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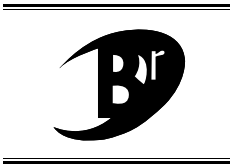

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REVIEW

New strategies of antifungal therapy in hematopoietic stem cell transplant recipients and patients with hematological malignancies

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Summary Invasive fungal infections (IFIs) are associated with considerable morbidity and mortality among high-risk individuals. Outcomes for IFI historically have been suboptimal and associated with a high mortality rate, hence global prophylaxis strategies have been applied to at-risk populations. Among certain populations, fluconazole prophylaxis has reduced systemic and superficial infections caused by ***Candida*** species. Newer azoles are currently being evaluated as prophylaxis and have the potential to provide protection against mould pathogens that are more troublesome to treat once they occur. Global prophylaxis strategies have the shortcoming of subjecting patients to therapy that ultimately will not need it. Targeted prophylaxis has the advantage of treating only patients at highest risk using some parameter of greater host susceptibility. Prophylaxis strategies are most suitable in patients at the highest risk for IFI. For patient groups whose risk is somewhat lower or when suspicion of IFI occurs in patients receiving prophylaxis, empirical antifungal therapy is often employed following a predefined period of fever. Again this approach subjects many non-infected patients to unnecessary and toxic therapy. A more refined approach such as presumptive or pre-emptive therapy whereby treatment is only initiated upon positive identification of a surrogate marker of infection in combination with clinical and radiological signs will subject fewer patients to toxic and expensive treatments.
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Introduction

Invasive fungal infections (IFIs) are common complications following treatment for hematological

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malignancies and hematopoietic stem cell transplantation (HSCT), occurring in 10 to 25% of patients. Not all patients are at the same risk for developing an IFI, with the greatest risk in patients undergoing allogeneic HSCT (who develop graft versus host disease (GVHD)), cord HSCT, and T-cell depleted HSCT. Patients receiving treatment for hematological malignancies are also at a higher risk for developing an IFI compared to patients with solid tumors. IFIs are associated with significant morbidity and mortality once they occur. Thus, clinicians are continually looking for alternative strategies to diagnose the infections earlier with the hope that earlier detection and more prompt initiation of treatment, as well as use of newer, more effective and less toxic antifungal agents, will lead to improvements in outcome. The majority of IFIs in patients with hematologic malignancies and HSCT recipients are caused by yeasts such as *Candida* spp, and moulds such as *Aspergillus* spp., and thus the approaches discussed in this manuscript will focus on these two pathogens.

There are several approaches to management of IFIs in immunocompromised patients. Three major strategies of antifungal therapy include: (1) prevention, the use of prophylactic antifungal therapy to prevent an infection from occurring; (2) empirical treatment, the use of a pre-defined time period (72 − 120 hours) of persistent fever despite broad-spectrum antibiotics to serve as a trigger for antifungal therapy for a suspected infection; and (3) treatment for a documented IFI. There are advantages and disadvantages of each of these treatment strategies.

Prophylaxis is most suitable for patient groups in which the risk of IFI is high. This has been used to great benefit for *Pneumocystis Jiroveci* (PCP) and *Candida* spp. The recent availability of extended spectrum azoles (such as itraconazole, voriconazole, and posaconazole) and the echinocandins (caspofungin, micafungin and anidulafungin) has led to new interest for *Aspergillus* infections. The major shortcoming is the exposure of many patients (who ultimately will never need antifungal drugs) to toxicity, and there is a fear about the emergence of resistant fungi. These issues will be addressed later in more detail.

Empirical antifungal treatment is more complicated. Patients who are neutropenic and develop fever are treated with broad-spectrum antibacterial agents since bacteria are the leading cause of the first febrile episode during neutropenia. A lack of response to these agents may lead one to fear that the initial fever was not bacterial, rather caused by fungal pathogens, or alternatively, that persistent (or recurrent) fever may be due to a fungal superinfection. Empirical antifungal therapy of persistent fever during neutropenia has become commonly used following the publication of two small studies conducted in the late 1970's and early 1980's.[1,2] In these studies the addition of an antifungal to broad-spectrum antibiotics following seven days (in one study)[2] and 96 hours (in the other study)[1] of refractory fever resulted in fewer breakthrough IFIs[2] and fungal-related deaths.[1] The major concern with empirical antifungal therapy is that, like prophylaxis, it exposes a large proportion of the patient population to unnecessary antifungal therapy when infection is not present. This may lead to various toxicities, including infusional toxicity, nephrotoxicity, hepatotoxicity, visual toxicity, CNS toxicity, and various drug interactions with associated toxicities.

Such limitations of both prophylaxis and empirical therapy have fueled an increasing interest in further efforts to give treatment to only those individuals who are infected and to spare those who do not. Treating only patients with well-documented IFIs has its limitations as well. Most notable is the fact that documentation of IFI early in the course of infection, while one is most apt to achieve control of the IFI, is notoriously difficult since diagnostic tools are less than adequate. Thus, while sparing patients not in need of treatment is achieved, this strategy has been associated with poor outcomes in general.

We believe that increasingly clinicians will move to targeted prophylaxis instead of global prophylaxis; to targeted empirical treatment, using surrogate markers to identify those patients who are in the very early in the invasive phase of infection or those most likely ''infected'' before the development of fulminant disease to trigger antifungal treatment, and earlier treatment of documented IFIs using new diagnostics and perhaps more potent combinations of drugs. The merits of each of these strategies will be discussed in details in the following pages.

Prophylaxis

Current Approach

Numerous studies have evaluated the use of antifungal agents in the prevention of IFIs in HSCT patients, including fluconazole,[3–12] amphotericin B,[8,9,13–16] lipid amphotericin B formulations,[17–19] miconazole,[20–22] ketoconazole,[23–26] itraconazole,[11,27–34] posaconazole,[35] and micafungin.[36] The role of voriconazole as is currently being evaluated[37] (www.bmtctn.net). The pertinent results of pivotal prophylaxis trials are outlined in Table 1.

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