Pulmonary Aspergillosis: A Review on Diagnosis and Management

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Abstract

Aspergillosis is acquired by inhalation of spores of Aspergillus, a ubiquitous species in the environment. In normal hosts, spore inhalation rarely causes lung disease.

Pulmonary aspergillosis covers a wide spectrum of clinical syndromes depending on the interaction between Aspergillus and the host (immune-status, prior bronchopulmonary disease). It runs the gamut from invasive aspergillosis to Aspergillus bronchitis and colonization.

Invasive aspergillosis occurs in severely immunocompromised patients, typically with neutropenia. Chronic pulmonary aspergillosis affects patients with chronic structural lung disease such as chronic obstructive pulmonary disease, mycobacterial lung disease, but without significant immunocompromise. Aspergillus bronchitis affects patients with bronchial disease such as bronchiectasis. Allergic bronchopulmonary aspergillosis affects patients with bronchial asthma or cystic fibrosis, and is due to an allergic response to Aspergillus.

In this review of literature, we discuss the pulmonary manifestations of Aspergillus infection, its diagnosis and treatments.

Introduction

Aspergillosis is a disease caused by fungi of the genus Aspergillus principally A. fumigatus, and less commonly A. flavus, A. terreus, and A. niger. The name Aspergillus is derived from its resemblance to the sporulating head of Aspergillus and the aspergillum/aspergill used to sprinkle holy water (from latin asperegere: to sprinkle.) Aspergilli are filamentous saprophytic molds ubiquitous in nature that grow in soil, decaying vegetation, and water. Direct examination of Aspergillus within tissue reveals septated hyphae which dichotomously branch at 45° as shown in Figure 1.

While Aspergillus can involve a variety of organ systems, including the respiratory (lung, sinuses), central nervous, ocular, gastrointestinal/hepatic and renal systems causing significant morbidity and mortality [1, 2]. This review of literature will focus on the pulmonary manifestations of Aspergillus infections.

Aspergillus causes a spectrum of pulmonary diseases (presented in Table 1) determined by the interplay between the pathogen Aspergillus, underlying lung disease and the host immunity [3-7]. On one end of the spectrum, invasive pulmonary aspergillosis (IPA) predominantly affects patients with severe immune dysfunction, while chronic pulmonary aspergillosis (CPA) affects patients with underlying lung disease but with an absence of, or mild immune dysfunction. Acute community-acquired Aspergillus pneumonia occurs in patients without significant immune deficits and normal lungs. Aspergillus bronchitis is a chronic bronchitis that is mostly seen in non-immunocompromised patients with bronchiectasis or cystic fibrosis. Allergic bronchopulmonary aspergillosis is due to an allergic response to inhaled Aspergillus in asthmatics.

I invasive Pulmonary Aspergillosis

Acute invasive pulmonary aspergillosis (IPA) is a rapidly progressive infection that occurs in highly immunocompromised patients and carries a mortality upwards of 50 to 80%. [8, 9]. The classic risk factor for IPA is neutropenia and the likelihood of IPA depends on the duration and severity of neutropenia. Histologically, IPA in neutropenic hosts shows angioinvasion (Figure 2), while IPA in non-neutropenic patients does not usually demonstrate angioinvasion and occurs in a wide range of conditions: allogeneic hematopoietic stem-cell transplantation after neutrophil recovery, solid organ transplantation, advanced AIDS, chronic granulomatous disease, and critically-ill ICU patients [10]. The most common risk factors for these patients is the use of chronic corticosteroid therapy.

IPA has been increasingly diagnosed in non-neutropenic ICU patients who have non-specific risk factors such as sepsis, chronic obstructive pulmonary disease (COPD), steroid therapy, multiple antibiotic treatments, and hepatic and/or renal failure.
Sepsis probably causes a state of ‘immunoparalysis’ and steroids cause an immunodeficient state that promotes the occurrence of IPA.

The diagnosis of IPA is based on the criteria mentioned in Table 2. Histopathologic visualization of fungal elements alone is not sensitive enough to diagnose invasive aspergillosis and should be accompanied by immunostains, cultures and where available, nucleic acid amplification tests (NAAT) [11, 12]. Assays for PCR and NAAT are not commercially available yet and require submission of samples to research or reference laboratories that have validated assays. The galactomannan assay is a fairly specific and sensitive test for the diagnosis of invasive pulmonary aspergillosis. Galactomannan is found in the cell wall of *Aspergillus* species and the assay can be performed in serum, BAL and pleural fluid, although the sensitivity is higher when performed in BAL fluid than in serum. Galactomannan assay results are always used in combination with culture and histopathology results. The sensitivity of the assay increases with repeated testing (one week apart) and has the highest sensitivity among patients with hematological malignancies or post-hematopoietic stem cell transplantation [13].

False positive serum and BAL galactomannan assays can be caused by several beta-lactam antibiotics including piperacillin-tazobactam and carbapenem [14]. Galactomannan is also found in the cell walls of *histoplasma capsulatum* and *fusarium* spp. The concurrent use of caspofungin has been associated with a higher sensitivity of the galactomannan assay likely due to the increase in galactomannan levels released from cell wall breakdown. In addition to the galactomannan, serum 1,3 beta-D-glucan test may be helpful, keeping in mind the cross-reactivity with pseudomonas can yield false positive results [13].

**Treatment of IPA**

Voriconazole is the recommended primary therapy for IPA based on a randomized trial that compared voriconazole with amphotericin B deoxycholate and showed improved survival with voriconazole [16]. Voriconazole can be given intravenously or orally. Alternative primary therapies are liposomal amphotericin B and isavuconazonium. Recently, the FDA has approved isavuconazonium (a pro-drug of isavuconazole) for intravenous and oral treatment of IPA[17]. The recommendation was based on a randomized trial of isavuconazonium vs voriconazole. All-cause mortality and overall response rates
Table 2. Diagnostic criteria for invasive pulmonary aspergillosis per the European Organization for the Research and Treatment of Cancer (EORTC) and the Mycosis Study Group [15].

<table>
<thead>
<tr>
<th>Proven Invasive Pulmonary Aspergillosis</th>
<th>Probable Invasive Pulmonary Aspergillosis</th>
<th>Possible Invasive Pulmonary Aspergillosis</th>
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<tr>
<td>• Sterile biopsy showing hyphae branching at 45° (morphologically suggestive of Aspergillus) with evidence of associated tissue damage</td>
<td>Clinical criteria (one of the following):</td>
<td>Clinical criteria (one of the following):</td>
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<td>OR</td>
<td>• Recent history of neutropenia (absolute neutrophil count &lt; 500 cells)</td>
<td>• Recent history of neutropenia (absolute neutrophil count &lt; 500 cells)</td>
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<td>• Aspergillus on culture of lung biopsy specimens</td>
<td>• Allogeneic stem-cell transplant recipient</td>
<td>• Allogeneic stem-cell transplant recipient</td>
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<td>• Prolonged corticosteroid exposure (mean dose &gt; 0.3mg/kg/day of prednisone equivalent for 13 weeks)</td>
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<td>• Therapy with known T-cell immunosuppressive agents (e.g., Cyclosporine, tacrolimus, etc.)</td>
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<td>• Hereditary severe immunodeficiency AND</td>
<td>• Hereditary severe immunodeficiency AND</td>
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<td>Radiologic criteria on CT (one of the following):</td>
<td>Radiologic criteria on CT (one of the following):</td>
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<td>• Well-circumscribed, dense lesions ± halo sign</td>
<td>• Well-circumscribed, dense lesions ± halo sign</td>
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<td>• Air-crescent sign</td>
<td>• Air-crescent sign</td>
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<td></td>
<td>• Cavitary lesion</td>
<td>• Cavitary lesion</td>
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<td></td>
<td>AND</td>
<td>AND</td>
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<td></td>
<td>Mycological criteria (one of the following):</td>
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<td></td>
<td>• Cytology, culture or microscopy of respiratory sample (BAL, bronchial brush) showing fungal elements or growing Aspergillus</td>
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<td></td>
<td>• Detection of antigen or cell-wall components (e.g., Galactomannan in serum, plasma or BAL)</td>
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<td></td>
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<td>Detection of antigen or cell-wall components (e.g., Galactomannan in serum, plasma or BAL)</td>
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were similar in both groups.

Patients who do not respond to monotherapy are considered for combination antifungal therapy usually with an echinocandin in addition to voriconazole or liposomal amphotericin B. The treatment of IPA should be continued for a minimum of 6 to 12 weeks, dependent on the duration and severity of immunosuppression and the clinical response to therapy [18].

Tracheobronchial Aspergillosis (TBA)

Tracheobronchial aspergillosis is a unique feature of IPA, representing isolated tracheobronchial invasion. Predisposing factors for TBA are similar to those for IPA, however it has been mainly described in lung transplantation recipients, and patients with AIDS. The diagnosis requires bronchoscopy. TBA has been classified into 3 forms (19). Obstructive TBA manifests as thick mucus plugs loaded with Aspergillus spp. without obvious bronchial inflammation. Pseudomembranous TBA is characterized by extensive involvement of the tracheobronchial tree with a membranous slough overlying the mucosa containing Aspergillus as shown in Figure 3.

Ulcerative TBA is a focal process usually found at the suture line of the tracheobronchial anastomosis in lung transplant recipients. The diagnosis of TBA is usually made by the characteristic findings on bronchoscopy (Figure 4) combined with microbiological and pathological analysis of the respiratory specimens obtained during bronchoscopy.

Treatment of TBA

Similar to IPA, voriconazole or lipid formulation of amphotericin B is used. Bronchoscopic debridement of airway lesions and minimization of immunosuppression when feasible are also considered [20]. In lung transplant recipients with anastomotic TBA, adjunctive inhaled amphotericin B is recommended. The duration of antifungal therapy is at least 3 months, or until TBA has completely resolved.

Neutropenic Fever in Patients with Cancer

Neutropenic patients can be classified as high-risk or low-risk [21]. Patients with any of the following are considered high-risk if they have:

- profound neutropenia (ANC < 100 cells/m3), anticipated to be prolonged (> 7 days), and
- the presence of medical comorbidities: hemodynamic instability, oral mucositis causing dysphagia, gastrointestinal symptoms (abdominal pain, nausea, vomiting or diarrhea), new-onset neurologic changes, pneumonia, intravascular catheter infections [21].
High-risk patients who have received intensive cytotoxic chemotherapy are at risk for "invasive" fungal infections; yeasts (primarily Candida species) and molds (primarily Aspergillus). They typically cause persistent or recurrent fever in patients with profound (≤ 100 cells/mm³) and prolonged (> 10-15 days) neutropenia. Fever may be the only sign in the early stages of fungal infections.

The Infectious Diseases Society of America (IDSA) recommends empiric antifungal therapy for high-risk neutropenia in patients with persistent or recurrent fever after 4-7 days of empirical broad spectrum antibiotic therapy [21].

**Chronic Pulmonary Aspergillosis (CPA)**

There are a multitude of chronic forms of CPA that may overlap as illustrated in Figure 5. The progression of CPA is slow with a duration of at least 3 months. It affects patients with underlying chronic lung conditions, namely tuberculous and non-tuberculous mycobacterial infections, COPD, bullous lung disease, ABO, asthma, pulmonary fibrocystic sarcoidosis, lung radiation, rheumatoid arthritis, and ankylosing spondylitis [3].

The key diagnostic test for CPA is the detection of IgG to *Aspergillus* (or the less sensitive serum *Aspergillus* precipitins). Positive anti-*Aspergillus* antibodies differentiate infected patients from colonized patients, with a positive predictive value of 100% for infection. Positive PCR, culture of *Aspergillus*, or galactomannan in respiratory samples provide supportive evidence. The diagnostic criteria for CPA are outlined in Figure 6.

The most common form of CPA is chronic cavitory pulmonary aspergillosis which occurs in non-immunocompromised patients with lung disease. When untreated, it may progress to chronic fibrosing pulmonary aspergillosis as shown in Figure 7. Less common forms of CPA are *Aspergillus* nodule(s) and single aspergilloma shown in Figure 8.

Sub-acute invasive aspergillosis also known as chronic necrotizing pulmonary aspergillosis. It develops over 4-12 weeks, usually affects mildly immunocompromised patients and manifests with variable radiological features including cavitation, nodules, progressive consolidation with ‘abscess formation’.

**Clinical Criteria:**
- Chronic pulmonary or systemic symptoms (duration >3 months) including at least one of the following symptoms: weight loss, productive cough or hemoptysis.
- No overt immunocompromised conditions (e.g. hematological malignancy, neutropenia, organ transplantation, chronic granulomatous disease)

**Radiological Criteria:**
- Cavitary pulmonary lesions with evidence of paracavitary infiltrates, new cavitary formation, or expansion of cavitory size over time.

**Laboratory Criteria:**
- Either positive result of serum precipitins or IgG to *Aspergillus* or isolation of *Aspergillus* species from pulmonary or pleural cavity.
- Elevated levels of inflammatory markers (C-reactive protein, erythrocyte sedimentation rate).
- Exclusion of other pulmonary pathogens, by results of appropriate cultures and serological tests, that are associated with similar disease presentation, including mycobacteria and endemic fungi.
Treatment of CPA

1. Treatment of chronic cavitary and fibrosing aspergillosis
   Patients with CPA and with pulmonary symptoms including progressive loss of lung function or radiographic progression should be treated with a minimum of 6 months of antifungal therapy [18]. Oral Itraconazole and voriconazole are the preferred oral antifungal agents; posaconazole is an alternative therapy for those with adverse effects or clinical failure. Patients with subacute invasive aspergillosis should be managed as invasive aspergillosis.

2. Treatment of simple aspergilloma
   Surgical resection is a definitive treatment for patients with adequate pulmonary function. Intracavitary instillation of amphotericin B is an effective short-term treatment to control severe hemoptysis [24]. Mild to moderate hemoptysis can be controlled with tranexamic acid that inhibits fibrinolysis of clots. Catheter embolization of the bronchial arteries may be a lifesaving procedure for severe hemoptysis, either as a temporizing measure before surgery or as a definitive treatment.

3. Treatment of Aspergillus nodule
   A single Aspergillus nodule that has been completely excised does not need antifungal treatment if the patient is immunocompetent. In immunocompromised patients, an oral azole such as oral itraconazole is indicated [3]. In a patient with multiple nodules who undergoes surgical excision of a single nodule, azole therapy is recommended and these patients require radiographic follow up with chest CT after excision of a single nodule. If the residual nodules are progressive, continued azole therapy is indicated and a repeat biopsy should be considered to rule out other etiologies [22].

Acute Community-Acquired Aspergillus Pneumonia

There appear to be 3 different presentations of community acquired Aspergillus pneumonia:

1. massive exposures to airborne Aspergillus spores that overwhelm the immunity of the lung to fight infection (‘mulch pneumonitis’)
2. lower levels of exposure following influenza infection
3. patients with COPD and those on chronic systemic corticosteroid therapy

Chest imaging shows a diffuse miliary pattern in cases of massive exposure, or unilateral upper-lobe cavitary disease. Aspergillosis may occur in the setting of severe influenza infections even among immunocompetent hosts and carries a mortality rate of almost 50% [25]. Diagnosis requires a high level of suspicion. Aspergillus can be isolated from optimal respiratory tract specimens (bronchoalveolar lavage and bronchial brushings) and galactomannan should be detectable in the bronchoalveolar lavage (BAL) fluid. Prompt therapy with voriconazole is recommended given the high mortality rates [26].

Aspergillus bronchitis

Aspergillus bronchitis is a chronic superficial Aspergillus infection of the bronchial tree in a non-immunocompromised patient, usually with bronchiectasis or cystic fibrosis. If the patient has significant immunocompromise (recent chemotherapy, transplantation, or AIDS) the term IA tracheobronchitis should be applied. Dr. Denning’s group proposed the following criteria for the diagnosis of chronic Aspergillus bronchitis [27].
Bronchiectasis

Suggested protocol for the diagnosis of allergic bronchopulmonary Aspergillosis (ABPA) adapted from Agarwal et al [29].

Table 3. A table comparing the diagnostic criteria for ABPA by the ABPA Working Group and those proposed by Agarwal et al [29]. (COPD: chronic obstructive pulmonary disease; kUA: kilounit of antibody; mgA: milligram of antibody; ABPA: Allergic bronchopulmonary Aspergillosis; Ig: immunoglobulin.)

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<thead>
<tr>
<th>ABPA Working Group Criteria</th>
<th>Criteria Proposed by Agarwal et al</th>
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<tr>
<td>Essential criteria:</td>
<td>Essential criteria:</td>
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<tr>
<td>• Bronchial asthma and cystic fibrosis</td>
<td>• Serum A. fumigatus specific IgE levels &gt; 0.35 kUA/L or positive type I Aspergillosis skin test</td>
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<tr>
<td>• Elevated serum total IgE levels &gt; 1000 IU/ml (an IgE value &lt;1000 IU/ml may be acceptable if all other criteria are met, especially if the serum A. fumigatus specific IgG level &gt; 27 mg/L).</td>
<td>• Elevated serum total IgE levels &gt; 1000 IU/ml (an IgE value &lt;1000 IU/ml may be acceptable if all other criteria are met, especially if the serum A. fumigatus specific IgG level &gt;27 mg/L).</td>
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Additional criteria [two of three must be met]:

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<tr>
<td>• Presence of precipitating (or IgG) antibodies against A. fumigatus in serum</td>
<td>• Serum A. fumigatus IgG level &gt; 27 mg/L OR Thoracic imaging findings consistent with ABPA</td>
</tr>
<tr>
<td>• Thoracic imaging findings consistent with ABPA</td>
<td>o Transient abnormalities: nodules, consolidation, mucoid impaction, hyper-attenuating mucus, fleeting opacities, toothpaste/gloved-finger opacities, or tram-track sign</td>
</tr>
<tr>
<td>• Bronchial asthma, cystic fibrosis, COPD, post-tuberculous fibrocavitary disease</td>
<td>o Permanent abnormalities: parallel lines, ring shadows, bronchiectasis, pleuropulmonary fibrosis</td>
</tr>
<tr>
<td>• High-resolution chest CT</td>
<td>OR Historical or current peripheral blood eosinophil count &gt; 500 cells/µL</td>
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Essential criteria
1. Microbiology: Demonstration of Aspergillus in the airways at least twice (sputum culture or PCR positive for Aspergillus)
2. Chronic (>4 weeks) pulmonary symptoms: Chronic productive cough, tenacious mucus production, recurrent bronchitis exacerbations with poor response to antibiotics and possible systemic symptoms.
3. No significant immune system deficiency.

Supportive Criteria
5. Bronchoscopy findings: Thick tenacious mucus with bronchial plugging, bronchial erythema, or ulceration. Superficial invasion of mucosa by Aspergillus hyphae.
6. Response to therapy: Good response to an eight-week course of antifungal therapy.

Treatment of Aspergillus bronchitis
Oral azole therapy (itraconazole, voriconazole, posaconazole) for 4 months is effective in the majority of patients, however, relapse risk is about 50% and these patients may need long-term therapy [27].

Allergic Bronchopulmonary Aspergillosis
ABPA is a pulmonary disorder caused by hypersensitivity to Aspergillus fumigatus that complicates the course of patients with asthma and cystic fibrosis. It presents with different clinical and radiological manifestations such as refractory asthma, recurrent fleeting pulmonary infiltrates with or without bronchiectasis. ABPA should be suspected in all patients with asthma and cystic fibrosis regardless of the severity or the level of disease control. A working group of ‘ABPA in asthmatics’ formed by the International Society of Human and Animal Mycology (ISHAM) convened an expert group that proposed new criteria for ABPA in 2015 [28]. Subsequently, Agarwal et al have recently proposed new criteria outlined in Table 3 [29]. Comparing the ABPA working group criteria to the criteria proposed by Agarwal et al, the proposed criteria include a larger array of lung disease (COPD, post-tuberculous fibrocavitary disease) and identifies a specific A. fumigatus IgG level. The diagnostic algorithm for ABPA is outlined in Figure 9.

Treatment of ABPA
ABPA has distinct stages of progression from an acute infection (stage 1) to advanced ABPA (stage 6) as listed in Table 4. The treatment of ABPA has been described by Agarwal et al [29], highlighted in the flowchart shown in Figure 10. Primary treatment of ABPA involves corticosteroids for asthma attacks associated with ABPA. The most frequently used schedule is the low-dose steroid regimen (prednisone 0.5mg/kg/day) for 2 weeks followed by 0.5/mg/kg every other day for 8 weeks, then tapered by 5mg every 2 weeks for a total duration of 3 to 5 months. Alternative treatments described oral Itraconazole 200mg twice daily for 16 weeks or longer. Itraconazole has been shown to decrease the number of exacerbations requiring steroids with improved lung function and exercise tolerance. [30, 31] Itraconazole can eliminate Aspergillus in the airways and can theoretically reduce the allergic responses in ABPA. The aim of the MIPA trial (Monotherapy of Itraconazole Versus Prednisolone in Allergic Bronchopulmonary Aspergillosis; clinicaltrials.gov: ID: NCT01321827), a prospective randomized controlled trial that is currently underway, is to evaluate the efficacy and safety of itraconazole monotherapy in patients with ABPA.
Conclusions

The different clinical syndromes caused by Aspergillus can be considered as a continuous spectrum of disease resulting from the interplay of Aspergillus, host immunity and underlying lung disease. The spectrum runs from invasive pulmonary aspergillosis to Aspergillus bronchitis. One form of aspergillosis may evolve from one form into another depending on the degree of immunity of the host. Prompt diagnosis and treatment with appropriate antifungals are essential for improved outcomes.

Funding Source: No funding sources to declare.  
Conflict of Interest: The authors listed do not have any pertinent financial disclosures or conflicts of interest.

References


