

An Official American Thoracic Society Statement: Treatment of Fungal Infections in Adult Pulmonary and Critical Care Patients

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With increasing numbers of immune-compromised patients with malignancy, hematologic disease, and HIV, as well as those receiving immunosuppressive drug regimens for the management of organ transplantation or autoimmune inflammatory conditions, the incidence of fungal infections has dramatically increased over recent years. Definitive diagnosis of pulmonary fungal infections has also been substantially assisted by the development of newer diagnostic methods and techniques, including the use of antigen detection, polymerase chain reaction, serologies, computed tomography and positron emission tomography scans, bronchoscopy, mediastinoscopy, and video-assisted thorascopic biopsy. At the same time, the introduction of new treatment modalities has significantly broadened options available to physicians who treat these conditions. While traditionally antifungal therapy was limited to the use of amphotericin B, flucytosine, and a handful of clinically available azole agents, current pharmacologic treatment options include potent new azole compounds with extended antifungal activity, lipid forms of amphotericin B, and newer antifungal drugs, including the echinocandins. In view of the changing treatment of pulmonary fungal infections, the American Thoracic Society convened a working group of experts in fungal infections to develop a concise clinical statement of current therapeutic options for those fungal infections of particular relevance to pulmonary and critical care practice. This document focuses on three primary areas of concern: the endemic mycoses, including histoplasmosis, sporotrichosis, blastomycosis, and coccidioidomycosis; fungal infections of special concern for

immune-compromised and critically ill patients, including cryptococcosis, aspergillosis, candidiasis, and *Pneumocystis pneumonia*; and rare and emerging fungal infections.

Keywords: fungal pneumonia; amphotericin; triazole antifungal; echinocandin

The incidence, diagnosis, and clinical severity of pulmonary fungal infections have dramatically increased in recent years in response to a number of factors. Growing numbers of immune-compromised patients with malignancy, hematologic disease, and HIV, as well as those receiving immunosuppressive drug regimens for the management of organ transplantation or autoimmune inflammatory conditions, have significantly contributed to an increase in the incidence of these infections. Definitive diagnosis of pulmonary fungal infections has also increased as a result of advances in diagnostic methods and techniques, including the use of computed tomography (CT) and positron emission tomography (PET) scans, bronchoscopy, mediastinoscopy, and video-assisted thorascopic biopsy. At the same time, the introduction of new treatment modalities has significantly broadened options available to physicians who treat these conditions. Once largely limited to the use of amphotericin B, flucytosine, and a handful of clinically available azole agents, today's pharmacologic treatment options include potent new azole compounds with extended antifungal activity, novel lipid forms of amphotericin B, and a new class of antifungal drugs known as echinocandins. In light of all these developments in the incidence, diagnosis, and treatment of pulmonary fungal infections, the American Thoracic Society convened a working group on fungi to develop a concise clinical summary of the current therapeutic approaches for those fungal infections of particular relevance to pulmonary and critical care practice. This document focuses on three primary areas of concern: the endemic mycoses, including histoplasmosis, sporotrichosis, blastomycosis, and coccidioidomycosis; fungal infections of special concern for immune-compromised and critically ill patients, including cryptococcosis, aspergillosis, candidiasis, and *Pneumocystis pneumonia*; and rare and emerging fungal infections.

METHODS

For each fungal infection evaluated, the available literature has been thoroughly reviewed and interpreted by the experts involved in this statement. In the search for published evidence, workgroup members reviewed journal articles and previously published guidelines, and conducted an evaluation of electronic databases, including PubMed and MEDLINE. In general, only articles written in English were used in the final recommenda-

TABLE 1. CATEGORIES INDICATING THE STRENGTH OF EACH RECOMMENDATION FOR OR AGAINST ITS USE IN THE TREATMENT OF FUNGAL INFECTIONS

Category	Definition
A	Good evidence to support a recommendation for use
B	Moderate evidence to support a recommendation for use
C	Poor evidence to support a recommendation for or against use
D	Moderate evidence to support a recommendation against use
E	Good evidence to support a recommendation against use

tions. The most relevant literature references are included in this publication. Discussion and consensus among workgroup members formed the basis for the recommendations made in this statement. The authors reviewed the evidence base for each major recommendation of this consensus statement and graded according to an approach developed by the U.S. Preventive Services Task Force (Tables 1 and 2). Although the American Thoracic Society (ATS) and Infectious Disease Society of America (IDSA) have recently adopted the GRADE approach to grading the quality of evidence and strength of recommendations for clinical guidelines, the current project was initiated and much of the work was completed prior to the official adoption of GRADE. The recommendations included were, therefore, graded according to the system used in prior guidelines (1–3). Each section also includes expert interpretations regarding the best approach for challenging clinical situations that have not been well studied in the literature, but that are the basis for frequent consultation of the members of the ATS working group on fungal infections. For convenience, a glossary of definitions of uncommon terms is also included at the end of the document.

Each member of the writing committee has declared any conflict of interest, and every effort was made by the Chair as adjudicator to ensure that recommendations were free of any real or perceived conflict of interest; however, it should be noted that the process predates the official development and adoption of the revised ATS Conflict of Interest guidelines in 2008 (4).

ANTI-FUNGAL AGENTS: GENERAL CONSIDERATIONS

In most cases, treatment of fungal infections must be based on the causative fungus, the severity of disease, and the clinical features of each patient. Specific guidelines for therapy, including dosing recommendations, are included in subsequent sections under specific organisms and infection site(s). This section will provide general comments about the major classes of available antifungal agents, including novel agents such as extended-spectrum triazoles and echinocandins.

Polyenes

The prototype of the polyenes is amphotericin B deoxycholate (amphotericin B), which continues to be a fundamental treatment option for severe fungal infections, particularly life-threatening illnesses, including aspergillosis, cryptococcosis, systemic candidiasis, and severe cases of histoplasmosis, blastomycosis, coccidioidomycosis, and zygomycosis. Polyenes act by binding to sterols in the fungal cell membrane, forming a transmembrane channel that precipitates cell leakage and death. Amphotericin B is administered intravenously, and is associated with a broad range of side effects. Careful monitoring during therapy should focus on serum creatinine, blood urea nitrogen, serum electrolytes (particularly potassium and magnesium), complete blood counts, and liver function tests, and monitoring should be conducted at least weekly during therapy, or even daily in the presence of renal insufficiency. Because the renal toxicity of amphotericin B can develop precipitously, we recom-

TABLE 2. GRADES OF EVIDENCE QUALITY ON WHICH RECOMMENDATIONS ARE BASED

Grade	Definition
I	Evidence from at least 1 properly randomized, controlled trial Evidence from at least 1 well-designed clinical trial without randomization, from cohort or case-controlled analytic studies (preferably from > 1 center), from multiple patient series studies, or from dramatic results of uncontrolled experiments
II	Evidence from opinions of respected authorities, that is based on clinical experience, descriptive studies, or reports of expert committees.
III	

mend that patients with any degree of renal insufficiency be more closely monitored. Many experienced clinicians pre-medicate patients with antipyretics, antihistamines, anti-emetics, or meperidine to decrease the common febrile reaction and shaking chills associated with infusion (BIII). Meperidine is most effective for ameliorating the severe rigors. Rapid intravenous administration of amphotericin B has been observed to precipitate life-threatening hyperkalemia and arrhythmias (5); therefore, the daily dose of amphotericin B deoxycholate should be infused over 2 to 6 hours. Hypotension and shock have also occasionally been observed during amphotericin B infusion. Amphotericin B should not be administered simultaneously with leukocytes, as this may possibly precipitate pulmonary toxicity (6). There appears to be an additive, and possibly synergistic, nephrotoxicity with other nephrotoxic agents such as aminoglycoside antibiotics (7). Adequate intravenous fluid hydration has been shown to reduce the risk of nephrotoxicity (8). In complicated patients, consultation with an experienced clinical pharmacist or use of tools such as software programs that delineate drug interactions, particularly those with suspected synergistic nephrotoxicity or those requiring renal clearance, is recommended. Additional side effects are common, and may include hypokalemia, phlebitis/thrombophlebitis, anorexia and weight loss, fever and chills, headache and malaise, and cardiac dysrhythmias. Liver toxicity may also occur, but its incidence is rare compared with renal toxicity. Nephrotoxicity and other untoward side effects of amphotericin B deoxycholate are largely dose-dependent. In clinical situations that require doses of amphotericin B deoxycholate greater than or equal to 1.0 mg/kg/day, strong consideration should be given to using lipid formulations of amphotericin to avoid the potentially high incidence of toxic side effects (*see below*) (BIII).

In addition to amphotericin B deoxycholate, two different lipid-associated formulations have been developed and are in current use: liposomal amphotericin B and amphotericin B lipid complex. These agents have variable dosing schedules and toxicities, but, in general are significantly less nephrotoxic than amphotericin B deoxycholate. Data concerning the improved efficacy of any amphotericin lipid formulation over amphotericin B deoxycholate are limited. So far, the clearest indication for use of a lipid formulation is to reduce renal toxicity (AII), which is an especially important consideration in patients who have underlying nephrotoxicity or in those who are receiving multiple concomitant nephrotoxic drugs. For diseases where dosing of amphotericin B at 1.0 mg/kg/day or higher is standard, the intrinsic nephrotoxicity of amphotericin B itself dictates preferred use of lipid formulations. As with standard amphotericin B formulations, monitoring for side effects during therapy should include measurement of serum creatinine, blood urea nitrogen, and serum electrolytes (particularly potassium and magnesium), complete blood counts, and liver function tests which should be performed at least weekly during therapy, or even daily in the presence of renal insufficiency. Theoretically, lipid formulations of amphotericin might have some benefit of higher central

nervous system (CNS) penetration, especially when given in higher doses, although conclusive clinical data to support this approach in treatment of fungal meningitis are lacking.

Recommendation. Among patients with renal insufficiency or among those individuals who are receiving multiple concomitant nephrotoxic drugs, we suggest a lipid formulation of amphotericin B to reduce renal toxicity (DII).

Remark. In certain clinical situations that require doses of amphotericin B deoxycholate greater than or equal to 1.0 mg/kg/day, the incidence of such toxicities is high, and lipid formulations of amphotericin are associated with fewer adverse effects, and therefore may be preferred.

Triazoles

The azole antifungal agents contain three nitrogen atoms within the basic ring. Triazoles in clinical use include ketoconazole, itraconazole, fluconazole, voriconazole, and posaconazole. Triazoles target the 14- α -demethylase enzyme, which mediates the conversion of lanosterol to ergosterol in the fungus. Interactions of azole drugs with human P450 cytochromes have been well documented (9). Therefore, azole-related drug interactions are especially problematic in immunocompromised hosts, particularly transplant patients and those infected with HIV. In these populations, decreased plasma concentration of the azole may occur as a result of increased metabolism, or of increases or decreases in concentrations of co-administered drugs. With most of the azole compounds, interactions occur with many such drugs, particularly cyclosporine, benzodiazepines, statins, and certain anti-HIV drugs, as a result of altered rates of drug metabolism and induction of the relative P450 enzymes (10). The use of azoles is contraindicated during pregnancy; in these patients, amphotericin is preferred, as amphotericin B and its lipid derivatives are rated class B for pregnancy. By contrast, fluconazole, itraconazole, and posaconazole are class C drugs, while voriconazole is a class D drug. Earlier generation azoles such as ketoconazole also have adverse effects on steroid hormone levels and adrenal function (11).

Itraconazole. Modifications to the azole structure have led to additional extended spectrum antifungals. For instance, itraconazole contains a four-ring lipophilic tail that enhances its interactions with the CYP51 cytochrome, rendering it active against molds. Itraconazole is effective for some *Aspergillus* infections, mucosal candidal infections, histoplasmosis, blastomycosis, coccidioidomycosis, and other fungal infections (12). Unfortunately, due to itraconazole's high protein binding and poor CNS penetration, it is not an optimal choice for CNS infections. Itraconazole is available as either oral capsules or an oral solution. The oral capsules require gastric acid for absorption, and so are usually taken with food or acidic beverages. In addition, concurrent use of proton pump inhibitors and antacids should be avoided. To overcome problems with variable drug absorption, particularly in settings in which proton pump inhibitors must be administered concurrently, itraconazole has been solubilized in a cyclodextrin solution, resulting in substantial improvement in absorption (13). In contrast to the capsule form, the oral solution requires an empty stomach. Because of the widespread use of antacids, H₂ blockers, and proton pump inhibitors, the committee recommends thoughtful consideration of the optimal form to use. When using oral itraconazole, it is important to routinely assure that adequate levels of itraconazole are present in serum (AII). The bioassays used to measure the antifungal activity of serum reflect all active antifungal substances that are present in the serum at the time of testing, and therefore may not specify the level of the unique agent of interest. In contrast, the high-performance liquid chromatography (HPLC) method measures the actual concentration of the specific compound in question in the serum

or other body fluids. The report usually provides the concentration of the parent compound and its active metabolites, but does not take into account binding of active drug, because of the extraction process, used before the assay. Thus, the target range provided by the lab for each particular assay should be followed when making dose adjustments. Dosage adjustments of orally administered itraconazole are not required in patients with renal impairment, and do not appear to be required during hemodialysis. Itraconazole is extensively metabolized in the liver, and caution should be employed in patients with significant liver insufficiency (12).

Contraindications to itraconazole use include previous hypersensitivity to itraconazole or co-administration of cisapride, dofetilide, midazolam, pimozide, levacetylmethadol, quinidine, statin medications, triazolam, and other agents. Precaution should be used in patients with severe congestive heart failure (CHF), achlorhydria, hepatic dysfunction, or hypersensitivity to other azoles. Side effects of itraconazole are rare and may include rash, diarrhea, and nausea. Serious, though uncommon, side effects include worsening of CHF, Stevens-Johnson syndrome, and hepatotoxicity. As with other azole compounds, interactions occur with many such drugs, particularly cyclosporine, benzodiazepines, statins, certain anti-HIV drugs, and many other agents related to its metabolism by the P450 cytochrome system (10). Pharmacy and medication cross-reference resources should be consulted whenever instituting treatment.

Fluconazole. In the 1990s, fluconazole joined this class of antifungals, offering a reduced lipophilicity that allows for easier administration. This agent has been shown to have good activity against *Candida albicans*, and is used for prevention and treatment of both mucosal and invasive diseases. Fluconazole also has significant activity in cryptococcosis and coccidioidomycosis. Dose adjustments are recommended in renal impairment, and dosages are reduced by 50% when the creatinine is less than 50 ml/minute. Patients on hemodialysis require replacement of the entire dosage after each dialysis session (14). Contraindications to fluconazole therapy include known hypersensitivity to the agent. Side effects are generally uncommon, but can include skin rash and pruritus, nausea and vomiting, increased liver enzymes, and headache. Anaphylactic reactions are generally rare for all azoles. Compared with other azole antifungal agents, such as itraconazole, voriconazole, and posaconazole, drug-drug interactions are relatively less common with fluconazole, as the drug is a relatively less active inhibitor of P450. Prescribing physicians should generally consult pharmacy and medication cross-reference resources when initiating treatment.

Voriconazole. Voriconazole is a newer azole antifungal that is increasingly being used for invasive aspergillosis and other mold infections. As with most other azoles, the drug is contraindicated in patients receiving co-administration of P450-CYP3A4 substrates, including fexofenadine, astemizole, pimozide, or quinidine, as these interactions may lead to increased plasma concentrations of these drugs, electrocardiographic Q to T wave interval (QT) prolongation and, rarely, torsades de pointes. In addition, coadministration of rifampin, carbamazepine, barbiturates, ritonavir, and efavirenz should be avoided. Voriconazole should be used with caution in patients with hypersensitivity to other azole antifungal agents, or with hepatic cirrhosis. Due to the cyclodextrin component, intravenous preparations of voriconazole should be used with caution in patients with renal insufficiency (creatinine clearance <50 ml/min), as the cyclodextrin vehicle may accumulate. Although there are no direct data that indicate that the cyclodextrin in intravenous voriconazole is in fact nephrotoxic, the oral form can be used instead. Dose adjustments are not necessary for oral voriconazole in patients with mild to moderate renal impairment. If intravenous

voriconazole is absolutely necessary in patients with moderate or severe renal insufficiency (creatinine clearance < 50 ml/min), serum creatinine should be monitored closely. For patients receiving hemodialysis, the removal of the drug by hemodialysis is not sufficient to warrant dosage adjustment. Voriconazole should not be used in patients with severe hepatic insufficiency, unless the benefits outweigh the risk of liver problems. Patients also need to avoid direct sunlight, since photosensitivity reactions can occur. Side effects include peripheral edema, rash, nausea, vomiting, and liver dysfunction. Severe liver dysfunction and failure have rarely occurred (15). Visual disturbance (scotomata) occurs in approximately one-third of patients, but the condition is rapidly reversible, and will abate within minutes to hours following discontinuation of the agent (16). Some reports suggest that cutaneous malignancies have been associated with voriconazole use. Metabolism of the drug can be variable, and recent experience indicates a potential need for monitoring of serum levels. Again, drug interactions are common, and medication cross-reference resources should be consulted when instituting therapy.

Posaconazole. Posaconazole has received FDA approval for use as prophylaxis against invasive fungal infections in severely immunocompromised patients and for treatment of oropharyngeal candidiasis that is refractory to fluconazole and itraconazole. In addition, this agent has proven effective when used as salvage therapy in severely immunocompromised patients with refractory infection with *Aspergillus* species (17), and as a treatment for coccidioidomycosis (18). The agent also displays activity against zygomycetes (19) and a variety of other fungi. Posaconazole is contraindicated in patients receiving ergot alkaloids, and in those receiving terfenadine, astemizole, pimozone, or quinidine, as these interactions may lead to increased plasma concentrations of these drugs with QT prolongation (20). Common adverse effects include diarrhea and abdominal discomfort, and serious side effects include occasional hepatic dysfunction, in addition to long QT syndrome. Posaconazole has saturable absorption, requiring adequate dietary fat that limits oral dosing to approximately 800 mg per day. The optimal way to provide the drug is 200 mg four times per day, and with fatty meals when possible. Dose adjustments for posaconazole are not necessary in patients with mild to severe hepatic insufficiency or renal impairment. Dose adjustments are also not necessary after dialysis. Appropriate clinical monitoring is indicated, including liver function tests at the start and during the course of therapy, and assessment of serum potassium, magnesium, and calcium levels, with rigorous correction of levels as needed before initiating therapy. As additional drug interactions may emerge, medication cross-reference resources should be consulted when instituting treatment.

Recommendations. In patients receiving itraconazole, voriconazole, or posaconazole, we recommend measurements of drug levels in serum to be certain that the drug is being absorbed and to guide treatment (AII).

In patients with renal insufficiency (creatinine clearance < 50 ml/min), we suggest reducing the dose of fluconazole by 50% (BIII).

Remark. Patients undergoing hemodialysis require redosing after each dialysis session.

Echinocandins

The echinocandins are an entirely novel class of antifungal agents that disrupt fungal cell walls through inhibition of the 1,3- β -glucan synthase complex. Thus, they have been referred to as the "penicillins of the antifungal armamentarium." Currently, three agents are available: caspofungin, micafungin, and anidulafungin.

Caspofungin. Caspofungin exhibits fungicidal activity against *Candida* species and fungistatic activity against *Aspergillus* species. Caspofungin has been used primarily for candidiasis, treatment of febrile neutropenia, and for salvage therapy of invasive aspergillosis. Laboratory studies support activity against *Pneumocystis* species and some other fungal infections, although clinical data are lacking (21, 22). Caspofungin is only administered via intravenous infusion, with dosage adjustment being required in the case of hepatic impairment. The medication is contraindicated in patients with hypersensitivity, and precaution should be exercised in patients with liver impairment, those who are pregnant, and those concomitantly receiving cyclosporine. Common side effects include increased liver enzymes, nausea, facial swelling, headache, and pruritus. Notably, caspofungin and the other echinocandins are not inhibitors or inducers of the cytochrome metabolism enzymes. However, drug-drug interactions may still be observed, especially with cyclosporine and tacrolimus, rifampin, and certain anti-HIV drugs.

Micafungin. Like caspofungin, micafungin also has activity against *Candida* and *Aspergillus* species. This agent has been approved for treatment of invasive candidiasis, for prophylaxis of stem cell transplantation patients against *Candida*, and for *Candida* esophagitis (23). Precaution should be used in patients with prior hypersensitivity to other echinocandins. Serious hypersensitivity reactions, including anaphylaxis and shock, have rarely occurred. Side effects include phlebitis; rash; abdominal discomfort with nausea, vomiting, or diarrhea; and hyperbilirubinemia.

Anidulafungin. Anidulafungin is the most recently approved echinocandin, and has received approval for use in candidemia, candidiasis, and candidal esophagitis, with additional activity exhibited against *Aspergillus* species (22). Studies of its relative activity in comparison to other agents are underway. This agent is generally well tolerated, but should be infused slowly. Common side effects include diarrhea and hypokalemia. Serious adverse reactions include deep vein thrombosis and, rarely, liver toxicity. The drug should be used cautiously in patients with liver dysfunction, and appropriate clinical monitoring should be implemented in these patients. At present, all three of the currently licensed echinocandins should be viewed as equally effective for candidemia.

TREATMENT OF HISTOPLASMOSIS

Histoplasma capsulatum is a dimorphic fungus that is endemic to the Ohio, Missouri, and Mississippi River valleys in the United States, as well as some river valleys in Central America. Severity of illness after inhalational exposure to *Histoplasma capsulatum* depends on the intensity of exposure, as well as the immune status and underlying lung architecture of the host, and plays a major role in treatment decisions (Table 3). The chronic manifestations of healed histoplasmosis will be briefly mentioned and, as a rule, do not require specific antifungal therapy. In all instances, severe progressive disseminated disease, as well as CNS involvement, require initial treatment with amphotericin B, while mild to moderate disease can usually be treated with itraconazole (AII).

Pulmonary Nodules

Although not treated with antifungal agents, asymptomatic pulmonary nodules due to recent or remote *Histoplasma* exposure are common and diagnostically challenging, as they mimic malignancy. Often these nodules are biopsied or excised, and may on occasion stain positively for *Histoplasma*. Universally, when *Histoplasma* cannot be cultured, antifungal treatment is not recommended (EIII). The time to calcification is variable and cannot generally be used alone to absolutely

TABLE 3. TREATMENT RECOMMENDATIONS FOR HISTOPLASMOSIS

Disease Manifestation	Treatment Recommendations	Comments
Mild pulmonary histoplasmosis; therapy deemed necessary	Itraconazole (200 mg twice daily for 12 wk)	Liposomal amphotericin is preferred in patients with renal insufficiency.
Moderately to severely ill pulmonary histoplasmosis	Amphotericin B (0.7 mg/kg/day) ± corticosteroids for 1–2 wk, then itraconazole (200 mg twice daily for 12 wk)	Consider itraconazole serum level at 2 wk of therapy. Monitor renal and hepatic function.
Chronic pulmonary histoplasmosis	Itraconazole (200 mg twice daily for 12–24 mo)	Continue treatment until no further radiographic improvement. Monitor for relapse after treatment is stopped. Itraconazole serum level at 2 wk, then every 3–6 mo recommended.
Progressive disseminated histoplasmosis	Lipid formulation amphotericin B (3–5 mg/kg/d) or amphotericin B (0.7–1.0 mg/kg/d for 1–2 wk), then itraconazole (200 mg twice daily for 12 mo)*	Chronic maintenance therapy may be necessary if immunosuppression cannot be reduced. Monitoring antigen levels may be useful. Monitor renal and hepatic function.

* For mild to moderate disease in progressive disseminated histoplasmosis, itraconazole 200 mg twice daily for 12 mo may be an option.

distinguish from malignancy, though some reveal typical central and concentric calcification on CT imaging, which is suggestive of being benign. Moreover, many nodules never calcify. PET scans can also show increased uptake in these histoplasma-induced lesions (24). The decision to pursue diagnosis in this patient population depends on many factors, including smoking status, chronicity, and patient preference. In patients who are symptomatic with pulmonary nodule(s) and associated chest adenopathy, recent infection is presumed and treatment with antifungal agents may be warranted depending on disease severity, as discussed below for the immunocompetent host.

Broncholithiasis

Broncholithiasis occurs when calcified lymph nodes erode into the airway, causing symptoms of dyspnea, wheezing, or hemoptysis. Many times these are managed conservatively and the patient may spontaneously cough the broncholith out of the airway. In instances in which the patient requires intervention, bronchoscopic evaluation is first recommended (BIII). Removing a partially or completely eroded broncholith can usually be safely performed at the time of bronchoscopic evaluation (25), but surgical intervention may be required if broncholithiasis is complicated by obstructive pneumonia, fistula formation, or massive hemoptysis (BIII) (26). Antifungal treatment is not generally recommended (BIII).

Fibrosing Mediastinitis

Fibrosing mediastinitis is uncommon, but is often progressive with distortion and compression of major vessels and central airways. It must be differentiated from granulomatous mediastinitis related to recent infections, malignancy, and chronic pulmonary thromboembolism. Patients may experience symptoms for years prior to diagnosis. Fibrosing mediastinitis can be fatal and, despite lack of proven therapy, some clinicians recommend a 12-week course of itraconazole at 200 mg twice daily (CIII) (27, 28). If radiographic or physiologic improvement is obvious, therapy should be considered for 12 months. The use of corticosteroids is not routinely recommended (DIII), and the role of antifibrotics (for example, tamoxifen) are unclear (CIII) (29). Intravascular stents may be useful in appropriately selected patients—typically those with advanced disease, open airways, and severe manifestations of vascular compromise (BIII) (30). The algorithm for compressive disease of the airway is complicated. The committee suggests considering balloon bronchoplasty, followed by consultation with a surgeon specializing in mediastinal disease, and endobronchial stenting (CIII). Stenting of the airway in benign disease is reserved for those with no other options, and a removable silicone stent is initially preferred (CIII). Endobronchial laser

therapy has been used for hemoptysis related to fibrosing mediastinitis and hyperemic airways (31).

Immunocompetent Hosts with Symptomatic Histoplasma Pneumonia, or with Progressive or Severe Disease

Because healthy individuals with progressive disease are uncommon, recommendations for treatment of immunocompetent patients are based primarily on expert opinion. In healthy individuals, asymptomatic infection follows low-intensity exposures and typically requires no therapy (32). Because effective and minimally toxic oral therapy is now available, 200 mg itraconazole twice daily for up to 12 weeks is appropriate therapy for patients who remain symptomatic after 3 weeks of observation (BIII). In contrast, inhalation exposure to a large inoculum may cause severe pulmonary infection with massive mediastinal lymphadenopathy, hypoxemia, respiratory failure, and acute respiratory distress syndrome (ARDS), even in healthy individuals. In patients with life-threatening pulmonary infections, including patients with severe gas-exchange abnormality, severe toxicity, and rapid progression, amphotericin B deoxycholate (0.7 mg/kg/d) or a lipid formulation of amphotericin (5 mg/kg/d) should be used initially in these severely ill patients (AIII), followed by itraconazole 200 mg twice daily to complete at least a 12-week course once the patient clinically improves (BIII). Initiating therapy with itraconazole 200 mg twice daily for 12 weeks is recommended for patients with mild or moderate disease (BIII). The role of corticosteroids in acute infection is controversial. Patients with hypoxemia associated with diffuse infiltrates and patients with massive granulomatous mediastinitis may benefit as long as steroid therapy is used in combination with antifungal therapy (CIII). The panel felt that prednisone 40–60 mg/day for 1 to 2 weeks was an appropriately conservative regimen (CIII).

Immunocompromised Hosts

In immunosuppressed patients, progressive disseminated histoplasmosis occurs and amphotericin B (0.7–1.0 mg/kg/d to clinical improvement or up to a total of 2 g), or a lipid formulation of amphotericin (3–5 mg/kg/d), is the initial recommendation for patients who are sufficiently ill to require hospitalization. This should be followed by itraconazole, 200 mg twice daily for 12 months once clinical improvement is noted (AII). In one study, initial treatment of patients with AIDS with liposomal amphotericin B (AmBisome) showed a survival benefit (33) (BI). However, patients treated with amphotericin B deoxycholate in this study inadvertently had more severe disease activity, which may have influenced the results in favor of liposomal amphotericin B. Patients with mild to moderate disease can be treated with itraconazole monotherapy. A loading dose of 200 mg three

times daily is recommended for the first 3 days of therapy, followed by 200 mg twice daily for 12 months (AII) (34). Monitoring of itraconazole levels is useful and should be performed using either the bioassay or HPLC methods. Therapeutic reference ranges should be obtained from the local laboratory and testing method, since the effective range will vary with the method employed. In general, the bioassay therapeutic range is believed to be between 1 and 10 $\mu\text{g/ml}$. The reference ranges for various HPLC assays vary by the methods used, though they are generally in ranges three to five times lower than those obtained through bioassay methods.

Patients with HIV and AIDS may require prolonged itraconazole maintenance therapy (e.g., itraconazole 200 mg twice daily) after appropriate initial therapy (35). However, when effective immune reconstitution occurs, maintenance therapy generally can be safely discontinued when CD4 counts greater than 200/ μl are achieved (36) (BII). In those patients who remain immunosuppressed and require lifelong maintenance therapy, *Histoplasma* polysaccharide antigen levels, checked several times a year, should be monitored in urine and serum, as a rise in antigen levels may predict relapse (BIII). The use of glucocorticoids in immunocompromised patients with severe hypoxemia and diffuse infiltrates, such as in the setting of immune reconstitution inflammatory syndrome which can occur with histoplasmosis, remains poorly studied and controversial (37). However, the writing group felt that prednisone 40–60 mg/day for 1 to 2 weeks was an appropriately conservative regimen if deemed useful on a patient-by-patient basis (CIII). Patients with AIDS who live in endemic areas, particularly those who do not exhibit significant immune reconstitution through HAART reflected by CD4 cells greater than 200/ μl , or those with a high likelihood of occupational or recreational exposure, may be considered for prophylaxis with itraconazole 200 mg/day (38); however, whether the benefits outweigh the cost and risk is not well established (BII). In addition, recent treatment with anti-tumor necrosis factor- α (TNF- α) agents has also been associated with histoplasmosis, as well as other endemic and opportunistic fungal infections (39). Clinicians should be aware of this association and have a high index of suspicion for this diagnosis in such patients. In addition, adrenal insufficiency has been estimated to complicate disseminated histoplasmosis in 7% of cases, and this possibility should be considered, particularly in patients who do not respond well to therapy (40).

Patients with underlying structural lung disease (particularly emphysema) may develop “chronic pulmonary histoplasmosis.” This condition has been observed during histoplasmosis outbreaks when acute infection occurs in patients with centrilobular emphysema or other forms of upper lobe structural disease. The clinical and radiographic findings may resemble those classically seen in reactivation tuberculosis, and infection is likely to progress if not treated (41). However, it needs to be emphasized that current concepts indicate that chronic pulmonary histoplasmosis does *not* represent reactivation of a prior infection (42). Treatment failures commonly occur and provide a rationale for prolonged treatment (43). Itraconazole given at 200 mg twice daily for 12 to 24 months is the current treatment of choice for chronic pulmonary histoplasmosis (AIII). Itraconazole levels should be monitored to verify that the patient is absorbing the agent. Amphotericin B can alternatively be used if clinical severity warrants (41). *Histoplasma* antigen testing, complement fixation titers, and gel diffusion tests have no role in following treatment efficacy in patients with chronic pulmonary histoplasmosis.

Although older studies suggest that fluconazole and ketocanazole can be used to treat both acute and chronic pulmonary histoplasmosis, they are inferior to itraconazole and should be used only in special circumstances or when itraconazole is not

tolerated (DII). Voriconazole and posaconazole are active against *H. capsulatum* and have been successfully used in salvage therapy (44–48). The echinocandins do not appear to be an effective treatment for *Histoplasma* infection (49).

Recommendations. IMMUNOCOMPETENT HOSTS WITH *HISTOPLASMA*-RELATED PULMONARY NODULES, BRONCHOLITHIASIS, OR FIBROSING MEDIASTITIS. Among asymptomatic patients with pulmonary nodules in whom *Histoplasma* cannot be cultured, we recommend that antifungal treatment not be used (DI).

In most patients with broncholithiasis, we recommend that antifungals not be used (BIII).

In selected patients with broncholithiasis who require intervention, such as those with significant hemoptysis, we suggest bronchoscopic evaluation and removal of the broncholith either bronchoscopically or surgically (BII).

Among selected patients with broncholithiasis complicated by obstructive pneumonia, fistula, or massive hemoptysis, we suggest surgical intervention (BII).

In patients with fibrosing mediastinitis, some clinicians recommend itraconazole 200 mg twice daily for 12 weeks (CIII). In patients with radiographic or physiologic improvement after an initial 12 weeks of therapy, we suggest longer treatment, up to 12 months (CIII). In these patients, we also suggest that antifibrotic agents and systemic glucocorticosteroids not be used (DII).

In selected patients with fibrosing mediastinitis and severe vascular or airway compromise, we suggest placing intravascular stents (BII), bronchoplasty, and/or placing endobronchial stents, if appropriate expertise is available (BIII). If a decision is made to place a stent, we suggest initially using removable stents (BIII).

IMMUNOCOMPETENT HOSTS WITH SYMPTOMATIC, PROGRESSIVE, OR SEVERE PULMONARY HISTOPLASMOSIS. In asymptomatic patients, we recommend that no antifungal treatment be used (BII).

In symptomatic patients with mild pulmonary histoplasmosis, who remain symptomatic after 3 weeks of observation, we suggest itraconazole 200 mg twice daily for up to 12 weeks (BIII).

In selected patients with mild to moderate pulmonary histoplasmosis, we suggest initiating treatment with itraconazole 200 mg twice daily rather than with amphotericin B (BIII).

In patients with severe pulmonary histoplasmosis, such as those with life-threatening pulmonary infections including patients with severe gas-exchange abnormality, severe toxicity, and rapid progression, we recommend amphotericin B 0.7 mg/kg/day until clinical improvement is observed or until a cumulative dose of 2 g of amphotericin B is reached (BI). In patients who improve clinically after initial treatment with amphotericin B, we suggest maintenance itraconazole 200 mg twice daily for at least 12 weeks (BII).

In patients with severe pulmonary histoplasmosis with diffuse pulmonary infiltrates or massive granulomatous mediastinitis, we suggest adjunctive systemic glucocorticosteroid therapy be used (CII).

Remark. Prednisone 40–60 mg/day (or equivalent) for 1 to 2 weeks seems appropriate in these patients.

In patients with pulmonary histoplasmosis, we suggest itraconazole rather than fluconazole or ketoconazole (CII).

Remark. In selected patients who do not tolerate itraconazole, fluconazole or ketoconazole may still be used.

IMMUNOCOMPROMISED HOSTS WITH PULMONARY HISTOPLASMOSIS OR WITH PROGRESSIVE OR DISSEMINATED DISEASE, OR WITH CHRONIC PULMONARY HISTOPLASMOSIS. In patients with mild to moderate histoplasmosis, we recommend itraconazole 200 mg three times daily for 3 days followed by 200 mg twice daily for 12 months (CI).

In patients with severe progressive disseminated histoplasmosis requiring hospitalization, we recommend amphotericin

B 0.7–1.0 mg/kg/day (or a lipid formulation of amphotericin B 3–5 mg/kg/d) until clinical improvement is observed or until a cumulative dose of 2 g of amphotericin B is reached (BII). In patients who improve clinically after initial treatment with amphotericin B, we suggest itraconazole 200 mg twice daily for 12 months (CI).

In patients with AIDS and progressive disseminated histoplasmosis who completed 12 months of initial itraconazole therapy, we suggest itraconazole 200 mg twice daily until effective immune reconstitution occurs (i.e., CD4+ T cell counts > 200/ μ l) (CII).

In patients with AIDS who remain immunosuppressed and require lifelong maintenance therapy, we suggest monitoring *Histoplasma* polysaccharide antigen levels in urine and serum several times per year (BIII).

In patients with chronic pulmonary histoplasmosis, we recommend itraconazole 200 mg twice daily for 12 to 24 months rather than no antifungal treatment (BI), and suggest that *Histoplasma* antigen is not monitored (BIII).

In patients with severe chronic pulmonary histoplasmosis, we recommend initial treatment with amphotericin B over itraconazole (BII).

In selected immunocompromised patients with severe pulmonary histoplasmosis and diffuse pulmonary infiltrates, we suggest adjunctive systemic glucocorticosteroid therapy (BII).

Remark. Prednisone 40–60 mg/day (or equivalent) for one to two weeks seems appropriate in these patients.

TREATMENT OF SPOROTRICHOSIS

Introduction

Sporotrichosis is an illness caused by the dimorphic fungus *Sporothrix schenckii*. The organism is found throughout the world, and is associated with various forms of vegetation. The most common form of the infection is caused by inoculation of the organism into skin and subcutaneous tissues. The usual presentation of the disease is the characteristic lymphocutaneous or ulcerative skin form of sporotrichosis. Occasionally patients will inhale the organism, leading to the development of pulmonary sporotrichosis, which may occasionally disseminate to various parts of the body, predominantly to large joints. The treatment recommendations for sporotrichosis are derived predominantly from nonrandomized trials, case series, and case reports (50–52). There have been no randomized controlled therapeutic trials. Itraconazole remains the drug of choice for most forms of sporotrichosis (53). Doses range from 200 mg/day for the lymphocutaneous form to 200 mg twice daily for pulmonary and osteoarticular disease (BIII). Conventional amphotericin B deoxycholate or a lipid formulation of amphotericin is used for meningeal disease and may be used for severe pulmonary and osteoarticular disease in a course of 1 to 2 g total dose (BIII). Relapse following therapy is unfortunately common.

Recommendations. In patients with mild to moderately severe pulmonary sporotrichosis, based on the extent of radiographic involvement and oxygenation status, we suggest itraconazole 200 mg twice daily, with a total duration of therapy generally of 3 to 6 months based upon overall clinical response (BIII).

In patients with severe pulmonary sporotrichosis, such as those with life-threatening pulmonary infections including patients with severe gas-exchange abnormality, severe toxicity, and rapid progression, we suggest amphotericin B 0.7 mg/kg/day until clinical improvement is observed or until a cumulative dose of 1 to 2 g of amphotericin B is reached, followed by itraconazole 200 mg twice daily, with total duration of therapy generally of 3 to 6 months based upon overall clinical response (BIII).

TREATMENT OF BLASTOMYCOSIS

Introduction

Blastomyces dermatidis is a dimorphic fungus endemic in the central and southeastern United States. Blastomycosis is acquired by inhalation and can present as an acute, subacute, or even chronic infection. A small number of cases present as an infectious ARDS with fulminant diffuse pneumonia (54). The wide range of less severe pulmonary presentations includes lobar pneumonia, mass lesions, single or multiple nodules, and chronic fibronodular or fibrocavitary infiltrates. Dissemination from the lung is generally believed to occur in a minority of cases, either concurrent with the pulmonary infection or after resolution of a clinical or subclinical primary infection (usually within 1 or 2 yr) (55). It is unknown whether these delayed cases represent a manifestation of reactivation of the primary infection. The usual pattern of spread is to skin and bone. Less than 5% of disseminated cases involve the central nervous system, the meninges, or, less commonly, the brain itself. In immunosuppressed patients, especially those with AIDS, the disease is more severe and the pace of illness is accelerated (56, 57). Considerations for treatment of blastomycosis have to be viewed in the context of this wide spectrum of clinical illness (Table 4).

Immunocompetent Hosts

The vast majority of clinically recognized cases are mild to moderate in severity, involving the lung and/or the skin and bones. For these infections, the usual treatment is itraconazole 200 mg orally twice daily for 6 months (AII) (43, 58, 59). This treatment is highly effective and is the same for pulmonary infections and for nonmeningeal dissemination (accompanying pulmonary disease or in isolation), except that treatment duration is extended to 12 months when bones are involved (BII) (59–63). Thus, a 6- to 12-month course of oral itraconazole is appropriate treatment for most patients who present with blastomycosis. The challenge is to define the range of treatment options for the small minority of patients with the most difficult and life-threatening infections. Because patients with very severe infection, including all patients with CNS disease, were excluded by protocol from the large clinical trials that showed itraconazole equal to amphotericin B deoxycholate, the latter agent remains the gold standard for such patients. It should be noted, however, that subsequent case reports do suggest efficacy of itraconazole for patients who are quite ill (63, 64).

Life-threatening pulmonary infections include patients with severe gas-exchange abnormality, severe toxicity, and rapid progression. The recommended treatment is intravenous amphotericin B deoxycholate (0.7–1.0 mg/kg/d) to a total cumulative dose of 1.5–2.5 g (AII) (58, 65). Treatment can be given daily until clinical improvement has been established, and then three times weekly to completion (AIII) (65). Lipid formulations of amphotericin should be used for patients with pre-existing renal failure or with renal complications from amphotericin B deoxycholate. The usual daily dosage is 5 mg/kg/day, but even higher dosing has been used (BIII). Although there is a large positive experience in clinical practice, there are no disease-specific clinical trial data proving equivalency of lipid formulations of amphotericin versus amphotericin B deoxycholate in blastomycosis, and the total cumulative dose and duration of required treatment have not been studied. In current clinical practice, sequential therapy is often used after initial therapy with either agent. Amphotericin B deoxycholate (or lipid formulation amphotericin) is used until clinical improvement is achieved (500–1,000 mg of amphotericin B deoxycholate or 1–3 wk of lipid formulation amphotericin),

TABLE 4. TREATMENT RECOMMENDATIONS FOR BLASTOMYCOSIS

Disease Manifestation	Treatment Recommendations	Comments
Mild to moderately ill patients with pulmonary and nonmeningeal disseminated blastomycosis	Itraconazole (200 mg twice daily for 24 wk)	Monitor levels to insure absorption. Consider liquid preparations.
Skin disease	Itraconazole (200 mg twice daily for 24 wk)	Monitor levels to insure absorption. Consider liquid preparations.
Bone disease	Itraconazole (200 mg twice daily for 12 mo)	Monitor levels to insure absorption. Consider liquid preparations.
Life-threatening severe blastomycosis, including ARDS	Liposomal amphotericin B (5 mg/kg/d) or amphotericin B (0.7–1.0 mg/kg/d) until clinical improvement, then itraconazole (200 mg twice daily for 6–12 mo)	Consider concurrent corticosteroids for severe gas-exchange abnormalities. For immune-suppressed patients, treat for a minimum of 12 mo and indefinitely for AIDS without immune reconstitution.
Meningeal infection	Liposomal amphotericin B (5 mg/kg/d) or amphotericin B (0.7–1.0 mg/kg/d) until clinical improvement, and concurrent or sequential itraconazole (400 mg/d) or fluconazole (400–800 mg/d) for 6–12 mo	For immune-suppressed patients, treat for a minimum of 12 mo and indefinitely for AIDS without immune reconstitution.

followed by itraconazole 200 mg orally twice daily for 6 months (BIII) (58). Thus, it is difficult to gauge the optimal duration of lipid formulation amphotericin B treatment, since it is seldom used for the entire treatment course. Six to eight weeks of amphotericin administration has been suggested depending on treatment response, only by comparison to the treatment of other fungal infections.

Meningeal infections are also treated differently due to high protein binding and poor CNS penetration of itraconazole. The recommended treatment is amphotericin B deoxycholate at a dose of 0.7 mg/kg/day, to a total dose of at least 2 g (BIII) (58, 65). Lipid formulations of amphotericin B may be used in patients who cannot tolerate the standard deoxycholate formulation. Lipid formulations of amphotericin B have the theoretical benefit of higher brain tissue levels (versus amphotericin B deoxycholate) in animal models. There are case reports of successful retreatment of CNS blastomycosis with lipid formulation amphotericin B after failure of amphotericin B deoxycholate (66, 67). Triazoles alone should not be used in blastomycotic meningitis (CIII). However, combination therapy may be useful. High-dose fluconazole (400–800 mg daily, either intravenous or oral) can be used together with amphotericin B deoxycholate (or lipid formulation amphotericin B) from onset, or used in sequence after initial improvement. The time course of fluconazole treatment should be extended to at least 6 months. Although fluconazole is less effective than itraconazole for pulmonary and nonmeningeal disseminated blastomycosis (68, 69), it has been used for meningitis because of better CNS penetration (CIII). Voriconazole, a newer triazole, is intermediate between itraconazole and fluconazole in terms of CNS penetration, and in animal models has efficacy against blastomycosis (70, 71). It is attractive conceptually as the triazole component of a combination or sequential strategy for meningitis (CIII), but supporting clinical data is limited to individual case reports and small series of patients (72, 73).

Treatment of Immunosuppressed Hosts

Blastomycosis in immunosuppressed patients is another setting in which the standard 6- to 12-month course of oral itraconazole is often altered, again based on very limited specific data. The basic principle is that immunosuppressed patients have higher mortality and likely require more aggressive and prolonged therapy (56, 57). Recommended treatment for pulmonary and nonmeningeal blastomycosis in moderately immunosuppressed patients, such as solid organ recipients, includes sequential therapy with amphotericin B deoxycholate (or liposomal amphotericin B in cases of renal insufficiency or intolerance

of amphotericin B deoxycholate) until clinical improvement, followed by oral itraconazole 200 mg twice daily for a minimum of 12 months. In mild to moderate clinical infections, itraconazole from the onset of therapy may be adequate. For patients with AIDS, lifetime maintenance, such as with itraconazole, is necessary unless immunity is fully restored, with CD4 lymphocytes greater than 200/ μ l for 3 months (BII).

CNS involvement may also occur in immunosuppressed patients, either isolated or more likely as part of widespread dissemination. Mortality is high and treatment should be aggressive. Combination therapy is often used, again without specific supporting data. One option is amphotericin B deoxycholate (or liposomal amphotericin B) together with high dose fluconazole (400–800 mg daily) from onset. The amphotericin B deoxycholate (or liposomal amphotericin B) component is continued to clinical improvement and then fluconazole is continued for at least an additional 12 months. Lifetime maintenance therapy, such as with fluconazole, is recommended when AIDS without immune reconstitution is the underlying immunosuppressive illness (AII). As discussed previously, liposomal amphotericin B has the theoretical benefit of achieving higher brain tissue levels in animal models and voriconazole has some attraction as a potential triazole component, but there are no disease-specific data comparing one regimen to another (CII).

There are two other specific clinical circumstances that merit comment. First, if CNS disease progresses on amphotericin B deoxycholate therapy or develops while a patient is being treated with itraconazole for pulmonary or non-CNS-disseminated disease, then a change in strategy is warranted (64, 67, 69, 74). A reasonable but unproven regimen might be combination therapy with liposomal amphotericin B plus fluconazole 800 mg daily to clinical improvement, followed by fluconazole for 6 months (immunocompetent), 12 months (immunocompromised/non-AIDS), or indefinitely (AIDS without satisfactory immune reconstitution) (BIII). Voriconazole 200 mg twice daily might be an alternative for fluconazole in the above regimen, based on pharmacokinetic properties and *in vitro* sensitivities (CIII). Surgical resection may play a role in some patients with focal CNS disease, in combination with aggressive antifungal chemotherapy.

Second, patients with highly unstable pulmonary or disseminated blastomycosis who require advanced physiologic support (including mechanical ventilation, advanced oxygenation techniques, and vasopressors) have a guarded prognosis. Many have severe ARDS. A reasonable but unproven regimen might be amphotericin B deoxycholate or liposomal amphotericin B plus itraconazole 200 mg twice daily until clinical

improvement, followed by oral itraconazole for 6 months (immunocompetent), 12 months (immunocompromised/non-AIDS), or indefinitely (AIDS) (CIII). Voriconazole 200 mg twice daily might be substituted for itraconazole in the above regimen, based on pharmacokinetic properties and *in vitro* activity (CIII). A role for corticosteroids for severe diffuse pulmonary disease is not proven, but they are sometimes used to try to improve severe hypoxemia during the initial and most unstable period, together with mandatory appropriate antifungal therapy (75). In addition, the use of glucocorticoids in immunocompromised patients with severe hypoxemia and diffuse infiltrates related to blastomycosis, such as in the setting of immune reconstitution inflammatory syndrome, also remains poorly studied and controversial. As discussed above for histoplasmosis, the writing group felt that adjunctive corticosteroid doses in the range of 40–60 mg prednisone daily for 1 to 2 weeks was an appropriately conservative regimen if deemed useful on a patient-by-patient basis (CIII).

Additional Treatment Considerations

1. Special consideration should be given for treating patients with blastomycosis who are pregnant. In these patients, amphotericin B is preferred over the azole agents. Amphotericin B and its lipid derivatives are rated class B for pregnancy, while fluconazole, itraconazole, and posaconazole are class C drugs, and voriconazole is a class D drug (76).
2. The high efficacy of itraconazole for the great majority of blastomycosis cases has been proven in large clinical trials that will not likely be repeated with voriconazole or with newer triazoles such as posaconazole, despite some theoretical advantages for those newer agents in absorption and tissue penetration. Since there likely will be no prospective studies comparing these agents to itraconazole for either standard cases or in special situations such as CNS disease, there also will likely be no strong evidence-based guidelines forthcoming that will advance current preferences beyond those outlined above.
3. Echinocandins likely have no role (either alone, in combination, or sequentially) in treatment of blastomycosis, even in situations warranting a nontraditional approach (DIII). Although the echinocandins have some activity *in vitro*, clinical efficacy of these agents against *Blastomyces* has not been demonstrated (77).
4. The prostate, like the CNS, can serve as a sanctuary site with respect to itraconazole with its high protein binding. Lipid formulations of amphotericin B and newer triazoles with less protein binding, sometimes in concert with surgery, have been used successfully in some cases (CII).

Recommendations. IMMUNOCOMPETENT HOSTS. In patients with mild to moderate pulmonary blastomycosis, we recommend oral itraconazole 200 mg twice daily for 6 months (AII).

In patients with severe pulmonary blastomycosis, we recommend amphotericin B 0.7–1.0 mg/kg/day daily until clinical improvement is observed (BII), followed by continuation of amphotericin B 0.7–1.0 mg/kg three times weekly, until a cumulative dose of 1.5–2.5 g is reached (BII). Once clinical improvement is observed, we suggest oral itraconazole 200 mg twice daily for 6 months (BII).

Remarks. In patients with renal failure, lipid formulations of amphotericin are preferred.

Because patients with very severe blastomycosis have been excluded from clinical studies that compared itraconazole to

amphotericin B, there is serious uncertainty about the relative efficacy of itraconazole compared with amphotericin.

In patients with pulmonary blastomycosis and bone involvement, we suggest prolonging treatment with itraconazole to 12 months (CII).

In patients with pulmonary blastomycosis and concomitant CNS involvement, we suggest:

- liposomal amphotericin B 0.7 mg/kg/day until a cumulative dose of 2 g is reached (BII);
- triazoles should not be used as monotherapy for meningeal blastomycosis (DII);
- high dose intravenous or oral fluconazole 400–800 mg daily may be provided as an add-on therapy to intravenous amphotericin B in patients with severe or refractory disease, with the total duration of fluconazole therapy extended for at least 6 months (BIII).

IMMUNOCOMPROMISED HOSTS. In patients with severe pulmonary blastomycosis without CNS involvement, we recommend amphotericin B 0.7 mg/kg/day until clinical improvement is observed (BII). Once clinical improvement is observed, we recommend oral itraconazole 200 mg twice daily for at least 12 months (BII).

In patients with mild to moderate pulmonary blastomycosis without CNS involvement, we suggest oral itraconazole 200 mg twice daily for at least 12 months (BIII).

When AIDS is involved, we suggest oral itraconazole 200 mg/day indefinitely or until immunity is fully restored (BII).

In patients with pulmonary blastomycosis and concomitant CNS involvement, we recommend:

- combined therapy with amphotericin B 0.7 mg/kg/day together with intravenous or oral fluconazole 400–800 mg daily from the onset until clinical improvement is observed (BIII);
- use of fluconazole for at least 12 months total after discontinuation of combined intravenous treatment with amphotericin B and high-dose fluconazole (BIII);
- use of liposomal amphotericin B rather than amphotericin B deoxycholate should be considered due to theoretic better CNS penetration (CIII);
- triazoles are not used as monotherapy (DII);
- patients with AIDS should continue to receive oral fluconazole 400 mg per day indefinitely or until immunity is restored (AII).

In patients with pulmonary blastomycosis with new or progressing CNS involvement despite amphotericin B monotherapy, we suggest:

- combined therapy with liposomal amphotericin B 5 mg/kg/day until clinical improvement is observed, together with intravenous or oral fluconazole 800 mg/day (CIII);
- fluconazole is used for at least 6 months in immunocompetent patients, and at least 12 months in immunocompromised patients, after discontinuation of combined treatment with amphotericin B and fluconazole (CIII);
- patients with AIDS receive oral fluconazole 400 mg daily indefinitely or until immunity is restored (AII).

In some carefully selected patients with blastomycosis and focal CNS lesions, consideration of surgical resection of the focal CNS lesions may occasionally be considered, if appropriate expertise is available (CIII).

In critically ill patients with pulmonary blastomycosis, we suggest:

- combined therapy with amphotericin B (0.7–1.0 mg/kg amphotericin B deoxycholate or 5 mg/kg daily liposomal amphotericin B) until clinical improvement is observed, together with oral itraconazole 200 mg/day (CII);
- following the initial intravenous therapy, oral itraconazole is used for at least 6 months in immunocompetent patients, and at least 12 months in immunocompromised patients, after discontinuation of combined treatment with amphotericin B and itraconazole (CII);
- after initial therapy is complete, patients with AIDS should receive oral itraconazole 200 mg/day indefinitely, or until immunity is restored (CII). Voriconazole 200 mg twice daily may be used as an alternative to itraconazole (CIII).

In selected critically ill patients with severe pulmonary blastomycosis, such as blastomycosis-associated ARDS, we suggest consideration of adjunctive systemic glucocorticosteroids (CIII). Prednisone 40–60 mg daily (or equivalent) for 1 to 2 weeks seems appropriate in these patients.

In patients with pulmonary blastomycosis with new or progressing CNS involvement despite amphotericin B monotherapy, we suggest:

- combined therapy with liposomal amphotericin B 5 mg/kg/day until clinical improvement is observed, together with intravenous or oral fluconazole 800 mg/day (CIII);
- fluconazole is used for at least 6 months in immunocompetent patients, and at least 12 months in immunocompromised patients, after discontinuation of combined treatment with amphotericin B and fluconazole (CIII);
- patients with AIDS receive oral fluconazole 400 mg daily indefinitely or until immunity is restored (AII).
- Voriconazole 200 mg twice daily may be considered as an alternative to fluconazole, though extensive disease-specific data are currently lacking (CIII).

In some carefully selected patients with blastomycosis and focal CNS lesions, consideration of surgical resection of the focal CNS lesions may occasionally be considered, if appropriate expertise is available (CIII).

In critically ill patients with pulmonary blastomycosis, we suggest:

- combined therapy with amphotericin B (0.7–1.0 mg/kg amphotericin B deoxycholate or 5 mg/kg daily liposomal amphotericin B) until clinical improvement is observed, together with oral itraconazole 200 mg/day (CII);
- following the initial intravenous therapy, oral itraconazole is used for at least 6 months in immunocompetent patients, and at least 12 months in immunocompromised patients, after discontinuation of combined treatment with amphotericin B and itraconazole (CII);
- after initial therapy is complete, patients with AIDS should receive oral itraconazole 200 mg/day indefinitely, or until immunity is restored (CII).
- Voriconazole 200 mg twice daily may be considered as an alternative to itraconazole, though this is based largely on *in vitro* sensitivities and limited case based data (CIII).

TREATMENT OF COCCIDIOIDOMYCOSIS

Coccidioidomycosis is caused by the soil-dwelling fungi *Coccidioides immitis* and *Coccidioides posadasii* that are localized to relatively arid regions of the Western hemisphere. The areas of highest endemicity in North America are the San Joaquin Valley of California, the south-central region of Arizona, and northwestern Mexico. The vast majority of cases of coccidioidomycosis are acquired by inhalation. Approximately 60% of infections are asymptomatic (78). Many of the remainder are associated with a pulmonary syndrome resembling other community-acquired pneumonia (CAP) syndromes or an upper respiratory tract infection. Acute pulmonary coccidioidomycosis may be distinguished from CAP by its lack of response to antibacterial therapy, and sometimes by hilar adenopathy, peripheral blood eosinophilia, severe fatigue, night sweats, and the presence of erythema multiforme or erythema nodosum. The diagnosis can be established by the presence of anticoccidioidal antibody in the serum, measurable by ELISA, immunodiffusion, or by tube precipitin and complement fixation assays. The diagnosis can also be established by the identification of coccidioidal spherules in tissue or by isolating the fungus by culture from a clinical specimen. Because acute primary pulmonary coccidioidomycosis is frequently self-limited, many cases appear to respond to antibacterial antibiotics and are consequently misdiagnosed as CAP. In endemic regions, coccidioidomycosis may be responsible for nearly one-third of patients presenting with lower respiratory tract symptoms (79).

Immunocompetent Patients

Most cases of primary pulmonary coccidioidomycosis in individuals without identified risk factors are self-limited and do not require treatment (BIII) (Table 5) (78). Therapy of primary pulmonary coccidioidomycosis should be considered when symptoms persist for more than 6 weeks or for especially severe acute disease (80). The principles of therapy in this group are identical to those discussed next for treatment of immunosuppressed patients and other patients at risk for disseminated disease.

Immunosuppressed Patients and Others at Risk for Disseminated Disease

Therapy for primary pulmonary coccidioidomycosis should be considered for patients with impaired cellular immunity, such as those with solid-organ transplants, those with HIV infection with peripheral blood CD4 cell counts less than 200/ μ l, and in those with co-morbidities likely to be adversely affected by ongoing primary infection, such as chronic lung disease, chronic renal failure, or congestive heart failure (BIII) (Table 5). Patients receiving TNF- α inhibitor therapy are also at increased risk for developing symptomatic coccidioidomycosis (81). Patients with diabetes mellitus are likely to develop chronic pulmonary coccidioidomycosis, particularly cavitary disease, and require close monitoring, with clinical assessment and radiography every 1 to 2 months until the cavity resolves or stabilizes (82). Cavitary disease can be complicated by hemoptysis, which independently represents an indication for therapy. All patients with primary pulmonary coccidioidomycosis should be followed for at least 1 year to assure complete resolution and absence of complications (BIII). A small fraction of patients develop persistent pulmonary disease or dissemination. Patients with solid-organ transplants and those with HIV infection and depressed CD4 cell counts are at particularly high risk for dissemination. African-American and Filipino-American men are also at increased risk for developing disseminated coccidioidomycosis, as are pregnant women who experience coccidioidal infection during the second or third trimester (83). The most

TABLE 5. RECOMMENDED INITIAL THERAPY FOR COCCIDIOIDOMYCOSIS

Disease Manifestation	Nonimmunocompromised Host	Immunocompromised Host
Primary pulmonary	No therapy in most; fluconazole (400 mg/d) or itraconazole (400 mg/d) for 3–6 mo in selected cases.*	Fluconazole (400 mg/d) or itraconazole (400 mg/d) for 3–6 mo or longer depending on clinical response.
Pulmonary nodule	No therapy.	Consider fluconazole (400 mg/d) or itraconazole (400 mg/d) during periods of significant immune suppression.
Pulmonary cavity	No therapy. Consider therapy in some cases [†] ; in those consider fluconazole (400 mg/d) or itraconazole (400 mg/d) for 3–6 mo or longer until cavity and symptoms stabilize.	Fluconazole (400 mg/d) or itraconazole (400 mg/d) for 12–18 mo or longer until cavity and symptoms stabilize.
Diffuse pulmonary	Liposomal amphotericin B (5 mg/kg/d) or amphotericin B (0.7–1.0 mg/kg/d) until clinical improvement, followed by fluconazole (400 mg/d) or itraconazole (400 mg/d) for at least another year.	Liposomal amphotericin B (5 mg/kg/d) or amphotericin B (0.7–1.0 mg/kg/d) until clinical improvement, followed by fluconazole (400 mg/d) or itraconazole (400 mg/d) for at least a year. [‡] For ongoing immune suppression consider long-term maintenance with azole.
Disseminated, nonmeningeal (including bone disease)	Fluconazole (400 mg/d) or itraconazole [‡] (400 mg/d) for at least a year and until clinical improvement and stabilization; in severe cases, liposomal amphotericin B (5 mg/kg/d) or amphotericin B (0.7–1.0 mg/kg/d) until clinical improvement followed by fluconazole (400 mg/d) or itraconazole (400 mg/d) for at least another year.	Fluconazole (400 mg/d) or itraconazole [‡] (400 mg/d) for at least a year and until clinical improvement and stabilization. In severe cases, liposomal amphotericin B (5 mg/kg/d) or amphotericin B (0.7–1.0 mg/kg/d) until clinical improvement followed by fluconazole (400 mg/d) or itraconazole (400 mg/d) for at least another year.
Meningitis	Fluconazole (400–1,000 mg/d) or itraconazole (400–600 mg/d) for life; intrathecal amphotericin B in some cases.	Fluconazole (400–1,000 mg/d) or itraconazole (400–600 mg/d) for life; intrathecal amphotericin B in some cases.

* Moderate, severe, or prolonged infection (> 6 wk), or for patient factors including chronic obstructive pulmonary disease, chronic renal failure, congestive heart failure, diabetes mellitus, and certain ethnicities and demographic factors as discussed in the text.

[†] In cases in which persistent productive cough or hemoptysis, continued pleuritic chest pain, or increasing size of cavity occurs or rising serologic titer.

[‡] Itraconazole preferred for bone disease.

common sites of disseminated coccidioidomycosis are the skin, soft tissues, bones and joints, and the meninges. A lumbar puncture with analysis of cerebrospinal fluid should be done in any patient with primary coccidioidomycosis presenting with headache, blurry vision, photophobia, meningismus, or any other CNS symptom, and should be considered in any patient who is severely ill or not likely to be subsequently followed.

Persistent pulmonary disease comprises nodules, cavities, and chronic infiltrates. Coccidioidal nodules are usually asymptomatic, presenting a problem only in distinguishing them from malignancies, and generally require no treatment. Cavities may occasionally be associated with pleuritic chest pain, productive cough, or hemoptysis. Patients with cavities should be considered for therapy, especially when hemoptysis is present, or with progressive enlargement of the cavity (BIII). Chronic pulmonary coccidioidomycosis, defined as symptoms ongoing for more than 3 months, frequently occurs in patients with underlying lung disease and should be treated (BIII).

All forms of disseminated coccidioidomycosis require antifungal therapy (AIII). Meningitis represents a special situation because currently available azole antifungal therapy should be continued throughout a patient's lifetime (AII) (84), given the extremely high relapse rate. Intravenous amphotericin B deoxycholate is considered ineffective for coccidioidal meningitis, but intrathecal amphotericin B has a role in its management in cases of azole therapy failure, or when a more rapid response is desired (AII) (85). Because of the risk of hydrocephalus and other complications even in the face of appropriate antifungal therapy, an expert should be consulted in the management of coccidioidal meningitis (BIII) (82).

Antifungal therapy for chronic coccidioidomycosis is generally prolonged, with a minimum course of 12 to 18 months (AII) (86–88). Courses beyond 18 months should be considered in patients with underlying immunocompromising conditions. Declining titers of serum anticoccidioidal antibody indicate treatment effectiveness. Available agents for the treatment of coccidioidomycosis include azole antifungals and amphotericin

B. The echinocandin class of antifungals has not been adequately assessed in coccidioidomycosis, but does not appear to possess efficacy. Azole antifungals that are well studied in coccidioidomycosis include ketoconazole, fluconazole, and itraconazole. There are small series and case reports suggesting efficacy of voriconazole and posaconazole in recalcitrant cases of coccidioidomycosis (18, 89–91). Ketoconazole has been largely supplanted by fluconazole and itraconazole, and the latter has greater efficacy than fluconazole for bone and joint coccidioidomycosis (AI) (87). When fluconazole and itraconazole are employed, the minimum dose is 400 mg/day (BII) (86–88).

Amphotericin B is currently reserved for the most severe cases of coccidioidomycosis or those that do not respond to azoles (AIII). Although there is no evidence that the newer lipid formulations of amphotericin B possess any greater efficacy than the conventional amphotericin B deoxycholate preparation, the lipid formulations are better tolerated and allow treatment with a reduction in renal and other toxicities (BIII).

Recommendations. IMMUNOCOMPETENT HOSTS. In most immunocompetent patients with primary pulmonary coccidioidomycosis and no additional risk factors for dissemination, we suggest no antifungal treatment (BII).

Remark. Additional risk factors for dissemination include COPD or other chronic structural lung disease, chronic renal failure, congestive heart failure, diabetes mellitus, pregnancy, African-American or Filipino-American heritage, HIV, and those patients receiving TNF- α antagonists.

In immunocompetent patients with primary pulmonary coccidioidomycosis and moderate to severe symptoms, or those in whom symptoms persist for more than 6 weeks, we suggest treatment with triazole antifungal drugs for at least 3 to 6 months or longer if symptoms and radiographic abnormalities persist (BII).

IMMUNOCOMPROMISED HOSTS AND OTHERS AT RISK FOR DISSEMINATED DISEASE. Therapy for primary pulmonary coccidioidomycosis should be considered for patients with impaired cellular immunity, such as those with solid organ transplants, those with HIV infection with peripheral blood CD4 cell counts less than

200/ μ l, and in those with comorbidities likely to be adversely affected by ongoing primary infection, such as chronic lung disease, chronic renal failure, or congestive heart failure, or those receiving TNF- α antagonists (BII).

In patients with primary coccidioidomycosis presenting with neurologic symptoms, we recommend lumbar puncture with analysis of cerebrospinal fluid for presence of *Coccidioides* spp. (BII).

Remark. Symptoms that may prompt performing analysis of cerebrospinal fluid for presence of *Coccidioides* spp. include headache, blurry vision, photophobia, meningismus, and other neurologic symptoms.

In many patients with pulmonary coccidioidomycosis and pulmonary nodules only, we suggest consideration of observation for at least 1 year without antifungal treatment. However, fluconazole (400 mg/d) or itraconazole (400 mg/d) may be considered during periods of significant immune suppression (i.e., chemotherapy, systemic corticosteroid therapy, or CD4 counts < 250/ μ l) (CII).

In patients with pulmonary coccidioidomycosis and pulmonary nodules who have additional risk factors for disseminated disease, patients with cavities, and those presenting with hemoptysis, we suggest treatment with triazole antifungal drugs, either fluconazole (400 mg/d) or itraconazole (400 mg/d) (BII).

Remark. Additional risk factors for more severe disease include COPD or other chronic structural lung disease, chronic renal failure, congestive heart failure, diabetes mellitus, pregnancy, African-American or Filipino-American heritage, HIV, and those patients receiving TNF- α antagonists.

Azole therapy for chronic pulmonary coccidioidomycosis (nodules or cavities with symptoms > 3 mo) is generally prolonged, with a minimum course of 12 to 18 months or longer until the cavities and symptoms stabilize (BIII).

For diffuse pulmonary coccidioidomycosis with significant impairment of gas exchange, we recommend initial liposomal amphotericin B (5 mg/kg/d) or amphotericin B (0.7–1.0 mg/kg/d) until clinical improvement, followed by fluconazole (400 mg/d) or itraconazole (400 mg/d) for at least another year (BIII). In patients with ongoing immune suppression, azole therapy may be continued indefinitely.

All patients, whether immunocompetent or immunocompromised, with any form of disseminated coccidioidomycosis require treatment. For nonmeningeal disseminated disease, we recommend treatment with fluconazole (400 mg/d) or itraconazole (400 mg/d) for at least a year and until clinical improvement and stabilization (BII). Itraconazole is preferred in bone disease. In severe or refractory cases, liposomal amphotericin B (5 mg/kg/d) or amphotericin B (0.7–1.0 mg/kg/d) may be initiated until clinical improvement, followed by fluconazole (400 mg/d) or itraconazole (400 mg/d) for at least another year (BIII).

In patients with meningitis, we recommend fluconazole (400–1,000 mg/d) or itraconazole (400–600 mg/d) for life (BII). In patients with meningitis in whom treatment with triazole antifungal drugs failed, we suggest consideration of intrathecal amphotericin B in selected cases (BIII).

Remark. We suggest that patients with disseminated coccidioidomycosis and meningitis be managed in conjunction with clinicians with appropriate expertise in the treatment of coccidioid meningitis (BIII).

TREATMENT OF PARACOCCIDIOIDOMYCOSIS

Paracoccidioidomycosis is caused by the dimorphic fungus *Paracoccidioides brasiliensis*. The organism is endemic in certain parts of South and Central America, including Mexico, but does not involve the Caribbean or any part of the United States. The presumed pathogenesis is via inhalation of airborne spores,

leading to pulmonary and disseminated disease. This disease is more common among male patients, and many infected individuals are manual laborers, suggesting that exposure is occupation-dependent.

The majority of diagnosed patients present with disseminated disease, involving lymph nodes producing painful mucocutaneous ulcers. The infection may also present as a chronic, tuberculosis-like infection with low-grade fever, weight loss, and upper zone infiltrates on chest radiogram. The less common juvenile form produces a rapidly progressive pulmonary disease with multiple areas of infiltrates, hepatosplenomegaly, and adenopathy. The infection may occur as an opportunistic infection in patients with HIV and/or AIDS, in which case it is usually widely disseminated.

Information regarding treatment of paracoccidioidomycosis is limited to case series and one randomized study. Critically ill patients are usually treated with amphotericin B, either as the deoxycholate or a lipid formulation (BIII). The more slowly progressive form of the infection may be treated with ketoconazole 200–400 mg daily, itraconazole 100–400 mg daily, or sulfadiazine 4–6 g daily. The last three agents were shown to be similarly effective (BII) (92, 93).

Recommendations. In critically ill patients with disseminated paracoccidioidomycosis, we recommend initial amphotericin B (0.7–1 mg/kg/d) therapy until clinical stabilization or until 2 g total dose administered (BI). This may be followed by azole therapy as listed below.

In patients with disseminated paracoccidioidomycosis and mild to moderate or slowly progressive symptoms, we recommend one of the following options until clinical stabilization and resolution of symptoms (BII). The total duration of therapy must be individualized to clinical response, but generally therapy for 6 to 12 months or longer is employed. Potential regimens include:

- ketoconazole 200–400 mg daily
- itraconazole 100–400 mg daily
- sulfadiazine 4–6 g daily

TREATMENT OF CRYPTOCOCCOSIS

The most common cause of cryptococcosis is *Cryptococcus neoformans*. The closely related organism *Cryptococcus gattii* (previously *C. neoformans* var. *gattii*) is emerging as an important pathogen in the Pacific Northwest of the United States and Vancouver Island in Canada, as well as tropical or subtropical climates such as Africa, India, Papua New Guinea, South America, and Australia (94). *Cryptococcus* is a basidiomycetous yeast that occurs in a minimally encapsulated form in nature and rapidly synthesizes a polysaccharide capsule upon entering the pulmonary environment (95). *C. neoformans* commonly produces disease in immunocompromised hosts, and patients with AIDS are particularly susceptible. By contrast, *C. gattii* more commonly infects immunocompetent hosts in unique geoclimatic regions (96–98).

Immunocompetent Hosts

While meningitis is the most serious and common manifestation of cryptococcosis, pulmonary disease occurs in both immunocompetent and immunocompromised individuals. Skin, prostate, eye, and bone infections are the most common secondary sites of infection (97). In immunocompetent patients, the pulmonary manifestations include asymptomatic colonization, often in patients with underlying structural lung disease (99, 100). In symptomatic patients, the most common abnormalities

TABLE 6. TREATMENT OF IMMUNOCOMPETENT PATIENTS WITH CRYPTOCOCCOSIS

Disease Manifestation	Treatment Recommendations	Comments
Colonized Mild localized pulmonary disease	No specific antifungal therapy Fluconazole (400 mg/d for 6 mo) OR Itraconazole (400 mg/d for 6 mo)	Therapy may need to be extended if the response is not complete
Central nervous system or disseminated disease	Amphotericin B (0.7–1.0 mg/kg/d) ± flucytosine (100 mg/kg/d) for 2 wk, then fluconazole or itraconazole (400 mg/d for 10 wk) OR Amphotericin B (0.7–1.0 mg/kg/d) ± flucytosine (100 mg/kg/d) for 6–10 wk	Therapy may need to be extended if the response is not complete

are pulmonary nodules, masses, or interstitial pneumonitis (100–102). However, pleural effusions, adenopathy, and even severe ARDS can occur with large fungal burdens (100, 103).

In immunocompetent patients that are asymptomatic and simply colonized with *C. neoformans* (asymptomatic with no evidence of disease), specific therapy may not be necessary (Table 6) (104) (AII). Although pulmonary cryptococcosis may resolve spontaneously, it may be difficult to define which patients are truly immunocompetent, or who may become immunosuppressed in the future. Since pulmonary cryptococcosis occasionally disseminates, it is prudent to treat infected patients with fluconazole (oral and nontoxic), and close follow-up is recommended for 1 year (BIII). Serum cryptococcal antigen titers should be obtained in all patients with suspected infection (AIII), and in patients with symptoms, persistent fever, evidence of progression, physiologic compromise, dissemination, or positive serum cryptococcal antigen titers, treatment should be promptly implemented (AI).

Cryptococcosis can be very serious, and certainly respiratory failure and death can occur (105). In all cases, a lumbar puncture should be considered, and in a patient with evidence of dissemination from the lung, symptoms referable to the CNS, or positive serum cryptococcal antigen titers, a lumbar puncture should be performed (BIII). When treatment is required for disease confined to the lung, fluconazole 400 mg/day initially, tapering to 200 mg/day, is often sufficient (100, 104, 106) (AII). Treatment should be given for 6 months and may have to be extended, particularly in patients with *C. gattii* infections, at least in part because of the slightly reduced susceptibility to fluconazole displayed by *C. gattii* (106–108) (CIII). For patients with CNS or disseminated disease, the treatment regimens for immunocompromised patients should be employed. In certain cases, surgical resection may be considered in patients with large mass lesions or areas refractory to medical therapy (BII) (109, 110).

Immunocompromised Hosts

Patients with defects in T cell function, such as those infected with HIV and having a CD4 T cell count less than 100/ μ l, patients with hematologic malignancies and immunosuppression due to chemotherapeutic agents or monoclonal antibodies, patients receiving corticosteroids for solid organ transplantation or inflammatory diseases such as sarcoidosis, and patients with diabetes mellitus are predisposed to cryptococcosis (106, 111). While the direct antifungal activity of cyclosporine/tacrolimus may reduce the risk of infection compared with other immunosuppressive regimens (112, 113), infections still occur in solid organ transplant patients that receive these agents (114). Recently, treatment with novel immunosuppressive agents such as infliximab and alemtuzumab has also been identified as a risk factor for cryptococcosis (115–118).

Although meningitis is the most common manifestation, the lung is involved in up to 39% of patients with AIDS with

cryptococcosis (119). However, the pulmonary manifestations in AIDS are quite varied. A pneumonitis with reticular or reticulonodular densities is most common (119, 120), but ground glass opacities, consolidation, hilar adenopathy, pleural effusions, and even miliary nodules have been reported (120, 121). By contrast, pulmonary nodules, parenchymal masses, and consolidation are somewhat more common in non-HIV-infected patients (121).

For immunocompromised patients with meningitis, disseminated disease, or severe symptoms, the standard therapy for cryptococcosis is amphotericin B (0.7 mg/kg/d) and flucytosine (100 mg/kg/d in four divided doses), except when reduced platelet or neutrophil counts preclude the use of flucytosine (Table 7). If cerebrospinal fluid (CSF) cultures are negative at 2 weeks, this therapy can be switched to fluconazole (400 mg/d) for an additional 8 weeks (122) (AI). The dose of flucytosine may be guided by serum levels if these are available (levels = 50–100 μ g/ml, with exact levels varying by the assay used), though the incidence of toxicity is low with dosing of 100 mg/kg/day in the setting of normal renal function (AIII). If fluconazole cannot be administered, itraconazole (400 mg/d) has been shown to be an option (123, 124) (BII). If azoles cannot be administered, then amphotericin B and flucytosine can be administered for 6 to 10 weeks (125–127) (AI). Single drug therapy with fluconazole is not generally recommended as initial therapy for immunocompromised patients with meningitis (128) (EI). While most experience supports this standard regimen as outlined, a recent small, randomized trial in HIV-infected patients with cryptococcal meningitis compared amphotericin B (0.7 mg/kg/d) plus flucytosine to amphotericin B (1.0 mg/kg/d) plus flucytosine in this disorder. While the higher dose amphotericin regimen was more rapidly fungicidal than the lower dose, the mortalities were not different. Because of study size, limited data were available to draw firm conclusions on differences in toxicity between the regimens (129).

While some have advocated for the use of concurrent therapy with amphotericin B and fluconazole (130), no benefit was shown with the combination in a small randomized clinical trial (131), and therefore the combination cannot be recommended routinely at this time (DI). In patients with renal insufficiency or who are unable to tolerate amphotericin B deoxycholate, lipid formulations of amphotericin B (3–5 mg/kg/d) are recommended (132–134) (BII).

HIV-positive patients with CD4 counts less than 200/ μ l should receive chronic maintenance therapy with fluconazole, generally at doses of 200 mg/day (135–137) (AI). Reports of resistance to fluconazole (138–141) to date have not altered this recommendation (BIII). Antiretroviral therapy should usually be delayed until 8 to 10 weeks after starting treatment for cryptococcosis to avoid an immune reconstitution syndrome (IRS) during initial control of infection (142–144) (BII). After the institution of antiretroviral therapy, chronic maintenance antifungal therapy can be discontinued when the CD4 T cell

TABLE 7. TREATMENT OF IMMUNOCOMPROMISED PATIENTS WITH CRYPTOCOCCOSIS

Disease Manifestation	Treatment Recommendations	Comments
Pulmonary with positive culture, asymptomatic or mild disease	Fluconazole (400 mg/d) or itraconazole (400 mg/d) for 6–12 mo, followed by secondary prophylaxis	Fluconazole secondary prophylaxis may be discontinued after institution of HAART therapy if disease-free and CD4 count is > 200/ μ l.
CNS or disseminated disease	Amphotericin B (0.7–1.0 mg/kg/d) + flucytosine* (100 mg/kg/d) for 2 wk [†] , then fluconazole or itraconazole (400 mg/d) for 8 wk [†] , followed by maintenance [‡] OR Amphotericin B (0.7–1.0 mg/kg/d) + flucytosine* (100 mg/kg/d) for 6–10 wk [†] , followed by maintenance [‡] OR Lipid formulation of amphotericin B (3–6 mg/kg/d) for 6–10 wk [†] , followed by maintenance [‡]	
Maintenance (Secondary prophylaxis)	Fluconazole (200 mg/d)	Fluconazole secondary prophylaxis may be discontinued after institution of HAART therapy if disease-free and CD4 count is > 200/ μ l.

* Except when reduced platelet or neutrophil counts preclude the use of flucytosine.

[†] Therapy may need to be extended if the response is incomplete.

[‡] Fluconazole secondary prophylaxis (maintenance) may be discontinued after institution of HAART therapy if disease-free and CD4 count is > 200/ μ l.

count is greater than 200/ μ l, an undetectable HIV RNA level is achieved and sustained for 3 months, and the patient is stable for 1 to 2 years (145, 146) (AI). Physicians should also be aware of the rare, paradoxical development of meningeal cryptococcosis (147) or intracranial cryptococcoma (148) after the institution of antiretroviral therapy.

The role of newer agents has not yet been determined. Echinocandins such as caspofungin are not active against *Cryptococcus* (149, 150) and should not be used (EIII). Despite the theoretical superiority of voriconazole and posaconazole (151, 152), no randomized clinical trials have been reported. Voriconazole and posaconazole may have contributed to success in anecdotal reports of treatment in refractory or intolerant patients (44, 153), but their routine use outside of refractory cases cannot be advocated until clinical trials are available (CIII). Treatment with adjuvant recombinant interferon- γ has been reported, but further trials are necessary to ensure its efficacy before it can be routinely recommended (154) (CI). However, this approach might be considered in refractory cases.

Management of raised intracranial pressure is a critical part of the care of patients with cryptococcal meningitis. The primary mode of therapy is drainage of CSF to reduce the intracranial pressure after imaging with CT or magnetic resonance imaging (MRI) to ensure that no cerebral mass effect is present (AII). Repeated lumbar punctures, lumbar drains, ventriculoperitoneal shunts, temporary ventriculostomy, and therapy with mannitol have all been employed (155–160) (AIII). Recently, particularly in resource-limited situations, placement of a lumbar drain has been preferred to repeat lumbar puncture despite the risk of infection, overdrainage, and the requirement to clamp the drain if the patient moves to alter the elevation of the head in relation to the collecting cylinder (161, 162). Acetazolamide and standard diuretic therapy should be avoided (163) (EI). While there are no studies to support the routine use of corticosteroids in the management of cryptococcal meningitis, and they have in fact been associated with poor prognosis in HIV-infected patients in retrospective studies, corticosteroids have been advocated in patients infected with *C. gattii* to avert the high incidence of visual loss, and in the presence of an immune reconstitution syndrome (IRS) (164) (CIII).

An IRS consisting of worsening signs and symptoms of meningitis, intrathoracic lymphadenopathy, cavitary pneumonia, worsening pulmonary infiltrates, or sterile abscess has been reported in patients receiving antiretroviral treatment, in transplant patients, and even in normal hosts (142–144, 165,

166). In this syndrome, histopathology may reveal organisms, but cultures are usually negative. Corticosteroids (i.e., prednisone 40–60 mg/d) may be used (BIII), and consultation with an expert in infectious diseases is encouraged for patients suspected of having IRS.

Recommendations. IMMUNOCOMPETENT HOSTS. In asymptomatic immunocompetent patients with respiratory tract colonization by *C. neoformans*, we recommend no antifungal treatment (AII).

In patients with pulmonary cryptococcosis and any concern of dissemination, neurologic symptoms, or positive serum cryptococcal antigen titers, we recommend lumbar puncture with analysis of cerebrospinal fluid for presence of *Cryptococcus* spp. (AI).

In immunocompetent patients with pulmonary cryptococcosis and no evidence of other organ involvement, we recommend fluconazole 400 mg/day initially, tapering to 200 mg/day after clinical improvement is assured and with total treatment for 6 months (AII). Alternatively, itraconazole 400 mg/day may be considered for 6 months (BII). We suggest fluconazole treatment longer than 6 months in patients with documented *C. gattii* infection, at least in part because of the slightly reduced susceptibility to fluconazole displayed by *C. gattii* compared with *C. neoformans* (88, 102, 106–108) (CIII).

In selected patients with pulmonary cryptococcosis and large mass lesions or areas refractory to medical therapy, we suggest consideration of surgical resection (CIII).

IMMUNOCOMPROMISED HOSTS AND IMMUNOCOMPETENT HOSTS WITH DISSEMINATED OR CNS INVOLVEMENT. In patients with disseminated cryptococcosis or CNS involvement, we recommend amphotericin B (0.7–1.0 mg/kg/d) plus flucytosine (100 mg/kg/d) for 2 weeks, then fluconazole or itraconazole (400 mg/d) for 8 to 10 weeks (AI). Alternatively, amphotericin B (0.7–1.0 mg/kg/d) plus flucytosine (100 mg/kg/d) may be administered for 6 to 10 weeks in patients in whom azoles cannot be used (AI).

Remark. If flucytosine is used, dosing should be guided by blood drug levels if available.

In patients with disseminated cryptococcosis or CNS involvement, we recommend that azoles not be used as monotherapy (DI).

In patients with refractory disease not responding to fluconazole and itraconazole, we suggest voriconazole or posaconazole be considered as salvage therapy on a case by case basis (BIII).

In patients with AIDS and CD4+ T cell count less than 200/ μ l who have disseminated cryptococcosis or CNS involve-

ment, we recommend that fluconazole 200 mg/day is used indefinitely, after successful primary therapy as outlined above, or until CD4 T cell count is greater than 200/ μ l, HIV RNA is undetectable and sustained for 3 months, and the patient is stable for 1 to 2 years (AI).

Remark. Antiretroviral therapy should usually be delayed until 8 to 10 weeks after starting treatment for cryptococcosis to avoid an IRS.

MANAGEMENT OF RAISED INTRACRANIAL PRESSURE AMONG PATIENTS WITH CRYPTOCOCCOSIS AND CNS INVOLVEMENT. In patients with cryptococcosis and raised intracranial pressure and with no confirmed cerebral mass effect on CT or MRI, we recommend drainage of CSF (AII).

We recommend that patients with cryptococcosis and raised intracranial pressure are managed in conjunction with clinicians with appropriate expertise in the treatment of cryptococcosis of the CNS, and neurosurgical consultation should be sought as indicated (BIII).

In patients with cryptococcosis and raised intracranial pressure, we recommend that acetazolamide and diuretic therapy not be used (EI).

In most patients with cryptococcal infection and raised intracranial pressure, we suggest that systemic glucocorticosteroids not be used (DII).

An IRS characterized by worsening meningitis, adenopathy, or pulmonary infiltrates can occur in patients receiving antiretroviral therapy. In these patients we recommend that adjunctive systemic glucocorticosteroid therapy be considered (CII).

Remark. Prednisone 40–60 mg/day (or equivalent) for 1 to 2 weeks seems appropriate in these patients.

TREATMENT OF ASPERGILLOSIS

Aspergilli are ubiquitous in the environment, with more than 150 recognized species. In tissues, aspergilli may be seen as septate hyphae. *Aspergillus* species are the most common cause of mortality due to invasive mycoses in the United States. The most common species infecting humans are *A. fumigatus* (64–67% in two series), *A. flavus*, *A. niger*, and *A. terreus* (167, 168). When invasive disease occurs, it is usually acute and life-threatening, and one or more of the following factors are present: neutropenia, glucocorticoid therapy, or cytotoxic chemotherapy. In addition, patients without the traditional risk factors for *Aspergillus* infection, particularly in ICU populations, are being increasingly encountered. Several diseases have been prominently implicated in this new group, including COPD, post-influenza, cirrhosis, alcoholism, various post-surgical settings, and adults presenting with heterozygous chronic granulomatous disease. Other pulmonary manifestations of *Aspergillus*-related disease, such as allergic bronchopulmonary aspergillosis, aspergilloma, and chronic necrotizing aspergillosis, can also occur (169).

Prophylaxis of susceptible patients, such as immunocompromised hosts, is often indicated, particularly in those with significant neutropenia using systemic antifungal drugs (170–174) (AII). Environmental measures such as high-efficiency particulate air (HEPA) filtration are also frequently employed to minimize exposure to *Aspergillus* species in the hospital (175). Recent studies indicate some utility of mold-active antifungals, including itraconazole, posaconazole, amphotericin B formulations, and echinocandins, in preventing invasive aspergillosis in patients with malignancies and hematopoietic stem cell transplant (HSCT) patients. The most compelling data come from large, randomized trials showing superiority of posaconazole compared with fluconazole or itraconazole in preventing invasive aspergillosis in neutropenic patients with acute myelogenous leukemia or myelodysplastic syndrome, and in recipients of hematopoietic stem cell transplantation (172, 173). Other experience suggests utility of itraconazole, micafungin, and inhaled liposomal amphotericin B. The committee believes that some anti-*Aspergillus* prophylaxis is warranted in a selected group of high-risk HSCT recipients and in patients with hematologic malignancies, particularly those associated with severe neutropenia. However, identifying the optimal drug and defining the most appropriate population are matters of controversy. In addition, lung transplantation patients exhibit particular risk for invasive aspergillosis, and prophylaxis, especially with inhaled amphotericin B formulation, is often employed in the absence of large, randomized trial data demonstrating efficacy.

The diagnosis of invasive aspergillosis is difficult, but recent studies suggest utility of diagnostic aides that detect *Aspergillus* galactomannan antigen in serum, or even bronchoalveolar lavage (BAL) fluid (176). Recently, strategies of pre-emptive therapy based on the detection of *Aspergillus* galactomannan antigen or polymerase chain reaction (PCR) testing on serial blood samples of high-risk patients have been suggested (177). Two recent randomized trials suggest potential utility of such measurements, although the results were not definitive (178, 179). More data are necessary to determine if these tests can be used to drive pre-emptive therapy or to withhold drugs in the setting of fever during neutropenia.

Invasive Aspergillosis

When invasive disease is suspected or confirmed, prompt, aggressive antifungal treatment is essential (Table 8). Reversal of neutropenia, if possible, is necessary for recovery in almost all patients. Surgical excision has an important role in the invasion of bone, burn wounds, epidural abscesses, and vitreal disease (BIII). Surgery may also be valuable when invasive pulmonary disease fails aggressive antifungal chemotherapy, particularly when disease impinges on major vascular structures with risk of major bleeding (CIII). These are individualized decisions based on the clinical presentation, but combined medical and surgical strategies can frequently be successful.

Invasive Aspergillosis

Therapy is often prolonged, lasting several months to more than a year, with duration individualized to an individual patient's clinical response (CIII). Prerequisites for discontinuing treatment include clinical and radiographic resolution, microbiologic clearance, and reversal of immunosuppression. Reinstating therapy in patients who have responded should be considered if immunosuppression is reinstated, or if the patient requires additional cytotoxic therapy or another HSCT (BIII). Although amphotericin B deoxycholate had historically been the "gold standard" for the treatment of invasive aspergillosis, most seasoned clinicians and the most recent IDSA guidelines recommend voriconazole as the primary treatment option (180). This decision was supported by at least one large randomized trial (181, 182) (AI).

Amphotericin B lipid formulations. There are no definitive data or consensus opinions indicating improved efficacy of any of the lipid amphotericin formulations over amphotericin B deoxycholate in the treatment of invasive aspergillosis (183–185). Thus, the best indication for using a lipid formulation appears to be for reducing renal toxicity (AII) to allow the administration of high doses of amphotericin for a prolonged time. Recently, a large randomized trial demonstrated no additional benefits of high-dose liposomal amphotericin B (10 mg/kg/d) compared with lower-dose liposomal amphotericin B regimens (3 mg/kg/d), and outcomes were generally good with the lower dose, suggesting utility of liposomal amphotericin B in doses of 3–5 mg/kg/day, and therapeutic risk associated with excessive toxicities at the higher doses (186).

TABLE 8. INITIAL RECOMMENDED THERAPY FOR PULMONARY *ASPERGILLUS* INFECTION

Disease Manifestation	Treatment Recommendations	Comments
Invasive aspergillosis	<p>Primary therapy:</p> <p>intravenous voriconazole (6 mg/kg every 12 h for 1 d, followed by 4 mg/kg every 12 h) until improvement, followed by oral voriconazole (200 mg every 12 h) or oral itraconazole (400–600 mg/d) until resolution or stabilization of all clinical and radiographic manifestations</p> <p>OR</p> <p>intravenous liposomal amphotericin B (3–5 mg/kg/d) until improvement, followed by oral voriconazole (200 mg every 12 h) or oral itraconazole (400–600 mg/d) until resolution or stabilization of all clinical and radiographic manifestation</p> <p>Salvage therapy:</p> <p>intravenous caspofungin (70 mg Day 1 and 50 mg/d intravenously thereafter) or intravenous micafungin (100–150 mg/d) until improvement, followed by oral voriconazole (200 mg every 12 h) or oral itraconazole (400–600 mg/d) until resolution of disease</p> <p>OR</p> <p>posaconazole (200 mg four times per day initially, then 400 mg twice daily orally after stabilization of disease)</p>	<p>Follow up serum galactomannan level</p> <p>Reversal of immune suppression (neutropenia)</p>
Chronic necrotizing (“semi-invasive”) pulmonary aspergillosis	<p>For mild to moderate disease, voriconazole (200 mg every 12 h) or itraconazole (400–600 mg/d) until resolution or stabilization of all clinical and radiographic manifestations.</p> <p>If clinically severe consider beginning with either liposomal amphotericin B or intravenous voriconazole as described above for invasive disease.</p> <p>Consider surgical resection</p>	<p>Reversal of immunosuppression (corticosteroids)</p> <p>Rule out dissemination.</p>
Allergic bronchopulmonary aspergillosis	<p>Corticosteroids (doses and durations vary widely, with doses adjusted on level of airflow obstruction, eosinophilia, and levels of IgE)</p>	<p>Itraconazole (200 mg twice daily for 16 wk initially) has been used as a steroid-sparing agent</p>
Aspergilloma	<p>No indication for antifungal agents</p> <p>Bronchial angiography and embolization</p> <p>Surgical resection</p>	<p>Can become chronic progressive pulmonary disease or invasive if immunosuppression given (i.e., sarcoid, chronic obstructive pulmonary disease)</p>
Hypersensitivity pneumonitis	<p>No indication for antifungal agents</p> <p>Corticosteroids</p>	<p>Avoidance measures</p>

Voriconazole. Voriconazole has recently emerged as a standard therapy for the treatment of invasive aspergillosis, based on the results of a randomized trial comparing the outcomes to amphotericin B deoxycholate; however, whether outcomes are superior to lipid formulations of amphotericin B has not been determined (181). In many instances voriconazole may be considered the treatment of choice (AII) (187). *In vitro* studies have generally shown greater activity of voriconazole over amphotericin B deoxycholate or itraconazole, though this is not a universal finding (188–192). *A. terreus* is frequently resistant to amphotericin B, but susceptible to voriconazole (187, 193). Management of potential drug–drug interactions, and attention to appropriate dosing to achieve measurable and optimal levels, are important clinical issues, although the exact role for therapeutic drug monitoring is currently being defined. After achieving adequate initial disease control with intravenous voriconazole, the patient can be transitioned to oral formulations of this drug.

Itraconazole. Oral itraconazole is not recommended for initial therapy for invasive aspergillosis. However, after disease progression is arrested with either voriconazole or amphotericin, the patient can be transitioned to oral itraconazole (180) (BIII). When using oral itraconazole in patients in whom clinical response is critical or in doubt, itraconazole levels should be documented in serum (AII).

Posaconazole. Posaconazole is highly active against *Aspergillus* species *in vitro* and in animal models (194–198), and recent data indicate good performance as salvage therapy of invasive aspergillosis (17). The drug is only available as an oral formu-

lation. As mentioned above, the efficacy and safety of posaconazole has been compared with fluconazole or itraconazole as prophylaxis for prolonged neutropenia in patients receiving chemotherapy for acute myelogenous leukemia or the myelodysplastic syndrome (173). Significantly fewer patients in the posaconazole group had invasive aspergillosis, and survival was significantly longer among recipients of posaconazole than among recipients of fluconazole or itraconazole. However, serious adverse events possibly or probably related to treatment were greater in the posaconazole group compared with the fluconazole or itraconazole group, with the most common adverse events being gastrointestinal tract disturbances. Monitoring posaconazole levels are useful, as with the other azoles. The exact target ranges are dependent on the methodology employed, and ranges for that particular assay should be followed when making dose adjustments.

Caspofungin. Caspofungin use in invasive aspergillosis is largely limited to salvage therapy, often in combination with other antifungal agents, after primary therapy with amphotericin-based regimens have failed (199, 200) (CII). Although the drug has been approved as a single-agent salvage therapy drug for invasive aspergillosis, the drug does not kill *Aspergillus* species *in vitro*, and robust clinical data are lacking.

Combination therapy. While each individual antifungal agent has limitations, combinations might prove more effective and create a widened spectrum of drug activity, more rapid antifungal effect, synergy, lowered dosing of toxic drugs, or a reduced risk of antifungal resistance (201, 202). Clinical therapy

with amphotericin B and azoles has been extensively reviewed (203). Despite theoretical concerns of amphotericin B potentially antagonizing azoles, amphotericin B plus itraconazole has been used effectively for invasive aspergillosis (168, 204).

Although the results of recent case series suggest a reason for optimism using the combination of voriconazole and caspofungin (205), outcomes need to be confirmed in a randomized trial. There is currently insufficient clinical support to recommend combination therapy, although many clinicians are employing this approach as a "last option," or in settings of particularly advanced disease (CII).

Sequential therapy. There are reports of various patterns of sequential antifungal therapy for aspergillosis (206). An earlier regimen used amphotericin B to treat a patient's acute disease until neutropenia recovers, and then oral itraconazole maintenance antifungal coverage (168, 207). Currently, however, a switch from an intravenous amphotericin B preparation or voriconazole to oral voriconazole deserves strong consideration.

Immunomodulatory therapy. Reversal of immunosuppression, such as with withdrawal of corticosteroids, results in better outcomes in allogeneic stem cell transplant patients, but is often not feasible. Immunotherapy, such as with granulocyte colony-stimulating factor (G-CSF) or granulocyte/macrophage colony-stimulating factor (GM-CSF), is designed to increase the number of phagocytic cells and shorten the duration of neutropenia, modulate the kinetics or actions of those cells at the site of infection, and/or activate the fungicidal activity of phagocytes to kill fungi more efficiently (208, 209). GM-CSF appeared to offer some protection against invasive aspergillosis in one clinical trial in patients with acute myelogenous leukemia, decreasing the fungal infection-related mortality from 19% to 2% (210) (CII). However, exuberant immune responses during the course of cytokine therapy may lead to tissue damage and potential worsening of disease (211, 212). IFN- γ may reduce the incidence of invasive aspergillosis in patients with chronic granulomatous disease (213). However, comparative studies are required, given concerns of complications in organ transplant recipients (i.e., provoking graft-versus-host-disease [GVHD] or organ rejection). There are anecdotal reports of granulocyte transfusions assisting treatment of fungal infections in neutropenic patients (CIII).

Chronic Necrotizing Aspergillosis ("Semi-Invasive Aspergillosis")

Chronic, "semi-invasive" pulmonary aspergillosis is infrequent, and may take cavitory, necrotizing, and/or fibrosing forms. The clinical picture most resembles chronic pulmonary coccidioidomycosis or histoplasmosis. Diabetes, prior pulmonary disease, and/or corticosteroid therapy are common underlying conditions, though other immunosuppressing conditions, including AIDS, have also been associated. In addition, patients with an aspergilloma may develop semi-invasive disease after prolonged courses of corticosteroids. Symptoms include cough with or without hemoptysis, dyspnea, weight loss, fatigue, and chest pain. Histopathology reveals chronic inflammation, necrosis, fibrosis and/or granulomas, with hyphae in the cavities or superficially in adjacent or necrotic tissue. Pleural thickening or intracavitary fungus balls may occur. IgG precipitating antibody to *Aspergillus* is very common. No randomized trials have been performed, but case series reporting therapeutic responses have included one or more of the following: voriconazole, itraconazole, amphotericin B, surgical resection, and adjunctive IFN- γ (214–219) (CII). The committee would, however, favor either voriconazole or itraconazole for mild to moderate disease until resolution or stabilization of the clinical and radiographic manifestations. Initial therapy with intrave-

nous amphotericin B or intravenous voriconazole should be considered in patients with severe disease, as described for invasive pulmonary aspergillosis. In addition, surgical resection may be necessary in some cases, based upon severity of disease, structural considerations, and response to antifungal treatment.

Allergic bronchopulmonary aspergillosis (ABPA). Since ABPA is a noninvasive, hypersensitivity disease, therapeutic recommendations differ significantly from those for invasive aspergillosis. The goal of therapy in ABPA is prophylaxis against, and treatment of, acute exacerbations, as well as prevention of end-stage fibrotic disease. Systemic corticosteroids are the cornerstone of therapy (AII) (220–226). The recommended starting dose is 0.5 mg/kg/day prednisone (or other steroid equivalent), with the dose tapering as indicated by symptom improvement. Mild exacerbations may be controlled with inhaled steroids and bronchodilators. Leukotriene antagonists may be useful adjuncts at such times (BII). For acute exacerbations of disease, a prednisone dose of 0.5–1.0 mg/kg/day for 1 to 2 weeks, followed by 0.5 mg/kg every other day for 6 to 12 weeks upon clinical remission is recommended, followed by tapering of the dose to the patient's original pre-exacerbation dose. Multiple asthmatic exacerbations in the face of such a management strategy will necessitate chronic steroid therapy, usually greater than 7.5 mg/day. It is noteworthy that ABPA is of particular concern to patients with cystic fibrosis, in which up to 10% of patients are affected. Specific recommendations on this particular population have previously been published, and the reader is referred to those previous recommendations for that group of patients (227).

Since lung damage can occur even in asymptomatic individuals, it is important to monitor serum IgE levels at regular intervals, such as every 1 to 2 months. The steroid dose should be adjusted upward if the serum IgE significantly increases (e.g., double the baseline value taken after initial stabilization on maintenance systemic steroids) (CIII). Serial monitoring of pulmonary function tests and chest imaging is also indicated, as is adjustment of the steroid dose if there is imaging evidence such as infiltrates, mucoid impaction, fibrosis, worsening bronchiectasis, or worsening physiology. Itraconazole at a dose of 200 mg twice daily may be instituted over a 6-month treatment trial in some of these patients. The results of a randomized trial suggest itraconazole therapy in addition to corticosteroids is associated with symptomatic improvement and lessening of steroid requirements compared with steroid treatment alone (AI) (228). The role of anti-IgE therapy in these patients is currently being studied, but remains unclear (229).

Aspergillomas

Aspergillomas are fungal balls within lung cavities. The natural history of affected patients is variable. Poor prognostic factors include severity of the underlying pulmonary disease, increasing size or number of aspergillomata, immunosuppression, increasing *Aspergillus*-specific IgG titers, HIV infection, chronic pulmonary sarcoidosis with cavitory changes, and lung transplantation (230, 231). Hemoptysis is a dangerous sequela. Antifungal therapy is of limited utility because of the lack of a blood supply (232–234). Randomized trials are lacking. In patients with massive hemoptysis, emergent bronchial artery embolization is required and can be life-saving (BII) (235–237). Re-bleeding is common after arterial embolization, and surgical consultation should be sought early. Surgical resection is the definitive treatment, but is associated with a high morbidity and mortality (BII) (238–241). Surgical interventions are often limited by patient co-morbidities and poor lung function. Percutaneous intracavitary instillation of antifungals has also been attempted in patients with contraindications to surgery, with only anecdotal success (242–244). The role of antifungal therapy is limited and

should be reserved for patients who are suspected of having a component of semi-invasive disease.

Hypersensitivity Pneumonitis Related to *Aspergillus* Species

Environmental exposure to *Aspergillus* species may result in hypersensitivity pneumonitis. Occasionally, chronic hypersensitivity may mimic usual interstitial pneumonia and progress to pulmonary fibrosis. When hypersensitivity pneumonitis is suspected, serum antibodies against *Aspergillus* species are detected in the serum, suggesting prior exposure. Antifungal therapy is not indicated for hypersensitivity pneumonitis. Treatment strategies include avoidance and, when necessary, corticosteroid therapy (up to 60 mg/d to taper over 1 mo) (245) (BIII).

Recommendations. IMMUNOCOMPETENT HOST. *ALLERGIC BRONCHOPULMONARY ASPERGILLOSIS.* In patients with allergic bronchopulmonary aspergillosis, we recommend prednisone (or other steroid equivalent) with a starting dose of 0.5 mg/kg/day, with the dose tapering as indicated by symptom improvement (AI).

In patients with acute exacerbations of allergic bronchopulmonary aspergillosis, we recommend prednisone 0.5–1.0 mg/kg/day daily for 1 to 2 weeks, followed by 0.5 mg/kg every other day for 6 to 12 weeks upon clinical remission, followed by tapering of the dose to the patient's original pre-exacerbation dose (AI).

In patients with mild exacerbations of allergic bronchopulmonary aspergillosis, we suggest that inhaled steroids and bronchodilators, as well as leukotriene antagonists, can be beneficial in some patients (BII) (221).

In patients with multiple asthmatic exacerbations despite the management strategies described above, we recommend/suggest that chronic steroid therapy, usually greater than 7.5 mg/day, may be required (BIII).

In all patients with allergic bronchopulmonary aspergillosis, we recommend regular monitoring of serum IgE levels, serial monitoring of pulmonary function tests, and chest imaging; when imaging evidence, such as infiltrates, mucoid impaction, fibrosis, or worsening bronchiectasis, is present, we recommend/suggest adjustment of the steroid dose (AII).

Remark. Itraconazole 200 mg twice daily for 16 weeks initially has been used as a steroid-sparing agent for allergic bronchopulmonary aspergillosis (BI).

ASPERGILLOMAS. In patients with aspergillomas, we generally recommend that antifungal agents not be used (DII). We suggest that antifungals be used only in patients suspected of having a component of semi-invasive disease (BIII).

Remark. Aspergillomas can develop into chronic necrotizing ("semi-invasive") pulmonary disease if immunosuppressive agents are administered.

In patients with aspergillomas with massive hemoptysis, we recommend emergent bronchial artery embolization (BII). In addition, thoracic surgical consultation should be obtained in the event of uncontrolled bleeding (BIII).

In some patients with aspergillomas with massive hemoptysis, we suggest that surgical resection may be necessary to control local disease and massive hemoptysis (BII).

HYPERSENSITIVITY PNEUMONITIS RELATED TO ASPERGILLUS. In patients with hypersensitivity pneumonitis, we recommend that antifungal therapy not be used. In these same patients, we recommend avoidance of *Aspergillus* exposure, and, when necessary, corticosteroid therapy up to 60 mg/day, tapering over 1 month (243)(BIII).

IMMUNOCOMPROMISED HOST. *INVASIVE PULMONARY ASPERGILLOSIS.* In patients with invasive pulmonary aspergillosis, we recommend either:

- intravenous voriconazole 6 mg/kg every 12 hours for 1 day, followed by 4 mg/kg every 12 hours until improvement,

followed by oral voriconazole 200 mg every 12 hours (preferred) or oral itraconazole 400–600 mg/day until resolution or stabilization of all clinical and radiographic manifestations (AI); or

- intravenous liposomal amphotericin B 3–5 mg/kg/day until improvement, followed by oral voriconazole 200 mg every 12 hours (preferred) or oral itraconazole 400–600 mg/day until resolution or stabilization of all clinical and radiographic manifestation (AI)

Remarks. Reversal of immune suppression, such as neutropenia, if possible, is generally necessary for successful treatment.

Currently, the best indication for using a lipid formulation appears to be for reducing renal toxicity (AII) to allow the administration of high doses of amphotericin for a prolonged time.

Monitoring of serum galactomannan levels can be useful to judge response of therapy and outcome.

In patients with refractory invasive pulmonary aspergillosis in whom aggressive antifungal chemotherapy has failed, and who have focal disease, we suggest consideration of surgical excision (CIII).

In patients with invasive pulmonary aspergillosis who have failed front line therapy and are requiring salvage therapy, we suggest either:

- intravenous caspofungin 70 mg on Day 1 and 50 mg/day intravenously thereafter, or intravenous micafungin 100–150 mg/day until improvement, followed by oral voriconazole 200 mg every 12 hours or oral itraconazole 400–600 mg/day until resolution of disease (CII); or
- posaconazole 200 mg four times per day initially, then 400 mg twice daily orally after stabilization of disease (CIII).

CHRONIC NECROTIZING ASPERGILLOSIS. In patients with chronic necrotizing aspergillosis, with mild to moderate disease, we suggest voriconazole (200 mg every 12 h) or itraconazole (400–600 mg/d) until resolution or stabilization of all clinical and radiographic manifestations (CII).

If clinically severe, consider beginning therapy of chronic necrotizing aspergillosis with either liposomal amphotericin B or IV voriconazole as described above for invasive disease (CII).

Surgical resection may be clinically indicated, based upon severity of disease, structural considerations, and response to antifungal therapy (CIII).

In select patients at high risk of invasive fungal infection, such as HSCT recipients and other patients with hematologic malignancies, particularly those with severe neutropenia, we suggest that some anti-*Aspergillus* prophylaxis is warranted (BII). Recent data support the use of posaconazole 200 mg orally three times daily, with a full meal or a liquid nutritional supplement, until recovery from neutropenia and clinical remission is established (AI). Other prophylaxis approaches have utilized itraconazole, micafungin, and inhaled liposomal amphotericin B.

Remark. Identifying the most appropriate population for prophylaxis remains an area of ongoing investigation.

TREATMENT OF CANDIDIASIS

Candida species are the fourth most common cause of nosocomial bloodstream infections in the United States (246, 247). Candidemia is the most common manifestation of systemic or invasive candidiasis, and is associated with significant prolon-

gation of hospital length-of-stay compared with length-of-stay in nonfungemic patients. The disease usually originates from colonization by *Candida* species of the gastrointestinal tract or the skin. Recent data indicate that approximately 10% of patients in intensive care units (ICUs) are at high risk for developing candidemia, based on these factors: (1) indwelling central venous catheter, prosthetic devices, or systemic antibiotics for 4 or more days; and (2) at least two of the following other risk factors: total parenteral nutrition on Days 1 to 4 of ICU stay, any dialysis on Days 1 to 4 of ICU stay, any major surgery in the 7 days prior to or on ICU admission, pancreatitis in the 7 days prior to or on ICU admission, systemic steroids in the 7 days prior to ICU admission, other systemic immunosuppressive agents in the 7 days prior to ICU admission, or neutropenia (248, 249) (BII).

Candida albicans remains the most common *Candida* species associated with candidemia. However, in the last decade, non-*albicans* species have accounted for about 40 to 50% of cases of candidemia (246, 247). Risk factors for increased incidence of non-*albicans* *Candida* bloodstream infection in the ICU include exposure to fluconazole, central venous catheters, and mean number of antibiotic days (250). Duration of ICU stay and exposure to specific antibiotics, such as to vancomycin, were not associated with increased risk (250). Data from the most recent epidemiologic series of candidemia cases indicate that *C. glabrata* is the most common non-*albicans* species, especially among immunocompromised patient populations. *Candida parapsilosis* is the third most common cause of candidemia, especially in patients with intravenous catheters, prosthetic devices, and those undergoing intravenous therapy. *Candida tropicalis* is the fourth most common cause of candidemia, and is often associated with leukemia, prolonged neutropenia, and prolonged ICU stay. Other non-*albicans* *Candida* species may rarely cause candidemia; these include *C. krusei*, *C. kefyr*, *C. guilliermondii*, *C. lusitanae*, and *C. stellatoidea*. In patients with fluconazole exposure, *C. krusei* may more commonly cause infection.

Candidemia

The strategy of labeling some patients with “benign” candidemia has not been successful. Since there is significant mortality rate associated with candidemia, and because less toxic antifungal drugs (such as fluconazole and the echinocandins) are now available, all patients with one or more positive blood cultures for *Candida* species should be treated for candidemia. Licensed antifungal drugs that have been used for treatment of candidemia include polyenes (amphotericin B deoxycholate and lipid formulations of amphotericin B), azoles (fluconazole, itraconazole, and voriconazole), and echinocandins (caspofungin, micafungin, and anidulafungin).

Over the past 15 years, a number of large comparative clinical trials to evaluate management strategies for candidemia have been conducted, comparing the relative effects of amphotericin B, azoles, and echinocandins, as well as combination therapies, for treatment of candidemia and other forms of invasive candidiasis (249–256, 258). Two separate, nonblinded randomized studies comparing fluconazole at 400 mg/day with amphotericin B at 0.5–0.6 mg/kg/day (251) resulted in similar success and mortality rates for both agents, and no differences in the rates of persistent candidemia (AI); however, in a third study comparing high-dose fluconazole (fluconazole 800 mg/d plus placebo) to a combination therapy (high-dose fluconazole, 800 mg/d, plus amphotericin B 0.7 mg/kg/d), the group receiving the combination regimen did experience a greater success rate and a lower rate of persistent candidemia than the group receiving fluconazole alone (251). Mortality rates for the two

groups were similar. The primary goal of demonstrating overall superiority of fluconazole was not achieved by these authors. In all three of these randomized trials, fluconazole was associated with less toxicity than amphotericin B. Two other nonrandomized trials comparing fluconazole to amphotericin B demonstrated similar outcomes to those in the randomized trials (252, 253).

In a recent open-label trial comparing voriconazole (6 mg/kg/12 h \times 2, then 3 mg/kg/12 h) to a regimen of amphotericin B (0.7–1.0 mg/kg/d for 3–7 d) followed by fluconazole (400 mg/d) in nonneutropenic patients with candidemia, success rates and primary analysis of efficacy, which compared the proportions of patients surviving with a successful response at 12 weeks after the end of therapy, were similar for both groups (258). The two regimens were similarly effective for candidemia, whether caused by *C. albicans* or non-*albicans* *Candida* species.

Four more recently completed studies exploring the use of echinocandins in treating candidemia provide interesting data and new treatment options. In one large, randomized, blinded trial, caspofungin (70 mg on the first day, then 50 mg/d) was better tolerated and resulted in a better success rate than amphotericin B (0.6–1.0 mg/kg/d) in treating patients with invasive candidiasis, mostly candidemia (254). Caspofungin was also superior to amphotericin B in a modified-intent-to-treat analysis (BI). Follow-up at 6 to 8 weeks revealed no difference in relapse or survival. In this trial, the predominant *Candida* species was *C. albicans* (45%), and other less common species were *C. parapsilosis*, *C. tropicalis*, and *C. glabrata*. The response rate was higher among patients with non-*albicans* candidemia in both groups of patients.

A second randomized study of 245 evaluable patients comparing anidulafungin (100 mg/d) to fluconazole (400 mg/d) showed superior success rates for patients treated with anidulafungin, and patients in this group also had lower rates of persistent candidemia (255) (AI). However, there was no difference in overall patient outcome and the significance in benefit was lost by Week 6.

In the third study comparing micafungin (100 mg/d) to liposomal amphotericin B (3 mg/kg/d), the two drugs exhibited similar rates of success, but micafungin was associated with fewer adverse events (AI). In addition, there was no difference in success rates across *Candida* species (254).

A recent study compared micafungin (100 mg/d) and micafungin (150 mg/d) with a standard dosage of caspofungin (70 mg/d followed by 50 mg/d) in patients with candidemia and other forms of invasive candidiasis (257). There were no significant differences in mortality, relapsing and emergent infections, or adverse events between the different regimens. The study concluded that micafungin was not noninferior to a standard dosage of caspofungin for the treatment of candidemia (255).

Based on the data from these and other studies (255, 256), the following approaches to management of documented candidemia are recommended (Table 9) (AI):

1. If feasible, all existing central venous catheters should be removed. Best evidence for this recommendation is found in the nonneutropenic patient population, including data in which catheter removal was associated with reduced mortality (252, 257, 258). However, there are no data obtained from randomized trials on which to base this recommendation (259, 260). In the event that ongoing central venous access is necessary for the acute management of the patient, a new site should be obtained.
2. Initial antifungal therapy should be with one of the following agents: fluconazole, an amphotericin B formu-

TABLE 9. INITIAL RECOMMENDED THERAPY FOR CANDIDEMIA

Disease Manifestation	Treatment	Comments
Candidemia, clinically stable	Fluconazole (400 mg/d or ~ 6 mg/kg/d)	Remove all central venous catheters. Switch to new site if central access is required. Eye exam by a skilled physician advised. Treatment to continue for 2 wk after last positive blood culture. If local incidence of non- <i>albicans</i> species > 10% consider an echinocandin.
	OR	
	Caspofungin (70 mg loading dose Day 1, then 50 mg/d)	
	OR	
Candidemia, clinically unstable and unknown species	Micafungin (100 mg/d)	Remove all central venous catheters. Switch to new site if central access is required. Eye exam by skilled physician advised. Treatment to continue for 2 wk after last positive blood culture. If local incidence of non- <i>albicans</i> species > 10%, or local frequency of fluconazole resistance in <i>C. albicans</i> is high, strongly consider an amphotericin- or echinocandin-based regimen.
	OR	
	Anidulafungin (200 mg on Day 1, then 100 mg/d)	
	OR	
	Amphotericin B deoxycholate (0.6–1.0 mg/kg/d) or lipid-based amphotericin B (3–5 mg/kg/d)	
	OR	
	Caspofungin (70 mg loading dose Day 1, then 50 mg/d)	
	OR	
	Micafungin (100 mg/d)	
	OR	
	Anidulafungin (200 mg on Day 1, then 100 mg/d)	
	OR	
	Voriconazole (6 mg/kg/12 h x 2, then 3 mg/kg/12 h)	
OR		
High-dose fluconazole (800 mg/d or ~ 12 mg/kg/d)		
OR		
A combination regimen with fluconazole (800 mg/d) and amphotericin B (0.6–1.0 mg/kg/d), for the first 5–6 d		

lation, an echinocandin (such as caspofungin, micafungin, or anidulafungin), or the combination regimen of fluconazole and amphotericin B (261, 262) (BII). In addition, voriconazole has now been approved as a first-line therapy of candidemia (AI). The choice among these agents depends on the clinical status of the patient, identification of the species and/or antifungal susceptibility of the infecting fungus, relative drug toxicity, presence of organ dysfunction that may affect drug clearance, and the patient's prior exposure to various anti-fungal agents (261) (BIII). Local epidemiologic data should be taken into consideration as well. In hospitals or practice areas where the incidence of non-*albicans* *Candida* blood isolates exceeds 10%, an initial empiric regimen other than fluconazole, such as either a polyene or an echinocandin-based regimen, should be considered due to the higher incidence of fluconazole resistance in these species. This would also apply to hospitals where primary resistance of *C. albicans* to fluconazole is high, owing to such factors as frequent use of fluconazole for prophylaxis. Our committee supports this recommendation, largely on the basis of the increasing resistance to fluconazole of non-*albicans* *Candida* spp, specifically, *C. glabrata* and *C. krusei*, and some *C. albicans* isolates. This recommendation deals with the initial empiric treatment regimen. If the *Candida* isolate is determined to be susceptible to fluconazole, then a switch to fluconazole should be made.

- For patients who are clinically stable and have not recently received azole therapy, either fluconazole (400 mg/d or ~ 6 mg/kg/d) or caspofungin (70 mg loading dose Day 1, then 50 mg/d) or micafungin (100 mg/d) or anidulafungin (200 mg on Day 1, then 100 mg/d), is an appropriate choice (BII).
- For patients who are clinically unstable and for whom identification of the *Candida* species in the blood is unknown, there is no definitive recommendation. Several options are available and include: amphotericin B deoxycholate

(0.6–1.0 mg/kg/d), a lipid formulation of amphotericin B (3–5 mg/kg/d), high-dose fluconazole (800 mg/kg/d or ~ 12 mg/kg/d), caspofungin (70 mg loading dose Day 1, then 50 mg/d), micafungin (100 mg/d), anidulafungin (200 mg on Day 1, then 100 mg/d), voriconazole (6 mg/kg/12 h x 2, then 3 mg/kg/12 h), and a combination regimen with fluconazole (800 mg/d) and amphotericin B (0.6–1.0 mg/kg/d, for the first 5–6 d) (BIII). The choice of options should consider the local epidemiology of *Candida* isolate, as noted above. The writing group consensus would choose either an amphotericin B formulation or an echinocandin for such patients (BIII).

- For patients whose *Candida* species is known, the efficacy of specific agents can be predicted. For patients with *C. albicans* and also possibly *C. tropicalis*, the drugs of choice are fluconazole (400 mg/d), amphotericin B (0.6–1.0 mg/kg/d), or an echinocandin (doses as specified above in number 4) (BII). For *C. parapsilosis*, the drugs of choice are fluconazole (400 mg/d) and amphotericin B (0.6–1.0 mg/kg/d). Echinocandins appear to have less activity against *C. parapsilosis*. For patients with candidemia caused by *C. glabrata*, an echinocandin or amphotericin B is recommended (BII). High-dose fluconazole (800 mg/d) may be a suitable alternative. For *C. krusei* candidemia, an echinocandin or amphotericin B is the drug of choice. For candidemia caused by *C. lusitanae*, fluconazole is the preferred therapy (BII).
- Lipid formulations of amphotericin B are usually indicated for patients intolerant of, or refractory to, conventional antifungal therapy (BII).
- For all patients with candidemia, treatment (regardless of the drug or regimen) should be continued for 2 weeks after the last positive blood culture (BII).
- Ocular findings may be the only sign for disseminated candidiasis and can result in blindness. Therefore, at least one formal ophthalmologic examination should be per-

formed in any patient with candidemia within 2 weeks of diagnosis (263). The examination should preferably occur when candidemia is controlled and new spread to the eye is unlikely. In neutropenic patients, this exam should be performed once the neutrophil count has recovered, as earlier exams can be misleading in neutropenic patients. Additional specific therapeutic strategies may be required when the vitreous is involved, including intraocular therapy and consultation with an ophthalmologist for consideration of vitrectomy. With eye involvement, parenteral therapy should also be prolonged, at least until endophthalmitis is arrested. Furthermore, ophthalmic infection may represent a sign of failure of the current selected regimen. In cases of endophthalmitis, expert consultation with infectious disease specialists should be obtained.

9. The topic of prophylaxis for critical-care patients at risk for candidemia remains controversial at the time of this document. A retrospective study identified factors associated with invasive candidiasis in patients hospitalized for at least 4 days (264). The factors included any systemic antibiotic or the presence of a central venous catheter and at least two of the following: total parenteral nutrition, any dialysis, any major surgery, pancreatitis, any use of steroids, or use of other immunosuppressive agents (264). These results have been used to support the initiation of empiric fluconazole for such patients at risk of candidemia. However, a recent control trial randomized 270 adult ICU patients with fever despite administration of broad-spectrum antibiotics, with all patients having central venous catheters and APACHE II scores greater than 16, to receive either intravenous fluconazole (800 mg/d) or placebo for 2 weeks (265). In these critically ill adults with risk factors for invasive candidiasis, empirical fluconazole did not clearly improve a composite outcome when compared with placebo after 4 weeks of follow-up.

Candida Pneumonia

Because invasion of the lung parenchyma by *Candida* species with resulting *Candida* pneumonia is a rare event, controversy surrounds this entity. In fact, the isolation of candidal species from respiratory secretions is most often not clinically significant. That said, two forms of *Candida* pneumonia have been rarely reported (266, 267): primary pneumonia, which follows aspiration of *Candida*-laden oropharyngeal secretions (268), and pneumonia secondary to hematogenously disseminated candidiasis, especially in immunocompromised hosts (269, 270). The second form is more common. There are no large clinical trial data to guide therapy for this disease. Most reported cases have received amphotericin B therapy, but with the availability of newer agents, several treatment options exist, as described under candidemia.

Recommendations. In patients with candidemia, we recommend:

- Removal of all existing central venous catheters (BI). In the event that ongoing central venous access is necessary for the acute management of the patient, a new site should be obtained (BIII).
- Candidemia should be treated with antifungal agents, selecting one of the following agents: fluconazole, an amphotericin B formulation, an echinocandin, voriconazole, or the combination regimen of fluconazole and amphotericin B, based upon specific considerations as outlined below (AI).

- Treatment should continue for 2 weeks after the last positive blood culture (BII).
- The committee advises that all patients with candidemia should receive an eye exam by a skilled physician (BIII).

Remarks. The choice among these agents depends on the clinical status of the patient, identification of the species and/or antifungal susceptibility of the infecting fungus, relative drug toxicity, presence of organ dysfunction that may affect drug clearance, and the patient's prior exposure to various antifungal agents (BIII). Local epidemiologic data should be taken into consideration as well. For hospitals or practice areas where the incidence of non-*albicans Candida* blood isolates exceeds 10%, an initial empiric regimen other than fluconazole should be used, such as either a polyene or an echinocandin-based regimen, due to the higher incidence of fluconazole resistance in these species (BII).

Remark. Recommendation for use of an agent other than fluconazole, such as either a polyene- or an echinocandin-based regimen, would also apply to hospitals where primary resistance of *C. albicans* to fluconazole is high, owing to such factors as frequent use of fluconazole for prophylaxis. This recommendation is largely based on the increasing resistance to fluconazole of non-*albicans Candida* spp, specifically, *C. glabrata* and *C. krusei*, and some *C. albicans* isolates. This recommendation specifically deals with the initial empiric treatment regimen. If the *Candida* isolate is determined to be susceptible to fluconazole, then a switch to fluconazole should be made (BII).

In patients with candidemia who are clinically stable and who have not recently received azole therapy, we recommend either fluconazole (400 mg/d or ~ 6 mg/kg/d) or caspofungin (70 mg loading dose Day 1, then 50 mg/d) or micafungin (100 mg/d) or anidulafungin (200 mg on Day 1, then 100 mg/d) (BII).

In patients with candidemia who are clinically unstable and for whom identification of the *Candida* species in the blood is unknown, we recommend either amphotericin B deoxycholate (0.6–1.0 mg/kg/d), or a lipid formulation of amphotericin B (3–5 mg/kg/d), or caspofungin (70 mg loading dose Day 1, then 50 mg/d), or micafungin (100 mg/d), or anidulafungin (200 mg on Day 1, then 100 mg/d) for initial therapy (BIII).

Remark. Additional treatment options include high-dose fluconazole (800 mg/kg/d or ~ 12 mg/kg/d) or voriconazole (6 mg/kg/12 h \times 2, then 3 mg/kg/12 h), or a combination regimen with high-dose fluconazole (800 mg/d) and amphotericin B (0.6–1.0 mg/kg/d, for the first 5–6 d) (BIII).

In patients with candidemia caused by *C. albicans* and also possibly *C. tropicalis*, we recommend fluconazole (400 mg/d) or amphotericin B (0.6–1.0 mg/kg/d) or caspofungin (70 mg loading dose Day 1, then 50 mg/d) or micafungin (100 mg/d) or anidulafungin (200 mg on Day 1, then 100 mg/d) (BII).

In patients with candidemia caused by *C. parapsilosis*, we recommend fluconazole (400 mg/d) and amphotericin B (0.6–1.0 mg/kg/d) (BIII).

Remark. Echinocandins appear to have less activity against *C. parapsilosis*.

In patients with candidemia caused by *C. glabrata*, we recommend an echinocandin or amphotericin B (BII). Dosing would include either caspofungin (70 mg loading dose Day 1, then 50 mg/d) or micafungin (100 mg/d) or anidulafungin (200 mg on Day 1, then 100 mg/d), or amphotericin B deoxycholate (0.6–1.0 mg/kg/d) or a lipid formulation of amphotericin B (3–5 mg/kg/d).

Remark. High-dose fluconazole (800 mg/d) may be a suitable alternative.

In patients with candidemia caused by *C. krusei*, we recommend an echinocandin or amphotericin B (BII). Dosing would

TABLE 10. TREATMENT OPTIONS FOR *PNEUMOCYSTIS JIROVECI* PNEUMONIA

Drug	Dose	Route	Comments
Trimethoprim plus sulfamethoxazole	15–20 mg/kg 75–100 mg/kg daily (in divided doses) generally for 3 wk	Oral or intravenous	First choice
Primaquine plus clindamycin	30 mg daily 600 mg three times daily, generally for 3 wk	Oral	Alternate option
Atovaquone	750 mg twice daily, generally for 3 wk	Oral	Alternate option
Pentamidine	4 mg/kg/d or 600 mg/d, generally for 3 wk	Intravenous or aerosol	Alternate option (Aerosol is rarely used)
Adjunctive corticosteroids (given in addition to antibiotic agent)	Prednisone (or equivalent dose of other corticosteroid) 40 mg twice daily for 5 d, then 40 mg daily on Days 6–11, and then 20 mg daily through Day 21	Intravenous or oral	Consider for use in patients with moderate to severe disease (P_{aO_2} on room air < 70 mm Hg or the alveolar–arterial oxygen gradient > 35)*

* Definitely recommended for HIV-associated *Pneumocystis* pneumonia. May consider in non–AIDS-associated *Pneumocystis* pneumonia as well.

include either caspofungin (70 mg loading dose on Day 1, then 50 mg/d) or micafungin (100 mg/d) or anidulafungin (200 mg on Day 1, then 100 mg/d), or amphotericin B deoxycholate (0.6–1.0 mg/kg/d) or a lipid formulation of amphotericin B (3–5 mg/kg/d).

In patients with candidemia caused by *C. lusitanae*, we recommend fluconazole (400 mg/d or ~ 6 mg/kg/d) (BII).

TREATMENT OF *PNEUMOCYSTIS* PNEUMONIA

Originally misclassified as a parasite, *Pneumocystis* species have now been definitively categorized as fungi based upon genetic and biochemical analyses. *Pneumocystis* continues to represent a major threat to immunocompromised patients (271). *Pneumocystis jirovecii*, the species infecting humans, is extremely resistant to traditional antifungal agents, including both amphotericin and azole agents (272, 273). Patient groups at risk for *Pneumocystis* pneumonia traditionally include those with HIV infection, hematologic and solid malignancies, organ transplantation, and those receiving immune-suppressive drugs for inflammatory disorders (274).

Immunocompetent Hosts

Clinically significant *Pneumocystis* pneumonia is virtually never observed in immunocompetent adults. Indeed, documentation of *Pneumocystis jirovecii* in a patient without known underlying disease should prompt a careful search for occult immune suppression, including previously unappreciated HIV infection, underlying solid or hematologic malignancy including myelodysplastic syndrome, and medication use, particularly corticosteroids, cytotoxic agents, TNF- α antagonists, and other immune suppressants (274).

Immunocompromised Hosts

All immunosuppressed patients with documented *Pneumocystis* pneumonia require treatment (Table 10). Despite newer agents, trimethoprim–sulfamethoxazole remains the most effective regimen for treating severe *Pneumocystis* pneumonia (AI) (274). This is dosed as trimethoprim 15–20 mg/kg/day and sulfamethoxazole 75–100 mg/kg/day in four daily divided doses. Documenting drug levels of either the sulfamethoxazole or trimethoprim component is useful, and the committee recommends verifying effective drug levels in all patients requiring intravenous therapy. Treatment is usually continued for 3 weeks. It is important to keep in mind that treatment responses

to *Pneumocystis* therapy often require at least 7 to 10 days before clinical improvement is documented. However, in the event that clinical improvement is not observed or clinical deterioration occurs over this timeline, then failure of the first-line treatment should be considered. In addition, adverse effects are common with the first-line agents, and patients with known allergies to sulfa often cannot tolerate this therapy. Second-line agents include primaquine (30 mg/d) plus clindamycin (600 mg three times per day) or atovaquone alone (750 mg twice daily). Alternatively, intravenous pentamidine (4 mg/kg/d) can be given. Aerosolized pentamidine (600 mg/kg/d) has fallen out of favor in recent years, and should only be reserved for those individuals with mild to mild-moderate disease who are intolerant of other therapies. Laboratory and animal data indicate that caspofungin and related compounds may have activity against *Pneumocystis* species (21, 22). However, controlled clinical trial data of the use of caspofungin in *Pneumocystis* pneumonia are lacking.

Adjunctive corticosteroids, given in addition to antibiotics, are of substantial benefit to HIV-infected patients with moderate to severe *Pneumocystis* pneumonia with hypoxemia (P_{aO_2} on room air < 70 mm Hg or the alveolar–arterial oxygen gradient > 35). Such patients should receive prednisone at a dose of 40 mg twice daily for 5 days, then 40 mg daily on Days 6 through 11, and then 20 mg daily through Day 21 (AI) (275). The California Collaborative Treatment Group studied 333 patients with AIDS and *Pneumocystis* pneumonia receiving standard treatment and randomly assigned to receive adjunctive corticosteroids. Those assigned to treatment with corticosteroids had a lower cumulative risk of respiratory failure and death within 84 days. The clinical benefit of reduced respiratory failure and death in patients with AIDS was limited to those with moderate to severe *Pneumocystis* pneumonia as defined above (276). In patients without AIDS who exhibit severe *Pneumocystis* pneumonia, a dose of 60 mg or more of prednisone daily was also associated with better outcome in one retrospective analysis (BII) (277). Although definitive randomized controlled trials addressing the role of adjunctive corticosteroids in *Pneumocystis* pneumonia in settings other than AIDS are lacking, the committee advises adding corticosteroids to the therapeutic regimens of such patients with moderate to severe pneumonia, using dosing regimens as advised for patients with AIDS (BIII).

Prophylaxis of immune-suppressed patients has substantially decreased the burden of this infection. Primary prophylaxis

TABLE 11. DRUGS USEFUL FOR PROPHYLAXIS OF *PNEUMOCYSTIS* PNEUMONIA

Drug	Dose	Route	Comments
Trimethoprim-sulfamethoxazole	1 double-strength tablet daily or 1 single-strength tablet daily or 1 double-strength tablet 3 times per week, for the duration of significant immune suppression*	Oral	First choice Alternate option Alternate option
Dapsone	50 mg twice daily or 100 mg daily	Oral	Ensure patient does not have glucose-6PD deficiency.
Dapsone plus pyrimethamine plus leucovorin	50 mg daily 50 mg weekly 25 mg weekly	Oral	
Dapsone plus pyrimethamine plus leucovorin	200 mg weekly 75 mg weekly 25 mg weekly	Oral	
Atovaquone	750 mg twice daily	Oral	Give with high-fat meals, for maximal absorption.
Pentamidine	300 mg monthly	Aerosol	Rarely used; may be associated with upper lobe relapse.

* In HIV, use prophylaxis if CD4 counts < 200/ μ l. In non-HIV immune-suppressed patients, consider prophylaxis during time periods in which prednisone dose exceeds 20 mg/day for greater than 1 month, especially if patient has associated T-cell defects, or is receiving other cytotoxic of anti-TNF agents. Some experts also recommend monitoring CD4 counts in patients without AIDS, again using the threshold of 200 CD4 cells/ μ l for determining need for prophylaxis.

against *Pneumocystis* pneumonia in HIV-infected adults, including pregnant women and those receiving highly active antiretroviral treatment (HAART), should begin when CD4+ counts less than 200 cells/ μ l or if there is a history of oropharyngeal candidiasis (AI) (278) (Table 11). Patients with previous *Pneumocystis* pneumonia should receive lifelong secondary prophylaxis, unless reconstitution of the immune system occurs. Prophylaxis should be discontinued in patients who have had a response to HAART, as shown by CD4+ cell counts greater than 200 cells/ μ l for a period of 3 months (AI). Ledergerber and colleagues analyzed episodes of recurrent *Pneumocystis* pneumonia in 325 HIV-infected patients after they had peripheral blood CD4 cell count greater than 200 cells/ μ l and found no cases of recurrent *Pneumocystis* during a follow-up period totaling 374 person-years (279). Prophylaxis should be reintroduced if the CD4+ count falls below 200 cells/ μ l (274, 280).

A variety of patients uninfected with HIV but who are receiving immunosuppressive medications, or who have an underlying acquired or inherited immunodeficiency, should also receive prophylaxis. These include patients with hematologic and solid malignancies receiving cytotoxic chemotherapies, organ transplantation, and those treated with immune-suppressive regimens for inflammatory conditions (274). Chronic corticosteroid therapy appears to be the single most common risk factor for patients without AIDS who develop *Pneumocystis* pneumonia. A corticosteroid dose greater than 20 mg of prednisone for a period of 8 weeks or more was associated with a significant risk of *Pneumocystis* pneumonia in patients who did not have AIDS in one series (BII) (281). Similar observations have been observed during cancer or connective tissue diseases that were also treated with corticosteroids (282, 283). However, in assessing a patient's overall risk for *Pneumocystis* pneumonia, the clinician also should consider the presence of immune derangement related to the underlying disease, as well as the presence of other immunosuppressive drugs, particularly cytotoxic agents (274). Recent studies further indicate that anti-TNF- α agents and methotrexate are also independently associated with increased risk of developing *Pneumocystis* pneumonia

(BII) (284, 285). Laboratory monitoring strategies to determine those patients without HIV who are at greatest risk for developing *Pneumocystis* pneumonia is an area of active investigation. While some have suggested monitoring CD4 cell counts in a fashion parallel to that employed with patients with HIV, such a strategy fails to identify all such patients at risk for developing *Pneumocystis* pneumonia (BIII) (274).

Trimethoprim-sulfamethoxazole continues to be the mainstay for *Pneumocystis* prophylaxis. This may be dosed as one double-strength (preferred) given three times per week or one single-strength tablet given once per day. A randomized control trial by Hughes and coworkers in 92 immune-suppressed patients demonstrated that double-strength trimethoprim-sulfamethoxazole was as effective in the prevention of *Pneumocystis* pneumonitis when given three days a week as it was when given daily (286) (AI). Compliance may be enhanced by a daily regimen, and double-strength dosing may be associated with lesser occurrence of other bacterial infections (274). Alternative *Pneumocystis* prophylaxis regimens include atovaquone (1,500 mg/d given as two, daily divided doses) or dapsone (100 mg/d) (AI) (274). Prophylaxis failures, however, have been associated with dapsone use in transplantation populations (287). Aerosolized pentamidine (300 mg once per month) is very rarely used in prophylaxis regimens, and is discouraged. There are data to indicate that aerosolized pentamidine prophylaxis may result in worse survival and higher risk for other infections when used in the bone marrow transplantation setting (288). In an open-label trial of 843 patients with HIV infection and fewer than 200 CD4+ cells/ μ l receiving one of three randomly assigned prophylactic agents (trimethoprim-sulfamethoxazole, dapsone, or aerosolized pentamidine), the lowest failure rates occurred in patients receiving trimethoprim-sulfamethoxazole, or high dose dapsone (100 mg/day), with the highest failure rate occurring with aerosolized pentamidine, with a predilection toward upper-lobe *Pneumocystis* infection (289). There are also no available data currently available on the use of caspofungin and related compounds in prophylaxis of patients at risk for *Pneumocystis* pneumonia.

Earlier concerns that trimethoprim-sulfamethoxazole may be contraindicated for prophylaxis among patients concurrently treated with methotrexate because of myelosuppression have not been supported by recent studies. For instance, in one large study of patients treated with up to 25 mg of methotrexate per week who also received trimethoprim-sulfamethoxazole prophylaxis, severe myelosuppression was not observed (BII) (290). Such patients should be treated with folate supplementation (1.0 mg/d), or leucovorin on the day after receiving methotrexate, and careful monitoring of complete blood counts and liver function tests should be performed at least once a week while receiving therapy.

Recommendations. IMMUNOCOMPETENT HOSTS. Since *Pneumocystis jirovecii* does not cause clinically significant pneumonia in immunocompetent adults, in patients with no apparent underlying disease, a careful search for occult immune suppression should be conducted (AII).

IMMUNOCOMPROMISED HOSTS. In patients with moderate to severe *Pneumocystis* pneumonia (Pa_{O_2} on room air < 70 mm Hg or an alveolar-arterial oxygen gradient > 35, or those requiring hospitalization), we recommend trimethoprim 15–20 mg/kg/day and sulfamethoxazole 75–100 mg/kg/day in four daily divided doses for 3 weeks (AI).

Remark. In patients requiring intravenous therapy, we recommend verifying effective drug levels (AI).

In patients who cannot tolerate the above therapy, we recommend primaquine 30 mg/day plus clindamycin 600 mg three times per day, or intravenous pentamidine 4 mg/kg/day (BI).

Remark. Aerosolized pentamidine 600 mg/kg/day for treatment of *Pneumocystis* pneumonia has fallen out of favor in recent years, and should only be reserved for those individuals with mild to mild-moderate disease who are intolerant of other therapies.

In HIV-infected patients with moderate to severe *Pneumocystis* pneumonia with hypoxemia, we recommend/suggest prednisone at a dose of 40 mg twice daily for 5 days, then 40 mg/day on Days 6 through 11, and then 20 mg/day through Day 21 (AI).

In patients without HIV with moderate to severe *Pneumocystis* pneumonia, we suggest adding corticosteroids to the therapeutic regimens, using dosing regimens as advised for patients with AIDS (BII).

In patients with mild to moderate *Pneumocystis* pneumonia (Pa_{O_2} on room air > 70 mm Hg or an alveolar-arterial oxygen gradient < 35, and not requiring hospitalization), we suggest either oral trimethoprim 15–20 mg/kg/day and sulfamethoxazole 75–100 mg/kg/day in four daily divided doses, oral primaquine 30 mg/day plus clindamycin 600 mg three times per day, or oral atovaquone (750 mg twice daily) for 3 weeks (AI).

Prophylaxis of *Pneumocystis Pneumonia*. In HIV-infected patients with *Pneumocystis* pneumonia with CD4+ counts less than 200 cells/ μ l, we recommend prophylaxis with trimethoprim-sulfamethoxazole dosed as one double-strength tablet or one single-strength tablet given once per day, or one double-strength tablet taken three times per week, until achieving CD4+ cell counts greater than 200 cells/ μ l for a period of 3 months (AI).

In HIV-infected patients with *Pneumocystis* pneumonia who have a history of oropharyngeal candidiasis, we recommend prophylaxis until achieving CD4+ cell counts greater than 200 cells/ μ l for a period of 3 months (AI).

In patients with hematologic and solid malignancies receiving cytotoxic chemotherapies, organ transplantation, and those treated with immune-suppressive regimens for inflammatory conditions, we recommend prophylaxis during the period of immune suppression with either:

- trimethoprim-sulfamethoxazole dosed as one double-strength tablet or one single-strength tablet given once per day, or one double-strength tablet taken three times per week (AI); or
- atovaquone 1,500 mg/day given as two daily divided doses (AI); or
- dapsone 50 mg twice daily or 100 mg/day (AI).
- Alternative regimens for prophylaxis include dapsone (50mg/d) plus pyrimethamine (50 mg/wk) plus leucovorin (25 mg/wk), or dapsone (200 mg/wk) plus pyrimethamine (75 mg wk) plus leucovorin (25 mg/wk) (BII).

Remarks. In immune-suppressed patients without HIV, consider prophylaxis during time periods where prednisone dose exceeds 20 mg/day for greater than 1 month, especially if the patient has associated T cell defects, or is receiving other cytotoxic drugs or anti-TNF agents. Some experts also recommend monitoring CD4 counts in patents without AIDS, again using the threshold of 200 CD4 cells/ μ l for determining need for prophylaxis.

Double-strength TMP-SMX dosing may be associated with lesser occurrence of other bacterial infections (274).

Aerosolized pentamidine (300 mg once per month) is very rarely used in prophylaxis regimens, and is generally discouraged.

In patients with concurrent methotrexate treatment or with other concerns for myelosuppression, and who are receiving anti-folate-based *Pneumocystis* regimens with either trimethoprim-sulfamethoxazole or dapsone-pyrimethamine regimens, we further suggest folate supplements of 1.0 mg/day, or leucovorin (25mg/wk) on the day following methotrexate treatment during the period of prophylaxis or treatment (BIII).

TREATMENT OF OTHER FUNGI

The management of emerging or rare fungi is supported by limited evidence-based studies with no randomized, blinded, comparative studies. The main mycoses in this category include zygomycoses (including diseases due to *Rhizopus*, *Mucormycosis*, *Cunninghamella*, and other species), hyalohyphomycoses (including diseases due to *Paecilomyces*, *Fusarium*, and *Scedosporium*), the phaeohyphomycoses (including diseases due to dematiaceous or black molds such as *Curvularia*, *Bipolaris*, *Exophiala*, and *Alternaria*), and infections related to *Trichosporon*. It is important to note that airway cultures can identify a variety of fungi, which may be contaminants, colonizers, or disease producers, particularly in immunocompromised hosts. Determination of their importance requires accurate fungal identification, work-up to rule out disease, and, in some cases, referral to infectious disease experts for evaluation. Certain principles based on substantial clinical experience, as well as results of some open clinical trials, can also help guide treatment strategies (Table 12). In the majority of infections, there is a three-part management strategy for eradication.

The vast majority of these rare and emerging fungal infections involve immunocompromised patients. Therefore, a primary strategy for management of these infections with underlying diseases is to maximally reduce immunosuppressive drugs, provide immunostimulants, and/or rapidly control the underlying diseases or conditions, such as HIV infection, diabetes, and/or chemotherapy-induced neutropenia. However, in allergic fungal sinusitis caused by dematiaceous molds, an alteration in host immunity might be considered in management, along with the use of immunosuppressive regimens, such as inhaled or

TABLE 12. TREATMENT RECOMMENDATIONS FOR OTHER RARE FUNGI

Fungus	Primary Therapy	Alternative Therapies
Zygomycosis	Lipid formulations of amphotericin B (5 mg/kg/d) or amphotericin B deoxycholate (0.7–1.0 mg/kg/d)* †	Posaconazole (400 mg orally twice daily or 200 mg orally four times per day) (only some strains fully susceptible)* †
<i>Paecilomyces/Trichosporon</i>	Voriconazole*†	Posaconazole*†
<i>Fusarium</i>	Voriconazole or posaconazole or lipid formulation of amphotericin B*†	
<i>Scedosporium apiospermum</i>	Voriconazole (200 mg intravenously or orally twice daily) or posaconazole (200 mg four times daily)	
<i>Scedosporium prolificans</i>	No consistent antifungal†	
Phaeohyphomycosis	Itraconazole or voriconazole at (200 mg orally twice daily)*†	Posaconazole (200 mg four times daily), flucytosine (100 mg/kg/d)* †

* Exact dose and duration of treatment for these emerging rare infections are not precise, and consultation with an expert in infectious diseases regarding these clinical decisions should be considered.

† None of these agents has evidence-based randomized, comparative trials for support. These recommendations are based on clinical experience and *in vitro* susceptibility testing.

systemic corticosteroids with or without an antifungal agent (291). A second therapeutic strategy is to debulk or debride necrotic tissues, cysts, or true abscesses. This surgery is particularly important in the angioinvasive zygomycoses, which produce devitalized tissue, and also in cysts or abscesses produced by dematiaceous molds. The third strategy for management of rare and emerging fungal infections involves the use of specific antifungal drugs, which can be delivered as local therapy for fungal keratitis and/or irrigated into the wound during a surgical procedure, or as a systemic antifungal drug for invasive disease. Although not necessarily correlated with clinical outcome, *in vitro* antifungal susceptibility by Clinical and Laboratory Standards Institute M38A method may help validate antifungal drug choices in these rare and emerging molds.

General guideline statements regarding antifungal drug treatments for emerging and rare fungi include amphotericin B deoxycholate at 0.7–1.0 mg/kg/day as the drug of choice for zygomycosis (AII). However, recent clinical experience supports the use of lipid formulations of amphotericin B (liposomal amphotericin B and amphotericin B lipid complex) at 5 mg/kg/day with similar efficacy, but less toxicity (292–294). In fact, these lipid preparations of amphotericin B can be considered first-line therapy (AII). An additional recent retrospective study further supports rapid initiation of amphotericin therapy in zygomycosis. Study results indicated that delayed amphotericin B–based therapy (i.e., initiating treatment \geq 6 d after diagnosis) resulted in a twofold increase in mortality rate at 12 weeks after diagnosis, compared with early treatment (82.9% vs. 48.6%; $P = 0.008$) (295). For intolerant or refractory patients with zygomycosis, an alternative treatment is posaconazole 400 mg orally twice per day or 200 mg orally four times per day for optimal drug exposure, and consideration of drug level measurements for monitoring therapy (BII) (296, 297). However, only some zygomycetes are fully susceptible to posaconazole. For fusariosis, lipid formulations of amphotericin B, voriconazole, or posaconazole appear to have similar efficacy and the antifungal choice is dictated by clinical conditions (BII) (44, 293, 296, 298, 299). For scedosporiosis, the treatment regimen depends on the species. For *S. apiospermum* (*Pseudallescheria boydii*), the drug of choice is voriconazole at 200 mg intravenously or orally twice per day (BII) (44, 298). Disease caused by *S. prolificans* will require individualized treatments and possibly a combination of drugs (such as azoles and terbinafine), since this fungal species is relatively resistant to all classes of antifungals (CIII) (44, 292, 298, 300). Infections with the dematiaceous molds (phaeohyphomycoses) can be successfully managed with either itraconazole or voriconazole at 200 mg orally twice per day or posaconazole 400 mg orally twice per day as first-line agents (BII) (44, 296, 298, 301, 302). Flucytosine at 100 mg/kg/day

and adjusted to renal function has been used in combination therapies for serious phaeohyphomycosis (CIII), and this combination strategy may be particularly relevant for phaeohyphomycosis of the central nervous system (303). For trichosporonosis (*Trichosporon* species and *Geotrichum capitatum*) (304) and *Paecilomyces* infections, attention to immune reconstitution is essential; however, it appears from case reports and *in vitro* testing that extended-spectrum triazoles, such as voriconazole, posaconazole, and itraconazole, may be successfully used in treatment, although failures can also occur with these agents (BIII) (44). A role for the echinocandins in the treatment of these uncommon infections has not yet been well established.

The exact dosing and duration of treatment for these emerging, rare infections are not precise, and consultation with an expert in infectious diseases regarding these clinical decisions should be considered. Case reports indicate that the use of adjunctive immune-stimulation agents, such as cytokines, has been successful (305). Thus, colony-stimulating factors or interferon- γ will need to be used on an individual, case-by-case basis. Treatment of infections with a very rare fungal species having less than a dozen reported cases will need to be guided by *in vitro* susceptibility testing and/or clinical experience within the literature, or from a consultant's opinion. It is most important to have a correct identification of the fungus to help guide treatment decisions.

Recommendations. In patients with zygomycosis, we recommend lipid formulations of amphotericin B at 5 mg/kg/day or amphotericin B deoxycholate at 0.7–1.0 mg/kg/day (BII).

In patients who are intolerant of, or refractory to, amphotericin B, we suggest posaconazole 200 mg orally four times per day (BII).

Remark. Only some zygomycetes are fully susceptible to posaconazole.

For patients with fusariosis, we suggest lipid formulations of amphotericin B, voriconazole, or posaconazole (BII). The exact dosing and duration of therapy is unclear, is not evidence-based, and is largely derived from *in vitro* susceptibility testing. Therefore, we recommend consultation with an expert in infectious diseases regarding these clinical decisions (BIII).

For patients with scedosporiosis associated with *S. apiospermum*, we suggest voriconazole 200 mg intravenously or orally twice per day (BII). The duration of therapy is not precise and depends on closely monitoring clinical response to therapy. For patients with scedosporiosis associated with *S. prolificans*, no consistent antifungal regimen can be recommended (CIII). Therefore, we recommend consultation with an expert in infectious diseases regarding these clinical decisions (BIII).

For patients with phaeohyphomycoses, we suggest either itraconazole or voriconazole 200 mg orally twice per day, or

posaconazole 400 mg orally twice per day (BII). The duration of therapy is not precise and depends on closely monitoring clinical response to therapy. Therefore, we recommend consultation with an expert in infectious diseases regarding these clinical decisions (BIII).

Remark. Flucytosine 100 mg/kg/day adjusted to renal function has been used in combination with the primary agents listed above in serious phaeohyphomycoses infections, and may be particularly relevant in treating phaeohyphomycosis of the central nervous system.

For trichosporonosis (*Trichosporon* species and *Geotrichum capitatum*) (304) and *Paecilomyces* infections, attention to immune reconstitution is essential. However, case reports and *in vitro* testing suggest that extended-spectrum triazoles, such as voriconazole, posaconazole, and itraconazole, may be successfully used in treatment, although failures can also occur with these antifungal agents (BIII) (44). The exact dosing and duration of therapy is unclear, and is not evidence-based. Therefore, we recommend consultation with an expert in infectious diseases regarding these clinical decisions (BIII).

Additional Treatment Considerations

In the majority of infections, there is a three-part management strategy for eradication:

1. Because the vast majority of these rare and emerging fungal infections involve immunocompromised patients, a primary strategy for management of these infections with underlying diseases is to maximally reduce immunosuppressive drugs, provide immunostimulants, and/or rapidly control the underlying diseases or conditions such as HIV infection, diabetes, and/or chemotherapy-induced neutropenia. However, in allergic fungal sinusitis caused by dematiaceous molds, an alteration in host immunity might be considered in management with the use of immunosuppressive regimens, such as inhaled, topical, or systemic corticosteroids with or without an antifungal agent, administered either topically or systemically (291).
2. A second therapeutic strategy is to debulk or debride necrotic tissues, cysts, or true abscesses. This surgery is particularly important in the angioinvasive zygomycoses, which produce devitalized tissue, and also in cysts or abscesses produced by dematiaceous molds.
3. The third strategy for management of rare and emerging fungal infections is the use of specific antifungal drugs, which can be delivered as local therapy for fungal keratitis and/or irrigated into the wound during a surgical procedure, or given systemically for invasive disease. Although not necessarily correlated with clinical outcome, *in vitro* antifungal susceptibility by CLSI (NCCLS) M38A method may help validate antifungal drug choices in these rare and emerging molds.

GLOSSARY OF TERMS

Azole antifungal—Azole antifungals are a class of agents that possess a five-member nitrogen heterocyclic ring structure containing at least one other noncarbon atom, such as nitrogen, oxygen, or sulfur. Azole antifungal drugs function by inhibiting 14 α -demethylase that synthesizes ergosterol in the plasma membrane of the fungus. Typical agents include itraconazole, fluconazole, voriconazole, and posaconazole.

Basidiomycetous yeast—These fungi possess spores on a basidium structure following sexual reproduction. Although this group includes rusts, smuts, and certain mushrooms, the *Cryptococcal* species are the members of this group most commonly associated with human disease.

Dimorphic fungus—Dimorphic fungi generally exist in mold (or hyphal/ filamentous) form at room temperature and grow in a yeast form at body temperatures. Various dimorphic fungi that are potential human pathogens include *Coccidioides immitis*, *Paracoccidioides brasiliensis*, and *Candida albicans*.

Echinocandin antifungals—These agents are large lipopeptide molecules that inhibit β -(1, 3)-glucan synthesis, thereby damaging fungal cell walls. Echinocandins are rapidly fungicidal against most *Candida* spp. and fungistatic against *Aspergillus* spp. Typical agents include caspofungin, micafungin, and anidulafungin.

Moulds—Moulds (or molds) are fungal microorganisms, which grow in the form of multicellular filaments, termed *hyphae*.

Polyene antifungals—These agents contain multiple conjugated double bonds, which bind to sterols in the fungal cell membrane, principally ergosterol, rendering the fungal cell leaky and resulting in cell death. Typical agents in this class include amphotericin B deoxycholate, and the lipid formulations of amphotericin.

Yeasts—Yeasts are eukaryotic fungal microorganisms. Most reproduce by asexual budding, although some also exhibit binary fission. Yeasts are generally unicellular, although some species exhibit multicellular forms through the generation of a string of connected budding cells known as *pseudohyphae*. At body temperature, *Candida albicans* is most commonly present in yeast form.

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