

Practice Guidelines for Diseases Caused by *Aspergillus*

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Executive Summary

Aspergillosis comprises a variety of manifestations of infection. These guidelines are directed to 3 principal entities: invasive aspergillosis, involving several organ systems (particularly pulmonary disease); pulmonary aspergilloma; and allergic bronchopulmonary aspergillosis. The recommendations are distilled in this summary, but the reader is encouraged to review the more extensive discussions in subsequent sections, which show the strength of the recommendations and the quality of the evidence, and the original publications cited in detail.

Invasive aspergillosis. Because it is highly lethal in the immunocompromised host, even in the face of therapy, work-up must be prompt and aggressive, and therapy may need to be initiated upon suspicion of the diagnosis, without definitive proof (BIII). Intravenous therapy should be used initially in rapidly progressing disease (BIII). The largest therapeutic experience is with amphotericin B deoxycholate, which should be given at maximum tolerated doses (e.g., 1–1.5 mg/kg/d) and should be continued, despite modest increases in serum creatinine levels (BIII). Lipid formulations of amphotericin are indicated for the patient who has impaired renal function or who develops nephrotoxicity while receiving deoxycholate amphotericin (AII). Oral itraconazole is an alternative for patients who can take oral medication, are likely to be adherent, can be demonstrated (by serum level monitoring) to absorb the drug, and lack the potential for interaction with other drugs

(BII). Oral itraconazole is attractive for continuing therapy in the patient who responds to initial iv therapy (CIII). Therapy should be prolonged beyond resolution of disease and reversible underlying predispositions (BIII). Adjunctive therapy (particularly surgery and combination chemotherapy, also immunotherapy), may be useful in certain situations (CIII).

Aspergilloma. The optimal treatment strategy for aspergilloma is unknown. Therapy is predominantly directed at preventing life-threatening hemoptysis. Surgical removal of aspergilloma is definitive treatment, but because of significant morbidity and mortality it should be reserved for high-risk patients such as those with episodes of life-threatening hemoptysis, and considered for patients with underlying sarcoidosis, immunocompromised patients, and those with increasing *Aspergillus*-specific IgG titers (CIII). Surgical candidates would need to have adequate pulmonary function to undergo the operation. Bronchial artery embolization rarely produces a permanent success, but may be useful as a temporizing procedure in patients with life-threatening hemoptysis. Endobronchial and intracavitary instillation of antifungals or oral itraconazole may be useful for this condition. Since the majority of aspergillomas do not cause life-threatening hemoptysis, the morbidity and cost of treatment must be weighed against the clinical benefit.

Allergic bronchopulmonary aspergillosis (APBA). Although no well-designed studies have been carried out, the available data support the use of corticosteroids for acute exacerbations of ABPA (AII). Neither the optimal corticosteroid dose nor the duration of therapy has been standardized, but limited data suggest the starting dose should be ~0.5 mg/kg/d of prednisone. The decision to taper corticosteroids should be made on an individual basis, depending on the clinical course (BIII). The available data suggest that clinical symptoms alone are inadequate to make such decisions, since significant lung damage may occur in asymptomatic patients. Increasing serum IgE levels, new or worsening infiltrate on chest radiograph, and worsening spirometry suggest that corticosteroids should be

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Table 1. Categories reflecting the strength of each recommendation for or against the use of therapy for diseases caused by *Aspergillus* species.

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

used (BII). Multiple asthmatic exacerbations in a patient with ABPA suggest that chronic corticosteroid therapy should be used (BIII). Itraconazole appears useful as a corticosteroid sparing agent (BII).

Although the frequency of these diseases is on the rise, there is a paucity of randomized comparative trials involving these entities; therefore, the recommendations represent a compromise and consensus among students of these diseases (i.e., the authors). They have synthesized the recommendations from published and personal experience, including case series, open trials, and any comparative trials, as indicated.

Introduction

Aspergillus species are saprophytic molds found worldwide. Diseases caused by *Aspergillus* species are most commonly caused by *Aspergillus fumigatus*, with *Aspergillus flavus* the second most frequently isolated pathogen. Other species reported to cause disease include *Aspergillus amstelodami*, *Aspergillus avenaceus*, *Aspergillus candidus*, *Aspergillus carneus*, *Aspergillus caesiellus*, *Aspergillus clavatus*, *Aspergillus glaucus*, *Aspergillus granulatus*, *Aspergillus nidulans*, *Aspergillus niger*, *Aspergillus oryzae*, *Aspergillus quadrilineatus*, *Aspergillus restrictus*, *Aspergillus sydowi*, *Aspergillus terreus*, *Aspergillus ustus*, and *Aspergillus versicolor*. The frequency and relative importance of these infections are on the rise in all developed countries, which is possibly related to increased numbers of immunocompromised patients, owing to improved survival from AIDS, malignancies and more intensive cytotoxic therapy, more transplantation (with immunosuppression) for organ dysfunctions, and better therapy and prophylaxis for candidal infections.

These guidelines are drafted to ensure appropriate and successful therapy for 3 main diseases caused by *Aspergillus* species. They include invasive aspergillosis, ABPA, and aspergilloma. The guidelines proposed initially are general and are followed by modifications for individual clinical settings. The guidelines are based on scientific publications and peer-reviewed information (this documentation is provided), and are largely concerned with therapy. The guidelines are not intended to be a comprehensive treatise on pathogenesis or diagnosis. The categories of ranking of the strength of the recommendation and the quality of the evidence are given in tables 1 and 2. Guidelines for prophylaxis and empirical therapy for invasive

aspergillosis in neutropenic hosts have recently been published [1] and will not be discussed here.

Antifungal Agents

General and specific commentary on antifungal drugs has been provided in a previous guideline in this series. The drugs available to treat aspergillosis presently include amphotericin B in deoxycholate [2–4], a familiar drug with 40 years' clinical experience; 3 lipid-based preparations of amphotericin B [5–12]; and itraconazole, an oral and iv triazole [13–18]. In general, the largest databases for therapy in aspergillosis concern amphotericin B deoxycholate and various surgical modalities. There is thus some concern about the efficacy of the newer therapies, particularly in patients with rapidly progressive invasive disease.

Itraconazole has many important drug interactions [19], which are particularly noteworthy in patients at risk of aspergillosis, because many such patients are receiving other drugs concomitantly for a variety of conditions. These patients often also have hypochlorhydria and/or enteropathy as a result of these conditions; therefore, when oral itraconazole is used, serum concentrations should be assayed to ensure adequate absorption (BII). Consideration should be given to the cyclodextrin oral suspension of itraconazole in such patients, because absorption is superior to that with itraconazole capsules [20–22]. An iv form has been released, but there is little information yet available about it.

Many clinicians recommend that any drug used for invasive disease be given at peak recommended doses: for example, 1–1.5 mg/kg/d of amphotericin B deoxycholate, ≥ 5 mg/kg/d of lipid formulations of amphotericin, and ≥ 400 mg/day of itraconazole (BIII). An increase in serum creatinine level associated with amphotericin B deoxycholate is common, and clinicians experienced with amphotericin use are reluctant to modify the dose because of a modest degree of nephrotoxicity.

New investigational triazoles, voriconazole and SCH 56592 (posaconazole), have activity against *Aspergillus* species and are currently undergoing phase II or III clinical trials. Lipid-complex nystatin (iv), another oral triazole BMS-207147 (ravuconazole), and 3 echinocandin derivatives (LY303366, cas-

Table 2. Categories indicating the quality of evidence for recommendations for antifungal therapy in diseases caused by *Aspergillus* species.

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

pofungin [MK991], and FK463) are also in earlier stages of clinical development.

Invasive Aspergillosis, Particularly Invasive Pulmonary Disease

Invasive aspergillosis is a devastating infection that usually affects patients with neutropenia [23] or neutrophil and/or macrophage dysfunction [24], cytotoxic chemotherapy, long-term corticosteroid therapy, bone marrow [25, 26] or organ [27] transplant, or congenital or acquired immunodeficiency [28]. An aggressive diagnostic approach in patients at risk and prompt institution of antifungal therapy may be essential for patient survival [29] (BIII). The lungs are the most common site of primary invasive disease, although sinus disease approaches it in frequency in some centers. The CNS is the most common secondary site of invasive disease. Consequently, most of the remarks in this section are focused on invasive pulmonary disease.

The progressive nature of this disease and its refractoriness to therapy are, in part, due to the organism's rapid growth and to its tendency to invade blood vessels.

Diagnosis. Case definitions for clinical trials [13, 14] have evolved and will continue to develop as multicenter clinical trials groups, such as the National Institute of Allergy and Infectious Diseases Mycoses Study Group, the European Organization for Research and Treatment of Cancer, and Cancer and Leukemia Group B, come together to evaluate results of previous trials and the newest diagnostic information, and attempt to shape a common lexicon. Definitive diagnosis requires both histopathologic evidence of acute-angle branching, septated nonpigmented hyphae measuring 2–4 μ in width, and culture(s) yielding *Aspergillus* species from specimens obtained by biopsy from the involved organs (or aspiration from a solid organ). Blood [30], CSF, and bone marrow specimens rarely yield *Aspergillus* species. The septated hyphae of *Aspergillus* are best detected by Gomori methenamine silver and Periodic acid–Schiff stains (AIII), and it would be desirable to include these stains in the initial tissue evaluation if invasive fungal disease is suspected. *Aspergillus* hyphae are difficult to distinguish from those of *Fusarium* species, *Pseudallescheria boydii*, agents of phaeohyphomycosis, and some other molds.

Aspergillus species recovered from cultures of the respiratory tract (e.g., sputum and nasal cultures) are usually a result of colonization in the immunocompetent host but may indicate invasive disease in the immunocompromised host. The positive predictive value may be as high as 80%–90% in patients with leukemia or bone marrow transplants [31, 32]. Radiographic studies [33, 34] may include characteristic findings such as wedge-shaped pleural-based densities or cavities on plain radiographs (both late findings). Findings on CT scans include the “halo sign” (an area of low attenuation surrounding a nodular lung lesion) initially (caused by edema or bleeding sur-

rounding an ischemic area) and, later, the “crescent sign” (an air crescent near the periphery of a lung nodule, caused by contraction of infarcted tissue). These studies may speed diagnosis and define the extent of infection in neutropenic patients, but the radiographic findings are not diagnostic, because other infections and conditions may sometimes produce similar pictures [35]. The CT abnormalities have been best documented in neutropenic marrow transplant recipients. CT abnormalities commonly precede plain chest radiograph abnormalities, particularly the later, more specific plain film findings, and chest CT should be considered in patients with a suspected infection. High resolution or spiral CT may offer an advantage over routine CT. Bronchoalveolar lavage, with assay of the fluid by smear, culture, and/or antigen detection, has excellent specificity and reasonably good positive predictive value for invasive aspergillosis in immunocompromised patients [36, 37] (BII). Transbronchial biopsy or brushings are too often false negative (CIII). Biopsies of endobronchial lesions have been useful when such lesions are encountered.

Because of the ubiquitous nature of the organism, establishing a definitive diagnosis of disease caused by *Aspergillus* is difficult. The use of antibodies against *Aspergillus* to diagnose invasive aspergillosis has produced conflicting results. Patients in high risk groups are too frequently falsely seronegative. With antibody or antigen testing, serial assays appear more valuable than isolated tests [38] (BII), but specific recommendations about frequency of testing have not been established. Several promising assays have been developed to detect *Aspergillus* galactomannan in urine, sera, CSF, and bronchoalveolar lavage specimens by EIA [39], ELISA [40], and immunoblot [41]. These appear more sensitive and reproducible than earlier latex agglutination methodology. Studies with an EIA system commercially available in Europe for detection of *Aspergillus* galactomannan [42] reported positive predictive values of 54% and negative predictive values of 95%, largely among bone marrow transplant recipients in France. A problem in some studies with antigen testing was that case detection occurred too late to be useful, although early detection has been noted in some studies with ELISA methodology [42–44]. In some studies, true positives were more frequent among the high titer results, and false positives more common in children. No antigen tests are currently approved for use in the United States.

In addition, assays that use PCR have been reported to detect fragments within the 18S rRNA of *Aspergillus* species [45, 46], the 135-bp fragment in the mDNA of *Aspergillus* species [47], and a 401-bp fragment in the rDNA complex of *A. fumigatus* [48], and PCR assays may prove more sensitive than antigen detection. However, few of these PCR assays have been tested with body fluids in prospective trials of invasive aspergillosis, and reproducibility must be verified. There is also interest in using metabolites, such as glucan [49] or mannitol [50], for diagnostic identification of invasive disease.

Therapy. Clinicians are often faced with some suggestive,

but not definitive, evidence of invasive pulmonary disease, and treatment may need to be initiated at that point, particularly in the more immunocompromised or ill patient. Investigations to substantiate or refute the diagnosis should continue, in such instances, after an empirical treatment decision.

The optimal duration of therapy is unknown and dependent on the extent of invasive aspergillosis, the response to therapy, and the patient's underlying disease(s) or immune status. A reasonable course would be to continue therapy to treat microfoci, after clinical and radiographic abnormalities are resolving, cultures (if they can be readily obtained) are negative, and reversible underlying predispositions have abated (BIII). Duration of therapy should be guided by clinical response rather than any arbitrary total dose. Continuation of antifungal therapy through reinduction cancer chemotherapy, or resumption of antifungal therapy in patients with apparently resolved fungal infection who are about to receive reinduction chemotherapy, is worthy of consideration. The ultimate response of these patients to antifungal therapy is largely related to host factors, such as the resolution of neutropenia and the return of neutrophil function, lessening immunosuppression and the return of graft function from a bone marrow or organ transplant, as well as the extent of aspergillosis when diagnosed.

Intravenous therapy may be preferred, at least initially, in patients who are acutely ill, because drug delivery is certain (BIII). Amphotericin B [2–4] has been the standard of treatment in invasive aspergillosis, particularly for life-threatening and severe infections. In well-characterized patients, the overall response rate has been 37% (range, 14%–83%) [51]. (Response rates to all agents vary because of underlying diseases, extent of infection, resolution of neutropenia or underlying immunodeficiency, definition of response, duration of follow-up, and other factors.) A study [52], consistent with *in vitro*–*in vivo* correlations made in other mycoses, suggests a favorable outcome is more likely with isolates susceptible *in vitro*. The lipid-based formulations are indicated for patients with invasive aspergillosis who develop nephrotoxicity while receiving amphotericin B [6–12] (AII). The lipid-based preparations may be preferred as initial therapy in patients with marginal renal function or in patients receiving other nephrotoxic drugs. The studies on the lipid preparations have been open-label or with historical conventional amphotericin B controls. Randomized, prospective, comparative clinical trials between amphotericin B and a specific lipid-based formulation for invasive aspergillosis, or comparing specific doses of each, remain to be done or have been presented only preliminarily thus far. Although most animal model studies have suggested that larger doses of the lipid preparations are required to produce therapeutic effects equivalent to deoxycholate amphotericin, a recent trial has questioned whether the larger lipid doses are needed [53].

Itraconazole has been studied as therapy for invasive aspergillosis in 2 recent studies [13, 14], which found complete response/improved rates of 39% and 63%, respectively. These

rates are representative of what has been reported in earlier series [15–18]. Relapse rates may be higher among the immunocompromised [13]. The oral form is an alternative to amphotericin in patients who are likely to adhere to prescribed therapy, unlikely to have problems with absorption, and who are not receiving drugs that interact with itraconazole or which cannot be easily managed. A logical and attractive sequence would be to use *iv* therapy first (e.g., amphotericin B), at least until disease progression is arrested, and then follow with oral therapy for prolonged treatment (CIII).

An investigational triazole, voriconazole, has been used in an open-label trial of invasive aspergillosis with >50% complete/partial response rate in ongoing studies [54]. No randomized, prospective study has been completed that compares a triazole with any amphotericin B preparation for invasive aspergillosis.

Combination therapy that uses amphotericin B with azoles, flucytosine, or rifampin has advantages *in vitro* and in animal models, although antagonism has also been shown *in vitro* and in animals [55, 56]. This approach has met with limited success in case reports, but the role or efficacy of such combinations has not been established in invasive aspergillosis. In addition, flucytosine may exacerbate myelosuppression in patients with neutropenia, and maintaining nontoxic blood levels may be difficult when concurrent amphotericin is given, owing to the latter's tendency to impair function of the excretory route (renal) of flucytosine. Rifampin may have significant drug interactions, owing to potent hepatic enzyme-induction, particularly in transplant recipients who are already receiving glucocorticoids, cyclosporine, or tacrolimus, and this property also precludes the possibility of itraconazole use for weeks [19].

Surgical excision has been successful for some cases of pulmonary infection [57]. Some clinicians emphasize prompt surgery as a modality for the centrally located lesion (near the mediastinum) because of the higher likelihood of catastrophic pulmonary hemorrhage [58]. Adjuvant modalities [59], such as granulocyte transfusions [60, 61], colony-stimulating factors such as granulocyte colony-stimulating factor, macrophage colony-stimulating factor, granulocyte-macrophage colony-stimulating factor [62–65], or interferon- γ [66] are under study, for prophylaxis or therapy, in the neutropenic or immunocompromised host, but are not recommended for routine therapeutic use (CIII). Proof of increased survival has not been demonstrated with any of these adjunct modalities.

Therapeutic Approaches, Other Invasive and Noninvasive Sites of Infection

Nonpleuropulmonary Infections

Infections due to *Aspergillus* species at other sites are less common than pulmonary parenchymal infections, and prospective treatment trials are lacking, with most previously reported treatment results being anecdotal. In this regard, the following therapeutic recommendations are based on reports

of cases or small series, in addition to extrapolation from the outcome of infections at more common sites, such as lung parenchyma.

Sinonasal infections. *Aspergillus* sinonasal infections may or may not be invasive and can follow a fulminant or an indolent course [67]. The disease manifestations and the subsequent treatment approach may also vary, depending on the degree of immunocompetence of the host.

Acute invasive infection is the subtype of sinonasal aspergillosis that occurs in the immunocompromised host. These infections are characterized by mucosal invasion with infarction and spread of infection in centrifugal fashion to contiguous structures. Mortality is high, ranging from 20% in patients with leukemia in remission who are undergoing maintenance therapy, to up to 100% in patients with relapsed leukemia or those undergoing bone marrow transplantation [68, 69]. A high index of suspicion is necessary in immunocompromised patients. Although surveillance nasal cultures are of questionable value (CIII), baseline sinus radiographs or limited CT should be considered in these high risk patients. Early diagnosis is imperative, and the onset of new local symptoms, such as epistaxis, naso-orbital pain, a positive nasal swab culture in a febrile, susceptible host, or an abnormal sinus radiographic finding should lead to immediate otolaryngologic evaluation, including careful inspection of the nasal turbinates (AIII). Biopsy and subsequent fungal culture of suspicious lesions are important not only to demonstrate mucosal invasion but also to differentiate *Aspergillus* infections from those caused by other isolates, such as those due to Mucorales or *Alternaria* species (AIII). Control of predisposing factors by decreasing corticosteroid dosage or resolution of neutropenia remains the most important factor that affects outcome. Treatment should combine medical with surgical approaches (BIII). Although surgical debridement alone may be curative in immunocompetent hosts, it may increase mortality among patients with neutropenia [4]. Endoscopic surgery has been used for ethmoid sinus disease, in which an ethmoidectomy is performed in an anterior to posterior direction, with debridement continued as far posteriorly as abnormal tissue is encountered; more extensive surgery is indicated when there is widespread involvement of the paranasal sinuses or lateral nasal wall, or when orbital, facial, or intracranial involvement is present [70] (BIII). Local amphotericin B sinonasal lavage or spray after debridement has been used by some clinicians [71].

Chronic indolent invasive sinonasal infections occur in immunocompetent hosts in regions with high levels of environmental spores, such as the Sudan, Saudi Arabia, and other tropical or desert areas, and occasionally in patients with diabetes in other locales. *A. flavus* is the most common causative agent of these infections, in contrast to the frequent isolation of *A. fumigatus* from sites of infection in immunocompromised hosts. These infections have a progressive clinical course over months to years, with invasion of the surrounding tissues: the

ethmoid sinuses, orbit, and subsequent cranial bone osteomyelitis and intracranial extension [72–74]. As with acute invasive infections in immunocompetent hosts, treatment consists of surgical debridement and drainage, which is sufficient in the majority of cases [75] (BIII). The role of antifungal therapy is secondary (CIII). Despite this approach, multiple recurrences are common.

Aspergillus sinus infections may also present as a fungus ball or mycetoma. These lesions usually remain confined to a single sinus cavity for months to years, with little tissue reaction and no invasive features. Treatment involves surgical removal of the mass to ensure adequate sinus drainage. Systemic antifungal therapy has no clear role in these infections (CIII). The prognosis is excellent.

Lastly, *Aspergillus* species are a cause of allergic fungal sinusitis, which typically occurs in immunocompetent, atopic young adults, with a long antecedent history of allergic rhinitis, nasal congestion, headache, nasal polyposis, asthma, and/or recurrent sinusitis. Bone destruction from erosion is seen in 30%–50% of cases, especially in the cribriform plate, posterior wall of the frontal sinus, ethmoid septa, lamina papyracea, and medial antral wall. Treatment is conservative surgical drainage with antibiotics as needed for secondary bacterial infection [76–78] (BIII). Systemic antifungal therapy is not used unless there is definite evidence of tissue invasion or orbital/intracranial extension (CIII). Nasal corticosteroids and saline douches may be used for symptomatic relief. There may be a potential role for systemic corticosteroids with allergic flare-ups in cases refractory to surgery and in the perioperative setting, although, postoperatively, there is a danger in corticosteroid use before healing is completed, because of possible corticosteroid impairment of re-epithelialization and wound healing.

Infections of the larynx, trachea, and bronchus. The small number of cases of *Aspergillus* infection of the larynx, trachea, and/or bronchi have been reported in immunocompromised hosts, such as patients with lymphoproliferative disorders or AIDS, solid organ transplant recipients, or patients receiving chronic corticosteroid therapy [79–83]. Localized infection that has commonly been limited to the anastomotic site has been described in heart-lung and lung transplant recipients [84]. Ulcerative or plaquelike lesions have been described in AIDS patients who present with fever, cough, and dyspnea [79]. Epiglottitis attributed to this fungus has rarely been reported [85].

Systemic antifungal therapy has been the mainstay of treatment in these cases. Although unproven, inhaled amphotericin B may have a role as adjunctive therapy [86]. In the several reported cases of laryngeal infection, surgical debridement or excision has been crucial for a successful outcome, in addition to systemic antifungal therapy. Lastly, in the setting of necrotizing *Aspergillus* bronchitis with the presence of a mycelial mass in the trachea, removal of the mass by bronchoscopic procedure may be necessary, given the poor penetrance of antifungals into the mass.

Ear infections. Both invasive and noninvasive (or saprophytic) otic infections have been described. *Aspergillus* species may colonize the ceruminous debris in the external canal, with no resulting infection. However, invasive infection of the external ear canal has been described in patients with AIDS and in patients with acute leukemia [4, 80, 81, 87, 88]. *Aspergillus* mastoiditis may follow *Aspergillus* otitis.

In immunocompromised patients, systemic antifungal therapy appears necessary [89] (BIII). However, infections of lesser severity (without tissue invasion) or those that occur in immunocompetent patients may be managed with local measures, including cerumen removal (BIII). A variety of such topical therapeutic options has been used, which includes cresylate, alcohol, nystatin (ointment, powder), amphotericin B 3% topical solution, boric acid, thymol, gentian violet, iodochlorhydroxyquin (powder, lotion), 5-fluorocytosine ointment, nitrofungin, clotrimazole, and ketoconazole [90]. In these cases, prolonged therapy may be necessary.

Ocular infections. *Aspergillus* endophthalmitis may occur by several mechanisms, including direct inoculation by trauma after surgical procedures, such as cataract extraction, or by hematogenous spread, which is seen most commonly in immunocompromised patients, injection drug abusers, or patients with *Aspergillus* endocarditis [91]. Diagnosis in these cases requires smear and culture of vitreous and/or aqueous humor. Penetration of systemic amphotericin B and itraconazole into the vitreous and aqueous humors is often inadequate and treatment is unsuccessful [90]. Because of this, intravitreal amphotericin B (10 μg dose) may be employed (BIII), usually after pars plana vitrectomy. Levels of flucytosine in aqueous fluid are 20%–30% that of serum levels; however, experience with this agent in ocular infections is limited. Vitrectomy may be necessary for the diagnosis and management of these infections, in conjunction with intravitreal amphotericin B or amphotericin B irrigation [92–95] (BIII).

Other ocular manifestations of *Aspergillus* infections are less common. Scleral abscesses may be treated with surgery and topical amphotericin B [96, 97]; it is not clear whether systemic antifungal therapy is necessary in these cases. Various approaches have been used for corneal infections, including the application of collagen shields impregnated with amphotericin B (0.5%), 0.15%–1% amphotericin B eye drops, amphotericin B corneal baths, topical clotrimazole (1%), pimaricin (5%), miconazole (1%), or ketoconazole (2%) [98–100]. Oral itraconazole may also play a role in these more superficial infections, since this agent penetrates the deeper corneal layers [101]. Surgery is sometimes required if there is progression while the patient is receiving medical therapy or if there is a threat of perforation. Surgical possibilities include debridement, lamellar keratectomy, formation of a conjunctival flap over a severe ulcer (to attempt to save the eye from rupture), or corneal grafting. If malignant glaucoma occurs, or to restore aqueous

fluid drainage, iridectomy, lens excision, or anterior vitrectomy may be needed [102].

CNS infections. *Aspergillus* infections of the CNS may manifest as single or multiple cerebral abscesses, meningitis, an epidural abscess, or a subarachnoid hemorrhage [103]. The published literature suggests that mortality in CNS infection exceeds 90% [4].

Intracranial abscesses occur as a result of hematogenous spread, with subsequent occlusion of intracranial vessels and infarction [104]. Biopsy of these lesions, if feasible, is warranted, to differentiate *Aspergillus* infections from those caused by other fungi, such as *Pseudallescheria*, dematiaceous fungi, Mucorales or *Fusarium*, which may alter one's choice of antifungal therapy (AIII). CSF has been reported to be antigen-positive in some cases. A surgical approach allows for laboratory characterization of the causative agent together with removal of nonviable tissue, which may not be well-penetrated by systemic antifungals [105, 106]. Stereotactic procedures for abscess drainage have also been used [107]. Although surgery alone may be sufficient in the setting of well-encapsulated single lesions in less immunocompromised patients, systemic antifungal therapy is also used in the majority of cases (BIII). Flucytosine in conjunction with amphotericin may have a role here because of its CNS penetration. There are reports of successes with lipid-complexed amphotericin, itraconazole, or voriconazole [108–111]; aggressive dosing may be important.

Aspergillus meningitis is unusual; cases are reported in injection drug abusers; neutropenic, diabetic, or tuberculosis patients; or patients on prolonged corticosteroid therapy. It may present as an extension of paranasal sinus disease, as a complication of intrathecal antibiotic therapy or in the postoperative setting after transsphenoidal surgery [112], and presents rarely in patients with no underlying disease. *Aspergillus* antigen may be detectable in the CSF and may be used for serial observations of the course of therapy [113]. Systemic and intrathecal (e.g., via an Ommaya reservoir) amphotericin B has been used for the treatment of these infections [4], as has itraconazole [114] and voriconazole [113]. Removal of infected tissue may be important [115].

Lastly, epidural abscesses caused by *Aspergillus* are usually secondary to a contiguous site of infection, such as in a vertebral body. Surgical drainage along with systemic therapy is indicated for treating these infections (BIII).

Bone infections. The mechanism for *Aspergillus* bone infections is by direct extension, traumatic injury, inoculation by a surgical intervention, or hematogenous spread, especially in patients with the previously described predisposing risk factors, particularly those with chronic granulomatous disease, or injection drug abusers [116–120]. Vertebral osteomyelitis or diskitis is the most frequent bone infection caused by *Aspergillus* species, with joint infections being distinctly uncommon [4, 120]. Surgical debridement is generally required for these infections. Although an occasional case may be cured by surgical

intervention alone, systemic antifungal therapy is generally used in addition [121, 122]. Amphotericin B levels in bone are low, which may necessitate the addition of drugs that have good penetrance into bone, such as rifampin or flucytosine. Itraconazole penetrates bone well and has also been used successfully [14, 123–127].

Cutaneous infections. Cutaneous infections caused by *Aspergillus* species are commonly a result of hematogenous seeding from a primary focus of infection, most often the lung, which occurs in highly immunocompromised patients. These lesions may be single or multiple, may not be tender, and occur most commonly on the extremities. They first appear as erythematous papules, then become pustular, and subsequently develop a central ulceration with an elevated border that is covered by a black eschar [128, 129]. Although this latter stage is characteristic of *Aspergillus* skin lesions, the appearance is not pathognomonic, and a skin biopsy with fungal culture is indicated to rule out other infections that may manifest in a similar fashion (AIII). The majority of cutaneous infections are caused by *A. fumigatus*, *A. flavus*, or *A. terreus*, but, more recently, *Aspergillus chevalieri* has been reported to cause morphologically distinct skin lesions, which appear erythematous, hyperkeratotic, and vesiculopapular in nature [130].

Primary invasive skin infections due to *Aspergillus* species have been reported in association with adhesive dressings for venous access devices which are contaminated with *Aspergillus* spores [129]. These erythematous indurated plaquelike lesions progress to necrotic ulcerative lesions. Direct cutaneous inoculation of delicate, macerated skin of newborns may occur. Burn wounds may also become secondarily infected by *Aspergillus* species. Lastly, onychomycosis may occasionally be caused by *Aspergillus* species.

The role of biopsy of cutaneous lesions for a definitive fungal diagnosis has been emphasized. Systemic antifungal therapy is the mainstay of therapy (BIII), and the results are generally good. Surgical excision may occasionally be necessary when the local infection cannot be controlled in the neutropenic setting [131]. In catheter site infections, removal of the catheter in addition to systemic antifungal therapy is indicated [129]. Burn wound aspergillosis and posttraumatic soft tissue infections are best managed by surgical debridement in addition to systemic therapy. Oral itraconazole, with or without topical therapy, such as 8% ciclopirox nail lacquer, is used for onychomycotic infections [15, 132, 133].

Endocarditis, pericarditis, and myocarditis. *Aspergillus* species have been reported as a cause of both native and prosthetic valve endocarditis [94], which is occasionally a manifestation of disseminated aspergillosis. The fungus is rarely isolated from blood cultures [30]. The resultant vegetations are often large and friable, and carry a high risk of embolic complications. Because of the poor penetration of amphotericin B into the vegetation, in addition to the risk of embolic complications, early surgical intervention with valve replacement is generally

undertaken, especially in the setting of prosthetic valve endocarditis [94, 134]. Perioperative amphotericin B appears prudent. An occasional case has been successfully managed with amphotericin B and flucytosine alone [135].

Pericarditis is a rare complication of disseminated infection [136–139]. It may result from hematogenous spread, rupture of a myocardial abscess, or contiguous spread from the lung. It usually presents with substernal pain, dyspnea, or arrhythmias. Antigen testing of the pericardial fluid may prove useful in diagnosis. One-third of patients with pericarditis develop cardiac tamponade. Constrictive pericarditis or pneumopericardium have been reported. Treatment consists of systemic antifungal therapy (CIII) and pericardial drainage, including pericardiectomy, where appropriate [4].

Myocarditis may be seen as an isolated entity or together with pericarditis [140–143].

Urinary tract infections. Urinary tract infections are generally a consequence of hematogenous spread. Infections that involve the renal parenchyma are more common in immunocompromised hosts, such as patients with leukemia or chronic granulomatous disease, or injection drug abusers. Drug abusers and patients with diabetes are at risk for infections that involve the renal pelvis. The appearance of a fungus ball usually represents renal papillary necrosis; prostatic abscesses with or without a fungus ball also occur [144]. Systemic antifungal therapy is generally used for parenchymal disease. For management of abscesses and fungus balls, surgical removal may be indicated. Therapy is confounded by the low concentrations achieved in urine by itraconazole or polyenes. Renal, ureteral, or prostatic disease has been managed with systemic amphotericin B or its liposomal preparations [145]; the addition of flucytosine may be helpful since this agent reaches high concentrations in the urine. Local irrigation with amphotericin B has also been used for urinary bladder and renal pelvic infections.

Intra-abdominal infections. Systemic antifungal therapy is necessary for hepatosplenic aspergillosis (AIII). The outcome of this infection with amphotericin B therapy has been poor. For this reason, either lipid amphotericin derivatives or itraconazole, both of which attain high concentrations in hepatic tissue, should be considered.

Aspergillus peritonitis has occurred as a complication of chronic ambulatory peritoneal dialysis [146–148]. Dialysis catheter removal is essential for eradicating these infections [4]. Antifungal therapy should be used in addition; both intraperitoneal and systemic amphotericin B have been used, as has itraconazole [90, 146].

Visceral organ involvement with *Aspergillus* species most often occurs in the setting of disseminated infection. The esophagus is the most common site of involvement in the gastrointestinal tract, then the colon and small intestine [4, 104]. Ulcerative lesions in these sites may result in perforation or infarction [149]. Systemic therapy is required, but the outcome is poor.

Lymph node infections. *Aspergillus* species may cause primary granulomatous infection of lymph nodes [150]. In cases refractory to systemic antifungal therapy, surgical excision of the node may be necessary to eradicate the infection.

Pleuropulmonary Infections

Pulmonary aspergilloma. An aspergilloma can be defined as a conglomeration, within a pulmonary cavity or ectatic bronchus, of intertwined *Aspergillus* hyphae matted together with fibrin, mucus, and cellular debris [151]. Patients usually have underlying pulmonary disease such as fibrocystic sarcoidosis, cavitary tuberculosis or histoplasmosis, bullous emphysema, or fibrotic lung disease [152]. The diagnosis of aspergilloma is usually made clinically without a lung biopsy, and the chest radiographic features are of utmost importance in making the presumptive diagnosis. On radiographs, pulmonary aspergilloma 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 [153]. If peripheral, pleural thickening is characteristic. The diagnosis of an aspergilloma is usually made when the above-mentioned radiographic features are found in a patient with serum precipitins that are positive for an *Aspergillus* species, a test with >95% sensitivity for aspergilloma [153, 154]; however, some patients who receive corticosteroids may be seronegative.

Although aspergillomas are often thought of as benign saprophytic colonizations of the lung with *Aspergillus*, the manifestations of *Aspergillus* lung disease overlap with a continuum between colonization and tissue invasion [151–154]. Invasive pulmonary aspergillosis may develop from an aspergilloma [155] and is often fatal. A chronic necrotizing form of *Aspergillus* infection has been described [156] in which systemic symptoms (e.g., fever and weight loss) are present, an aspergilloma is present on chest radiograph, and evidence of tissue invasion is found on evaluation of lung biopsy.

Hemoptysis is a common symptom of aspergilloma and may result in fatal asphyxiation [155, 157, 158]. Hemoptysis is the cause of death in up to 26% of patients with aspergilloma [151, 158]. Therapeutic decisions that involve aspergilloma hinge on preventing life-threatening hemoptysis, although patients with systemic symptoms are deemed high-priority candidates for therapy. Certain risk factors have been identified that suggest a poor prognosis with aspergilloma. These include the severity of the underlying lung disease, increasing size or number of aspergillomas on chest radiograph [153], immunosuppression (including corticosteroids) [154], increasing *Aspergillus*-specific IgG titers [155], underlying sarcoidosis [156], and HIV infection [157]. Although not specifically studied, it seems, intuitively, that patients who have an episode of large volume hemoptysis would be at especially high risk of a life-threatening episode.

There is no consensus concerning the treatment of aspergil-

loma. No double-blind, placebo-control, or randomized trials have been undertaken. Data concerning treatment have been generated from uncontrolled trials and case reports. The first major decision in the management of aspergilloma is whether therapy is required. Since life-threatening hemoptysis occurs in a minority of patients, it may be inappropriate to subject all patients with aspergilloma to therapy, especially since therapy is often associated with significant morbidity and mortality.

Definitive treatment for aspergilloma is surgical resection [152]. However, surgery has been associated with a high morbidity and mortality [158–166]. Pulmonary resection is hazardous, owing to the presence of dense vascular adhesions and the possibility of aspergillus infection of the postsurgical space. Operative mortality is >7% [167], and serious postoperative complications, such as hemorrhage and bronchopleural fistulae, are common. An important factor that contributes to the high surgical risk of resection is that aspergillomas tend to develop in clinically ill individuals with poor pulmonary function [167]. Indeed, in many patients, surgery is contraindicated because of severe underlying pulmonary dysfunction. It has been suggested that surgical resection of aspergilloma be restricted to patients with severe hemoptysis and adequate pulmonary function [167], and considered for patients with underlying sarcoidosis, immunocompromised patients, and those with increasing *Aspergillus*-specific IgG titers (CIII). The unpredictable course of the illness in the absence of surgery confounds decisions about surgical intervention.

Bronchial artery embolization (BAE) has been used to occlude the vessel that supplies the bleeding site in patients experiencing hemoptysis from aspergilloma [168]. Sometimes other arteries are involved in abnormal vascular connections and can be targeted. Unfortunately, BAE is usually unsuccessful or only temporarily effective and requires a patient who can lie still for 3–4 h. Collateral vascular channels from the pulmonary and systemic circulation eventually supply enough blood flow to the involved area where hemoptysis often recurs; re-embolization then often will not be successful [169, 170]. BAE should be considered as a temporizing procedure in a patient with life-threatening hemoptysis, who might be eligible for more definitive therapy if the hemoptysis were stabilized (BIII).

Additional treatments for aspergillomas have included radiation therapy [171], intracavitary or endobronchial instillation of antifungal agents [167, 172–174], inhaled nebulized antifungals [167], and systemic antifungals [17, 18, 175–178]. When symptoms (e.g., fever or cough) are present, they may be related in part to concomitant infection with another agent or to allergic manifestations. Symptomatic abatement has been noted in patients with evidence of allergy (e.g., eosinophilia, total IgE elevation, and aspergillus scratch test positivity, etc.) given systemic corticosteroid therapy [179]; however, such therapy raises the risk of conversion to invasive or disseminated disease [154] and/or exacerbation of an undiagnosed concurrent

infection. Several of these studies deserve comment. Intravenous amphotericin B for aspergilloma provided no benefit over routine pulmonary toilet [175]. One study [173] that used endobronchial or intracavitary instillation of amphotericin B for aspergilloma was particularly promising: 12 of 14 patients achieved resolution or clinical improvement. This modality is more problematic in the patient with compromised pulmonary function. The use of itraconazole for aspergilloma has been reported in several studies [17, 18, 109, 176–178]. Most of these studies were retrospective, unblinded, and did not contain a control group. Furthermore, the dose and duration of itraconazole therapy was not standardized. Nevertheless, the results of these studies suggest that itraconazole may be efficacious in the treatment of aspergilloma (BIII).

APBA. APBA is a hypersensitivity disease of the lungs almost always caused by *A. fumigatus*. It was initially described [180] as a disease characterized by episodic wheezing, pulmonary infiltrates, sputum and blood eosinophilia, pyrexia, and sputum containing brown flecks or plugs. Two decades later, 7 primary diagnostic criteria for ABPA were proposed [181]: episodic bronchial obstruction (asthma), peripheral blood eosinophilia, immediate scratch test reactivity to *Aspergillus* antigen, precipitating antibodies to *Aspergillus* antigen, elevated serum immunoglobulin E (IgE) concentrations, history of pulmonary infiltrates (transient or fixed), and central bronchiectasis. The diagnosis of ABPA was felt likely if the first 6 diagnostic criteria were present, and the presence of all 7 made the diagnosis certain [181]. Secondary diagnostic criteria included repeated detection of *Aspergillus* in sputum by use of stain and/or culture, a history of expectoration of brown plugs or flecks, elevated specific IgE directed against *Aspergillus* antigen, Arthus reaction (late skin reactivity) to *Aspergillus* antigen, and characteristic defects on intrabronchial challenge with *Aspergillus*.

ABPA has been reported to be present in 7%–14% of corticosteroid-dependent patients with asthma in the United States [182]. Many patients with cystic fibrosis have airway colonization with *Aspergillus* species, and ~7% develop ABPA [183]; these patients may be particularly at risk for invasive aspergillosis if lung transplantation is performed.

Typically the chest radiograph in ABPA reveals transient areas of consolidation that predominate in the upper lobes and may be bilateral [184]. These opacifications are presumably commonly caused by bronchial obstruction with mucus plugs. The bronchus filled with mucus may form a band shadow or a glove-finger shadow [184]. These fleeting shadows are a characteristic feature of the disease and may be relieved by coughing up a mucus plug. A “ring sign” or parallel shadows (“tram lines”), representing inflamed bronchi, may be seen on chest radiographs. The diagnosis of ABPA should be considered in a corticosteroid-dependent asthmatic or an asthmatic with any of the above-mentioned radiographic features.

ABPA may progress through clinical stages of acute corticosteroid-responsive asthma to corticosteroid-dependent

asthma to fibrotic end-stage lung disease with honeycombed lung [185]. Therapy in ABPA is directed at treating acute asthmatic exacerbations and avoiding of end-stage fibrotic disease.

Although corticosteroid therapy is the mainstay of therapy for ABPA, there is a paucity of data concerning its use. The few studies of corticosteroids for ABPA have involved small numbers of patients and have neither been double-blind nor controlled, and the corticosteroid dose has varied. However, despite these methodologic problems, data strongly support the usefulness of corticosteroids in the management of acute ABPA (AII). Rosenberg et al. [186] treated 22 ABPA patients with 0.5 mg/kg/d of prednisone for 1 week, followed by 0.5 mg/kg every other day. An attempt was made to discontinue prednisone after 6 weeks. The symptoms of wheezing, dyspnea, and cough remitted rapidly with this regimen. As the dose of prednisone was decreased, most patients developed symptoms of mild asthma that was controlled with inhaled bronchodilators and/or corticosteroids in most instances. Serum IgE levels correlated with disease activity since they declined with a clinical response to corticosteroids and often increased before exacerbations of ABPA.

There have been few studies that examine the treatment of chronic ABPA with corticosteroids, and all have been retrospective. Safirstein et al. [187] observed ABPA patients for 5 years and found that untreated patients had a chronic course characterized by airway obstruction, recurrent pulmonary consolidations with eosinophilia, and, in many cases, severe lung destruction. Symptoms were not a good guide to predict outcome, as several asymptomatic patients developed eosinophilia and lung consolidation that resulted in chronic lung damage. Daily prednisone doses >7.5 mg/d resulted in fewer episodes of recurrent consolidation. Middleton et al. [188] described 65 patients with “asthmatic pulmonary eosinophilia,” 32 of whom had ABPA. ABPA patients given chronic corticosteroid therapy were less likely to develop further radiographic opacities than those given intermittent corticosteroids. These investigators found that 10 mg/d of prednisone was required for an indefinite period to avoid the recurrence of pulmonary infiltrates. Capewell et al. [189] studied the clinical course of 33 patients with ABPA over a mean of 14 years. Twenty-eight (85%) of 33 were treated with long-term prednisone at a mean daily dose of 7.4 mg. There was no statistically significant change in spirometry over the observation period. These data are promising since pulmonary function did not deteriorate over the observation period, although a prospective study would be required to obviate the problems posed by using a historical control group in a retrospective study.

Increasing serum IgE levels, new or worsening infiltrate on chest radiograph, and worsening spirometry suggest that corticosteroids are needed (BII). Multiple asthmatic exacerbations in an ABPA patient suggest that corticosteroid therapy should be used, usually at a dose of ≥ 10 mg/d of prednisone (BIII). The decision to gradually reduce the dosage of corticosteroids

should be made on an individual basis, depending on the clinical course (BIII).

Another approach to the treatment of ABPA is to eradicate *Aspergillus* species from the airways. Inhaled natamycin [190] and oral clotrimazole [191] are not efficacious, particularly in preventing recurrences. In a placebo-control, double-blind study [192], ketoconazole did decrease *Aspergillus*-specific IgG and improve asthma symptoms in 7 ABPA patients. A subsequent communication [193] of an open, unblinded trial that was not randomized showed no benefit from ketoconazole. Several non-randomized trials [18, 194–196] have indicated that itraconazole is useful as adjunctive therapy in ABPA, because the corticosteroid dose can be lowered, pulmonary function is improved, and IgE levels decline. A recently completed double-blind, randomized, placebo-controlled trial [197] for ABPA showed that itraconazole, 200 mg twice daily for 16 weeks, resulted in statistically significant differences in ability to ameliorate disease, as assessed by the reduction in corticosteroid dose and IgE and the improvement in exercise tolerance and in pulmonary function. Itraconazole may be useful as a corticosteroid-sparing agent (BII).

Inhaled corticosteroids (beclomethasone) were not shown to be efficacious for ABPA [198], although some clinicians feel this may be a useful modality in some patients [199], and anecdotal reports suggest higher doses may be efficacious [200]. Mold counts in ambient air seem to correlate with exacerbations of ABPA [201, 202]. However, there have been no studies of environmental manipulation to attenuate ABPA, and the utility of such therapy remains conjectural. Hyposensitization therapy or avoidance of sites in the environment have not been productive strategies.

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