

MOULDS – INDOOR ALLERGENS AND THEIR ROLE IN ATOPIC DISEASE

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ABSTRACT

Fungi are both indoor and outdoor allergens. Fungal spore levels vary between regions in South Africa and are affected by seasons and weather conditions. Hypersensitivity conditions to fungi are asthma, allergic rhinitis, hypersensitivity pneumonitis, allergic bronchopulmonary aspergillosis and allergic fungal rhinosinusitis. A number of conditions have been attributed to inhalational fungal exposure, but evidence is lacking to substantiate these associations.

Key words: moulds, fungi, fungal spore, indoor allergen, atopic disease, hypersensitivity disorders

INTRODUCTION

Moulds or, more accurately, fungi are cited by patients and some doctors as the cause of a number of complaints, varying from nasal and respiratory allergy to the less measurable effects such as lethargy, headaches and nausea. Allergic sensitisation to fungi was first described by Blackley in the 1860s.¹ Individual fungi can produce a number of potentially allergenic proteins which are cross-reactive between the species, but their clinical significance is uncertain.²

These fungi may be found both indoors and outdoors, but clinical significance requires individual evaluation of each

patient and knowledge of which fungi are present in the region where individuals work and which are problematic for atopic individuals.

Local aerobiology data from the Cape Town and Gauteng spore traps demonstrate that outdoor fungal counts are variable and weather-dependent, but that increased levels are detected in spring and autumn.³ *Alternaria*, *Cladosporium* and *Epicoccum* are recorded at consistently significant levels at the four spore traps in Cape Town.^{3,4} Only one single spore trap showed a *Curvularia* peak in autumn. Ascospores peaked after rainy weather and Basidiospore levels increased in the autumn months.^{3,4}

Fungal species commonly found indoors are *Cladosporium*, *Alternaria*, *Epicoccum*, *Penicillium* and *Aspergillus*.⁵ These indoor species usually result from contamination of the indoor environment by those species found in the vicinity.⁶ Fungi are carried indoors through open windows or through transfer by pet hair or contaminated clothing.⁷ The indoor levels of fungal spores are usually less than simultaneously measured outdoor levels. If the indoor fungal spore levels are higher than the outdoor spore count, then indoor fungal proliferation is present.

Mycotoxicosis is the result of ingestion of food contaminated by fungi which have produced mycotoxins.⁸ All fungi are able to produce mycotoxins. Ergotism is a result of the production of ergot by the fungus *Claviceps purpurea*.⁹ This is sometimes found on contaminated millet or rye. Ergotism can be either the convulsive or the gangrenous type. Aflatoxin is produced by some *Aspergillus* species which contaminate stored peanuts, feed or grains.¹⁰ This toxin is implicated in the development of hepatocellular carcinoma.



Figure 1: Spore trap, Observatory, Cape Town

Fungal mycelia or fungal balls are non-invasive and may accumulate in areas of previous damage or anatomical abnormality after colonising the respiratory epithelium. These collections require surgical excision. In the South African context, an *Aspergillus* fungal ball may grow in a post-tuberculosis lung cavity.

Hypersensitivity disorders related to fungi are asthma, allergic rhinitis (AR), hypersensitivity pneumonitis, allergic bronchopulmonary aspergillosis (ABPA) or mycosis, and allergic fungal rhinosinusitis (AFRS).

FUNGI AND ASTHMA

Sensitisation and exposure to fungi, particularly *Alternaria*, is associated with asthma;¹¹ fungal allergy carries a higher risk of severe or fatal asthma attacks.¹²

Indoor fungal spore counts have been difficult to correlate with asthma symptoms and there are conflicting studies as to whether indoor fungal loads correlate with increased asthma symptoms.^{13–15} These studies often relied on self-reported visible fungus or damp in the living areas but actual fungal spore counts were not obtained in the home. Outdoor fungal exposure has been associated with asthma symptoms in a paediatric group¹⁶ and an increased risk of wheezing in the first three months of life.¹⁷ An association between damp and asthma symptoms has been found in a number of studies,^{18–20} but the issue of the proliferation of bacteria and dust mites in this environment was not accounted for.

Severe asthma with fungal sensitisation (SAFS) is likely to be part of the same disease spectrum as ABPA. Patients with SAFS will have severe asthma with positive skin tests for fungal sensitisation and may have other criteria such as mucus impaction and atelectasis, peripheral eosinophilia and raised serum immunoglobulin E (IgE). The differentiating feature is that the serum IgE does not exceed 1 000 kU/L and ABPA may occur in mild or moderate asthma. SAFS and ABPA are treated in the same manner: with glucocorticoids ± systemic azoles.²¹

ALLERGIC RHINITIS

Local studies on fungal sensitisation in patients with clinically diagnosed AR have shown sensitisation to *Alternaria alternata*, *Candida albicans* and *Aspergillus fumigatus* in Free State province, South Africa.²² A study from the Western Cape province found the highest rates of sensitisation to three fungi: *Alternaria*, *Aspergillus* and *Cladosporium*.²²

Allergic sensitisation to fungi may be the cause of some cases of AR; however, further research is required to support this.⁵

HYPERSENSITIVITY PNEUMONITIS

The diagnosis of hypersensitivity pneumonitis (HP) is based on a combination of criteria, including exposure to known antigens, a compatible clinical and radiological pattern of disease, altered spirometry, compatible broncho-alveolar lavage and histopathology result with or without a positive inhalational challenge.²³

HP usually arises with occupational exposure to fungal antigens, but there are reports of HP from indoor fungal contamination of showers, air-conditioning systems and humidifiers. *Epicoccum*, *Aspergillus* and *Penicillium* are the fungi most commonly implicated.^{24–26}

ALLERGIC BRONCHOPULMONARY ASPERGILLOSIS

ABPA is a hypersensitivity reaction to colonisation of the airways by the fungus *Aspergillus fumigatus*. The estimated prevalence in persistent asthmatics is 1–2%,^{27,28} but it has been reported in up to 28% of asthma clinic patients hospitalised with an acute exacerbation.²¹ The prevalence in patients with cystic fibrosis (CF) is reported to be between 7% and 15%.^{29,30}

Long-term sequelae of chronic ABPA may be recurrent episodes of mucous impaction and airway obstruction leading to bronchiectasis and lung fibrosis.

Aspergillus fumigatus is a ubiquitous mould found in garden waste which colonises the airways after inhalation of the airborne spores. In the asthmatic and, less commonly, in the patient with CF, this results in Th2 production of *Aspergillus*-responsive T-cells which stimulate the production of IL-4, IL-5 and IL-13.

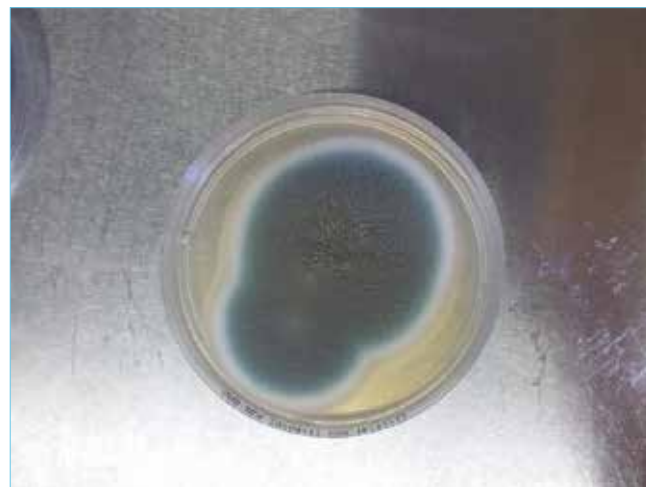


Figure 2: Culture of *Aspergillus* species (Courtesy of Dr Chad Centner)

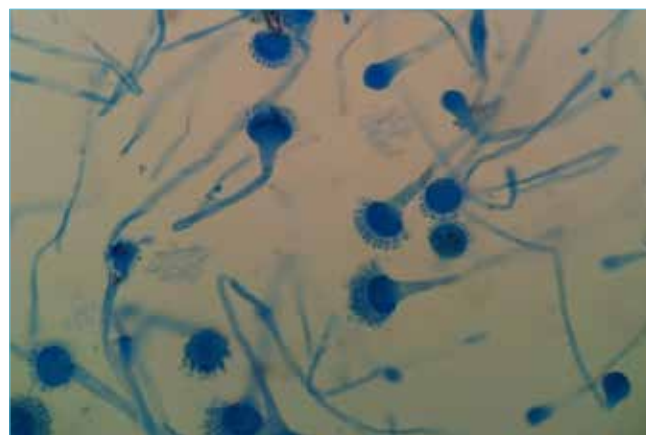


Figure 3: Lactophenol cotton blue stain of *Aspergillus* species (Courtesy of Dr Chad Centner)

This leads to an increase in eosinophils and IgE. IgE and IgG antibodies to *Aspergillus* are also formed. The fungus releases mycotoxins and proteolytic enzymes, which, in addition to the neutrophilic and eosinophilic inflammation, results in airway damage with or without central bronchiectasis.²¹

These patients may present with asthma with recurrent exacerbations or symptoms of *Aspergillus* rhinosinusitis or they be systemically unwell with fever, malaise, haemoptysis and expectorating brown mucous plugs.

No single test is available to diagnose ABPA. Responsible clinicians should be aware of the possibility of it being present in their patients who present with frequent exacerbations and an abnormal chest X-ray. Issues regarding adherence, technique and other co-morbidities should be addressed before ABPA is considered.

The International Society for Human and Animal Mycology (ISHAM) criteria of 2013 (see Table 1)³¹ simplified the criteria making what is often a complicated diagnosis, easier to make.

TABLE 1: ISHAM2013

• Predisposing conditions
▫ Asthma
▫ Cystic fibrosis
• Obligatory
▫ Skin-prick test positive to <i>Aspergillus</i>
▫ Specific IgE to <i>Aspergillus fumigatus</i>
▫ Increased total serum IgE
• Other criteria
▫ Precipitating antibodies to <i>Aspergillus fumigatus</i>
▫ Radiographic pulmonary opacities
▫ Total eosinophil count >500 cells/microlitre

Allergic bronchopulmonary mycosis (ABM) is an ABPA-like syndrome associated with fungi other than *Aspergillus fumigatus*. The diagnostic criteria are the same except specific IgE should be measured for the following fungi: *Curvularia*, *Candida*, *Fusarium*, *Penicillium*, *Drechslera*, *Stemphylium*, *Pseudallescheria* and *Helminthosporium*.³² The author has treated one patient in the South African setting with ABM secondary to *Alternaria*.

ABPA may be difficult to diagnose in patients with CF, but clinicians should have a high clinical suspicion in patients older than six years and do surveillance with total IgE levels annually. The diagnostic criteria of ABPA in CF comprise:³³

1. Acute or subacute deterioration.
2. Serum IgE >2 400 ng/mL or 500 kU/L.
3. Positive skin-prick test to *A. fumigatus* or positive specific IgE.
4. One of the following:
 - a. Precipitins to *Aspergillus* or IgG *A. fumigatus*;
 - b. New or recent abnormalities on chest radiograph.

Treatment of ABPA targets the hypersensitivity response to limit inflammation and prevent lung damage. Currently, there are two schools of thought on the treatment of patients with ABPA:

- (1) steroids only – reserving antifungals for those who fail or relapse on the steroid wean; or
- (2) steroids with concomitant antifungals.

Various steroid regimens have been published, but the objective should always be to treat the condition with the least number of side-effects. Those patients on long-term glucocorticoids should have their blood pressure and blood glucose measured at follow-up visits, and the prescribing clinician should ensure calcium and vitamin D supplementation. Greenberger initially used 0.75 mg/kg prednisone for six weeks, then 0.5 mg/kg for six weeks, followed by a slow wean by decreasing the steroid dose by 5 mg every six weeks.³⁴ Whereas this regimen was effective, the long duration of therapy must be noted and consequently the risk for increased glucocorticoid side-effects. In fact, the updated regimen by Greenberger prescribing 0.5 mg/kg prednisone for two weeks, then 0.5 mg/kg on alternate days with a wean to stop over three months³⁴ has a more favourable side-effect profile with no difference in relapse rates.

The 2016 practice guidelines by the Infectious Diseases Society of America (IDSA) advocate concomitant glucocorticoids and azole therapy;³⁵ however, the significant metabolic effects of glucocorticoids are potentiated by concomitant itraconazole. An alternative practice is to limit azoles for those that have rebound IgE elevation or symptoms as the steroids are weaned. If an azole is required, it is added for 16 weeks.^{36,37}

Itraconazole is started at high dose for three days to allow enzyme induction and then decreased to twice a day. The recommended adult dose is 200 mg three times a day for three days, which is then tapered to 200 mg twice daily. The paediatric dose is 5 mg/kg/day. Liver-function tests and drug levels should be monitored, but the drug levels are unavailable in state practice in South Africa. Important patient information is that the drug be taken with food, and that no acid-blocking drugs may be taken if the patient is taking the capsule preparation of the drug.³³

The loading dose of voriconazole is 400 mg twice daily for two doses and then 200 mg twice daily. It is recommended that liver-function tests and drug levels also be monitored for this drug.³³

Serum IgE levels should be monitored every two months for six months to establish the patient's new IgE setpoint when symptoms are controlled. A 100 per cent increase in the IgE and symptoms with changes in the chest X-ray should alert the treating physician to possible ABPA relapse.³⁸ There is no evidence regarding repeating the specific IgE or IgG to *Aspergillus*.

Omalizumab has shown some benefit in patients without CF. A small randomised-control trial that administered omalizumab allowed a washout phase and then crossed over to the placebo arm. This showed fewer exacerbations in the treatment group. A paediatric case series has also shown benefits, but more definitive trials are needed. A systematic review concluded that there was a lack of evidence for the safety and efficacy of omalizumab in patients with ABPA and CF.³³

Complications of APBA may be invasive *Aspergillus* infections, chronic pulmonary aspergillosis, aspergilloma and bronchiectasis.

ALLERGIC FUNGAL RHINOSINUSITIS

Allergic fungal sinusitis (AFRS) is a chronic rhinosinusitis with allergic inflammation attributed to fungi that have colonised the paranasal sinuses. The fungi most commonly involved are *Bipolaris*, *Curvularia*, *Aspergillus*, *Exserohilum* and *Drechslera*.³⁹

The cardinal symptoms of chronic rhinosinusitis are:³⁹

1. Anterior and/or posterior nasal mucopurulent drainage.
2. Nasal obstruction and congestion.
3. Facial pressure and pain.
4. Reduced or loss of sense of smell.

The Bent and Kuhn diagnostic criteria⁴⁰ for AFRS are still widely applied, but newer criteria were proposed in a 2016 consensus statement. The Bent and Kuhn criteria are:

- type-1 hypersensitivity to fungi;
- elevated total serum IgE;
- nasal polyposis
- characteristic CT scan findings;
- eosinophilic mucous without fungal tissue invasion, mucosal necrosis, granulomas or giant cells;
- positive fungal stain of sinus contents removed at surgery;
- exclusion of other fungal rhinosinusitis disorders.

The proposed diagnostic criteria for AFRS are:⁴¹

1. Symptoms of CRS.
2. Eosinophilic mucin in one or more sinus cavity found at surgery.
3. Histology must confirm that the fungal hyphae found in the mucin have not invaded the nasal mucosa.
4. Immunocompetent patient.
5. Characteristic CT changes: nasal polyposis, one or more sinuses involved, unilateral or bilateral disease, central hyperattenuation of the fluid within the sinuses, bone demineralisation of the sinus wall with possible sinus expansion, possible mucocoele formation, erosion of bone of the orbits or base of skull.
6. Specific fungal IgE positive at allergy evaluation.

Co-infection with staphylococcus aureus has been observed in some patients with AFRS.

The treatment of AFRS involves both medical and surgical intervention.^{42,43} If the treating physician feels that invasive fungal rhinosinusitis is unlikely, then the medical management may focus on the treatment of CRS with nasal polyposis. If medical management fails, then:

- Endoscopic sinus surgery for diagnosis, polypectomy, drainage and clear-out is indicated.
- Surgery is usually required to remove polyps and clear out fungal material that may obstruct sinus drainage and prevent intranasal steroids from being fully efficacious.
- Oral glucocorticoids may be administered prior to surgery

and should continue post surgery in the form of prednisone 0.5 mg/kg.³⁸

- Glucocorticoid nasules are administered concurrently to limit local nasal-allergic inflammation.
- Oral glucocorticoids are weaned after one to three months to a maintenance dose that limits nasal symptoms, with local nasule instillation continuing.
- Nasule instillations are weaned after two to three years if the nasal mucosa remains normal.³⁶
- Steroid nasules are not on code in state facilities and the cost may be prohibitive in the private healthcare sector. An alternative is a high-dose corticosteroid intranasal spray.
- Adjunctive fungal immunotherapy is advocated by some, but is of uncertain benefit.^{44–46}
- Post-operative antifungals have been evaluated, but there is paucity of supportive data.

The recurrence of AFRS is common if post-surgical glucocorticoids are either not used or the patient experiences adherence challenges.³⁶ Total IgE levels are useful for follow-up of patients post surgery, and an increase of 10 per cent or more is associated with additional surgery required.⁴⁷

CONTROVERSIES SURROUNDING FUNGAL EXPOSURE

It is known that ingested mycotoxins may cause disease, but the lay press is rife with articles suggesting 'toxic mould' exposure or indoor exposure to *Stachybotrys chartarum* may cause a variety of symptoms in human beings.

Mycotoxin can be inhaled, but the particles need to be aerosolised, as in an occupational setting.⁵ Pulmonary mycotoxicosis, also known as 'grain fever syndrome', has been described in workers who clean large grain silos. These patients may present with 'flu-like' symptoms, shortness of breath, fever, headache and myalgia. These symptoms are self-limiting, with no long-term health effects. This condition is more correctly termed 'organic toxic dust syndrome', as it is not known which component of the dust causes the symptoms. This dust contains a variety of bacteria, fungi, organic debris and even endotoxins.⁵

Stachybotrys chartarum is a fungus that is found worldwide and requires a high moisture content to thrive. It is not easily aerosolised as the particles are sticky, and not all species produce mycotoxins. This fungus has previously been implicated in acute idiopathic pulmonary haemorrhage, but study analysis revealed that the association could not be upheld.⁴³ There is no evidence that the *S chartarum* mycotoxin is causative of 'mould-induced immune dysregulation', nor is there objective evidence of any neurologic dysfunction. No literature supports the contention that inhalational exposure causes spontaneous abortions, malignancy, hepatobiliary, renal or endocrine disease.

ENVIRONMENTAL CONTROL OF FUNGI

Common indoor fungi are *Alternaria alternata*, *Cladosporium herbarum* and *Penicillium notatum*.⁵ *A Alternata* is found on foodstuffs and in damp areas such as bathrooms. *P notatum* is found both indoors and outdoors and is commonly found on stale bread, cheese, cereals and fruit, and in vineyards and wine

cellars. *C. herbarum* grows in houses with poor ventilation, on windows and window frames and in unclean refrigerators. It is commonly found in dead plants and soil.

Aspergillus fumigatus is found predominantly outdoors in decaying leaves and plant matter, but may be found in stored tubers.

Patients with demonstrated fungal allergy should have their home environment cleansed if the home contains visible mould or smells of mould. Fungi thrive in homes with high humidity, water damage or stagnant water.^{48,49}

The 2007 randomised trial that examined at-home eradication of fungus in the homes of mould-sensitised patients showed significant benefit in the form of patient-perceived improvement in breathing and medication reduction.⁵⁰ By 12 months the intervention group showed a significant reduction in both controller and reliever use as well as in rhinoconjunctivitis.⁵⁰

A prospective randomised control trial that looked at both environmental control and patient behaviour modification showed a lower rate of asthma exacerbations compared to asthma controls. The environmental modification involved building repairs and remedying ventilation or air-conditioning as opposed to educating the control group about household cleaning and cleanliness.⁵¹

The management of fungal allergy relies on reducing exposure to fungi by limiting humidity and increasing ventilation in the dwellings of allergic individuals. General living space should have the windows opened as often as possible, but especially while cooking, and the bathroom window should be opened after bathing or showering. Visible fungus should be removed with a bleach-containing cleaning solution and fungus-resistant paint should be applied. Other measures could include limiting the presence of indoor plants and the use of dehumidifiers, where possible.

Additional measures to consider for the bedrooms would be to:

- remove all carpets;
- ensure humidifiers are not used in the bedroom;
- remove indoor plants;

- remove visible condensation on windows and window frames;
- use chemical dehumidifiers in cupboards;
- allow bedroom cupboards to air; and
- not to store leather goods in these cupboards.

Outdoor fungus exposure can be limited by not allowing the allergic person to rake decaying leaves or dispose of garden waste. Windows should be closed on dry and windy days, when fungal spores may contaminate the indoor environment. Care should be taken in heavily wooded areas or forests in autumn, when piles of leaves accumulate. Wine-cellar tours and exposure to functions on farms and in barns should be approached with caution.

Occupational mould allergy may occur in farm workers, bakers, brewers, florists, carpenters, wine-makers and wallpaper hangers.

CONCLUSION

- Fungi are found both indoors and outdoors, but clinical significance requires individual patient evaluation and testing for sensitisation to the local common fungi.
- Simplified diagnostic criteria are available for ABPA and treating clinicians need to decide on whether glucocorticoids-only or glucocorticoids plus concomitant azoles are the suitable treatment required for individual patients.
- AFRS must be considered in patients who have chronic rhinosinusitis, in which case early referral to an ENT surgeon is warranted.
- There are no rigorously conducted studies that support inhalational fungal exposure that causes spontaneous abortions, immune dysregulation, idiopathic pulmonary haemorrhage malignancy, hepatobiliary, or renal or endocrine disease.
- There is evidence that reducing the mould in the environment of those sensitised to fungi has an impact on respiratory health.

DECLARATION OF CONFLICT OF INTEREST

The author declares no conflict of interest.

This article has been peer reviewed.

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