

Advances in antifungal therapy

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The frequency of invasive, opportunistic mycoses has increased significantly over the past 2 decades (1-3). This increase in infection is associated with excessive morbidity and mortality (2,3) and is directly related to the increasing numbers of patients who are at risk for the development of serious fungal infections, including patients undergoing blood and marrow transplantation (BMT), solid-organ transplantation, and major surgery (especially gastrointestinal surgery); patients with AIDS, neoplastic disease, and advanced age; patients receiving immunosuppressive therapy; and premature infants (2,3).

Candida species remain the most important fungal pathogens, but infections due to *Candida* species increasingly occur among patients in intensive care units, rather than among patients who are profoundly immunosuppressed as a result of receiving therapy for hematologic malignancies. Recent trends show marked changes in the species causing fungemia in some medical centers but not in others. These changes in the epidemiological profile of yeast infections are tied to the use of antifungal agents, and, conversely, these changes directly affect the antifungal agents that are most appropriate for treatment of these infections. Mould infections continue to occur predominantly

among highly immunosuppressed patients. Patients who have hematologic malignancies, patients who have received a solid-organ or hematopoietic stem cell transplant, and patients receiving corticosteroids are at the greatest risk of acquiring mould infections. *Aspergillus* species are the most common cause of mould infections, but even within this genus, new species that are resistant to standard anti-*Aspergillus* agents have emerged during the past few years. Other environmental moulds, including *Scedosporium* and *Fusarium* species and various *Zygomycetes* (e.g., *Rhizopus* and *Mucor* species), are increasingly reported as the cause of invasive infection among highly immunosuppressed hosts in some, but not all, medical centers (4).

As the number of fungal infections has increased and as hosts have become more vulnerable, newer diagnostic tests to more quickly identify the responsible pathogens are needed. The standard remains the combination of growth in culture and histopathologic analysis revealing fungal invasion, but clinical circumstances make this combination unattainable for many highly immunosuppressed patients. Detection of antigen, as sought in the galactomannan and β -D-glucan assays, is desirable, but the role of these noninvasive tests is not yet clear. As is often the case when the use of new diagnostic tests increases, clinical use of the galactomannan assay has revealed previously unsuspected reasons for both false-positive results (i.e., the administration of certain antimicrobial

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agents contaminated with galactomannan during the manufacturing process) and false-negative results (i.e., the early administration of mould-active antifungal agents) (5).

The role of antifungal susceptibility testing remains controversial. Although antifungal susceptibility testing has never been as simple as the testing of antibacterial agents, the issues of appropriate antifungal agent is challenging.

The introduction during the past 5 years of the first expanded-spectrum triazole, voriconazole, and a new class of cell-wall active agents, the echinocandins, quickly changed the approach to treatment of invasive fungal infections. These agents are safer than and equally effective as the prior reference standard, amphotericin B; for some organisms, these agents are even more effective than amphotericin B. The new agents have proved to be extremely beneficial in the treatment of infection with resistant yeasts and moulds that have become more prevalent in recent years.

The expanded-spectrum triazole, voriconazole, has become the agent of choice for the treatment of invasive aspergillosis. It also has activity against many of the moulds that have emerged as pathogens in recent years and is effective against *Candida* infections. The broad spectrum of activity and the availability of both an intravenous formulation and a well-absorbed oral formulation are advantages of voriconazole. However, a significant number of drug-drug interactions and adverse effects (e.g., visual changes, hepatitis, and rash) are disadvantages. The anticipated approval of another broadspectrum triazole, posaconazole, will likely provide, for the first time, a nonpolyene option for the treatment of infections due to the Zygomycetes. The echinocandins (i.e., caspofungin, micafungin, and anidulafungin) damage the cell walls of *Candida* and *Aspergillus* species. The echinocandins are limited in spectrum and are available only as intravenous formulations but they appear to be extremely well tolerated. Their role in the treatment of candidiasis will

undoubtedly expand, but they likely will remain second-line agents, used as salvage therapy or in combination with other antifungal agents, for the treatment of invasive aspergillosis (6).

In Iran, despite significant development in the management of immunocompromised and organ-transplanted patients and with respect to the fact of further patients with solid organ transplantation than hematological malignancies, mould-induced infections are much less frequently detected when compared with *Candida*-induced infections. Few consultations with infectious disease specialists, lack of adequate diagnostic facilities including galactomannan and culture of opportunistic moulds are associated with more complex situation. On the other hand, unavailability of new antifungal drugs, even in academic centers in Iran, might complicate these patients' management. Therefore, recognizing fungal infections in immunocompromised subjects, developing laboratory facilities, and easier access to new antifungal drugs could inevitably pave the way for better management.

REFERENCES

1. Pfaller MA, Diekema DJ. Rare and emerging opportunistic fungal pathogens: concern for resistance beyond *Candida albicans* and *Aspergillus fumigatus*. *J Clin Microbiol* 2004; 42:4419–31.
2. Wisplinghoff H, Bischoff T, Tallent SM, Seifert H, Wenzel RP, Edmond MB. Nosocomial bloodstream infections in US hospitals: analysis of 24,179 cases from a prospective nationwide surveillance study. *Clin Infect Dis* 2004; 39:309–17.
3. Marr KA, Carter RA, Crippa F, Wald A, Corey L. Epidemiology and outcome of mould infections in hematopoietic stem cell transplant recipients. *Clin Infect Dis* 2002; 34:909–17.
4. Pfaller MA, Pappas PG, Wingard JR. Invasive fungal pathogens: current epidemiological trends. *Clin Infect Dis* 2006; 43(Suppl 1): S3–14.
5. Alexander BD, Pfaller MA. Contemporary tools for the diagnosis and management of invasive mycoses. *Clin Infect Dis* 2006; 43(Suppl 1): S15–27.
6. Dodds Ashley ES, Lewis R, Lewis JS, Martin C, Andes D. Pharmacology of systemic antifungal agents. *Clin Infect Dis* 2006; 43(Suppl 1): S28–39.