Diagnosis and treatment of allergic bronchopulmonary aspergillosis

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Allergic bronchopulmonary aspergillosis (ABPA) is a pulmonary disorder caused by immune reactions against *Aspergillus fumigatus*. It usually complicates the course of patients with bronchial asthma and cystic fibrosis manifesting with uncontrolled asthma, recurrent pulmonary infiltrates, and bronchiectasis**.** The interest in this entity stems from the fact that early diagnosis and treatment can prevent the occurrence of bronchiectasis, a marker of irreversible lung damage. As the disorder needs to be detected before onset of bronchiectasis, all patients with predisposing conditions need to be routinely screened for ABPA. *Aspergillus* sensitization (AS) defined as the presence of an immediate-type cutaneous hypersensitivity or elevated IgE levels against crude or specific antigens of *A. fumigatus* is probably the first step in the development of ABPA, and ABPA can be conceptualized as an exaggerated form of AS.

The diagnosis of ABPA is usually made using a combination of clinical, radiological and immunological criteria, and can be easily remembered by the mnemonic ARTSPICE (**A**sthma, **R**adiographic opacities, **T**ype I skin test against *Aspergillus* antigen, **S**pecific *A fumigatus* IgG and IgE levels elevated, **P**recipitins against *A fumigatus*, **I**gE levels raised, **C**entral bronchiectasis, **E**osinophilia). The significance of CB as a specific diagnostic marker for ABPA is controversial

as it has been shown that almost 40% of involved lobes have bronchiectasis extending to the periphery. The presence of elevated *A. fumigatus* specific IgE (>0.35 kUA/L) and total IgE (>1000 IU/mL) strongly points towards the diagnosis of ABPA in a patient with asthma.

While investigating a patient with asthma, an *Aspergillus* skin test should be used for screening. Once it is positive, total serum IgE levels are done. If the value is >1000 IU/mL, other tests should be done including high-resolution computed tomography (HRCT) of the chest, IgE and IgG specific to *A. fumigatus*, total eosinophil count and serum precipitins to *A. fumigatus*. If the IgE levels are 500-1000 IU/mL, the next step is analysis of *A. fumigatus* specific IgE and/or IgG antibodies. If the levels are raised, the patient is followed every six weeks with total IgE levels especially if there is bronchiectasis. If the absolute value rises >1000 IU/mL or there is a rising trend, then other investigations for ABPA are performed. If the IgE value is 500-1000 IU/mL and IgE and/or IgG specific to *A. fumigatus* are not raised, the patient is then followed up with annual IgE levels.

The management of ABPA includes two important aspects namely institution of glucocorticoids to control the immunologic activity, and close monitoring for detection of relapses. Another target is to use antifungal agents to attenuate the fungal burden secondary to the fungal colonization in the airways. The clinical effectiveness of therapy is reflected by decrease in the patient's total IgE levels (there seems to be no correlation between serum levels of *A. fumigatus* specific IgE levels and disease activity) along with improvement in symptoms and radiology. The goal of therapy is not to attempt normalization of IgE levels but to decrease the IgE levels by 20-50% which in most cases leads to clinical and radiographic improvement. One should also establish a 'new' baseline total IgE level for an individual patient, which serves as a guide to future detection of relapse and helps in follow-up of the patient.

Oral corticosteroids (CS) are the drug treatment of choice for ABPA. They not only suppress the immune hyperfunction but are also anti-inflammatory. Different regimens of CS have been used in literature as there is no robust data to guide the dose and duration of CS. They are especially beneficial in those with mucoid impaction and poorly controlled asthma. A randomized controlled trial on the efficacy and safety of two different glucocorticoid dose regimens (Prednisolone 0.5 mg/kg/day for 2 weeks, 0.5 mg/kg/day for alternate days for eight weeks, taper by 5 mg every 2 weeks and discontinue; vs. 0.75 mg/kg/day for 6 weeks, 0.5 mg/kg/day for 6 weeks, taper by 5 mg every 6 weeks and discontinue) in allergic bronchopulmonary aspergillosis has been completed (NCT00974766). The results of this trial will help in answering the question regarding dose of glucocorticoids in ABPA. Inhaled CS have minimal systemic side-effects but achieve high concentrations in the tracheobronchial tree. However, evidence suggests that inhaled CS alone have no role in the management of ABPA and should not be used as first-line therapy. However inhaled CS can be used for the control of asthma once the oral prednisolone dose is reduced to <10 mg/day.

The results of two randomized controlled trials suggest that itraconazole could significantly decrease the IgE levels by >25% compared to placebo but does not cause significant improvement in lung function. However, the major limitation of these studies is the fact that neither study reported long-term outcomes in terms of relapses of ABPA. Thus, longer term trials are required before a firm recommendation can be made for the use of itraconazole as adjunctive treatment for patients with ABPA. Itraconazole should be used only in cases of ABPA who relapse despite glucocorticoid therapy or in patients with glucocorticoid-dependent ABPA. Itraconazole has also been used as monotherapy in ABPA. However, more trials are required to confirm the efficacy of itraconazole monotherapy. A randomized controlled trial comparing

monotherapy of itraconazole versus prednisolone in ABPA (MIPA study: NCT01321827) is underway, which aims to answer to this question. Recently, voriconazole and posaconazole have also been tried in ABPA.

There are case reports of ABPA treated with inhaled amphotericin and inhaled steroids. Similarly there are single patient case-reports or small case-series on the use of omalizumab in ABPA. Pulse doses of intravenous methylprednisolone have been used for treatment of severe exacerbations of ABPA. All these therapies can be tried in those with steroid-dependent ABPA or in patients who develop treatment-related adverse reactions.