

Fungi in Cystic Fibrosis and Non-Cystic Fibrosis Bronchiectasis

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Abstract

Keywords

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- *Aspergillus fumigatus*
- allergic bronchopulmonary aspergillosis
- allergic bronchopulmonary mycosis

Bronchiectasis is a pathologic bronchial dilatation with loss of function that can result from multiple inflammatory and infectious injuries to the conducting airways of the lung. Molds, particularly the filamentous fungus *Aspergillus fumigatus*, have been implicated as a common cause of both cystic fibrosis (CF) and non-CF bronchiectasis, the latter primarily in patients with severe asthma. The pathogenesis of mold-associated bronchiectasis is usually due to atopic sensitization to mold allergens in the presence of active chronic endobronchial fungal infection with host innate and adaptive immune deviation to a Th2-dominated inflammation, a condition known as allergic bronchopulmonary aspergillosis (ABPA) (or allergic bronchopulmonary mycosis if a non-*Aspergillus* mold is implicated). Diagnostic criteria of ABPA continue to evolve, while treatment relies upon downregulation of the allergic inflammatory response with immunomodulatory agents and antifungal pharmacotherapy.

Bronchiectasis is a pathologic condition, not a disease.^{1,2} It is defined by the clinical presence of chronic sputum production and the pathologic finding of inflamed, dilated airways. Diagnosis of bronchiectasis changed dramatically in the 1980s and 1990s when high-resolution computed tomography [HRCT] of the chest replaced bronchography and plain chest radiography in investigation of structural airway disease, becoming the diagnostic tool of choice.^{3–5} In recent years, primarily through studies employing chest HRCT, it has become increasingly understood that the condition of bronchiectasis can complicate common pre-existing lung diseases such as asthma, chronic bronchitis, and chronic obstructive pulmonary disease (COPD)^{6,7}; this, together with wider use of CT imaging, probably accounts for the rising incidence of bronchiectasis in the general population.⁸

Causation

Causation of bronchiectasis is often multifactorial and inapparent.⁹ Bronchiectasis appears to represent a final common

pathway of lung damage in situations where an inflammatory stimulus, usually due to infection or injury, is both persistent and contained to the airways and surrounding parenchyma. The host side of the equation lies in an initial vulnerability to chronic localized infection that retards or obstructs normal repair (e.g., in someone with preexisting structural damage from a prior infection or noninfectious insult, or someone with a disease predisposing to airway mucus stasis) often coincident with airway obstruction and some form of innate or adaptive host defense deficiency compromising normal mechanisms of airway secretion and microbial clearance—the “vicious cycle” model first proposed by Cole in 1986.¹⁰ This model has held up well.¹¹ Social development, geography, ethnicity, gender, age, and smoking history have important roles in the distribution of imputed causative and associated factors in the occurrence of bronchiectasis.¹² In addition, bronchiectasis uncommonly occurs as an isolated lung pathology but more typically it is accompanied by a variety of other structural abnormalities such as airway mucus plugging, air trapping, parenchymal infiltrates, nodules, atelectasis, and fibrosis.

The contribution of infection to bronchiectasis is well appreciated, but the identification of a specific pathogen as a causative agent is often obscure, and in addition the initiating infectious insult can be impossible to distinguish from subsequent rounds of apparently new infectious exacerbations.⁷ Most historical investigation has focused on aerobic bacterial pathogens easily detected using standard aerobic culture techniques: these demonstrate the common presence of *Haemophilus*, *Pseudomonas*, and *Streptococci* in bronchiectatic airways of non-cystic fibrosis (non-CF) patients, with *Staphylococcus aureus* and *Pseudomonas aeruginosa* playing a prominent role in CF. More recent studies have noted the emergence of nontuberculous mycobacteria (NTM) and fungi as potentially important contributors to bronchiectasis.^{12–14} Within the last decade, the emerging use of nonculture methods for detection of microbial DNA has led to a more nuanced appreciation of the wider diversity of polymicrobial infection in bronchiectasis with a mixed community of aerobic and anaerobic bacteria.^{15,16}

Fungi in Causation of Bronchiectasis

The particular role of fungi in bronchiectasis is at best incompletely understood, with the exception of a particular form of immune-mediated bronchiectasis, allergic bronchopulmonary mycosis (ABPM), the best known example of which is allergic bronchopulmonary aspergillosis (ABPA).¹⁷ Even in this instance, as will be discussed later, there are well-described cases of ABPA where bronchiectasis is not present. Few studies of bronchiectasis outside of asthma and CF have systematically examined the role of fungi, and the study of the mycobiomic contribution to the total microbiome of lung disease, still in its infancy, has to date only investigated CF.^{18–20} In general, pathogenesis of bronchiectasis due to fungal infection seems to occur when the host has a significant airway clearance defect allowing endobronchial fungal growth (i.e., localized airway infection) and a genetic predisposition to immune deviation toward a Th2-dominated response, a feature common to severe atopic asthma and CF.²¹

The Role of *Aspergillus fumigatus* in Fungal Bronchiectasis

Investigation of mold-associated bronchiectasis has focused almost entirely upon *Aspergillus fumigatus* [Af], a filamentous fungus whose dominance of ABPM appears a result of its unique repertoire of virulence factors and environmental adaptability.^{22,23} Af has been demonstrated as the causative agent in more than 90% of all fungal-associated ABPM, although a wide variety of other fungi have been reported (–Table 1).^{24,25} These relatively uncommon cases of ABPM due to non-*Aspergillus* fungi have displayed some interesting geographical clustering, for example, in Japan there appears to be a higher incidence of ABPM caused by *Schizophyllum commune* than elsewhere,²⁵ while in India there seems to be some predilection for *Candida albicans*.²⁴ In addition, there have been numerous case reports or small series published on non-*fumigatus* *Aspergillus* species (i.e., *A. terreus*, *A. niger*,

Table 1 Non-*Aspergillus fumigatus* fungi associated with allergic bronchopulmonary mycoses

Yeasts
<i>Candida albicans</i>
<i>Candida glabrata</i> (aka <i>Torulopsis</i>)
<i>Saccharomyces cerevisiae</i>
<i>Trichosporon beigeli</i>
Moulds
Ascomycota:
<i>Aspergillus</i> spp. (<i>A. niger</i> , <i>flavus</i> , <i>terreus</i> , <i>nidulans</i> , <i>oryzae</i> , <i>glaucus</i> , <i>ochraceus</i>)
<i>Bipolaris</i> spp. (<i>B. hawaiiensis</i> , <i>australensis</i> , <i>spicifera</i>)
<i>Curvularia</i> spp. (<i>C. lunata</i> , <i>senegalensis</i>)
<i>Scedosporium apiospermum</i> (aka <i>Pseudallescheria boydii</i> species complex)
<i>Penicillium</i> spp.
<i>Alternaria alternata</i>
<i>Fusarium vasinfectum</i>
<i>Cladosporium cladosporioides</i>
<i>Stemphylium</i> spp.
<i>Paecilomyces</i> spp.
<i>Geotrichum candidum</i>
<i>Helminthosporium</i> spp.
<i>Cochliobolus hawaiiensis</i> (aka <i>Bipolaris</i> , <i>Drechslera</i>)
Basidiomycota:
<i>Schizophyllum commune</i>
Mucoromycotina:
<i>Rhizopus oryzae</i>

A. flavus, *A. ochraceus*) causing ABPM.^{24–37} There have also been documented cases of occupational ABPA due to *A. fumigatus* in compost workers in the United Kingdom and due to *A. oryzae* in workers in the soy food industry in Japan.^{38–41} A suggestion of a higher proportion of patients with ABPM without underlying asthma in these non-*A. fumigatus* ABPM cases needs to be interpreted cautiously, as the diagnostic evaluations in many cases were incomplete and the case ascertainment appears subject to bias with respect to a lack of investigation of the local asthma population.²⁴ Based on the overwhelming predominance and importance of *A. fumigatus* in causing bronchiectasis due to ABPM, the remainder of this article will focus upon recent developments in pathogenic mechanisms, clinical manifestations, diagnosis, and treatment of ABPA proper.

Cystic Fibrosis Transmembrane Conductance Regulator, *Aspergillus* and Bronchiectasis

The role of cystic fibrosis transmembrane conductance regulator (CFTR) dysfunction in the pathogenesis of bronchiectasis has emerged as an area of considerable interest, as the clear

conventional distinction between CF and non-CF bronchiectasis is blurred by the findings of frequent CFTR mutations or CF-like respiratory epithelial ion transport abnormalities in people with bronchiectasis who lack criteria for a formal CF diagnosis.^{42,43} In one such study, CFTR mutations or abnormal CFTR function were found in 66% of 72 patients with chronic sinopulmonary disease of unknown origin; 83% of these patients whose evaluation included HRCT had bronchiectasis.⁴⁴ This is important because an innate defense role for CFTR against airway Af infection, deranged in CF, has been shown,⁴⁵ and an apparent causal link between CFTR dysfunction and a Th2-dominated proinflammatory immune response to Af airway challenge has been repeatedly found in murine models of CF.^{46–48}

Pathogenesis of Allergic Bronchopulmonary Aspergillosis in CF

Clinically, current concepts regarding the pathogenesis of ABPA as the major example of immune-mediated fungal bronchiectasis posit innate immune defects in CF predisposing the host to immune deviation and Th2-dominated inflammation leading to the development of fungal bronchiectasis.^{49–51} However, in addition to numerous host genetically determined susceptibility factors such as CFTR genotype,¹⁷ the role of the fungal pathogen is also implicated in the pathogenesis of ABPA, at least in CF, by infecting strains genetically dominated by *A. fumigatus sensu stricto* species.⁵² Thus, people with CF form one important group susceptible to ABPA partly on the basis of CFTR dysfunction. A recent study, using single-center patient data generated from a novel diagnostic algorithm developed at the University of Manchester in the United Kingdom,⁵³ and applying this to available CF registries, projected a population of approximately 5,500 adult CF patients with ABPA (i.e., 18% of the adult CF population) in those countries—far in excess of actual reported cases in almost all of those registries.⁵⁴ Fungal infection with Af thus appears to substantially contribute to CF bronchiectasis through a CFTR-dependent pathway that phenotypically manifests as a badly dysregulated allergic response and which, incidentally, is greatly underdiagnosed. Several studies have linked allergic responses to Af in CF to accelerate decline in lung function compared with nonsensitized CF patients.^{55–60} Progression from atopic sensitization to Af (i.e., demonstration of immediate skin test reactivity and/or elevated blood Af-specific IgE antibodies) to full-blown clinical ABPA is associated with further acceleration of lung disease progression.^{53,61}

It is possible that non-Af molds found in respiratory secretions of some patients with CF, such as *Scedosporium apiospermum* and *Exophiala dermatitidis*, may also produce a similar syndrome of sensitization and potential progression to ABPM, although this has not been demonstrated to date.^{62–64} While both *Scedosporium* and *Exophiala* have been described in cases of non-CF bronchiectasis, available evidence suggests this may be a secondary saprophytic process occurring in cavitation produced from previously injured airways.^{65–69}

Fungal-associated allergic bronchiectasis probably occurs as a later exacerbating factor in the overall pathogenesis of CF bronchiectasis, which starts early in life, is associated with a hyperinflammatory response to a broad array of inhaled or aspirated microbial pathogens (especially *P. aeruginosa*), and for which onset is predicted in early infancy by elevation of free neutrophil elastase activity in airway lining fluid.^{70–73} The finding of a complex microbiota containing bacterial, fungal, and viral elements supports the polymicrobial origin and nature of bronchiectasis in CF in which dysfunctional CFTR linked to chronic inflammation is paramount and in which exacerbations or accelerated disease progression may be due to bacterial, fungal, or viral infection.^{18–20,74,75} Although fungi have not yet been specifically investigated with respect to early onset of CF bronchiectasis, it is notable that the Australian AREST CF consortium recently noted that recovery of Af in bronchoalveolar lavage fluid of children with CF younger than 2 years (13% of their birth cohort) was an independent predictor of lower spirometric pulmonary function at ages 4 to 8 years.⁷⁶ In older CF patients, the persistent recovery of Af has been specifically linked to more severe bronchiectasis on HRCT, suggesting a unique contribution to inflammatory remodeling by Af colonization.⁷⁷ This comports with the in vitro data demonstrating the potency of Af as a proinflammatory stimulus to CF respiratory epithelial cells.^{45,78}

Aspergillus and Non-CF Bronchiectasis

In somewhat of a contrast to the picture in CF, the occurrence of non-CF bronchiectasis is generally associated with more discrete and restricted microbial pathogens, at least as assessed by conventional cultures. In children, *Haemophilus influenzae* was found to be the dominant early pathogen recovered by bronchoalveolar lavage soon after diagnosis; although a variety of other pathogens were recovered, fungi were not among them.⁷⁹ The occurrence of bronchiectasis in asthma is generally uncommon and limited to one or two lobes.^{80,81} However, it is much more prevalent when specifically associated with fungal infection (usually but not solely with *A. fumigatus*) and allergic responses to molds in patients with asthma.^{21,80–84} Moreover, bronchiectasis in asthma appears mostly restricted to patients with severe asthma.^{85–87} Here, the contributing factors appear to focus on the role of host atopy and unique virulence capabilities of Af when an allergic host with poorly controlled asthma develops localized endobronchial Af colonization and infection. In one study, 42% of asthmatics had bronchiectasis with a strong trend to higher incidence of bronchiectasis if fungal cultures were positive,⁸⁶ while in another study bronchiectasis was present in 68% of asthmatics sensitized to Af compared with 35% of nonsensitized asthmatics, a significant difference.⁸³

What virulence factors in Af may contribute to development of bronchiectasis in the susceptible host? Many candidates with plausible biologic activity have been identified. Some are widely shared with other organisms, such as chitin, a critical cell wall component of filamentous fungi including Af, which can induce eosinophilic pulmonary inflammation,^{88,89} other

cell wall components such as β -glucan,⁹⁰ and exoproducts such as gliotoxin that exert cyto- and ciliotoxic activity.^{23,91} Although Af conidia are immunologically inert,⁹² they can be internalized by airway epithelial cells, triggering an innate inflammatory response.⁹³ Moreover, if conditions prevent normal rapid clearance of conidia by airway macrophages,⁹⁴ germination of Af conidia and subsequent hyphal growth in the airways trigger a complex interaction between distinct Af hyphal moieties and human respiratory epithelial, dendritic, and phagocyte cell and soluble pattern recognition receptors including C-type lectin and Toll-like receptors.^{51,95–97} These interactions play a key role in initiating innate inflammatory responses and adaptive immune deviation to a Th2-dominant response in genetically susceptible hosts.^{50,98,99} As efficient immunity to Af relies on a Th1-dominant response,¹⁰⁰ a deviation to Th2 dominance results in faulty clearance and sustained granulocytic inflammation with eosinophil and neutrophil influx allowing evolution of airway remodeling into ultimate development of bronchiectasis.^{101–103} A clinical association of Th2-dominant allergic respiratory disease with airway fungal colonization does not prove causality of the latter for the former but does support the likelihood of a directly pathogenic role.¹⁰⁴ A recent in vitro study of human bronchial epithelial cells challenged with Af found a dose-dependent suppression of interferon signaling, offering one potential path for skewing the immune response to Th2¹⁰⁵; this provides an additional mechanism to those found in earlier studies implicating epithelial and dendritic cell Th2-skewing chemokine response pathways.^{50,98,106}

Fungal proteases are strong candidates for a causal role in the evolution of fungal bronchiectasis. During hyphal growth Af and other filamentous fungi produce abundant secreted proteases. Various animal models and in vitro studies with human airway cells demonstrate profound proinflammatory cytokine responses when challenged with Af proteases, which is in part dependent on epithelial protease-activated receptor signaling.^{107–110} Many of the two dozen or so cloned Af allergens are proteases.^{14,85} A murine Af chronic challenge model with recombinant fungal serine protease or metalloprotease resulted in Th2 inflammation, airway hyperreactivity, and prominent airway remodeling.¹¹¹ In addition, as mucus impaction is together with bronchiectasis, a major radiographic finding in ABPA,^{112,113} it is noteworthy that Af protease activity induces strong mucin and MUC5AC production in human bronchial epithelial cells.¹¹⁴ Earlier, clinical bronchiectasis sputum was shown ex vivo to have similar mucus secretagogue activity,¹¹⁵ and while the majority of this activity was attributed to neutrophil elastase, it is plausible that Af proteases contribute to this effect in cases of bronchiectasis associated with Af infection and allergy.

In addition to pathogen-related virulence factors, development of fungal bronchiectasis in the setting of ABPM is likely facilitated by host factors in driving Th2-dominated responses. An expanding number of host genetic susceptibility factors identified with increased risk of developing ABPA/ABPM include a large number of innate immune system molecular polymorphisms.¹⁷ We may speculate that different distributions of these polymorphisms in different ethnicities

and geographic regions may explain some of the variability in rates of ABPM disease found in the literature.^{54,116}

Polymicrobial Infection, Disease Spectrum, and Fungal Bronchiectasis

Beyond Af or other fungal pathogens and the susceptible host, a third factor that adds yet more complexity to the occurrence of fungal bronchiectasis is the role of other, nonfungal, pathogens.¹¹⁷ It has been well established that underlying tuberculosis, for example, can lead to development of aspergilloma and chronic pulmonary aspergillosis, presumably due to initial tuberculous cavitory structural damage that facilitates fungal colonization and infection.^{118,119} Tuberculosis can also lead to Af sensitization and ABPA in the susceptible host.¹²⁰ With increasing rates of NTM pulmonary infection including bronchiectasis,^{13,121} it has now also been recognized that NTM lung disease is another predisposing condition to development of ABPA and fungal bronchiectasis. In a case-control study of 30 patients with NTM and non-CF bronchiectasis, positive Af serology and radiographic features of Af-associated pulmonary diseases were more commonly found in NTM than in control cases.¹²² In CF patients, there is also an association between ABPA and recovery of Af and NTM from respiratory cultures.^{123,124} As more is learned about the pulmonary microbiome in CF and non-CF bronchiectasis, it seems likely that the complexity of polymicrobial infection will be increasingly appreciated and how these microbes interact for good, ill, or indifference in the host will eventually be unraveled.¹²⁵

Diagnosis and Treatment

In this article, I have placed fungal bronchiectasis mainly into the diagnostic entity of ABPA/ABPM. However, it is important to always keep in mind the essential truth that distinct nosologic Af-related lung disease entities actually exist along a spectrum of structural and functional pulmonary derangements due to infection and/or allergy; this presents a diagnostic difficulty that has been recognized for over 30 years.^{126,127} A single patient may evolve over time from one *Aspergillus*-associated disease to another, or simultaneously may exhibit several such diseases.^{127–130} This can create considerable confusion. For example, patients may exhibit serologic signs and clinical symptoms of ABPA but not have developed bronchiectasis on HRCT; this condition is termed allergic bronchopulmonary aspergillosis-serologic (ABPA-S).^{131–133} It is unclear whether ABPA-S represents an earlier detection of ABPA whose natural history is progression to bronchiectasis or perhaps a milder self-limited disease, and therefore whether ABPA treatment is needed or effective in the prevention of bronchiectasis in such patients. On the other side of the ABPA spectrum, certain HRCT radiographic features of ABPA such as hyperattenuating mucoid impaction (seen in 20–25% of ABPA) appear to represent a more aggressive disease with a more intense allergic response and a greater propensity to relapse.¹¹² In addition, occurrence of ABPA and fungal bronchiectasis may precede, follow, or be

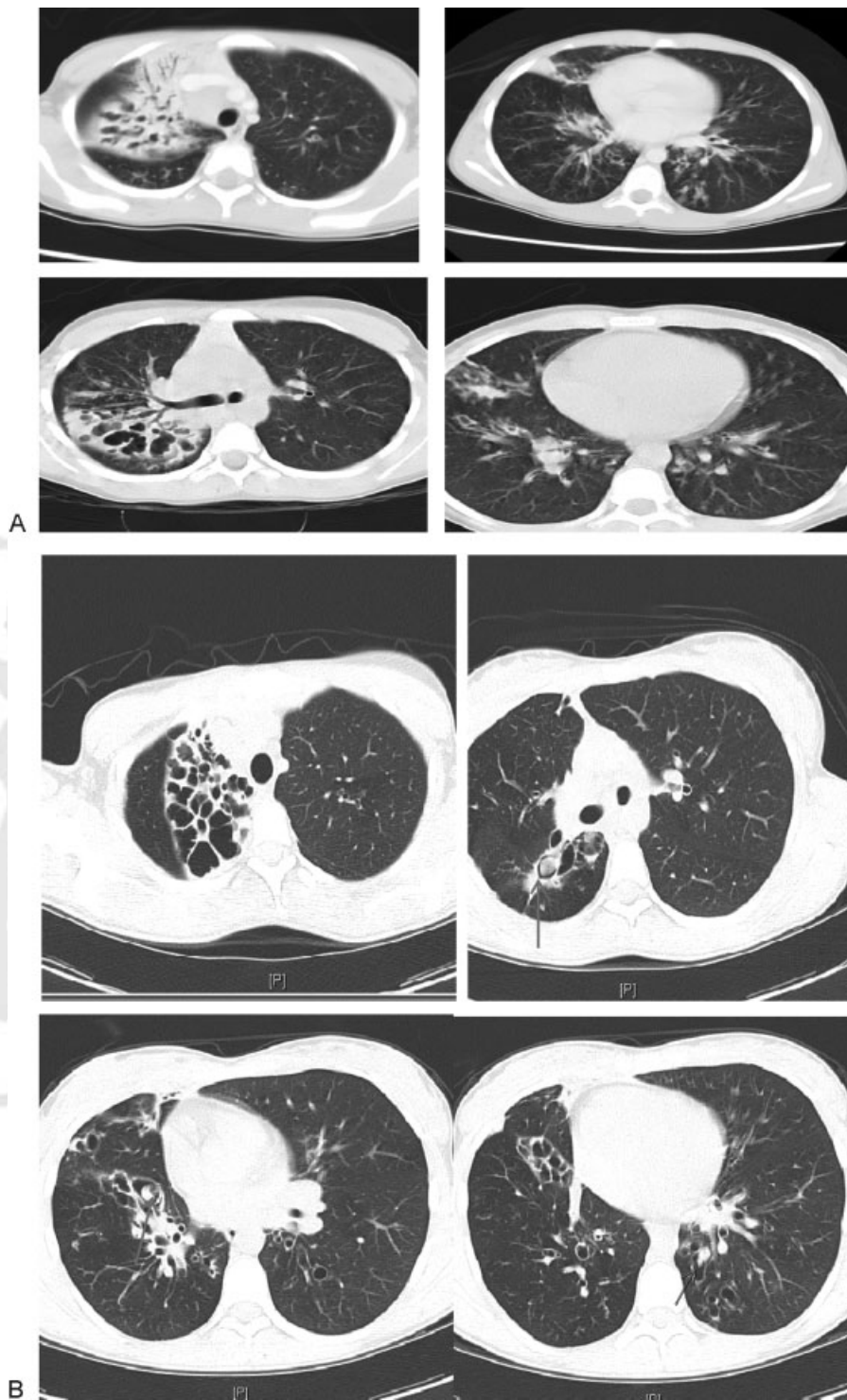


Fig. 1 Evolution of chest HRCT findings in a child with cystic fibrosis, *Aspergillus* bronchiectasis and several *Aspergillus*-associated lung diseases occurring concomitantly. (A) *Top*: Upon diagnosis of cystic fibrosis at the age of 6 years, this patient's bronchoscopic cultures grew mucoid *P. aeruginosa* but no fungus from bronchoalveolar lavage and transbronchial biopsy samples. Chest CT at diagnosis shows lymphadenopathy, bronchiectasis, and atelectasis. *Bottom*: Follow-up CT 3 years later shows marked progression of right upper lobe bronchiectasis as well as multilobar mucoid impaction. Expanding cavitation with surrounding infiltrate suggests chronic pulmonary aspergillosis. Culture was now positive for *A. fumigatus*. Voriconazole was initiated. (B) *Top*: Criteria for diagnosis of ABPA were met 2 years later. Right-sided bronchiectasis and cavitation has progressed. Now a presumptive aspergilloma can be seen (arrow). The patient was treated with a 3-month course of prednisone (successfully tapered and discontinued) along with ongoing voriconazole. *Bottom*: Further CT slices from same study show multiple aspergillomas bilaterally (arrows). Inhaled amphotericin B was added to the chronic treatment program and caspofungin was added when hospitalized for exacerbations. The patient, now a mid-teenager, has been stable over the subsequent 4 years but continues to be culture positive for *A. fumigatus* and remains on voriconazole.

Table 2 Criteria for diagnosis of allergic bronchopulmonary aspergillosis

Predisposing conditions
• Asthma or cystic fibrosis
Obligatory criteria (both present)
• Total baseline serum IgE >1,000 IU/mL ^a
• Positive immediate hypersensitivity skin test or elevated in vitro specific IgE to <i>Aspergillus fumigatus</i>
Supportive criteria (≥ 2 present)
• Eosinophilia > 500 cells/μL ^b
• Serum precipitating or IgG antibodies to <i>Aspergillus fumigatus</i>
• Consistent radiographic opacities ^c

Note: A positive respiratory culture or DNA test for *Aspergillus fumigatus* is supportive but not necessary for the diagnosis of ABPA.

Source: Adapted from Agarwal et al¹⁷ and Moss.²¹

^aIf all other criteria met, IgE < 1,000 IU/mL may be acceptable.

^bSteroid naive or historical.

^cTransient (consolidation, nodules, tram-track, finger-in-glove) or permanent (bronchiectasis, fibrosis) pulmonary opacities.

coincident with other nonallergic forms of pulmonary aspergillosis, including *Aspergillus* bronchitis, chronic pulmonary aspergillosis, aspergilloma, and (rarely) invasive pulmonary aspergillosis (► Fig. 1).^{127–130,134–139}

Classic criteria for diagnosis of ABPA were developed in the context of asthma. With recognition of the importance of the disease in patients with CF, diagnostic modifications were made to account for overlap between manifestations of ABPA and underlying CF, such as shared features of bronchiectasis and allergic responses to infection with Af.¹⁴⁰ Recently, a working group of the International Society for Human and Animal Mycology (ISHAM) proposed a unifying revision of diagnostic criteria for ABPA after critical review of the global literature (► Table 2).^{17,21} Even so, the ISHAM working group report acknowledged that uncertainties regarding optimal cutoffs for levels of various serological tests and interpretation of radiographic abnormalities are likely to require further refinements, as diagnostic tests are standardized and applied in different populations.^{53,141–143} At present, a uniform diagnostic algorithm is recommended to increase case ascertainment and initiate treatment as early as possible (► Fig. 2).

Treatment of fungal bronchiectasis, occurring as it almost always does in the context of allergic inflammation, has for decades relied upon immunomodulation of Th2 disease with systemic corticosteroids, and recently on increasing use of the humanized monoclonal anti-IgE antibody omalizumab, which allows steroid sparing while reducing relapses.^{21,144–149} Although both of these therapies lack the evidence of randomized controlled trials, both approaches have accumulated much empirical albeit uncontrolled reports of efficacy.^{21,144,150} Due mainly to concerns about steroid toxicity and dependence, and also to accumulating evidence of the underlying presence of chronic endobronchial fungal infection, antifungal agents have been added to immunomodulation as second tier agents. Both oral triazoles with anti-Af activity (itraconazole, voriconazole, and posaconazole) and amphotericin B delivered by nebulization have

been successfully employed, although the evidence base is not robust.^{150–154} Finally, elimination of avoidable environmental exposure may be of benefit when feasible.

Many questions remain. A task force of the European Academy of Allergy and Clinical Immunology has recently published a summary of the current understanding of fungal allergy in asthma, identifying large knowledge gaps regarding the complex relationships between fungal infection, allergy, polymicrobial infection, environmental and host risk factors, and diagnostic and therapeutic approaches.¹⁵⁵ This serves as a sobering reminder of our current ignorance and a good introduction to the substantial research program required to better recognize and treat fungal allergic respiratory disease, including one of its most serious consequences, bronchiectasis.

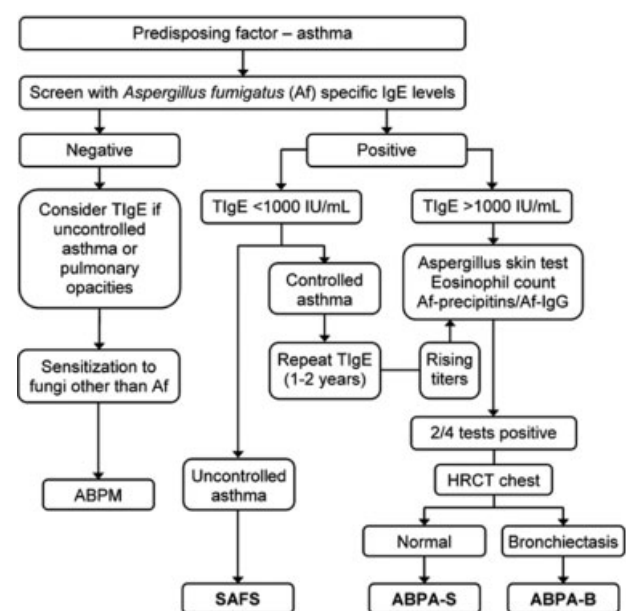


Fig. 2 Diagnostic algorithm for allergic bronchopulmonary aspergillosis.¹⁷

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