New Antifungal Drugs for Pulmonary Myces*

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Abbreviations: CNPA=chronic necrotizing pulmonary aspergillosis; CSF=cerebrospinal fluid; PDH=progressive disseminated histoplasmosis

Amphotericin B has been the standard therapy for most serious fungal infections since the 1950s. However, amphotericin B use is frequently limited by adverse effects such as fever, rigors, hypotension, and nephrotoxicity.1 With the increasing numbers of immunocompromised patients due to cytotoxic chemotherapy, organ transplantation, and AIDS, the number of invasive fungal diseases due to the endemic mycoses, histoplasmosis, and coccidioidomycosis, as well as to the opportunistic fungi, Cryptococcus, Aspergillus, and unusual pathogens, has increased markedly. The need for new antifungal drugs that are well tolerated, orally administered, and have a broad spectrum of activity has resulted in the development of the new azole antifungal agents, fluconazole and itraconazole. The nephrotoxicity of amphotericin B has been reduced in the novel formulations of liposomal amphotericin B, amphotericin B colloidal dispersion, and amphotericin B lipid complex, but improved clinical outcomes have not yet been convincingly demonstrated. These new antifungal agents offer alternative therapy to amphotericin B for many invasive fungal diseases, and in some instances have become the preferred agents for the treatment of disseminated fungal infection.

Antifungal Agents

The azole antifungal agents are comprised of the imidazole and triazole groups. These agents are structurally similar with a five-numbered azole ring containing either two or three nitrogens (Fig 1). The imidazoles, miconazole and ketoconazole, have been available for many years but have a narrower spectrum of activity, more adverse effects, and a shorter half-life than the newer triazole agents, fluconazole and itraconazole.

All azole drugs have the same mechanism of action, i.e., interfering with ergosterol synthesis in the cell membrane of yeasts and fungi by binding to the cytochrome P-450 mediated enzyme, 14 alphamethylase. This results in the accumulation of 14-methylated ergosterol precursors that destabilize the cell membrane leading to inhibition of cell growth and ultimately to cell death.2 The first oral azole drug, ketoconazole, has been useful for the treatment of various forms of candidiasis, nonmeningeal histoplasmosis, blastomycosis, paracoccidioidomycosis, and nonmeningeal coccidioidomycosis. Activity against nonalbicans species of Candida, Cryptococcus, aspergillosis, and extracutaneous sporotrichosis is poor or nonexistent. Ketoconazole has been associated with a number of troublesome adverse effects, including anorexia and GI intolerance, hepatitis, depression of testosterone and adrenocorticotropic hormone-stimulated cortisol response, gynecomastia, impotence, and rash, limiting its use.3-7 The absorption of ketoconazole requires an acidic environment, and is limited by the use of H2-receptor-blocking agents such as cimetidine, ranitidine, or famotidine.8,9

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FIGURE 1. Structure of ketoconazole, fluconazole, and itraconazole.
A number of drug interactions occur with ketoconazole. Drugs such as rifampin and phenytoin, which increase hepatic P450-dependent enzymes, increase the metabolism of ketoconazole reducing plasma levels of the drug.10 Ketoconazole can inhibit the metabolism of cyclosporine, prolonging its half-life and increasing the risk of nephrotoxicity.11,12 The concomitant administration of ketoconazole with terfenadine or cisapride inhibits cytochrome P450 3A4 metabolism resulting in high levels of unmetabolized terfenadine or high cisapride blood levels, which may prolong the QT interval resulting in serious cardiac arrhythmias.13,14

The newer triazoles, fluconazole and itraconazole, have improved therapeutic and safety profiles when compared with ketoconazole15,16 (Table 1). Fluconazole is highly water soluble, is minimally protein bound, and is distributed throughout the body water.15,17 Itraconazole like ketoconazole is almost totally insoluble in water, highly lipophilic, and highly protein bound.15-17 Therefore, itraconazole plasma levels are low and negligible amounts of itraconazole are found in cerebrospinal fluid (CSF), but high concentrations of the drug are found in most tissues, especially skin, nails, adipose tissue, endometrium, and cervical and vaginal tissues.18

In contrast to ketoconazole and itraconazole, high concentrations of fluconazole are achieved in the CSF and urine.19,20 Fluconazole penetrates well into peritoneal fluid and has been used successfully to treat fungal peritonitis.21 While the oral absorption of both ketoconazole and itraconazole is decreased by antacids or H2-blockers, gastric acid is not required for the absorption of fluconazole.22 The presence of food and gastric acid increases the bioavailability of itraconazole.23 Fluconazole is primarily excreted renally, while itraconazole undergoes extensive hepatic metabolism and at least one metabolite, hydroxyitraconazole, has in vitro antifungal activity.24,25 Therefore, fluconazole dosing must be adjusted in patients with renal failure, while no dose adjustment of itraconazole is necessary in patients receiving dialysis or patients with renal insufficiency.26

The serum half-life of both fluconazole and itraconazole is approximately 24 h, so both drugs can be administered once daily. An IV form of fluconazole can be used in patients unable to take oral medications.

Less frequent adverse effects have been reported for both fluconazole and itraconazole than ketoconazole. GI complaints, including nausea, vomiting, diarrhea, and abdominal complaints, occur in less than 10% of patients.7,27 Other less common adverse reactions reported include rash, headache, fatigue, edema, hypokalemia, and abnormal results of liver function tests. Abnormal results of liver function tests occurred in 7% of patients receiving long-term itraconazole therapy but were reversible on discontinuing treatment with the drug.27 Mild transient elevations of liver function test values have been reported in patients taking fluconazole, but severe hepatotoxicity is extremely rare.7 Drug interactions with both fluconazole and itraconazole are similar to those occurring with ketoconazole. Like ketoconazole, the coinadministration of terfenadine, astemizole, or cisapride with itraconazole and possibly fluconazole, can result in prolongation of the QT interval and life-threatening cardiac arrhythmias and should be avoided.28 Rifampin, phenytoin, phenobarbital, and carbamazepine administration can enhance hepatic metabolism of itraconazole leading to treatment failures.29 Administration of fluconazole with phenytoin may result in toxic serum phenytoin levels.30 Both fluconazole and itraconazole may enhance the anticoagulant effect of warfarin and the hypoglycemic effect of oral hypoglycemic agents.30,31 The administration of itraconazole to patients receiving digoxin may increase serum digoxin concentrations leading to toxic levels.31,32 Like ketoconazole, coadministration of cyclosporine with itraconazole and possibly fluconazole can result in increased concen-
trations of serum cyclosporine leading to nephrotoxicity.\textsuperscript{33} Cyclosporine doses should be reduced by 50% when concurrent itraconazole is administered, and serum cyclosporine levels should be monitored.\textsuperscript{33}

**Spectrum of Activity**

The triazoles, fluconazole and itraconazole, have broad spectrum in vitro antifungal activity against most fungal pathogens.\textsuperscript{15,16,34} (Table 2). Itraconazole is the first azole drug with activity against Aspergillus species. In vitro studies show itraconazole compares favorably to amphotericin (with minimum inhibitory concentration \(\leq 1\) \(\mu\)g/mL) against *Aspergillus fumigatus*.\textsuperscript{35,36} Itraconazole also has excellent activity against *Sporothrix schenckii*, *Blastomyces dermatitidis*, *Paracoccidioides brasiliensis*, and *Histoplasma capsulatum*.\textsuperscript{36,37} Fluconazole has excellent activity against *Candida albicans*, *Cryptococcus neoformans*, and *Coccidioides immitis*; however, some non-albicans species such as *Candida krusei*, and *Candida glabrata* are resistant.\textsuperscript{38,39} Ketoconazole, fluconazole, and itraconazole are not active against the agents of mucormycoses.

**Pulmonary Mycoses**

Fungal pneumonia occurs in both immunocompetent and immunocompromised hosts. The major pulmonary fungal diseases seen in the United States are the endemic mycoses, histoplasmosis, coccidioidomycosis, and blastomycoses, and the opportunistic pathogens Cryptococcus, Candida, Aspergillus, and the agents of Mucormycoses. Paracoccidioidomycosis is a common cause of pulmonary fungal disease in Central and South America. Unusual fungi such as *Pseudallescheria boydii*, *Penicillium marneffei*, and the pulmonary phaeohyphomycosis may cause lung infection in the immunocompromised host. *S. schenckii* is an endemic fungi that occasionally causes pulmonary sporotrichosis in normal or immunosuppressed persons. Amphotericin B has been the treatment of choice for most serious systemic fungal disease. The new azole drugs, fluconazole and itraconazole, are effective alternatives to amphotericin B for the treatment of many fungal lung infections (Table 3).

**Aspergillosis**

Aspergillus, a ubiquitous mold and an important pathogen in immunosuppressed patients and patients with preexisting lung disease, is responsible for four types of pulmonary disease, allergic bronchopulmonary aspergillosis, aspergillosis, chronic necrotizing pulmonary aspergillosis (CNPA), and invasive aspergillosis. Allergic bronchopulmonary aspergillosis characterized by eosinophilia, fleeting pulmonary infiltrates, a positive immediate type skin test response to Aspergillus, elevated serum IgE, and anti-Aspergil-

\[\text{Table 3—Therapy of the Pulmonary Fungal Mycoses}\]

<table>
<thead>
<tr>
<th>Pulmonary Syndrome</th>
<th>Therapy of Choice</th>
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<tr>
<td>Aspergillosis</td>
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<tr>
<td>Allergic bronchopulmonary aspergillosis</td>
<td>Corticosteroids, itraconazole</td>
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<td>Aspergiloma</td>
<td>Surgical resection, itraconazole</td>
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<tr>
<td>Chronic necrotizing pulmonary aspergillosis</td>
<td>Itraconazole or amphotericin B</td>
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<td>Invasive aspergillosis</td>
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<td>Blastomycosis</td>
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<td>Acute pulmonary disease</td>
<td>Itraconazole</td>
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<td>Chronic pulmonary disease</td>
<td>Itraconazole</td>
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<td>Coccidioidomycosis</td>
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<tr>
<td>Acute pulmonary disease</td>
<td>Ketoconazole or itraconazole</td>
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<tr>
<td>Chronic pulmonary disease</td>
<td>Itraconazole or ketoconazole</td>
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<tr>
<td>Pulmonary cryptococcosis</td>
<td>Fluconazole or amphotericin B</td>
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<tr>
<td>Histoplasmosis</td>
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<tr>
<td>Acute pulmonary histoplasmosis</td>
<td>No therapy</td>
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<tr>
<td>Chronic pulmonary histoplasmosis</td>
<td>Itraconazole or ketoconazole</td>
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<tr>
<td>Disseminated histoplasmosis</td>
<td>Amphotericin B or amphotericin B</td>
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<td>Maintenance therapy for AIDS patients</td>
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<tr>
<td>Paracoccidioidomycosis</td>
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<tr>
<td>Mild pulmonary disease</td>
<td>Itraconazole</td>
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<td>Severe pulmonary disease</td>
<td>Amphotericin B or sulfadiazidine or itraconazole</td>
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<td>Sporotrichosis</td>
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<tr>
<td>Mild pulmonary disease</td>
<td>Itraconazole</td>
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<tr>
<td>Severe pulmonary disease</td>
<td>Amphotericin B</td>
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racic intracavitary instillation of amphotericin B with questionable benefit.\textsuperscript{43-45} Itraconazole has been used with some success for the treatment of aspergillosis.\textsuperscript{46-48} In one series of 14 patients treated with itraconazole, 2 patients were cured and 8 patients had improved conditions, while 4 remained unchanged or their conditions deteriorated.\textsuperscript{47} In two other reports of patients with aspergilomas, half the patients (three of six) showed improvement after therapy with itraconazole.\textsuperscript{46,48} Itraconazole has also been used effectively to treat or suppress CNPA.\textsuperscript{46,47,49} Of 19 patients in one series, 9 were cured and 9 showed improvement.\textsuperscript{46,47} Three patients with CNPA were clinically successfully suppressed with itraconazole; however, tissue at autopsy or at operation showed residual CNPA.\textsuperscript{49}

The therapy of choice for invasive aspergillosis in immunocompromised, especially neutropenic patients, remains amphotericin B. However, itraconazole has been used with success in several series of patients with invasive disease. Of 3 series, a total of 42 of 54 patients treated with from 100 to 400 mg itraconazole per day were considered cured of the disease.\textsuperscript{46,47,50}

**Pulmonary Blastomycosis**

Blastomycosis is a systemic disease most often involving the lungs, skin, bones, and genitourinary system caused by the dimorphic fungus \textit{B dermatitidis}. The endemic areas in the United States include the southeastern and south central states, especially the areas bordering the Mississippi and Ohio Rivers, an area in New York State along the St. Lawrence River, and the midwestern states.

Acute pulmonary blastomycosis is a nonspecific illness characterized by flu-like symptoms such as fever, chills, and myalgias accompanied at first by a nonproductive cough that usually becomes productive of purulent sputum. Pleuritic pain may be present, pleural effusions are not common, and the chest radiograph usually shows segmental or lobar consolidation.\textsuperscript{51} Although there are reports of spontaneous resolution of acute infection, most patients with pulmonary disease develop an indolent, progressive chronic pneumonia characterized by productive cough, hemoptysis, pleuritic chest pain, weight loss, low-grade fever, and most often upper lobe infiltrates that may cavitate.\textsuperscript{50-53} Complications of chronic pulmonary disease include miliary disease, diffuse pneumonitis, and respiratory failure.\textsuperscript{54,55}

Amphotericin B remains the drug of choice for all forms of blastomycosis in the immunosuppressed host and for patients with CNS disease or life-threatening illness.\textsuperscript{56,57} Itraconazole is an effective alternative therapy for both acute and chronic pulmonary disease in the immunocompetent patient, but should be avoided in patients with CNS or genitourinary disease. Itraconazole at doses of 200 to 400 mg/d for approximately 6 months was effective in treating 43 of 48 patients with nonmeningeal non-life-threatening blastomycosis.\textsuperscript{58}

**Candidiasis**

Candida pneumonia does not occur in normal or compromised hosts. Candidal lung involvement occurs only as part of a disseminated invasive candidiasis that may occur in patients receiving steroids, prolonged antibiotic therapy, prolonged hospitalization, following major surgical procedures, or in leukopenic patients. Candida pneumonia without associated invasive disease does not occur. Candidal mycetomas have been reported rarely in the literature and are clearly not any more related to candidal pneumonia than aspergilomas are related to Aspergillus pneumonia. The recovery of Candida via protected brush or BAL specimens is common in patients receiving antimicrobial or corticosteroid therapy, as well as in diabetics, alcoholics, and HIV-infected patients. Therefore, the recovery of Candida from a bronchoscopy specimen, even with a protected tip, in a normal or compromised host with pulmonary infiltrates is not diagnostic of Candida pneumonia and should not be used as the basis for empiric antifungal therapy.\textsuperscript{59-65} A Candida culture obtained via bronchial specimen should prompt the clinician to look for another explanation for the pulmonary infiltrates. Candidal lung involvement, even in systemic invasive disease, is rarely made antemortem. Therefore, if the diagnosis is made antemortem, the patient should be treated for systemic disease and not for an isolated pulmonary infection.

**Coccidioidomycosis**

\textit{C immitis} causes the systemic illness coccidioidomycosis that is endemic in the southwestern United States. Approximately 60% of infected patients are asymptomatic while 40% will develop primary infection after an incubation period of 1 to 3 weeks. Most symptomatic patients with primary coccidioidomycosis develop a lower respiratory tract infection associated with a flu-like illness characterized by fever, chills, cough, malaise, anorexia, and night sweats. Erythema nodosum or erythema multiforme may occur. Chest radiographs are often abnormal with infiltrates, pleural effusions, or hilar adenopathy.\textsuperscript{66} Five percent of patients with primary disease have a residual pulmonary cavity or nodule, while 0.5% develop disseminated disease usually involving the meninges, bones, or joints.

In some patients, primary acute pneumonia may progress to chronic pulmonary coccidioidomycosis, a disease that closely mimics pulmonary tuberculosis. Most forms of acute pulmonary coccidioidomycosis are
self-limited and require no therapy. However, patients with severe primary disease, high complement-fixing antibody titers, symptoms lasting more than 6 weeks, or immunosuppression should receive therapy, usually with ketoconazole or itraconazole. Itraconazole has been used to treat patients with chronic nonmeningeal coccidioidomycosis effectively. In one series, 57% of patients with pulmonary disease and 90% of patients with bone, joint, skin, or soft-tissue involvement responded to itraconazole. In another study, 15 of 16 patients with pulmonary coccidioidomycosis treated with 400 mg itraconazole daily achieved clinical remission. Although itraconazole appears effective in the treatment of pulmonary coccidioidomycosis, to our knowledge, there are no data available comparing the efficacy of itraconazole, fluconazole, ketoconazole, or amphotericin B in the treatment of pulmonary disease.

Cryptococcosis

C neofor mans, an encapsulated yeast-like fungus, ubiquitous in nature, is the causative agent of cryptococcosis, a disease occurring primarily in patients with defects in the T-cell-mediated host defense mechanism, such as AIDS, patients with transplants, and patients receiving high-dose corticosteroids. The most common clinical presentation of cryptococcal disease is CNS cryptococcosis; however, pulmonary cryptococcosis also may occur. Patients with cryptococcal pneumonia may present with a wide spectrum of clinical findings ranging from asymptomatic patients to those with cough and dyspnea to severe progressive pneumonia.

Pulmonary cryptococcosis in nonimmunosuppressed patients is a diagnosis often made by surgical biopsy. Surgical excision may be curative. In most patients with normal CSF findings, negative CSF urine cultures, and a normal immunologic system, pulmonary disease is usually self-limited and may not require antifungal therapy.

Immunosuppressed patients with pulmonary cryptococcosis should be treated with amphotericin B (with or without flucytosine) or fluconazole. Lifelong maintenance therapy with fluconazole is necessary in AIDS patients. There are little data on the use of itraconazole in the treatment of patients with pulmonary cryptococcosis; however, several small series have shown that itraconazole is effective in the treatment of cryptococcal meningitis.

Histoplasmosis

H capsulatum is a dimorphic fungus that is endemic in the areas surrounding the central river valleys of the United States. Most individuals exposed to a low inoculum of conidia do not develop illness, while more than 50% of persons develop symptoms after a heavy exposure.

Approximately 80% of acute primary pulmonary infections are asymptomatic. Some patients develop a flu-like illness with fever, chills, headache, arthralgias, myalgias, nonproductive cough, and pleuritic or substernal chest pain. Erythema multiforme and/or erythema nodosum may occur in up to 5% of patients. Patients with mild or no symptoms usually have normal chest radiographs while the chest radiographs of symptomatic patients often show one or more patchy or nodular infiltrates, hilar or mediastinal adenopathy, pleural effusions if pericarditis is present, and occasionally cavities. Pulmonary complications of primary histoplasmosis that may develop include mediastinal granulomatosis and fibrosis and histoplasmosa. Chronic pulmonary histoplasmosis mimics tuberculosis, is characterized by chronic upper lobe cavities and systemic complaints of low-grade fever, weight loss, and persistent cough. Progressive disseminated histoplasmosis (PDH) occurs in immunocompromised adults and young children. Pulmonary findings are rarely seen in adults with chronic or subacute PDH, while almost all infants and adults with acute PDH have prominent pulmonary symptoms and abnormal chest radiographs showing diffuse nodular infiltrates and/or hilar adenopathy. Patients who have AIDS and who have acute PDH often present with fever, weight loss, cough, dyspnea, and diffuse pulmonary infiltrates that may progress to ARDS.

Most patients with acute pulmonary histoplasmosis require no specific treatment; however, ketoconazole or itraconazole has been used to treat patients with prolonged symptoms or severe disease. Itraconazole has been used effectively for the treatment of chronic pulmonary histoplasmosis, disseminated nonmeningeal disease, and disseminated histoplasmosis in patients with AIDS. In one series, 7 of 12 AIDS patients treated with 400 mg itraconazole daily went into remission, 2 clinically improved, and three failed therapy. In another study, 23 of 27 AIDS patients clinically improved with itraconazole. Itraconazole has also been used as maintenance therapy in AIDS patients after induction therapy with amphotericin B. Amphotericin B remains the drug of choice for life-threatening histoplasmosis or for infections not responding to itraconazole.

Paracoccidioidomycosis

P brasiliensis is the causative agent of paracoccidioidomycosis, an important systemic mycosis in Latin America. Most primary infections are asymptomatic and occur in normal hosts. However, severe infections may occur in immunosuppressed patients such as those with AIDS. Pulmonary complaints of cough and
dyspnea and chest pain are prominent and are frequently accompanied by mucosal ulcerations, dysphagia, cutaneous lesions, and lymphadenopathy. Chest radiographs most often show bilateral basilar, patchy, or nodular infiltrates with sparing of the apices. The treatment of choice for severe disease is amphotericin B, often combined with sulfadiazine or itraconazole for maintenance therapy. Itraconazole appears superior to ketoconazole for milder disease.

Sporotrichosis

S. schenckii, the causative agent of sporotrichosis, most commonly causes a nodular lymphangitis at the site of inoculation of the fungus into the skin. Rarely, pulmonary sporotrichosis can occur, usually in patients who have chronic medical problems such as diabetes mellitus, alcoholism, chronic lung disease, or corticosteroid use. Chest radiographs typically show cavitory disease. The treatment of choice for lymphocutaneous disease is itraconazole. Itraconazole also appears effective in treating patients with pulmonary disease; however, life-threatening cases should be treated initially with amphotericin B. In some patients, surgical resection is required for cure. A recent study showed fluconazole to be a second-line drug for the treatment of sporotrichosis and should be reserved for patients unable to take itraconazole.

Conclusion

The newest triazoles, itraconazole and fluconazole, provide broad spectrum activity against many fungal infections. These drugs have fewer and less severe reactions than amphotericin B. Itraconazole or ketoconazole can be administered orally and are effective in many fungal pulmonary infections. Although amphotericin B remains the preferred drug for the treatment of life-threatening pulmonary mycoses in the compromised host, the new triazole antifungals have an important place in the therapeutic armamentarium against many pulmonary mycoses. Itraconazole is especially useful in the prolonged treatment of CNPA, pulmonary blastomycosis, chronic pulmonary histoplasmosis, chronic pulmonary coccidioidomycosis, pulmonary paracoccidioidomycosis, and pulmonary sporotrichosis.

Currently, clinicians may choose from ketoconazole, fluconazole, and itraconazole, depending on the severity and type of pulmonary mycoses. Itraconazole is a great therapeutic advance in treating most pulmonary mycoses and is less toxic and oral alternative to amphotericin B therapy. Fortunately, with the exception of P. boydii, virtually all fungi resistant to the triazoles remain responsive to amphotericin B.

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