Fungal Infections

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Over the last decade, there have been changes in the epidemiology of fungal infections as well as dramatic improvements in the antifungal armamentarium. *Candida* species are an increasingly important cause of infection among patients in intensive care units. Mold infections continue to occur predominantly among highly immunosuppressed patients, such as those who have acute leukemia and those undergoing hematopoietic stem cell or solid organ transplantation. *Aspergillus* species remain the most common molds to cause invasive infection, but other environmental molds, such as *Scedosporium, Fusarium,* and various zygomycetes, including *Rhizopus* and *Mucor,* appear to be increasing in some medical centers. We now have available a new class of antifungal agents, the echinocandins, that act to damage the cell walls of *Candida* and *Aspergillus* species. Although limited in spectrum and only available in intravenous formulations, these agents are very safe and extremely well tolerated. Another new agent is the expanded spectrum triazole voriconazole. This agent has a very broad spectrum of activity, is available in both oral and intravenous formulations, and is approved for treatment of aspergillosis, other molds, and candidiasis. The major drawbacks with voriconazole are the number of drug–drug interactions and side effects, including rash, hepatitis, and visual disturbances. Treatment with amphotericin B, long the mainstay of antifungal therapy despite its inherent toxicity, is required much less often since the introduction of these new antifungal agents.

Keywords: asperigillosis; candidiasis; echinocandins; triazoles; zygomycosis

There have been changes in the epidemiology of fungal infections in the last decade. *Candida* infections, once a major cause of death in patients with leukemia and recipients of stem cell or solid organ transplants, are now seen more often in patients in the intensive care unit (ICU). The species of *Candida* causing infection are more diverse: *Candida albicans* does not predominate as it once did; *Candida glabrata*, an organism often resistant to fluconazole, has become prevalent in some hospitals. Changes in the epidemiology of mold infections have also occurred. *Aspergillus* species remain the most common cause of mold infections in humans, but there has been an increase in infections due to other molds, such as *Scedosporium apiospermum*, *Fusarium* species, and zygomycetes, such as *Rhizopus* and *Mucor*. These molds are angioinvasive, infiltrating through blood vessels and leading to extensive tissue infarction and widespread dissemination. Many of the emerging molds are resistant to amphotericin B.

Paralleling these changes in the epidemiology of fungal infections has been the introduction of new antifungal agents. The expanded spectrum triazole voriconazole has become the agent of choice for the treatment of invasive aspergillosis. It also has activity against many of the molds that have emerged as pathogens in recent years and is effective for *Candida* infections. The broad spectrum of activity and the availability of both intravenous and a well-absorbed oral formulation are advantages of voriconazole; disadvantages are more drug–drug interactions and side effects than noted with other azoles. The echinocandins caspofungin and micafungin are members of an entirely new class of antifungal agents that are increasingly used for the treatment of *Candida* infections and are effective agents for aspergillosis that has become refractory to other therapy. A major advantage of the echinocandins is that they have very few side effects; the disadvantages are that they are available only as intravenous formulations and the spectrum of activity is relatively narrow. The new antifungal agents have led to many fewer patients requiring treatment with amphotericin B.

Candida INFECTIONS

In the past, the major groups at risk for serious *Candida* infections were patients who were neutropenic, had received a transplant, or had been treated with corticosteroids or cytotoxic agents. Currently, serious *Candida* infections are more likely to be seen in patients who are in the ICU. Those most at risk are patients who have a central venous catheter in place, are receiving parenteral nutrition, have had a surgical procedure, are on broad-spectrum antibiotics, require hemodialysis, and have high Acute Physiology and Chronic Health Evaluation (APACHE) scores (1–3). *Candida* species are the fourth most common cause of nosocomial bloodstream infection; among ICU patients, they are the third most common cause of nosocomial bloodstream infections (4). The attributable mortality from candidemia remains close to 40% (5). *C. albicans* is the most common human pathogen. *C. glabrata* is the second most common infecting species, followed by *C. tropicalis* and *C. parapsilosis;* other species are found much less often.

A recent trend noted in many hospitals is an increase in the prevalence of *C. glabrata* as a cause of serious *Candida* infections (6–10). There are several reasons for this increase, including geography, age, the patient population studied, and the use of fluconazole. *C. glabrata* has been noted more commonly in adults older than 60 yr (9, 10) and in centers caring for patients who have leukemia or have received a stem cell transplant (7, 8), and has been correlated with increasing use of fluconazole (7, 8). The importance of this epidemiologic trend is that *C. glabrata* is often resistant to fluconazole, the agent used most often for the treatment of candidemia.

Although candidemia is the most common manifestation of invasive candidiasis, extensive visceral invasion with *Candida* can occur with persistently negative blood cultures. Virtually all organs can be involved, but the eyes, kidneys, liver, spleen, and brain are most commonly affected. Signs of invasive candidiasis that should be sought clinically include chorioretinitis or endophthalmitis and the appearance of painless, nonpruritic pustular skin lesions.

All patients with documented candidemia or invasive candidiasis should be treated with an antifungal agent (11). The high rate of dissemination to major organs once *Candida* gains entrance to the bloodstream provides the rationale for this approach. Multiple antifungal agents are available for the treatment of candidiasis. These include fluconazole, caspofungin, voriconazole, amphotericin B, and lipid formulations of amphotericin

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B. Micafungin, a new echinocandin, has not yet received U.S. Food and Drug Administration approval for invasive candidiasis but is likely to be efficacious also. It has been shown that fluconazole, voriconazole, and caspofungin are as effective as amphotericin B deoxycholate in the treatment of candidemia (12, 13). It is assumed that lipid formulations of amphotericin B are as efficacious as the deoxycholate formulation, but clinical trials to compare lipid agents with standard amphotericin B have not been performed.

The preferred treatment for candidemia is fluconazole. This agent is active against most species of *Candida,* has been shown to be as effective as amphotericin B in nonneutropenic patients, has few side effects, and is now the least expensive agent available for this indication. However, fluconazole has limited activity against *C. glabrata* and is not active against *C. krusei*, an uncommonly isolated species. Physicians should be aware of the most common species of *Candida* causing bloodstream invasion in their hospital. If *C. albicans*, *C. parapsilosis*, and *C. tropicalis* cause most candidemias, fluconazole remains the agent of choice. If *C. glabrata* accounts for more than 15 to 20% of isolates, fluconazole should not be used as first choice for candidemia, and caspofungin, which has activity against all *Candida* species and very few side effects, should be used (11). If the laboratory identifies the organism as *C. albicans*, *C. parapsilosis*, or *C. tropicalis*, therapy should be changed to fluconazole. The echinocandins are likely to emerge as the agents of choice for candidemia if they become less costly. Currently, the echinocandins are much more costly than generic fluconazole, and many hospitals restrict their use for that reason.

Removal of all vascular catheters hastens the clearance of yeasts from the blood (14). Daily cultures of blood should be obtained to document that fungemia has resolved, and treatment should continue for 2 wk after the date of the first negative blood culture.

ANGIOINVASIVE MOLD INFECTIONS

Filamentous fungi cause fewer infections than *Candida*, but the mortality from invasive mold infections is far greater. These organisms are ubiquitous in the environment, but cause invasive infection almost entirely among immunosuppressed patients, including those who have received stem cell or solid organ transplants, those who are neutropenic, and those who have been treated with corticosteroids or other immune-modulating agents. Among the angioinvasive fungi, the most common pathogens in humans are *Aspergillus* species. *A. fumigatus* and *A. flavus* are the most common pathogens (15), but *A. terreus*, which is resistant to amphotericin B, is increasingly reported as a cause of infection in immunosuppressed patients (16).

A variety of other molds, including *S. apiospermum*, *Fusarium* species, and the zygomycetes, appear to be causing an increasing number of infections in immunosuppressed patients (17). All of these fungi have in common the propensity to invade through blood vessel walls, cause tissue infarction and necrosis, and disseminate widely.

Aspergillus, *Scedosporium*, and *Fusarium* are hyaline molds. In tissues, their hyphae are colorless, have septae, and branch at acute angles, and it is very difficult to differentiate these organisms from each other. However, it is important to do so because each of these organisms has different susceptibilities to antifungal agents.

S. apiospermum is an environmental mold that is present in soil, water, and sewage (18). In its sexual state, it is known as *Pseudallescheria boydii*. It is an increasing cause of pneumonia in patients who have leukemia and in those who have received a stem cell or solid organ transplant (Figures 1 and 2) (19). The other major *Scedosporium* species is *S. prolificans*, which is more common in Spain and Australia than in the United States (20). It, too, infects mostly immunocompromised patients, but this species is resistant to almost all antifungal agents, and the mortality with pulmonary or disseminated infection is exceedingly high.

Fusarium species are plant pathogens, but increasingly they have been described as a cause of infections in patients with leukemia and stem cell transplant recipients (21). *Fusarium* and a few other genera of molds actually sporulate *in vivo*, a phenomenon that allows them to grow in cultures taken from blood. *Fusarium* species disseminate through the bloodstream after entry through the lungs or through a cutaneous source, such as a simple paronychia. Painful nodular skin lesions occur frequently with hematogenous spread (Figure 3).

The class Zygomycetes is composed of common environmental fungi that are angioinvasive. The most commonly isolated species belong to the genera *Rhizopus* and *Mucor.* These organisms form broad, nonseptate hyphae that branch at right angles, thus appearing very different in tissues from the thinner hyaline septate molds described above (Figure 4). The zygomycetes are most commonly seen in diabetics, patients with leukemia, and those who have received an organ or stem cell transplant (22).

The conidia of most angioinvasive fungi are inhaled into the upper or lower respiratory tracts and invade from these sites. Not surprisingly, the most common clinical manifestations of infection with angioinvasive fungi are pneumonia and sinusitis. Nodules, lobar infiltrates, wedge-shaped infarction, and cavitary lesions are common radiographic and pathologic manifestations of invasive pulmonary infection. Sinusitis can be localized, but more often is complicated by invasion into the orbit, the major cranial vessels, or the brain. Widespread hematogenous dissemination is common.

Diagnosis of infection with angioinvasive molds remains problematic. Biopsy evidence of tissue invasion is preferred but not easily obtained in immunosuppressed patients who are often thrombocytopenic. These organisms are ubiquitous in the environment so that a culture that yields one of these molds from sputum or bronchoalveolar lavage fluid may merely reflect contamination or colonization (15). On the other hand, in a markedly immunosuppressed host, a positive culture from sputum or bronchoalveolar lavage fluid is highly associated with invasive disease and provides firm evidence to initiate therapy (23). Rather than simply noting that a mold or an *Aspergillus* species has been isolated, the laboratory should be able to identify the specific species of *Aspergillus* and at least the genus of non-*Aspergillus* molds. This allows the clinician to choose the appropriate antifungal agent.

High-resolution chest computed tomography (CT) scans have assumed increasing importance in the diagnosis of angioinvasive fungal infection in patients in high-risk groups. Multiple nodular lesions are often found on CT scan when the chest radiograph reveals no abnormalities. The presence of nodular lesions that are surrounded by a ground glass appearance, the so-called halo sign, is an early finding in angioinvasive mold infections (24). Cavitation is a late sign of infection and not helpful for early diagnosis (25). CT scans of the sinuses and magnetic resonance imaging scans of the brain are helpful in establishing the extent of invasion into the orbit and the brain.

The treatment of mold infections has changed markedly in recent years. Previously, amphotericin B and itraconazole were the only available agents, but many non-*Aspergillus* molds were resistant to these agents and the mortality rate for aspergillosis remained over 80% for the highest risk groups (26). Voriconazole has become the agent of choice for invasive aspergillosis, based on superior outcomes in a controlled, randomized, blinded

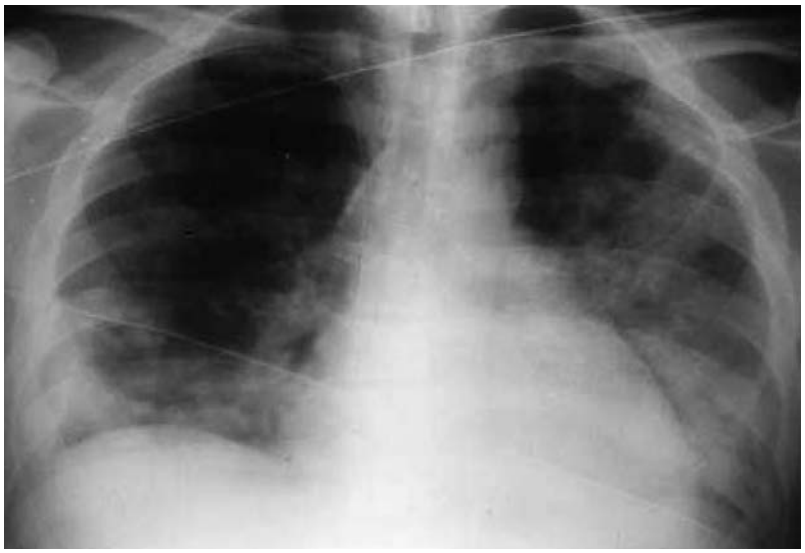

Figure 1. Chest radiograph of a liver transplant patient who developed infection with *Scedosporium apiospermum.*

treatment trial that compared voriconazole with amphotericin B (27). Voriconazole is also effective for the treatment of infections with *Scedosporium*, *Fusarium*, and other molds (28). However, the zygomycetes are resistant to voriconazole and must be treated with amphotericin B.

The echinocandins are useful in the treatment of aspergillosis, but not other angioinvasive fungi. They are most useful as second-line therapy and have not been studied as first-line therapy for invasive aspergillosis (29). Echinocandins are often combined with other agents, such as voriconazole, to treat seriously ill patients with aspergillosis (30). However, there are no controlled clinical trials showing that combination therapy is beneficial.

NEW ANTIFUNGAL AGENTS

Voriconazole

Voriconazole is a broad-spectrum triazole agent that is active against all species of *Candida*, including *C. krusei* and *C. glabrata*, and *Cryptococcus neoformans.* The drug is fungicidal for *Aspergillus* and other molds, including *S. apiospermum*, and many *Fusarium* species. The zygomycetes are resistant to voriconazole (31).

Voriconazole is available as both an intravenous and an oral formulation. Bioavailability of the oral formulation is approximately 95% when administered in the absence of food (32). Steady-state concentrations are reached quickly with either formulation by giving a loading dose twice that of the daily dose on the first day of therapy. Voriconazole distributes into many tissues and body fluids, including the eye, brain, and cerebrospinal fluid (33). However, because of extensive metabolism, active drug is not excreted into the urine. Voriconazole is extensively metabolized in the liver by several cytochrome P450 enzymes. Because of genetic differences in the activity of the major cytochrome enzyme that metabolizes voriconazole, the serum concentrations may vary considerably from person to person.

Dosage adjustments are necessary for patients with liver dysfunction. For those with mild to moderate liver disease, it is recommended that the daily dose be cut by half after administering the standard loading dose (32). The safety of voriconazole has not been studied in patients with severe liver disease. Voriconazole is not nephrotoxic. However, because the cyclodextrin vehicle in which the intravenous formulation is solubilized is cleared by glomerular filtration, patients with a creatinine clearance of less than 50 ml/min should not be treated with the intravenous formulation. They can be treated with the oral formulation.

The potential for drug–drug interactions with voriconazole is high (31). Inducers of cytochrome (CY)P450, such as rifampin, long-acting barbiturates, and carbamazepine, decrease voriconazole concentrations significantly and should be avoided. Voriconazole interferes with the metabolism of many drugs through inhibition of CYP450 enzymes. Sirolimus and ergot alkaloids produce life-threatening toxicity and are contraindicated. Other agents, such as tacrolimus, cyclosporine, and warfarin, should have the dosage reduced and levels monitored carefully (34, 35). Before prescribing voriconazole, advice from a knowledgeable clinical pharmacist should be sought.

The most common side effect of voriconazole, noted in almost a third of patients, is photopsia, which is manifested by bright spots, wavy lines, altered color discrimination, or blurred vision (36). These visual disturbances occur with both the intravenous and oral formulations. Symptoms usually occur during the first week of therapy, and in many patients will disappear in a few weeks even though therapy is continued.

Rash occurs in as many as 8% of patients treated with voriconazole. This can manifest as photosensitivity, and Stevens-Johnson syndrome also has been reported.

All azoles can cause hepatitis, and voriconazole may be more likely to cause this than other azoles (37). Patients should have liver function tests monitored before starting therapy, within the first 2 wk, and then every 4 wk throughout therapy. Mild asymptomatic elevation of hepatic enzymes can be monitored carefully and the drug continued. If enzyme elevations rise higher than fivefold the upper limit of normal, the drug should probably be discontinued. The risk of developing hepatitis appears to increase with increased serum voriconazole levels. Because of the potential for dose-related hepatotoxicity, the dosage of voriconazole should not be increased above that recommended by the manufacturer.

Voriconazole has become the drug of choice for the treatment of invasive aspergillosis. The move from amphotericin B to voriconazole followed the publication of a large, multinational, randomized trial that compared amphotericin B with vorioconzole in 277 patients with proved or probable invasive aspergillosis (27). At Week 12, complete or partial responses were noted in 53% of the voriconazole group and in 32% of the amphotericin B group. Survival was 71% in the voriconazole group and 58%

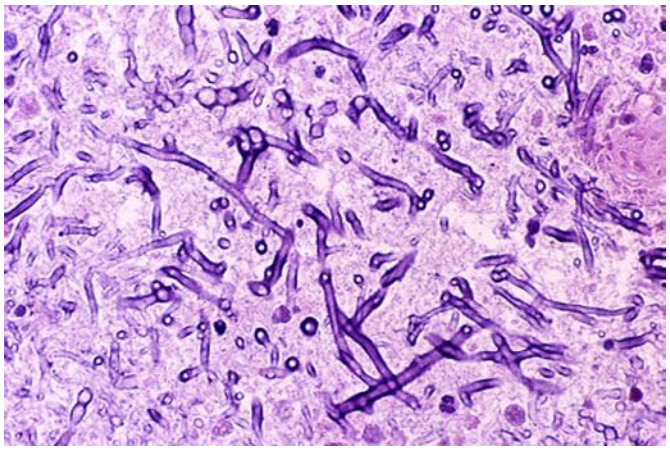

Figure 2. Histopathologic appearance of *S. apiospermum* in tissue from an open lung biopsy in this patient. The hyphae, which are septate and branch at acute angles, are indistinguishable from those seen with tissue invasion by *Aspergillus* species (silver methenamine stain).

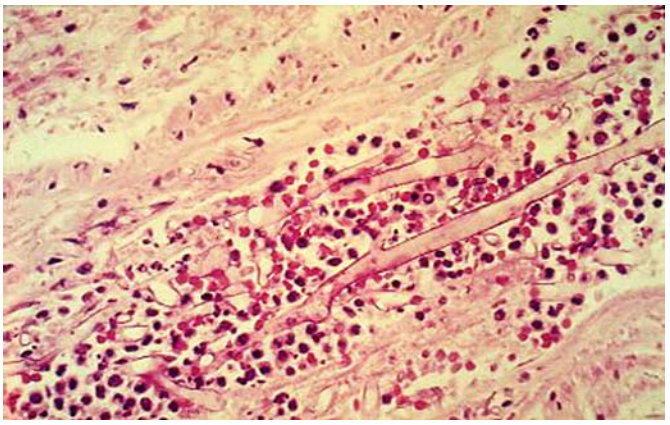

Figure 4. Broad, nonseptate right-angle branching hyphae of *Rhizopus* species invading an artery in the lung of a patient who died of zygomycosis (hematoxylin and eosin stain).

in the amphotericin B group. These results showed voriconazole to be more effective than amphotericin B as initial therapy for patients with invasive aspergillosis. Voriconazole is also the preferred treatment for *Scedosporium* and *Fusarium* infections and other angioinvasive fungal infections, with the exception of the zygomycocetes (28).

Voriconazole is approved for the treatment of invasive candidiasis and candidemia on the basis of recently published results of a multinational, randomized, blinded treatment trial that compared voriconazole to amphotericin (38). It appears to be effective for all species of *Candida*.

Echinocandins

The echinocandins are a new class of antifungal agents that act to inhibit synthesis of glucans present in the cell wall of certain fungi, leading to lysis and death of the organism (39). Echinocandins are cidal for all *Candida* species and are static against *Aspergillus* species. They are not active against other molds, *C. neoformans*, or the endemic mycoses. Three echinocandins, caspofungin, micafungin, and anidulafungin, have been developed; caspofungin and micafungin have been approved for use, and anidulafungin likely soon will receive approval.

All of the echinocandins are available only as intravenous formulations that generally are infused over an hour. These agents distribute into liver, spleen, lungs, and kidneys, but penetrate brain, eye, and cerebrospinal fluid very poorly. Active drug is not excreted into the urine.

Although there are some differences in metabolism of the three echinocandins, in general, these compounds are hydrolyzed and then acetylated to metabolites that have no antifungal activity. There are few if any drug interactions with micafungin and anidulafungin; there are a few interactions that occur with caspofungin and drugs, such as rifampin and phenytoin, that induce CYP450 enzymes (40).

A strong point in favor of the echinocandins is that they have minimal side effects (40, 41). Infusion-related reactions, such as flushing, fever, and chills, occur uncommonly and are lessened by slowing the infusion rate. Rash, pruritus, headache, nausea, vomiting, and phlebitis have been reported infrequently. It is not clear if the echinocandins cause hepatitis. Elevations of serum liver enzyme values have been reported in 11 to 24% of patients in clinical trials, but were no more common than in patients treated with fluconazole or amphotericin B. It is prudent to monitor serum liver enzyme levels in patients receiving these drugs.

Caspofungin has been shown to be as effective as amphotericin B for the treatment of candidemia and invasive candidiasis. Overall, 73% of caspofungin-treated patients versus 62% of amphotericin B–treated patients had a successful outcome in one multinational, blinded, randomized treatment trial (13). Caspofungin is also approved for the treatment of aspergillosis in patients whose disease is refractory to standard therapy or who are unable to tolerate other antifungal therapy on the basis of the results of a salvage treatment trial. The success rate of 41% reported in that trial compared favorably with that noted in historical control subjects (29). There have been no prospective, comparative trials of caspofungin or the other echinocandins as primary therapy for invasive aspergillosis, and thus most recommendations are to use these agents as second-line therapy.

It is possible that the echinocandins will become useful agents when used in combination with either amphotericin B formulations or triazoles. Given their unique mechanism of action on the cell wall, combining an echinocandin with an agent that acts at a different target, the cell membrane, may produce synergistic

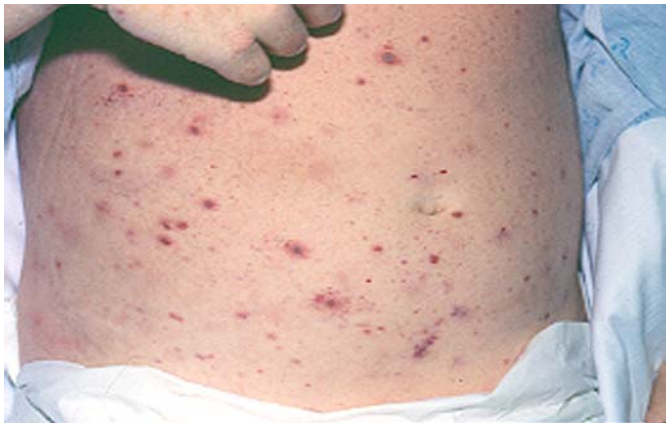

Figure 3. Multiple nodular skin lesions noted in a patient who had acute leukemia and who developed disseminated infection with *Fusarium* species. (Photo coutesy of Dimitrios Kontoyiannis, M.D., University of Texas M.D. Anderson Cancer Center, Houston, TX.).

killing of the fungal organism. Reports from several cancer centers have noted improved outcomes when combination therapy was used, but these studies all compared results with historical control subjects treated with one agent (30, 42, 43). It is clear that antagonism does not occur, and with the exception of increased risk for drug-related side affects, combination therapy is unlikely to be harmful. Currently, no firm recommendations can be made about combination therapy; physicians must decide when and if this might be useful for individual patients.

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