

# Diagnosis and Treatment of Pulmonary Aspergillosis Syndromes

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Both inherited and acquired immunodeficiency and chronic pulmonary disease predispose to the development of a variety of pulmonary syndromes in response to *Aspergillus*, a fungus that is ubiquitous in the environment. These syndromes include invasive aspergillosis, which is now recognized to occur in patients with critical illness without neutropenia and in those with mild degrees of immunosuppression, including from corticosteroid use in the setting of COPD. Chronic pulmonary aspergillosis includes simple aspergilloma, which is occasionally complicated by life-threatening hemoptysis, and progressive destructive cavitory disease requiring antifungal therapy. Allergic bronchopulmonary aspergillosis occurs almost exclusively in patients with asthma or cystic fibrosis. Recent advances in each of these syndromes include a greater understanding of the underlying pathophysiology and hosts at risk; improved diagnostic algorithms; and the availability of more effective and well-tolerated therapies. Improvement in outcomes for *Aspergillus* pulmonary syndromes requires that physicians recognize the varied and sometimes subtle presentations, be aware of populations at risk of illness, and institute potentially life-saving therapies early in the disease course.

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**ABBREVIATIONS:** ABPA = allergic bronchopulmonary aspergillosis; IFN- $\gamma$  = interferon  $\gamma$ ; SAFS = severe asthma with fungal sensitization; Th = T-helper

Pulmonary aspergillosis refers to a spectrum of diseases that result from *Aspergillus* becoming resident in the lung. These include invasive aspergillosis from angioinvasive disease, simple aspergilloma from inert colonization of pulmonary cavities, and chronic cavitory pulmonary aspergillosis from fungal germination and immune activation (Table 1). Allergic bronchopulmonary aspergillosis (ABPA), driven by allergic responses, has an important place along this spectrum as well.

*Aspergillus* is a ubiquitous and hardy organism. It grows best in moist environments, although spore aerosolization and dispersion occur most effectively in dry climates. Spores survive harsh external conditions and adapt to a range of internal environments.<sup>1-3</sup> Although there are hundreds of *Aspergillus* species, *Aspergillus fumigatus* is by far the most common pathogenic species in humans, where the small size and hydrophobicity of its spores confer a dispersion advantage.<sup>4-6</sup> Although less common,

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**TABLE 1 ] Pulmonary Aspergillosis Syndromes**

<i>Aspergillus</i> Syndrome	Syndrome	Clinical Features	Recent Updates
Allergic aspergillosis	ABPA	Worsening of underlying asthma Markedly elevated total IgE Sensitization: (+) skin testing and/or elevated <i>Aspergillus</i> -specific IgE Bronchiectasis	Cystic fibrosis is a risk factor for ABPA Bronchiectasis may be absent early in the disease course Antifungal agents benefit some patients Case reports of benefit from anti-IgE therapy
Chronic pulmonary aspergillosis	Simple aspergilloma	Quiescent mycetoma in a preexisting lung cavity Hemoptysis may occur	Small case series suggests benefit of percutaneous intracavitary amphotericin for refractory hemoptysis
	Chronic cavitary pulmonary aspergillosis	Systemic symptoms: malaise, fevers, weight loss Elevated <i>Aspergillus</i> -specific IgG New or expanding cavities in setting of chronic lung disease ± Intracavitary mycetoma ± Extensive parenchymal destruction ± Fibrosis	Immune dysfunction may contribute to risk of disease Long-term antifungal therapy generally recommended Surgical resection is often risky but may benefit those with focal disease and limited pleural involvement
Invasive disease	Angioinvasive disease	Seen in neutropenia and stem cell transplant Presentation ranges from asymptomatic macronodules to overt respiratory failure CT scan more sensitive than plain chest radiograph	Expanded populations at risk Positive <i>Aspergillus</i> respiratory culture may require further evaluation Serum and BAL galactomannan testing may aid in diagnosis Voriconazole first-line therapy; dual therapy in some
	Invasive tracheobronchial disease	Neutropenia and lung transplant are risk factors Ulcerative, pseudomembranous, and obstructive variants Atelectasis and unilateral wheeze are suggestive	Expanded populations at risk: COPD, critical illness, HIV infection Requires bronchoscopy for diagnosis

ABPA = allergic bronchopulmonary aspergillosis.

*Aspergillus flavus* and *Aspergillus niger* also contribute to the total burden of pulmonary aspergillosis. When inhaled, spores deposit by sedimentation in distal airways and alveolar spaces. In healthy hosts, spores are eliminated by mucociliary clearance and immune defenses. Germination is the conversion of dormant spores into growing hyphal elements.

*Aspergillus* is an inadvertent human pathogen, and pulmonary aspergillosis is largely the result of impaired airway clearance from a compromised immune function or a chronic lung disease such as COPD and sarcoidosis. Advances in the domains of stem cell transplant and immunosuppressive therapies and an increased prevalence of chronic pulmonary diseases have inadvertently led to a rise in pulmonary aspergillosis syndromes. Now commonly encountered by pulmonologists and intensivists worldwide, these syndromes have a high associated morbidity and can be fatal. In this review, we highlight

advances in the diagnosis and treatment of pulmonary aspergillosis relevant to clinical care. These include the recognition of additional hosts at risk of invasive disease, as well as an expanded array of diagnostic and treatment options; a delineation of the features and outcomes of chronic pulmonary aspergillosis; and, updated diagnostic criteria and an evolving understanding of the role of triazole and anti-IgE treatment options in ABPA.

### Invasive Aspergillosis: Epidemiology, Diagnostic Testing, and Treatment Updates

Invasive aspergillosis has been described classically in patients with neutropenia in the setting of hematologic malignancy but is seen increasingly in patients with even milder immune compromise from immunosuppression, chronic pulmonary or liver disease, or critical illness.<sup>7</sup> As the portal of entry, the upper and lower respiratory tracts are most commonly infected, although dissemination to any organ may occur. *Aspergillus*

tracheobronchitis and CNS infection are associated with especially poor outcomes. An informative review of the pathogenesis of invasive aspergillosis has been published.<sup>8</sup> The diagnosis may be delayed from lack of awareness of the expanded patient populations at risk and because of failure to recognize the significance of positive *Aspergillus* respiratory cultures or to use available diagnostic tests. Early diagnosis of invasive aspergillosis, along with the use of therapeutic agents with greater tolerability and efficacy, have the potential to decrease mortality, which remains high.

Criteria for the diagnosis of invasive fungal disease were formulated in 2002 and updated in 2008.<sup>9</sup> Although intended for research purposes, they serve as a useful conceptual framework for the physician at the bedside. Proven invasive aspergillosis requires histopathologic or cytologic evidence of fungus, or culturing *Aspergillus* from a sterile site regardless of immune status. The criteria for probable disease include clinical upper or lower respiratory tract involvement with direct (identification of fungus by microscopy, cytology, or culture) or indirect (detection of antigen or cell-wall constituents) mycologic evidence of infection in a predisposed patient. The criteria for possible invasive aspergillosis are similar, but mycologic evidence is not required.

The revised 2008 definition added solid organ transplant, inherited immunodeficiencies, connective tissue diseases, and immunosuppressive therapy to the list of host factors that characterize patients predisposed to invasive disease (Table 2). More recent studies suggest additional populations at risk, including patients with critical illness, COPD, end-stage liver disease, or alcoholic hepatitis.<sup>10-13</sup> The incidence of invasive aspergillosis among patients without malignancy in the ICU may be as high as 4%.<sup>14</sup> In a retrospective multicenter study of 1,209 randomly selected patients with a culture from any body

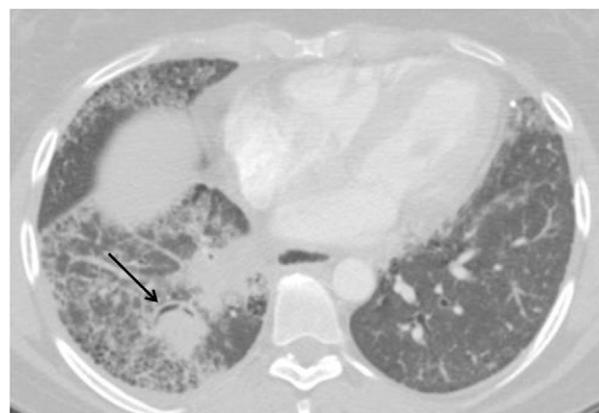
site positive for *Aspergillus*, 12% had evidence for invasive disease.<sup>15</sup> Although patients with hematologic malignancy or transplant or neutropenia accounted for the majority of cases, malnutrition (27%), corticosteroid use (20%), HIV infection (19%), diabetes mellitus (11%), and chronic pulmonary disease (9%) were associated with invasive infection as well. In a single-center retrospective study of 239 patients hospitalized with COPD who had *Aspergillus* isolated from a lower respiratory tract sample, 22% had probable invasive aspergillosis.<sup>12</sup> Multivariate regression identified the following predictors of invasive aspergillosis: ICU admission, heart failure, 3 months of antibiotics use, and > 700 mg cumulative prednisone from admission to *Aspergillus* isolation. Inhaled corticosteroids may increase the risk of invasive aspergillosis in patients with COPD.<sup>16,17</sup> Importantly, mortality may be increased in critically ill patients when *Aspergillus* is isolated, irrespective of evidence for invasive disease.<sup>11,18</sup>

The clinical presentation of invasive aspergillosis includes fever, cough, dyspnea, chest discomfort, and hemoptysis. Chest CT imaging is more sensitive than plain chest radiography.<sup>8,9</sup> Signs on CT scans constituting clinical evidence for invasive pulmonary disease by the 2008 criteria include dense, well-circumscribed lesion(s) with or without a surrounding "halo" of ground-glass gray attenuation, air-crescent sign, and cavity formation (Fig 1). A retrospective study of chest CT imaging in 235 patients with invasive aspergillosis demonstrated at presentation one or more macronodules (94%), halo sign (61%), consolidation (30%), infarct

**TABLE 2 ] Populations Predisposed to Invasive Aspergillosis**

Host Factors by EORTC/MSG Criteria	Additional Patients at Risk
Allogeneic stem cell transplant Neutropenia > 10 d Anti-T-cell agents; calcineurin and tumor necrosis factor- $\alpha$ inhibitors; purine analogs Systemic corticosteroid use > 3 wk Inherited severe immunodeficiencies	Solid organ transplant Critical illness Chronic liver disease COPD Diabetes mellitus HIV infection

EORTC/MSG = European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group.



**Figure 1 – Chest CT scan demonstrating the typical radiographic findings of invasive aspergillosis with both the air crescent sign (arrow) and the cavity formation. This patient had an autoimmune interstitial lung disease treated with low doses of prednisone and azathioprine. The patient presented with fever, right pleuritic chest pain, and an elevated WBC count. Previous respiratory cultures positive for *Aspergillus* had been presumed to represent “colonization.” Galactomannan antigen was detected in both serum and BAL fluid. Pleural fluid analysis was culture positive for *Aspergillus fumigatus*. The patient recovered with discontinuation of immunosuppressive therapy and 6 mo of treatment with voriconazole.**

shaped nodules (27%), cavitory lesions (20%), and air-crescent signs (10%).<sup>19</sup>

*Aspergillus* tracheobronchitis is a form of invasive aspergillosis recognized increasingly in critically ill patients with a minority having little in the way of formal immunosuppression (Fig 2, Table 1).<sup>7,11</sup> The diagnosis requires bronchoscopy, and it is associated with poor outcomes because recognition is often delayed, except in patients undergoing lung transplant who are monitored with periodic surveillance bronchoscopies.<sup>11</sup> Characteristic findings on bronchoscopy include tracheobronchial ulceration, nodules, pseudomembranes, plaque, or eschar (Fig 2). *Aspergillus* tracheobronchitis should be suspected in patients with suggestive imaging and hemoptysis or in patients with lobar atelectasis or unilateral wheeze, which result from thick mucus plugs containing *Aspergillus* that fill the central airways.

Tests that may aid in the diagnosis of invasive infection include an enzyme immunoassay that detects galactomannan antigen, a constituent of the *Aspergillus* cell wall, and quantitative polymerase chain reaction assay. The sensitivity and specificity of these tests vary depending on the host (immunocompromised vs nonimmunocompromised), the specimen tested (serum or BAL fluid), and the presence of antifungal therapy, which can decrease assay sensitivity.<sup>8,20,21</sup> There may be a role for serial tests both in screening high-risk patients and in assessing response to therapy. A meta-analysis evaluating diagnostic serum galactomannan testing in immunocompromised patients demonstrated a sensitivity of 78% and a specificity of 82% at an optical density index cutoff of 0.5. The accuracy of galactomannan testing of BAL fluid in a more recent meta-analysis, in which most patients had a hematologic malignancy, showed a summary estimate sensitivity of 90% and specificity of 94%, when studies had a range of cutoff indexes.<sup>22</sup> In a single-center prospective study of 110 patients in the ICU, 26 of whom had proven invasive aspergillosis, the sensitivity of galactomannan in BAL fluid was 88%, with a specificity of 87% using a cutoff index of 0.5.<sup>23</sup> The sensitivity of the serum assay was 42% in this same series. However, not all studies have confirmed a high sensitivity of galactomannan testing. In a large, hematologic cohort, the test sensitivity for BAL fluid was 50%, and agreement with the gold standard diagnostic algorithm was only modest.<sup>24</sup> False-positive galactomannan tests have been reported in patients receiving piperacillin/tazobactam antibiotics, but this may be less likely to occur with current antibiotic formulations.<sup>25</sup> Quantitative polymerase

chain reaction assay in BAL fluid has theoretical advantages but is not validated for clinical use.<sup>26,27</sup> Testing for serum 1,3- $\beta$ -D-glucan antigen is not specific, because this antigen is present in other fungi.<sup>8,11</sup>

Although the 2008 criteria provide a useful and partially validated diagnostic algorithm, in practice therapy for invasive aspergillosis is often started empirically in patients in whom invasive aspergillosis is suspected on clinical grounds. Management requires a multipronged approach that includes reversal of immunosuppression when possible. Immunomodulatory therapy with granulocyte colony stimulating factor may be useful in neutropenic patients. A single-center retrospective study demonstrated that surgical excision of an isolated pulmonary site of infection can be carried out safely in neutropenic and thrombocytopenic patients who have progressive disease despite antifungal therapy.<sup>28</sup>

Agents with efficacy against invasive aspergillosis include amphotericin B and its lipid formulations; the triazoles itraconazole, voriconazole, and posaconazole; and caspofungin and micafungin.<sup>29,30</sup> Guidelines favor voriconazole as the initial treatment of invasive aspergillosis based on its greater activity in vitro and a randomized trial showing improved outcomes and a lower rate of adverse reactions compared with amphotericin B.<sup>29,30</sup> Voriconazole is started IV, then switched to oral therapy when clinical improvement occurs (Table 3). According to expert opinion, monitoring serum trough levels to adjust dosing to achieve a therapeutic serum concentration may improve efficacy and decrease toxicity. Monitoring for liver toxicity and recognizing the potential for drug interactions is necessary. In particular, visual changes and hallucinations may occur. If required, salvage therapy consists of IV caspofungin or micafungin or oral posaconazole, which is highly active against *Aspergillus*. Combination therapy may be of benefit, but data to support this are limited.

Medical therapy is often prolonged, with duration dependent on response, which includes assessment of clinical and radiographic resolution, microbiologic clearance, and improvement in immune function. Therapy may need to be restarted if immunosuppression, chemotherapy, or stem cell transplant is required. Several studies suggest that survival (64% at 12 weeks in one prospective study) may be higher than in the past.<sup>31</sup> In a retrospective cohort study of patients in the ICU without traditional risk factors for invasive aspergillosis, a delay in initiating antifungal therapy was associated with a longer hospital stay.<sup>32</sup>

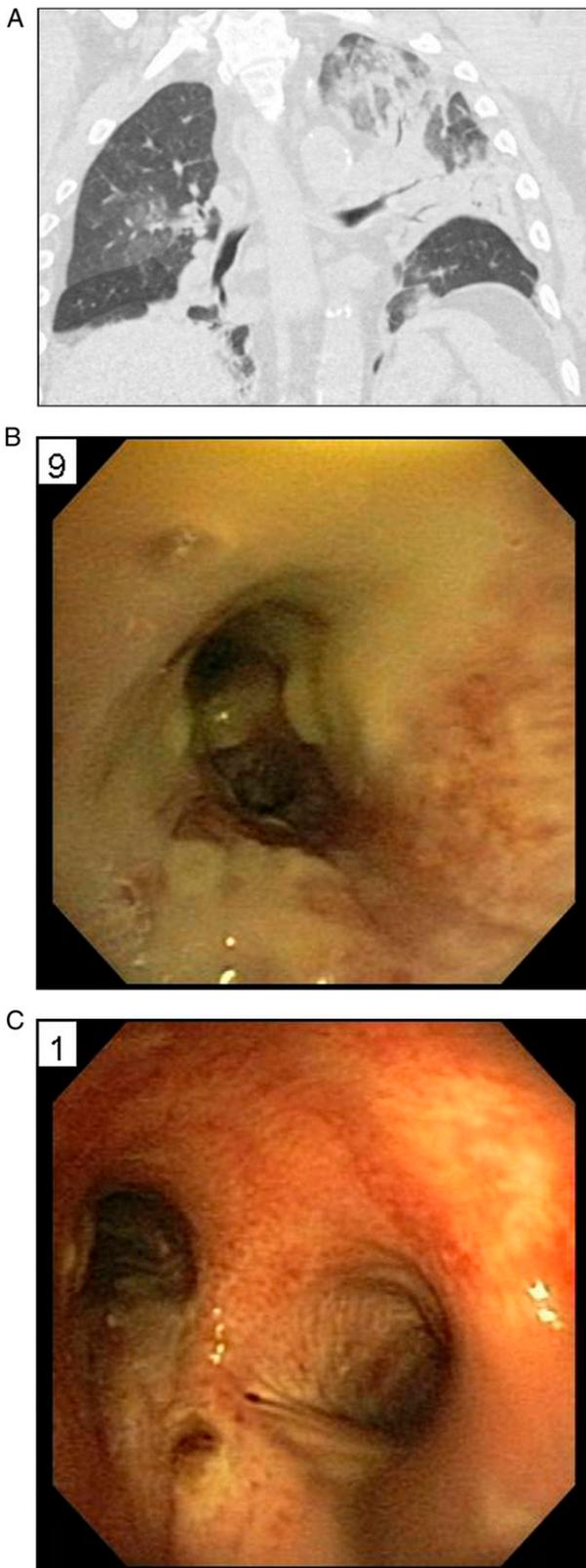


Figure 2 – Chest CT scan and bronchoscopic images of invasive tracheo-bronchial aspergillosis. The patient was on immunosuppression for a prior heart transplant. He presented with dyspnea, hemoptysis, and hypoxemia. A, Imaging revealed a dense consolidation in the left upper lobe with peripheral nodular opacities. B, C, Bronchoscopic airway inspection revealed patchy areas of white adherent plaques and airway

## Chronic Pulmonary Aspergillosis

Chronic pulmonary aspergillosis refers to a spectrum of diseases, from simple aspergilloma to progressive cavitary aspergillosis (Table 1). Simple aspergillomas form in preexisting cavities, which sequester spores from clearance and the resulting fungus ball from immune responses (Fig 3). Positive precipitins or elevated serum IgG titers to *Aspergillus* are often observed.<sup>7,33</sup> Except when hemoptysis occurs, the clinical course is typically benign with long-term radiographic stability. Patients generally do not require or benefit from medical therapy, although the instillation of intracavitary antifungal treatment may lead to a short-term benefit in patients with hemoptysis.<sup>34</sup>

In contrast to simple aspergilloma, syndromes of progressive cavitary aspergillosis are highly morbid (Fig 4). Over 30 years ago, Gefter and colleagues<sup>35</sup> coined the term “semi-invasive aspergillosis” for this clinical entity. Since then, it has been variably referred to as “complex aspergilloma,” “chronic cavitary pulmonary aspergillosis,” “chronic necrotizing pulmonary aspergillosis,” and “subacute invasive disease.”<sup>30,36-38</sup> “Chronic cavitary pulmonary aspergillosis” and “chronic necrotizing pulmonary aspergillosis” have been the more commonly used terms in recent years, and many authors distinguish the two entities by cavity features, host immune status, and the degree of suspected tissue invasion.<sup>37,39</sup> Specifically, the term “chronic necrotizing pulmonary aspergillosis” is often reserved for quickly progressing disease in patients with compromised immune function, in whom local tissue invasion is suspected. However, the terms continue to be used interchangeably in the literature, the clinical features demonstrate significant overlap, and parenchymal invasion is rarely demonstrated. Although a consensus on terminology is still lacking, we refer to this syndrome as “chronic cavitary pulmonary aspergillosis.”<sup>37</sup> Cavities may be single or multiple, thin-walled or thick-walled, and progress in a dramatic or indolent fashion (Fig 4). Discrete mycetomas were observed in only 25% of patients in one study.<sup>40</sup> Pleural thickening is common. Progressive pulmonary fibrosis develops in a subset of patients.<sup>37</sup> Symptoms include dyspnea, cough, hemoptysis, chest pain, weight loss, fever, and malaise. Nonspecific serum inflammatory markers such as C-reactive protein and the erythrocyte sedimentation rate are often elevated.

sloughing in the trachea (B) and left and right bronchial trees (C). Endobronchial biopsy with Grocott stains was positive for septating fungal organisms with tissue invasion. *Aspergillus fumigatus* grew from BAL cultures. Voriconazole treatment resulted in marked clinical improvement, including resolution of hemoptysis.

**TABLE 3 ] Management of Pulmonary Aspergillosis Syndromes**

Syndrome	Therapy	Dose	Comments
Invasive aspergillosis	Voriconazole IV	6 mg/kg every 12 h for 1 d then 4 mg/kg every 12 h	Preferred therapy Consider dose adjustment based on serum levels Duration depends on clinical and/or radiographic response
	Liposomal amphotericin B IV	3-5 mg/kg/d	Alternate therapy
	Caspofungin IV	70 mg on day 1 then 50 mg/d	Salvage therapy, usually in combination with other antifungal agents
	Micafungin IV	100-150 mg/d	Salvage therapy
	Voriconazole po	200 mg every 12 h	Once improved on IV therapy
Chronic pulmonary aspergillosis	Itraconazole po	400-600 mg/d	Alternate therapy once improved on IV therapy
	Voriconazole or liposomal Amphotericin B IV	As above	If severe disease
	Voriconazole po	200 mg every 12 h	Mild to moderate disease
	Itraconazole po	400-600 mg/d	Alternate therapy
	Surgical resection		For nonresponsive disease in patients with adequate cardiopulmonary reserve
Aspergilloma	Observation		Limit immunosuppression if possible
	Bronchial artery embolization		If hemoptysis
	Surgical resection		Consider for persistent hemoptysis
ABPA	Corticosteroids (prednisone)	0.5-0.75 mg/kg/d for 2-4 wk	Taper as patient responds; follow total serum IgE levels, which fall with treatment
	Itraconazole po	200 mg bid × at least 16 wk	Monitor serum levels
	Voriconazole po	150-300 mg bid × 6 mo	Dose based on serum levels; consider if itraconazole failure or intolerance
	Omalizumab sq	Based on total IgE level and weight	Case reports suggest benefit

sq = subcutaneous injection. See Table 1 for expansion of other abbreviation.

In the largest published review of comorbidities, all patients with chronic cavitary pulmonary aspergillosis had at least one underlying pulmonary disease, of which COPD was the most common.<sup>41</sup> A history of mycobacterial disease, split between TB and non-TB infection, was present in one-third of patients. Fibrotic sarcoidosis and ABPA were other important comorbidities. The nature of these underlying lung diseases suggests that mechanical impediments to *Aspergillus* elimination are an important element of disease. Defects in innate immunity and exogenous immunosuppression likely also contribute to increased susceptibility.<sup>33</sup> Specific polymorphisms in Toll-like receptors and mannose-binding lectin, both involved in pathogen pattern recognition and innate immune responses, continue to be explored.<sup>42-45</sup> How-

ever, the mechanisms of tissue destruction, where local tissue invasion is rarely observed, remain poorly understood.

Diagnosing chronic cavitary pulmonary aspergillosis can be challenging. Imaging abnormalities may be mistaken for underlying parenchymal disease, and cavitation may not be evident early in the disease course. Serum IgG testing by quantitative or precipitins assays establishes sensitization and is positive in most patients.<sup>46</sup> Total IgE and *Aspergillus*-specific IgE levels are often, although not consistently, elevated.<sup>37,39</sup> Cultures of expectorated sputum or BAL fluid are often positive for *Aspergillus*, but negative cultures do not rule out disease when it is suspected on clinical grounds.<sup>47</sup> Because *Aspergillus* antigens may access the circulation,

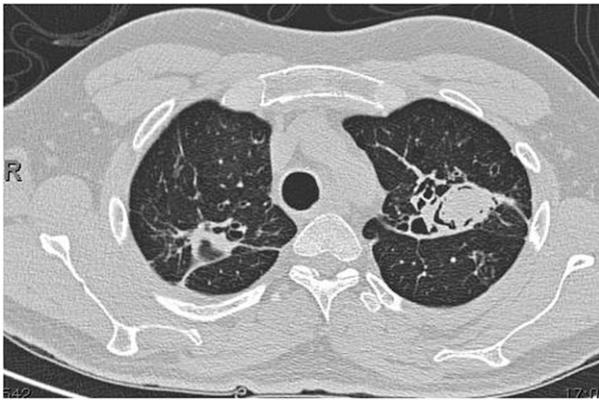


Figure 3 – Chest CT scan of a patient with biapical scarring from previous infection with *Mycobacterium tuberculosis* who developed a simple aspergilloma in the left upper lobe scar. Hemoptysis was initially treated with bronchial artery embolization, but, at recurrence some years later, resection of the left upper lobe was performed after pretreatment with voriconazole to reduce the risk of local postoperative *Aspergillus* infection.

serum galactomannan testing is positive in some patients. Reported sensitivities have increased with the liberalization of the cutoff index in recent years.<sup>48</sup> Serum

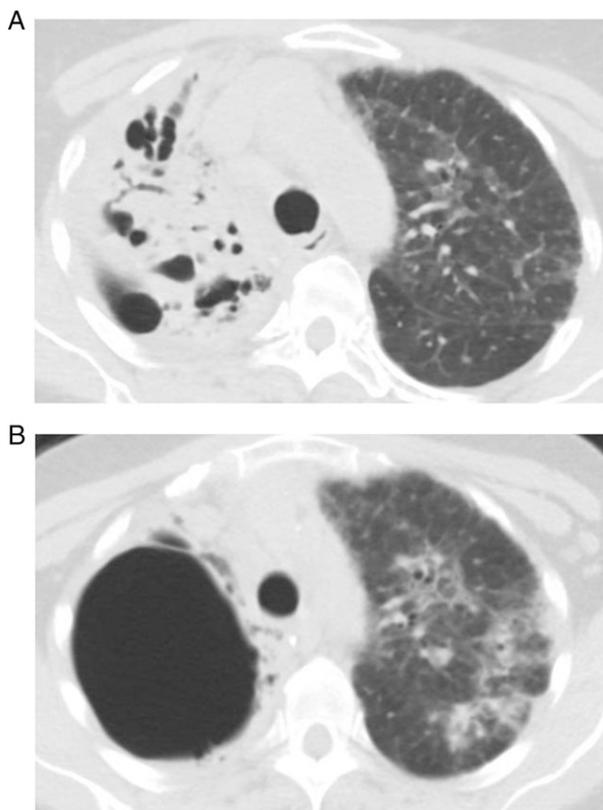


Figure 4 – A, Chest CT scan demonstrating chronic cavitary pulmonary aspergillosis in the setting of underlying fibrocystic sarcoidosis. After years of stable sarcoidosis, this patient developed dyspnea, hemoptysis, and hypoxemia. Sputum cultures grew *Aspergillus niger*. Serum IgG for *Aspergillus* was positive. Imaging revealed extensive right-sided consolidation with discrete areas of cavitation and mycetoma. B, Extensive tissue destruction ensued in the following year. Hemoptysis has not recurred since itraconazole was started.

1,3  $\beta$ -D glucan testing is unreliable and in one study was positive in only 21% of patients with chronic progressive pulmonary aspergillosis.<sup>48</sup> Histology reveals chronic inflammation; granulomas are a variable finding. Fungal hyphae are more commonly observed within cavities than in surrounding parenchyma.<sup>35,49</sup> Ultimately, the diagnosis rests in the combination of clinical features, imaging, serologies, and cultures, with consideration of predisposing patient factors (Table 1).

With a high attributable morbidity, outcomes in chronic cavitary pulmonary aspergillosis are generally poor.<sup>50,51</sup> Survival likely increases with treatment, although mortality is also high, even among treated patients.<sup>52</sup> Several retrospective and prospective case series, and limited data from randomized controlled studies, support a protracted course of treatment in patients with symptomatic disease (Table 3).<sup>40,53-55</sup> IV amphotericin or voriconazole are options for severe disease, and oral voriconazole or itraconazole is typically used in stable patients. Radiographic and clinical improvements typically accompany decreases in fungal burden, but serum *Aspergillus*-IgG levels may remain elevated, and serologic normalization is not a reliable end point of treatment.<sup>56</sup> Not all patients improve with treatment; in patients with progressive disease, a positive response to therapy may be reflected in stabilization rather than in radiographic improvement.<sup>55</sup> Azole resistance is of increasing concern and has been associated with treatment failure.<sup>57</sup> In addition to antifungals, a therapeutic role for interferon  $\gamma$  (IFN- $\gamma$ ), an important cytokine in the containment of fungal infections, has been explored. Similar to the results observed in a small series of patients with invasive aspergillosis, a positive response to exogenous IFN- $\gamma$  therapy was noted in a report of two patients with chronic cavitary pulmonary aspergillosis.<sup>58,59</sup> Notably, these patients had demonstrated reduced IFN- $\gamma$  production and had failed antifungal therapy alone.<sup>59</sup>

Subacute or massive hemoptysis can complicate both simple aspergilloma and chronic cavitary pulmonary aspergillosis. Bronchial artery embolization is an important treatment option for short-term control of hemoptysis that threatens clinical stability. However, long-term recurrence is common. Intracavitary instillation of amphotericin has been tried in some patients. Although typically delivered via bronchoscopic technique, in a recently published series of patients with simple aspergilloma or chronic cavitary pulmonary aspergillosis, percutaneous installation of intracavitary treatment was associated with good short-term control of hemoptysis

in 25% of patients.<sup>34</sup> Surgical resection is generally reserved for fit patients who fail medical management and/or bronchial artery embolization and who have disease favorable to resection.<sup>60,61</sup> Concomitant antifungal treatment is not recommended universally but should be considered for patients with contamination of the pleural space during resection or with residual disease postoperatively.<sup>61,62</sup> Recurrent disease is not uncommon, even in those with a good initial response to medical and/or surgical treatment.<sup>60,63</sup> Schweer and colleagues<sup>39</sup> recently published an elegant treatment algorithm emphasizing the need for careful long-term follow-up.

### ABPA: Diagnostic and Treatment Options

ABPA is the result of immune-mediated damage to, and dysfunction of, the airways triggered by *Aspergillus* (Fig 5). Modifications to diagnostic criteria developed decades ago have been proposed in recent years (Table 4).<sup>64,65</sup> *Aspergillus*-specific IgE levels may be more sensitive than skin testing for establishing sensitization. In a recent evaluation of diagnostic criteria, *Aspergillus*-specific

IgE levels were increased in 100% of patients with ABPA.<sup>66</sup> This was the most sensitive finding for ABPA. Although asthma is the most common comorbidity, patients with cystic fibrosis have a higher rate of *Aspergillus* colonization, and up to 15% of patients develop ABPA.<sup>67</sup> For patients with asthma, spirometry may be normal and ABPA should be considered even in mild disease when serologies and imaging are otherwise suggestive.<sup>64,68</sup> The usefulness of bronchiectasis as a diagnostic criterion has been questioned recently.<sup>53</sup> The possibility of ABPA should not be dismissed in patients without bronchiectasis, which can be a late-stage event, who otherwise have suggestive clinical findings. Although typically central, peripheral bronchiectasis may be evident.<sup>64</sup> High-attenuation mucous, when present, is highly suggestive of ABPA over other causes of bronchiectasis and predicts relapse among patients with ABPA (Fig 5B).<sup>64,69</sup> Finally, positive respiratory cultures are supportive but are not a formal diagnostic criterion. Even when stains or cultures are negative, *Aspergillus* DNA may be detected in respiratory samples.<sup>70</sup>

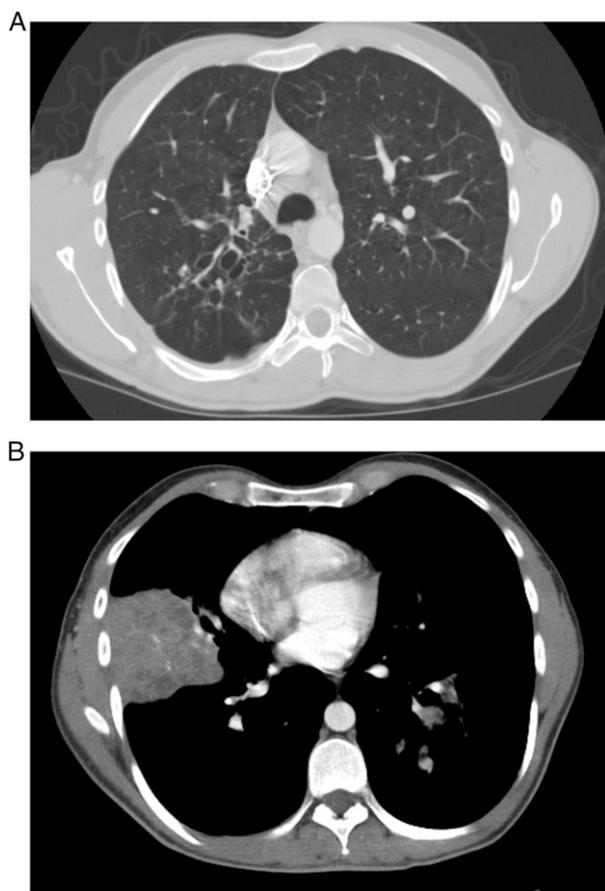


Figure 5 – Chest CT scan demonstrating typical features of allergic bronchopulmonary aspergillosis. A, Central bronchiectasis. B, Plugging of airways with mucus.

The pathogenesis of ABPA is complex. In basic terms it involves (1) noninvasive growth of *Aspergillus* aided by poor airway clearance, and (2) a hypersensitive response in predisposed individuals. The activation of lymphocytes occurs along a T-helper (Th) 2 pathway, rather than the Th1 pathway for sensitization in patients without ABPA.<sup>53</sup> Th2 cells recruit eosinophils, which, along with fungal enzymes, contribute to epithelial damage. A more detailed unifying model of the essential immunologic events in ABPA across cystic fibrosis and asthma subtypes is still evolving. In patients with cystic fibrosis, human leukocyte antigen alleles have been associated with the development of ABPA.<sup>71</sup> In addition, in patients with cystic fibrosis, regulatory T cells were reduced in patients with ABPA compared with patients with asymptomatic colonization.<sup>72</sup> In this same study, vitamin D levels were also lower in patients with ABPA.<sup>72</sup> Vitamin D attenuates innate immune responses and enhances regulatory T cells, and research on Vitamin D and ABPA is ongoing.<sup>73</sup>

Corticosteroids are the mainstay of treatment (Table 3). However, therapies that attenuate fungal burden are used increasingly for augmentation or second-line therapy.<sup>53,74-76</sup> In ABPA due to asthma or cystic fibrosis, the addition of a triazole antifungal agent has been associated with improvements in lung function, serologic markers, rates of exacerbation, and corticosteroid requirements. Although important for combination

**TABLE 4 ] Diagnosing ABPA**

Diagnostic Criteria	Historically Included	Recent Modifications Highlight
Predisposing condition	Asthma	Cystic fibrosis
Demonstration of fungal sensitization	Sensitization to <i>Aspergillus fumigatus</i> Positive <i>Aspergillus</i> skin test or elevated IgE levels against <i>Aspergillus fumigatus</i>	Sensitization can be to a variety of <i>Aspergillus</i> species or other fungal organisms Intradermal testing is more sensitive than skin prick The combination of serum <i>Aspergillus</i> IgE and skin testing is most sensitive
Elevated total serum IgE	Levels >1,000 IU/mL	Levels may be lower for patients on corticosteroids or in a less active phase of disease
Positive <i>Aspergillus</i> -specific serologies	Elevated serum <i>Aspergillus</i> IgE and positive precipitins	Quantitative <i>Aspergillus</i> IgG titers often replace precipitins testing
Radiographic changes	Opacities from mucous plugging Central bronchiectasis	High attenuation mucous plugging is pathognomonic Not all patients have bronchiectasis, particularly early in disease

See Table 1 for expansion of abbreviation.

regimens, the role of antifungals as a sole, first-line treatment remains to be determined. A placebo-controlled study is underway, and case reports and series suggest that omalizumab, a monoclonal antibody to IgE, may be effective in some patients.<sup>53</sup> Treatment end points in ABPA remain a reduction in, although not normalization of, total IgE levels associated with clinical and radiographic improvement. Following a treatment course, patients may remain in remission, relapse and require long-term treatment, and/or progress to end-stage lung disease. Therefore, close long-term follow-up with serial assessments of total serum IgE is advised for all patients.

### Other Syndromes Caused by *Aspergillus* Sensitization

*Aspergillus* sensitization can cause hypersensitivity pneumonitis or can complicate asthma. The features of hypersensitivity pneumonitis have been reviewed elsewhere.<sup>77</sup> Severe asthma with fungal sensitization (SAFS) is an emerging disease concept. Although fungal sensitization can be associated with severe asthma, a direct role of sensitization in the disease process remains unclear. Unlike the syndromes described earlier, *Aspergillus* germination is not thought to be a feature of SAFS. SAFS is distinguished from ABPA by sensitization to an array of fungal species, a lower total IgE, normal *Aspergillus*-IgG levels, and a lack of bronchiectasis and other radiographic changes of ABPA.<sup>78,79</sup> It has been suggested that SAFS and ABPA occur along a spectrum, with a more pronounced inflammatory response in ABPA, but it remains to be established that patients with SAFS are at predictable risk of progressing to ABPA. A role for antifungal therapy in SAFS has not been established, and an

aggressive asthma regimen remains the mainstay of treatment.<sup>78</sup>

### Conclusions

*Aspergillus* is a ubiquitous organism that is encountered regularly in the environment. Although preexisting lung disease or immune dysfunction have long been recognized as prerequisites for the development of pulmonary disease in response to *Aspergillus*, recent studies demonstrate that even a modest degree of immunosuppression increases this risk, where the type of pulmonary response is often a function of host factors. Invasive pulmonary aspergillosis is encountered in patients with chronic lung disease exposed to oral or inhaled corticosteroids and in critically ill patients. The diagnosis of invasive aspergillosis is aided by an understanding of the populations and settings that predispose to infection, the recognition that positive cultures may indicate invasive disease; the use of noninvasive galactomannan testing may be helpful, although test sensitivity is variable across studies and the clinical utility remains unclear. Chronic cavitary pulmonary aspergillosis occurs most often in patients with preexisting lung disease. Outcomes are generally poor, particularly without antifungal treatment. Patients with asthma or cystic fibrosis may develop ABPA from a Th2 response to germinated *Aspergillus* in the airway. For invasive and chronic cavitary pulmonary aspergillosis, and potentially for ABPA, patients benefit from antifungal therapy, most often with triazole medications. Future work to further identify the immune alterations that mediate the inflammatory responses to *Aspergillus*, or the lack thereof, will advance our understanding of the pathogenesis of these syndromes.

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