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Fungal bronchitis is a distinct clinical entity which is responsive to antifungal therapy

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Abstract

Chronic productive cough in the context of exacerbations of airway disease can be associated with positive sputum cultures for fungi, in particular *Aspergillus fumigatus* and *Candida* spp., suggesting fungal bronchitis, a condition not widely recognised, as a possible cause for the exacerbation. Our objective was to determine the response to antifungal therapy in patients with suspected fungal bronchitis. Retrospective analysis of data extracted from case records of patients under secondary care respiratory clinics who had been treated with triazole therapy for suspected fungal bronchitis between 2010–2017. Primary outcome was lung function response after 1 month of treatment. Nineteen patients with fungal bronchitis due to *A. fumigatus* and 12 patients due to *Candida* spp., were included in the study. Most of the patients, particularly in the *Aspergillus* group, had allergic fungal airway disease on a background of asthma. All but one of the patients in each group were recorded as showing clinical improvement with antifungal therapy. In the majority of patients this was reflected in an improvement in lung function. *Aspergillus* group: FEV_1 (1.44 $\pm$ 0.8 L vs 1.6 $\pm$ 0.8 L: $p < 0.02$), FVC (2.49 $\pm$ 1.08 L vs 2.8 $\pm$ 1.1 L: $p = 0.01$), and PEF (260 $\pm$ 150L/min vs 297 $\pm$ 194ml/min: $p < 0.02$). *Candida* group: FEV_1 (1.6 $\pm$ 0.76 L vs 2.0 $\pm$ 0.72 L: $p < 0.004$), FVC (2.69 $\pm$ 0.91 L vs 3.13 $\pm$ 0.7 L: $p = 0.05$), and PEF (271 $\pm$ 139L/min vs 333 $\pm$ 156 L/min: $p = 0.01$). Side effects of treatment were common, but resolved on stopping treatment. This service improvement project supports the idea that fungal bronchitis is a distinct clinical entity which is responsive to treatment. Controlled clinical trials to confirm the clinical impression that this is relatively common and treatable complication of complex airway disease are required.

Keywords

Fungal bronchitis, antifungal, allergic fungal airway disease, *Aspergillus*, *Candida*

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Introduction

Fungi can cause a number of respiratory conditions due to either allergic or infective mechanisms. Allergic conditions include asthma and rhinitis, allergic fungal airway disease (AFAD), (which includes allergic bronchopulmonary aspergillosis (ABPA) and severe asthma with fungal sensitisation (SAFS)), and extrinsic allergic alveolitis.[1] Infection related conditions include the semi-invasive chronic pulmonary aspergillosis, aspergilloma and lung focused consequences of systemic infection due to immunosuppression.[2] Apart

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from avoidance of fungal exposure, the mainstay of the treatment of allergic manifestations of fungal disease are corticosteroids. Antifungal therapy is used for infection related problems, but is problematic because of variable drug concentrations in the lung, cost, adverse events, drug interactions, and drug resistance. The mycological confirmation of infection is confounded by limited biomarkers and the difficulty in distinguishing colonisation from infection. Allergic conditions can be caused both by thermotolerant fungi that can grow at body temperature and therefore germinate in the lung, and mesophilic fungi such as *Alternaria* spp., whose spores act as aeroallergens, but which do not cause infection.[3] Lung infection is only caused by thermotolerant fungi such as the genera *Candida, Aspergillus, Talaromyces* and *Penicillium*. Some patients show an overlap between allergic and infection related manifestations where signs of infection are associated with immunological markers of allergy, including raised total and specific IgE for the fungal species in question. This is particularly the case for AFAD where *A. fumigatus* is the major culprit.[4] While the role of systemic antifungal therapy is established in invasive fungal infections there is considerable uncertainty about the value of these drugs in non-invasive conditions such as AFAD.[1] We undertook a trial of voriconazole in AFAD which showed no overall benefit.[5] However, it appeared on close investigation that a small number of subjects demonstrated clinically significant improvement with voriconazole. These subjects had a productive cough whose sputum cultured strongly positive for *A. fumigatus*. In addition, we identified patients in our secondary care respiratory clinics with exacerbations of asthma where the sputum culture showed a heavy growth of *Candida* spp. We hypothesised that in a proportion of patients with airway disease, exacerbations are caused by a non-invasive infection of the airways by thermotolerant fungi, particularly *Aspergillus* and *Candida* spp., which would be responsive to antifungal therapy. We have called this complication of airway disease 'fungal bronchitis', a term coined by others to describe a similar picture in cystic fibrosis.[6] This paper represents a service improvement project (SIP) of the response to antifungal therapy in these patients.

Methods

Study design

This was a retrospective service improvement project registered in line with the governance arrangements set out by the University Hospitals of Leicester NHS Trust Clinical Audit Policy (registration number 8959e). Patients were identified from a database of patients who had been treated with antifungal therapy for suspected fungal bronchitis between 2010 and 2017 held by one of the authors (AJW), and pharmacy records. Information was extracted by one of the authors (LP), who had not been involved in their management, from case notes, the University of Leicester Mycology Laboratory, a bespoke, speciality specific, electronic record developed by the NIHR respiratory Biomedical Research Centre (BRC) (ADD database), and the UHL electronic records of laboratory tests (ILAB) and radiology (PACS). Data was recorded onto a structured proforma recording demographic and clinical details together with the physiological and clinical response to treatment. The primary outcome was the change in FEV_1 after 1 month of treatment. An improvement in lung function was defined as a 100 ml or more increase in either FEV_1 or FVC. A secondary outcome was the overall impression of the treating clinician as to whether there had been a clinical improvement in the patient's condition (annotated as improved, no change or worse). This assessment was based on the outcome in terms of symptoms of cough and sputum production, breathlessness and general well-being. Patients were included in the SIP if there was data on clinical and lung function response after a minimum of 30 days treatment. There was no randomisation or placebo group.

Treatment protocol for fungal bronchitis

Patients with suspected fungal bronchitis whose sputum cultured *A. fumigatus*, were first prescribed itraconazole (200 mg bd). If there was no benefit after 1 month or there were significant adverse reactions voriconazole (200 mg bd) was the next line of therapy. Posaconazole was used in one patient who was intolerant of itraconazole and voriconazole. For predominantly yeast bronchitis we initially used fluconazole (up to 400 mg daily). As the response was generally disappointing and some patients also grew *A. fumigatus* in their sputum, in subsequent patients we followed the same protocol as for *Aspergillus* bronchitis. Some patients had more than one episode of treatment for fungal bronchitis and in this case the best response was selected, unless one episode was for a positive yeast culture and one was for a positive *A. fumigatus* culture in which case both episodes were

included. Patients gave written informed consent for their clinical data to be reported anonymously (DAC: The value of measuring airway inflammation in the management of asthma: EDGE ID: 248, UHL Ref: 07066, Ethics Ref: 6307).

Patients

All patients were diagnosed and their treatment managed by AJW as part of their routine care associated with two specialist clinics, (difficult asthma and AFAD). The majority of subjects had asthma as their underlying airway disease. Fungal bronchitis was diagnosed when the following criteria were present: (1) A persistent cough productive of purulent or mucoid sputum, associated with a clinical exacerbation of the underlying airways disease, unresponsive to broad spectrum antibiotics or a course of high dose oral prednisolone (usually 30 mg daily for 2 weeks), (2) A positive sputum culture for *A. fumigatus* or *Candida* spp. Any culture of *A. fumigatus* was considered clinically significant, but either recurrent cultures of *Candida* spp. in the routine UHL clinical laboratory, or greater than 100 colonies of yeast per 100 mg of sputum in the University Mycology Laboratory was regarded as significant. In three patients in the *Aspergillus* group there was no data available on the sputum culture at the point treatment was started and treatment was commenced on the basis of a history of previous episodes of culture positive fungal bronchitis together with a consistent clinical picture. The advantages and risks of treatment with antifungal therapy were explained to the patients before treatment was commenced. Patients were seen 1 month after starting therapy and where possible at 3 months. The decision to treat with itraconazole was taken by AJW, but written permission from the clinical microbiologists was required for the prescription of voriconazole and posaconazole.

Laboratory and clinical investigations

All tests were undertaken for clinically indicated reasons using the routine laboratories and lung physiology service in UHL, with the exception of some sputum samples which were cultured in the University of Leicester mycology research laboratory. The UK NHS clinical microbiology protocol (hereafter referred to as the NHS protocol) is to homogenise sputum, in some instances dilute the homogenate, then plate out a small quantity ($\sim$10 µl) onto fungal growth media. In contrast, the University of Leicester protocol (hereafter referred to as the University protocol) separate sputum plugs from saliva and plate out a large volume (150 mg) of sputum plug. The University protocol has been shown to be far more sensitive for detecting filamentous fungi and allows a semi-quantitative assessment based on colony counting.[7] Spirometry was performed using a dry bellows spirometer (Vitalograph Gold Standard, Vitalograph Ltd, Maids Moreton, UK), according to standards set by the Association of Respiratory Technicians and Physiologists (ARTP).

Statistics

Data was analysed using PRISM software for a Macintosh computer using the Wilcoxon matched pairs signed rank test as the lung function data was not normally distributed.

Results

Demographics

Patients were divided into two groups based on sputum culture, those in whom *A. fumigatus* was the dominant pathogen and those in whom *Candida* spp., was dominant. There were 19 patients in the *A. fumigatus* group and 12 in the *Candida* spp., group. Demographically there was little difference between the two groups with a strikingly high percentage of patients with underlying bronchiectasis in both groups (*Aspergillus* 85%, *Candida* 73%) (Table 1).

Immunology and culture

Aspergillus group. More patients in the *Aspergillus* group were IgE sensitised to fungal allergens and had higher levels of total IgE and specific IgE to *A. fumigatus* and *Candida* spp., than the *Candida* group (Tables 1 and 2). 100% of the 11 patients who had sputum samples cultured in the University laboratory were positive for *A. fumigatus* and 4 of these 11 grew more than 100 colonies of *Candida* spp. In the NHS laboratory 50% of samples (7 of 14) were positive for *A. fumigatus* and 8 of 14 grew *Candida* spp. In the nine samples where there was paired data between the two laboratories all were positive in the university laboratory but only two were positive for *A. fumigatus* in the NHS laboratory (Table 2).

Candida group. Of the nine patients where a baseline sputum was cultured in the University laboratory seven grew greater than 100 colonies of *Candida* spp.

Table 1. Demographics.

Group (number of subjects)	*Aspergillus* predominant (19)	*Candida* spp. predominant (12)
Age (range)	66 (48–80)	59 (44–77)
Gender (f) (%)	11 (58%)	6 (50%)
Fungal sensitised (%)	16 (85%)	5 (42%)
Smoking current/past	1/7	1/5
Smoking p/y those who smoked	5–30	5–40
Average BMI (SD)	26.5 (5.07)	29 (5.6)
Bronchiectasis	16 (85%)	8 (73%)

Table 2. Fungal allergy and sputum culture.

Group (number of subjects)	*Aspergillus* predominant (19)	*Candida* spp. predominant (12)
Mean total IgE (range)	2121 (88–5000)	596 (5–2736)
Mean *AF* specific IgE (range)	19.4 (0.03–77.3)	4.96 (0–51)
Mean *AF* specific IgG (range)	54.3 (13–140)	30 (0–77)
Mean *Candida* IgE (range)	5.9 (0.01–38)	1.85 (0–16)
University *AF* +ve culture	11/11	3/9
University >100 colonies *Candida spp.*	4/11	7/9
Colonies *AF* (range)	31 (2–124)	0–3
Colonies *Candida* spp. (range)	85 (0–380)	262 (3–600)
NHS *AF* +ve	7/14	0/12
NHS lab *Candida spp.* (+ve)	8/14	10/12
Matched *AF* UHL/University	2/9	6/9
Matched *Candida* spp. UHL/University	6/9	6/9

AF: *Aspergillus fumigatus.*

Three sputum samples also grew *A. fumigatus*. In the NHS laboratory 10 of the 12 patients grew *Candida* spp. In six of the nine patients where there were paired samples from the two laboratories the sputum culture was in agreement. The majority of *Candida* species identified were *C. albicans* with *C. glabrata* and *C. tropicalis* also identified. Some patients had sputum cultures with more than one *Candida* species present.

Treatment

Thirteen of the 19 patients in the *Aspergillus* group completed at least 1 month of treatment with itraconazole, 5 required voriconazole and 1 posaconazole. We had lung function data after 3 months of treatment on eight patients treated with itraconazole, and two with voriconazole. Seven of the 12 patients in the *Candida* group completed 1 month of itraconazole, 3 of voriconazole and 2 of fluconazole. We had insufficient data to make reporting a longer period of treatment meaningful in this group (Table 3).

All but one of the patients in each group had evidence of clinical improvement assessed as described in the methods. This was maintained at 3 months of treatment in the patients where we had data. There was an improvement in lung function in 14 of the 19 patients in the *Aspergillus* group and 9 of the 12 patients in the *Candida* group after 1 month of treatment which was maintained in the 10 patients in the *Aspergillus* group where we had lung function data at 3 months (Table 3). Adverse effects were common, occurring in 10 of the 19 *Aspergillus* group, although just 1 of the *Candida* group.

Spirometry

Aspergillus group. In the *Aspergillus* group there was a significant improvement 1-month post treatment compared to baseline in FEV_1 ($p < 0.02$), FVC ($p = 0.01$), and PEF ($p < 0.02$) (Table 4). There was a further modest increase in lung function at 3 months in the 10 subjects where data was available, but this was not significantly greater than the improvement at 1 month (Table 4). The improvement in lung function was more striking in the FVC than the FEV_1. PEF was a relatively unresponsive measure. Using the definition of a 100 ml or greater improvement in either FEV_1 or FVC at 1 month 14 patients improved, 3 got

Table 3. Treatment and clinical response.

Group (number of subjects)	*Aspergillus* predominant (19)		*Candida* spp. predominant (12)
Duration (number of subjects)	One month (19)	Three months (10)	
Itraconazole treated	13	8	7
Voriconazole treated	5	2	3
Posaconazole treated	1 (0)	0	0
Fluconazole treated	0	0	2
Duration treatment (days)	30–390		35–360
Side effects (%)	10 (50%)		1 (8%)
Clinical improvement (%)	18 (95%)	10 (100%)	11 (92%)
Lung function improvement (%)	14 (74%)	10 (100%)	9 (75%)

Table 4. Spirometry *Aspergillus* group.

	AF at 1 month (19)			AF at 3 months (10)				
	Pre	Post	Sig	Pre	One month	Three months	Sig, b vs 1	Sig, 1 vs 3
FEV_1 (L)	1.44 ± 0.8	1.6 ± 0.8	$p < 0.02$	1.47 ± 0.9	1.67 ± 0.94	1.79 ± 0.8	$p < 0.02$	ns
FVC (L)	2.49 ± 1.08	2.8 ± 1.1	$p = 0.01$	2.46 ± 1.23	2.79 ± 1.26	3.00 ± 1.27	$p = 0.01$	ns
PEF (L/min)	260 ± 150	297 ± 194	$p < 0.02$	261 ± 154	297 ± 166	311 ± 149	$p < 0.02$	ns

AF: *Aspergillus fumigatus*; b: baseline; 1: 1 month; 3: 3 months; Pre: pre-treatment; Post: post-treatment; Sig: significance; ns: non-significant.

worse and 2 remain unchanged. Eleven patients improved by more than 200mls in one or other measure. At 3 months all 10 patients improved. The magnitude of the change in those where there was an increase was quite striking in some cases (Figure 1).

Candida group. In the *Candida* group there was a similar degree of improvement at 1 month in FEV_1 ($p < 0.004$), FVC ($p = 0.05$), and PEF ($p = 0.01$), (Figure 1). Nine patients improved by at least 100 mls in FEV_1 or FVC with one deteriorating and two remaining the same. Eight of the nine had a greater than 200 ml improvement.

Discussion

Fungal bronchitis describes chronic purulent sputum production due to non-invasive infection with thermotolerant fungi in the context of a relatively immunocompetent host. It is not widely used in the medical literature and the role of fungi in causing exacerbations of airway disease characterised by a productive cough is usually not considered, despite thermotolerant fungi, in particular *Candida* spp. but also *Aspergillus* spp. often being found in sputum cultures. The term '*Aspergillus* bronchitis' has been occasionally used in the context of cystic fibrosis and has also been reported in patients with COPD.[8,9] *Candida* bronchitis has also been recognised as a distinct entity and reported in acute severe asthma. However the lack of reports of antifungal agents demonstrating improvement in suspected fungal bronchitis hampers its recognition as a significant clinical condition.[10,11]

As part of a tertiary service for patients with difficult asthma and allergic fungal airway disease (AFAD), we recognised a clinical presentation of often chronic exacerbations of airway disease which were unresponsive to standard treatment with broad spectrum antibiotics or high dose oral corticosteroids, in which sputum culture was positive for either *A. fumigatus* or *Candida* spp. Usually the sputum was white/creamy or brown rather than the green associated with bacterial infection, and was very mucoid or rubbery in consistency. Treatment with antifungal agents appeared to be beneficial in these patients. We believe our paper offers convincing support for the relevance of sputum fungal growth in the context of exacerbations of airway disease, with clinical improvement in nearly all patients and objective improvement in lung function in the majority, which could be striking, especially considering this is a group of people where fixed airflow obstruction is a common finding.[12] Cough and sputum production

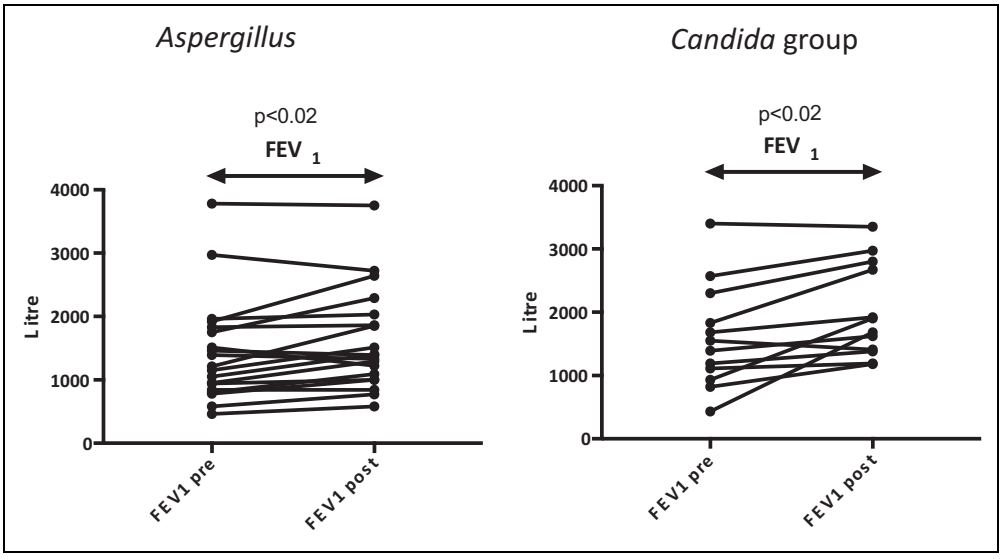

Figure 1. FEV1(in litres) before and after one month treatment with anti-fungal therapy in patients diagnosed with fungal bronchitis due to Aspergillus(1a) and Candida spp. (1b). There was a significant improvement in both groups ($p<0.02$ Wilcoxon matched pairs signed rank test).

were reduced and general well-being enhanced. Improvement in some patients was maintained long term, whereas others appeared vulnerable to repeated events. Improvement where it occurred, was generally evident within 1 month of treatment. This was in contrast to the FAST study of itraconazole in AFAD where improvement in quality of life took several months to become evident, but consistent with the marked reduction in fungal burden after the first month of treatment that occurred in the EVITA[3] study of voriconazole in AFAD.[5,13]

A positive sputum culture for thermotolerant fungi is critical for the diagnosis of fungal bronchitis. Unfortunately, the UK wide standardised methodology for fungal culture is insensitive so that many cases are missed.[7] Furthermore, *Candida* spp., which are commonly cultured in sputum, are usually disregarded as being a commensal, even where recurrent positive cultures are present and the patient suffers from chronic sputum production.[14] Quantification and species identification of the *Candida* isolates would be helpful as we found quite high rates of non-*C. albicans* species in our patients which may have more pathogenic potential. In addition, we have found that counts of >50 colonies Candida spp., per 100 mg sputum are rarely seen in healthy subjects, but is common in airway disease, particularly COPD (CHP pers. obs.). It is likely that treatment with inhaled corticosteroids, which all the patients were taking, increases the likelihood of a positive sputum culture for *Candida* and possibly for *A. fumigatus*.[15] It is also possible that inhaled corticosteroids increase the risk of fungal bronchitis, but considering the near universal use of these drugs in asthma and related airway diseases it can only be a minor effect. It is therefore clear from our service improvement project that in some patients the *Candida* is contributing to a persistent bronchitis with impaired lung function. Most of the *Aspergillus* group had underlying AFAD, whereas the *Candida* had a more mixed profile of airway disease.

Even when confidently diagnosed, treatment of fungal bronchitis is not straightforward. Itraconazole is sometimes not effective and is poorly tolerated. Resistance can occur, particularly if patients have had several courses. It is important to monitor blood levels and biochemistry and blood counts for potential adverse events. Other triazoles have similar problems and are more restricted in their use because of expense. This discourages physicians from prescribing, and patients from accepting antifungal therapy.

This study has a number of weaknesses consistent with its retrospective and uncontrolled design. Recruitment bias was possible. For example patients who improved may have been recalled more readily than those where treatment has failed. All the patients who fitted the criteria for the study (as noted in the study design section of the methods) were offered treatment irrespective of whether their positive culture was from the NHS or University laboratory and

the great majority took up the offer. One or two patients declined because of concern about side effects and for the purposes of this study they were lost to follow up. There was a significant amount of missing data and the measurement of clinical improvement based on an overall clinical impression rather than standardised measurements lack robustness. The numbers of patients were relatively small. Nonetheless the clear improvement in lung function in many subjects is objective evidence of a positive response to treatment. This could reflect regression to the mean or a response to the corticosteroid enhancing effect of itraconazole, but most of the patients had been under the clinic for some months with exacerbations which were resistant to oral corticosteroids, so neither of the above would be a satisfactory explanation for the relatively rapid improvement seen with antifungal therapy.

The role of antifungal therapy in the treatment of AFAD is controversial, with the small number of controlled studies showing minor benefit at best. Against this there are a number of case reports and series suggesting improvement with treatment with antifungal agents in AFAD related conditions.[16] The main consequence of fungal involvement in the lung in AFAD is damage which we would suggest is primarily due to allergic mechanisms.[17] However, we suggest that a small sub-set of patients, particularly those where lung damage has already occurred leading to local weaknesses in host-defence, can develop overgrowth of fungi in the bronchi leading to an infective bronchitis which is responsive to antifungal therapy. This paper supports the need for controlled, prospective studies of antifungal therapy in this group of patients to test this hypothesis.

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