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Pulmonary and sinus fungal diseases in non-immunocompromised patients

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The human respiratory tract is exposed daily to airborne fungi, fungal enzymes, and secondary metabolites. The endemic fungi *Histoplasma capsulatum*, *Coccidioides* spp, *Blastomyces dermatitidis*, and *Paracoccidioides brasiliensis*, and occasionally *Aspergillus fumigatus*, are primary pulmonary pathogens of otherwise healthy people. Such infections resolve in most people, and only a few infections lead to disease. However, many fungi are directly allergenic by colonising the respiratory tract or indirectly through contact with cell wall constituents and proteases, causing or exacerbating allergic disease. Increasing evidence implicates high indoor fungal exposures as a precipitant of asthma in children and in worsening asthma symptoms. Lung or airways infection by endemic fungi or aspergillus can be diagnosed with respiratory sample culture or serum IgG testing. Sputum, induced sputum, or bronchial specimens are all suitable specimens for detecting fungi; microscopy, fungal culture, galactomannan antigen, and aspergillus PCR are useful tests. Antifungal treatment is indicated in almost all patients with chronic cavitary pulmonary infections, chronic invasive and granulomatous rhinosinusitis, and aspergillus bronchitis. Most patients with fungal asthma benefit from antifungal therapy. Adverse reactions to oral azoles, drug interactions, and azole resistance in *Aspergillus* spp limit therapy. Environmental exposures, genetic factors, and structural pulmonary risk factors probably underlie disease but are poorly understood.

Introduction

Different species of fungi are inhaled; some are capable of surviving at body temperature and evading the host defences of healthy individuals. A very small number of the fungi that cause pulmonary infection are true pathogens—the most notable are those pathogens that cause endemic mycoses: *Coccidioides* spp, *Histoplasma* spp, *Blastomyces dermatitidis*, and *Paracoccidioides brasiliensis*. Other pathogens, such as *Aspergillus* spp and *Cryptococcus* spp, can overwhelm innate defences when inhaled in substantial quantities or when patients have defects in the innate immunity. Most of these defects are subtle and poorly understood.

In this Series paper, we introduce the common fungal diseases of the upper and lower airways in non-immunocompromised patients, their prevalence, the clinical and radiological presentation, the mode of diagnosis, and therapy options (figure 1). Rare manifestations of these infections are not addressed in depth. We also explore some less well understood issues about the presentation of fungal exposure in buildings or through occupation.

Fungal rhinosinusitis

Fungal rhinosinusitis is now more commonly recognised and is somewhat controversially separated into different phenotypes, each with a separate treatment strategy. About 10% of the adult population has chronic rhinosinusitis, a proportion of which are various types of fungal rhinosinusitis, which means that many millions of people are affected. A dysfunctional interplay between the human host and fungi at the nasal and sinus mucosa results in a wide range of clinical presentations.

Fungal rhinosinusitis can be classified into four broad clinical presentations: immunocompromised, an acute invasive phenotype with fulminant course; mild or no discernible impairment of immunity, a chronic invasive or granulomatous phenotype with a chronic course; colonisation of nasal passage and sinus, a fungal ball phenotype with a chronic course; and atopic or genetic susceptible host, eosinophil-related fungal rhinosinusitis including allergic fungal rhinosinusitis with chronic or occasionally acute course. Fungi can be present on nasal mucosa of any healthy person and invade the mucous membrane in immunocompromised patients and patients with chronic invasive disease.

Chronic invasive or granulomatous fungal rhinosinusitis

Whether chronic invasive rhinosinusitis and granulomatous fungal rhinosinusitis are separate diseases or different presentations of the same phenotype is unclear. Chronic invasive fungal rhinosinusitis is seen worldwide in patients with diabetes or who are on steroid therapy, whereas the granulomatous type is seen in apparently healthy people in a geographically confined region between Sudan and India. Abundant hyphae with mixed inflammation and isolation of *Aspergillus fumigatus* are hallmarks of chronic invasive fungal rhinosinusitis. Dematiaceous fungi, including *Alternaria* spp and *Curvularia* spp, are occasionally isolated. In granulomatous fungal rhinosinusitis, *Aspergillus flavus* is the most common species indicated, and hyphae are sparse in tissue and usually present inside giant cells. Both diseases have a chronic course with marked orbital involvement. Diagnosis is established by histopathology...
of endoscopically removed samples and culture. IgG antibodies to aspergillus or precipitins can be useful in monitoring therapy. Management consists of surgical debridement, preferably endoscopically, and antifungal therapy. Amphotericin B, itraconazole, or voriconazole for 6–12 weeks are effective post-debridement.

Fungal ball

Fungi colonise the sinus mucosa and produce a dense conglomeration of hyphae in one sinus cavity, most typically the maxillary sinus but occasionally the sphenoid sinus. The disease occurs worldwide but is most prevalent in elderly women in southern France. Management consists of endoscopic removal. Antifungal therapy is not necessary for maxillary fungal ball but can be advisable post-operatively for patients with disease in the sphenoid sinus.

Allergic fungal rhinosinusitis

Akin to allergic bronchopulmonary aspergillosis, a profound Th2 lymphocyte response with eosinophilic mucin in the sinus is the hallmark of allergic fungal rhinosinusitis. Allergic fungal rhinosinusitis is prevalent in arid and tropical regions of the world. The prevalence in north India is reported to be 110 patients per 100 000 population during the wheat-thrashing season (March to April). In Israel, a prevalence of up to 500 patients per 100 000 population has been reported. Allergic fungal rhinosinusitis and allergic bronchopulmonary aspergillosis can co-occur in the same patient.

Patients present with symptoms of chronic sinusitis, which might include facial pressure, headache, nasal stuffiness, and discharge. Patients often have a history of multiple surgeries and incomplete responses to antibacterial therapy; allergic fungal rhinosinusitis should be suspected in intractable sinusitis with nasal polyposis. Some patients present with proptosis. CT scans of the sinuses will reveal opacification with concretions or calcifications, or both. Positive type 1 hypersensitivity is common, and the presence of eosinophilic mucin containing fungal hyphae is diagnostic. Dematiaceous fungi including Alternaria, Bipolaris, and Curvularia spp are often isolated from patients in developed countries. By contrast, A flavus is isolated from patients in south Asia, the Middle East, and Sudan.

The cornerstones of infection management are removal of nasal polyps combined with topical corticosteroids immediately after surgery, short-term antibiotic therapy for concurrent bacterial infection (notably for Staphylococcus aureus), and nasal irrigation with saline. Relapse is common but can be prevented, in part, by long-term nasal steroids and saline. In double-blind, placebo-controlled studies, local and systemic antifungal agents have been shown to have limited benefit—the benefit is in relapsing cases (ie, preventing relapse). Some patients benefit from a salicylate-free diet.

Community-acquired aspergillus pneumonia

Massive exposures to aspergillus conidia can overwhelm the innate immunity of the lung and cause acute disease. Low levels of exposure after influenza, a history of
lung disease, chronic obstructive pulmonary disease, and corticosteroid therapy also predispose patients to community-acquired aspergillus pneumonia. An acute or subacute onset is typical. Chest imaging will reveal a miliary, bilateral diffuse pattern or unilateral, upper lobe cavitary disease. Aspergillus spp can be isolated from respiratory tract specimens, and galactomannan is detectable in bronchoscopic fluid. IgG antibodies to aspergillus become detectable, but the time course is uncertain. Outcome is poor in patients with concurrent viral infection and who are taking corticosteroids. Other patients will either have complete resolution or develop chronic pulmonary aspergillosis. Antifungal therapy is advised, with corticosteroids in bilateral diffuse disease, but data are scant.

**Chronic pulmonary aspergillosis**

Chronic pulmonary aspergillosis is a challenging disorder, complicating several respiratory diseases. The global burden is estimated at about 3 million people, of whom about 1-2 million have had pulmonary tuberculosis. These patients are not immunocompromised but have a history of lung defects (table 1). Chronic pulmonary aspergillosis progresses slowly, and by convention, will have been present for at least 3 months before diagnosis. Most patients with chronic pulmonary aspergillosis are men aged 50–75 years (60%) with long-standing constitutional symptoms of profound fatigue and weight loss, pulmonary symptoms of productive cough, haemoptysis of variable degree, chest discomfort, and shortness of breath. Imaging reveals at least one cavity, which can be small or large, thick or thin-walled. Most often, the cavity appears with or without an aspergilloma (conglomerates of fungal hyphae as biofilm within pulmonary cavities) or with solid or cavitating nodules (table 2). Occasionally, a large mass lesion or extensive consolidation with limited air spaces will have appeared (figure 2). Pleural thickening is a characteristic feature of chronic pulmonary aspergillosis but not universal. Patients often have recurrent infections with *Streptococcus pneumoniae* or *Haemophilus influenzae*. Differential diagnosis includes the other fungal pathogens discussed in this Review, as well as tuberculosis, non-tuberculous mycobacterial infection, and lung carcinoma.

Subacute invasive pulmonary aspergillosis (previously known as chronic necrotising pulmonary aspergillosis) develops in 4–12 weeks, usually affects moderately immunocompromised patients, and should be managed as invasive aspergillosis.

The key diagnostic test for chronic pulmonary aspergillosis is the detection of IgG to aspergillus (or the less sensitive precipitins), which is detectable in more than 90% of patients with cavitary disease but only in about 60% of patients with aspergillus nodules. Almost all patients show an increased production of inflammatory markers. Positive PCR or culture of aspergillus or the detection of galactomannan in respiratory samples is supportive evidence if the radiological findings are typical. Some patients have increased production of total IgE or IgE to aspergillus but might not have asthma or allergic bronchopulmonary aspergillosis.

Simple aspergillomas should be resected, if possible, preferably with the video-assisted thoracic surgery technique. Surgery might be necessary in complex cases, such as patients with haemoptysis.
unresponsive unilateral disease, or azole resistance. Each patient should be carefully risk assessed, as summarised by Farid and colleagues.44

Long-term oral antifungal therapy is recommended for most patients (table 3).45,46 The objectives of therapy are to minimise symptoms,46 notably cough, sputum production, fatigue, weight loss, and risk of haemoptysis. Antifungal therapy does not improve breathlessness appreciably unless the patient is very deconditioned and can exercise more; pulmonary rehabilitation might be helpful. Follow-up without therapy is recommended for patients with resected Aspergillus spp nodules and for patients with minimal symptoms and no radiological progression in several months.

Haemoptysis can be controlled with tranexamic acid and bronchial artery embolisation; surgical resection is usually unnecessary. Haemoptysis can be a sign of therapeutic failure or antifungal resistance, or both. Acquired azole resistance can develop, as is more likely, during prolonged therapy (especially in patients for whom inadequate dosing or drug bioavailability leads to suboptimum serum concentrations of azole), poor compliance, and high burden of infection. These patients might need intermittent or long-term intravenous therapy.47

Pulmonary histoplasmosis

Histoplasmosis has three main pulmonary manifestations: acute disease after substantial exposure to Histoplasma capsulatum (especially after cave explorations), chronic cavitary diseases in immunocompetent people, and disseminated disease in immunocompromised people (figure 1). Most exposures are subclinical and leave small calcified granulomata in the lungs or spleen.

Acute pulmonary histoplasmosis appears a few days after a point exposure. The diagnosis is usually made clinically, with consolidation on chest radiograph.48 Serological diagnosis is based on histoplasma antigen or antibody (especially antibody seroconversion), or both.49

The annual incidence of symptomless infections can only be estimated by skin test conversion and varies substantially by geography. For example, in Mexico, the number of people who had a positive skin test varied from 11.2 to 56.2 million of the estimated 112 million population (based on a 2010 census).46 Primary infection, with or without symptoms, appears to confer some immunity from re-infection, unless the patient is profoundly immunocompromised.

Chronic cavitary pulmonary histoplasmosis is uncommon. Cavitation is most common in patients with emphysema and can, initially, represent focal areas of consolidation surrounding bullae.45 Disease is usually bilateral, involving the upper lobes. Patients present with productive cough, increasing shortness of breath, weight loss, night sweats, and sometimes fever that has lasted many months or years. Chest radiographs show gradually expanding cavities that progress to local fibrosis.44 For more than 90% of patients, respiratory samples usually yield a positive culture for H capsulatum and IgG antibody is detectable in serum.46 Histoplasma is a class 3 pathogen, so the laboratory should be prepared to handle this fungus safely. Long-term itraconazole therapy is advised (table 3).45,46 Fibrosing mediastinitis and airway-obstructing lymphadenopathy are rare complications, typically without concurrent pulmonary disease.

Pulmonary coccidioidomycosis

Coccidioidomycosis is caused by Coccidioides immitis or Coccidioides posadasii, which exist in the environment in southwestern USA, northern Mexico, and in geographical pockets throughout Central America and South America.1 In the USA, about 60% of cases occur in Arizona, but sporadic, imported cases are reported across the world. Infection follows inhalation of one or more arthroconidia.

Infection is asymptomatic in about 60% of cases.3 However, primary infection, often referred to as Valley Fever, presents as influenza-like symptoms, which include fever, chest pain, cough, or weight loss, and is sometimes associated with erythema nodosum or erythema multiforme (figure 1). Discrete nodules in the lower lobes or consolidation can occur.50 Primary pulmonary coccidioidomycosis can be severe with a prolonged, debilitating course. About 90% of patients have detectable IgM antibody within 2 weeks of illness. Primary coccidioidomycosis either resolves or progresses to chronic and progressive pulmonary disease. Dissemination can lead to meningitis or skin, bone, or lymph node disease.

Patients with chronic pulmonary coccidioidomycosis present with persistent cough, weight loss, and malaise. Patients usually have a single, thin-walled cavity, but some patients can have enlarging or multiplying nodules or cavities.50 Cavitary pulmonary disease usually yields a positive sputum or bronchoalveolar lavage culture.44

Figure 2: CT of moderate emphysema and a thin-walled right upper lobe cavity containing intra-cavitary material and irregular wall laterally, with pleural thickening
High titre IgG antibodies to Aspergillus fumigatus were found.
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A specific manifestation of coccidioidomycosis is the pulmonary nodule, which is usually single, asymptomatic, and benign (table 2). Radiologically, the nodules do not resemble carcinoma but are usually removed from patients living in non-endemic areas because only histological confirmation minimises anxiety about the diagnosis.

*Coccidioides* spp are classified as class 3 pathogens, so laboratories should be have the appropriate facilities. The fungus is white on agar and produces infectious arthroconidia (rectangular microscopic structures). Tissue can contain spherules, which are large, thick walled circular structures containing endospores. The complement fixation test for IgG antibodies is the usual diagnostic test for chronic pulmonary coccidioidomycosis since the titre correlates with the severity of disease and decreases with successful therapy.

Primary coccidioidomycosis is usually treated symptomatically; itraconazole or fluconazole can shorten the duration of disease, but do not affect relapse. Antifungal therapy is not necessary for pulmonary nodules, whereas prolonged antifungal therapy is necessary for chronic cavitary pulmonary coccidioidomycosis (table 3), and relapse is reported even after 1 year of therapy. No convincing data exist to support the use of any one particular azole, and echinocandins are ineffective. Severe disease is treated with amphotericin B. Relapse is more likely if the antibody titre in the complement fixation test is greater than 1/256. Long-term azole therapy is appropriate if relapse occurs.

**Pulmonary paracoccidioidomycosis**

Paracoccidioidomycosis occurs in certain areas of Central America and South America. About 3500 new cases occur in Brazil each year. The dimorphic fungus *Paracoccidioides brasiliensis* is acquired through inhalation. Initial infection is usually subclinical; poorly understood factors or immunosuppression allow reactivation.

A rare manifestation of paracoccidioidomycosis in patients younger than 30 years is acute, progressive infection (figure 1). This so-called juvenile form of disease is characterised in the lung by adenopathy, unilateral pleural effusion, and miliary-like shadows. Disseminated infection to other organs is typical, and untreated cases could be fatal.

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**Table 2: Therapies for pulmonary fungal disease in non-immunocompromised patients**

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Initial therapy</th>
<th>Duration</th>
<th>Alternative therapy</th>
<th>Cautions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic pulmonary aspergillosis</td>
<td>Surgical resection</td>
<td>...</td>
<td>None</td>
<td>Sufficient respiratory reserve, relapse is possible</td>
</tr>
<tr>
<td>Aspergillus nodule</td>
<td>None if asymptomatic</td>
<td>...</td>
<td>Azole therapy if progressive</td>
<td>If multiple, continued imaging and possibly repeat biopsy if progressive</td>
</tr>
<tr>
<td>Chronic cavity and fibrosis</td>
<td>Itraconazole or voriconazole</td>
<td>&gt;6 months, typically long term</td>
<td>Posaconazole, liposomal amphotericin B (about 3 mg/kg), micafungin</td>
<td>Drug interactions, especially rifampicin; long-term toxicity include peripheral neuropathy and skin photosensitivity (voriconazole)</td>
</tr>
<tr>
<td>Histoplasmosis</td>
<td>None</td>
<td>...</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Acute pulmonary</td>
<td>None if minor symptoms</td>
<td>...</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Acute pulmonary</td>
<td>Liposomal amphotericin B, itraconazole</td>
<td>1-3 months</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Chronic cavity</td>
<td>Itraconazole</td>
<td>12-24 months</td>
<td>Posaconazole</td>
<td></td>
</tr>
<tr>
<td>Coccidioidomycosis</td>
<td>None</td>
<td>...</td>
<td>Fluconazole, itraconazole (2 months)</td>
<td>Not of proven value but might be helpful in severe cases, no effect on relapse</td>
</tr>
<tr>
<td>Coccidioidomycosis nodule</td>
<td>None</td>
<td>...</td>
<td>Posaconazole, liposomal amphotericin B</td>
<td>Relapse risk about 50%</td>
</tr>
<tr>
<td>Chronic pulmonary</td>
<td>Fluconazole, itraconazole</td>
<td>12 months</td>
<td>Posaconazole, liposomal amphotericin B</td>
<td>Relapse risk about 50%</td>
</tr>
<tr>
<td>Paracoccidioidomycosis</td>
<td>Itraconazole</td>
<td>3-6 months</td>
<td>Liposomal amphotericin B</td>
<td>--</td>
</tr>
<tr>
<td>Juvenile</td>
<td>Itraconazole</td>
<td>6 months</td>
<td>Liposomal amphotericin B</td>
<td>--</td>
</tr>
<tr>
<td>Chronic pulmonary</td>
<td>Itraconazole</td>
<td>2-6 months</td>
<td>Liposomal amphotericin B if very unwell</td>
<td>--</td>
</tr>
<tr>
<td>Blastomycosis</td>
<td>None or itraconazole</td>
<td>6-12 months</td>
<td>Itraconazole or voriconazole</td>
<td>Asymptomatic colonisation does not need therapy</td>
</tr>
<tr>
<td>Cryptococcal pneumonia</td>
<td>Fluconazole</td>
<td>6-12 months</td>
<td>Itraconazole or voriconazole</td>
<td></td>
</tr>
<tr>
<td>Fungal asthma</td>
<td>Itraconazole</td>
<td>4-8 months</td>
<td>Nebulised amphotericin B, voriconazole, posaconazole</td>
<td>Relapse risk about 50%</td>
</tr>
<tr>
<td>Aspergillus bronchitis</td>
<td>Itraconazole</td>
<td>4 months</td>
<td>Voroconazole, posaconazole</td>
<td>Relapse risk about 50%</td>
</tr>
</tbody>
</table>

*Monitor azole serum concentrations and possible toxicities and avoid drug interactions. †Includes allergic bronchopulmonary aspergillosis and severe asthma with fungal sensitisation.
Chronic pulmonary paracoccidioidomycosis is often associated with disease in other organs, notably the skin and mouth, lymph nodes, spleen, liver, and adrenal glands. Pulmonary lesions are granulomatous nodules that often cavitate but rarely calcify. Co-existent pulmonary tuberculosis is common. Itraconazole is superior to compounded preparations of trimethoprim and sulphamethoxazole (table 3).

**Pulmonary blastomycosis**

Pulmonary blastomycosis is usually seen with cutaneous blastomycosis. Almost all cases occur in North America, with rare cases reported from Africa and India. The most common presentation is with cough, weight loss, chest pain, skin lesions, and fever; haemoptysis is seen occasionally (figure 1). Primary pulmonary blastomycosis might be asymptomatic or present as acute or subacute pneumonia, ranging from mild to severe. Itraconazole therapy is curative (table 3).

**Cryptococcal pneumonia**

Pulmonary cryptococcosis is rare, but probably underdiagnosed, and is most common in immuno-compromised patients (figure 1). It is most often caused by *Cryptococcus neoformans* var *grubii* (worldwide) or *Cryptococcus gattii* (geographically confined). *C gattii* is found in eucalyptus and other large trees in tropical and subtropical regions in Australia, Asia, Europe, and the northwestern Pacific.

Patients might be asymptomatic and present with an abnormal chest radiograph. The most common symptoms are cough, which is usually productive, and haemoptysis. Single or multiple peripheral nodules, sometimes in association with areas of consolidation, are common, but pleural effusion and consolidation are seen occasionally. Airway colonisation also occurs. *C gattii* pulmonary infection includes multifocal areas of consolidation, both solid and cavitary nodules, pleural effusion, and endobronchial lesions. Hypoxaemia is rare. Patients might have disseminated disease with meningitis or a cerebral cryptococcoma.

CT-guided or video-assisted thoracoscopy lung biopsy or resection is the most common means of establishing the diagnosis. Culture from respiratory samples is often negative, but cryptococcal antigen is occasionally detected in serum or cerebrospinal fluid. Most patients with *C gattii* infection are not immunocompromised but might have ill-defined immune deficits. If not suspected, antifungal therapy with fluconazole (table 3) is advised, unless meningitis is also present, in which case combination amphotericin B and flucytosine is strongly recommended.

**Fungal asthma**

Current evidence links a proportion of asthma cases to fungal infections in two ways. First, substantial indoor dampness, mould odour, and visible mould exposure can trigger asthma, with an increased risk of 30–50%. Second, many patients with asthma are sensitive to several fungi, including *Aspergillus* spp, *Alternaria* spp, and *Cladosporium* spp, and this sensitivity is usually linked to poor asthma control. The latter sensitivity is often referred to as fungal asthma. Fungal sensitisation is common in severe asthma, occurring in at least 33% of patients. Genetic factors are probably important in fungal asthma. Severe airway inflammation and multiple hospital admissions are common.

Fungal asthma has a broad range of clinical phenotypes and includes allergic bronchopulmonary aspergillosis. Fungal asthma can manifest as fungal sensitisation or fungal allergy. Whereas fungal sensitisation is an exaggerated immune response to a fungus, without inflammation or tissue damage, and is clinically recognised by an increased production of fungus-specific IgE, fungal allergy is an immune-mediated inflammatory response to a fungus causing tissue damage. Although many fungi can cause sensitisation, fungal allergy is predominantly due to thermotolerant fungi, especially *A fumigatus*. Allergic bronchopulmonary aspergillosis is the most well characterised form of fungal asthma.

Severe asthma with fungal sensitisation denotes a phenotype of severe asthma characterised by severe asthma and fungal sensitisation but no allergic bronchopulmonary aspergillosis.

Allergic bronchopulmonary aspergillosis presents as poorly controlled asthma, with exacerbations consisting of increased amounts of sputum containing mucous plugs, malaise, and weight loss. Chest imaging might reveal mucous plugging, and, in later stages, central bronchiectasis. Hyperattenuated mucus is visible in a substantial proportion of patients in India but is uncommon elsewhere, for unknown reasons. The diagnosis of various forms of fungal asthma is based on a combination of clinical, radiological, and immunological findings. IgE to *A fumigatus* is required for a diagnosis of allergic bronchopulmonary aspergillosis. A total IgE of more than 1000 IU/L arbitrarily distinguishes allergic bronchopulmonary aspergillosis from severe asthma with fungal sensitisation.

Management of fungal asthma includes inhaled or oral corticosteroids, or both, immunisation against *S pneumoniae* and *H influenzae*, management of excess mucus with therapeutic bronchoscopy (if plugging is severe), and hypertonic saline nebulisers and azithromycin as an airway anti-inflammatory agent. Oral or inhaled antifungal therapy, if tolerated, is beneficial for most patients (table 3). Complications of allergic bronchopulmonary aspergillosis include bronchiectasis and pulmonary fibrosis (including chronic pulmonary aspergillosis).

**Thunderstorm asthma**

Thunderstorm asthma refers to an association between high fungal spore counts, thunderstorms, and severe asthma attacks. Increased humidity and high winds...
trigger increased spore or conidia release and dissemination. Several fungi have been implicated in thunderstorm asthma, including *Didymella extistalis*, *Sporobolomyces* spp, and *Alternaria* spp as well as grass allergens. Affected patients might become so ill as to need intensive care. Whether antifungal therapy could be beneficial is unclear.

**Occupational asthma**

Occupational asthma has been attributed to fungi in a few cases. Examples include mushroom workers with positive IgE and IgG to *Pleurotus cornucopiae*; people working in condom manufacturing, where *Lycopodium clavatum* was used as a dusting agent; a research microbiologist with asthma and with specific IgE antibodies to *Dictyostelium discoideum*; a coal miner who developed occupational asthma with specific IgE antibodies to *Rhizopus nigricans* after a mine was contaminated with this fungus; people working in the coffee grinding industry or the plywood industry who have specific IgE to *Neurospora* species; and orchid growers with sensitivity to *Cryptostroma corticale*, which is found in the bark chips used to cultivate orchids.

**Aspergillus bronchitis**

Aspergillus bronchitis is a chronic superficial infection of the lower airways, characteristically in non-immunocompromised patients. Any of the pathogenic *Aspergillus* spp can cause this form of bronchitis, and most patients have bronchiectasis or cystic fibrosis. About 10000 adults are estimated to have cystic fibrosis and aspergillus bronchitis, but the burden of aspergillus bronchitis in people who do not have cystic fibrosis has not been estimated. The most common clinical presentations in patients who do not have cystic fibrosis are either chronic productive cough with tenacious mucus production and dyspnoea or recurrent exacerbations of pre-existing airway disease with incomplete response to antibiotics. Mucous impaction necessitating therapeutic bronchoscopy is a rare, dramatic presentation.

Since *Aspergillus* spp can colonise the respiratory tree, the combination of symptoms with microbiological demonstration of aspergillus in the airways at least twice is required for diagnosis. Some patients have airway ulceration or membrane formation, whereas other patients have obstructing, thick mucus. Detection of fungus by microscopy and either galactomannan assays or PCR is sufficient for diagnosis. Some patients show increased production of IgG to aspergillus.

Oral azole therapy for about 4 months is effective in most patients (table 3); however, relapse is common, and some patients need long-term therapy.

**Cystic fibrosis**

Patients with cystic fibrosis are at risk of acquiring fungi in their sputum, commonly *Candida* spp, which is of limited importance, *A fumigatus*, which might represent allergic bronchopulmonary aspergillosis, aspergillus bronchitis or transient colonisation, *Exophiala dermatitidis*, which is of uncertain importance, and *Scedosporium* spp. Those patients with aspergillus in their airways have a slightly more rapid decrease in lung function than those without. Infection of the airways manifests as aspergillus bronchitis and allergic bronchopulmonary aspergillosis, but many patients are not affected or only sensitised to *A fumigatus*. The optimal management of fungal infection and allergy in patients with cystic fibrosis is uncertain.

**Mouldy building exposure and building sickness syndrome**

Poor quality buildings, water leaks, and inadequate ventilation can lead to excess fungal growth inside a building. In addition to precipitating or worsening asthma, some patients develop other symptoms, referred to as building sickness syndrome. Other names for this collection of syndromes include sick building syndrome, sick house syndrome, or the evocative toxic black mould. This syndrome might affect patients with chemical intolerance (multiple chemical sensitivity). Since many of the symptoms are non-specific and no diagnostic test is available, the diagnosis relies on a careful history.
of the patient’s symptoms and environmental exposures and exclusion of other causes of common symptoms such as fatigue (figure 3).83–85 Clinical clues to a positive diagnosis of building sickness syndrome related to fungal or mould exposure include three elements: a history of exposure to visible mould or smell, usually with improvement after leaving the building (eye, nose, or throat irritation and hoarseness combined with difficulty in concentration and sensitivity to odours is characteristic of exposure to volatile organic compounds); headache, dizziness, nausea, dry skin or pruritus, nasal stuffiness, and lethargy are common, and weight loss and muscle pains are reported occasionally; and exacerbation or initiation of allergic rhinitis or asthma.

In addition to an empathetic ear and eradication of dampness and mould from the house or office, patients need to be thoroughly examined, checked for alternative diagnoses with an initial screen for inflammatory markers, anaemia, liver, renal and thyroid abnormality, and have a chest radiograph. Comorbidity, especially psychological, is common.84 If allergic or pulmonary symptoms are prominent, then testing for fungal sensitisation or IgG, or both, is appropriate. Preferably, these tests should be combined with a careful assessment of fungal exposure in the home or workplace by an experienced professional. The Quick Environmental Exposure and Sensitivity Inventory questionnaire is valuable in assessing patients.85

The cornerstone of management is avoidance. Repair of leaks, reduction in condensation, and improvement in ventilation are key to clinical improvement. Patients with evidence of chemical intolerance need advice on avoidance, which can be challenging, so cognitive behavioural therapy might be helpful.86 No evidence exists for any particular therapeutic strategy, partly because of the highly individual nature of the exposures.

Extrinsic allergic alveolitis and other symptoms caused by fungi

Extrinsic allergic alveolitis caused by fungi is probably more common than realised because fungal exposure can be unobtrusive. A well documented example was an outbreak of pulmonary symptoms and skin-prick positivity to aspergillus in several workers producing citric acid from Aspergillus niger.83,84 Fungal exposure is also problematic for workers in the malt,9 tobacco,9 tobacco,9 baking,9 and esparto manufacturing industries.9 Many individual case examples have not been given disease names yet, and many occupational exposures lead to pulmonary symptoms that do not fulfil criteria for asthma or extrinsic allergic alveolitis.75–78 Antifungal therapy has not been tested in patients with either extrinsic allergic alveolitis or occupational asthma related to fungi. Some patients present late with interstitial lung disease or pulmonary fibrosis. Avoidance is generally recommended but could have serious economic consequences for some patients. A trial of itraconazole, as a corticosteroid-sparing agent, might be sensible if subtle exposure continues and is unavoidable.

Conclusion

Airborne fungi cause a wide range of disease in the lung and upper and lower airways, some acute and others indolent or chronic. High exposure is a common factor. Underlying lung or airway disease is a common antecedent factor, and the course of fungal disease is highly variable—probably attributable to local airway and lung immune defences and genetic factors, which are not well understood. Most infectious syndromes and some allergic manifestations improve with antifungal therapy.

Contributors

DWD and AC contributed equally to the writing of this paper.

Declaration of interests

DWD and family hold Founder shares in F2G Ltd, a University of Manchester spin-out antifungal discovery company. He acts or has recently acted as a consultant to Astellas, Sigma Tau, Basilea, Sycamex, Cidara, Bioseragen, Quintiles, Pulmatix, Pulmocide, and Zambon. In the past 3 years, he has been paid for talks on behalf of Astellas, Dynaminke, Gilead, Merck, and Pfizer. He is a longstanding member of the Infectious Disease Society of America Aspergillus Guidelines group, the European Society for Clinical Microbiology and Infectious Diseases Aspergillus Guidelines group, and the British Society for Medical Mycology Standards of Care Committee. AC declares no competing interests.

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References


See Online for appendix