



CLINICAL AUDIT ARTICLE

Audit on the Management of ABPA in CF patients at Alder Hey Children's Hospital

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Abstract

Background: Allergic bronchopulmonary aspergillosis (ABPA) is a persistent problem for many cystic fibrosis (CF) patients. It is a challenging condition to diagnose and manage.

Aim: The CF team at Alder Hey Children's Hospital aimed to assess how consistently and effectively they were managing the condition. A diagnosis and management monitoring tool was used to systematically draw data for auditing.

Methods: Out of 87 patients under the care of the CF team, 20 had previously been diagnosed with ABPA. 60% had 4 out of the 4 minimal diagnostic criteria. 75% grew cultures positive for *A. fumigatus* at some point since their diagnosis of ABPA. All patients had received prednisolone therapy at some point since diagnosis, with 7 patients receiving the maximum starting dose of 40 mg and 1.29 mg/kg for those below maximum dose. 14 patients were prescribed antifungal therapy. 5 patients had levels ordered when they started the therapy, 5 had levels ordered between 45 and 1149 days after prescription, and 3 have had no levels ordered to date. A second audit was performed one year later to complete the audit cycle.

Results: This cohort of patients had a much higher prevalence of ABPA than the general CF population.

Discussion: Research into the relationship between ABPA exacerbation and concurrent infections or antibiotic therapy could help identify risk factors for developing an exacerbation. There should be discussions about how to improve the consistency in initial dosing of prednisolone, considering guidelines.

Conclusion: There should be more itraconazole levels taken to ensure safety and effectiveness of antifungal therapy.

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Introduction

Allergic bronchopulmonary aspergillosis (ABPA) in cystic fibrosis (CF) patients is the colonization by the fungus *Aspergillus fumigatus* in the lungs with an allergic response. ABPA occurs in approximately 10% of CF patients and accounts for about 10% of pulmonary exacerbations in these patients.¹

A. fumigatus spores are largely found in soil but may become airborne. When inhaled by a susceptible host, the fungus can colonize and produce toxic and allergenic products. The clinical features are included in Box 1.

Box 1. Clinical features of ABPA²

Symptoms: Increased wheeze, cough, production of dark sputum plugs, fever, malaise, and general deterioration.

Other features: Pulmonary deterioration that is not responding to antibacterial treatment; pulmonary infiltrates, mucoid impaction or central bronchiectasis on chest radiography; an elevated serum immunoglobulin E (IgE) (> 1000 IU/mL); presence of specific IgE anti-*A. fumigatus*; and elevated eosinophil count. The patient may have a positive skin-prick test result to *A. fumigatus* allergen.

Early symptom recognition and initiation of effective treatment are important in reducing long-term complications. There is discrepancy between various organizations' use of diagnostic criteria as patient presentation can be atypical and still show a

response to ABPA treatment. The minimum diagnostic criteria used for reference in this paper are displayed in Box 2.

Box 2. Diagnostic criteria for ABPA in CF as according to Cystic Fibrosis Consensus³

- Acute or subacute clinical deterioration (cough, wheeze, exercise intolerance, exercise-induced asthma, change in pulmonary function, or increased sputum production) not attributable to another aetiology.
- Total serum IgE concentration of 1500 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 cutaneous reactivity to *Aspergillus* (skin-prick test wheal of 13 mm in diameter with surrounding erythema, while the patient is not being treated with systemic antihistamines) or *in vitro* demonstration of 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 radiography (infiltrates or mucus plugging) or chest computerized tomography (CT) scan (bronchiectasis) that have not cleared with antibiotics and standard physiotherapy.

Diagnosing ABPA can be a significant challenge because there are a wide range of infections that CF patients are vulnerable to that can present with similar respiratory symptoms. The management of ABPA, according to the Cystic Fibrosis Trust guidelines, starts with an oral corticosteroid (prednisolone) usually given at around 0.5–2 mg/kg up to a maximum dose of 40 mg. This is then weaned down on the basis of IgE levels, chest radiography, spirometry, and pulmonary symptoms, ideally within in

2–3 months. If there is a slow or poor response to corticosteroid therapy or a second episode occurs, antifungal therapy (itraconazole) is prescribed. For patients under 12 years of age, 5 mg/kg daily is recommended, up to a maximum of 200 mg twice daily. If the patient is over 12 years of age, 200 mg twice daily is given.⁴ Individuals with ABPA often respond well to oral prednisolone, but prolonged and repeated corticosteroid use increases the risk of diabetes mellitus, osteoporosis, and impaired growth.⁵ There is also evidence that oral itraconazole is poorly absorbed by children with CF⁶; therefore, it is recommended that drug serum levels are measured during therapy.⁷ This is also important in recognizing when levels are too high, because adverse events will occur more often.⁸ It is therefore extremely important to find and maintain the balance between optimizing treatment while minimizing the risk of side effects.

The purpose of this audit is to assess the management of ABPA in CF patients treated at Alder Hey Children's Hospital. The CF team aimed to assess the rates of consistency of managing the condition and assess the importance of any trends highlighted during the audit process. The aim is to provide recommendations based on any trends or discordance with guidelines.

Methods

An ABPA “diagnosis and follow-up” form for each patient was used as the audit tool for this retrospective audit. It was formulated by the CF team at Alder Hey, and will be used throughout each ABPA patient's treatment. It includes an entry for each ABPA therapy adjustment with inclusion of measurements of IgE, lung function testing (specifically, FEV₁), liver function tests (LFTs), respiratory cultures, clinical features, and dose changes. This document helps track these test results and allows an overview of clinical response to treatment.

Data were systematically extracted from patient notes, using clinic letters, inpatient notes, and investigation results from the hospital database to retrieve IgE, LFTs, FEV₁, culture testing, and dose changes. Raw data were processed using a spreadsheet program to produce tables and graphs for data presentation. The Cystic Fibrosis Consensus Conference 2003 guidelines for ABPA diagnosis were used for diagnostic criteria.⁴ The Cystic Fibrosis Trust guidelines for treatment was used as the audit standard.⁵ A prospective second audit was performed 1 year later after discussion with the team about recommendations and changes to implement. These included further itraconazole level monitoring, improved

consistency of prednisolone dosing, and improved record keeping. Inclusion criteria included patients with a diagnosis of CF and patients with a previous diagnosis of ABPA. There were no exclusion criteria used.

Results

Demographics

Of the 87 patients with CF, 20 (23%) had previously been diagnosed with ABPA. 60% of the cohort were boys. The mean current age of the patients was 13.53 years (range 5.58–18.33) with a mean age at diagnosis of ABPA of 8.98 years (range 2.91–16.75).

Figure 1. Number of episodes experienced by each patient

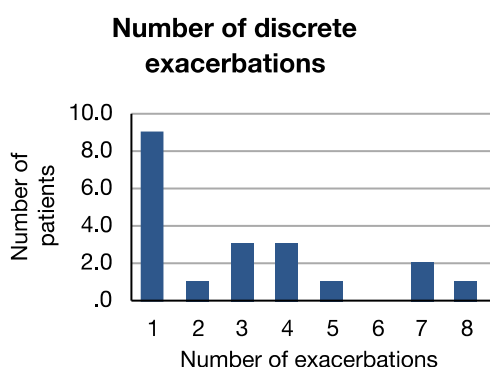


Table 2. Distribution of exacerbations

Total exacerbations	59
Mean exacerbations per patient (range)	2.95 (1–8)
Number of patients with < 0.5 episodes/year	5
Number of patients with 0.5–0.99 episodes/year	8
Number of patients with > 1 episodes/year	7
Mean number of exacerbations/year (SD)	0.93 (± 0.62)

Figure 1 and Table 2 show data on the number of exacerbations experienced by each patient.

Diagnosis

Table 1 shows a summary of the demographic data. Ages are rounded to the last month.

Figure 2 shows the proportions of patients who met the 4 minimal diagnostic criteria for ABPA diagnosis, as included above.

Figure 2. Proportions of diagnostic criteria met

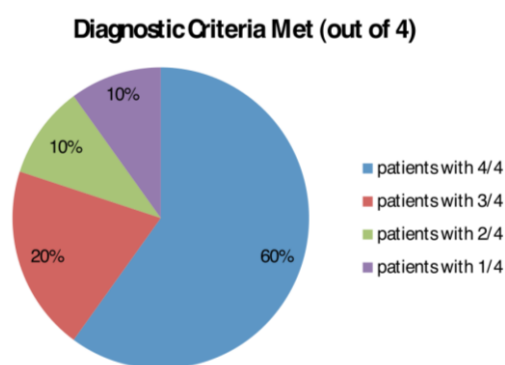


Figure 3. Prescribed doses of prednisolone on diagnosis

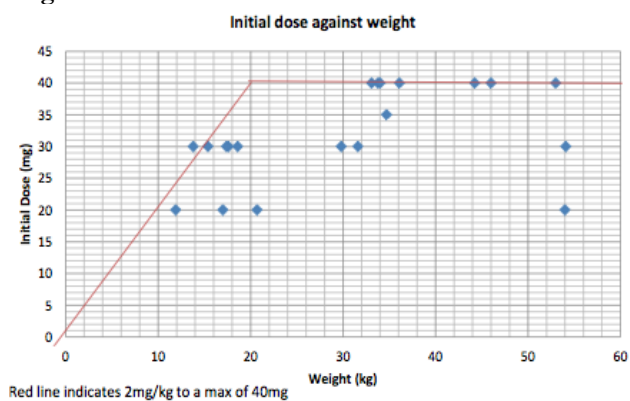


Table 1. Demographic data of patients included in this audit

Patient	Sex	Age	Age at diagnosis of ABPA	Years since diagnosis of ABPA	IgE at diagnosis is	Diagnostic criteria met	Ever grown <i>A. fumigatus</i> ?	Number of episodes
1	F	13.58	11.50	2.08	1751	1	N	2
2	M	14.33	4.08	9.75	1049	4	N	5
3	M	14.58	3.33	11.25	878	4	Y	7
4	M	12.17	3.83	8.33	199	4	Y	2
5	M	13.92	12.25	1.67	941	2	Y	1
6	M	13.00	10.50	2.50	54.7	4	Y	1
7	M	15.08	5.42	9.67	304	4	N	4
8	F	14.58	12.92	1.67	1108	2	N	2
9	F	14.42	12.83	1.58	326	3	Y	3
10	M	8.50	8.08	0.42	375	4	Y	1
11	F	18.33	8.42	9.92	2962	1	Y	7
12	F	14.50	13.92	0.58	1320	4	Y	1
13	F	5.58	3.58	2.00	224	4	Y	1
14	F	17.25	16.75	0.50	436	4	Y	1
15	M	16.92	15.50	1.42	675	4	Y	1
16	M	8.42	2.92	5.50	1312	4	Y	2
17	M	15.92	6.25	9.67	175	3	Y	2
18	M	16.92	11.17	5.75	175	3	Y	4
19	M	8.33	7.42	0.92	489	4	N	1
20	F	14.33	9.08	5.25	162	3	Y	4

6 (30%) patients had an IgE over 1000 IU/mL at diagnosis, 3 (15%) had an IgE between 500 IU/mL and 1000 IU/mL, and 11 (55%) had an IgE below 500 IU/mL. Fifteen (75%) had grown *A. Fumigatus* in respiratory cultures at some point throughout their treatment.

Prednisolone prescribing

All patients were started on prednisolone once diagnosed. Figure 3 displays the initial doses prescribed.

15 (75%) were given alternate day doses at some point during their prednisolone therapy. The total days on prednisolone during each patient's first episode ranged from 36 to 945 days, with an average of 285.95 days. 14 (70%) had their doses reduced within 2 weeks and 4 (20%) patients had not had any dose reduction by 4 weeks after first dose. 4 (20%) patients were never completely weaned off their first

prednisolone course due to a new exacerbation or because weaning was ongoing at the time of the study. During subsequent episodes 11 (55%) patients had their dose reduced within 2 weeks but 5 (25%) patients had not had a dose reduction by 4 weeks after their first dose.

Figure 4. A table to show the initial doses of prednisolone

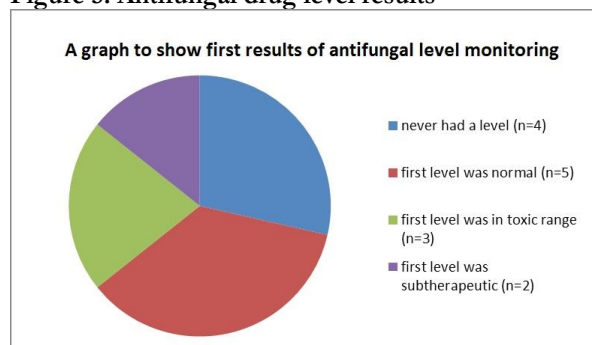
Mean starting dose mg/kg (excluding those given max dose)	1.29 (± 0.53)
No. given at maximum 40 mg	7
Number given at > 2 mg/kg	1
Number given at 1.50–1.99	5
Number given at 1.0–1.49	4
Number given at < 1 mg/kg	4

Itraconazole prescribing

14 patients were on antifungal therapy, 8 (57%) of whom were started on it at their second exacerbation. 13 patients were taking itraconazole with a mean starting dose of 260 mg a day. The average length of time patients were on itraconazole was 1282 days.

1 patient was prescribed voriconazole due to itraconazole intolerance. Figure 5 displays the results of antifungal drug level monitoring.

Figure 5. Antifungal drug level results



In patients who had an unsatisfactory antifungal medication level, the dose was changed and levels repeated until a satisfactory level was recorded.

Discussion

Key findings

This audit studied a population of patients who have a greater prevalence of ABPA than is reported in previous studies. There are significant challenges in diagnosing ABPA due to the number of differential diagnoses that could be causing an exacerbation of respiratory symptoms in a CF patient. There are challenges in achieving optimal management of the condition; it is important to achieve a balance between symptom control and the side effects that prolonged steroid use and antifungal therapy pose. The data showed inconsistencies in steroid prescribing and a

lack of therapy level monitoring for patients on this antifungal agent.

Record keeping

Only 1 patient had a “diagnosis and follow-up” form completed. The form could be an important tool in monitoring the progression of ABPA and managing it effectively, and should be filled in regularly following any change of ABPA treatment. The form displays an overview of ABPA features, treatment and investigation results. Most of the records reported the symptoms and signs that lead to suspicion of ABPA but many lacked investigation results.

Diagnosis

It is interesting to observe that prevalence of ABPA in this cohort was significantly higher than has been previously reported, at 2–10%.^{1,9} It would be useful to investigate risk factors specific to this cohort by researching their level of exposure to the fungus.

The growth of *A. fumigatus* in respiratory cultures was common (75%) but is sporadic and not related to exacerbations, so appears a weak indicator of disease. However, it may be worthwhile to see if it relates to an exposure to the fungus.

It is stated in the guidelines that when diagnosing ABPA, the clinician should be particularly suspicious if the child is over 6

years of age. However, these results show that 25% of the patients were diagnosed when under 5 years of age. This study found increased prevalence over 6 years of age, but high clinical suspicion may still be maintained in the under 5 group.

Chest imaging at diagnosis was performed in 45% of cases. Suboptimal levels of imaging could lead to misdiagnosis and the missing of bronchiectasis.

11 patients (55%) fulfilled the criteria regarding IgE levels (IgE over 1000 IU/mL or 4 times the previous level). This could suggest that it is a weaker diagnostic indicator and the level could be set lower if the criteria should still be used.

Prednisolone prescribing

The prednisolone dose chart suggests clinicians are generally prescribing prednisolone at lower doses than recommended without consistency. It appears that different clinicians may choose varying doses based on their own experience rather than on an evidence base or by using guidelines. Administering to a dose at recommended levels may improve outcomes.

It was noted that weaning off prednisolone during the first episode was more successful and took less time, than weaning in following subsequent episodes. However, it would be useful to see whether a faster

wean off medication leads to an increased likelihood of relapse. Guidelines indicate that an attempt should be made to taper off the medication by 2 to 3 months and although all patients had some dose reduction by 3 months, some of these dose reductions were small.

Itraconazole prescribing

It is stated in guidelines that itraconazole levels must be measured due to varying rates of absorption in children, and to prevent liver damage due to excess levels. 3 patients had no measurements of their levels, which is poor practice. Guidelines state the length of itraconazole therapy should be 3–6 months, with results of therapy withdrawal monitored. The mean treatment length (1282 days) greatly exceeded this. The long duration indicates a greater need for itraconazole level and LFT monitoring.

Limitations

The small sample size ($n = 20$) of the audit means any conclusions may not be reliable; however, there is a paucity of data published on the subject of ABPA. The lack of specialist knowledge of the auditors may have meant that certain important factors may have been missed, but regular discussions with the CF team were held to ensure all key features were included.

Conclusion

There are several recommendations that can be drawn from the first evaluation. Firstly, it is important that documentation fully states any diagnoses, any change of dose and the date. Furthermore, it would be useful to complete the proforma of ABPA treatment fully, to allow easy monitoring of progress.

It would be beneficial for the team to discuss a consistent method of prescribing prednisolone, whilst considering the guidelines provided on prescribing as well as clinicians' own experience of the efficacy and safety of various doses.

The team should discuss how to improve monitoring of itraconazole levels to prevent children from either being below therapeutic levels, or having high levels and risking liver damage.

Changes implemented

After presenting the conclusion and recommendations, it was agreed that the team would use the "diagnosis and follow-up" form for all patients with a diagnosis of ABPA, updating information at each outpatient clinic. The team took names of those who still needed itraconazole levels so they could be ordered at their next clinic. It was also agreed to discuss the variations in prednisolone prescribing between clinicians and agree a consistent method of deciding initial doses.

Second audit

Upon the second audit, there had been no new CF patients diagnosed with ABPA. 18 patient notes were available for data extraction. Of these, 3 had moved to adult services and as such were not included and 2 patients' notes were not available. From the remaining 15 patients, 3 episodes of ABPA had been treated within the last year, all 3 with prednisolone starting doses of 40 mg. The dosing of prednisolone was still unrelated to the patients' weight and so further discussion may be needed to elicit the reasoning of the healthcare team. Of these 3 patients, only 1 had the ABPA form completed fully, which meant that tracking prednisolone dosing and episodes was difficult. Furthermore, only 3 of the 9 patients remaining on itraconazole had their levels measured within the last year. This is still an area which needs improvement and it is recommended that all patients on itraconazole should be recalled for levels at the next clinic.

Learning points

What is already known?

- ABPA is a challenging condition for patients and for clinicians who manage it.
- Diagnostic criteria are difficult to define, with many patients not fitting the full criteria, despite responding positively to ABPA therapy.
- There are guidelines on how to manage ABPA effectively, as published by the Cystic Fibrosis Trust.

What this study adds

- Insight into the demographics of patients who have been diagnosed with ABPA in CF in the Mersey area.
- Further information on diagnostic criteria to be used in the discussion of how to define ABPA.
- Recommendations on the consistency of prednisolone dosing, based on existing guidelines.

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