

# Pulmonary aspergillosis: infection, diagnosis and treatment

## Abstract

Pulmonary Aspergillosis is a group of lung disorder occurs due to the infection of *Aspergillus* species. It has wide range of clinical indications based on the interaction of *Aspergillus* with the host. The understanding of pathophysiological mechanism of *Aspergillus* infection is essential in order to minimize the chances of infection as well as to develop treatment strategies. Aspergillosis is found to be associated with various health conditions such as Asthma, Chronic Obstructive Pulmonary Disease (COPD) and Cystic fibrosis. The chances of *Aspergillus* infection increased in the transplant patient and the patient having immunocompromised state. Diagnosis is mostly done through sputum culture, serological and molecular diagnostic tools. Antifungal therapeutics is considered as treatment strategies along with monoclonal anti Immunoglobulin E (IgE) antibody. In some cases surgery is also preferred.

**Keywords:** Aspergillosis, antifungal therapeutics, treatment strategies, diagnostics

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**Abbreviations:** COPD, chronic obstructive pulmonary disease; IgE, immunoglobulin E; IA, invasive aspergillosis; IPA, invasive pulmonary Aspergillosis; EMA, European medicines agency; FDA, food and drug administration

## Introduction

Aspergillosis is a group of infections caused by the various species of filamentous fungus *Aspergillus* including *A. fumigatus*, *A. flavus*, *A. terreus* and *A. niger*.<sup>1</sup> *Aspergillus* species cause a wide range of diseases, from allergy syndromes to chronic pulmonary problems and invasive infections.<sup>2</sup> Various species of *Aspergillus* found in the surrounding environments out of which *Aspergillus fumigatus* causes pulmonary illness, with variety of clinical symptoms.<sup>3</sup> Though the *Aspergillus* is a saprophytic in soil but the species of this organism learned to adapt and proliferate in human host by invading human immune system.<sup>4</sup>

Pulmonary Aspergillosis encompasses a wide range of clinical indications based on the interaction of *Aspergillus* with the host.<sup>5</sup> Severity of Aspergillosis determined by the degree of immunological compromise, the form and intensity of the inflammatory host response, and/or the presence of underlying pulmonary disease.<sup>6</sup> The importance of this infection has grown dramatically as the number of patients with compromised immune systems associated with the management of cancer, organ transplantation, autoimmune and inflammatory conditions has increased.<sup>3</sup> The most commonly reported fungal infections in patients with COVID-19 include Aspergillosis, invasive candidiasis, and mucormycosis.<sup>7,8</sup> Significant progress has been achieved in the categorization, diagnosis, and management of pulmonary Aspergillosis in recent years.<sup>9</sup> Search for novel antifungal drugs is needed for the further management of disease.<sup>10</sup>

## Pathophysiological mechanism of *Aspergillus* infection

The understanding of pathophysiological mechanism of *Aspergillus* infection is essential in order to minimize the chances of infection as well as to develop treatment strategies as *Aspergillus* spp. infections continue to be associated with substantial morbidity and death.<sup>11</sup> *Aspergillus* conidia are breathed by immunocompetent individuals and taken up by phagocytes in the lungs where, the spores are suppressed by immune system. However, in immunocompromised

people, *Aspergillus* spores germinate and colonize successfully. In immunocompromised people, neutrophils and macrophages, which are primary responders to *Aspergillus* spores in immunocompetent individuals, became ineffective, leading to the advancement of Aspergillosis. It has been observed that the persistence of *Aspergillus* in the host cells is due to the fungal adherence to the host surface, extracellular matrix, or basal lamina.

## Clinical gamut of pulmonary aspergillosis

Patients with atopy, asthma, or cystic fibrosis are more likely to develop hypersensitivity to *Aspergillus* antigens.<sup>3</sup> Patients with chronic pulmonary Aspergillosis have chronic structural lung disease, such as COPD, or prior mycobacterial lung illness, but no other major immuno compromise. *Aspergillus* bronchitis affects those who have bronchial diseases like bronchiectasis. Allergic bronchopulmonary Aspergillosis is caused by an allergic reaction to *Aspergillus* and affects people with bronchial asthma or cystic fibrosis.<sup>5</sup>

## Association of pulmonary aspergillosis with other health conditions

Invasive Aspergillosis (IA) is becoming more common in critically ill patients in the intensive care unit, particularly those with severe influenza and severe coronavirus disease 2019 (COVID-19).<sup>12-14</sup> Biomedical waste is a big source of infection in hospital setting and its surroundings which also give rise to associated infections.<sup>15</sup> Granulocytopenia lasting more than three weeks is the most common risk factor for developing invasive pulmonary Aspergillosis in patients with acute leukemia.<sup>16</sup> Transplant recipients with a liver, lung, heart, or kidney have both shared and distinct risk factors for the development of Invasive Aspergillosis.<sup>17</sup>

## Diagnosis of aspergillosis

Noninvasive biomarkers have simplified the suspicion and diagnosis of invasive pulmonary Aspergillosis.<sup>18</sup> However, the diagnosis of Aspergillosis comprises an amalgamation of clinical valuation, laboratory tests, imaging studies and sometimes invasive procedures. Because pulmonary Aspergillosis can range from a moderate allergic reaction to a severe and invasive infection that can be life-threatening, prompt and precise diagnosis is critical for commencing the proper treatment.

Allergic bronchopulmonary Aspergillosis should be considered in individuals with moderate-severe chronic asthma and a skin prick test positive for *Aspergillus fumigatus*, regardless of age.<sup>19</sup> Histopathological evaluation of lung tissue acquired via thoracoscopic or open-lung biopsy is the gold standard in the diagnosis of invasive pulmonary Aspergillosis (Table 1).<sup>3</sup>

Chest computed tomography scans and innovative non-culture-based techniques like antigen detection and polymerase chain reaction may help with early detection of invasive Aspergillosis, although they have limits.<sup>20</sup>

**Table 1** Diagnosis methods for pulmonary aspergillosis

Method of diagnosis	Details of assessment	Reference
Clinical assessment	Assessment of patient's immune health, chronic disease condition and history lung surgery	-
Radiological detection	Assessment of presence of nodule, mass or cavity in lungs (Aspergilloma)	Segal and Walsh, 2006; Yeghen et al., 2000 <sup>20,21</sup>
Culture of Sputum or Bronchoalveolar Lavage (BAL)	Assessment of presence of <i>Aspergillus</i> in sputum sample	Ohara et al., 2016 <sup>22</sup>
Serological test	Assessment of presence of antibody or antigen associated with <i>Aspergillus</i> and detection of serum Ig E levels	Brandt et al., 2018 <sup>23</sup>
Polymerase chain reaction (PCR)	Detection of <i>Aspergillus</i> DNA	Brandt et al., 2018, Bhange et al 2022 <sup>23,24</sup>

## Treatment strategies

The therapy goals are to regulate inflammation, reduce the number of exacerbations, and slow the course of lung damage.<sup>25</sup> Treatment with oral corticosteroids is used for management, and the majority of patients respond well.<sup>26</sup> An extended-spectrum triazole, Isavuconazole considered as treatment drug for the treatment of invasive pulmonary Aspergillosis (IPA) by European Medicines Agency (EMA) and the Food and Drug Administration (FDA).<sup>9</sup> Additionally, Voriconazole is still the preferred treatment, while isavuconazole and posaconazole have comparable efficacy with reduced toxicity. As a treatment for invasive Aspergillosis, there is considerable interest in combination antifungal therapy that combines an echinocandin with either an azole or an amphotericin B formulation.<sup>20</sup> Combination therapy is utilized in cases of severe immunosuppression and widespread infection.<sup>2</sup> Amphotericin B, the oldest and most commonly used antifungal, has been used prophylactically in a variety of doses and schedules, but has been largely supplanted by its lipid and liposomal versions, which have a better safety profile.<sup>27,28</sup> The high relapse rate following therapy withdrawal is a common feature of all kinds of this semi-continuous spectrum of disorders.<sup>9,29</sup> Few studies have looked at therapy choices for chronic pulmonary Aspergillosis (CPA), where long-term oral itraconazole or voriconazole is still the gold standard.<sup>11</sup> It has been researched that omalizumab, a monoclonal anti-IgE antibody, has improved asthma management in severely allergic asthmatics.<sup>30</sup> In some circumstances, surgical intervention may be required to remove contaminated tissue.<sup>31</sup> If physically possible, surgical excision of a simple aspergilloma is suggested, ideally via video-assisted thoracic surgery.<sup>32</sup> Search for the new antifungal drugs should be continued for effective treatment strategies.<sup>33,34</sup>

## Conclusion

Aspergillosis could be life threatening and the infection of *Aspergillus* can frequently occur with other diseases. Thanks to modern diagnostic tests which help the healthcare professional to assess the accurate condition of patient with Aspergillosis. Antifungal therapy may alleviate respiratory indications and improve lung function. Early detection and management are critical in reducing the disease's course and severity. However the prevention of Aspergillosis is always a good option.

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## Conflicts of interest

The authors declare that there are no conflicts of interest.

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