Update on Epidemiology of and Preventive Strategies for Invasive Fungal Infections in Cancer Patients

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Changes in antineoplastic treatments and transplant practices are driving shifts in the epidemiology of invasive fungal diseases (IFDs). Patients with acute myelogenous leukemia (AML) and those undergoing bone marrow transplant (BMT) are at greatest risk for contracting IFDs. Unfortunately, there are few large population studies that can be used to track trends and help us to better understand why certain individuals within recognized high-risk groups are at greater risks than others for contracting IFDs. The growing use of antifungals in prophylaxis and treatment influences which species will cause an IFD as well as the resistance patterns of these fungi. On the one hand, antifungal prophylaxis has mitigated, but not eliminated, the threat of candidiasis. Furthermore, prophylaxis trials have shown trends of reduced aspergillosis in BMT patients; however, no survival benefits were seen, and 1 trial indicated a lower rate of aspergillosis and survival benefits in patients with AML. Future prophylaxis trials should reduce the heterogeneity of risk in study participants in order to better assess benefit; these trials should also incorporate fungal biomarkers into their design. The threat of emerging fungal resistance in prophylaxis strategies is real and must be monitored.

Keywords. fungal infections; cancer; prophylaxis; resistance.

Epidemiology

The epidemiology of invasive fungal diseases (IFDs) in cancer patients continues to evolve while treatment of underlying malignancies with chemotherapies and new biological agents negatively impact the protective immune responses. Although IFDs are known as life-threatening "collateral damage" that result from managing cancers, the appearance of these diseases and the outcome for patients depend on the type of cancer and its treatment. Furthermore, from a diagnostic and preventive standpoint, it is essential that clinicians assess both the general risks of IFDs in a particular patient and the specific local risks within the context of hospital practices, patient populations, and local infection control effectiveness. There are subgroups within cancer risk groups that have even higher or lower risks for IFDs. For instance, a patient who received a bone marrow transplant (BMT) for management of acute myelogenous leukemia (AML) may carry added risks compared with another patient who received BMT for a different indication. Another example is a patient who had a prior IFD and displays an added risk for the next stage of chemotherapy [1].

Large population studies of cancer patients with IFDs are necessary to calculate robust risk incidences for individual cancers and for transplant recipients in order to inform guidelines [2]. However, each hospital system should track their epidemiology of IFDs; with computerized systems, this tracking should be more facile. Local epidemiological insights may be of even greater importance because cancer patients receive outpatient care involving different infection control practices.
These local insights will drive the diagnostic and therapeutic agenda for IFDs in cancer.

Several trends persist regarding the epidemiology of IFDs and cancer. These include an increasing number of IFDs because of an increasing “at-risk” population; a variable clinical integration of biomarkers vs radiographic screenings in the early diagnosis of IFDs; a high associated mortality with IFDs despite treatments; a negative impact of delayed antifungal therapy on patient outcome; a confluence of prophylaxis strategies that are spiraling empiricism in antifungal drug use and long-term antifungal treatment regimens with unclear endpoints, creating a prescription for the appearance of drug-resistant strains and/or superinfections; and the fact that all cancers and their treatments do not have equal risk of resulting in an IFD.

Models for examining cancers and IFDs include patients with hematological malignancies and allogeneic BMT because such malignancies are considered the highest-risk cancers and these patients are at the highest risk for IFDs. Despite many evidence-based studies and national guidelines for these risk groups, protocols are not always followed consistently within hospitals. For example, in one hospital, despite the multicenter comparative success of posaconazole over fluconazole/itraconazole for AML/Myelodysplastic Syndrome (MDS) prophylaxis [3], patients were receiving either fluconazole or posaconazole. When azole prophylaxis use was retrospectively reviewed outside of a clinical study, it was confirmed that the mold-active agent, posaconazole, prevented more IFDs than did fluconazole; however, there was no difference in mortality as observed in the definitive study [4]. Thus, studies and the resulting guidelines are not always fully adopted and followed at all medical centers for a variety of reasons. However, it is clear that the combination of severe neutropenia, mucositis, long-term intravenous catheters, and broad-spectrum antibiotics allows for the frequent appearance of IFDs in the high-risk cancer group, and strategies to prevent and/or manage IFDs must be in place.

Currently, data confirm that our use of antifungals has changed the fungal patterns of IFDs. For example, an autopsy study of hematological malignancies at a cancer hospital noted a drop in aspergillosis but an increase in mucormycosis and a resurgence of Candida infections [5]. Furthermore, up to 3% of bloodstream fungal isolates at that hospital were caused by rare yeast strains with variable in vitro susceptibility patterns to azoles and echinocandins [6]. Is this occurrence of IFDs a reflection of more outpatient management of cancers and/or the widespread use of azoles and echinocandins in this cancer population? There is no precise answer; however, it is clear that we are observing more fungal strains with direct resistance to azoles and echinocandins [7]. Diagnostically, in advanced hematologic malignancies, the clinician must be aware of the frequent occurrence of superinfections such as mucormycosis caused by drug-resistant molds and associated with voriconazole use [8].

In addition, clinicians must be aware of echinocandin-resistant Candida glabrata infections [7] that result after widespread and prolonged antifungal drug exposure. It is necessary to start antifungal therapy at an early stage of IFD for a better outcome. If, through genetics, we can more precisely assess the specific risk for a patient to contract an IFD, we can move toward precise, targeted strategies for preventing disease and treating patients early. Furthermore, with our biomarker strategies, we are challenged to identify early cases of IFDs under the umbrella of prophylaxis [9–11].

Prophylaxis

The considerations for prophylaxis must carefully balance the likelihood of IFD and the types of fungi that are likely to cause IFD with the risks and benefits of the antifungal agents. Historically, Candida has been the most important cause of IFD encountered in BMT and acute leukemia patients as well as a major cause of persistent or unexplained fever during neutropenia. In multiple studies, fluconazole prophylaxis was shown to be a safe and effective prophylaxis for BMT and leukemic patients, showing consistent reductions in IFDs (mostly Candida); in some studies, reduced mortality from IFDs was also seen [12, 13].

IFDs due to non-albicans Candida species have increased proportionately in other patient populations exposed to widespread fluconazole use. Yet, surprisingly, emergence of IFDs due to fluconazole-resistant non-albicans Candida species has been less problematic for BMT patients despite more than 2 decades of azole prophylaxis. However, in vitro antifungal susceptibility testing is still useful in epidemiological studies to guide therapy and identify emergence of resistant strains in these patients.

With the emergence of invasive aspergillosis (IA), which is a primary cause of IFD in cancer patients, efforts have shifted to identifying patients at greatest risk for IA and determining how to manage them. The occurrence of prior IA was recognized as the major risk factor for subsequent IA and once was considered a contraindication for BMT. However, it is recognized that “secondary” prophylaxis with voriconazole makes it possible to safely perform BMT in patients with prior IA [14]. However, caution is needed since breakthrough IA can still occur, particularly in patients with such risk factors as intensive conditioning regimens, prolonged neutropenia, and graft-versus-host disease (GVHD) [15].

Polyenes have not been evaluated as prophylaxis in high-quality studies due to toxicity of the systemic formulations and the need for parenteral administration. However, one trial of aerosolized liposomal amphotericin B did suggest a protective benefit [16]. The extended-spectrum azoles (itraconazole, voriconazole, and posaconazole) for mold protection have been well studied [3, 17–20]. In one trial with AML/MDS patients, posaconazole was used to effectively reduce IFDs.
(including IA), plus a survival benefit was noted [3]. In contrast, in BMT patients, nonsignificant trends of lower IFD rates were noted in clinical trials with all 3 mold-active azoles; however, no significant improvement in survival was noted. Issues relating to drug tolerance, particularly with itraconazole, variable blood levels with all 3 agents, and the presence of breakthrough IFDs, particularly in very high-risk patients, indicate that we have yet to devise the optimal anti-Aspergillus prophylaxis. For instance, although the oral mold-active azoles have variable systemic exposure, the new formulation of posaconazole appears to be an improvement for thisazole. However, it is unclear if drug monitoring is as important for prophylaxis success as it has been shown to be in treatment.

It is important to note that participants enrolled in certain prophylaxis studies had a variable risk for IFD. It is possible that benefits would have been more evident had patients with specifically higher risk been enrolled. For example, in one study, the patients receiving BMT for AML were at highest risk, and voriconazole prophylaxis was associated with fewer IFDs in that subgroup [20]. It is known that those with GVHD as well as the subgroup treated with high-dose steroids given for IFDs in that subgroup [20]. It is known that prolonged neutropenia is a major risk factor for IA after AML induction therapy [21]; therefore, patients who require a second course of induction therapy would be the most likely to develop IA and benefit from prophylaxis. Future trials should take the heterogeneity of risk into consideration and focus on patients at the highest risk.

The potential for emergence of drug-resistant molds, particularly those that cause mucormycosis, is real. Early single-center studies noted significantly more instances of mucormycosis in patients given prophylactic voriconazole [23–25]. Such observations were limited because the use of voriconazole was not standardized and patients at high risk for all IFDs were generally given voriconazole and compared with individuals at lower risk for IFDs. In fact, the best estimates of risk have come from randomized trials that compared rates of mucormycosis using various azoles with and without activity against mucormycosis [3, 19, 20, 26], as well as longitudinal observational studies of IFD trends in BMT centers over time [27]. These studies suggest that the rates of mucormycosis remain relatively low in most centers and that rates vary from center to center. Generally, rates of mucormycosis have not increased significantly over time and do not appear to be higher in patients given voriconazole. However, there is variability in how aggressive diagnostic assessment is from center to center, which complicates the estimation of both risks and trends. In addition, the risk is subject to change over time and therefore warrants careful surveillance of IFDs in each cancer center. Moreover, azole resistance is being detected in Aspergillus isolates [28] and its presence should be monitored.

**Preemptive (Biomarker-Driven) Therapy**

Finally, the best way to incorporate fungal biomarkers into an individually targeted treatment approach is a major concern that requires additional study of high-risk cancer patients. Several studies have examined the use of galactomannan or polymerase chain reaction to guide preemptive antifungal therapy as an alternative to antifungal prophylaxis. Unfortunately, although a pilot study [29] suggested promise for preemptive therapy; in other studies, the picture was not so clear [30]. Because of methodological limitations of these studies, including lack of standardized anti-yeast prophylaxis, use of a high threshold of positivity for the galactomannan assay, and lapses in adherence to the monitoring schedule, we are unable to determine the best way to combine biomarker monitoring with preemptive therapy as an alternative to prophylaxis. Biomarkers must be studied and considered. It is essential that we are careful stewards of our limited antifungal armamentarium because resistance development can make them obsolete and there are few new antifungal agents in the pipeline.

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