CF Guidelines - Fungal & Aspergillus Lung Disease

Fungal & Aspergillus Lung Disease in CF:

Aspergillus is a spore releasing fungus found widely in the environment, particularly in rotting compost. Species most likely to cause disease - Aspergillosis - include Aspergillus Fumigatus (90%) and Aspergillus Flavus.

Disease classification:

- Allergic (IgE) - Asthma.
- Extrinsic allergic alveolitis.
- Allergic Bronchopulmonary Aspergillosis - ABPA.
- Non-invasive Aspergilloma - fungal ball in the lung cavity or sinus.
- Invasive - especially in those immunosuppressed included those post-transplantation, those on steroids or those with severe debility.

Colonisation of sputum has a prevalence of 40%. This does not necessarily cause disease. Culture of respiratory tract specimens for fungi may need to be specifically requested in some units. Repeated isolations, even in the absence of disease may prompt specific anti-fungal or yeast treatment and prophylaxis should be considered against yeast and fungi during intravenous or prolonged courses of antibiotics - e.g. Nystatin solution - 1ml every 6 hours, or Amphoteracin lozenges - 10mg every 12 hours. Symptomatic candidal - oral or perineal - infections require active treatment using Fluconazole - 6mg/kg loading dose followed by 3mg/kg daily for 7 - 14 days.

Asthma:

Sensitivity to inhaled Aspergillus antigen causing wheezing and bronchial hyperactivity. Symptoms can overlap with those of ABPA making diagnosis difficult. Treatment is the same as for asthma in non CF patients with the provision of a written self management plan.

Allergic Bronchopulmonary Aspergillus - ABPA:

ABPA is a serious potential cause of lung damage and is not uncommon in CF - prevalence up to 11%. Features include wheezing, pulmonary infiltrates and bronchiectasis with fibrosis. Early detection depends on screening and high clinical suspicion. Diagnosis can be difficult because atopy and a variety of serological responses to Aspergillus antigens in early life complicate the interpretation of serological markers.

Screening - based on CF foundation consensus, 2003:

- Maintain high clinical suspicion in those suffering an exacerbation but showing poor clinical response to antibiotics and physiotherapy.
- Minimum annual total IgE concentration and specific IgE to Aspergillus.

If IgE is rising, especially if over 500UI/ml or a four-fold rise in association with a high specific Aspergillus RAST consider the diagnosis of ABPA on the basis of minimal criteria - provided below.

Classical diagnosis - requires all of the following features:

- Acute/sub acute clinical deterioration with cough, wheeze, a decline in lung function and increase sputum not attributable to another cause. Suspicion is increased if clinical improvement is not observed with standard physiotherapy and antibiotics for Pseudomonal or other chest infections.

- Serum total IgE above 1,000UI/ml or a recent four fold increase rise to more than 500UI/ml. Steroids may dampen the evolution of serological markers.
- Positive skin prick test to Aspergillus - > 3mm wheel diameter with surrounding erythema whilst not on antihistamine treatment - or a positive Aspergillus RAST - grade 3 or above.
- Precipitating antibodies to Aspergillus or serum IgG antibodies to Aspergillus.
- New or recent chest X-ray infiltrates or mucus plugging or CT changes - central bronchiectasis, obliterative bronchiolitis.

Minimal diagnostic criteria - all must be present:

- Acute/sub acute clinical deterioration with cough, wheeze, a decline in lung function and increase sputum not attributable to another cause.
- Total serum IgE > 500UI/ml. If 200UI/ml - 500UI/ml and clinical suspicion of ABPA repeat in 4 - 6 weeks. If on steroids repeat when discontinued.
- Positive skin prick test to Aspergillus or positive Aspergillus RAST.

One of the following must also form part of the minimal diagnostic criteria:

- Precipitins to Aspergillus.
- New or recent chest X-ray showing infiltrates or mucus plugging.
- Not improving with standard treatment.

Supportive features of ABPA - but not diagnostic:

- Eosinophillia - above normal range.
- Sputum culture positive for Aspergillus.
- Brown/Black rubbery sputum plugs expectorated.

Treatment for Allergic Bronchopulmonary Aspergillus - ABPA:

- Oral corticosteroids:
  - Commence treatment with a dose of 2mg/kg/d for 2 weeks - max 60mg, although there are reports of higher doses being needed to achieve remission in some patients. Then lower the dosage to 1mg/kg/d for 2 weeks, finally reducing the dose further still to 1mg/kg on alternate days. Re-evaluate clinical response with a chest X-ray, IgE and lung function. Tapir the dosage on basis or response, which may take several months. A continuing low dose is required in some previously relapsing patients to prevent further relapse. Be aware of steroid side effects - mental disturbance, gastric erosions, glucose intolerance or diabetes, weight gain, osteoporosis, growth suppression, cataracts, immuno-suppressive There are case reports where Invasive Aspergillus develops during steroid treatment of ABPA.
  - Relapse is common within 2 - 3 years of the first episode. If relapse occurs, the steroid dose should be increase again and a small percentage of patients require long term steroid treatment. There is no evidence for the use of inhaled bronchodilators or asthmatic drugs - inhaled corticosteroids or leukotriene antagonists. However, they may be used for asthmatic symptoms that overlap frequently with ABPA.

- Antifungal treatment - Itraconazole:
  - Many prescribe this routinely for initial ABPA treatment - caution with adult patient. However, if not routine, consider using if sputum is positive

on a specific culture of Aspergillus, if there is a poor or a slow response to steroids and relapse episodes. Theoretically antifungal treatment reduces the fungal burden and might reduce antigenic stimulation and inflammatory response. It may reduce the long term risk of disease progression. Start with a dose of 5mg/kg/d - can be used once a day unless > 200mg per day in which case, twice daily dosing is needed. Maximum of 400mg per day. Treatment should last between 3 - 6 months in children. Liver function needs to be monitored before and during with a minimum repeat at one month an then three monthly thereafter. Itraconazole is poorly absorbed so should be given with an acid liquid - orange juice or fizzy drink. Antacids prevent absorption.

- Voriconazole:
  - There are several reports, mainly international conferences of Aspergillus Lung Disease with borderline criteria for diagnosing ABPA, responding well to Voriconazole. Consider if no clinical improvement with standard therapy and Aspergillus found on sputum specimens or BAL sample - as part of an investigation of illness being unresponsive to usual treatments. Discuss the use of Voriconazole with the microbiologist. Also consider if any radiological evidence of Aspergillus is present. There is a risk of hepatotoxicity and a range of other potential toxic reactions - See BNF 5.2

  Dosage for Voriconazole should be as follows:
  - Loading dose - day 1:
    - Intravenous - 6mg/kg bd.
    - Less than 40kg (orally) - 200mg bd.
    - Greater than 40kg - 400mg bd.

  - Maintenance dose - day 2 onwards:
    - Intravenous - 4mg/kg bd.
    - Less than 40kg (orally) - 100mg bd.
    - Greater than 40kg - 200mg bd.

Several concomitant drugs contraindicated including Rifampicin and Terfenadine. Dose adjustment may be required with Cyclosporine, Omerprasole, Tacrolimus - check on prescribing. Response should be checked weekly. Voriconazole requires renal, hepatic and FBC monitoring and may cause photo-sensitivity.

- Nebulised Amphotericin - non-liposomal:
  - This has been used in difficult cases and for recurrent sputum isolation at a dose of 5mg bd after physiotherapy - check for bronchospasm with first administration and use pre-dose bronchodilator if necessary. Late complications of ABPA include amyloidosis which should be considered if proteinuria develops occasionally with other sighns of goitre, hepatosplenomegaly, renal dysfunction and cardiomyopathy.

Invasive Aspergillosis:

Invasive disease may occur, heralded by worsening of symptoms and progression of X-ray sometimes with cavitation, haemoptysis and pleuritic pains. Fever and malaise are common, as is a rising CRP. Metastatic fungal spread is associated with severe debility and under nutrition, immunosupression, including steroids for neotropenic patients. Systemic fungal infection may be difficult to detect but blood cultures and fungal PCR’s should be requested after discussion with the microbiologists. The

treatment for Invasive Aspergillosis requires specialist microbiological input and options including intravenous liposomal Amphotericin, 1 - 3 mg/kg per day for 4 - 6 weeks and Voriconazole. Oral Flucytosine is sometimes given at the same time as Amphotericin - named patient basis only. The treatment is potentially very toxic and renal hepatic function needs to be monitored carefully, especially for hypokalaemia, hypomagnesaemia and anaemia.

Systemic Candidal Infections:

These can be associated with debility, steroids or systemic immunosupressive therapy, central line infection and diabetes. Blood cultures, candidal PCR or positive blood candidal antigens may help diagnosis. Fever, a high CRP, ocular and renal foci of infection may be found. Treatment is with intravenous Liposomal Amphotericin and the removal of infected ports - replacement should be delayed until the infection is under control, with a period of treatment between removal of old system and replacement with the new system.

Infections with organisms other than cadida alliances may occur and are more common in patients with diabetes.

References:

1, ABPA in CF - State of the Art: CF Foundation Consensus Conference, Stevens et al. Clinical infectious diseases, 2003:37 (supplement 3) S225-64
2, Ref from CF Journal Gerberk, Oades, Sheldon - Infection in Patients etc.

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