4.4 Allergic bronchopulmonary aspergillosis (ABPA)

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1. INTRODUCTION

- Allergic bronchopulmonary aspergillosis (ABPA), the most common form of allergic bronchopulmonary mycosis, is a complex specific immunological response to antigens of *Aspergillus* species colonizing the bronchi of CF patients **(see also Chapter *"Fungi"*)**. Recurrent episodes of bronchial obstruction, inflammation and mucoid impaction lead to bronchiectasis, pulmonary infiltrates and fibrotic changes.
- The prevalence of ABPA in CF is 2 to 15 % but the rates of colonization (up to 75 % when new molecular and selective culture techniques are used) and of sensitization (~ 30 %) are much higher. As the pathogenesis of ABPA remains incompletely understood, it is still unclear why some colonized CF patients become sensitized and others not, and why some sensitized CF patients develop ABPA and others not.
- Factors associated with ABPA in CF include
  - age (peaking in adolescence)
  - atopy
  - severity of lung disease
  - colonization with *Pseudomonas aeruginosa*
- The diagnostic criteria used in non-CF patients with ABPA cannot be applied to CF patients with ABPA, as bronchiectasis is a pathological feature of both CF and ABPA.

2. DIAGNOSIS

- Pursuing diagnosis when ABPA is suspected or by a screening approach in subjects at risk, such as CF patients, is very important because :
  - this condition responds to steroids and
  - its early detection and treatment may decrease the risk of evolution to irreversible fibrotic changes
- There is not a specific single diagnostic test for ABPA but diagnosis is traditionally based on the combination of clinical, radiological and immunological criteria. **In CF, recognizing and diagnosing ABPA is difficult and often delayed because some criteria overlap with CF itself (e.g. presence of bronchiectasis)**. Therefore, diagnostic criteria used in non-CF patients with ABPA cannot be applied to CF patients with ABPA.
- Due to these difficulties, a Cystic Fibrosis Foundation Consensus Conference has identified diagnostic **(Table 1)** and screening criteria **(Table 2)** for ABPA in CF.

Table 1: Diagnostic criteria of ABPA in CF[1]

Classic case

– Acute or subacute clinical deterioration (cough, wheeze, exercise intolerance, exercise-induced asthma, decline in pulmonary function, increased sputum) not attributable to another etiology
– Serum total IgE > 1000 IU/ml (> 2400 ng/ml), unless the patient is receiving systemic corticosteroids; if so, retest when steroid treatment is discontinued
– Immediate skin test reactivity to *Aspergillus* species or *in vitro* presence of serum IgE antibody to *A. fumigatus*
– Precipitating antibodies to *A. fumigatus* or serum IgG antibody to *A. fumigatus*
– New or recent abnormalities on chest radiograph (infiltrates or mucus plugging) or chest CT (bronchiectasis) that have not cleared with antibiotics and standard physiotherapy

Minimal diagnostic criteria

– Acute or subacute clinical deterioration (cough, wheeze, exercise intolerance, exercise-induced asthma, decline in pulmonary function, increased sputum) not attributable to another etiology
– Total serum IgE > 500 IU/ml (> 1200 ng/ml). If ABPA is suspected and the total IgE level is 200-500 IU/ml, repeat testing in 1-3 months is recommended. If the patient is taking steroids, repeat when steroid treatment is discontinued.
– Immediate skin test reactivity to *Aspergillus* species or *in vitro* presence of serum IgE antibody to *A. fumigatus*
– One of the following :
  a) precipitins to *A. fumigatus* or in vitro demonstration of IgG antibody to *A. fumigatus*; or
  b) new or recent abnormalities on chest radiograph (infiltrates or mucus plugging) or chest CT (bronchiectasis) that have not cleared with antibiotics and standard physiotherapy.

Note: Although it may be present in some cases, eosinophilia is not one of the diagnostic criteria of ABPA in CF, as it is not a specific finding in this context.

Table 2: Screening criteria for ABPA in CF[1]

Maintain a high level of suspicion for ABPA
Determine the total serum IgE concentration annually:

– If the total serum IgE concentration is > 500 IU/ml, → determine immediate cutaneous reactivity to *A. fumigatus* or use an *in vitro* test for IgE antibody to *A. fumigatus* → if results are positive, consider diagnosis on the basis of minimal criteria.
– If the total serum IgE concentration is 200-500 IU/ml → repeat measurement if there is increased suspicion for ABPA, such as disease exacerbation, and perform further diagnostic tests (immediate skin test reactivity to *A. fumigatus*, *in vitro* test for IgE antibody to *A. fumigatus*, *A. fumigatus* precipitins, or serum IgG antibody to *A. fumigatus*, and chest radiography).

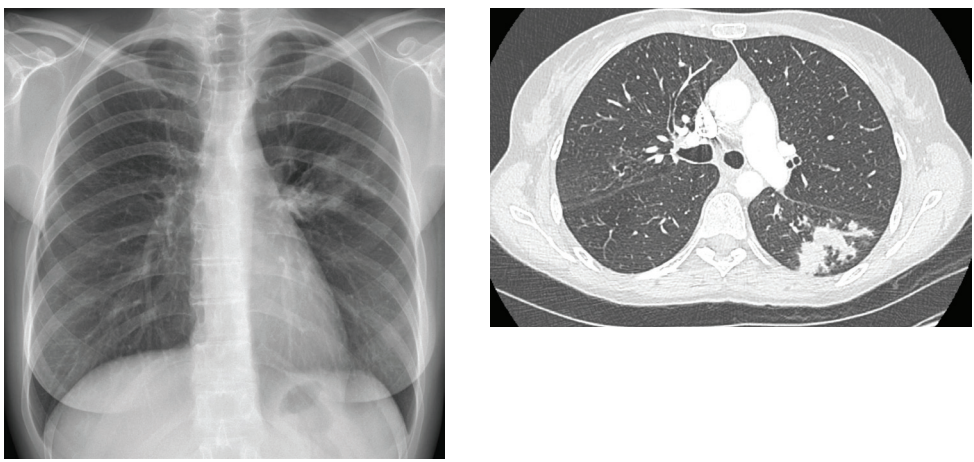
2.1 Recombinant antigens for the diagnosis of ABPA

- For therapeutic reasons, ABPA has to be clearly distinguished from sensitization to *Aspergillus*.
- A panel of recombinant antigens including Asp f2, Asp f4 and Asp f6 may allow the two conditions to be distinguished and thus it may be a useful diagnostic tool.
  - Serological investigations using Asp f4 and Asp f6 showed that specific IgE against these two allergens are detected exclusively in sera of patients with ABPA. However, larger studies are required to fully assess the diagnostic value of these new antigens.

2.2 Imaging

- CT is more sensitive than chest radiography for the detection of ABPA abnormalities (**Figure 1**).
- Radiological assessment of ABPA in patients with CF is very limited by overlapping findings in the two diseases.
- The only reported imaging abnormality seen in ABPA and not in CF is the presence of high-attenuation mucus plugs, but it is not always present.

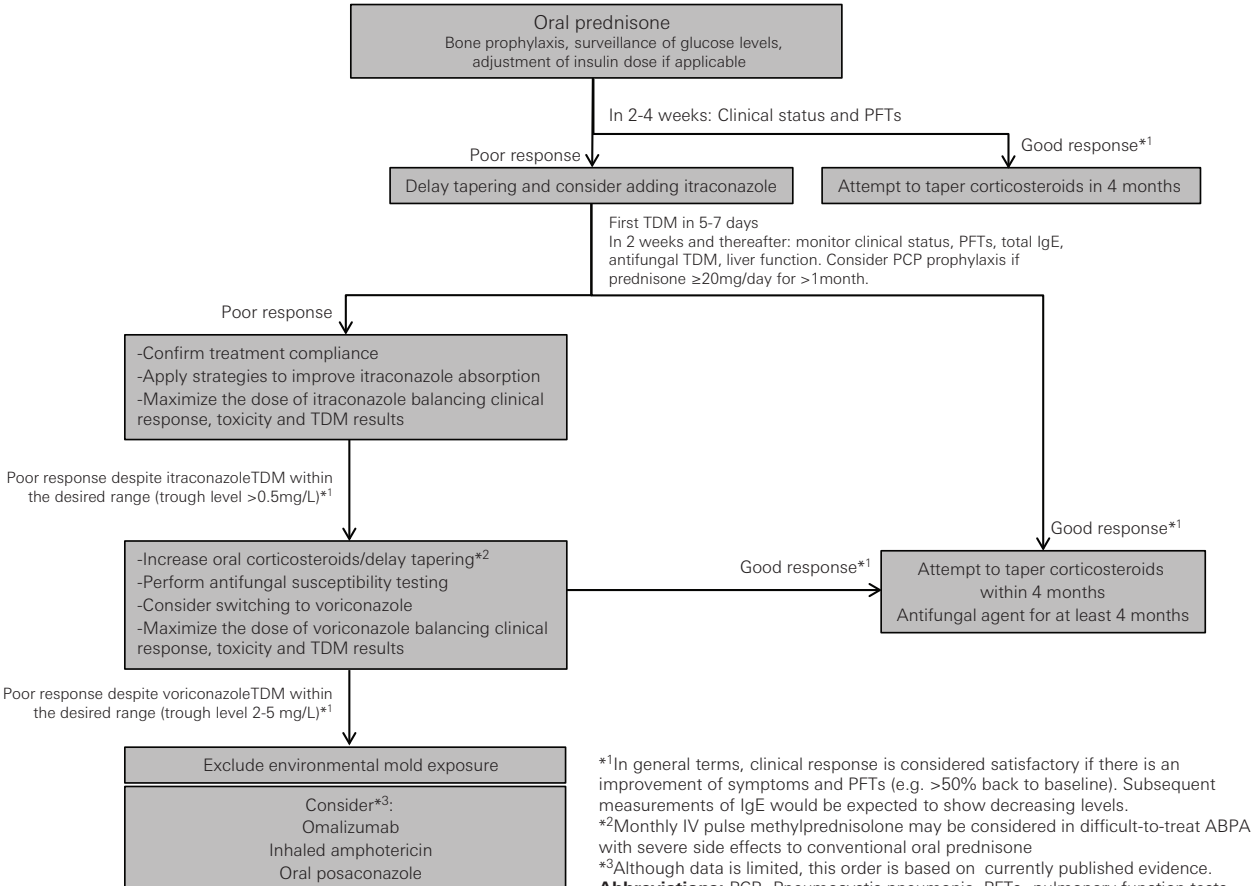
Figure 1: ABPA in a 40 year old CF female patient (delF508/R851L)



3. TREATMENT

- **Figure 2** presents a therapeutic strategy that may be applied for ABPA in CF patients and **Table 3** summarizes information on agents used for ABPA.
- **Systemic corticosteroids**: the few studies on ABPA in CF patients are small and non-controlled. Nevertheless, these limited data suggest that steroids are efficient.
  - Although precise doses and treatment duration remain unclear, currently **oral corticosteroids are considered the mainstay treatment of ABPA**.

Figure 2: Therapeutic strategy for ABPA in CF patients



*1In general terms, clinical response is considered satisfactory if there is an improvement of symptoms and PFTs (e.g. >50% back to baseline). Subsequent measurements of IgE would be expected to show decreasing levels.
*2Monthly IV pulse methylprednisolone may be considered in difficult-to-treat ABPA with severe side effects to conventional oral prednisone
*3Although data is limited, this order is based on currently published evidence.
Abbreviations: PCP=Pneumocystis pneumonia, PFTs=pulmonary function tests, TDM=therapeutic drug monitoring

- Monthly IV pulse of methylprednisolone has been administered in some patients who had difficult to treat ABPA and severe side effects to conventional oral prednisone.

- **Antifungal therapy**: steroids have no effect on Aspergillus burden. Several studies showed that antifungal therapy seems to be effective and steroid-sparing, but these studies included small numbers of patients and very few patients with CF.
  - As for steroids, precise doses and duration of the antifungal therapy remain unclear. Pragmatically and by analogy to the recommended treatment of ABPA in non-CF patients, when a combination of oral corticosteroids and antifungal therapy is used, the recommended treatment duration is at least 4 months.
  - Regarding the choice of the antifungal agent, although no comparative efficacy or safety studies exist in CF patients with ABPA usually itraconazole is the 1st choice. Although of uncertain clinical usefulness, antifungal susceptibility testing may be considered in selected cases (e.g. refractory, difficult to treat cases) to aid the choice of antifungal agent.
- **Omalizumab** (Xolair®): is a recombinant monoclonal anti-IgE antibody that has been used in patients with moderate to severe allergic asthma as a corticosteroid-sparing agent. Since elevated IgE is a central finding in ABPA, omalizumab has been used to provide symptom control and allow corticosteroid tapering in patients with poor response to the conventional ABPA treatment.
  - Case-reports in CF pediatric patients with ABPA, suggest that omalizumab may be associated with improved lung function, reduced frequency of respiratory symptoms and decreased use of systemic corticosteroids.
  - For adult CF patients, data on treatment efficacy and safety are extremely limited.
- **Inhaled corticosteroids**: Given the limited information available, inhaled corticosteroids cannot be recommended in the treatment of ABPA in CF or for prevention of fibrotic changes. However, they may be considered for the asthmatic component of ABPA.
  Note: itraconazole may enhance the adrenal suppressant effect of inhaled corticosteroids.
- **Environmental manipulation** (modification of environmental mold exposure): may be considered in refractory cases.

4. MONITORING OF TREATMENT EFFICACY

- Generally, when the therapeutic response is good, total IgE is expected to decrease after 1-2 months of treatment, eosinophilia (if initially present) to resolve, and PFTs and radiological abnormalities to improve. Imaging should not worsen under therapy.
- In addition to the evaluation of symptoms and PFTs, serial measurements of total serum IgE are used to monitor treatment efficacy
  - During treatment for ABPA: IgE levels should be measured every 1-2 months.
  - In ABPA remission: IgE levels should be measured every 3-6 months

  Note (for patients receiving omalizumab): the majority of commercially available IgE assays measure free as well as omalizumab-bound IgE. At the moment of writing the role of total serum IgE to monitor omalizumab treatment is not established.
- Follow-up chest imaging should be considered in a case-by-case basis balancing treatment implications and radiation exposure.

Table 3: Pharmaceutical agents used for ABPA

Drug	Route	Dose	Duration	Comment
Systemic corticosteroids				
Prednisone	Oral	0.5-1 mg/kg/day (max 60 mg/day) for 2-4 weeks and then consider tapering	Attempt to taper over 4 months to the lowest dose associated with no rebound in IgE, clinical symptoms, eosinophilia or new infiltrates	– After prednisone initiation, follow-up patients at least every two weeks for the first month to assess response to treatment. – Monitor and treat corticosteroid-induced adverse effects such as diabetes, bone loss, infections*[1], adrenal suppression
Methylprednisolone	IV	10-15 mg/kg/day (max 1g) for 3 consecutive days once a month	Until clinical and laboratory resolution of ABPA (6-10 courses in the literature)	– It may be considered for selected cases presenting severe adverse effects to oral corticosteroids. – It seems to be an effective and relatively safe alternative in this context; however, no long-term efficacy and safety data are currently available in the literature.

Antifungal agents*[2]				
Itraconazole	Oral	5mg/kg/day (max 600 mg/day) When daily dose exceeds 200 mg/day administer 2x/day	At least 4 months	– 1st choice antifungal agent – Monitor liver function tests, QT interval, drug interactions*[3] – Strategies to increase absorption a) Preferential use of the liquid formulation b) For the liquid formulation: administration on an empty stomach, concomitant administration with a low pH drink (e.g. orange juice, coca cola) and avoidance/spaced use of acid-blocking agents and proton pump inhibitors. c) For capsules: administration with food – TDM is required. In case of infratherapeutic levels check treatment adherence and optimize absorption. If despite these measures levels remain infratheurapeutic see footnote**[2]**
Voriconazole	Oral	Loading dose 400mg every 12h for two doses (optional) and then 200 mg 2x/day	At least 4 months	– 2nd choice antifungal agent (compared to itraconazole, voriconazole has improved gastrointestinal tolerance, better bioavailability but has been studied less, is associated more often with adverse effects and is more expensive) – Monitor liver function tests, visual disturbances, photosensitivity, QT interval, drug interactions*[3]. Voriconazole may increase the dose concentration of PPIs and vice versa (pre-emptive omeprazole dose reduction by half should be considered in patients receiving omeprazole 40mg/day or greater) – TDM is required. In case of infratherapeutic levels check treatment adherence. If levels remain infratheurapeutic see footnote*[2] – **Off-label use:** before treatment initiation, obtain approval by patient's insurance.

(continued)

Posaconazole	Oral	**Tablets:** Loading dose 300mg every 12h for two doses and then 300mg 1x/day **Solution:** 600-800mg 1x/day	Unknown	– Case report evidence (patients who did not tolerate itraconazole and voriconazole) – **The bioavailability of solution and tablets is NOT similar! During prescription always specify if the dose refers to tablets or solution.** – Monitor liver function tests, QT interval, drug interactions*[3] – TDM is required – **Off-label use:** before treatment initiation, obtain approval by patient's insurance.
Amphotericin B	Nebulized[2,3]	Liposomal, L-AMB (AmBisome®): 25 mg twice a day 3 days/week in the first month and 2 days/week for several months followed by 1 day/week [50 mg in 12 ml of WFI (4mg/ml)→nebulisation using a dedicated jet nebulizer such as PARI-Turboboy® over 15 min] or Conventional, AMB-d (Fungizone®): 10 mg twice a day 3days/week [50 mg of AMB-d dissolved in 10 ml of WFI (5mg/ml)→ nebulisation of 10mg (2ml) using a dedicated such as PARI-Turboboy® over 15 min]	Unknown	– Limited evidence in ABPA (extensive use for antifungal prophylaxis in immunocompromized patients). Different forms, doses and administration intervals have been used in the literature. – May be considered in difficult cases not tolerating oral antifungal agents or cases presenting recurrent relapses that render tapering of corticosteroids and maintenance of remission difficult. In these cases, it may replace oral antifungals (switching) or added to the oral antifungal agent. – Risk of bronchospasm: perform spirometry before and after the first dose, administer bronchodilators before each dose, consider administering inhaled or nebulized budesonide (0.5-1mg) after each dose. – Incompatible with NaCl: reconstitution with WFI only! – Reconstituted L-AMB can be stored for a maximum of 24h at 2-8°C. – Reconstituted AMB-d can be stored for a maximum of 7 days at 2-8°C. – **Off-label use:** before treatment initiation, obtain approval by patient's insurance.

Omalizumab	SC	Dose administered every 2 or 4 weeks depending on patient weight and pre-treatment IgE levels*[4]	Unknown	– No randomized controlled studies in CF patients with ABPA. – The majority of commercially available IgE assays measure free as well as omalizumab-bound IgE. At the moment of writing the role of total serum IgE to monitor omalizumab treatment is not established. – Observe patient for a minimum of 2 h following each administration (hypersensitivity/anaphylactoid reactions) – **Off-label use:** before treatment initiation, obtain approval by patient's insurance.

AMB-d=amphotericin B deoxycholate, L-AMB= liposomal amphotericin B, TDM=therapeutic drug monitoring, WFI=water for injection **(see Chapter *"Therapeutic drug monitoring")***

*[1]There is a lack of evidence for the role pneumocystis pneumonia (PCP) prophylaxis in this clinical context. In general terms, PCP prophylaxis with TMP/SMX should be considered in cases of prolonged treatment with high dose corticosteroids (e.g. ≥20mg/day of prednisone equivalent for >1month).

*[2]When itraconazole or voriconazole levels are consistently infratherapeutic in TDM, higher doses (e.g. itraconazole 200mg 3x/day or voriconazole 250-300mg 2x/day) may be considered in selected cases under close surveillance of TDM, clinical and biological toxicity. However this strategy is generally not recommended due to the risk of toxicity (variable absorption, non-linear pharmacokinetics and risk of accumulation).

*[3]Itraconazole and voriconazole inhibit CYP3A4. They may enhance the adrenal-suppressant effect of systemic or inhaled corticosteroids.

*[4]Dose calculator can be found in http://www.xolair.com/allergic-asthma/hcp/determining-the-dose.html and dose tables in http://www.xolair.com/allergic-asthma/hcp/determining-the-dose.html . These dosing recommendations were established for asthma patients. Pre-treatment IgE levels and patient weight are used to determine the dose. In these calculators, the upper limit of IgE before treatment is 700 IU/ml, which is usually lower to the IgE levels observed in CF patients with ABPA. In this case the administered dose of omalizumab should NOT exceed the maximal dose recommended for 700 IU/ml.

5. REFERENCES

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