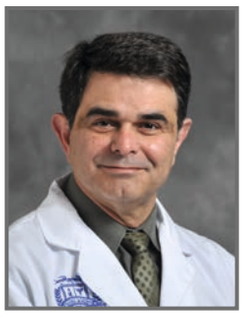
How can we improve the management of fungal infections in immunocompromised patients?



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Q Which fungal infections pose the highest risk to immunocompromised patients?

Over the past 30 years, the frequency and variety of invasive fungal infections (IFIs) have risen markedly in parallel with the rapid developments in medical technology [1]. *Candida* spp. are the most common cause of opportunistic IFIs throughout the world [1]. However, during the past two decades, the frequency of infections due to the non-*albicans Candida* spp., especially *Candida glabrata* and *Candida krusei* have increased [1]. *Aspergillus* spp. accounts for the second most commonly seen fungal infection in immunocompromised patients [1,2]. However, in patients with malignancy or patients undergoing transplants, *Aspergillus* is the most common mold causing IFIs [2]. This is followed by infections due to *Mucor* spp., *Fusarium* spp. and *Scedosporium* spp. [1,2].

Q Generally, is treatment or prevention the priority?

Prevention of IFI is the utmost priority. The high rate of morbidity and mortality in immunocompromised patients, along with the difficulty in establishing a diagnosis has led to the strong recommendation of antifungal prophylaxis in high-risk individuals [3].

Q What strategies are in place to help prevent fungal infections in immunocompromised patients?

The current recommendation in individuals undergoing intensive chemotherapy and developing neutropenia and in hematopoietic stem cell transplantation (HSCT) recipients is to use antifungal prophylaxis [3]. These recommendations have been evaluated in several large clinical trials and are currently recommended by the European Organisation for Research and Treatment of Cancer (EORTC)/Mycoses Study Group (MSG). Several clinical trials have shown that these high-risk patients benefit from systemic antifungal prophylaxis with either fluconazole, itraconazole, posaconazole, voriconazole or micafungin [3]. In contrast, although frequently recommended, there are few data that address the best approach for systemic antifungal prophylaxis in solid organ transplant recipients.

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In addition to systemic prophylaxis, prevention of exposure to possible pathogens is also recommended especially in the neutropenic and HSCT recipients. Although environmental exposure to *Candida* is not possible, it is feasible for some of the more common mold infections especially *Aspergillus* spp. In fact, a review of nosocomial *Aspergillus* spp. cases found that the most common sources of infection were clusters associated with hospital construction and renovation projects [4]. Use of high-efficiency particulate air filters and positive pressure rooms have become common practice and can significantly decrease conidial exposure. Additionally, there is new evidence that contaminated water distribution systems in hospitals may increase exposure to molds, such as *Aspergillus* spp. and *Fusarium* spp. [5]. Although uncommon, exposure to soil, plants, fruits and vegetables should also be avoided [6].

Q What steps do you think should be taken in developing countries to protect immunocompromised individuals?

As stated previously, specifically in the neutropenic and HSCT recipient population [3], systemic antifungal prophylaxis should be considered. The best approach for antifungal prophylaxis in the solid organ transplant recipients is yet unknown, but fluconazole prophylaxis appears to be warranted in many OLT. Furthermore, if possible, use of high-efficiency particulate air filters and positive pressure rooms have also proven to be beneficial. Additionally, a decreased exposure to water distribution systems and avoidance of exposure to soil, plants, fruits and vegetables is recommended [6].

Q How has therapy developed over the past 10 years to protect these individuals?

Advances in antifungals as well as advances in establishing high-risk patient populations have improved the early detection and early therapeutic intervention in patients. Over the past 10 years several antifungals have been approved for use in these populations. These include voriconazole intravenous and oral formulations, which have become the mainstay of invasive aspergillosis in the majority of situations [7]. In addition, posaconazole, another triazole antifungal has also been approved for prophylaxis of IFIs in those patients who are at risk due to their immunocompromised condition [8].

The echinocandins are the newest class of antifungal approved in the management of fungal infections [9]. These antifungals are unique in that their mechanism of action is at the cell wall instead of the cell membrane of the fungus. There are three currently available, caspofungin, micafungin and anidulafungin. Of these, caspofungin has been approved for empiric therapy for presumed fungal infections in febrile neutropenic patients.

Q How big a problem is antifungal treatment resistance?

Infections with strains of yeast and molds that are resistant or less susceptible to antifungal agents have primarily been described in patients with HIV/AIDS, but rarely in other immunocompromised groups [10,11]. Resistance can be classified into two levels: clinical and cellular (*in vitro*). Clinical resistance is not necessarily caused by a failure of the antifungal or associated with decreased *in vitro* susceptibility. Clinical failure is usually due to low levels of the drug in serum/tissues, which can be due to poor patient adherence, drug–drug interactions that decrease drug levels, or severe immunosuppression. In fact, in a severely immunocompromised host, when the immune system is impaired or nonfunctional, even high doses of fungicidal agents will not be able to eradicate the fungal infection.

In contrast, cellular resistance is independent of the host, and involves strains that are less responsive to antifungals at conventional doses. There are several well known cellular mechanisms of resistance. Primary (intrinsic) resistance is demonstrated by organisms that are naturally resistant to antifungals (i.e., *Aspergillus terreus* is resistant to amphotericin B or *C. krusei* is resistant to fluconazole). The

term secondary resistance (acquired) is used when an initially susceptible isolate becomes resistant to an antifungal agent. This form of resistance is uncommon, but is generally seen in *Candida* spp. recovered from patients with advanced AIDS [10,11].

Q When is combination antifungal therapy considered the best option for managing these infections?

To date, more than 200 *in vitro* and animal studies evaluating the activity of different antifungal combinations against *Candida* species have been published [12]. Recently, in several of these studies several different antifungal combinations have demonstrated significant synergistic and/or additive activity against many different fungi. However, caution must also be exercised since several of these studies have also demonstrated antagonistic activity. In addition, there are no well-designed clinical trials that have shown any survival benefit to combination antifungal therapy versus monotherapy in any form of fungal infection. Well-controlled clinical trials are still necessary to define the most efficacious antifungal combination regimen. In conclusion, combination therapy is not recommended for infections due to yeast and molds.

Q What have been the most revolutionary therapies in recent clinical trials?

Over the past decade, there have been several clinical trials that have made an impact in the management of IFIs in the compromised host. The most significant step taken recently has been the use of voriconazole as first-line therapy for invasive aspergillosis [7,13]. These recommendations are based on results from a randomized, multicenter study that evaluated amphotericin B deoxycholate versus voriconazole as primary therapy of invasive aspergillosis [7]. The results demonstrated that patients randomized to voriconazole had a 53% successful outcome compared with a successful outcome of 32% in the amphotericin B group. Additionally, the survival rate was also higher in the voriconazole group, 71% compared to a rate of 58% in the amphotericin B group.

Another revolutionary change has been the addition of the echinocandins to the antifungal armamentarium [7]. Caspofungin, micafungin and anidulafungin are relatively safe and effective antifungal agents for the management of *Candida* infections and *Aspergillus* spp. They are similar with respect to their broad spectrum of activity, including all *Candida* and *Aspergillus* spp. evaluated thus far. Finally, they have few to no drug–drug interactions making them easy to use in a complicated immunocompromised host. They have been approved for esophageal candidiasis, candidemia, candidiasis, as empiric therapy against IFI in neutropenic patients, prophylaxis against *Candida* in HSCT recipients, and for invasive aspergillosis in patients refractory or intolerant to other antifungal therapy.

Conclusion

There are a growing number of immunocompromised patients due to an increasing number of transplants, more intensive chemotherapy and seriously ill patients living longer. Consequently, the number of patients at risk of IFIs has increased. Despite amazing therapeutic advances in the antifungal treatment of IFIs, improvement in the diagnostic techniques, the routine availability and use of rapid diagnostic assays and the development of criteria for the early and adequate initiation of antifungal therapy has not kept pace. The delays in the diagnosis and early initiation of antifungal therapy consequently lead to continued high morbidity and mortality of patients with IFIs.

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