Treatment of Aspergillosis: Clinical Practice Guidelines of the Infectious Diseases Society of America

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EXECUTIVE SUMMARY

Aspergillus species have emerged as an important cause of life-threatening infections in immunocompromised patients. This expanding population is composed of patients with prolonged neutropenia, advanced HIV infection, and inherited immunodeficiency and patients who have undergone allogeneic hematopoietic stem cell transplantation (HSCT) and/or lung transplantation. This document constitutes the guidelines of the Infectious Diseases Society of America for treatment of aspergillosis and replaces the practice guidelines for *Aspergillus* published in 2000 [1]. The objective of these guidelines is to summarize the current evidence for treatment of different forms of aspergillosis. The quality of evidence for treatment is scored according to a standard system used in other Infectious Diseases Society of America guidelines. This document reviews guidelines for management of the 3 major forms of aspergillosis: invasive aspergillosis, chronic (and saprophytic) forms of aspergillosis, and allergic forms of aspergillosis. Given the public health importance of invasive aspergillosis, emphasis is placed on the diagnosis, treatment, and prevention of the different forms of invasive aspergillosis, including invasive pulmonary aspergillosis, sinus aspergillosis, disseminated aspergillosis, and several types of single-organ invasive aspergillosis.

There are few randomized trials on the treatment of invasive aspergillosis. The largest randomized controlled trial demonstrates that voriconazole is superior to deoxycholate amphotericin B (D-AMB) as primary treatment for invasive aspergillosis. Voriconazole is recommended for the primary treatment of invasive aspergillosis in most patients (A-I). Although invasive pulmonary aspergillosis accounts for the preponderance of cases treated with voriconazole, voriconazole has been used in enough cases of extrapulmonary and disseminated infection to allow one to infer that voriconazole is effective in these cases. A randomized trial comparing 2 doses of liposomal amphotericin B (L-AMB) showed similar efficacy in both arms, suggesting that liposomal therapy could be considered as alternative primary therapy in some patients (A-I). For sal-

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It is important to realize that guidelines cannot always account for individual variation among patients. They are not intended to supplant physician judgment with respect to particular patients or special clinical situations and cannot be considered inclusive of all proper methods of care or exclusive of other treatments reasonably directed at obtaining the same results. Accordingly, the Infectious Diseases Society of America considers adherence to these guidelines to be voluntary, with the ultimate determination regarding their application to be made by the physician in light of each patient's individual circumstances.

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vage therapy, agents include lipid formulations of amphotericin (LFAB; A-II), posaconazole (B-II), itraconazole (B-II), caspofungin (B-II), or micafungin (B-II). Salvage therapy for invasive aspergillosis poses important challenges with significant gaps in knowledge. In patients whose aspergillosis is refractory to voriconazole, a paucity of data exist to guide management. Therapeutic options include a change of class using an amphotericin B (AMB) formulation or an echinocandin, such as caspofungin (B-II); further use of azoles should take into account host factors and pharmacokinetic considerations. Refractory infection may respond to a change to another drug class (B-II) or to a combination of agents (B-II). The role of combination therapy in the treatment of invasive aspergillosis as primary or salvage therapy is uncertain and warrants a prospective, controlled clinical trial.

Assessment of patients with refractory aspergillosis may be difficult. In evaluating such patients, the diagnosis of invasive aspergillosis should be established if it was previously uncertain and should be confirmed if it was previously known. The drug dosage should be considered. Management options include a change to intravenous (IV) therapy, therapeutic monitoring of drug levels, change of drug class, and/or combination therapy.

Antifungal prophylaxis with posaconazole can be recommended in the subgroup of HSCT recipients with graft-versus-host disease (GVHD) who are at high risk for invasive aspergillosis and in neutropenic patients with acute myelogenous leukemia or myelodysplastic syndrome who are at high risk for invasive aspergillosis (A-I). Management of breakthrough invasive aspergillosis in the context of mould-active azole prophylaxis is not defined by clinical trial data. The approach to such patients should be individualized on the basis of clinical criteria, including host immunosuppression, underlying disease, and site of infection, as well as consideration of antifungal dosing, therapeutic monitoring of drug levels, a switch to IV therapy, and/or a switch to another drug class (B-III).

Certain conditions of invasive aspergillosis warrant consideration for surgical resection of the infected focus. These include but are not limited to pulmonary lesions contiguous with the heart or great vessels, invasion of the chest wall, osteomyelitis, pericardial infection, and endocarditis (B-III). Restoration of impaired host defenses is critical for improved outcome of invasive aspergillosis (A-III). Recovery from neutropenia in a persistently neutropenic host or reduction of corticosteroids in a patient receiving high-dose glucocorticosteroids is paramount for improved outcome in invasive aspergillosis.

A special consideration is made concerning recommendations for therapy of aspergillosis in uncommon sites, such as osteomyelitis and endocarditis. There are very limited data on these infections, and most involve D-AMB as primary therapy simply because of its long-standing availability. Based on the strength of the randomized study, the panel recommends voriconazole for primary treatment of these very uncommon manifestations of invasive aspergillosis (B-III).

Management of the chronic or saprophytic forms of aspergillosis varies depending on the condition. Single pulmonary aspergillomas may be best managed by surgical resection (B-III), whereas chronic cavitary and chronic necrotizing pulmonary aspergillosis require long-term medical therapy (B-III).

The management of allergic forms of aspergillosis involves a combination of medical and anti-inflammatory therapy. For example, management of allergic bronchopulmonary aspergillosis (ABPA) involves the administration of itraconazole and corticosteroids (A-I).

INTRODUCTION

Heretofore considered to be an unusual cause of infection, *Aspergillus* species have emerged as important causes of morbidity and mortality in immunocompromised patients [2–4]. Invasive aspergillosis currently constitutes the most common cause of infectious pneumonic mortality in patients undergoing HSCT and is an important cause of opportunistic respiratory and disseminated infection in other immunocompromised patients [5–11]. Furthermore, *Aspergillus* species also produce a wide range of chronic, saprophytic, and allergic conditions. Although other forms of aspergillosis, such as ABPA, allergic sinusitis, and saprophytic infection, are also causes of morbidity, they are seldom life-threatening. Throughout this document, treatment recommendations are rated according to the standard scoring system of the Infectious Diseases Society of America and United Stated Public Health Service for rating recommendations in clinical guidelines, as summarized in table 1.

MICROBIOLOGY AND EPIDEMIOLOGY OF ASPERGILLOSIS

Organisms. *Aspergillus fumigatus* is the most common species recovered from cases of invasive aspergillosis [12]. The next most commonly recovered species are *Aspergillus flavus, Aspergillus niger,* and *Aspergillus terreus* [13]. Some institutions may have a predominance of *A. flavus* or *A. terreus* as the most frequently recovered species of *Aspergillus* [14]. *A. terreus* is clinically resistant to AMB, but species, including *A. flavus, Aspergillus lentulus, Aspergillus nidulans, Aspergillus ustus, Aspergillus glaucus,* and others, can also demonstrate resistance [15–20].

Classification and definitions. Aspergillosis causes patient afflictions that are classically defined as invasive, saprophytic, or allergic [21]. Invasive diseases caused by *Aspergillus* species include infections of the lower respiratory tract, sinuses, and skin as portals of entry. The CNS, cardiovascular system, and other tissues may be infected as a result of hematogenous dis-

Table 1. Infectious Diseases Society of America–United States Public Health Service grading system for ranking recommendations in clinical guidelines.

Category, grade	Definition
Strength of recommendation	
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
Quality of evidence	
I	Evidence from ⩾1 properly randomized, controlled trial
II	Evidence from ⩾1 well-designed clinical trial, without randomization; from cohort or case-controlled analytic studies (preferably from >1 center); from multiple time-series; or from dramatic results from uncontrolled experiments
III	Evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees

semination or direct extension from contiguous foci of infection. Saprophytic involvement includes *Aspergillus* otomycosis and pulmonary aspergilloma. Allergic conditions encompass allergic *Aspergillus* sinusitis and allergic bronchopulmonary aspergillosis [22]. Although other classifications have been proposed, reference to the above clinical conditions will be made throughout these guidelines.

Members of the European Organization for Research in Treatment of Cancer–Invasive Fungal Infection Cooperative Group and National Institute of Allergy and Infectious Diseases Mycoses Study Group formed a Consensus Committee to develop standard definitions for invasive fungal infections for clinical research [23]. Based on a review of the literature and an international consensus, a set of research-oriented definitions for invasive fungal infections (including invasive aspergillosis), as observed in immunocompromised patients with cancer, was developed. Three levels of certainty of invasive aspergillosis were defined: proven, probable, and possible. Although the definitions are intended for use in the context of clinical and/or epidemiological research, they provide a standard set of criteria by which guidelines can be developed for the treatment of invasive aspergillosis.

The definition for proven aspergillosis requires histopathological documentation of infection and a positive result of culture of a specimen from a normally sterile site. The definition of probable aspergillosis requires the fulfillment of criteria within 3 categories: host factors, clinical manifestations (symptoms, signs, and radiological features), and microbiological evidence. Throughout these guidelines, the term "invasive aspergillosis" will assume a diagnostic certainty of proven or probable invasive aspergillosis. With 2 important exceptions, proven or probable infection requires the recovery of an organism. The first exception includes the fairly frequent occurrence of histopathological demonstration of hyphae consistent with *Aspergillus* species in patients with negative culture results. The other exception consists of fulfilling the diagnostic criteria for probable invasive aspergillosis with a surrogate non–culture-based method (i.e., a positive galactomannan assay or β-glucan assay result and radiologically compatible CT findings) in an immunocompromised host with clinical findings of infection that constitute the definition of probable invasive aspergillosis.

Several other points bear note concerning these definitions of aspergillosis. First, the term "probable" denotes a relatively high degree of certainty that the signs and symptoms of infection in the immunocompromised host are truly due to an *Aspergillus* species. A study by Stevens and Lee [24] that examined response of invasive aspergillosis to itraconazole using Mycoses Study Group definitions found similar outcomes for proven and probable invasive aspergillosis, suggesting that combining these 2 categories is appropriate for outcomes analyses. Second, the European Organization for Research in Treatment of Cancer–Mycoses Study Group document clearly articulates that the consensus definitions are not intended to be a direct guide to practice [23]. Third, the definitions are principally applicable to immunocompromised patients with cancer and HSCT recipients. These definitions are currently being refined to reflect increasing understanding of the patterns of invasive aspergillosis in an expanded population of immunocompromised patients.

Diagnosis. *Aspergillus* species grow well on standard media and can be identified to species level in most laboratories. Culture confirmation, where possible, is important to differentiate aspergillosis from other filamentous fungal infections, such as fusariosis and scedosporiosis. Blood cultures are of limited utility, because the results are often not positive even in disseminated infection. Bronchoalveolar lavage, transthoracic percutaneous needle aspiration, or video assisted thoracoscopic biopsy are standard procedures for establishing a diagnosis of invasive pulmonary aspergillosis. Fluid and tissue specimens from these procedures may reveal characteristic angular dichotomously branching septate hyphae on direct microscopic examination and/or *Aspergillus* species on culture. Where fea-

sible, specimens obtained from these procedures are cultured on fungal media for optimal growth of *Aspergillus* species [25, 26]. However, results of cytologic examination, pathologic examination, direct smears, and culture may be falsely negative for clinical specimens from patients who are already receiving systemic antifungal therapy and in cases in which the diagnostic procedure could not be performed directly in the affected area (e.g., when the bronchoscopic examination or washing could not be performed directly in the affected area or when the bronchoscope or biopsy needle could not reach the infected tissues). Thus, lack of a positive culture or direct smear result does not rule out the diagnosis of invasive aspergillosis. Moreover, recovery of *Aspergillus* species from clinical specimens by invasive procedures may be impractical in patients who are hemodynamically unstable, are severely hypoxic, have low platelet counts, or have advanced coagulation deficits. Thus, other markers of infection are often used in the assessment of patients at risk for invasive aspergillosis.

Increasing recognition of the halo sign and air-crescent sign by improved CT technology in immunocompromised patients has greatly facilitated the diagnosis of invasive pulmonary aspergillosis in patients with hematologic conditions [27–31]. Although these radiological features are characteristic, they are not diagnostic of invasive pulmonary aspergillosis. Infections due to other angioinvasive filamentous fungi, such as Zygomycetes, *Fusarium* species, and *Scedosporium* species, as well as to *Pseudomonas aeruginosa* and *Nocardia* species, may cause a halo sign and other radiological features described for aspergillosis. Although these more characteristic radiological patterns of invasive pulmonary aspergillosis have been well described in neutropenic hosts, less is known about the features of these lesions in other immunocompromised patients [27, 29].

The availability of the galactomannan EIA also may contribute substantially toward a non–culture-based diagnosis of invasive aspergillosis. EIA for galactomannan has been validated in animal models and in patients as a surrogate marker for detection of invasive aspergillosis [32–42]. Galactomannan antigen has also been detected in CSF samples from patients with CNS aspergillosis [43–45] and in bronchoalveolar lavage fluid specimens from patients with invasive pulmonary aspergillosis, although the use of EIA for galactomannan in such contexts is investigational [46, 47]. In addition to facilitating early detection, serial assessment of galactomannan antigenemia may facilitate therapeutic monitoring [48, 49]. However, the use of serial galactomannan for therapeutic monitoring remains investigational. Thus, duration of therapy should be determined, not solely by normalization of antigenemia, but also by resolution of clinical and radiological findings.

Several well-conducted studies of this EIA system have demonstrated good sensitivity in the detection of invasive aspergillosis in patients with hematological malignancy [33, 35, 50–52]. However, the sensitivity in nonneutropenic patients may be lower, possibly because of a lower residual fungal burden or anti-*Aspergillus* antibodies [53, 54]. The combined use of serum galactomannan antigen measurement and detection of pulmonary infiltrates by early use of CT should improve detection of invasive pulmonary aspergillosis and permit earlier initiation of antifungal therapy [55]. Several variables, including antifungal therapy or prophylaxis, significantly reduce levels of circulating galactomannan [35, 52]. False-positive results have been reported in several contexts, including in patients who have received certain antibiotics (pipercillin-tazobactam and amoxicillin-clavulanate), in cases of neonatal colonization with *Bifidobacterium,* the in cases in which plasmalyte is used in bronchioalveolar lavage fluids, and in patients with other invasive mycoses (including *Penicillium,* histoplasmosis, and blastomycosis) [36, 56–61]. Despite these limitations, this assay is a useful adjunctive test to establish an early diagnosis, particularly when used in serial screening of patients at high risk of infection.

Other potential circulating markers for detection of aspergillosis include (1→3)-β-D-glucans detected by the Tachypleus or Limulus assay [62–66]. The Tachypleus or Limulus assay used to detect the presence of (1→3)-β-D-glucans is a variation of the limulus assay used to detect endotoxin. The presence of (1→3)-β-D-glucans in serum signifies the presence of fungal invasion but is not specific for *Aspergillus* species [67]. False-positive results can occur in a variety of contexts, such as through glucan contaminated blood collection tubes, gauze, depth-type membrane filters for blood processing, and in vitro tests using various antibiotics (e.g., some cephalosporins, carbapenems, and ampicillin-sulbactam) [68]. The Fungitell assay (Associates of Cape Cod) for detection of (1→3)-β-D-glucans is approved by the US Food and Drug Administration (FDA) for the diagnosis of invasive mycoses, including aspergillosis [66, 69]. One study reported that, among 283 patients with acute myeloid leukemia and myelodysplastic syndrome who were receiving antifungal prophylaxis, the (1→3)-β-D-glucan assay was sensitive and specific in early detection of 20 proven or probable invasive fungal infections, including candidiasis, fusariosis, trichosporonosis, and aspergillosis [66, 69]. The database for this assay in other populations at high risk for invasive aspergillosis is limited, and more research is required in these populations [66, 69]. PCR-based diagnosis, which amplifies *Aspergillus*-specific fungal genes (usually ribosomal DNA genes), has shown considerable promise for invasive aspergillosis [70–79]. However, these systems have not been standardized, are not commercially available, and remain investigational [80]. Combining non–culture-based diagnostics (e.g., PCR and GM and GM and [1→3]-β-D-glucan) is an important research

direction that may improve the overall predictive value of these systems.

The development of standardized methodology for antifungal susceptibility testing is another recent advance in the laboratory evaluation of *Aspergillus* species. Interpretive breakpoints have not been established for any of the antifungal agents against filamentous fungi. However, new developments through the Clinical and Laboratory Standards Institute provide reproducible methods for antifungal susceptibility testing. Further studies using these in vitro methods may lead to improved rationale for selection of antifungal compounds in the treatment of invasive aspergillosis. Although azole resistance by *Aspergillus* species is unusual, patients exposed chronically to antifungal triazoles have been reported to have refractory infection caused by isolates with elevated MICs [81, 82].

Recognizing that other filamentous fungi, such as *Fusarium* species, *Scedosporium* species, various dematiaceous (pigmented) moulds, and Zygomycetes, may cause similar patterns of infection, a definitive microbiological diagnosis should be established where possible. Non-*Aspergillus* filamentous fungi may require different antifungal agents and may carry a prognosis that is distinct from those of *Aspergillus* species.

ANTIFUNGAL COMPOUNDS USED FOR TREATMENT OF INVASIVE ASPERGILLOSIS

Over the past decade, a considerable expansion in antifungal drug research and the clinical development of several new compounds and strategies targeted against invasive aspergillosis have occurred [83]. The following FDA-approved compounds have in vitro, in vivo, and clinical activity against *Aspergillus* species and are licensed for treatment of invasive aspergillosis: D-AMB and its lipid formulations (AMB lipid complex [ABLC], L-AMB, and AMB colloidal dispersion [ABCD]), itraconazole, voriconazole, posaconazole, and caspofungin.

Voriconazole and D-AMB are the only compounds licensed in the United States for primary treatment of invasive aspergillosis. The LFABs, itraconazole, and caspofungin are approved for salvage therapy of invasive aspergillosis. Posaconazole is licensed for prophylaxis of invasive aspergillosis in neutropenic patients with leukemia and myelodysplasia and in allogeneic HSCT recipients with GVHD. Posaconazole also was approved in the European Union for treatment of invasive aspergillosis that is refractory to an AMB formulation or to itraconazole. Micafungin and anidulafungin, which are also members of the class of echinocandins, have in vitro, in vivo, and clinical activity against aspergillosis but are not licensed in the United States for this indication. Antifungal management of invasive aspergillosis is summarized in table 2. A comprehensive review of antifungal compounds is beyond the scope of these guidelines and is covered in detail elsewhere [84–86]. Because the experience of administration of these agents is predominantly in adults, specific notice is given to the need for adjustment of dosages in pediatric patients, to obtain plasma exposures comparable to those of adults. These pharmacological differences in pediatric and adult dosing are discussed in more detail elsewhere [87, 88].

AMB

AMB is a natural polyene macrolide antibiotic that consists of 7 conjugated double bonds, an internal ester, a free carboxyl group, and a glycoside side chain with a primary amino group. It is not orally absorbed. For IV use, AMB has been solubilized with deoxycholate as micellar suspension (D-AMB). AMB primarily acts by binding to ergosterol (the principal sterol in the cell membrane of most medically important fungi), leading to the formation of ion channels and fungal cell death. AMB also binds to cholesterol (the main sterol of mammalian cell membranes), although with less avidity than for ergosterol, resulting in cellular injury and end organ dysfunction. A second mechanism of action of AMB may involve oxidative damage of the cell through a cascade of oxidative reactions linked to lipoperoxidation of the cell membrane. AMB has in vitro and in vivo activity against most *Aspergillus* species. Most isolates of *A. terreus* are resistant to AMB in vitro, in vivo, and in patients.

Following IV administration, AMB becomes highly protein bound before distributing predominantly into the reticuloendothelial tissues (liver, spleen, bone marrow, and lung) and the kidney. Peak plasma concentrations of 2–4 μg/mL are achieved following IV infusion of 1 mg/kg of D-AMB. Clearance from plasma is slow, with a β half-life of 24–48 h and a terminal half-life of $\geqslant$15 days. Despite mostly undetectable concentrations in the CSF, D-AMB is active in the treatment of some fungal infections of the CNS because of its penetration into infected brain tissue via a disrupted blood-brain barrier.

D-AMB causes acute infusion-related reactions and dose-limiting nephrotoxicity. Infusion-related reactions include fever, rigors, chills, myalgias, arthralgias, nausea, vomiting, headaches, and bronchospasm. D-AMB–induced nephrotoxicity is characterized by azotemia, urinary wasting of potassium and magnesium, renal tubular acidosis, and impaired urinary concentration ability. Azotemia attributable to D-AMB is particularly common in the doses required for treatment of invasive aspergillosis. D-AMB–related azotemia is exacerbated by concomitant nephrotoxic agents, particularly cyclosporine and tacrolimus. Renal toxicity associated with the use of D-AMB has the potential to lead to renal failure and dialysis, particularly in HSCT recipients and in patients with diabetes mellitus, patients with underlying renal impairment, and patients receiving concomitant nephrotoxic agents. Hospitalized patients receiv-

Table 2. Summary of recommendations for the treatment of aspergillosis.

Condition	Therapy[a]		Comments
	Primary	Alternative[b]	
Invasive pulmonary aspergillosis	Voriconazole (6 mg/kg IV every 12 h for 1 day, followed by 4 mg/kg IV every 12 h; oral dosage is 200 mg every 12 h)	L-AMB (3–5 mg/kg/day IV), ABLC (5 mg/kg/day IV), caspofungin (70 mg day 1 IV and 50 mg/day IV thereafter), micafungin (IV 100–150 mg/day; dose not established[c]), posaconazole (200 mg QID initially, then 400 mg BID PO after stabilization of disease[d]), itraconazole (dosage depends upon formulation)[e]	Primary combination therapy is not routinely recommended based on lack of clinical data; addition of another agent or switch to another drug class for salvage therapy may be considered in individual patients; dosage in pediatric patients for voriconazole is 5–7 mg/kg IV every 12 h and for caspofungin is 50 mg/m^2/day; limited clinical experience is reported with anidulafungin; dosage of posaconazole in pediatric patients has not been defined; indications for surgical intervention are outlined in table 3
Invasive sinus aspergillosis	Similar to invasive pulmonary aspergillosis	Similar to invasive pulmonary aspergillosis	Similar to invasive pulmonary aspergillosis
Tracheobronchial aspergillosis	Similar to invasive pulmonary aspergillosis	Similar to invasive pulmonary aspergillosis	Similar to invasive pulmonary aspergillosis
Chronic necrotizing pulmonary aspergillosis (subacute invasive pulmonary aspergillosis)	Similar to invasive pulmonary aspergillosis	Similar to invasive pulmonary aspergillosis	Because chronic necrotizing pulmonary aspergillosis requires a protracted course of therapy measured in months, an orally administered triazole, such as voriconazole or itraconazole, would be preferred over a parenterally administered agent
Aspergillosis of the CNS	Similar to invasive pulmonary aspergillosis	Similar to invasive pulmonary aspergillosis	This infection is associated with the highest mortality among all of the different patterns of invasive aspergillosis; drug interactions with anticonvulsant therapy
Aspergillus infections of the heart (endocarditis, pericarditis, and myocarditis)	…[f]	Similar to invasive pulmonary aspergillosis	Endocardial lesions caused by *Aspergillus* species require surgical resection; aspergillus pericarditis usually requires pericardiectomy
Aspergillus osteomyelitis and septic arthritis	…[f]	Similar to invasive pulmonary aspergillosis	Surgical resection of devitalized bone and cartilage is important for curative intent
Aspergillus infections of the eye (endophthalmitis and keratitis)	Intraocular AMB indicated with partial vitrectomy[f]	Similar to invasive pulmonary aspergillosis; limited data with echinocandins	Systemic therapy may be beneficial in management of aspergillus endophthalmitis; ophthalmologic intervention and management is recommended for all forms of ocular infection; topical therapy for keratitis is indicated

(continued)

Table 2. ***(Continued.)***

Condition	Therapy[a]		Comments
	Primary	Alternative[b]	
Cutaneous aspergillosis	…[f]	Similar to invasive pulmonary aspergillosis	Surgical resection is indicated where feasible
Aspergillus peritonitis	…[f]	Similar to invasive pulmonary aspergillosis	…
Empirical and preemptive antifungal therapy	For empirical antifungal therapy, L-AMB (3 mg/kg/day IV), caspofungin (70 mg day 1 IV and 50 mg/day IV thereafter), itraconazole (200 mg every day IV or 200 mg BID), voriconazole (6 mg/kg IV every 12h for 1 day, followed by 3 mg/kg IV every 12 h; oral dosage is 200 mg every 12 h)	…	Preemptive therapy is a logical extension of empirical antifungal therapy in defining a high-risk population with evidence of invasive fungal infection (e.g., pulmonary infiltrate or positive galactomannan assay result)
Prophylaxis against invasive aspergillosis	Posaconazole (200 mg every 8h)	Itraconazole (200 mg every 12 h IV for 2 days, then 200 mg every 24 h IV) or itraconazole (200 mg PO every 12 h); micafungin (50 mg/day)	Efficacy of posaconazole prophylaxis demonstrated in high-risk patients (patients with GVHD and neutropenic patients with AML and MDS)
Aspergilloma[g]	No therapy or surgical resection	Itraconazole or voriconazole; similar to invasive pulmonary aspergillosis	The role of medical therapy in treatment of aspergilloma is uncertain; penetration into preexisting cavities may be minimal for AMB but is excellent for itraconazole
Chronic cavitary pulmonary aspergillosis[g]	Itraconazole or voriconazole	Similar to invasive pulmonary aspergillosis	Innate immune defects demonstrated in most of these patients; long-term therapy may be needed; surgical resection may lead to significant complications; anecdotal responses to IFN-γ
Allergic bronchopulmonary aspergillosis	Itraconazole	Oral voriconazole (200 mg PO every 12 h) or posaconazole (400 mg PO BID)	Corticosteroids are a cornerstone of therapy; itraconazole has a demonstrable corticosteroid-sparing effect
Allergic aspergillus sinusitis	None or itraconazole	Few data on other agents	…

NOTE. ABLC, AMB lipid complex; AMB, amphotericin B; AML, acute myelogenous leukemia; BID, twice daily; GVHD, graft-versus-host disease; IV, intravenous; L-AMB, liposomal AMB; MDS, myelodysplastic syndrome; PO, orally; QID, 4 times daily.

[a] Duration of therapy for most conditions for aspergillosis has not been optimally defined. Most experts attempt to treat pulmonary infection until resolution or stabilization of all clinical and radiographic manifestations. Other factors include site of infection (e.g., osteomyelitis), level of immunosuppression, and extent of disease. Reversal of immunosuppression, if feasible, is important for a favorable outcome for invasive aspergillosis.

[b] Alternative (salvage) therapy for patients refractory to or intolerant of primary antifungal therapy.

[c] Micafungin has been evaluated as salvage therapy for invasive aspergillosis but remains investigational for this indication, and the dosage has not been established.

[d] Posaconazole has been approved for the salvage treatment of invasive aspergillosis in the European Union but has not been evaluated as primary therapy for invasive aspergillosis.

[e] Dosage of itraconazole in treatment of invasive pulmonary aspergillosis depends on formulation. The dosage for tablets is 600 mg/day for 3 days, followed by 400 mg/day. Although used in some case reports, oral solution is not licensed for treatment of invasive aspergillosis. Parenteral formulation has been studied in a limited series using a dosage of 200 mg every 12h IV for 2 days, followed by 200 mg daily thereafter (whether this is an optimal dosage has not been defined).

[f] Most of these cases have been treated primarily with deoxycholate AMB in individual case reports. Although the preponderance of cases treated with voriconazole in the randomized trial consisted of pulmonary invasive aspergillosis, successful treatment of other cases of extrapulmonary and disseminated infection allows one to infer that voriconazole would also be effective in these cases, so that voriconazole is recommended as primary therapy for most of these patients.

[g] A more recent classification divides aspergilloma into 2 categories: chronic cavitary and single aspergilloma. The latter does not require antifungal therapy but does require surgical therapy under some circumstances, and the former requires long-term antifungal therapy.

ing D-AMB have been reported to sustain a high frequency of renal insufficiency and an excess mortality [89, 90].

LFAB

Three LFABs have been approved in the United States and the European Union: ABCD (Amphocil or Amphotec), ABLC (Abelcet), and a small unilamellar vesicle L-AMB (AmBisome). Because of their reduced nephrotoxicity in comparison with D-AMB, these compounds allow for the infusion of higher dosages of AMB. Higher dosages are required for equivalent antifungal efficacy, because amphotericin has to be released from the synthetic phospholipids when in close proximity to ergosterol, allowing for delivery of enough AMB to the site of infection.

Each of the lipid formulations has plasma pharmacokinetic properties that are distinct from those of AMB. All 3 LFABs preferentially distribute to reticulo−endothelial system tissues and functionally spare the kidney. In the kidney, less AMB is released from the lipid carrier, because the synthetic phospholipids have a greater affinity for AMB than does cholesterol in renal epithelial cell membranes.

Infusion-related adverse effects of fever, chills, and rigor are less frequent with L-AMB, compared with D-AMB. However, individual cases of substernal chest discomfort, respiratory distress, and sharp flank pain have been noted during infusion of L-AMB, and in a comparative study, hypoxic episodes associated with fever and chills were more frequent in ABCD recipients than in D-AMB recipients. Mild increases in serum bilirubin and alkaline phosphatase levels have been observed with all 3 formulations. Idiosyncratic reactions to one LFAB do not preclude the use of another LFAB.

ABLC and ABCD are approved at dosages of 5 mg/kg/day and 3–4 mg/kg/day, respectively, and L-AMB is approved at a dosage of 3–5 mg/kg/day for salvage therapy of invasive aspergillosis. A dosage of 3 mg/kg/day of L-AMB is used initially for empirical antifungal therapy in persistently febrile neutropenic patients. The optimal dosage for treatment of invasive aspergillosis has not been defined for any of the LFABs. Although many experts would use the higher dosage range for treatment of documented infection, there are no data from controlled trials supporting higher dosages. Although L-AMB has been safely administered at dosages as high as 15 mg/kg/day, one study did not demonstrate a trend to a dose-response relationship [91]. That higher dosages of L-AMB are not necessarily equivalent to greater response rate was recently demonstrated by Cornely et al. [92]. This recent prospective, randomized trial of L-AMB, which compared a dosage of 3 mg/kg/day with a dosage of 10 mg/kg/day for primary treatment of proven and probable invasive aspergillosis in 201 patients, found similar survival rates and overall response rates; greater toxicity was seen in the higher-dosage group. The dose-response relationships for ABLC and ABCD have not been well studied. Whether higher dosages of LFABs are beneficial in the treatment of CNS aspergillosis, in other sites of infection, or in certain conditions is also not well defined. Dosages of LFABs in pediatric and adult patients achieve similar plasma exposures of AMB.

Antifungal Triazoles

The antifungal triazoles are synthetic compounds that have ⩾1 triazole ring attached to an isobutyl core (e.g., voriconazole, ravuconazole, and isavuconazole) or to an asymmetric carbon atom with a lipophilic complex mixed functional aromatic chain (e.g., itraconazole and posaconazole). These 2 classes of anti-*Aspergillus* triazoles vary in their pharmacology and mechanisms of resistance. Fluconazole, which also is an antifungal triazole, is not active against invasive aspergillosis. Voriconazole is FDA approved for the primary treatment of invasive aspergillosis. Itraconazole is licensed for treatment of invasive aspergillosis in patients who are refractory to or intolerant of standard antifungal therapy. Posaconazole is FDA approved for prevention of invasive aspergillosis in neutropenic patients receiving remission induction chemotherapy for acute myelogenous leukemia or myelodysplastic syndrome and for HSCT recipients with GVHD. The antifungal triazoles target ergosterol biosynthesis by inhibiting the fungal cytochrome P450–dependent enzyme lanosterol 14-α-demethylase, resulting in altered cell membrane function and cell death or inhibition of cell growth and replication. The triazoles also inhibit cytochrome P450–dependent enzymes of the fungal respiration chain. The anti-*Aspergillus* triazoles are active in vitro and in vivo against all common species of *Aspergillus.* Although some isolates of *A. fumigatus* have been found to be resistant to itraconazole, resistance to the anti-*Aspergillus* triazoles has been unusual thus far; however, recent studies suggest that the rate may be increasing [82, 93].

Voriconazole. Voriconazole is formulated as tablets or as a sulfobutyl-ether cyclodextrin solution for IV administration. Sulfobutyl-ether cyclodextrin and voriconazole dissociate in plasma and follow their own disposition. As the cyclodextrin molecule is renally cleared, accumulation of the vehicle occurs in individuals with renal insufficiency. The consequences of plasma accumulation of sulfobutyl-ether cyclodextrin are uncertain at this time, and caution is advised when using the IV formulation in patients with renal impairment (C-III). The relative benefits and uncertain risks of the sulfobutyl-ether cyclodextrin parenteral solution of voriconazole in the context of invasive aspergillosis and renal failure should be determined on an individual patient basis. This concern does not apply to orally administered voriconazole. The oral formulation has good bioavailability in the fed or fasted state. Voriconazole is widely distributed in mammalian tissues, with CSF levels of

~50% in plasma levels. The elimination half-life of ~6 h warrants twice-daily dosing. Voriconazole is hepatically metabolized, with only 5% of the drug appearing unchanged in the urine. This agent exhibits nonlinear pharmacokinetics, with maximum concentration in plasma and area under the curve increasing disproportionally with increasing dose. Voriconazole is both a substrate and an inhibitor of CYP2C19, CYP2C9, and CYP3A4. The patient's current medications should be reviewed for potentially deleterious drug interactions. Allelic polymorphisms in CYP2C19 may result phenotypically in rapid or slow metabolism of voriconazole, possible resulting in significant variation in plasma concentrations. Single-nucleotide polymorphisms contributing to slow metabolism are represented in higher frequencies among non-Indian Asian populations than among other populations.

Treatment of invasive aspergillosis with voriconazole is initiated with a loading dose of 6 mg/kg IV every 12 h for 2 doses, followed by 4 mg/kg every 12 h. These dosages are greater than those routinely administered for oral therapy (200 mg every 12 h). Oral therapy can be approximated to the standard IV dosage by using 4 mg/kg/dose rounded up to convenient pill sizes (B-III), although use of oral voriconazole in these doses is investigational and has not been carefully studied. Because patients initially received IV therapy in the original randomized clinical trial of voriconazole, parenteral therapy, where feasible, is recommended to approximate the results of that study. Because of the more accelerated metabolic clearance in pediatric patients, the doses of voriconazole may be higher [94]. A maintenance dosage of 7 mg/kg twice daily in pediatric patients is recommended by the European Medicines Agency for the attainment of plasma levels comparable to those of adults. Loading regimens in pediatric populations have not been adequately studied. Measurement of serum levels, especially in patients receiving oral therapy, may be useful in some patients, either to evaluate for potential toxicity or to document adequate drug exposure, especially in progressive infection (B-III) [95].

Voriconazole's profile of adverse reactions includes transient visual disturbances (characterized principally by photopsia); hepatotoxicity, which may be dose limiting (manifested by elevated serum bilirubin, alkaline phosphatase, and hepatic aminotransferase enzyme levels); skin rash (usually in sunlight-exposed areas), visual hallucinations; and others [85].

Itraconazole. Itraconazole is a high molecular weight, highly lipophilic compound that is formulated as capsules, oral solution in hydroxypropyl-β-cyclodextrin (HPCD), and parenteral solution that also uses HPCD as solubilizer. Absorption from the capsular formulation, which is enhanced by low gastric pH and dietary lipids, may be erratic or negligible in the fasting state, particularly in granulocytopenic patients with cancer and in patients with hypochlorhydria, and its use in seriously ill patients with life-threatening infection is not recommended. Absorption is improved when the capsules are taken with food or an acidic cola beverage. HPCD solution of itraconazole provides more-uniform oral bioavailability that is further enhanced in the fasting state. Systemic absorption of the cyclodextrin carrier is negligible.

Itraconazole is extensively metabolized in the liver and is excreted in metabolized form into bile and urine. The major metabolite, hydroxy-itraconazole, possesses antifungal activity that is similar to that of itraconazole [96–98]. Most observed reactions to itraconazole are transient and include nausea and vomiting, hypertriglyceridemia, hypokalemia, and elevated hepatic aminotransferase enzyme levels. Gastrointestinal intolerance appears to be more frequent with oral HPCD itraconazole solution. Because itraconazole use may infrequently cause negative inotropic effects, it should be administered with caution to patients with ventricular dysfunction. Itraconazole is a substrate of CYP3A4 but also interacts with the heme moiety of CYP3A4, resulting in noncompetitive inhibition of oxidative metabolism of many CYP3A4 substrates. Serious interactions with some chemotherapeutic agents (e.g., cyclophosphamide) further limit its use [99].

The recommended dosage range of oral itraconazole in adults is 400 mg/day (capsules) and 2.5 mg/kg twice daily (HPCD solution). In pediatric patients aged >5 years, a dosage of oral itraconazole HPCD solution of 2.5 mg/kg twice daily has been recommended [100]. The approved adult dosages of IV HPCD itraconazole are 200 mg twice daily for 2 days, followed by 200 mg once daily for a maximum of 12 days. Because of the erratic bioavailability of itraconazole, measurements of plasma concentrations of itraconazole by bioassay or by HPLC are recommended during oral therapy of invasive aspergillosis (A-III).

Posaconazole. Posaconazole is structurally similar to itraconazole but has been studied in the treatment of invasive aspergillosis only in the oral formulation. Posaconazole exhibits not only linear kinetics but also saturable absorption; thus, oral loading doses are not possible. Steady-state levels may not be achieved for up to a week with posaconazole therapy, which may impact its use in primary therapy. Posaconazole undergoes hepatic metabolism via glucuronidation and also has the capacity for drug-drug interactions through inhibition of CYP450 3A4 isoenzymes. Significantly more toxicity was observed in patients with acute leukemia or myelodysplasia who were receiving posaconazole for prophylaxis than in such patients receiving prophylactic fluconazole or itraconazole [92].

Laboratory animal studies demonstrate activity of the oral formulation in the prevention and treatment of experimental pulmonary and disseminated aspergillosis [101, 102]. Recently completed clinical trials are consistent with these laboratory findings, demonstrating activity in the prevention of invasive aspergillosis in neutropenic patients with acute myelogenous

leukemia and in HSCT recipients with GVHD, as well as in salvage therapy for refractory invasive aspergillosis [103–105].

The dosage of the oral suspension of prophylaxis is 200 mg 3 times per day, and the dosage for salvage treatment is 800 mg administered in 2 or 4 divided doses. The dosage in pediatric patients is not established. Limited data are available on the use of therapeutic drug monitoring, but in one study, improved efficacy occurred with higher posaconazole drug levels [103].

Therapeutic drug monitoring. A growing body of evidence suggests patient-to-patient variability in the pharmacokinetics of triazoles used for treatment or prophylaxis in invasive aspergillosis [95, 103, 106, 107]. Absorption issues (for itraconazole and posaconazole), drug-drug interactions (for all triazoles), and pharmacogenetic differences (for voriconazole) all contribute in various degrees to this variability [84]. Although the available data do not allow consensus and specific recommendations for therapeutic drug monitoring, accumulating reports suggest that plasma drug level monitoring may play an important role in optimizing the safety (for voriconazole and flucytosine) and efficacy (for itraconazole, posaconazole, and possibly, voriconazole) of antifungals with significant interpatient pharmacokinetic variability among a complex patient population, such as patients at risk for or who have invasive aspergillosis. The necessity of documenting or continuing therapeutic drug monitoring (once therapeutic concentrations are documented) should be individualized as determined by the clinical status of the host (e.g., specific organ function, comorbidities, and receipt of concomitant medications) and the overall treatment plans. Although further work is needed to validate therapeutic drug monitoring approaches for antifungals, the committee recommends that determination of a plasma drug level, in conjunction with other measures of clinical assessment, may be another factor in evaluating reasons for therapeutic failure attributable to suboptimal drug exposures or for toxicity attributable to the drug (B-III).

Echinocandins: Caspofungin, Micafungin, and Anidulafungin

The echinocandins are a novel class of semisynthetic amphiphilic lipopeptides composed of a cyclic hexapeptide core linked to a variably configured N-acyl side chain [108]. The echinocandins act by noncompetitive inhibition of the synthesis of 1,3-β-glucan, a polysaccharide in the cell wall of many pathogenic fungi. Together with chitin, the rope-like glucan fibrils are responsible for the cell wall's strength and shape. They are important in maintaining the osmotic integrity of the fungal cell and play a key role in cell division and cell growth. Because of their distinct mechanism of action, the echinocandins have the potential for use in combination regimens with currently available standard antifungal agents.

All current echinocandins are only available for IV administration. They exhibit dose-proportional plasma pharmacokinetics with a β half-life of 10–15 h that allows for once-daily dosing. All echinocandins are highly (>95%) protein bound and distribute into all major organ sites, including the brain; however, concentrations in uninfected CSF are low. Caspofungin and micafungin are metabolized by the liver and slowly excreted into the urine and feces. Anidulafungin is slowly degraded nonenzymatically in plasma and then hepatically excreted.

At the currently investigated dosages, all echinocandins are generally well tolerated, and only a small fraction of patients enrolled in the various clinical trials have discontinued therapy because of drug-related adverse events. The most frequently reported adverse effects include increased liver aminotransferase enzyme levels, gastrointestinal upset, and headaches. As with other basic polypeptides, the echinocandins have the potential to cause histamine release; however, histamine-like symptoms have been observed only in isolated cases, which may be related to infusion rates that are more rapid than recommended. The current echinocandins appear to have no significant potential for drug interactions mediated by the CYP450 enzyme system. Caspofungin can reduce the area under the curve of tacrolimus by ~20% but has no effect on cyclosporine levels. However, cyclosporine increases the area under the curve of caspofungin by ~35%; because of transient elevations of hepatic aminotransferase enzyme levels in single-dose interaction studies, the concomitant use of both drugs should be done with caution (B-III). Finally, inducers of drug clearance and/or mixed inducer/inhibitors, namely efavirenz, nelfinavir, nevirapine, phenytoin, rifampin, dexamethasone, and carbamazepine, may reduce caspofungin concentrations.

Caspofungin is indicated in patients with probable or proven invasive aspergillosis that is refractory to or intolerant of other approved therapies. The currently recommended dosage regimen of caspofungin in adults consists of a single 70-mg loading dose on day 1, followed by 50 mg/day thereafter, administered by slow IV infusion of ~1 h. Maertens et al. [109] reported the use of higher doses of caspofungin (70 mg/day) for use in salvage combination therapy of invasive aspergillosis. In cases of markedly reduced hepatic function, adult patients should receive a daily dose of 35 mg. Caspofungin administration at 50 mg/m^2/day in children provides exposure that is comparable to that obtained at a dosage of 50 mg/day in adults [110]. Micafungin and anidulafungin have activity against *Aspergillus* species but are not approved for that indication, and optimal doses for aspergillosis have not been established. Micafungin at a mean daily dose of 111 mg was used in one open-label trial. However, on a mg/kg basis, higher doses may be needed in young children and infants to achieve a plasma exposure that is comparable to that in adults [111, 112]. Although anidulafungin is active in experimental pulmonary aspergillosis,

there is relatively little reported experience describing its use in the treatment of invasive aspergillosis.

TREATMENT GUIDELINE OVERVIEW

The following practice guidelines provide recommendations for treatment of the different forms of aspergillosis. For each form of aspergillosis, the objective, treatment options, outcome of treatment, evidence, values, benefits and harms, and key recommendations are specified, where appropriate. The panel performed extensive review of all the randomized, controlled, and observational trials published in the English-language literature. Final recommendations were discussed by the panel and determined by consensus. Because invasive pulmonary aspergillosis is the most common life-threatening form of invasive aspergillosis, more emphasis is placed on its management than on other aspects of clinical infection. Many of the statements concerning treatment of invasive pulmonary aspergillosis are also applicable to other forms of invasive aspergillosis.

INVASIVE ASPERGILLOSIS

INVASIVE PULMONARY ASPERGILLOSIS

Without adequate therapy, invasive pulmonary aspergillosis will almost always progress to relentless fatal pneumonia. In neutropenic patients, this pneumonia may be characterized by devastating hemorrhagic infarction or progressive necrotizing pneumonia. Without adequate therapy, invasive pulmonary aspergillosis is further complicated by dissemination to the CNS or by extension to contiguous intrathoracic structures, including the great vessels and the heart. Because of the potential progression of this infection, the early administration of antifungal therapy while diagnostic evaluation is undertaken is critical.

Key Recommendations

Early initiation of antifungal therapy in patients with strongly suspected invasive aspergillosis is warranted while a diagnostic evaluation is conducted (A-I) [29, 92]. The decision of medical therapy for treatment of invasive pulmonary aspergillosis has been greatly facilitated by a randomized, controlled trial of voriconazole versus D-AMB.

Because of better survival and improved responses of initial therapy with voriconazole, primary therapy with D-AMB is not recommended (A-I). **For primary treatment of invasive pulmonary aspergillosis, IV or oral voriconazole is recommended for most patients (A-I). Oral therapy can be maximized by using a dose of 4 mg/kg rounded up to convenient pill sizes (B-111). For seriously ill patients, the parenteral formulation is recommended (A-III).** A randomized trial compared 2 initial dosages of L-AMB (3 mg/kg/day and 10 mg/kg/day) and showed similar efficacy in both arms but greater toxicity in the higher-dose arm. **These results suggest that L-AMB may be considered as alternative primary therapy in some patients (A-I). For salvage therapy, agents include LFABs (A-II), posaconazole (B-II), itraconazole (B-II), caspofungin (B-II), or micafungin (B-II).** In that context, the diagnosis should be confirmed. **Therapeutic options include a change of class using an AMB formulation or an echinocandin (B-II)**; additional use of an azole should take into account prior therapy, host factors, and pharmacokinetic considerations.

In the absence of a well-controlled, prospective clinical trial, routine administration of combination therapy for primary therapy is not routinely recommended (B-II). The committee recognizes, however, that in the context of salvage therapy, an additional antifungal agent might be added to current therapy, or combination antifungal drugs from different classes other than those in the initial regimen may be used (B-II). In addition, management of breakthrough invasive aspergillosis in the context of mould-active azole prophylaxis or suppressive therapy is not defined by clinical trial data but would suggest a switch to another drug class (B-III). Paramount to the successful treatment of invasive pulmonary aspergillosis is the reversal of immunosuppression (e.g., reduction in the dosage of corticosteroids) or recovery from neutropenia. **Surgical resection of *Aspergillus*-infected tissue may be useful in patients with lesions that are contiguous with the great vessels or pericardium, lesions causing hemoptysis from a single focus, and lesions causing erosion into the pleural space or ribs (B-III).**

Duration of antifungal therapy for invasive pulmonary aspergillosis is not well defined. We generally recommend that treatment of invasive pulmonary aspergillosis be continued for a minimum of 6–12 weeks; in immunosuppressed patients, therapy should be continued throughout the period of immunosuppression and until lesions have resolved. Long-term therapy of invasive aspergillosis is facilitated by the availability of oral voriconazole in stable patients. **For patients with successfully treated invasive aspergillosis who will require subsequent immunosuppression, resumption of antifungal therapy can prevent recurrent infection (A-III)** [113, 114].

Therapeutic monitoring of invasive pulmonary aspergillosis includes serial clinical evaluation of all symptoms and signs, as well as performance of radiographic imaging, usually with CT, at regular intervals. The frequency with which CT should be performed cannot be universally defined and should be individualized on the basis of the rapidity of evolution of pulmonary infiltrates and the acuity of the individual patient. The volume of pulmonary infiltrates may increase for the first 7–10 days of therapy—especially in the context of granulocyte recovery [27]. The use of serial serum galactomannan assays for therapeutic monitoring is promising but remains investi-

gational [48, 49]. Progressive increase in *Aspergillus* antigen levels over time signifies a poor prognosis. **However, resolution of galactomannan antigenemia to a normal level is not sufficient as a sole criterion for discontinuation of antifungal therapy (B-III).** Further data elucidating the prognostic and therapeutic value of serial galactomannan levels in patients with invasive pulmonary aspergillosis are needed.

Evidence

Data on antifungal therapy. There are few randomized clinical trials on the treatment of invasive aspergillosis. Invasive pulmonary aspergillosis is a life-threatening infection associated with severe morbidity and mortality. Invasive pulmonary aspergillosis may be the source for dissemination to the CNS and other critical organs. This infection has been extremely difficult to study in prospective, randomized trials. The largest prospective, randomized trial for the treatment of invasive pulmonary aspergillosis demonstrated that voriconazole was superior to D-AMB, followed by other licensed antifungal therapy [115]. All patients had proven or probable invasive aspergillosis, and most of them had pneumonia. Voriconazole was administered at a dosage of 6 mg/kg every 12 h for 2 doses as a loading dose, followed by 4 mg/kg every 12 h IV for the first 7 days, followed by 200 mg twice daily thereafter. D-AMB was administered at 1.0–1.5 mg/kg/day IV; other licensed antifungal therapy was permitted if the initial therapy failed or if the patient had intolerance to the first drug. This study demonstrated significantly improved survival, improved overall response rate at 12 weeks of therapy, and improved overall response at end of therapy. Successful outcome was achieved in 53% of patients in the voriconazole arm and 32% of patients in the D-AMB arm, resulting in an absolute difference of 21%. Survival rate at 12 weeks was 71% among voriconazole-treated patients and 58% among D-AMB–treated patients. Recipients of voriconazole had fewer severe drug-related adverse events. However, transient visual disturbances occurred more frequently with voriconazole, as discussed in the earlier section on antifungal compounds in this article. The efficacy of voriconazole was further demonstrated in pediatric and adult patients receiving voriconazole for treatment of invasive aspergillosis who were refractory to or intolerant of conventional antifungal therapy [116–118]; the overall response rate was 43% and 48% for pediatric and adult patients, respectively.

Two earlier and smaller randomized trials of the primary treatment of invasive aspergillosis [119, 120] and another recent dose comparison study of L-AMB [92] have been reported. An earlier prospective, randomized trial of 2 dosages of L-AMB (1.0 mg/kg/day vs. 4.0 mg/kg/day) for treatment of invasive aspergillosis was conducted by the European Organization for Research in Treatment of Cancer [120]. Although this study found no difference in response rate or survival between the 2 treatment groups, the patient population included those with possible aspergillosis. When those patients with possible aspergillosis are excluded from the analysis, the data reveal a trend toward improved response in patients with proven and probable aspergillosis who were treated with the higher dosage, which is consistent with the data from animal models demonstrating a dose-response relationship [32, 121]. Another study randomized patients with documented invasive aspergillosis to receive ABCD (6 mg/kg/day) versus D-AMB (1 mg/kg/day) for primary treatment of invasive aspergillosis [119]. This study found that patients randomized to either arm had similar outcomes but poor overall responses (patients with complete and partial responses, 17% in the ABCD group vs. 23% in the D-AMB group), and those receiving ABCD had less nephrotoxicity (25% vs. 49%). More recently, Cornely et al. [92] compared an initial dosage of L-AMB of 10 mg/kg/day for 2 weeks with a dosage of 3 mg/kg/day. In that study, among 201 patients, overall outcomes in the 2 arms were similar (46% in the high-dose arm vs. 50% in the low-dose arm), but there was more toxicity (32% vs. 20%) in the high-dose arm, suggesting that higher doses were not beneficial in these patients, the majority of whom had early invasive pulmonary aspergillosis diagnosed by CT.

For patients who are intolerant of or refractory to voriconazole, a formulation of AMB is an appropriate alternative. D-AMB historically has been used in the treatment of invasive aspergillosis. However, the available data indicate that the LFABs are as effective as D-AMB but less nephrotoxic [119, 122–125]. That LFABs are effective against invasive pulmonary aspergillosis and other forms of invasive aspergillosis is also demonstrated in several large, open-label, compassionate-release studies with a response rate of ~40% [124–126]. For those patients with underlying hepatotoxicity or other contraindications to voriconazole, an LFAB is less toxic than is D-AMB and is likely to be at least as effective as D-AMB as an alternative for primary therapy.

A study of caspofungin for patients who are intolerant of or refractory to conventional therapy also demonstrated a favorable response rate of ~40% [127]. Higher responses (50%) occurred with invasive pulmonary aspergillosis than with disseminated aspergillosis (23%). Drug-related nephrotoxicity and hepatotoxicity occurred in <5% of patients.

Orally administered itraconazole has also been used to treat patients with invasive aspergillosis who are refractory to or intolerant of D-AMB [24, 128]. In a study of 76 evaluable patients, all of whom were able to take oral therapy, 30 patients (39%) had a complete or partial response, with success rates varying widely according to site of disease and underlying disease group [128]. More recent studies of the parenteral formulation of β-hydroxy-propyl-cyclodextrin itraconazole in the treatment of invasive pulmonary aspergillosis that was refrac-

tory to various forms of AMB have been reported, with overall response rates of 52% [129, 130]. **Measurement of itraconazole serum levels are generally recommended to document absorption of drug (B-II).** Although evidence to support a correlation between higher drug levels and efficacy is limited, levels >250 ng/mL have been associated with more-favorable outcomes. **Salvage therapy of itraconazole for treatment of invasive pulmonary aspergillosis that is refractory to primary therapy with voriconazole is not recommended because of the same mechanism of action or possible resistance and because of the erratic bioavailability and toxicity (B-II).**

Posaconazole was approved in Europe for salvage treatment of patients with invasive aspergillosis who are refractory to AMB or itraconazole. The overall success rate in an externally controlled, open-label trial using Data Review Committee–assessed global response at end of treatment was 42% for the posaconazole group and 26% for the control group [103]. The differences in response between the treatment groups were preserved across additional, prespecified subsets, including infection site (pulmonary or disseminated), hematological malignancy, HSCT, baseline neutropenia, and enrollment reason (refractory or intolerant). A difference in response was also seen in a confirmatory analysis subpopulation (patients who received prior antifungal therapy for 7–30 days before the start of salvage therapy). As with other salvage trials, patients enrolled in this study were a selected population who had received prior therapy, and for posaconazole salvage studies, patients were also selected on the basis of their ability to receive the oral formulation of posaconazole. The salvage study also demonstrated a direct relationship between serum concentration and response rate. One should note, however, that these serum concentrations were achieved in patients receiving the highest adult dosage (800 mg administered in divided doses over 24 h) at which maximum absorption of compound is known to occur. Thus, further increases in the oral adult dosage are unlikely to yield higher plasma concentrations.

Most of the prospective studies of second-line therapy have been conducted by replacing the compound to which the patient is intolerant or against which the infection is progressing. Whether both drugs should be administered simultaneously has seldom been prospectively studied [111], nor are there compelling prospective clinical data to support combination antifungal therapy over single-agent therapy for primary therapy of invasive aspergillosis [131]. The addition of a second antifungal agent to a first agent that is failing or toxic is usually practiced out of understandable desperation. Nevertheless, limited in vitro, in vivo, and nonrandomized clinical trial data suggest the benefit of some forms of combination therapy against invasive aspergillosis [109, 131–137]. However, not all antifungal combinations are beneficial, and some may be deleterious [138, 139]. There are insufficient clinical data to support combination therapy as routine primary treatment of invasive pulmonary aspergillosis. Although initial laboratory studies, case reports, and retrospective case series indicate encouraging findings, the efficacy of primary combination antifungal therapy requires a prospective, randomized clinical trial to justify this approach. Additional questions of optimal dosing, pharmacokinetic interactions, potential toxic interactions, and cost-benefit ratios of primary combination antifungal therapy also require further investigation.

Impact of* Aspergillus *species. Consideration should be given to the infecting species of *Aspergillus.* Most isolates of *A. fumigatus* are susceptible in vitro and responsive in vivo to AMB, voriconazole, posaconazole, itraconazole, and caspofungin. However, most isolates of *A. terreus* are resistant in vitro and in vivo to AMB. **The aggregate body of data thus far warrants that an antifungal triazole should be used instead of AMB in the primary treatment of infection due to *A. terreus* (A-II)** [18]. Although uncommon, some isolates of *A. fumigatus* that are resistant to itraconazole have been reported. Other species of *Aspergillus* may also be resistant to AMB, including *A. lentulus, A. nidulans, A. ustus,* and *Aspergillus versicolor.* Known itraconazole-resistant isolates of *A. fumigatus* were recovered from patients who were not profoundly immunosuppressed and otherwise should have responded to itraconazole [140]. Multiazole-resistant *Aspergillus* species have also been recently reported [82]. Antifungal susceptibility testing, especially in the context of prior azole therapy, may be warranted as a guide to therapy, although very limited clinical data support this approach. Pending susceptibility data, the administration of a different class of agent (AMB formulation or echinocandin) may be warranted.

Use of colony-stimulating factors. Reversal of immunosuppression is an important factor in successful treatment of invasive pulmonary aspergillosis. Persistent neutropenia and chronic GVHD are 2 of the most important variables for poor outcome in invasive aspergillosis [6, 141]. Failure to recover from neutropenia is often associated with a fatal outcome of invasive pulmonary aspergillosis. Although colony-stimulating factors are widely used to attempt to reduce the duration of neutropenia, there are limited data from randomized, controlled trials to demonstrate that granulocyte colony-stimulating factor or granulocyte-macrophage colony-stimulating factor prevents the development of invasive pulmonary aspergillosis in patients with prolonged neutropenia (duration of neutropenia, >10 days) [142]. **Although high-risk neutropenic patients with invasive aspergillosis may already be receiving granulocyte colony-stimulating factor or granulocyte-macrophage colony-stimulating factor as a component of their cancer chemotherapy, those neutropenic patients who are not receiving a colony-stimulating factor may benefit from the addition of granulocyte colony-stimulating factor**

or granulocyte-macrophage colony-stimulating factor (B-III).

Cytokines, such as granulocyte colony-stimulating factor, granulocyte-macrophage colony-stimulating factor, and IFN-γ, also augment functional properties of phagocytic cells through upregulation of chemotaxis, phagocytosis, oxidative metabolism, and/or degranulation of neutrophils, and granulocyte colony-stimulating factor, granulocyte-macrophage colony-stimulating factor, and IFN-γ upregulate phagocytosis and the respiratory burst of monocytes and macrophages [143, 144]. The clinical data suggest a potential role of IFN-γ in selected hosts for prevention or treatment of invasive aspergillosis [145]. Although clinical data supporting its use specifically for aspergillosis are sparse, IFN-γ is widely used for prevention of bacterial and fungal infections in patients with chronic granulomatous disease (CGD) [146]. **Individual case reports suggest a role for IFN-γ as adjunctive antifungal therapy for invasive aspergillosis in immunocompromised nonneutropenic patients, particularly those with CGD (B-III).**

Role of granulocyte transfusions. Granulocyte transfusions may be another resource for the treatment of patients with invasive pulmonary aspergillosis [147, 148]. Although use of this modality for management of invasive pulmonary aspergillosis has been controversial, the key element for improved outcome appears to be an adequate number of granulocytes transfused to the profoundly neutropenic patient. The advent of granulocyte colony-stimulating factor mobilization of granulocyte donors results in the strikingly (~10-fold) increased number of granulocytes that can be recovered and subsequently administered to patients. In an open-label pilot study, Dignani et al. [147] have reported the use of granulocyte colony-stimulating factor–mobilized granulocyte transfusions administered to patients with invasive aspergillosis and other mycoses due to filamentous fungi. Stabilization of invasive pulmonary aspergillosis was demonstrated in some of the patients who were otherwise experiencing refractory invasive fungal infection. Unless patients recover from neutropenia, granulocyte transfusions will not stabilize invasive aspergillosis indefinitely.

Granulocyte transfusions can be accompanied by transfusion reactions, including pulmonary dysfunction evidenced by hypoxia and the acute onset of adult respiratory distress syndrome–like pulmonary infiltrates. Granulocyte transfusions are also associated with the transmission of cytomegalovirus infection. In cytomegalovirus-seronegative HSCT recipients, only cytomegalovirus-seronegative donors should be used for granulocyte transfusions. Because there has been an association between some of these reactions and simultaneous infusion of AMB, patients undergoing granulocyte transfusion with concurrent use of AMB products usually have the AMB staggered by several hours from the granulocytes, with careful monitoring for this complication. Moreover, this limited blood product resource should only be implemented for those patients with proven or probable infection who are anticipated to require this bridge as a temporary measure until recovery from neutropenia. Granulocyte transfusions have also been used in the treatment of refractory invasive aspergillosis and other infections in patients with CGD [17].

Management of immunosuppressive therapies. **Withdrawal of corticosteroids or reduction of dosage is often critical for successful outcome in invasive aspergillosis (A-III).** The failure to reduce an immunosuppressive dosage of systemic corticosteroids usually results in relentless invasive fungal infection. However, because control of underlying diseases, such as GVHD, may only be achieved by intense immunosuppression, corticosteroid-sparing immunosuppressive strategies are being used increasingly. TNF-α blockade with infliximab is one such strategy. However, because TNF-α is a key molecule in the initial innate host defense against *A. fumigatus,* its inhibition also may have deleterious immunological consequences leading to invasive aspergillosis [149–151].

For patients with chronic immunosuppression, continuation of antifungal therapy throughout the duration of immunosuppression seems to be associated with a more favorable outcome (A-III). For patients with successfully treated invasive aspergillosis who will require subsequent immunosuppression, resumption of antifungal therapy may prevent recurrent infection from residual foci of infection that may or may not be demonstrated by current imaging techniques [113].

Hemoptysis and surgical management. Hemoptysis is a serious complication of invasive pulmonary aspergillosis that may lead to exsanguination and respiratory arrest. Hemoptysis in the course of invasive aspergillosis may occur during profound pancytopenia or upon recovery from neutropenia [152, 153]. Early aggressive therapy and eradication of infection may prevent this complication; however, there are no data to definitively support this hypothesis. Because life-threatening hemoptysis complicating invasive aspergillosis is reported most often in patients already receiving antifungal chemotherapy, surgical resection may be the only recourse to eradicate the focus.

Surgical resection of pulmonary lesions due to *Aspergillus* species can provide a definitive diagnosis and can potentially completely eradicate a localized infection (table 3) [28, 154–158]. **Surgical therapy may be useful in patients with lesions that are contiguous with the great vessels or the pericardium, hemoptysis from a single cavitary lesion, or invasion of the chest wall (B-II). Another relative indication for surgery is the resection of a single pulmonary lesion prior to intensive chemotherapy or HSCT (B-II).** Although a successful course of voriconazole may preclude the need for surgical resection of pulmonary lesions, adjunctive surgical intervention is usually warranted for treatment of aspergillosis involving the heart,

Table 3. Relative indications for surgery in treatment of invasive aspergillosis.

Condition	Surgical procedure	Comment
Pulmonary lesion in proximity to great vessels or pericardium	Resection of pulmonary lesion	May prevent erosion of pulmonary lesions into great vessels and into pericardial space
Pericardial infection	Pericardiectomy	Pericardiectomy reduces organism burden around heart and prevents tamponade
Invasion of chest wall from contiguous pulmonary lesion	Resection of pulmonary lesion	Resection of lesion may relieve pain and prevent pleurocutaneous fistula
Aspergillus empyema	Placement of chest tube	Reduces burden of organism in closed space
Persistent hemoptysis from a single cavitary lesion	Resection of cavity	May prevent exsanguinating hemoptysis; other measures to reduce hemoptysis include embolization of involved blood vessel and cauterization; however, recurrence of bleeding is possible
Infection of skin and soft tissues	Debridement, wide margin surgical resection	Surgical judgment used in extent of debridement and resection, if indicated
Infected vascular catheters and prosthetic devices	Removal of catheters and devices	Removal of infected catheters and devices provides definitive eradication
Endocarditis	Resection of vegetation and infected valve	Vegetations may be valvular or mural; single mural lesions are resectable, particularly if pedunculated
Osteomyelitis	Debridement of infected bone	Debridement of necrotic and infected bone reduces organism burden and allows better drug penetration; surgical judgment determines extent of debridement
Sinusitis	Resection of infected tissues	Extent of debridement may vary from no intervention to wide resection, depending on surgical judgment
Cerebral lesions	Resection of infected tissue	Extent of debridement may vary from no intervention to complete resection, depending on location, neurological sequelae, accessibility, and surgical judgment

NOTE. Indications depend on multiple variables, severity of lesion, surgical judgment, and the ability of the patient to tolerate the operative procedure, as well as the potential role of alternative medical therapy.

great vessels, pleural space, and bone. However, recent favorable experience of using secondary antifungal prophylaxis after initial successful primary therapy prior to HSCT in patients with prior invasive aspergillosis suggests that antifungal therapy alone may be effective [159, 160]. Early surgical evaluation and close CT monitoring may be warranted during medical therapy, to intervene if a lesion further encroaches upon a critical structure. Decisions concerning surgical therapy should be individualized to account for a number of variables, including the degree of resection (e.g., wedge resection vs. pneumonectomy), potential impact of delays in chemotherapy, comorbidities, performance status, the goal of antineoplastic therapy (e.g., curative vs. palliative), and unilateral versus bilateral lesions.

Pharmacoeconomics and costs. The complex issues of pharmacoeconomics and fiscal costs of antifungal therapy are beyond the scope of these guidelines; however, these issues often occur in the context of LFABs versus D-AMB. The poor outcomes and fiscal costs of D-AMB–induced renal impairment in compromised hosts are well documented. Whether there is a population for whom D-AMB can be used as first-line therapy is an important question. Some pediatric patients, particularly neonates, may tolerate D-AMB with minimal or reversible renal impairment. The use of D-AMB in adult patients needs to be assessed on an individual basis for the relative risks and consequences of renal impairment. In many resource-limited settings, D-AMB may be the only agent for primary treatment of invasive aspergillosis and, as such, may be considered to be the standard of care.

TRACHEOBRONCHIAL ASPERGILLOSIS

Early treatment of tracheobronchial aspergillosis may result in the prevention of anastomotic disruption and loss of the lung graft, as well as resolution of ulcerative tracheobronchial lesions in lung transplant recipients.

Key recommendations. **Voriconazole is recommended as initial therapy in the treatment of tracheobronchial aspergillosis (B-II).** Little experience is available with caspofungin or other echinocandins in treating this infection. **Because the use of D-AMB may result in increased nephrotoxicity in association with calcineurin inhibitors, an LFAB is recommended if a polyene is considered in the patient (e.g., lung transplant recipient) (B-III).** Bronchoscopic evaluation is the most important aspect of initial diagnosis; CT will assess the

lack of progression to the remainder of the pulmonary tree. Reduction of immunosuppression, where possible, is an important element in improving therapeutic outcome. **Aerosolized D-AMB or LFAB may have some benefit for delivering high concentrations of polyene therapy to the infected (often anastomotic) site; however, this approach has not been standardized and remains investigational (C-III).** Cases of tracheobronchial aspergillosis in immunocompromised patients who have not received a transplant may be managed with a similar approach.

Evidence. Heart-lung and lung transplant recipients are at high risk for the development of invasive aspergillosis at the site of anastomosis between the recipient trachea and the donor trachea or at the site of the junction of the main bronchus [161, 162]. Tracheobronchial aspergillosis has also been described in the absence of an anastomotic site in other patient populations, including patients who have undergone HSCT and patients with lymphoma, acute leukemia, or AIDS [163, 164]. The spectrum of disease encompasses simple colonization, bronchitis, obstructing trachoebronchitis, ulcerative tracheobronchitis, and pseudomembranous tracheobronchitis. Because this form of pulmonary aspergillosis is not usually associated with pulmonary infiltrates in its initial stages, radiographic images may not identify the infection, which is otherwise easily seen during bronchoscopic examination. Bronchoscopic evaluation is necessary for early diagnosis. Voriconazole and itraconazole have been used successfully in the treatment of this form of pulmonary aspergillosis [116]. Parenteral AMB also has been used in this context. Direct instillation of AMB has been administered as an alternative approach to treatment of this form of pulmonary aspergillosis, in association with systemic therapy [165, 166]. Inhalational AMB in the form of ABLC has also been used for the prevention of invasive aspergillosis in lung transplant recipients, in whom tracheobronchial aspergillosis is especially important [167, 168]. However, this modality remains investigational.

CHRONIC NECROTIZING PULMONARY ASPERGILLOSIS (CNPA; SUBACUTE INVASIVE PULMONARY ASPERGILLOSIS)

Treatment of this infection may prevent progressive destruction of lung tissue in patients who are already experiencing impaired pulmonary function and who may have little pulmonary reserve.

Key recommendations. **The greatest body of evidence regarding effective therapy supports the use of orally administered itraconazole (B-III). Although voriconazole (and presumably posaconazole) is also likely to be effective, there is less published information available for its use in CNPA (B-III).** Because long-term treatment is required, oral antifungal therapy is preferred over parenteral therapy.

Evidence. CNPA is a distinct clinical and radiological form of pulmonary aspergillosis that most commonly causes a slowly progressive inflammatory destruction of lung tissue in patients with underlying lung diseases and low grade immunosuppression (e.g., prolonged use of systemic corticosteroids) [169, 170]. The previous literature regarding CNPA included both subacute invasive aspergillosis and other chronic forms of aspergillosis. Because of their underlying primary chronic respiratory disease, these patients are also at risk for succumbing to pulmonary comorbidities.

There are a limited number of small, nonrandomized, open-label studies that have been conducted for treatment of CNPA [171–175]. Although variable responses have been reported in the small number of patients treated with itraconazole [171], itraconazole appears to be suppressive in CNPA [173]. Other patients with CNPA have been treated with intracavitary instillation of AMB and, more recently, with voriconazole [172, 174, 175]. In general, the principles for treatment of CNPA are similar to those for invasive pulmonary aspergillosis described above, with a greater emphasis on oral therapy.

SINGLE-ORGAN, EXTRAPULMONARY FORMS OF INVASIVE ASPERGILLOSIS

Focal extrapulmonary invasive aspergillosis can develop as a single-organ infection or can occur in the context of disseminated infection. Because these are uncommon infections and occur in a wide spectrum of clinical conditions, no randomized clinical trials have been completed to assess therapeutic approaches in patients with these infections. Thus, there are very limited data on the treatment of these infections, and most involve D-AMB as primary therapy simply because of its long-standing availability. **However, based on the strength of the randomized study comparing voriconazole to D-AMB [115], the panel recommends voriconazole for primary treatment of these uncommon manifestations of invasive aspergillosis (B-III).** The use of voriconazole in these contexts is further supported by case series and anecdotal cases documenting the efficacy of voriconazole in extrapulmonary infections, some of which have historically been associated with abysmal responses, including CNS infection [176], osteomyelitis [177], and endocarditis [178, 179]. The use of alternative agents and salvage therapy can be approached in a manner similar to that described for invasive pulmonary aspergillosis.

ASPERGILLOSIS OF THE CNS

Treatment of CNS aspergillosis may reduce morbidity associated with neurological deficits and improve survival.

Key recommendations. Aggressive diagnostic and therapeutic intervention is important in patients with otherwise documented invasive pulmonary aspergillosis and signs of neurological deficits or unexplained abnormalities by CT or MRI.

The weight of evidence supports voriconazole as the primary recommendation for systemic antifungal therapy of CNS aspergillosis (A-II). Itraconazole, posaconazole, or LFAB are recommended for patients who are intolerant or refractory to voriconazole (B-III). There are few data supporting the use of echinocandins as a single agent in salvage treatment of CNS aspergillosis. Combination therapy with voriconazole and caspofungin is used for CNS aspergillosis but with minimal data to date. Surgical resection of lesions may be the definitive treatment and may prevent serious neurological sequelae. Surgical resection of lesions that would not result in worsening of neurological deficits also may improve outcome. Treatment of contiguous infections of the paranasal sinuses or vertebral bodies is a necessary part of management of this infection. Reversal of any underlying immune deficits is paramount for successful outcome of CNS aspergillosis. Because there may be progression of neurological deficits, there may be a tendency to use corticosteroids. The role of corticosteroids in this context, however, is deleterious and should be avoided where possible (C-III). The practice of intrathecal or intralesional antifungal chemotherapy is not recommended for treatment of CNS aspergillosis (B-III). Intrathecal administration of AMB does not allow penetration beyond the pia mater and may induce chemical arachnoiditis, seizures, severe headache, and altered mental status. Instead, high-dose systemic antifungal therapy is recommended to achieve higher parenchymal concentrations.

Evidence. *Aspergillus* dissemination to the CNS is a devastating complication of invasive aspergillosis [2, 180, 181]. This complication of invasive pulmonary aspergillosis has historically been associated with a mortality rate of >90%. Arising most commonly as hematogenous dissemination from a pulmonary focus or from direct extension of paranasal sinus infection, CNS aspergillosis is the most lethal manifestation of infection due to *Aspergillus* species [180]. Compared with candidiasis or cryptococcosis of the CNS, focal neurological deficits or focal seizures are the most common clinical manifestation of CNS aspergillosis [182]. Direct extension from the paranasal sinuses, particularly the ethmoid sinuses, may also cause involvement in frontal and temporal lobes or involvement of the cavernous sinus and, potentially, the internal carotid artery. Focal neurological deficits may be irreversible once established. Early recognition and treatment may limit neurological injury. Definitive diagnosis of CNS aspergillosis is often presumptive and based on the presence of documented invasive aspergillosis in other sites, in association with the presence of compatible clinical and radiological findings. Recent reports indicate that galactomannan antigen may be detected in CSF, thereby enhancing diagnostic certainty and potentially sparing an invasive neurological procedure for histological diagnosis [43–45].

Most observations of treatment of CNS aspergillosis are based on open-label studies. The one randomized trial for invasive aspergillosis demonstrated a trend toward improvement of CNS aspergillosis in patients who were treated with voriconazole [115]. The open-label studies of voriconazole in adult and pediatric patients also demonstrate activity of the triazole in treatment of CNS aspergillosis [116, 176]. Among patients with CNS aspergillosis who received voriconazole combined with surgical intervention, responses were favorable in 35% (with long-term survival in 31%); thus, voriconazole is the recommended therapy for CNS aspergillosis [176]. Among the LFABs, favorable responses have been achieved in case reports with L-AMB, ABLC, and ABCD [183–185]. Itraconazole and posaconazole have also been successfully used in treatment of CNS aspergillosis [103, 186–188]. The recent open-label, compassionate release study of caspofungin demonstrated response of CNS aspergillosis that was refractory to AMB [127]. The impact of these agents in the management of CNS aspergillosis appears to be beneficial. However, because of continued high rates of mortality, surgical resection of infected lesions may be an important adjunct to improve antifungal therapy (A-II). Several reports underscore the role of surgical resection of CNS aspergillosis [176, 186, 189]. Other strategies for treatment of CNS aspergillosis have included higher doses of single agents, combinations of antifungal agents, and use of immunomodulators [190]; however, there are no data from prospectively controlled clinical studies to suggest the superiority of these approaches, compared with standard single-agent therapy at approved dosages.

Epidural aspergillosis is an unusual manifestation of CNS aspergillosis that most often arises from extension into the epidural space from vertebral abscess [191]. Systemic antifungal therapy and surgical drainage are considered to be standards of practice for management of epidural aspergillosis; however, most of the experience in managing epidural aspergillosis is based on individual case reports and brief case series. *Aspergillus* osteomyelitis is discussed later in this article.

INVASIVE SINONASAL ASPERGILLOSIS

Key recommendations. Early recognition and therapeutic intervention with systemic antifungal therapy and surgical resection and/or debridement (where indicated) is important. The patient's immune status, extent of surgery necessary, concomitant coagulopathy, and morbidity associated with the surgical procedure(s) should be carefully weighed. Although randomized trials are lacking for this indication, AMB, itraconazole, voriconazole, or presumably, posaconazole are reasonable choices for initial therapy. **If the infection is known to be due to *Aspergillus* species, voriconazole should be initiated (B-III).** If one selects voriconazole or itraconazole as primary therapy, recognition of sinonasal zygomycosis is critical, because these triazoles lack clinical activity against this group of fungal organisms. **Thus, if the etiological organism is not known or**

histopathologic examination is still pending, an AMB formulation should be initiated in anticipation of possible sinus zygomycosis (A-III). Posaconazole demonstrates salvage activity in extrapulmonary aspergillosis and offers the theoretical advantage of activity against Zygomyetes in this context, although published clinical experience is limited (B-III). There are limited data supporting echinocandin use in *Aspergillus* sinusitis.

Evidence. Sinus aspergillosis is classified as invasive or noninvasive. Noninvasive aspergillosis may be further classified as saprophytic sinus aspergillosis or allergic sinus aspergillosis. This section will address the guidelines for treatment of invasive sinus aspergillosis. Subsequent sections will review the guidelines for management of noninvasive sinus aspergillosis.

Several studies involving immunocompromised patients indicate that this infection may be associated with invasive pulmonary aspergillosis or complicated by CNS aspergillosis [192–194]. Infection of the maxillary sinus may be complicated by direct invasion into the palate, with necrosis and perforation into the oral cavity or perforation of the nasal septum. Aspergillosis of the ethmoid and frontal sinuses carries the ominous implication of direct extension into the veins that drain these structures into the cavernous sinuses, resulting in cranial nerve deficits and internal carotid artery thrombosis. Aspergillosis of the ethmoid sinuses also may result in periorbital infection and extension into the extraocular muscles and globe of the eye, resulting in loss of vision. Infection of the sphenoid sinuses may result in direct extension into the cavernous sinuses. Infection of the mastoid sinus cells may occur as a result of a chronic *Aspergillus* otitis media. Aspergillosis of the mastoid sinus may subsequently extend into the transverse sinus, resulting in venous thrombosis and severe neurological sequelae.

Although there are no randomized trials investigating systemic antifungal therapy for treatment of invasive sinonasal aspergillosis, general principles emerge from reports using a combination of medical and surgical interventions [194]. The role of surgical therapy, however, is tempered by the extent of resection necessary, the potential hemorrhagic diathesis of the patient, the surgical candidacy of the patient, and the extent of infection. Diagnostic imaging using CT (including bone windows) will define the soft-tissue and bony extent of disease. The presence of sinus air-fluid levels or sinus opacification in an immunocompromised host should prompt otolaryngological evaluation and sinus endoscopic examination. Brushings and culture of necrotic or ulcerative lesions on the turbinates or in the paranasal mucosa may demonstrate *Aspergillus* species, but the differential diagnosis includes other filamentous fungi, such as the various Zygomycetes, which can appear distinctive histopathologically. Tissue samples should be cultured without homogenization to increase viability of Zygomycetes.

Systemic antifungal therapy is necessary for treatment of most cases of invasive sinus aspergillosis. Favorable responses have been achieved with AMB [189, 195–197], voriconazole [198], itraconazole [189], and caspofungin [199, 200]. Although surgical debridement occupies an important role in management of invasive *Aspergillus* sinusitis and may be curative in some circumstances, extensive resections or repeated surgical debridements may increase morbidity and mortality among neutropenic patients. Recent advances in surgery for maxillary and ethmoidal infection may be beneficial and may avoid more-disfiguring surgery. Local irrigations with AMB are often administered by the surgical teams as an adjunct to systemic antifungal therapy after debridement. However, the use of this strategy is unclear in the context of systemic antifungal therapy. As previously mentioned, the reversal of immunosuppression is paramount to successful outcome of this infection and to prevention of extension and dissemination to the CNS.

Chronic invasive sinonasal aspergillosis and chronic granulomatous *Aspergillus* sinusitis have also been documented in immunocompetent patients living in dry-air climates, such as India, Saudi Arabia, and Sudan [201, 202]. Invasive aspergillosis in Sudanese patients has been predominantly due to *A. flavus* and has been treated with surgical drainage in most cases. Invasive sinonasal aspergillosis in such patients tends to progress in a more indolent manner over the course of months to years in relation to its granulomatous histological characteristics. Although it is more indolent, this infection may progress to invasion of the orbit and other craniofacial structures and, ultimately, to intracranial involvement. Aggressive therapy with combined surgical debridement and chronic antifungal therapy is necessary. Because of the propensity for recurrent infections, long-term antifungal therapy for $\geq$1 year may be warranted.

ASPERGILLUS ENDOCARDITIS, PERICARDITIS, AND MYOCARDITIS

Key recommendations. Early recognition, followed by rapid, aggressive medical and surgical intervention is critical to preventing embolic complications and valvular decompensation. **Voriconazole has been successfully used in case reports and may be the preferred agent (B-III)** [179, 180], based on data from a randomized trial data conducted mostly in pulmonary infection. D-AMB historically has been recommended as the preferred initial treatment, and D-AMB therapy should be continued for a minimum of 6 weeks after surgical intervention (B-III). **Because of the potential for recurrent infections following replacement of an infected prosthetic valve, strong consideration should be given to lifelong antifungal therapy with an antifungal triazole, such as oral voriconazole or posaconazole (C-III).**

Evidence. Cardiac invasion by *Aspergillus* species may present as pericarditis, endocarditis, or myocarditis [203–208]. *Aspergillus* endocarditis may occur as a valvular or mural endo-

cardial infection. Valvular vegetations most commonly develop on prosthetic valves; however, *Aspergillus* endocarditis is reported to occur on normal valves, particularly in injection drug users. Valvular vegetations and, occasionally, mural vegetations may be large and pedunculated, with a high-risk of embolic complications, particularly CNS-related complications. Indeed, embolization to large arteries is a common hallmark of *Aspergillus* endocarditis. When manifesting as mural endocarditis, *Aspergillus* infection of the heart may be the result of dissemination or involvement of the mitral valve annulus.

Aspergillus myocarditis may manifest as myocardial infarction, cardiac arrhythmias, or myoepicarditis [203]. This infection generally occurs in the context of disseminated disease and requires systemic antifungal therapy.

Aspergillus pericarditis arises as the result of direct extension from a contiguous focus of invasive pulmonary aspergillosis, extension from a myocardial lesion, or intraoperative contamination [203]. Pericardial tamponade may rapidly ensue, leading to hemodynamic deterioration and cardiac arrest.

The literature of reported cases consistently underscores the poor prognosis of cardiac aspergillosis. The cornerstones of management of *Aspergillus* endocarditis are antifungal chemotherapy and surgical resection of the infected valve or mural lesion. Attempts to manage cases with medicine alone are rarely successful [203, 209, 210]. As a general principle, in management of fungal endocarditis, early and aggressive surgical resection is endorsed before the onset of valvular destruction, potentially fatal embolic events, or rupture of chordae tendinae leading to acute mitral valvular decompensation [189]. Most cases of *Aspergillus* endocarditis have been treated with AMB [209, 211, 212]. Because of the relative infrequency with which cardiac aspergillosis occurs, there are insufficient data on the use of antifungal triazoles or echinocandins for this infection, although success of voriconazole in cases of tricuspid and prosthetic valve endocarditis has been reported [178, 179]. An extended course of antifungal therapy postoperatively is recommended to eradicate residual cardiac foci and metastatic lesions.

D-AMB has been used for treatment of most cases of *Aspergillus* pericarditis, often with fatal outcome [203]. Of paramount importance to successful treatment of *Aspergillus* pericarditis is aggressive surgical pericardial resection or drainage to treat the rapid development of pericardial tamponade.

ASPERGILLUS OSTEOMYELITIS AND SEPTIC ARTHRITIS

Key recommendations. **Combined medical and surgical intervention is recommended, where feasible, for management of *Aspergillus* osteomyelitis and arthritis (B-III).** Diagnostic imaging with CT and/or MRI is essential for staging disease and for providing a guide for orthopedic and/or neurosurgical intervention. **Although there is currently limited experience with voriconazole for treatment of *Aspergillus* osteomyelitis, voriconazole appears to be effective for this indication (B-II). Historically, AMB has been used and would be appropriate therapy in this context (B-II).** Treatment for a minimum of 6–8 weeks is warranted in nonimmunocompromised patients. For immunocompromised patients, consideration for long-term suppressive therapy or treatment throughout the duration of immunosuppression is appropriate.

Evidence. *Aspergillus* osteomyelitis may develop by hematogenous dissemination, traumatic inoculation, direct extension from a visceral focus, or contamination at the time of surgery [213–215]. Hematogenous *Aspergillus* osteomyelitis may occur, especially in neutropenic patients, injection drug users, and patients with inherited immunodeficiency, such as CGD. The vertebral bodies and intervertebral disks are the most common site of *Aspergillus* osteomyelitis [216]. Successful outcomes have been achieved with combined surgical debridement and systemic antifungal therapy (B-III). Most cases of successful antifungal therapy have been achieved with AMB [215]. Medical treatment alone (L-AMB, followed by oral itraconazole) has rarely been successful in management of *Aspergillus* osteomyelitis [217]. Although successful primary itraconazole therapy of *Aspergillus* osteomyelitis has been reported [218], itraconazole has been more widely used subsequent to a course of AMB [217]. More recently, voriconazole has been successfully used as salvage and primary therapy, either alone or in combination with surgical debridement [177, 219]. There is little reported experience of the use of posaconazole [220] or echinocandins in treatment of *Aspergillus* osteomyelitis.

Aspergillus arthritis may develop from hematogenous dissemination in immunocompromised patients and in illicit injection drug users or by direct traumatic inoculation in immunocompetent hosts [221]. In many cases, *Aspergillus* arthritis arises as an extension from a contiguous focus of *Aspergillus* osteomyelitis [221]. Most of the successfully treated cases of *Aspergillus* arthritis have responded to combined medical therapy and drainage of the joint [215]. Most reported cases of *Aspergillus* arthritis have used AMB as primary therapy; azoles have less commonly been used in this role [221].

ASPERGILLUS ENDOPHTHALMITIS AND *ASPERGILLUS* KERATITIS

Aspergillus endophthalmitis and *Aspergillus* keratitis are 2 sight-threatening infections that require rapid ophthalmologic and medical intervention to preserve and restore sight. *Aspergillus* keratitis is an excruciatingly painful process; treatment of this process may also considerably alleviate pain. If not recognized and treated promptly, *Aspergillus* keratitis may require a corneal transplant or may be complicated by endophthalmitis.

Key recommendations. **Following a diagnostic vitreal tap, IV AMB and, where appropriate, intravitreal AMB plus pars**

plana vitrectomy may be sight saving in *Aspergillus* endophthalmitis (B-III). Voriconazole administered intravitreally or systemically is an alterative regimen (B-III). Management of *Aspergillus* keratitis requires emergency ophthalmologic intervention with ophthalmologic examination, topical antifungal therapy, and systemic antifungal therapy with AMB, voriconazole, or itraconazole (B-III). Ophthalmologic surgical intervention has been warranted in cases with potential corneal perforation or progression despite medical therapy.

Evidence. *Aspergillus* endophthalmitis is a devastating infection that may result in irreparable loss of vision and rapid destruction of the eye. Infection may occur by one of several mechanisms: hematogenous dissemination, direct inoculation by trauma, and contamination by surgical procedure [222–224]. Hematogenous dissemination occurs most commonly in injection drug users and immunocompromised patients with disseminated aspergillosis and endophthalmitis. Definitive clinical diagnosis requires direct ophthalmoscopic examination and culture of vitreous humor or aqueous humor specimens. AMB has been used most widely as the systemic agent in treatment of *Aspergillus* endophthalmitis. Concentrations of AMB-based compounds in the aqueous and vitreous humor are relatively low; intravitreal administration of AMB is also used following pars plana vitrectomy as a standard of care in management of *Aspergillus* endophthalmitis and has resulted in successful outcomes [223, 225]. Voriconazole has recently been found to be successful in isolated cases of *Aspergillus* endophthalmitis and has been administered intravitreally and systemically [226, 227]. Panresistant organisms, such as *A. ustus,* have also been reported [228]. Vitrectomy may be sight saving by removing the bulk of inflammatory debris and infectious organisms. More conservative measures, such as subconjunctival injection, are seldom successful. Direct macular involvement is a poor prognostic indicator for recovery of visual acuity [225]. Itraconazole has been used as systemic therapy, in conjunction with pars plana vitrectomy and AMB intravitreal injection, in a few reported cases. Systemic antifungal therapy with AMB and 5-flourocytosine has also been reported in several cases. Although 5-flourocytosine penetrates well into the vitreous humor, its role in enhancing the antifungal combination therapy against aspergillosis is not established, and it has been noted to be antagonistic in vitro against some *Aspergillus* strains [229].

Aspergillus keratitis is a locally invasive fungal infection of the cornea that is characterized by ocular pain, potentially rapid loss of vision, and potential development of endophthalmitis if not recognized and treated promptly [230–232]. The cornea is the critical structure for visual acuity and integrity of the anterior chamber. *Aspergillus* keratitis most commonly develops as a result of traumatic inoculation of *Aspergillus* into the cornea through injury or surgical procedures [233, 234]. *Aspergillus* keratitis is commonly encountered in agricultural workers, who may suffer abrasions of the cornea from branches and leaves during the course of their work in the fields [230].

Aspergillus keratitis constitutes an ophthalmologic emergency requiring careful slit lamp examination, assessment of the depth of infection, and prompt initiation of topical antifungal therapy. Topical antifungal therapy with AMB drops or pimaricin is most widely used, although there are no controlled data to support their use. Intracameral injection of AMB (i.e., into the anterior chamber) has been reported to be a suitable alternative in patients who are refractory to topical antifungal therapy [235]. Oral itraconazole has been successfully used in the treatment of *Aspergillus* keratitis, possibly because it penetrates into the deeper corneal layer of the eyes, but itraconazole has also been used as a topical solution [236, 237]. Voriconazole, administered topically, systemically, or via intracameral injection has also been successfully used in *Aspergillus* keratitis [238, 239] Surgical intervention, which may include debridement, lamellar keratectomy, or a conjunctival flap, is often required. Topical therapy may be unsuccessful, and surgical resection of the infected cornea may be the only recourse. A corneal transplantation may be necessary in the context of progressive *Aspergillus* keratitis despite medical therapy or if there is a threat of corneal perforation.

CUTANEOUS ASPERGILLOSIS

Cutaneous aspergillosis may develop in the context of hematogenous dissemination or can occur in the context of traumatic or nosocomial device-related infection

Key recommendations. **Therapy for secondary cutaneous lesions reflects that of disseminated infection, with systemic voriconazole (A-I) recommended as primary therapy. Alternative agents include L-AMB (A-I), posaconazole, itraconazole, or an echinocandin (B-II).** Surgical intervention, particularly for primary cutaneous infection, may be useful; biopsy for confirmation of mycological diagnosis is very important to distinguish other potential pathogens (e.g., *Fusarium* species and Zygomycetes).

Evidence. Cutaneous aspergillosis may be a primary process or, more frequently, may develop as a result of secondary hematogenous dissemination in immunocompromised patients [240–242]. Cutaneous aspergillosis rarely occurs as an infection in immunocompetent patients. Nosocomial cutaneous aspergillosis may also be a sentinel of environmental contamination, as exemplified by cutaneous infections occurring with arm boards, direct contamination of vascular sites in the operating room, contamination of dressings used for burn wounds, and percutaneous infection in newborn infants [241–244]. Itraconazole is concentrated in skin and skin structures, which theoretically may increase its use in treating cutaneous aspergillosis.

ASPERGILLUS PERITONITIS

Key recommendation. **Removal of peritoneal dialysis catheter and intraperitoneal dialysis with AMB, in addition to IV administration of AMB, are recommended (B-III). Itraconazole or an extended-spectrum azole (voriconazole or posaconazole) may be used as a salvage therapy (C-III).**

Evidence. *Aspergillus* peritonitis may occur as a complication of chronic ambulatory peritoneal dialysis [245]. Although *Candida* species are the most common cause of fungal peritonitis complicating chronic ambulatory peritoneal dialysis, *Aspergillus* species are a well-established cause of this infection [246]. Removal of the dialysis catheter, combined with the administration of intraperitoneal and IV AMB, has been associated with successful outcome [245, 247]. Itraconazole has also been used for systemic antifungal therapy in the management of *Aspergillus* peritonitis complicating chronic ambulatory peritoneal dialysis [248]. Evidence for other compounds is limited.

ESOPHAGEAL AND GASTROINTESTINAL ASPERGILLOSIS

Key recommendation. Once a diagnosis is established, medical and, where appropriate, surgical therapy is needed to prevent the complications of potentially fatal hemorrhage, perforation, obstruction, and infarction. Systemic antifungal therapy, as used for disseminated invasive aspergillosis, is appropriate.

Evidence. Aspergillosis of the esophagus and gastrointestinal tract has been found to be relatively common in advanced cases of disseminated invasive aspergillosis [249, 250]. Young et al. [250] described the esophagus and gastrointestinal tract as the third most common site of infection in autopsy-documented invasive aspergillosis. The few well-documented cases have been associated with high morbidity and mortality. There is no clear indication of optimal therapy. Because of the paucity of data for esophageal and gastrointestinal aspergillosis, a rational approach is to combine medical and surgical therapy.

HEPATIC ASPERGILLOSIS

Key recommendation. **Medical therapy of hepatic aspergillosis should be considered as initial therapy (C-III). For extrahepatic or perihepatic biliary obstruction, surgical intervention is warranted (C-III).** For localized lesions that are refractory to medical therapy, surgical consultation is recommended.

Evidence. Occurring as single or multiple parenchymal lesions, hepatic aspergillosis may occur as a process of dissemination from the gastrointestinal tract along the portal venous system or as a component of general systemic dissemination [17, 251]. Hepatic aspergillosis may also develop as a process of cholangitis [252]. Reports of therapeutic interventions are limited. Medical therapy for hepatic abscesses may be effective and preclude the need for surgical resection.

RENAL ASPERGILLOSIS

Key recommendations. A combined approach of medical and urological management of renal aspergillosis allows flexibility for the various patterns of renal aspergillosis. Nephrostomy may reduce the complications of ureteral obstruction and allow for AMB lavage of the pelvicalyceal system. All of the available antifungal agents with activity against aspergillosis penetrate renal parenchyma. **However, because none of these agents is excreted primarily into the pelvis of the kidney or urine, the management of pelvicalyceal and ureteral infection may require nephrostomy with instillation of AMB (C-III).**

Evidence. Renal aspergillosis may develop as single or multiple parenchymal abscesses, usually as a result of hematogenous dissemination or, less commonly, as the result of contamination of a surgical procedure or as fungal balls in the pelvis of the kidney [253–256]. This form of *Aspergillus* infection may cause hematuria, ureteral obstruction, perinephric abscess with extension into surrounding tissues, or passing of $\geqslant$1 fungal ball or fungal elements in the urine. Reports of management are limited to individual cases. Medical management alone may be successful if abscesses are relatively small. Management of larger abscesses may require surgical drainage. Nephrectomy is performed only as a last option.

EMPIRICAL ANTIFUNGAL THERAPY OF NEUTROPENIC PATIENTS WITH PROLONGED FEVER DESPITE ANTIBACTERIAL THERAPY AND PRESUMPTIVE THERAPY FOR INVASIVE ASPERGILLOSIS

Key recommendation. **Empirical antifungal therapy with AMB, an LFAB, itraconazole, voriconazole, or caspofungin is recommended for high-risk patients with prolonged neutropenia who remain persistently febrile despite broad-spectrum antibiotic therapy (A-I). Empirical antifungal therapy is not recommended for patients who are anticipated to have short durations of neutropenia (duration of neutropenia, <10 days), unless other findings indicate the presence of an invasive fungal infection (B-III).**

Evidence. This area has been reviewed in a related 2002 Guideline from the Infectious Diseases Society of America [257]. Early reports from the National Cancer Institute and the European Organization for Research and Treatment of Cancer underscored the importance of early initiation of D-AMB for treatment of invasive aspergillosis and other invasive fungal infections [258, 259]. These randomized, nonplacebo, open-label clinical trials demonstrated that neutropenic patients with

persistent fever despite broad-spectrum antibacterial therapy have an increased risk of developing an overt invasive fungal infection. In these studies, empirical antifungal therapy reduced the frequency of the development of clinically overt invasive fungal infection and provided prophylaxis against subsequent infections in high-risk neutropenic patients. L-AMB was found to be as effective as but less nephrotoxic than D-AMB in a randomized, double-blind multicenter trial; a secondary analysis demonstrated a significant reduction of invasive fungal infections in the L-AMB arm [260]. A randomized control study of IV and oral formulations of itraconazole also found this agent to be as effective as but less nephrotoxic than D-AMB in empirical antifungal therapy [261]. A randomized, controlled trial of voriconazole versus L-AMB did not fulfill prespecified criteria for the overall population but was comparable to L-AMB in the high-risk neutropenic population, with a significant reduction in the rate of emergent invasive aspergillosis during neutropenia in prespecified secondary analyses [262]. Although not FDA approved for empirical use in patients with fever and neutropenia, the use of voriconazole in treating both infection due to *Aspergillus* species and infection due to *Candida* species—the leading fungal pathogens in most patients with fever and neutropenia—provides evidence to support the recommendation for its use in patients at high risk for these infections while a diagnostic evaluation is conducted. Most recently, caspofungin was compared with L-AMB in a randomized, double-blind, multinational trial for empirical antifungal therapy. This trial found that caspofungin was as effective as L-AMB in overall response; prespecified secondary analyses found that caspofungin was more active in prolongation of survival and in primary treatment of baseline invasive fungal infections [263]. Empirical antifungal therapy appears to be most beneficial in patients with prolonged neutropenia (duration of neutropenia, >10 days). The initiation of antifungal therapy still warrants an aggressive approach to establishing a microbiological diagnosis where feasible.

Preemptive antifungal therapy is a logical extension of empirical antifungal therapy, in that it defines a high-risk patient population on the basis of more than persistent fever and neutropenia (i.e., with a surrogate marker of infection, such as abnormal CT findings or a positive result of assay for *Aspergillus* antigen). Because ~40% of patients receiving empirical antifungal therapy have pulmonary infiltrates, there is considerable overlap between the approaches of empirical and preemptive therapy. In an open-label feasibility study, Maertens et al. [55] used serum galactomannan assay and CT to detect invasive aspergillosis in a population of patients with leukemia who received fluconazole prophylaxis. This strategy, which used more extensive serum galactomannan and radiographic monitoring than is typically performed in routine practice, reduced the use of empirical therapy and successfully treated cases of invasive aspergillosis diagnosed using surrogate markers.

For persistently febrile neutropenic patients who may be receiving anti-*Aspergillus* prophylaxis, the causes of persistent fever are less likely to be of a fungal origin [264]. Careful evaluation for nonfungal causes, as well as the possibility of breakthrough invasive fungal infections that are resistant to the prophylactic regimen, should be considered in this patient population. Thus, routine initiation of empirical antifungal therapy in this context merits reevaluation.

PROPHYLAXIS AGAINST INVASIVE ASPERGILLOSIS

Key recommendation. **Antifungal prophylaxis with posaconazole can be recommended in HSCT recipients with GVHD who are at high risk for invasive aspergillosis and in patients with acute myelogenous leukemia or myelodysplastic syndrome who are at high risk for invasive aspergillosis (A-I). Itraconazole may be effective, but tolerability limits its use (B-I).** Further investigation of antifungal prophylaxis is recommended in this population and other high-risk groups.

Evidence. Prophylactic strategies may be useful in patients who are at high risk for invasive aspergillosis; selection of the patient population in whom this strategy may be applied remains a challenge. Selected high-risk patient groups may include patients with prolonged neutropenia and severe GVHD, lung transplant recipients, patients receiving long-term high-dose corticosteroid therapy, some liver transplant recipients, and those with certain inherited immunodeficiency disorders (e.g., CGD).

A clinical trial of posaconazole therapy has recently been reported that demonstrated its superiority versus fluconazole or itraconazole in prevention of invasive aspergillosis in patients with acute myeloid leukemia and myelodysplasia [105]. This study demonstrated higher survival in the posaconazole arm, but there was greater toxicity in recipients of posaconazole than in fluconazole recipients. Because of the heterogeneity of risk for invasive aspergillosis in published series of acute myelogenous leukemia therapy, further study is needed to determine which populations of patients with leukemia and myelodysplasia might benefit most from this approach. Risk factors for invasive aspergillosis during acute myeloid leukemia therapy from published series include the need for >1 treatment course to achieve remission or chemotherapy for relapsed or refractory acute myeloid leukemia. A separate study of posaconazole prophylaxis during GVHD in HSCT recipients also found a significant reduction in proven and probable invasive fungal infections and similar toxicity in posaconazole recipients, compared with those receiving fluconazole [104]. Because of the heterogeneity of risk for invasive fungal infection in patients receiving anti-GVHD therapy, fur-

ther study is needed to define which patients would benefit most from this approach. Risk factors for invasive aspergillosis in patients with GVHD include the need for prolonged high-dose steroid therapy (>1 mg/kg/day of prednisone for 2–3 weeks) and the use of certain anti-GVHD therapies, such as infliximab and antithymocyte globulin. Earlier studies of antifungal prophylaxis in hematological malignancies are summarized in a large meta-analyses [265–269].

A key distinction should be made between primary and secondary prophylaxis. Primary prophylaxis involves administration of antifungal chemotherapy to patients who have no evidence of infection but whose epidemiological risk profile indicates a high propensity for the development of invasive aspergillosis. Secondary prophylaxis involves the administration of antifungal therapy to a patient who is undergoing a period of immunosuppression and who has a history of invasive aspergillosis. This section focuses on primary prophylaxis. However, several studies indicate that secondary prophylaxis against invasive aspergillosis can be successful when an anti-*Aspergillus* azole (voriconazole, posaconazole, or itraconazole) or LFAB is given to patients receiving ongoing immunosuppressive therapy following treatment of a documented episode of invasive aspergillosis [113, 270–272].

Among the studies that investigated parenterally administered D-AMB or L-AMB for prophylaxis, most have been historically controlled, and some have suggested a reduction in invasive aspergillosis. Several prospective, randomized trials using polyene therapies have demonstrated a reduction in the number of invasive fungal infections, but none have demonstrated a significant reduction of invasive aspergillosis in a prospective, randomized study [273–276]. Studies of aerosolized AMB have revealed conflicting results, in part because of limitations of study design and selection of patients at risk [277–279].

Itraconazole has been evaluated in several prospective trials, but conclusions regarding efficacy have been limited, because study designs have not included patients at significant risk for aspergillosis [269, 280–284]. Although itraconazole oral capsules are ineffective for prophylaxis because of erratic bioavailability and dose-limiting toxicity, itraconazole oral solution or IV itraconazole in neutropenic patients with hematological dysfunction is partially effective in reducing the incidence of invasive aspergillosis, with a mean hazard ratio of 0.52 (range, 0.3–0.91) [265]. However, the use of itraconazole solution for prophylaxis against *Aspergillus* is also reduced by dose-limiting toxicity [285, 286]. Although micafungin showed a trend towards a decreased incidence of *Aspergillus* infection (compared with fluconazole) in HSCT, there were small numbers of breakthrough infections in the patients studied, and the requirement for daily IV therapy further limited widespread use [287]. Itraconazole has been successfully used as prophylaxis in patients with CGD [288]. Voriconazole has not been studied in this context, although clinical trials are in progress.

CHRONIC AND SAPROPHYTIC FORMS OF ASPERGILLOSIS

ASPERGILLOMA AND CHRONIC PULMONARY ASPERGILLOSIS

Key recommendation. **Antifungal chemotherapy with itraconazole, voriconazole, or presumably, posaconazole provides some potential for therapeutic benefit with comparatively minimal risk (B-III).** Surgical resection or intracavitary antifungal therapy may be appropriate in selected patients with a single aspergilloma who are carefully evaluated for the risks mentioned below. **Long-term, perhaps lifelong, antifungal treatment is required for chronic cavitary pulmonary aspergillosis (CCPA; B-III).**

Evidence. One or more pulmonary cavities with detectable serum *Aspergillus* antibodies are characteristic of pulmonary aspergilloma or chronic pulmonary aspergillosis. Patients usually have underlying pulmonary disease, such as cavitary tuberculosis or histoplasmosis, fibrocystic sarcoidosis, bullous emphysema, or fibrotic lung disease. Among the serious complications of chronic pulmonary aspergillosis are potentially life-threatening hemoptysis, pulmonary fibrosis, and rarely locally, invasive aspergillosis. Pulmonary aspergilloma is defined as a conglomeration of intertwined *Aspergillus* hyphae, fibrin, mucus, and cellular debris within a pulmonary cavity or an ectatic bronchus [289]. The diagnosis of aspergilloma is usually made clinically and radiographically without a lung biopsy. Pulmonary aspergilloma radiographically appears as a solid rounded mass, sometimes mobile, of water density, within a spherical or ovoid cavity, and separated from the wall of the cavity by an airspace of variable size and shape. Local pleural thickening is highly characteristic. CCPA is defined as the occurrence of multiple cavities, which may or may not contain an aspergilloma, in association with pulmonary and systemic symptoms and raised inflammatory markers. Over years, untreated, these cavities enlarge and coalesce, and aspergillomas may appear or disappear. A distinction between CNPA (previously known as subacute invasive pulmonary aspergillosis) and CCPA is the prolonged time frame and genetic predisposition described in the latter; defects in innate immunity are described in CCPA [290]. Apparent aspergillomas (which is better termed mycotic lung sequestrum) also may develop in consolidated lesions during recovery from neutropenia, but preexisting cavities are not present in these cases.

The data guiding management of single aspergillomas are based on uncontrolled trials and case reports. Therapeutic decisions that involve aspergilloma are predicated on preventing or treating life-threatening hemoptysis. The first major decision

in the management of aspergilloma is whether therapy is required.

Surgical resection is a definitive treatment for aspergilloma [156, 291]. However, pulmonary resection for aspergilloma is a difficult surgical procedure. Attempts to resect CCPA (referred to in the surgical literature as complex aspergilloma) have been associated with high morbidity and mortality. Postoperative complications include hemorrhage, bronchopleural fistulae, and *Aspergillus* infection of the pleural space. Further contributing to the high risk of surgical resection of an aspergilloma is the often preexisting poor pulmonary function that may preclude thoracotomy. The optimal candidates for surgical resection are those with a single aspergilloma.

Bronchial artery embolization has been used to occlude the putative vessel that supplies the bleeding site in patients experiencing hemoptysis caused by chronic pulmonary aspergillosis [292]. Unfortunately, bronchial artery embolization is usually unsuccessful or only temporarily effective because of complex collateral vascular channels. Thus, bronchial artery embolization should be considered as a temporizing procedure in a patient with life-threatening hemoptysis who might be eligible for more medical therapy or surgical resection (single aspergilloma) if the hemoptysis were stabilized (B-III). Endobronchial or transthoracic intracavitary resection instillation of antifungal agents, particularly AMB, has been attempted with some success [156, 293]. However, this modality may be difficult in patients with compromised pulmonary function.

Medical therapy has limited activity in treatment of aspergilloma [156]; in some cases, however, it may be of some use [289]. Medical therapy is the standard of care for CCPA [174, 175, 294, 295]. IV administered D-AMB appears to have minimal activity in treatment of aspergilloma. Response in CCPA to systemically administered itraconazole or voriconazole is favorable, with improvement in symptoms and stabilization or improvement in *Aspergillus* antibody titers and radiologic findings [170, 175]. Terbinafine has been suggested to have activity in one report, but lack of clinical data limits recommendation for its use [296]. The benefits of surgical resection of aspergilloma may offer definitive treatment; however, the risks of compromised pulmonary function, bronchopleural fistula, and infection of the pleural space may outweigh the benefits, depending on the individual patient. Bronchial artery embolization carries modest risk and only transient benefit. Transthoracic, intracavitary instillation of AMB may be effective, but it carries a risk of pneumothorax, hemoptysis, and pleural seeding. Oral systemic antifungal therapy is unnecessary for single aspergilloma but important for CCPA. Adverse events associated with azole antifungal drugs are infrequent but are problematic for those who develop them. If the drug is tolerated, no additional long-term risks of azole therapy have been identified.

ASPERGILLUS OTOMYCOSIS (OTIC ASPERGILLOSIS)

Key recommendations. **Topical therapy with irrigating solutions of boric acid, acetic acid, or azole cream may be effective in eradicating *Aspergillus* otomycosis (C-III). For refractory cases and in contexts of perforated tympanic membranes, use of voriconazole, posaconazole, or itraconazole may be appropriate (C-III).**

Evidence. *Aspergillus* otomycosis is a saprophytic process that usually involves the external auditory canal [297]. Symptoms include pruritus, pain, hypoacusis, and otic discharge. *Aspergillus* otomycosis may involve the middle ear if the tympanic membrane has been perforated. Perforation of the tympanic membrane does not usually occur as a result of *Aspergillus* otomycosis but more often ensues as the result of recurrent bacterial otitis media. Patients with impaired mucosal or cutaneous immunity, such as those with hypogammaglobulinemia, diabetes mellitus, chronic eczema, or HIV infection and those who receive corticosteroids, are susceptible to recurrent bacterial otitis media, otitis externa, and *Aspergillus* otomycosis. If the otomycotic process is not successfully treated and the underlying predisposing immune impairment and anatomic defects are not corrected, *Aspergillus* hyphae and conidia may extend into the mastoid sinus, creating a chronic fungal mastoiditis. *Aspergillus* otomycosis is most commonly attributable to *A. niger* and *A. fumigatus* [297, 298]. *A. niger,* which is a known cause of in vivo production of oxalic acid, may locally elaborate this toxic metabolite in the necrotic debris of the external auditory canal [299]. Erosion and disruption of the epidermis may serve as a portal of entry for superinfection by opportunistic bacterial infections in immunocompromised patients. Data describing treatment outcomes are anecdotal or uncontrolled. Topical therapy using irrigations with acetic acid or boric acid are described as being beneficial. Topical antifungal creams and ointments are not well studied but may be useful for this condition. Orally administered itraconazole, voriconazole, or posaconazole may be effective; however, there are no published studies that support their use.

ALLERGIC FORMS OF ASPERGILLOSIS

ALLERGIC BRONCHOPULMONARY ASPERGILLOSIS

Key recommendation. **Treatment of allergic bronchopulmonary aspergillosis (APBA) should consist of a combination of corticosteroids and itraconazole (A-I).**

Evidence. APBA is a hypersensitivity disease of the lungs that is associated with inflammatory destruction of airways in response to *Aspergillus* species [300]. ABPA is defined through 7 primary diagnostic criteria: episodic bronchial obstruction

(asthma), peripheral eosinophilia, immediate scratch test reactivity to *Aspergillus* antigen, precipitating antibodies to *Aspergillus* antigen, elevated serum IgE concentrations, history of pulmonary infiltrates (transient or fixed), and central bronchiectasis. Secondary diagnostic criteria include repeated detection of *Aspergillus* species in sputum samples using stain and/or culture, a history of expectoration of brown plugs or flecks, elevated specific IgE concentration directed against *Aspergillus* antigen, and Arthus reaction (late skin reactivity) to *Aspergillus* antigen. ABPA may progress through clinical stages of acute corticosteroid-responsive asthma to corticosteroid-dependent asthma to fibrotic end-stage lung disease with honeycombed lung.

Corticosteroid therapy is the mainstay of therapy for ABPA [301–303]. However, the few studies of corticosteroid therapy for ABPA have involved small numbers of patients and have been neither double-blind nor controlled [304]. Nevertheless, the current findings support the usefulness of corticosteroids in the management of acute ABPA, with improved pulmonary function and fewer episodes of recurrent consolidation. However, because chronic administration of corticosteroids causes severe immune impairment and multiple metabolic abnormalities, alternative approaches to management of ABPA have been developed.

An example of such an approach is to eradicate *Aspergillus* species from the airways using itraconazole as a corticosteroid-sparing agent. The mechanism of this effect is to diminish the antigenic stimulus for bronchial inflammation. Two double-blind, randomized, placebo-controlled trials for ABPA demonstrated that itraconazole (200 mg twice daily orally for 16 weeks) resulted in significant differences in ability to ameliorate disease, as assessed by the reduction in corticosteroid dose, increased interval between corticosteroid courses, eosinophilic inflammatory parameters, and IgE concentration, as well as improvement in exercise tolerance and pulmonary function [305, 306]. Similar benefits of itraconazole were observed in patients with cystic fibrosis and ABPA [307]. Other azoles (voriconazole and posaconazole) have not been studied in this context. The benefits of short-term corticosteroid treatment of ABPA include reduced frequency of acute exacerbations, preservation of pulmonary function, and improved quality of life. However, the long-term adverse effects of corticosteroid therapy may result in profound immunosuppression and debilitating metabolic abnormalities, including diabetes mellitus, hyperlipidemia, and osteoporosis. Corticosteroid-induced immunosuppression may very rarely result in progression of ABPA to invasive pulmonary aspergillosis. Itraconazole spares the effect of corticosteroids but may interact with inhaled corticosteroids, leading to iatrogenic Cushing syndrome in rare cases. The benefits of the addition of itraconazole outweigh the risks of long-term administration of high-dose prednisone.

ALLERGIC *ASPERGILLUS* SINUSITIS

Key recommendations. **Endoscopic drainage may be useful in patients with obstructive symptoms (C-III). Itraconazole is recommended for consideration in allergic *Aspergillus* sinusitis (AAS; C-III). Nasal or systemic corticosteroids may be useful in some patients (C-III).** The benefits of endoscopic surgical sinus drainage outweigh the risks of surgery in cases of AAS that present with complications of sinus obstruction. Systemic corticosteroids are beneficial but may be fraught with serious systemic complications with long-term use. Nasal corticosteroids are partially effective and well absorbed but, when used continuously in high doses, can damage or atrophy the nasal mucosa. **The benefits of itraconazole in AAS outweigh the potential for toxicity (C-III).** Because patients with either AAS and ABPA may be receiving nonsedating antihistamines, caution is required to assess the potential for adverse drug interactions with some of those agents associated with prolonged QT interval and torsades de pointe.

Evidence. Katzenstein et al. [308] first described the clinical and pathologic features of AAS in 1983 in 7 cases presenting as chronic sinusitis. Most patients were young adults with a history of asthma; all had chronic nasal polyps and opacification of multiple sinuses. Recurrent sinusitis was common. Several patients underwent repeated surgical drainage procedures. A distinct mucinous material containing eosinophils, Charcot-Leyden crystals, and hyphal elements morphologically compatible with *Aspergillus* species was found histologically in tissue resected from the sinuses. The condition of AAS shares similar histopathological features with ABPA but affects the paranasal sinuses instead of the lung. Waxman et al. [309] later described the immunologic features of AAS to include an immediate cutaneous reactivity to *Aspergillus* species in 60% of patients, elevation of total serum IgE concentration in 85%, and serum precipitins to *Aspergillus* species in 85%. The conditions of AAS and ABPA may coexist in some patients. These investigators and others have reported beneficial responses to variable courses and doses of prednisone in nonrandomized, noncontrolled, observational studies [309]. Because of the obstruction caused by inspissated mucinous secretions, surgical drainage and aeration is considered to be an essential component of management, in conjunction with intranasal or systemic corticosteroid therapy. Advanced forms of AAS may present with proptosis and optic neuropathy, necessitating prompt surgical intervention [309]. Fang [310] more recently introduced the use of endoscopic sinus surgery in the management of AAS, thus affording reduced risk, compared with that associated with more-invasive drainage procedures. Recent case reports suggest a benefit of itraconazole in the management of AAS and may spare the use of steroids [311, 312]. Other azoles have not been evaluated.

FUTURE DIRECTIONS AND GAPS IN KNOWLEDGE IN INVASIVE ASPERGILLOSIS

There are many unanswered and unresolved epidemiological, laboratory, and clinical questions that need to be addressed and understood in the diagnosis, treatment, and prevention of aspergillosis. Better diagnostic tests are needed, both to facilitate more accurate identification of patients with invasive aspergillosis and to permit earlier initiation of therapy. The availability of more-active and better-tolerated antifungal agents has significantly improved therapy of patients at risk for serious *Aspergillus* infection. However, critical gaps in knowledge remain regarding management of these infections, including the use of combination therapy, tools for early detection of these infections, evaluation of response, therapy for patients with breakthrough or refractory infection, and the patient population for whom prophylaxis would be most beneficial.

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