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Fungal Infections

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INTRODUCTION

Fungal infections are an increasingly important cause of morbidity and mortality, especially among the growing numbers of immunocompromised patients. Until recently, the armamentarium of drugs available to treat these frequently life-threatening diseases was extremely limited. Although the discovery of the azole drugs has significantly increased therapeutic options, additional approaches are still needed—agents currently under study allow considerable optimism for the future. Unfortunately, as with antibacterial drugs, the expanding use of antifungal therapies has led to the emergence of resistant organisms *(1)*. Selection of mutants resistant to the azole drugs and even to amphotericin B, as well as the emergence of microbes with intrinsic resistance to available antifungal therapies, raise imposing challenges. Clinicians should be aware of the appropriate management of fungal infections, including recommended empiric therapies, indications for susceptibility testing, and options for treatment of resistant pathogens.

ORGANISMS

The classification of fungi can be quite confusing, especially when toxonomic debates continue among mycologists. For example, the recent reclassification of *Pneumocystis carinii* as a fungus has caused considerable stir. It is most important to recognize that fungi can be categorized as either yeasts or molds. Yeasts are typically round in shape and reproduce by budding, whereas molds are typically composed of tubular structures called hyphae and grow by extension. Many human pathogens are dimorphic fungi, so called because they are yeasts or yeastlike in the human body, but grow as molds outside the body. Table 1 lists the major fungal pathogens.

Candida Species

Candida organisms are yeasts, and several species cause human disease. *Candida albicans* accounts for the majority of human disease, and is responsible for mucocutaneous disease (thrush, vaginitis), as well as invasive disease. However, other *Candida* species are being recognized as important pathogens. *Candida tropicalis* is responsible for up to one fourth of systemic candidiasis and may be more virulent than *C. albicans* in immunocompromised patients. *Candida krusei* and *Candida glabrata* (formerly

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Table 1
Major Fungal Pathogens

Category	Disease	Usual Pathogens
Classic fungal infections	Aspergillosis	*Aspergillus fumigatus,* other *Aspergillus* spp.
	Candidiasis	*Candida albicans,* other *Candida* spp.
	Cryptococcosis	*Cryptococcus neoformans*
Endemic fungal infections	Sporotrichosis	*Sporothrix schenkii*
	Histoplasmosis	*Histoplasma capsulatum*
	Blastomycosis	*Blastomyces dermatitidis*
	Coccidioidomycosis	*Coccidioides immitis*
	Paracoccidioidomycosis	*Paracoccidioides brasiliensis*
	Penicilliosis	*Penicillium marneffii*
Other invasive fungal infections	Zygomycosis	*Rhizopus arrhizus (oryzae),* other *Rhizopus* spp.; *Absidia* spp., *Cunninghamella* spp., *Mucor* spp., others
	Hyalohyphomycosis	*Fusarium* spp., *Paecilomyces* spp., *Trichoderma* spp.; *Acremonium* spp., *Geotrichum* spp., *Scopulariopsis* spp.
	Phaeohyphomycosis	*Bipolaris* spp., *Exophilia* spp.; *Alternaria* spp., *Curvularia* spp., *Exserohilum* spp., *Phialophora* spp., *Scedosporium* spp.
	Miscellaneous	*Pneumocystis carinii, Pseudallescheria boydii, Malassezia furfur, Trichosporon beigelii, Saccharomyces cerevisiae*
Other usually noninvasive fungal infections	Chromomycosis	Various fungi
	Mycetoma (Madura foot)	Various fungi
	Dermatophytes	*Trichophyton* spp., *Microsporum* spp., Epidermophyton floccosum

Torulopsis glabrata) were quite uncommon in the past, but are observed now more frequently, especially in patients with hematologic malignancies and recipients of bone marrow/stem cell transplants *(2).* Both of these organisms may demonstrate resistance to fluconazole and other azole drugs. *Candida parapsilosis* may cause disease in neonates, oncology patients, and individuals in intensive care units, sometimes due to exogenous acquisition from indwelling catheters or other invasive devices *(3).* A feared emerging pathogen is *Candida lusitaniae,* owing to its inherent resistance to amphotericin B.

Aspergillus Species

These molds are found throughout the environment and can cause serious disease, especially among immunocompromised patients. *Aspergillus fumigatus* and *Aspergillus flavus* are the most frequent pathogens in humans, but a variety of other species can cause clinical disease.

Cryptococcus

The only species of *Cryptococcus* that causes major disease in humans is *Cryptococcus neoformans.* This yeast is ubiquitous in the environment and has emerged as an important cause of infection, especially meningitis in human immunodeficiency virus (HIV)-infected patients.

Endemic Fungi

Endemic fungi are responsible for a large burden of disease. In the United States, *Blastomyces dermatitidis, Histoplasma capsulatum, Coccidioides immitis,* and *Sporothrix schenckii* are important pathogens. In other countries, *Paracoccidioides basiliensis* and *Penicillium marneffii* are endemic, the latter emerging as a major opportunistic pathogen among acquired immunodeficiency syndrome (AIDS) patients.

Other Fungi Causing Invasive Disease

A number of *Zygomycetes,* molds in the order Mucorales, including *Rhizopus, Absidia,* and *Mucor,* can cause zygomycosis. These subcutaneous or deep tissue fungal infections occur predominantly in immunocompromised patients, especially neutropenic individuals, patients treated with steroids, and those with HIV or transplants. Rhinocerebral mucormycosis classically occurs in patients with poorly controlled diabetes. *Rhizopus arrhizus (oryzae)* causes 60% of all cases and 90% of rhinocerebral infections; *Rhizopus microsporus* is the second most common pathogen.

Hyalohyphomycosis refers to disease caused by a number of different fungi with hyaline, septate, branched hyphae. Both noninvasive and invasive infections can occur in immunocompromised hosts. The most common causative organisms are *Fusarium* species and *Paecilomyces* spp. A number of other agents have been described, including *Trichoderma* spp. These emerging infections are of particular concern as some, such as *Paecilomyces* spp., are resistant to amphotericin B.

Several different dematiaceous, that is, darkly pigmented, fungi cause a group of infections referred to as phaeohyphomycoses. Localized or disseminated disease can occur in immunocompromised patients. *Bipolaris* spp. and *Exophilia* spp. are the most common pathogens. Various species have demonstrated resistance to antifungal therapy including *Scedosporium prolificans,* which is resistant to all known antifungal drugs.

Other important fungi include *Pneumocystis carinii,* the causative agent of *P. carinii* pneumonia; *Pseudallescheria boydii,* an important cause of disease in immunocompromised patients that may be resistant to amphotericin; *Malassezia furfur,* which can be transmitted via fatty acid containing hyperalimentation solutions and cause sepsis in neutropenic patients; *Trichosporon beigelii,* a cause of invasive disease in severely immunocompromised individuals; and *Saccharomyces cerevisiae* or Brewer's yeast, a cause of vulvovaginitis, as well as disseminated disease in immunocompromised patients.

Other, Usually Noninvasive, Fungi

A multitude of fungi can cause chromomycosis, a chronic fungal infection usually occurring on an extremity that remains localized within the cutaneous or subcutaneous layers. *Fonsecaea pedrosi* is the most common isolate throughout the world. A variety of other fungi can cause mycetoma, also known as Madura foot, a localized, destructive infection of the skin, fascia, bone, and muscle. The most frequent cause of the disease in the United States is *P. boydii* while *Madurella mycetomatis* predominates in Africa and India. Fungal mycetoma must be distinguished from comparable disease caused by aerobic actinomycetes. Molds, including *Trichophyton* spp., *Microsporum* spp., and *Epidermophyton floccosum,* are the causes of dermatophytosis. Classification schemes for these fungi are somewhat controversial, but there are approx 39 species that cause human disease. A fungus of special note is *M. alassezia furfur,* the cause of pityriasis or tinea versicolor, which also causes invasive disease in immunocompromised patients.

RESISTANCE

A major concern is the emergence of fungal strains resistant to antifungal drugs *(4)*. (*see* Table 3). While not yet as widespread as antibacterial resistance, antifungal resistance is noteworthy because of the limited options available for treating these infections and the frequently life-threatening nature of these illnesses. Antifungal resistance can be either intrinsic or acquired. Intrinsic resistance occurs regardless of previous drug exposure. For example, *Aspergillus* spp. and *C. krusei* are never inhibited by fluconazole and thus exhibit intrinsic resistance. Fungi that are intrinsically resistant to antifungal therapies may be selected in patients receiving antifungal drugs, for example, the selection of *C. krusei* in patients on azole prophylaxis *(5)*. Acquired resistance occurs when the organisms mutate to become resistant to a drug that the patient has been taking. The emergence of fluconazole-resistant *C. albicans* in HIV-infected patients receiving azole prophylaxis is an example that has generated concern. Fortunately, unlike antibacterial resistance, fungi do not appear to transfer resistance genes from one species to another, presumably predicting a slower rise in resistant fungi than has been observed with bacteria.

Azole Resistance

Most *C. albicans* are sensitive to fluconazole and other azole drugs *(6,7)*. However, the growing use of these drugs for treatment and prophylaxis, especially in AIDS patients and on transplant units, has led to emergence of isolates resistant to azole drugs. Recent reports suggest that nearly one third of patients with advanced AIDS can develop azole-resistant *Candida* infection *(8)*. Most often, the *C. albicans* demonstrates progressively rising minimum inhibitory concentrations (MICs) to fluconazole over time, becoming more resistant the longer the patient has taken the drug *(9)*. Case reports of acquisition of fluconazole-resistant strains by HIV-infected individuals have also appeared. Furthermore, HIV-infected patients receiving chronic fluconazole therapy may develop infections with other *Candida* species that are characterized by relative resistance to azole drugs, especially *C. glabrata* and *C. krusei.*

Additional cases of fluconazole-resistant *Candida* species have been reported in neonates, recipients of prosthetic devices, and ICU patients with monitoring devices. In

Table 2
Mechanisms of Action and Mechanisms of Antifungal Resistance

Drug	Mechanisms of Action	Mechanisms of Resistance
Amphotericin B	• Binds to ergosterol in fungal membrane → pore formation → leakage of intracellular contents • ?–Oxidative damage	• Altered ergosterol content in fungal membrane • Altered β-1, 3-glycan composition in fungal membrane → decreased drug permeability
Azoles	• Binding to the enzyme lanosterol 14α-demethylase which is required for ergosterol synthesis • Azole-induced changes in cell membrane also interfere with other membrane-bound enzymes such as those required for chitin synthesis • Interference with other enzymes required for synthesis of ergosterol surrogates	• Altered 14α-demethylase production or affinity for fluconazole • Altered ergosterol content in fungal membrane • Incorporation of alternate sterols in fungal membrane. • Decreased permeability of fungal membrane → reduced intracellular accumulation of drug • Drug efflux pumps

some cases, these patients had never received azole therapy, suggesting acquisition of the resistant strain rather than selection of a resistant mutant. Rarely, immunocompetent individuals may develop fluconazole-resistant candidiasis *(10)*. A recent report describes a patient with diabetes and a history of intravenous drug abuse (IVDA) who developed community-acquired fungemia due to a multiple azole resistant strain of *C. tropicalis (11)*. Depending on the resistance mechanism, fungi that became resistant to fluconazole may or may not demonstrate cross-resistance to other azole drugs.

Less frequently, other fungi may be resistant to fluconazole and/or other azole drugs. Fluconazole-resistant isolates of *H. capsulatum* and *C. neoformans* have been reported. Most of these have been in patients with AIDS who were receiving fluconazole prophylaxis. A fluconazole-resistant *C. neoformans* was isolated from an immunocompetent patient without prior exposure to azole drugs *(12)*. Recently, itraconazole-resistant isolates of *A. fumigatus* were documented.

The mechanisms responsible for azole resistance are an active area of investigation (Table 2). The major mechanism of action of azole drugs appears to be interference with the enzyme 14α-demethylase which is required for synthesis of ergosterol in the fungal wall. Fungi may become resistant to azole drugs by mutations resulting in altered 14α-demethylase production or affinity or mutations causing altered ergosterol content in the fungal membrane. Decreased permeability of the fungal membrane and efflux pumps that remove azole drugs from the cell are also potential mechanisms of resistance.

Flucytosine Resistance

Although most *Candida* species and *C. neoformans* are susceptible to flucytosine, about 10% of *Candida* isolates may be resistant prior to therapy. *C. lusitaniae* isolates

Table 3
Fungi with Frequent Resistance to Usual Therapies

Organism	Resistance
Candida albicans	Increasing emergence of resistance to azole drugs, especially to fluconazole in patients receiving long-term prophylaxis or treatment with fluconazole
Candida glabrata	Intrinsic decreased susceptibility to fluconazole, other azoles
Candida krusei	Intrinsic resistance to azoles drugs; may be selected in BMT patients on fluconazole prophylaxis
Candida lusitaniae	Usually resistance to amphotericin B and flucytosine
Candida tropicalis	Case reports of azole resistance
Aspergillus spp.	Resistant to fluconazole (itraconazole has activity)
Cryptococcus neoformans	Case reports of fluconazole resistance
Agents of zygomycosis	Resistant to azole drugs
Agents of hyalohyphomycosis	Some resistant to amphotericin B; most resistant to azole drugs
Paecilomyces lilacinus	Resistant to amphotericin B and flucytosine in vitro
Trichoderma spp.	Some resistant to fluconazole
Agents of phaeohyphomycosis	Increasing recognition of resistance to various antifungal agents
Scedosporium prolificans	Intrinsic resistance to all available drugs
Pseudallescheria boydii	Intrinsic resistance to amphotericin B
Trichosporon beigelii	Intrinsic resistance to amphotericin B
Saccharomyces cerevisiae	Resistant to fluconazole in vitro; may be resistant to other azoles.

are intrinsically resistant to flucytosine. In most cases, resistance to flucytosine usually emerges quickly when the drug is used as monotherapy. Therefore, when indicated, flucytosine should be used in combination with amphotericin B.

Amphotericin B Resistance

C. lusitaniae and *C. guilliermondii* are characterized by resistance to amphotericin B. *T. beigelii, P. boydii,* and some of the dematiacious fungi exhibit marked intrinsic resistance to amphotericin B. Development of secondary resistance to amphotericin B is still infrequently reported.

Amphotericin B exerts its predominant antifungal effect by binding to ergosterol in the fungal membrane and thus causing formation of pores in the fungal cell wall, leakage of intracellular contents, and cell death. Fungi can be resistant to amphotericin B if they have altered ergosterol content in the fungal membrane. Alternatively, resistance

can be due to altered β-1, 3-glycan composition in the fungal membrane, leading to decreased drug permeability.

Antifungal Susceptibility Testing

Traditionally, antifungal susceptibility testing was flawed by lack of standardization and inconsistency. In 1997, the National Committee for Clinical Laboratory Standards (NCCLS) approved standardized broth macrodilution and microdilution methods for the antifungal susceptibility testing of yeasts *(13).* The currently approved version (M27-A) can be used to determine susceptibility of *Candida* species and *C. neoformans* to amphotericin B, flucytosine, fluconazole, ketoconazole, and itraconazole. *Candida* species are classified as susceptible, susceptible-dose dependent, or resistant to fluconazole or itraconazole *(14,15).* Breakpoints have been established for *Candida* species for fluconazole (for all sites of infection) and for itraconazole (for mucosal sites only). For fluconazole, an MIC ≤ 8 mg/mL is considered susceptible, while ≥ 64 μg/mL implies resistance. MICs of 16–32 μg/mL are considered susceptible, depending on the dose of drug given. It is important to note that the standard breakpoints do not apply to *C. krusei,* which is considered intrinsically resistant to azoles. Breakpoints for amphotericin B are less clear, but MICs > 1 μg/mL may be associated with a poorer prognosis. Other methodologies such as E test strips are under investigation but are not yet reproducible or adequately standardized. Currently, no standardized antifungal susceptibility testing methods are available for any of the other fungi. However, a proposed standard for susceptibility testing for molds was recently published by the NCCLS, but the clinical significance remains unclear and breakpoints have not been determined *(16).* Currently, routine susceptibility testing of *Candida* spp. or *C. neoformans* is not recommended. However, when patients, especially immunocompromised patients, fail to respond to appropriate empiric therapy, susceptibility testing may be useful to guide therapy. In vitro susceptibility does not always predict successful therapy, as other factors such as underlying immune defects may be more important clinically. However, in vitro resistance usually predicts a high likelihood of therapeutic failure. At present, antifungal susceptibility testing should probably still be reserved for exceptional patient care situations and research purposes.

TYPES OF INFECTIONS

Candidiasis

Candida spp. can cause superficial (mucocutaneous) or deep infections *(17).* Candidal infections are extremely common, ranging from oral thrush to disseminated disease. Thrush most often occurs in patients on steroids or chronic antibiotics and in immunocompromised patients, especially those with HIV infection. In addition to the classic creamy white coating of the tongue and oral mucosa, oral candidiasis can present as an atrophic form, as angular cheilitis, or as *Candida* leukoplakia. In immunocompromised patients, *Candida* esophagitis can occur and usually presents with odynophagia. In HIV patients, painful swallowing can often be treated with an empiric course of antifungal therapy, reserving diagnostic workup for patients who fail.

Candida vaginitis is an extremely common condition; up to 70% of women will experience a "yeast infection" at some time in their lives (*see* Chapter 11, this volume). Severe and/or recurrent disease may signal underlying diabetes mellitus or HIV

infection, or be secondary to antibiotic use which alters the normal flora. Cutaneous candidiasis can present as *Candida* balantis, folliculitis, intertrigo, perianal involvement, or generalized skin eruptions. *Candida albicans* is frequently implicated as a cause of paronychia and onychomycosis. A condition termed chronic mucocutaneous candidiasis presents with persistent *Candida albicans* infections which are quite recalcitrant to treatment owing to the inability of the patients' T cells to respond to this yeast.

Candida spp. can also cause a wide range of invasive infections, usually in immunocompromised patients, including candidemia and deep infections of the eyes, liver, spleen, genitourinary tract, central nervous system (CNS) or other sites. *Candida* spp. are now the fourth most common isolate in nosocomial bloodstream infections, and blood cultures may be negative in an additional 50% of all cases *(18,19)*.

Candida organisms are normal commensals colonizing the skin and gastrointestinal (GI) tract. Most cases of candidiasis reflect proliferation of these colonizers in the setting of immunosuppression or alteration of the other normal flora by antibiotic therapy or steroids. However, *Candida* infections can be transmitted from human to human, as evidenced by thush of the newborn. In addition, acquisition from exogenous sources is increasing, for example, nosocomially due to catheters, monitoring devices, or prosthetic implants.

Aspergillosis

Aspergillus species can cause superficial infections, involving skin or the upper respiratory tract. For example, *Aspergillus* sinusitis is a serious problem in bone marrow/stem cell recipients, patients with hematologic malignancies, and individuals with HIV infection. Invasive disease can occur in immunocompromised patients and is a harbinger of poor prognosis; correction of the underlying disease process is critical to survival. Involvement of the lung, CNS, GI tract, and multiple other organs can occur. Histopathologic evaluation will reveal fungal invasion of blood vessels with thrombosis and infarction of involved tissues.

As the number of patients immunocompromised by HIV, transplantation, and cytotoxic therapies has increased, the incidence of invasive aspergillosis has grown accordingly. Risk factors include quantitative or qualitative defects of neutrophils, steroid therapy, and diabetes. As many as 40% of patients with chronic granulomatous disease will suffer from *Aspergillus* infection, as well as ~10% of patients with transplants, HIV infection, or hematologic malignancies. *Aspergillus* spores are most commonly acquired via the respiratory tract and may manifest in several ways in the lungs, often reflecting host immune conditions. Allergic bronchopulmonary aspergillosis represents an allergic reaction to *Aspergillus* antigen, and occurs most often in individuals with asthma. Manifestations include eosinophilia and fleeting lung infiltrates. Aspergillosis can also present as a fungus ball or aspergilloma, often developing in patients with preexisting lung cavities due to tuberculosis or previous bacterial lung abscess. These patients may present asymptomatically when routine chest films are obtained or can have massive hemophysis. Invasive pulmonary aspergillosis occurs in immunocompromised patients and rarely in immunocompetent patients exposed to a heavy inoculum of *Aspergillus* spores. Prognosis is most dependent upon recovery from the underlying disease, usually correction of neutropenia.

Cryptococcosis

C. neoformans is ubiquitous in the environment and can cause disease in immunocompetent individuals as well as patients with abnormal cell-mediated immunity, especially those with HIV infection, bone marrow/stem cell transplants, or hematologic malignancies. The AIDS pandemic has been associated with a dramatic increase in cryptococcal infections. *C. neoformans* has a clear-cut prediction to cause CNS infections and cryptococcal meningitis is the most common invasive mycosis in AIDS, afflicting 5–10% of patients.

Cryptococcal infection usually presents as pneumonia or meningitis, but disseminated cases with multiorgan involvement can occur. Pulmonary cryptococcosis may be asymptomatic or cause frank pneumonia. The severity of cryptococcal pneumonia relates to the severity of underlying host immune defects, often remaining indolent in immunocompetent patients but potentially progressing rapidly in AIDS patients *(20).* Cryptococcal meningitis can present with a range of symptoms. Onset is often insidious with headache and somnolence, usually without obvious nuchal rigidity. Diagnosis depends upon the demonstration of the encapsulated yeast cells by India ink examination of cerebrospinal fluid and/or detection of capsular antigen. The severity and rapidity of the course of disease as well as the response to therapy appears to correlate with the immune status of the host.

Endemic Mycoses

These diseases (*see* Table 1) are endemic to specific geographic areas and cause widespread infection and disease. Blastomycosis and histoplasmosis are endemic to the Ohio River Valley states, coccidioidomycosis to the southwestern United States, while paracoccidioidomycosis is most frequent in Latin America and penicilliosis occurs in Southeast Asia and China. However, the mobility of patients around the globe necessitates the awareness that these diseases may have been acquired years earlier and manifest later during periods of immunosuppression after the individual has moved to a nonendemic area.

Blastomycosis is usually acquired by the respiratory route, and when symptomatic is manifested as pneumonia. Pulmonary involvement can be asymptomatic or cause nonspecific signs of fever, cough, and myalgias. Large inocula or underlying defects in immunity can result in severe pneumonia, including an adult respiratory distress syndrome (ARDS) picture. Later, patients can develop chronic pulmonary disease or can present with evidence of disseminated disease, especially skin or bone involvement. Complaints of bone or joint pain after a bout of blastomycosis should be investigated carefully with plain films and/or bone scan. Whether reactivation of blastomycosis due to immunosuppression occurs is controversial, but if it does it is clearly very unusual.

Coccidioidomycosis is increasing in incidence in the United States and has been classified as an emerging disease. The etiologic agent, *C. immitis,* is transmitted by inhalation of spores, especially in hot, dusty conditions. While many cases are asymptomatic, patients exposed to a heavy inoculum may develop nonspecific symptoms of fever, cough, and myalgias, with pneumonic infiltrates common. Individuals of African or Asian descent, Hispanics, Filipinos, pregnant women, and patients immunocompromised by HIV or other cell-mediated immune defects are at increased risk of severe, disseminated disease. Dissemination can result in involvement of bone, joints, skin, and visceral organs. CNS disease is a dreaded complication. Cutaneous hypersensitivity reactions including erythema nodosum or erythema multiforme are frequent.

Histoplasmosis is also acquired by the airborne route, often after exposure to bird or bat droppings. Patients who are spelunkers, who have worked in old barns or chicken coops, or who have been involved in renovating old homes are at particular risk. Histoplasmosis can cause a range of syndromes in the immunocompetent host, from asymptomatic infection to nonspecific flulike illness to frank pneumonia. In most cases, recovery will be complete, often without specific therapy. Infection can cause severe pneumonia if the inoculum is high and can progress to chronic pulmonary infection, particularly in patients with preexisting lung disease. Rarely, progressive fibrosis can develop, leading to mediastinal fibrosis and potentially compromising the esophagus, airways, or the superior vena cava and other blood vessels. Progressive, disseminated histoplasmosis can occur, especially in infants and immunocompromised adults. Patients with defective cell-mediated immunity, especially those with AIDS, are at particular risk. In addition, HIV-infected patients are at significant risk of developing reactivation of *Histoplasma* infection as immunosuppression progresses. Manifestations of disseminated disease include fever, pneumonia, sepsis syndrome, and visceral organ involvement.

Sporotrichosis is an endemic fungal infection that most often presents with cutaneous disease but extracutaneous syndromes can occur, especially in immunocompromised patients. Classically acquired by inoculation through the skin, infection most often presents with a lesion at the site of injury and lymphangitic spread of painless nodules. In unusual circumstances, the fungus disseminates hematogenously and causes bone, CNS, lung, or eye disease in the immunocompetent host or multifocal disease in immunocompromised individuals.

Zygomycosis

The zygomycetes, *Rhizopus* spp., *Absidia* spp., and *Mucor* spp., can cause subcutaneous or deep infections in immunocompromised patients. Neutropenic patients and those receiving steroid or cytotoxic therapy are at particular risk of disseminated disease. Infection may be rhinocerebral involving the sinuses and brain, pulmonary, or disseminated. The fungi invade blood vessels and cause thrombosis and infarction of tissue, resulting in black necrotic lesions and drainage. In patients immunocompromised by AIDS, disseminated infection can involve the lung, skin, and visceral organs. Pulmonary involvement is most characteristic of disease in renal transplant patients.

Hyalohyphomycosis

These mold infections occur almost exclusively in severely immunocompromised patients. Risk factors include cytotoxic chemotherapy, prolonged antibiotic therapy, organ transplantation, and HIV infection. Infection can present as noninvasive infection, especially of the skin, or as deep infection with pneumonia, sinusitis, or dissemination. *Fusarium* species may cause invasive sinus infections, skin involvement, pneumonia, or bloodstream infection and may disseminate to cause multifocal disease. *Paecilomyces* spp. have an interesting prediliction for ocular involvement and can manifest as keratitis and endophthalmitis. In other patients, disseminated disease with pneumonia, sinusitis, and fungemia may occur.

Phaeohyphomycosis

The dematiacecus fungi can cause a variety of diseases in immunocompromised patients. Initially, disease may manifest as skin, sinus, lung, or CNS involvement, but

can progress to disseminated disease with involvement of multiple sites. Disease mimics that of other invasive fungal infections, but the diagnosis can be made with special stains of tissue samples to demonstrate the melanin characteristic of these organisms.

Other Serious Fungal Diseases

P. carinii has recently been reclassified as a fungus but clinical management of infections caused by this organism differs significantly from that of other fungi. *P. carinii* can be found in the lungs of many normal humans, but can cause severe pulmonary and extrapulmonary disease in immunocompromised individuals. Long recognized as a pathogen in malnourished or very premature babies and in patients with marked defects in cell-mediated immunity due to cytotoxic therapy, *P. carinii* has risen to prominence in the era of AIDS. *P. carinii* pneumonia (PCP) occurring in homosexual men was one of the first signals of the HIV pandemic and was the most important opportunistic infection early in the epidemic. Although interventions for prophylaxis and treatment of PCP are now widely available, it remains an important cause of morbidity and mortality in this population. *Pneumocystis* most often manifests as pneumonia. Although interstitial infiltrates are classic, it is important to remember that a wide variety of chest film findings can be present, including normal films. PCP should be included in the differential diagnosis of AIDS patients with shortness of breath and hypoxia, regardless of the X-ray findings. Extrapulmonary involvement with *Pneumocystis* may manifest in the lymph nodes, spleen, liver, bone marrow, GI tract, eyes, or thyroid. AIDS patients receiving PCP prophylaxis with aerosolized pentamidine are at particular risk of extrapulmonary involvement, as the drug protects only locally in the lung. As a result other systemic approaches to PCP prophylaxis are now preferred by many.

P. boydii has emerged as an important cause of disease in severely immunocompromised patients. Infection manifests most commonly as pneumonia, but sinusitis, skin infection, CNS or eye involvement, or disseminated disease can occur. Because this species is often resistant to amphotericin, prognosis is poor unless the underlying disease process can be corrected.

Other emerging infections are being recognized in severely immunocompromised patients. *M. furfur* is a lipophilic fungus that causes dermatophytosis in the normal host. However, as a result of its lipophilic nature, it can grow in lipid-rich solutions, including parenteral hyperalimentation supplemented with fatty acids. Immunocompromised, especially neutropenic patients receiving such therapy, may develop *Malassezia* infection, manifested by follicular skin lesions or disseminated disease in the lungs and other organs. *T. beigelii* has also emerged as a feared fungal infection in neutropenic patients. Skin, lung, or sinus involvement can progress to disseminated disease with multifocal infection. Reversal of the neutropenia is critical to survival. *Saccharomyces cerevisiae* or Brewer's yeast has been recognized as a cause of vaginitis and can also rarely cause disseminated infection.

Chromomycosis

This chronic fungal infection occurs throughout the world, especially in tropical regions and manifests as verrucous lesions at a site of inoculation of the organism, usually on an extremity. Infection remains localized within the cutaneous and subcutaneous tissues but can cause disfiguring lesions that may interfere with function. Over

time, the lesions can enlarge and become clumped together. Lesions can be pruritic but are rarely painful. Medical attention is usually sought because of bacterial superinfection, lymphedema, bulky lesions, or for cosmetic reasons. Invasion of bone does not occur, in contrast to mycetoma.

Mycetoma

Also known as Madura foot, mycetoma is a chronic, slowly progressive fungal infection of skin, fascia, muscle, and bone. Infection is generally acquired via accidental inoculation, usually into an extremity. The localized swelling and granuloma formation can progress to produce a disfigured, swollen foot with multiple sinuses, usually over the course of years. Medical care is usually sought because of secondary bacterial infection or for cosmetic requests. Because mycetoma can also be caused by actinomycetes, it is important to establish whether the etiology is fungal.

Dermatophytes

These mold infections are extremely common causes of superficial fungal lesions of the skin throughout the world *(21)*. The annual cost in the United States exceeds $400 million. Dermatophytoses can be acquired from other people, animals, or the environment. Although they do not generally cause life-threatening illness, they do affect quality of life and social embarassment is a concern. Lesions may appear as annular patches with raised margins and inflammation. Clinical appearances varies with the site and host immune response, as well as with the causative fungal species. Tinea pedis is most often caused by *T. rubrum* and *T. mentagrophytes* and results in the well-known lesions of "athlete's foot." Tinea cruris may be caused by *T. rubrum* and *E. flaccosum* and manifests groin lesions. Tinea corporis or ringworm may be caused by several dermatophytes, and clinical patterns vary with the site of infection and causative organism. Scalp ringworm or tinea capitis is a disease of children and is widespread in the United States. Scaling of the scalp skin is associated with erythema and alopecia. Onychomycosis usually occurs in patients with adjacent dermatophyte infection of the toes or fingers, and should be distinguished from onychomycosis due to *Candida* spp. The dermatophyte infections may be associated with "id reactions," leading to additional rash, which have been attributed to delayed-type hypersensitivity reactions to intradermal trichophyton.

TREATMENT

Antifungal Drugs

Antifungal agents are much more limited in number than are antibacterial drugs *(22–24)*. Unfortunately, many of the available agents have significant cost and toxicity. Currently available drugs for the treatment of fungal infections are amphotericin B and the newer liposomal forms of amphotericin, flucytosine, and the azole drugs *(25,26)*.

The polyene amphotericin B is the mainstay of therapy for serious fungal infections and remains the most broad-spectrum antifungal agent available. Its broad spectrum of activity and clinician experience with its use make it the drug of choice for *Aspergillus* infections and most other deep mycoses, despite its associated nephrotoxicity and other side effects. New liposomal amphotericin products are available that have less nephrotoxicity than the deoxycholate form *(27,28)*. While effective in treating many serious

fungal infections, their high cost has prompted many organizations to limit their use. Indeed, the cost–benefit comparison of amphotericin B vs. the new liposomal preparations has been the subject of much debate. Many institutions have restricted the use of liposomal preparations to patients who have developed nephrotoxicity in response to amphotericin B.

The new azole drugs represent an exciting advance for the treatment of serious fungal diseases *(29,30)*. For the first time, oral agents with reliable efficacy are now available for the treatment of several of the fungal diseases. Fluconazole is a relatively nontoxic drug that has good efficacy in the treatment of *Candida* and some other fungal infections. It is available in both an oral and an intravenous form. Itraconazole has a broader spectrum of activity, including activity against some *Aspergillus* organisms, as well as *Candida, Blastomyces,* and *Histoplasma.* New azole drugs such as voriconazole appear promising. Azoles have effects on the P450 system, and other medications should always be reviewed to prevent adverse drug interactions.

Flucytosine is less widely used than amphotericin B or the azoles, owing to its more limited spectrum of activity and potential toxicity. However, flucytosine can play an important role in treatment of cryptococcal meningitis when used in combination with amphotericin B. To prevent toxicity, especially bone marrow suppression, serum drug levels must be monitored. Suggested therapeutic choices for the major fungal infections are outlined in Table 4, based on recent practice guidelines suggested by the Infectious Disease Society of America (IOSA) *(31)*.

Treatment of Specific Fungal Infections

Candidiasis

Guidelines for the treatment of mucocutaneous candidiasis have been published by the American Academy of Dermatology *(21)*. Thrush due to *Candida* spp. can be treated with many different agents, including clotrimazole troches, nystatin swish and swallow, amphotericin suspension, or the oral azoles. The widespread use of fluconazole for treatment and prevention of thrush in patients with HIV has led to the emergence of azole-resistant strains *(32)*. For this reason, many experts now urge use of nonazole drugs as a first choice, with fluconazole reserved for cases in which other drugs such as nystatin have failed. However, the efficacy and ease of use of fluconazole have interfered with widespread acceptance of this approach.

Many agents are available for the treatment of *Candida* vaginitis. A single dose of fluconazole is often effective. Because concerns about resistance are much lower in the situation in which short-term therapy is needed, this practice has been widely adopted. However, in some patient populations in which fluconazole prophylaxis has been used, especially HIV patients, vaginitis resistant to azoles has been recognized.

The management of serious *Candida* infections has given rise to much debate. A consensus publication on an approach to management and prevention of severe *Candida* infections has been published *(33)*. Practice guidelines for treatment of candidiasis have recently been issued by the IOSA *(34)*. The need for a more aggressive approach to management of *Candida* infections was advocated, including emphasis of the need to treat all patients with candidemia. In most cases, fluconazole was considered appropriate first-line therapy for stable patients, while amphotericin B should still be used for those with life-threatening disease.

Table 4
Approach to Treatment of Fungal Infections

Disease	Treatment Options
Classic Infections	
Aspergillosis	
Allergic bronchopulmonary aspergillosis	None or—itraconazole
Aspergilloma	Observation; surgery; itraconazole
Invasive	Amphotericin B or liposomal amphotericin, then consider itraconazole
Candidiasis	
Mucocutaneous	Thrush-clotrimazole troches, nystatin swish and swallow, fluconazole, amphotericin solution, itraconazole if refractory; esophagitis—fluconazole, amphotericin if severe; vaginitis—fluconazole; topical preparations such as nystatin, miconazole
Invasive	Amphotericin B; fluconazole effective for most *C. albicans*
Cryptococcosis	
Nonmeningeal	Fluconazole
Meningitis	Amphotericin B + flucytosine followed by fluconazole
Sporotrichosis	Potassium iodide if limited; itraconazole; amphotericin B
Endemic infections	
Histoplasmosis	Observation if not severe; itraconazole; amphotericin B if severe
Blastomycosis	Itraconazole; amphotericin B if severe
Coccidioidomycosis	
Nonmeningeal	Observation if acute, not severe; fluconazole or itraconazole; amphotericin B if severe
Meningitis	Amphotericin B or fluconazole
Paracoccidioidomycosis	Itraconazole; amphotericin B if severe
Penicilliosis	Amphotericin B; itraconazole

Other invasive infections	
Zygomycosis	Correct predisposing disease process plus amphotericin B or liposomal amphotericin plus surgical debridement if possible (azoles not effective)
Hyalohyphomycosis	Correct predisposing disease process including growth factors for neutropenia, plus amphotericin B or liposomal amphotericin, itraconazole (for some species)
Phaeohyphomycosis	
Keratitis	Topical antifungal drugs
Skin	Surgical debridement plus itraconazole ± flucytosine
Other	Amphotericin B plus itraconazole ± flucytosine; plus surgical debridement if possible
Miscellaneous	
Invasive	
Pneumocystis carinii	Trimethoprim–sulfamethoxyzole; intravenous pentamidine; others
Pseudallescheria boydii	Surgical drainage if possible; Optimal treatment unknown—? azole drugs (often resistant to amphotericin B)
Malassezia furfur	Fluconazole; remove catheter
Trichosporon beigelii	Correct predisposing disease process including growth factors for neutropenia plus fluconazole.
Saccharomyces cerevisiae	Amphotericin B ± flucytosine (azoles usually not effective)
Chromomycosis	Surgical excision if possible; optimal treatment unknown—trial of itraconazole often warranted
Mycetoma	Itraconazole effective in some cases. Surgical debulking if possible (R/O disease due to actinomycetes)
Dermatophytes	
Onychomycosis	Terbinafine or itraconazole (intermittent therapy)
Tinea skin infection	Topical azole drugs or terbinafine if localized; oral terbinafine or itraconazole

Uncomplicated candidemia can usually be treated successfully with fluconazole for 21 d *(33)*. Complicated cases, such as those in immunocompromised patients or involving resistant organisms, require use of amphotericin B or longer courses of fluconazole. Given the difficulty with treating established fungal infections, prevention should be emphasized. The benefit of fluconazole prophylaxis in patients undergoing bone marrow/stem cell transplantation is widely accepted *(36)*. Studies are underway to determine the benefit of azole or amphotericin prophylaxis in other high-risk populations, such as solid organ recipients, patients with hemotologic malignancies receiving cytotoxic therapy, and patients in surgical ICUs. However, the emergence of resistant fungal infections in patients prescribed fluconazole prophylaxis makes this an area of ongoing controversy *(37)*.

The timing of initiation of empiric therapy for candidiasis in high-risk patients is also a subject of debate. Neutropenic patients with fever who fail to respond after 5–7 d of empiric antibacterial therapy may benefit from empiric treatment with antifungal agents. Furthermore, the high risk of candidemia in surgical ICU patients, and the high rate of failure to isolate the organisms from blood cultures in that setting, has led many clinicians to use empiric antifungal therapy in this population as well; further study is needed to define the optimal approach.

Aspergillosis

The IOSA has issued practice guidelines for the treatment of aspergillosis *(38)*. Invasive infections due to *Aspergillus* spp. should usually be treated with amphotericin B. Recovery from disseminated disease is most often dependent on correcting the underlying immune defect, especially neutropenia. The use of liposomal amphotericin B should be considered in patients unable to tolerate amphotericin B deoxycholate, especially those with nephrotoxicity. Treatment of aspergillosis most often requires use of high daily doses (0.8–1 mg/kg) and significant total doses (1.5–2 g). Itraconazole has efficacy against *Aspergillus* and consideration can be given to switching to the azole drug once the infection has been controlled. Decisions on when to switch from amphotericin B to itraconazole and duration of therapy must be tailored to the individual, keeping in mind the status of the underlying disease. Combination therapy with amphotericin B and flucytosine has been advocated by some experts, especially if infection occurs at sites not well penetrated by amphotericin B, such as the CNS. Rifampin may provide some synergistic benefit as well. Surgical therapy can be considered as an adjunct for patients with isolated foci of disease.

Much controversy has been raised about the use of combined amphotericin B and itraconazole. Potential antagonism has been postulated, possibly mediated by azole-induced alterations in ergosterol content of the fungi, making them less susceptible to amphotericin. However, there is little documentation of clinically significant detrimental interactions and many clinicians use amphotericin B and itraconazole together for life-threatening infections. Further study is needed.

Cryptococcosis

The IOSA has issued practice guidelines for the treatment of cryptococcosis *(39)*. Amphotericin B with or without flucytosine remains the drug of choice for serious cryptococcal disease. Renal function and blood counts must be monitored closely with these potentially toxic drugs. Prolonged therapy may be necessary to prevent relapse.

Fluconazole also has efficacy, and may be considered in less severely ill patients. In AIDS and probably other immunosuppressed patients, cryptococcal meningitis is never cured, just controlled. Therefore, in HIV-infected individuals, lifelong maintenance therapy with fluconazole is indicated. All patients should be followed closely for signs of relapse, which can occur in the CNS or in sequestered foci such as the prostate.

Endemic Mycoses

The IOSA has issued practice guidelines for the treatment of blastomycosis *(40)*, histoplasmosis *(41)*, coccidoidomycosis *(42)*, and sporotrichosis *(43)*.

The introduction of itraconazole has significantly simplified the management of blastomycosis. While amphotericin B remains the drug of choice for treatment of severe disease, itraconazole is effective in treating less serious illness. Monitoring after completion of therapy for evidence of skin or bone involvement is necessary. Prolonged treatment courses may be needed for treatment of chronic pulmonary disease or disseminated disease.

Histoplasmosis also responds to either amphotericin B or itraconazole, with the former required for severe disease, especially if it occurs in immunocompromised patients. Itraconazole can be used for most disease in immunocompetent hosts and in nonsevere disease in immunocompromised patients. Because of the frequency of reactivation, especially in AIDS patients, HIV-infected individuals should receive lifelong maintenance therapy with itraconazole.

Disseminated coccidioidomycosis should be treated with amphotericin B in cases of severe disease in immunocompromised or other high-risk individuals. Both fluconazole and itraconazole have activity against *Coccidioides immitis* and can be used for treatment of mild disease in immunocompetent individuals and for prolonged therapy after response to amphotericin B.

Localized sporotrichosis may respond to potassium iodide but the azole drugs, particularly itraconazole, are more reliable. Amphotericin B should be used for treatment of disseminated disease. Amphotericin B is the drug of choice for treatment of disseminated penicilliosis in AIDS patients, although itraconazole may also be effective.

Zygomycosis

Azoles are not effective and amphotericin B is the drug of choice for treatment of zygomycete infections. However, antifungal therapy will be effective only if correction of the predisposing disease process can be accomplished. The need for high doses of amphotericin B has led to interest in the use of liposomal preparations, but studies are limited, and concerns have been raised about CNS penetration. Surgical debridement should be undertaken if possible. Mucormycosis with rhinocerebral involvement in diabetics should be treated by correction of the diabetic ketoacidosis, amphotericin B, and surgery.

Hyalohyphomycosis

Successful treatment of these infections is usually dependent on correction of the predisposing immune deficits. The use of growth factors to urgently reverse neutropenia has been advocated. For fusariosis, amphotericin B or liposomal amphotericin with or without flucytosine have been used most often, and a role for itraconazole is being investigated. Although some *Paecilomyces* species are susceptible to amphotericin B, other species are not. Use of experimental drugs such as voriconazole should be considered.

Phaeohyphomycosis

When agents of phaeohyphomycosis cause isolated ocular involvement, topical antifungal agents may be effective. Optimal treatment regimens for disseminated disease have not been established and response to amphotericin B or azole drugs is variable. Surgical debridement should be considered whenever possible.

Pneumocystis carinii

The treatment of *P. carinii* pneumonia is quite distinct from that of most fungal infections. Trimethroprim–sulfamethoxyzole is the drug of choice for both prophylaxis and treatment. Unfortunately, a significant proportion of AIDS patients have allergies to sulfa agents and require the use of alternative agents. Dapsone, atovaquone, and aerosolized pentamidine are effective prophylactic drugs and intravenous pentamidine and atovaquone can be used for treatment. In AIDS patients, prophylaxis should be instituted for all patients with CD4 counts < 200 cells/mm^3 and patients with previous PCP episodes. It is possible that prophylaxis can be discontinued in AIDS patients whose CD4 counts increase significantly to > 200 cells/mm^3 after institution of highly active antiretroviral therapy, but further study of such immune reconstitution is needed before definite recommendations can be made.

Other Invasive Mycoses

Disseminated infection with *M. furfur* should be treated with fluconazole. Removal of the catheter used to administer the fatty acid containing hyperalimentation solution is critical. *T. beigelii* infections can be very difficult to treat and reversal of neutropenia with growth factors should be considered. Aggressive therapy with fluconazole and possibly amphotericin B is necessary. Invasive *Saccharomyces* infection should be treated with amphotericin B, with or without flucytosine. Symptomatic vulvovaginitis may also require therapy with amphotericin, as azoles are usually ineffective.

Chromomycosis

These infections are usually not life threatening, and the goal of therapy is often cosmetic improvement. Surgical excision for debulking or cryotherapy for small lesions may be helpful. Optimal treatment is incompletely defined, but consideration can be given to a trial of itraconazole.

Mycetoma

Because these infections can progress to bony destruction, improved therapy is desirable. Surgical excision may be helpful for debulking but amputation should be avoided. It is critical to ensure that disease is truly of fungal origin and is not due to actinomycetes which should be more amenable to antimicrobial therapy. A trial of itraconazole is reasonable.

Dermatophytes

The American Academy of Dermatology has published guidelines to assist the clinician in management of superficial mycotic infections of the skin. The guidelines cover six areas related to superficial mycoses: (1) mucocutaneous candidiasis; (2) tinea capitis and tinea barbae; (3) onychomycosis; (4) pityriasis versicolor; (5) piedra; and (6) tinea corporis, tinea cruris, tinea faciei, tinea manuum, and tinea pedis *(21)*. Pityriasis (tinea) versicolor often responds to therapy with topical imidazoles or other antifungals, but

severe disease may require therapy with oral azole drugs. In contrast, tinea capitis and tinea barbae usually require management with oral azoles, with topical agents relegated to an adjunctive role only. The addition of corticosteroids or antibacterial drugs may be necessary. Family members should be evaluated. Tinea corporis, cruris, faciei, manuum, and pedis will respond to topical antifungal agents if the condition is noninflammatory and mild. Oral azole drugs should be used if lesions are inflammatory.

Onychomycosis can be a challenging clinical problem, but new drugs offer improved options. Itraconazole has good efficacy in treatment of onychomycosis but traditional prolonged treatment courses can be quite expensive. Terbinafine is a more cost-effective agent and is now recommended as the first-line agent by many experts. The recent recognition of the efficacy of intermittent therapy with either drug can further reduce cost. Aggressive management is particularly important in immunocompromised patients, including those with HIV infection or diabetes.

Special Considerations for Treatment of Resistant Fungi

Because *C. krusei* is inherently resistant to fluconazole, treatment with amphotericin B is mandatory. *C. glabrata* also demonstrates reduced susceptibility to azoles and amphotericin B may be necessary. Isolates resistant to azoles, especially fluconazole, are rising for *C. albicans,* and case reports of resistance in non-*albicans Candida* spp. are increasing in frequency. When patients fail to respond to azole therapy, the possibility of resistant organisms should be considered, and switching to amphotericin B may be appropriate. Although not widely routinely available, *Candida* susceptibility testing is an option and standards have been established by the NCCLS *(13,15,26).* Testing may be indicated for patients who fail to respond to appropriate empiric therapy. Finally, *C. lusitaniae* is remarkably resistant to amphotericin B and flucytosine, but usually remains susceptible to fluconazole.

If patients with candidiasis fail to respond to therapy with fluconazole, alternative agents should be considered. Increasing the dose of fluconazole may be effective in treating some infections caused by *C. albicans* and non-*albicans Candida* spp. (e.g., *C. glabrata*) with relative resistance to fluconazole. Dosages as high as 800 mg/d have been used in recalcitrant cases. For fungi without cross-resistance to other azoles, itraconazole may be effective. Oral amphotericin can be used for oropharyyngeal candidiasis in HIV patients with disease unresponsive to azoles. Intravenous amphotericin B may be necessary in severe cases. New experimental drugs such as voriconazole offer hope for the future.

Aspergillus species will not respond to fluconazole, and amphotericin B should be used for treatment of serious disease. Itraconazole does have efficacy and can be used for less severe disease or for completion of therapy after initial response to amphotericin B.

Case reports of fluconazole resistance to *C. neoformans* have been reported, although the drug has good efficacy in most cases. Amphotericin B and flucytosine remain the mainstay of initial therapy, although fluconazole is occasionally used for the entire treatment course in some patients and is an important drug for maintenance therapy. If patients fail on fluconazole, a switch to amphotericin B is appropriate. Consideration can be given to susceptibility testing of *Cryptococcus* organisms in cases of nonresponse to the azole drugs.

Table 5
Potential New Antifungal Drugs

- Echinocandins (1, 3-β-D-glucan synthase inhibitors)
- New azole drugs
  Voriconazole
  SCH56592 (derivative of itraconazole)
- Chitin synthase inhibitors
- Sodarins (protein synthesis inhibitors)
  Nikkomycin
- Dicationic aromatic compounds

The zygomycetes and many of the agents of hyalohyphomycosis and phaeohyphomycosis are generally resistant to the azole drugs. In addition, some fungi causing hyalohyphomycosis are resistant to amphotericin B. For example, *Paecilomyces lilacinas* is resistant to amphotericin B and flucytosine in vitro. Azole drugs should be used. *Sedosporium prolificans,* which causes disease in the category of phaeohyphomycosis, demonstrates intrinsic resistance to all currently available antifungal drugs. *P. boydii* and *T. beigelii* also are resistant to amphotericin B. Azoles can be used but treatment is difficult and prognosis poor unless the underlying immune defects can be reversed. New, investigational drugs are under study and are urgently needed for management of these challenging diseases.

New Antifungal Drugs

The increase in fungal infections caused by well-recognized pathogens, the expanded recognition of resistant fungal strains, and the emergence of infections due to strains previously considered nonpathogenic highlight the need for development of innovative approaches to antifungal therapy. Several new drugs are under investigation and initial results portend an exciting future *(1,22,23,29)* (Table 5).

A number of new azole drugs are currently being studied. Voriconazole is a new triazole derivative of fluconazole currently in phase III trials that has a broad spectrum of activity against *Candida* spp., *Aspergillus* spp., dimorphic fungi, and other molds *(29).* Voriconazole seems to have activity against *Candida* spp. such as *C. krusei* which are resistant to fluconazole. Voriconazole also appears to have better activity against *Aspergillus* spp. than itraconazole. SCH 56592 is a derivative of itraconazole. This new drug appears to have better activity against *Aspergillus* spp. than itraconazole and broad-spectrum activity against a variety of yeasts, dimorphic fungi, and molds, including the zygomycetes and dematiaceous fungi. Other azole drugs are in earlier stages of development.

An exciting new class of antifungal function is the echinocandins. These drugs are fungicidal due to their inhibition of 1, 3β-D glucan synthase and consequent inhibition of β-glucan synthesis in the fungal cell wall. These compounds appear to have activity against *Candida* spp., *Aspergillus* spp., fungi causing endemic mycoses, and *P. carinii,* as well as other yeasts and molds. Nikkomycin is a fungicidal compound that inhibits chitin synthesis in the fungal cell wall. It may particularly prove useful in treatment of infections due to the endemic fungi, especially coccidioidomycosis. Studies are needed to determine if fungal cell membrane active agents (azoles and polyenes) and

cell wall active agents (nikkomycin and echinocandins) might be synergistic if used in combination.

Other Approaches

Other approaches to optimizing antifungal therapy include use of growth factors to correct underlying neutropenia and cytokines and other immunomodulatory interventions. Further studies to determine which patient populations will benefit from antifungal prophylaxis are also needed *(44–46)*.

Key Points

- While most *Candida albicans* remain sensitive to fluconazole and amphotericin B, fluconazole-resistant *C. albicans* and non-*albicans Candida* spp. that may be less susceptible to azoles are being recognized with increased frequency.
- *C. krusei* is resistant and *C. glabrata* demonstrates decreased susceptibility to fluconazole. *C. lusitaniae* is resistant to amphotericin B and flucytosine, but remains susceptible to azoles.
- *Aspergillus* spp. do not respond to fluconazole, but amphotericin B and itraconazole may have efficacy, especially if predisposing immune defects can be corrected.
- Itraconazole now plays an important role in management of blastomycosis and histoplasmosis, although amphotericin B is still used for severe disease.
- Treatment of zygomycosis, hyalohyphomycosis, and phaeohyphomycosis is challenging and involves aggressive antifungal therapy, adjunctive surgery if possible, and correction of underlying immune defects.
- Guidelines for management of dermatomycoses have been published by the American Academy of Dermatology.
- Susceptibility testing for *Candida* species and *Cryptococcus neoformans* has now been standardized but is still used predominantly for exceptional patient care decisions and research purposes.
- New antifungal drugs are urgently needed and several are currently being studied.
- Practice guidelines are available from the IOSA to guide treatment of many fungal diseases *(31)*.

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