylaxis in AML/MDS patients with neutropenia during remission-induction chemotherapy; retrospective, single-center observational study	IA, unspeciated mold infection, scedosporiosis	8.2% (4/49)	[18]
Primary prophylaxis in AML/MDS patients with neutropenia during remission-induction chemotherapy; retrospective, single-center observational study	IA	5.3% (6/114)	[19]
Primary prophylaxis in HSCT recipients; prospective, randomized, open-label, multicenter clinical trial	IA	2.1% (5/241)	[26]
Primary prophylaxis in AML patients during remission-induction or consolidation chemotherapy; retrospective, single-center observational study	IA	2.3% (4/175)	[27]

Table 1. Continued

Patient Population, Indication of Antifungal Use and Study Design	Type of bIMIs	Frequency of bIMIs[b]	Reference
Primary prophylaxis in hematological malignancy patients with prolonged neutropenia; retrospective, single-center observational study	IA most common, unspeciated mold infection	10.6% (18/170)	[28]
Primary prophylaxis in HSCT recipients with GvHD; prospective, randomized, open-label, single-center study	IA most common	10.9% (16/147)	[29]
Primary prophylaxis in HSCT recipients; prospective, randomized, open-label, multicenter study	IA most common, mucormycosis	5.6% (4/71)	[30]
Secondary prophylaxis in hematology patients with neutropenia; prospective, multinational registry observational study	Probable bIMI, IA, fusariosis	17% (8/47)	[31]
Echinocandin-associated bIMIs			
Primary prophylaxis, empirical or directed treatment for IFIs in hematological malignancy or HSCT; retrospective, multicenter observational study	IA most common, mucormycosis, fusariosis, *Hormographiella aspergillata* infection	7.3% (7/96)	[32]
Primary prophylaxis during neutropenia in HSCT recipients; prospective, double-blind, randomized, multicenter clinical trial	IA, mucormycosis and fusariosis	0.7% (3/425)	[33]
Primary prophylaxis in HSCT recipients; prospective, randomized, single-center clinical trial	Probable bIMIs most common, IA	7.3% (12/165)	[34]
Twice/thrice-weekly high-dose micafungin primary prophylaxis in HSCT recipients; retrospective, single-center observational study	IA most common, mucormycosis	4.8% (4/83)	[35]
Primary prophylaxis in HSCT recipients; retrospective, single-center observational study	IA most common, mucormycosis, *Exserohilum* infection, unspeciated mold infection	4.9% (6/123)	[36]
Primary prophylaxis in HSCT recipients with GvHD; retrospective, single-center observational study	Mucormycosis	4.8% (1/21)	[37]
Secondary prophylaxis in hematology patients with neutropenia; prospective, multinational registry observational study	Probable bIMI, IA	28.6% (8/28)	[31]
Parenteral AMB[c]-associated bIMIs			
Twice-weekly L-AMB primary prophylaxis in ALL patients during remission-induction chemotherapy; prospective, double-blind, randomized, multicenter clinical trial	Probable pulmonary bIMIs	7.5% (17/228)	[38]
Once-weekly L-AMB secondary prophylaxis in leukemia patients; retrospective, single-center observational study	IA	7.1% (1/14)	[39]
AMB-deoxycholate primary prophylaxis in autologous HSCT recipients with neutropenia; prospective, blinded, randomized, single-center clinical trial	IA	1.1% (1/91)	[40]
Aerosolized AMB-associated bIMIs			
Primary prophylaxis in hematological malignancies or autologous HSCT during prolonged neutropenia; prospective, randomized, multicenter clinical trial	IA	4.4% (10/227)	[41]

Abbreviations: AMB, amphotericin B; ALL, acute lymphogenous leukemia; AML, acute myelogenous leukemia; bIMI, breakthrough invasive mold infection; GvHD, graft-versus-host disease; HSCT, hematopoietic stem cell transplantation; IA, invasive aspergillosis; IFI, invasive fungal infection; IMI, invasive mold infection; L-AMB, liposomal formulation of AMB; MDS, myelodysplastic syndrome; N/A, not available.

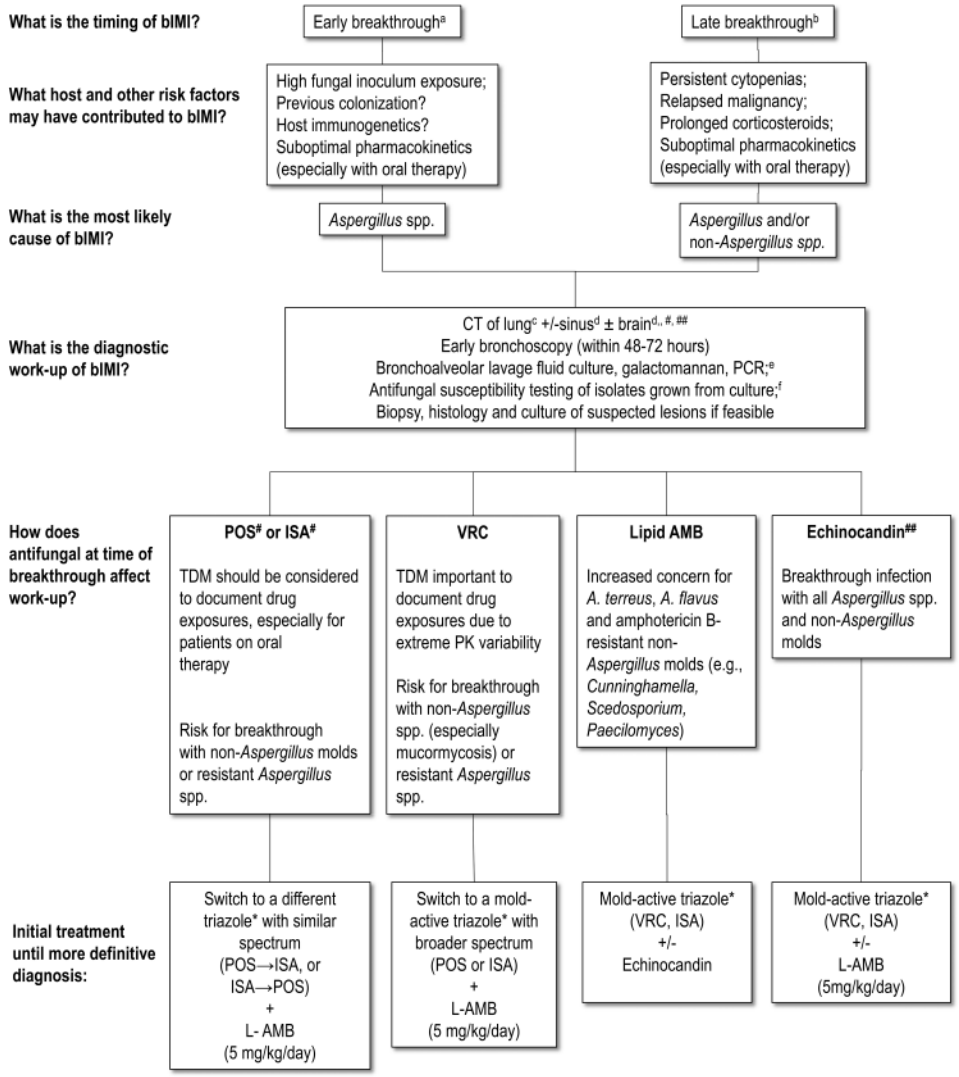
[a]We excluded studies of empiric antifungal treatment.

[b]Percentages reflect documented (proven/probable) cases of IMIs as per the EORTC/MSG criteria.

[c]AMB-deoxycholate or liposomal formulation of AMB.

and when they occur, high fungal inoculum exposures, suboptimal antifungal pharmacokinetics, and perhaps innate immune gene polymorphisms predominate as drivers [42]. In the latter setting, bIMIs are more frequent, innately resistant non-*Aspergillus* molds are more common, and host failure due to active hematologic cancer, cumulative immunosuppression (e.g., prolonged corticosteroids) and persistent neutropenia play a role (Figure 1) [2, 3, 10, 11, 43, 44]. Finally, as most cases of IA are currently diagnosed based on galactomannan (GM) positivity in serum and/or bronchoalveolar lavage fluid (BAL), the true etiology of bIMIs at the microbiology level is becoming increasingly uncertain as other hyalohyphomycetes such as *Fusarium* produce GM [45]. This overreliance on biomarkers might have implications when considering de-escalation of pre-emptive antifungal therapy in patients who develop triazole-associated bIMIs.

In this viewpoint that reflects the opinions of the authors, we synthesize our understanding of the current status of the complex field of bIMIs in the hematology patient receiving mold-active antifungal prophylaxis, we present common clinical scenarios of bIMIs in these patients, and we propose diagnostic and therapeutic algorithms that may aid in optimizing patient management.



[a] Primary prophylaxis during initial remission-induction chemotherapy; [b] Prophylaxis during re-induction for relapsed leukemia, prolonged corticosteroid treatment for graft-versus-host disease; [c] CT pulmonary angiography used in some centers to identify angioinvasive process (vessel occlusion sign) inside nodular infiltrates or consolidations; highly suggestive of invasive mold disease and not affected by antifungal prophylaxis; [d] If suggestive signs of involvement; [e] PCR test for *Aspergillus* spp. with or without detection of L98H, tandom repeat 34, T289A, and Y1212F triazole resistance mutations. Not approved in U.S. or available in most centers; [f] Susceptibility testing is not available in many centers and clinical breakpoints are not established for non-*Aspergillus* molds; [g] although ISA and POS achieve lower concentrations in the CNS compared to VRC, it is unclear whether more CNS bIMIs are seen with the first 2 triazoles; [h] echinocandins are considered to achieve suboptimal CNS concentrations; [*] starting with an IV formulation is favored, especially for VRC. Less convincing data exist that IV POS results in better levels than POS tablets, no data exist regarding ISA.
AMB, amphotericin B; CNS, central nervous system; CT, computed tomography; ISA, isavuconazole; IV, intravenous; PCR, polymerase chain reaction; POS, posaconazole; PK, pharmacokinetic; TDM, therapeutic drug monitoring; VRC, voriconazole.

Figure 1. Flowchart for assessment and management of breakthrough invasive mold infections in patients receiving mold-active antifungal agents. Abbreviations: bIMI, breakthrough invasive mold infection; L-AMB, liposomal formulation of AMB.

COMMON CLINICAL SCENARIOS OF BIMIS IN THE SETTING OF MOLD-ACTIVE ANTIFUNGAL PROPHYLAXIS: DIFFERENT DRUGS, DIFFERENT CONSIDERATIONS

bIMIs have been reported to occur in hematology and HSCT patients receiving mold-active prophylaxis with all classes of modern antifungals, including the newer triazoles, the echinocandins or the lipid formulations of AMB (Table 1). The spectrum of antifungal activity, the pharmacokinetic/pharmacodynamic properties, and the intrinsic and acquired antifungal resistance differ among the aforementioned classes of antifungal agents, and distinct differences also exist even among the newer triazole compounds. Below, we highlight common clinical scenarios and we propose diagnostic and therapeutic algorithms for patients who develop bIMIs, mainly pneumonia, while receiving different mold-active agents, with emphasis on bIMIs developing on mold-active triazoles (especially posaconazole). Because of space constraints, we will not be discussing bIMIs to itraconazole [18, 19, 26–31] (Table 1) or bIMIs in pediatric patients with hematological cancer.

The Approach to bIMIs in Patients Receiving Posaconazole or Other Mold-active Triazoles

The two pivotal clinical trials that led to the Food and Drug Administration (FDA) approval of posaconazole for prophylaxis in neutropenic patients with acute myelogenous leukemia (AML)/myelodysplastic syndrome (MDS) during remission-induction chemotherapy and allogeneic HSCT recipients with severe GvHD showed a significant decrease of IFIs (mainly IMIs) compared to the conventional prophylactic strategy of fluconazole and/or itraconazole. Improvements in IFI-attributable mortality and overall mortality were appreciated in HSCT recipients with severe GvHD or neutropenic patients with AML/MDS, respectively [4, 5]. Proven/probable bIMIs developed in 1–3.7% of posaconazole-treated patients, often in the setting of relapsed disease, compared to ~7–7.5% of fluconazole (or itraconazole)-treated individuals. The majority of posaconazole-associated bIMIs were due to IA with few cases of scedosporiosis and IMIs by unspeciated molds; no mucormycosis or fusariosis were documented in these initial trials that included 605 posaconazole-treated patients [4, 5].

Enrollment of patients in the randomized clinical trial setting is based on stringent criteria that often exclude complex "real-life" situations such as patients in the intensive care unit (ICU), elderly or with major comorbidities such as renal or liver dysfunction, those with relapsed/refractory leukemia, or individuals receiving medications that result in significant drug-drug interactions [46]. Therefore, postmarketing observational cohort studies are critical in developing a broader understanding of the safety and efficacy of any medication. Several cohort studies following the 2 landmark posaconazole prophylaxis clinical trials further highlighted the development of posaconazole-associated bIMIs with variable incidence rates depending on the study (0–10.9%) [6, 13, 16, 18–21]. IA caused by *A. fumigatus* is most often represented among these bIMIs, but IA caused by non-*fumigatus Aspergilli* and bIMIs caused by non-*Aspergillus* molds have also been reported including several cases of mucormycosis and fusariosis [6, 8, 13, 16]. Some studies have suggested a correlation between suboptimal serum posaconazole levels (<300–700 ng/mL) and the development of bIMIs [13, 14, 47, 48]; however, other studies have failed to demonstrate a direct relationship between the probability of bIMI with individual posaconazole levels, indicating that other factors may contribute to the emergence of these infections (discussed below). The introduction of the tablet formulation of posaconazole is associated with significantly greater serum levels relative to the suspension formulation [48, 49]. A recent single-center retrospective analysis of 343 patient courses of prophylaxis with the tablet formulation of posaconazole showed that 6 patients (1.7%) developed bIMI, predominantly IA, although their serum posaconazole levels exceeded 1100 ng/mL [17], further underscoring the lack of direct linear correlation between posaconazole levels and the probability of bIMI.

The differential diagnosis of bIMI presenting with nodular opacities on chest computed tomography (CT) imaging in a patient receiving posaconazole includes:

a) IA caused by posaconazole-susceptible *Aspergillus*. This scenario may be explained by low serum posaconazole levels caused by patient noncompliance and/or suboptimal drug absorption in the context of severe intestinal disease and/or increased posaconazole hepatic metabolism caused by interactions with concomitant drugs that are metabolized via the cytochrome P450 or by auto-induction of posaconazole metabolism upon chronic azole exposure. Alternatively, and/or in parallel, breakthrough IA by posaconazole-susceptible *Aspergillus* during posaconazole prophylaxis may be accounted for by an underlying severe net state of immunosuppression of the patient or exposure to a high fungal inoculum; indeed, progression of IMIs may be seen despite appropriate antifungal treatment in patients with profound inherited or acquired defects in host innate immunity [1, 44, 50].

b) IA caused by posaconazole-resistant *Aspergillus*. This scenario may be explained by infection with strains of *A. fumigatus* or non-*fumigatus Aspergillus* species that acquired azole resistance or tolerance during prolonged azole exposure in the environment or within the patient [51–53] or by infection with strains of cryptic *Aspergillus* species that have intrinsic azole resistance such as *A. ustus* [8]. Hence, knowledge of the local hospital epidemiology is of paramount importance in determining the probability of infection with such azole-resistant fungi. The recent emergence of azole-resistant *A. fumigatus* clinical strains driven by the widespread use of azole fungicides in agriculture is of global health concern. Indeed, certain medical centers in Europe have reported such azole-resistant *A. fumigatus* strains in up to 20% of *Aspergillus* isolates recovered from their patients; these infections have exceedingly high fatality rates (>80–90%) with azole treatment [52]. Azole-resistant IA appears to be quite rare currently in the United States [53, 54].

c) bIMI caused by intrinsically resistant non-*Aspergillus* molds including *Mucorales* or hyalohyphomycetes such as *Fusarium*, *Scedosporium*, or black molds [8]. Certain radiographic characteristics are more common in patients with mucormycosis over IA (reversed halo sign, multiple [>10] pulmonary nodules, pleural effusion, pansinusitis, ethmoid sinusitis [55, 56]), bearing in mind that the prevalence of some IMI-associated radiographic findings vary depending on the timing of imaging [57]. Instead, the presence of airway-invasive radiographic features including bronchial wall thickening, peribronchial consolidations and centrilobular nodules appear less common in mucormycosis relative to IA [58]. With regard to fusariosis, suspicion should

be raised by the presence of necrotic cutaneous lesions, including onychomycosis with accompanying interdigital intertigo or periungueal cellulitis [59].

d) Polyfungal infection or mixed fungal-bacterial infections. Notably, concomitant mucormycosis, fusariosis or other IMI may occur in up to 5–10% of heavily immunosuppressed patients with IA [10]. Similarly, nonfungal infections or noninfectious conditions may simulate radiographically as IMIs in the immunosuppressed hematology patient (Figure 2).

The diagnostic and therapeutic approach to the patient with posaconazole-associated bIMI is challenging as no robust information is available from existing clinical trials to guide decisions. Notably, the prompt initiation of treatment is critical for the successful outcome of IMIs as demonstrated for both IA and mucormycosis [57, 60]; this observation underscores the importance for instituting an aggressive diagnostic work-up and an early effective treatment plan for patients with bIMIs, particularly because of the high mortality associated of these infections. In all scenarios, whenever possible, efforts should be made to enhance immune restoration by tapering iatrogenic immunosuppression. Critical elements for improved outcome include: a) the timely performance of bronchoscopy with harvesting of BAL for culture and GM measurement, given that BAL culture sensitivity declines when bronchoscopy is delayed [61], and the timely measurement of b) BAL GM, the most sensitive biomarker currently available for the diagnosis of IA [62] whose sensitivity may not be affected by prior mold-active exposure [63], c) serum GM that can be an acceptable adjunct diagnostic for IA in patients on mold-active agents who develop a compatible clinical syndrome [64] and d) serum posaconazole levels. In addition to the prompt availability of CT, the availability of performing GM and posaconazole level in-house (relative to send-out testing that has a turnaround time of several days) are important variables that may influence both the yield of the diagnostic work-up and the choice of a targeted over a pre-emptive treatment approach.

Although the decision of what to start should be highly individualized based on many factors, we believe that, at least in tertiary care oncology centers that have complex epidemiology of IMIs, changing the "class" of antifungal with the initiation of liposomal AMB with or without a different mold-active triazole with a comparable spectrum should enable early broad-spectrum pre-emptive coverage against azole-susceptible and -resistant IA, mucormycosis, fusariosis, and other hyalohyphomycoses, while minimizing pharmacological variability encountered with the use of azoles (Figure 1). Liposomal AMB is particularly crucial when the aforementioned clinical and radiographic features that favor mucormycosis are evident. After initiation of preemptive treatment, rapid—within 1–2 weeks—reassessment of clinical and radiographic responses and appraisal of the diagnostic test results obtained for reaching an IMI and/or alternative diagnoses should be pursued with a goal, when feasible, to de-escalate to triazole monotherapy in the context of documented azole-susceptible IA or to AMB-based therapy in the context of mucormycosis, or other azole-resistant IMIs. The proposed preemptive approach of AMB/triazole combination

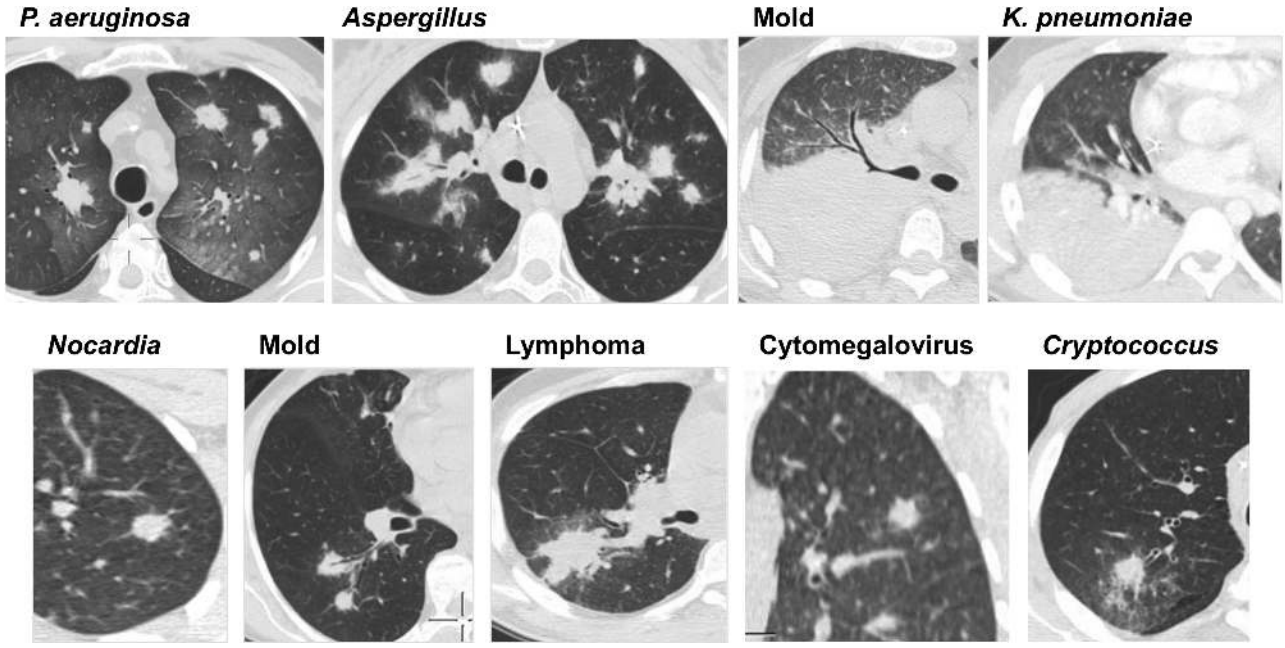


Figure 2. Limited specificity of chest CT imaging findings for invasive mold disease. Images are courtesty of Claudia Sassi, MD, Department of Radiology, S. Orsola-Malpighi Hospital, University of Bologna, Italy. Abbreviation: CT, computed tomography.

until diagnostic information becomes available requires clinical investigation (see Table 2) in comparison to the strategies of switching to AMB monotherapy versus continuing triazole prophylaxis; the latter approach did not exhibit differential efficacy in a very small retrospective study of 11 bIMIs [66].

Besides posaconazole, bIMIs also occur in patients receiving prophylaxis or treatment with voriconazole or isavuconazole. Similar considerations apply for voriconazole- and isavuconazole-associated bIMIs as with posaconazole-associated bIMIs, but certain triazole-specific distinct features are worthwhile highlighting as they may impact diagnosis and treatment. The incidence of proven/probable bIMIs following voriconazole use has been reported between 0.4 and 7.9% depending on the study [9, 10, 12, 24–26]. Voriconazole-associated bIMIs can be due to azole-susceptible or -resistant IA but are particularly enriched for mucormycosis (incidence of up to 7.2%) given the lack of in vitro activity of voriconazole against *Mucorales* (Figure 1) [7, 9, 10, 12, 24]. When breakthrough azole-susceptible IA occurs in voriconazole-exposed patients, it is often accounted for by the significant patient-to-patient variability in serum levels and the sizeable proportion of patients with low voriconazole levels (<1 μg/mL), especially in the pediatric population, critically ill patients in the ICU, and/or by severe underlying immunosuppressive state.

Less is known about bIMIs that develop in patients receiving isavuconazole. No such bIMIs were reported in 295 isavuconazole-treated patients in the 2 clinical trials that led to isavuconazole's FDA approval for the treatment of IA and mucormycosis [67, 68]. A recent single-center retrospective analysis revealed that documented bIMIs occurred up to 6% of 100 isavuconazole-treated patients, comprising predominantly mucormycosis, all occurring in the setting of refractory leukemia, prolonged cytopenias, and extended isavuconazole use [22]. Moreover, Fung et al recently reported 5 patients with isavuconazole-associated bIMIs in the setting of primary or secondary prophylaxis, with representation of both non-*fumigatus Aspergillus* resistant species, and non-*Aspergillus* molds [23]. Therefore, more data are needed from future studies to accurately define the spectrum and incidence of bIMIs in patients receiving isavuconazole, which will help devise optimal therapeutic approaches in these patients.

The Approach to bIMIs in Patients Receiving Echinocandins

The echinocandins have fungistatic activity against *Aspergillus* species, but exert no activity against non-*Aspergillus* mold fungi [69]. Micafungin is FDA-approved for IFI prophylaxis in HSCT recipients during the pre-engraftment neutropenic period [33]. The echinocandins are also used as prophylaxis in hematology

Table 2. Controversies in the Management of Breakthrough Invasive Mold Infections that Develop on Mold-active Antifungal Prophylaxis

Epidemiology/Risk factors/Screening strategies
Do we really know what a GM+, culture-negative bIMI really is in light of other hyalophyphomycetes such as *Fusarium* that can produce GM?
What is the role of clinical and/or immunogenomic-based risk stratification models to predict bIMIs and how do they differ in patients with leukemia versus HSCT?
What is the relationship between posaconazole, voriconazole or isavuconazole levels and the risk for developing bIMIs?
Is there a cost-effective strategy for screening for bIMIs? Assuming that performance of GM is impaired by mold-active antifungal agents, would periodic chest CT imaging (eg, low-dose radiation CT [65]) be an optimal strategy?
Does the prior sequential use of triazoles (eg, voriconazole followed by posaconazole, or posaconazole followed by isavuconazole) influence the frequency and type of bIMIs?
Diagnostic work-up
What is the best diagnostic approach for bIMIs presenting with pulmonary nodules (BAL versus CT-guided FNA versus VATS)?
What is the role of PCR in the diagnosis of bIMIs, including the new commercially-available tests for detection of TR34/L98H mutations in the Cyp51A gene?
What is the role of combining PCR with GM as a diagnostic approach to bIMI diagnosis?
What is the role of CT angiography in the diagnosis of bIMIs?
Management
What is the role of *in vitro* susceptibility testing for mold isolates in guiding the management of bIMIs?
What is the role of combination AMB/triazole versus switching to AMB in patients with triazole-associated bIMIs?
What is the role of adding an echinocandin in the pre-emptive treatment of triazole- and AMB-associated bIMIs?
What is the role of switching triazoles as monotherapy in voriconazole- or posaconazole-associated bIMIs?
What is the role of increasing the dose of triazoles or AMB as monotherapy in bIMIs?
What is the optimal timing of de-escalation after the onset of pre-emptive treatment of bIMIs?
What is the optimal antifungal management in patients with bIMIs and baseline or antifungal drug-induced liver and/or renal dysfunction?
What is the role of adjunct immunotherapy (eg, M-CSF versus GM-CSF versus G-CSF versus other) in the management of bIMIs?
What is the role of immune restoration via corticosteroid tapering in patients with bIMIs?
What is the role of surgical de-bulking of isolated pulmonary (or central nervous system) lesions, especially in the setting of drug-resistant IMIs?
What is the optimal timing of resuming chemotherapy (a critical element in achieving remission of hematological disease and long-term survival) after diagnosis of bIMIs?

Abbreviations: AMB, amphotericin B; BAL, bronchoalveolar lavage fluid; bIMI, breakthrough invasive mold infection; CSF, colony stimulating factor; CT, computed tomography; FNA, fine needle aspiration; GM, galactomannan; HSCT, hematopoietic stem cell transplantation; PCR, polymerase chain reaction; VATS, video-assisted thoracoscopic surgery.

patients during induction chemotherapy and in HSCT recipients in whom triazole use is hindered by pharmacokinetic, drug-drug interaction and/or toxicity problems. Proven/probable bIMIs have been reported in up to ~7.5% of hematology or HSCT patients during echinocandin prophylaxis [31, 32, 34–37, 70, 71]. IA accounts for the vast majority of these bIMIs (Table 1). This observation is in keeping with the relatively lower response rates of echinocandin primary therapy for IA in immunosuppressed hematology and HSCT patients [72], and the reported greater risk of bIMIs with echinocandin-based versus triazole-based prophylaxis in leukemia patients during remission-induction chemotherapy [73]. Less often, mucormycosis and fusariosis have also been reported as echinocandin-associated bIMIs [32, 34, 70, 71].

Taken together, although the differential diagnosis of presumed bIMI in patients receiving echinocandins is similar to that discussed above for triazole-associated bIMIs, the likelihood of IA appears greater in the setting of prior echinocandins. As outlined earlier for triazole-associated bIMIs, a prompt systematic work-up is warranted to establish a bIMI and/or alternative diagnoses. We propose that initiation of voriconazole or isavuconazole provides the preferred treatment modality to cover for breakthrough IA (Figure 1) [67, 74]. Consideration to continue the echinocandin in combination with the triazole may be given in patients with positive GM based on the study by Marr and colleagues [75]; nonetheless, most patients in that clinical trial were naive to mold-active antifungals; therefore, its results are difficult to extrapolate to the setting of echinocandin-associated breakthrough IA. In patients that present with clinical and radiographic features that may be suggestive of mucormycosis or fusariosis, strong consideration should be given to adding liposomal AMB as preemptive therapy.

The Approach to bIMIs in Patients Receiving AMB

Parenteral or aerosolized AMB is currently used infrequently as antifungal prophylaxis in hematology and HSCT patients, primarily because of its renal toxicity and availability of triazoles and echinocandins, evidence that parenteral AMB may not protect against bIMIs over placebo in patients with leukemia during remission-induction chemotherapy (incidence, 7.5%) [38] and that aerosolized AMB may not protect against IA in patients with relapsed hematological malignancies (incidence, ~4.5%) [41], and the demonstrated inferiority of AMB over voriconazole in the primary treatment of IA [74]. Consistent with the latter, the most common bIMI in the setting of prophylaxis with AMB-deoxycholate or liposomal AMB formulations is IA [39, 40]. Interestingly, a recent surveillance study in the United States showed higher than expected nonsusceptibility of *Aspergillus* species to AMB [76]. Documented mucormycosis or fusariosis rarely develop during AMB prophylaxis in agreement with the in vitro activity of AMB against *Mucorales* and *Fusarium* [77]. Notable gaps in antimold activity of AMB that may allow for developing corresponding bIMIs in AMB-treated patients include *Aspergillus terreus, Scedosporium apiospermum, Lamentospora prolificans*, and *Paecilomyces lilacinus*. Initiation of intravenous voriconazole or isavuconazole should cover for breakthrough IA and scedosporiosis in AMB-treated patients who present with a bIMI (Figure 1) [67, 74]. An echinocandin may be considered in combination with voriconazole during the first 2 weeks of treatment in patients who have positive GM, although the voriconazole-anidulafungin combination treatment study did not include AMB-exposed patients [75].

CONCLUSIONS, REMAINING CONTROVERSIES, AND FUTURE PERSPECTIVES

In recent years, bIMIs that occur in the setting of mold-active prophylaxis have emerged to cause significant real-life management dilemmas in profoundly immunocompromised hematology and HSCT patients. As there is lack of consensus data from clinical studies, many controversies remain unanswered (Table 2). The discovery of sensitive and IMI-specific diagnostic modalities that perform well in the setting of prior exposure to mold agents [78, 79], the introduction of novel antifungal compounds that have in vitro and in vivo activity against molds "experienced" to prior conventional regimens [80], and the improvement of our understanding of host immunogenetics that may lead to personalized risk stratification, prognostication and treatment strategies in these patients are promising future directions that may improve the patient prognosis [43]. The preclinical modeling of bIMIs that occur during mold-active drug exposure in clinically relevant mouse models of IMIs and multicenter clinical studies in these complex patient populations should shed more light on optimizing the diagnostic and therapeutic algorithms of bIMIs. While we await better clinical data, individualized, principle-driven, decisions are the best means to improve the outcomes of patients who develop bIMIs while receiving mold-active antifungal drugs.

Notes

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