Lassoing a chimera: the semantics of allergic fungal airway disease

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Acknowledgements

The authors are supported by the National Institute for Health Research Leicester Respiratory Biomedical Research Unit. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health.
Fungi are one of the kingdoms of life and represent a diverse group of eukaryotic organisms that occupy every ecological habitat including the healthy human body. From the perspective of human disease in general and allergy in particular fungi can be divided into two groups; those that are thermotolerant and can therefore colonise humans and those that cannot grow at body temperature, but act as aeroallergens in IgE sensitized individuals. The property of thermotolerance is relevant to those fungi which are involved in decomposition where temperatures are often high and are exemplified by members of the *Aspergillus* and *Penicillium* genera, particularly *Aspergillus fumigatus*. Yeasts, particularly members of the *Candida* genera, as well as filamentous fungi (moulds) can be thermotolerant and colonise mucocutaneous surfaces. Generally they are commensals causing no symptoms but can readily cause troublesome symptoms in people taking antibiotics or inhaled corticosteroids (IHC). Non-thermotolerant species include plant pathogens such as members of the *Alternaria* and *Cladosporium* genera can cause exacerbations of asthma and rhinitis when spore levels in ambient air are high, for example during harvesting. However they are unable to colonise the human airway and therefore have a limited and predictable impact on human health which is directly related to spore concentrations in inhaled air. Lung host defense is very effective at preventing invasive fungal infection unless there is profound immunosuppression, but lesser degrees of immune vulnerability associated with airways diseases such as asthma, COPD and cystic fibrosis where macrophage function and the mucociliary escalater is compromised can result in semi-invasive infection such as fungal balls in pre-existing cavities, fungal bronchitis and fungal associated pleurisy.

Measurement of adaptive fungal immunity in a clinical setting is generally limited to humoral responses to a small number of fungi. Th1 responses are typified by raised specific IgG and Th2 responses by a positive skin prick test (or less commonly intradermal test), a raised specific IgE and a raised total IgE. Cell mediated immunity or innate immune responses
although of critical importance are not usually measured unless immunodeficiency is suspected. Considering the number of fungi potentially involved in allergic fungal disease relatively few reagents are available to measure fungal immunity and fungal extracts, some of which are bespoke rather than commercially available, are not well standardised and can be unreliable. This may be one reason for the lack of correspondence between skin tests and in vitro measurements of specific IgE (1). The methodology for culturing fungi from human secretions is often insensitive and at best semi-quantitative (2, 3). Fungal allergens are complex and poorly characterized and component resolved approaches to diagnosing fungal allergy are in their infancy(4). The population epidemiology of fungal IgE sensitization is not well described and generally relies on SPT to a limited number of fungi which may underestimate the true level. However in healthy controls it is generally quoted as <5% increasing to about 10% in mild asthma (5). IgE sensitisation to Candida and Malazessia species is common in atopic dermatitis as is IgE sensitization to Trichophyton species in people with fungal nail or skin infections (6, 7). Sensitisation to moulds is much more common in severe asthma and cystic fibrosis where up to 50% of patients are sensitised to A. fumigatus (8, 9). Multiple sensitization to fungi is the rule rather than the exception (1). Whether this is due to a shared tendency to have a Th2 type of response to fungi or cross-sensitisation between fungal allergens, which seems more likely, is not clear (10). It is therefore difficult to ascribe causal links between sensitization and disease to individual fungal species. Fungal allergy is characterized by high levels of polyclonal IgE and a marked peripheral blood eosinophilia. This is reminiscent of the immune response to helminthic parasites and there are interesting parallels between these two types of human interacting eukaryotes. However, as with parasitic infection, the degree of immune response as measured by the peripheral blood eosinophil count or total IgE is not closely related to clinical outcomes. In addition in our cohort of patients total IgE relates at least as closely to sensitization to Candida and Malassezia as A. fumigatus complicating interpretation of the
clinical significance of a high total IgE. It is worth noting that an IgE of >1000KU/L in the absence of infection with helminthic parasites almost always denotes fungal sensitization and fungal allergy is a common cause of a hypereosinophilic blood count.

Taking the above comments into account it is perhaps not surprising that there has been a long standing and unresolved debate about how to determine when IgE sensitization to fungi, in particular *A. fumigatus*, is clinically important. The term allergic bronchopulmonary aspergillosis (ABPA) was first coined in the 1950s to describe a florid form of fungal allergy caused by *A. fumigatus* (11). A number of case series and reports generally involving relatively small numbers of patients describing the clinical and immunological features of ABPA, over time has become elevated into a set of diagnostic criteria with considerable importance attached to the total serum IgE concentration (12, 13). The features that were regarded as helpful in distinguishing ABPA from sensitization were a diagnosis of asthma or cystic fibrosis, fleeting lung shadows (rarely encountered these days), IgE sensitization to *A. fumigatus* either by SPT or specific IgE, *A. fumigatus* specific precipitins (now generally measured as specific IgG), a total IgE of >417 IU/L (equivalent to 1000ng/ml), and a marked peripheral blood eosinophilia. Central or proximal bronchiectasis was recognized as an important feature although a sub-group without bronchiectasis was also described (ABPA-S). Culture of *A. fumigatus* in sputum was a minor criteria. The difficulty of telling the difference between ABPA and asthma with sensitization to *A. fumigatus* was appreciated and a number of stages of ABPA from mild disease to severe lung damage was described (14). Although based on anecdote these criteria have been remarkably influential and clinicians have tried to squeeze their patients into the boxes created by these rather arbitrary rules ever since, with limited success. Thus only about 10% of the patients who are IgE sensitized to *A. fumigatus* meet all the major criteria for ABPA and inclusion criteria for clinical trials of anti-fungal agents in ABPA have not been consistent in following these criteria (15-17). Attempts have
been made to update the criteria consistent with modern practice. Denning and colleagues coined the term severe asthma with fungal sensitization (SAFS), to describe patients with ABPA in the context of severe asthma who had an IgE below 1000KU/L, a cut off which has been preferred over the Patterson-Greenberger cut of of 417IU/L in recent years for reasons that are obscure (18). However many patients with clinically significant fungal allergy do not have obviously severe asthma and SAFS includes asthmatics with sensitization to non-thermotolerant fungi which as noted above are unlikely to cause significant persistent lung disease. Other attempts to revise the criteria for ABPA have been hampered by the lack of a gold standard for what is in essence a rather ill-defined syndrome. This has resulted in circularity where patients selected on the basis of the criteria are then measured against the same criteria (19). The problems associated with tying down ABPA in relation to fungal sensitization are illustrated by a systematic review of the criteria used to diagnose ABPA in cystic fibrosis (CF) carried out by Venkata and Agarwal and published in this issue. Their two main conclusions were that IgE sensitization to A. fumigatus in CF was very common occurring in 40% of patients although <10% were diagnosed with ABPA, and that only 50% of studies (post 2005) followed criteria laid out by the CF foundation for the diagnosis of ABPA in 2003 (20). They highlight in their discussion many of the problems associated with diagnosing fungal allergy in CF that have been discussed above.

Establishing criteria for ABPA is like trying to lasso a chimera. The presentation of fungal allergy is too protean to submit to a set of fixed rules, especially when these are largely based on the strength of the immunological response which does not obviously relate to clinical outcomes. Not only does fungal allergy complicate airway diseases other than asthma and CF, it is associated with a range of thermotolerant fungi (although dominated by A. fumigatus) and presents heterogeneously, ranging from lobar collapse to fixed airflow obstruction. Allergic fungal airway disease represents a continuous spectrum of disease severity and
drawing an arbitrary line in the sand on one side of which is ABPA and on the other harmless
*A. fumigatus* sensitization is unhelpful, either in terms of immediate management or long term
prognosis. Diagnostic criteria are helpful when they guide to a distinct approach to
management or predict future harm (risk). Neither apply to ABPA which in the absence of
strong evidence for anti-fungal treatment is not managed much differently from patients with
the underlying condition whether they are sensitized to fungi or not. Similarly there is no
convincing evidence that patients who fit the criteria for ABPA are at any greater risk of
coming to long term harm than patients matched for severity of asthma or COPD who are
sensitized to fungi but do not fit the criteria for ABPA. ABPA as a term has outlived its
usefulness. The starting point of any discussion about the role of fungi in airway disease
should be what are the clinically important pathophysiological abnormalities that relate
directly and specifically to fungal allergy? We propose that the hallmark of allergic fungal
involvement in airway disease are changes that can be grouped under the term ‘lung damage’
with bronchiectasis, fixed airflow obstruction and upper lobe fibrosis prominent features
(21). These are likely to be the result of chronic mucus plugging of the large and small airways
as result of a persistent and strong allergic stimulus. Determining the relationship between
the immunology of allergic fungal airway disease and clinically relevant outcomes should be
based on their relationship to the presence or absence of these features. The concentration of
serum total IgE, which is given centre stage in all the various criteria for ABPA-SAFS, does not
relate significantly to any of these abnormalities (paper in preparation). We need to
recognise that all people with fungal allergy in the context of airway disease are potentially at
risk of progressive lung damage. Until this occurs progress in understanding why only some
people with fungal sensitisation develop lung damage and the role of anti-fungals in
management will continue to be compromised.


