EMERGING OPPORTUNISTIC FUNGAL INFECTIONS: WHERE ARE WE HEADING?

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Medical mycology involves the study of pathogenic fungi and their identification in the laboratory. Mycology has developed into a field that demands the attention of all clinicians treating patients in hospitals. Interest in medical mycology has grown in recent years due to a dramatic rise in the rates of fungal infections. An overview of well-known medically significant opportunistic fungi, such as *Candida*, *Cryptococcus*, *Aspergillus* and Zygomycetes, as well as emerging fungal pathogens, are discussed. Antifungal failures in these individuals are high; consequently, mortality rates are also high, despite standard therapy with amphotericin-B, lipid-associated formulation of amphotericin-B and the azoles. This underscores the need for new approaches and therapies to improve outcomes in high-risk individuals. (*J Natl Med Assoc.* 2003;95:1211–1215.)

Key words: opportunistic fungi ♦ emerging fungi ♦ treatment

Medical mycology involves the study of pathogenic fungi and their identification in the laboratory. Interest in medical mycology has grown in recent years due to a dramatic rise in the rates of fungal infections. During the 1980s to early 1990s, systemic mycoses became the seventh leading cause of death among infectious diseases in the United States, while mortality related to these infections rose three-fold.[1]

Fungi of medical importance grow as yeasts or molds. Yeasts are single-celled fungi that multiply by budding, while molds are multicellular, filamentous fungi. Fungi cause a wide spectrum of disease states—the most common being relatively minor, localized infections of the skin or mucous membranes. Familiar examples are athlete's foot, tinea corporis, onychomycosis, and vaginal infections. However, an increasing number of fungi are able to cause systemic infections with involvement of internal organs.[1]

Invasive fungal infections are more prevalent than before, due to increasingly large populations of patients at high risk secondary to immunosuppression. Additionally, any of the following are underlying risk factors: increased numbers of organ or bone marrow transplants,[2] complicated surgical procedures and use of prosthetic devices,[2] more-aggressive intensive care medicine in premature infants and adults,[3] more-aggressive cancer chemotherapy,[4] administration of broad-spectrum antibiotics,[5] and increased intravenous drug use and human immunodeficiency virus (HIV) pandemic with longer survival of patients with acquired immune deficiency syndrome (AIDS).[6]

Most fungi are harmless to healthy individuals, but to patients with underlying medical problems or immunosuppression, fungi can become devastating, opportunistic pathogens. The most common invasive fungal infections in immunocompromised hosts are candidiasis, aspergillosis, cryptococcosis, and zygomycosis.[7] Since the 1950s, and until recently, the key opportunistic fungal pathogens with which clinicians had to contend were *Candida albicans*, *Aspergillus fumigatus*, and the Zygo-

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mycetes, which cause mucormycosis. Today, non-*albicans Candida* have become more frequent, as have other *Aspergillus* species.

Candida species are the most common opportunistic pathogens in immunocompromised patients.[7] *Candida* species can cause deep-seated, invasive infections and account for the majority of all major systemic mycoses. Manifestations of infection range from candidemia to disseminated disease with involvement of multiple organs. Candidemia is usually a nosocomial infection with multiple predisposing factors, including high-risk surgery requiring total parenteral nutrition, dialysis, or prolonged stay in the intensive care unit;[3] premature neonates; and patients with hematologic malignancies receiving potent mucotoxic antineoplastic regimens.[4]

Aspergillosis refers to diseases caused by *Aspergillus*, most commonly *Aspergillus fumigatus* and *Aspergillus flavus*. These organisms are ubiquitous in the environment, and the portal of entry is most commonly the lung. *Aspergillus* has a predilection for vascular tissue and often invades blood vessels to the extent that the supplied organ is infarcted. Pulmonary involvement is the most common manifestation of invasive aspergillosis and develops as acute pneumonia.[2] Patients at highest risk for invasive aspergillosis are those with prolonged neutropenia, allogeneic hematopoietic transplant recipients (particularly in the setting of intensive immunosuppressive therapy to treat graft-versus host disease,[8] and lung transplant recipients.

Cryptococcosis refers to disease caused by *cryptococcus neoformans*. This fungus is ubiquitous in the soil, and infection usually occurs by inhalation of airborne organisms. The incidence of clinically significant infection in the general population is very low, but immunosuppressed individuals are prone to more serious infections and rapid progression. Cryptococcosis occurs principally in patients with severe T-cell compromise, especially in AIDS patients and transplant recipients.

Zygomycosis (also called mucormycosis) is caused by a number of molds, and the leading pathogens in this group are species of the genera *Mucor*, *Rhizopus*, *Rhizomucor*, and *Absidia*. These fungi are ubiquitous in the environment and found in soil, on decaying matter, as well as on fruit and bread. The most common form of zygomycosis is rhinocerebral disease, in which the fungi proliferate in the nasal sinuses and invade surrounding tissues, extending into the facial soft tissues, nerves, blood vessels, orbits, and brain.[9] Invasive infections by zygomycetes occur in a similar patient population, like aspergillosis, and additional risk factors for zygomycosis are diabetic ketoacidosis and iron overload states.

A wide variety of fungi isolated from neutropenic patients were not previously recognized as human pathogens. Many of these are soil or plant fungal pathogens that clinicians have not been trained to recognize. With more widespread use of intensive cytotoxic antineoplastic regimens and allogeneic hematopoietic and solid organ transplantation, these growing numbers of unusual fungi of low virulence may become significant opportunistic pathogens.[10] These fungi are often referred to as "emerging pathogens" and include the class of phaeohyphomycosis, hyalohyphomycosis, the recently reclassified *Pneumocystis carinii*, and other yeasts.

Many fungi appear histologically identical to *Aspergillus*. *Fusarium* is one of them. It is the most prevalent plant fungus worldwide and now recognized as a human pathogen. *Fusarium* infection usually follows inhalation, but some have originated from cutaneous lesions associated with infected nails. *Fusarium* infection is life threatening and associated with poor prognosis.

Many other fungi, such as *Pseudallescheria boydii*, *Penicillium marneffei*, and *Malassezia furfur,* are gaining attention as human pathogens.[10] *Pseudallescheria boydii* causes a soft-tissue and pulmonary disease in immunosuppressed individuals, and it resembles aspergillosis histologically. *Penicillium marneffei* is an environmental fungus, endemic in Southeast Asia, that can cause serious, life-threatening infections in immunosuppressed individuals. *P. marneffi* has gained particular attention during this era of the AIDS pandemic.

Pneumocystis causes pneumonia in immunocompromised patients and is a common opportunistic infection in AIDS. This organism was originally thought to be a protozoan; however, further study has proven it to be a yeast-like fungus closely related to organisms of the class Ascomycota.[11,12] Each species of *Pneumocystis* appears to be specific for the mammal in which it is found.[13] The species that infects humans is *Pneumocystis jiroveci.*[13] Based on the phenotypic differences between human strains of *Pneumocystis* and other mammalian strains, the name *Pneumocystis jiroveci* was first proposed by

Frenkel in 1976.[13] However, the name was not published under the prevailing specifications of the International Code of Zoological Nomenclature.[13] DNA analysis has now demonstrated that *Pneumocystis jiroveci* is found only in humans, while *Pneumocystis carinii* is a species found only in rats.[13] Even though it is still acceptable today to refer to the disease caused by *Pneumocystis jiroveci* as *Pneumocystis carinii* pneumonia, the correct designation for the human form of *Pneumocystis* should be *Pneumocystis jiroveci*.

Currently, in the developed world, the incidence of AIDS-associated opportunistic mycoses has dramatically declined, primarily as a result of treatment with highly active antiretroviral therapy (HAART).[14] Subsequently, discontinuation of secondary prophylaxis against selected systemic fungi is feasible in individuals with satisfactory CD4 lymphocyte count and decreased viral load responses to HAART. However, characteristics of the responses to antifungal agents in individuals with opportunistic mycoses have changed, in that some patients may develop "paradoxical" exacerbations of disease, if they respond favorably to HAART. This may be due to immune reconstitution and is often referred to as "Immune Reconstitution Inflammatory Syndrome" (IRIS).[15] Paradoxical deterioration in clinical status attributable to the recovery of the immune system during HAART is now been reported to be associated with some fungal pathogens.[16,17]

Mycology has developed into a field that demands the attention of all clinicians treating patients in hospitals. Systemic mycoses are more prevalent than ever. The diagnosis of these infections remains largely dependent on clinical presentation, the signs and symptoms of which result from angioinvasion of the organism. Now, fungi represent a substantial proportion of the pathogens in hospitals with significant high mortality[1,6] due to the fact that there are no rapid, accurate diagnostic tests that can confirm with certainty the presence of invasive fungal disease. Fungal infections are also difficult to distinguish from many bacterial or other infections. Clinical manifestations of many fungal infections are shared among a variety of fungal pathogens as well.

Treatment Overview

Several new antifungal agents have been developed because of limitations among the already available agents. The ideal antifungal agent should have a broad spectrum of activity, be fungicidal rather than fungistatic, available in oral and injectable formulations, safe at efficacious doses, cost effective, stable to resistance, and cause minimal drug interactions. However, the development of antifungal agents is a challenge, because there are very few potential drug targets unique to fungi. Also, because diagnosis and identification of fungal species is indefinable, it may be difficult to find an adequate-sized patient population to test experimental agents in large-scale trials.

Amphotericin-B remains the most effective broad-spectrum fungicidal agent employed today. It acts directly on sterol ergosterol to increase the permeability of the fungal cell membrane.[18] Unfortunately, infusion-related side effects and significant nephrotoxicity have always been problematic. These adverse effects have become increasingly troublesome in the era of complex patients, such as transplant recipients receiving nephrotoxic drugs. A significant achievement has been the development of "lipid-associated formulation of amphotericin-B."[19] These include liposomal amphotericin-B, amphotericin-B lipid complex, and amphotericin-B colloidal dispersion. All three products of lipid-associated formulation of amphotericin-B are generally less nephrotoxic than amphotericin-B, and they can effectively manage deep-seated, invasive mycoses.[19] The proper doses and durations of treatment are still uncertain, but higher daily doses than those of standard amphotericin-B should be given.[18,19] The lipid-associated formulation of amphotericin-B products are relatively expensive compared to the standard product of amphotericin-B deoxycholate and often leads to the less frequent usage of the lipid formulations of amphotericin-B products.

The systemically acting azoles are another widely used class of antifungal agents. Chemically, they are categorized as imidazoles—ketoconazole—or the triazoles—fluconazole, itraconazole, and voriconazole. This class inhibits the cytochrome P450 (CYP)-dependent C-14 ademethylase, the enzyme necessary for the conversion of lanosterol to ergosterol. This activity eventually depletes ergosterol and ultimately compromises cell membrane integrity. The second-generation antifungal triazole, voriconazole, is a new standard of care for invasive aspergillosis based on its superiority and survival benefit over conventional amphotericin-B.[20] With the success of the triazole antifungals, more broad-spectrum and

potent antifungal triazoles, such as posaconazole and ravuconazole, are already in development.

The newer class of fungal agents, the echinocandins, is lipopeptides derived from natural fungal fermentation products. Caspofungin is the only marketed compound in this class, and several others are in various stages of development. The echinocandins inhibits β-(1,3) glucan synthase.[21] Glucans are the most abundant polysaccharides, comprising the greater part of the fungal cell wall, thus β-(1,3) glucan synthase inhibition ultimately compromises fungal cell wall integrity. Caspofungin has been shown to be at least as effective as conventional amphotericin-B but less toxic in patients with candidemia.[22] Clinical trials have been initiated for other echinocandins, such as micafungin and anidulafungin.

New classes of antifungal agents, combined with drug target developments through genomics, promise to increase the antifungal armamentarium. Present treatment regimens, however, still need improvement.

A number of challenges remain. We have not yet optimized the strategies for early diagnosis, including serologies and DNA diagnostics. Nonculture-based early detection methods, including serology and antigen detection, have been successfully used for diagnosis of some fungal pathogens (histoplasmosis, coccidioidomycosis, and *C. neoformans*), and polymerase chain reaction and galactomannan antigen detection are promising strategies for early diagnosis of invasive aspergillosis. Studies on antifungal drug combinations are preliminary.[18] Also, we are yet to incorporate the potential of our cytokines and immune modulators into successful treatment strategies with our current antifungal agents. In this era of HIV pandemic, and immunity-improving HAART regimen, we need to study the HIV-infected population with deep-seated mycoses so as to avoid indefinite suppressive antifungal therapy in these individuals.

CONCLUSION

The prevalence of invasive fungal infections has increased significantly since the late 1970s. Of the most common invasive infections, candidiasis and aspergillosis disproportionately affect critically ill surgical patients and immunocompromised individuals. Fungal infections are a major cause of morbidity and mortality in the increasing numbers of immunocompromised patients. Early diagnosis is essential to successful therapy of these infections, many of which are caused by angioinvasive molds, including *Aspergillus* species, *Fusarium*, Zygomycetes, and others. Despite the unprecendented increase in both the frequency and the intensity of infection of emerging opportunistic fungal pathogens, the number of available antifungal agents is small.

Amphotericin-B has been the standard therapy for critically ill patients with invasive fungal disease, but lipid-associated formulation of amphotericin-B, the newer azoles, and new classes of antifungal agents, such as the echinocandins, have shown activity against a broad spectrum of pathogens. Combinations of antifungal therapies with immune reconstitution may further improve responses to treatment.

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