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REVIEW

Foiling fungal disease post hematopoietic cell transplant: review of prophylactic strategies

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Hematopoietic cell transplantation (HCT) offers definitive management for a wide variety of malignant and nonmalignant diseases. Conditioning regimens and therapies used to prevent and treat GvHD are immune suppressive, often increasing the risk of developing fungal disease due to yeasts or molds. Antifungal prophylaxis may be useful in preventing morbidity and mortality during and after HCT. In this article, we review the epidemiology and current literature regarding strategies for prevention of invasive fungal disease (IFD) in the pre-engraftment and post-engraftment settings, and propose future direction for scientific discovery.

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INTRODUCTION

Since its inception in the 1960s, hematopoietic cell transplantation (HCT) has revolutionized the management of a spectrum of malignant and nonmalignant diseases. An increasing number of patients is eligible for HCT with the development of protocols using reduced-intensity conditioning regimens and alternate donor sources, such as haploidentical donors and cord blood.[1–3] Although more patients are achieving cures of their underlying hematologic conditions, a large number is now living with complications of HCT.[1] Infectious complications following HCT are a frequently encountered morbidity, with an incidence of bacterial or fungal infections approaching 70% in patients undergoing HCT for acute leukemia.[4] Infections after HCT can be secondary to chemotherapy-related neutropenia, immunosuppression caused by medications used for prophylaxis and treatment of GvHD and GvHD itself.[2] Fungal disease is particularly severe and carries a very high morbidity and up to 60% mortality for patients diagnosed with invasive aspergillosis.[3,5]

Despite the high index of suspicion for fungal disease in HCT patients, diagnosis remains challenging. The clinical presentation of patients with fungal infections following HCT is often nonspecific and difficult to distinguish from bacterial infections. Initial cultures may be negative, as the sensitivity of fungal blood cultures for neutropenic cancer patients with invasive *Candida* infections can be as low as 30%.[6,7] Fungal antigen testing such as serum 1,3-β-D-glucan and *Aspergillus* galactomannan have aided in early diagnosis of fungal disease, with reported sensitivities in the 70–77% and 71–95% range, respectively, for diagnosis of invasive *Aspergillus* infection, but still have significant false negative rates.[8–11] Several meta-analyses have shown higher sensitivity and specificity, 86% and 89–95% respectively, associated with bronchoalveolar lavage galactomannan assay in the setting of proven or probable invasive aspergillosis.[12,13] Despite the improved performance of the bronchoalveolar lavage galactomannan assay, testing is frequently not feasible for HCT patients because of severity of illness and significant thrombocytopenia.[14,15] Although certain findings on chest imaging, such as the halo sign (defined as a mass surrounded by a lower density ring), are sensitive for invasive pulmonary *Aspergillus* infections, there is a variety of fungal infections that can also produce diffuse infiltrates that require a tissue diagnosis.[16] Unfortunately, obtaining tissue is often impractical because of the risks associated with an invasive biopsy, including bleeding, pneumothorax and, potentially, death. Because of the above limitations, consideration should be given for targeted antifungal prophylaxis. This article aims to review the current literature regarding the epidemiology and strategies for antifungal prophylaxis in patients undergoing HCT.

EPIDEMIOLOGY OF FUNGAL DISEASE IN HCT

Before the advent of antifungal prophylaxis, invasive *Candida* infections were prevalent in as many as 18% of HCT patients.[17] The initial prophylactic drug, fluconazole, was primarily used to prevent *Candida* infections.[18,19] This resulted in a significant decrease in transplant-related mortality secondary to *Candida* infections, but has shifted the prevalent organisms toward more resistant species.[20] Although the overall rates of *Candida* infections are low at most centers, disease due to fluconazole-resistant *Candida* species, such as *C. glabrata* and *C. krusei*, are now responsible for as much as 55% of Candidemia in patients with hematologic malignancies.[21] Over the past 2 decades, invasive fungal disease (IFD) secondary to molds such as *Aspergillus* and Mucorales has become more prevalent than *Candida*, with an incidence as high as 23%.[2,22,23]

High-risk periods for IFD include: (1) the pre-engraftment period when neutropenia is most profound, (2) the early post-engraftment period when the new T-cell armamentarium has yet to fully expand and patients are at highest risk for acute GvHD and (3) the late post-engraftment period complicated by chronic

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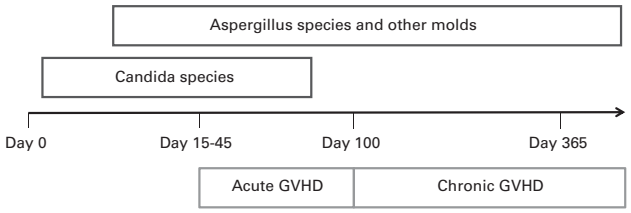

Figure 1. Epidemiology of fungal disease after hematopoietic cell transplantation. A full colour version of this figure is available at the *Bone Marrow Transplantation* journal online.

GvHD.[24,25] The pre-engraftment neutropenic period and the early post-engraftment period confer highest risk of *Candida*, whereas invasive *Aspergillus* is most common during the pre-engraftment period and the late post-engraftment period, as GvHD is a risk factor for IFD,[24,25] (Figure 1).

Genetic factors in both the donor and recipient may also alter a patient's risk of fungal infection with HCT.[26–29] In the coming era of personalized medicine, additional observations may help identify patients at increased risk for fungal disease, guiding the decision on whom to initiate targeted antifungal prophylaxis.

ANTIFUNGAL PROPHYLAXIS IN HCT

Early clinical trials examining antifungal prophylaxis in HCT demonstrated that fluconazole prophylaxis was superior to placebo in reducing the incidence of mortality due to systemic fungal infections in the pre-engraftment setting.[30–32] A 2007 meta-analysis of 64 randomized trials corroborated these findings and demonstrated a 38% reduction in all-cause mortality for both autologous and allogeneic HCT patients receiving pre-engraftment antifungal prophylaxis, although the majority of this effect was seen in allogeneic HCT patients.[20] Antifungal prophylaxis targeting yeast is now used universally during the pre-engraftment period for patients undergoing allogeneic HCT.[33,34]

A limitation of these data is their applicability to patients undergoing autologous HCT. In the above meta-analysis, the mortality benefit observed in autologous HCT patients was not attributable to reduced mortality from fungal infection.[20] Although there is some evidence that *Candida* colonization in patients undergoing autologous HCT is an independent risk factor for transplant-related mortality,[22] routine antifungal prophylaxis in patients undergoing autologous HCT is not currently recommended.[25,35]

POTENTIAL INDICATIONS FOR MOLD-ACTIVE PROPHYLAXIS

Routine mold-active prophylaxis in the pre-engraftment setting remains controversial, and choosing such patients can be challenging, as risk factors for yeast and mold infections often overlap. There is a select group of patients undergoing autologous and allogeneic HCT who may benefit from mold-active prophylaxis. These include patients with an anticipated duration of neutropenia of $\geqslant 10$ days or those who have had prior fungal disease.[23,24] Patients who have had IFD before HCT have as high as a 33% risk of fungal disease recrudescence post HCT.[36,37] Suppressive treatment with an antimold agent after the initial infection has resolved has been shown effective at preventing life-threatening relapsed fungal infection. In one prospective study of 41 patients with acute leukemia and proven or probable IFD who received prophylactic dose voriconazole 200 mg twice daily after resolution of their primary infection during allogeneic HCT, only one died because of relapsed fungal disease.[38] Although the sample size is small, it demonstrates that 'secondary prophylaxis' is effective in the pre-engraftment setting for patients undergoing HCT with prior IFD. Ideally, the prophylactic medication should be tailored to susceptibility data of the initial organism and should be chosen with careful consideration of drug interactions with the conditioning regimen.

Important risk factors for IFD post engraftment include respiratory viruses, escalating doses of glucocorticoids, grade 3 or higher GvHD and CMV infection.[39,40] Both acute and chronic GvHD are important risk factors for IFD in patients undergoing HCT.[2,39,41–43] Acute GvHD carries a hazard ratio of 2.4–5.7 for the development of IFD, with post-engraftment invasive *Aspergillus* occurring more frequently in patients who have acute GvHD.[39,41–43] Although this effect has been shown in some studies to be independent of the doses of glucocorticoids used to treat GvHD, other studies have shown glucocorticoid doses of >3 mg/kg daily to confer a high independent risk of IFD, with doses >2 mg/kg at the time of IFD diagnosis being a risk factor for mortality due to IFD in HCT patients.[2,5,42] CMV infection has been shown to be an independent risk factor for IFD in the HCT setting in numerous studies.[39,41,44] Data are lacking regarding the direct link between CMV infection and fungal disease in the HCT population, and the precise mechanism of this relationship has not been elucidated, although immunomodulatory effects of CMV as well as its treatments have been proposed.[41] Current guidelines do not identify CMV infection as an indication for mold-active prophylaxis.

OPTIONS FOR ANTIFUNGAL PROPHYLAXIS

Yeast-active agents that can be used for prophylaxis include fluconazole and echinocandins (micafungin or caspofungin). Mold-active agents that can be used for prophylaxis include second-generation (itraconazole, voriconazole) and third-generation (posaconazole) triazoles and amphotericin B (Table 1).

A 2012 meta-analysis evaluated IFD in 20 studies of patients being treated for hematologic malignancy with chemotherapy or HCT.[34] Itraconazole was the most commonly used mold-active agent (10 studies), followed by amphotericin B (4), micafungin (3), posaconazole (2) and voriconazole (1). This analysis demonstrated significant reductions in fungal infections and fungal infection-related mortality for patients receiving mold-active prophylaxis. However, mold-active prophylaxis also resulted in a significant increase in adverse side effects and no change in overall mortality. The benefits and adverse effects of the mold-active agents were not separated by class, and thus it is unclear whether the increase in adverse effects seen in the group receiving mold-active prophylaxis was restricted to poorly tolerated agents such as amphotericin B. Furthermore, the study in this meta-analysis that demonstrated the greatest benefit of mold-active prophylaxis did not include patients undergoing HCT, questioning the external validity of the observed benefit to the HCT population.[47] As a result, routine mold-active prophylaxis for patients undergoing HCT is not typically indicated.

Several trials have examined the use of amphotericin B for prophylaxis of IFD.[48–53] Smaller studies have demonstrated that amphotericin is safe and effective in preventing IFD in HCT patients.[48,49] However, trials comparing amphotericin to posaconazole have demonstrated higher rates of adverse effects with amphotericin, such as nephrotoxicity.[50,53] Retrospective trials using aerosolized amphotericin B have shown this to be a safe and effective strategy for fungal prophylaxis in HCT, but there are no published prospective trials examining its efficacy.[51,52]

Voriconazole has been studied extensively as a prophylactic agent in the HCT setting.[33,54–58] Adverse effects of voriconazole include hepatotoxicity, prolongation of the QTc interval and visual disturbances.[59] In addition, prophylaxis with voriconazole often requires consideration of drug–drug interactions, notably with immunosuppressive drugs such as calcineurin inhibitors. These drug–drug interactions warrant significant dose reductions, closer therapeutic drug monitoring of calcineurin inhibitors and may

Table 1. Guidelines for prophylaxis of fungal infections during and after hematopoietic cell transplantation

Organization	*Recommended agents for autologous HSCT*	*Recommended agents for allogeneic HSCT*	*Recommended agents for GvHD*
National Comprehensive Cancer Network (NCCN)[45]	No routine prophylaxis (2B) Fluconazole or an echniocandin if mucositis (1)	Fluconazole or an echinocandin (1) Can consider voriconazole, posaconazole or amphotericin B (2B)	Posaconazole (1) Can consider voriconazole, amphotericin B or an echinocandin (2B)
American Society of Bone Marrow Transplantation (ASBMT)[25]	No routine prophylaxis (C3) Fluconazole if prolonged neutropenia, mucositi, or fludarabine/2-CDA within 6 months before HSCT (B3)	Fluconazole (A1) unless colonized with resistant *Candida* Can consider micafungin (B1)	Posaconazole (B1) Can consider aerosolized amphotericin B (B2)
European Council on Infections in Leukemia (ECIL)[46]	No recommendations	Fluconazole (A1) or voriconazole (provisional A1) Aerosolized amphotericin B+fluconazole (B3) Micafungin or IV amphotericin B (C1)	Posaconazole (A1) or voriconazole (provisional A1) Itraconazole (B1) IV amphotericin B or fluconazole (C1)
Infectious Diseases Society of America (IDSA)[35]	None if neutropenia <7 days (A3) Aspergillus prophylaxis (itraconazole, posacaonazole or voriconazole) if prior IFD (A3), prolonged neutropenia either anticipated or immediately before HSCT (C3)	*Candida* prophylaxis (Fluconazole, itraconazole, voriconazole, posaconazole, micafungin or caspofungin) (A1) Aspergillus prophylaxis (itraconazole, posacaonazole or voriconazole) if prior IFD (A3), prolonged neutropenia either anticipated or immediately before HSCT (C3)	No recommendations

Abbreviations: HSCT = hematopoietic stem cell transplantation; IFD = invasive fungal disease.

warrant therapeutic drug monitoring even at prophylactic doses. Single-arm, safety studies have shown that voriconazole is well tolerated, with use resulting in low (2–5%) rates of IFD. Prospective trials comparing voriconazole with itraconazole showed improved tolerability of voriconazole in patients randomized to either drug for 100 days post-myeloablative or reduced-intensity allogeneic HCT and a trend toward fewer infections caused by *Aspergillus* in patients who were randomized to voriconazole versus fluconazole for at least 100 days post-myeloablative allogeneic HCT.[33,54] Surrogate benefits, such as reduced need for alternate treatment dose antifungals when compared with itraconazole, and lower rates of IFD when compared with fluconazole or itraconazole have been seen with voriconazole use. However, clinical trials have not shown improvements in IFD-free survival or overall survival with use of voriconazole over itraconazole or fluconazole.[33,34,54]

Posaconazole, which is felt to be the best tolerated of the triazole class of medications, is available orally (both as a solution and a delayed-release tablet) and intravenously.[60] Common toxicities seen with posaconazole include gastrointestinal upset as well as hepatoxicity, QTc prolongation and drug–drug interactions.[12] Therapeutic drug monitoring of posaconazole is usually not necessary in the prophylactic setting, as administration of the delayed-release tablet results in therapeutic concentrations.[61] The oral delayed-release form is also preferred to the solution as it has superior bioavailability, is minimally affected by food or gastric pH and requires once daily dosing after a 1-day loading dose. Posaconazole has been shown to be safe and effective as an agent for long-term prophylaxis of fungal infections when started on day 1 of HCT.[62] Posaconazole has also demonstrated superior prophylactic efficacy to fluconazole and itraconazole in the setting of GvHD, although there were more adverse events in posaconazole-treated patients.[47] One randomized controlled trial found a reduction in IFD (specifically with *Aspergillus* species) and IFD-related mortality in patients with grade II–IV acute GvHD or extensive, chronic GvHD who received posaconazole versus fluconazole. In this study, there was no change in overall mortality.[21] Breakthrough IFD with non-*Aspergillus* molds as well as resistant *Candida* has also been reported in HCT patients receiving posaconazole prophylaxis.[62–64] Posaconazole has not yet been studied for antifungal prophylaxis in the pre-engraftment period and more data are needed to establish its efficacy in this setting.

Isavuconazole, the latest triazole to be approved by the Food and Drug Administration for the treatment of fungal infections, has yet to be studied as antifungal prophylaxis in the HCT setting. It is well tolerated, and unlike other triazoles, may shorten the QTc interval. As with other triazoles, isavuconazole has numerous drug–drug interactions, including similar interactions with calcineurin inhibitors as other triazoles.[65] This agent has shown promise for treatment of IFD. In one randomized controlled trial, isavuconazole had similar efficacy to voriconazole for treatment of invasive *Aspergillus* with a lower incidence of adverse events.[66] In a single-arm, open-label trial, isavuconazole had similar efficacy to amphotericin B for treatment of Mucormycosis with a lower incidence of adverse events.[67] Given the morbidity associated with cessation of antifungal prophylaxis and resultant IFD, consideration should be given to randomized, controlled trial of prophylactic isavuconazole in HCT patients at high risk for IFD, such as those with severe GvHD or those requiring large doses of glucocorticoids.

Echinocandins are well tolerated and have been shown to have inhibitory activity *in vitro* and clinical activity against *Aspergillus* species in the salvage setting.[68] Recent guidelines recommend considering micafungin as an alternate agent for antiyeast prophylaxis in the early post-engraftment setting.[25,69–71] The use of micafungin as opposed to fluconazole for antifungal prophylaxis has been associated with modest reductions in the cost of HCT hospitalizations, potentially because of lower need for empiric antifungal therapy and a lower rate of breakthrough infections.[72,73] A limitation of routine echinocandin use is that they are currently only available as IV agents and continuation in the outpatient setting may be inconvenient, requiring daily clinic attendance or home infusion therapy. Echinocandins have no activity against non-*Aspergillus* molds such as Mucorales[74,75] and may provide superior prophylactic activity against yeasts rather than molds.

DURATION OF ANTIFUNGAL PROPHYLAXIS

The duration of antifungal prophylaxis for patients undergoing HCT is not well defined, but the evidence suggests that patients

benefit from continued prophylaxis even after resolution of neutropenia. In one study, patients were randomized to fluconazole or placebo for 75 days following HCT.[76] Although randomization occurred at the time of HCT rather than at engraftment, patients receiving prolonged prophylaxis suffered fewer late (>110 days post transplant) deaths from fungal disease, lower rates of severe gastrointestinal GvHD and improved overall survival after 8 years of follow-up.[77] In practice, antifungal prophylaxis is often administered for longer and possibly until cessation of significant immunosuppressive therapy.[78]

CURRENT GUIDELINES AND FUTURE DIRECTIONS

Several guidelines discuss fungal prophylaxis in HCT[25,35,45,46,79] (Table 1), but many have not been updated to reflect new data and changes in clinical practice.

There is no consensus regarding the optimal strategy for antifungal prophylaxis during autologous HCT. Patients who are expected to experience neutropenia beyond 7 days, colonized with yeast such as *Candida*, and who have had IFD before autologous HCT may represent the higher-risk groups who will benefit from antifungal prophylaxis.[22,25,35] Prospective clinical trials in which these patients are randomized to receive antifungal prophylaxis may help to clarify whether there is a morbidity or mortality benefit.

There is a paucity of data regarding the optimal antifungal prophylaxis strategy for patients undergoing a second or third allogeneic HCT or haploidentical HCT. Haploidentical HCT has been identified as an independent risk factor for IFD in one retrospective analysis,[80] but IFD following haploidentical HCT is uncommon, with rates as low as 3% for patients receiving post transplant high-dose cyclophosphamide.[80–83,82] Patients undergoing haploidentical HCT may not benefit from routine mold-active prophylaxis, although more prospective data are needed to better understand the rates of IFD in this HCT group.

In addition, there is no clear guidance regarding which mold-active agent is most useful if mold-active prophylaxis is deemed necessary, as all guidelines provide different recommendations.[25,35,45,46,79] This is in part because of a dearth of trials directly comparing mold-active agents, with one exception being a single trial comparing posaconazole to itraconazole in the setting of GvHD.[47] This trial offered sufficient clarity to warrant a recommendation for the routine use of posaconazole in the context of severe GvHD in all guidelines except the IDSA (Infectious Diseases Society of America) that does not provide any specific recommendations for mold-active prophylaxis in this setting. A potential prospective study could compare isavuconazole with available prophylactic agents in HCT, as this azole has broad-spectrum activity against yeasts and molds.[67]

A variety of host and donor genetic risk factors have been associated with increased risk of *Candida* colonization and invasive *Aspergillus*, but routine clinical use of this information is not yet standard of care.[26–29] As genetic testing becomes less expensive and more readily available, it may become plausible to screen recipients and donors for common genetic risk factors for IFD. Prospective trials should be designed to evaluate whether screening for these genetic risk factors with introduction of targeted mold-active prophylaxis during HCT is one strategy to reduce IFD-related transplant mortality.

CONCLUSIONS

In the era of routine antifungal prophylaxis during HCT, fungal disease remains a major source of transplant-related morbidity and mortality. As HCT is offered to more patients at higher risk for poor outcomes related to IFD, risk stratification is critical to selecting an appropriate prophylactic regimen. Patients undergoing uncomplicated autologous HCT who do not have prior fungal infections or are not expected to experience prolonged neutropenia may benefit from administration of antiyeast prophylaxis, such as fluconazole or micafungin. Although routine mold-active prophylaxis during HCT has not shown universal benefit, this may be because of poor adverse effect profiles of older mold-active agents. Additional trials are needed to evaluate the efficacy of newer agents. Clinicians should have a low threshold to use better-tolerated mold-active agents, such posaconazole, for antifungal prophylaxis in patients at high risk for IFD, including those patients with IFD before HCT, prolonged neutropenia or severe GvHD requiring augmented immune suppression. Further prospective studies are needed to determine whether these agents would be beneficial if used universally. Antimold prophylaxis should be continued long after engraftment to prevent late-onset fungal disease or, in the case of GvHD, until high-dose immunosuppression has ceased.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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