Cystic fibrosis (CF) is a systemic chronic disease and abnormalities in CFTR (Cystic fibrosis transmembrane conductance regulator) function affect interactions between the epithelial surface and microorganisms such as fungi. Conidial spores are usually cleared by airway epithelium; however, in CF due to disruption of epithelial barrier and germination of the fungi induce inflammatory response. Increased mucus viscosity and lung injury result in an ongoing cycle of infection, inflammation and pulmonary damage. Aspergillus, the most commonly detected filamentous fungi in CF induces this abnormal pulmonary inflammation. The main Aspergillus- associated clinical manifestations include allergic bronchopulmonary aspergillosis (ABPA), Aspergillus colonization, Aspergillus bronchitis, and Aspergillus sensitization.

**Diverse clinical characteristics of Aspergillus growth in patients with cystic fibrosis**

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**Abstract**

**Background and objectives.** Patients with cystic fibrosis (CF) have a varying spectrum of clinically significant Aspergillus disease in addition to allergic bronchopulmonary aspergillosis (ABPA). Here we aimed to review the different clinical phenotypes related with Aspergillus growth on the airway culture of patients with CF, we also aimed to investigate the effect of Aspergillus growth on lung function tests.

**Method.** The medical records of 100 patients with CF who had Aspergillus growth on airway culture within the period of April 2001 and June 2016 were retrospectively analyzed. Age, gender, symptoms, physical examination findings, pulmonary function tests, the diagnosis of ABPA, and airway culture results were recorded for every visit. Patients with Aspergillus growth on airway cultures were classified into different groups as ABPA, Aspergillus sensitization, Aspergillus colonization and Aspergillus bronchitis.

**Results.** Medical records of 83 patients and 147 sputum cultures were attained from 100 patients. The mean age of the patients was 17.6±7.6 years and the mean age of the first Aspergillus growth in sputum was 12.5±6.7 years. At first isolation, Aspergillus fumigatus SC was the most common Aspergillus SC in sputum (76.3%) and 14.5% of these patients required hospitalization. Aspergillus sensitization was diagnosed in 3.6% (n= 3) of the patients. Aspergillus colonization was diagnosed in 18.1% (n= 15) of all patients and led to a decline in FEV1%, FVC% and FEF25-75% which was not statistically significant, furthermore. ABPA was detected in 9.6% (n= 8) of all patients and led to a statistically significant decline in FEV1% (p= 0.02); nonsignificant decline in FVC% and FEF25-75%. Aspergillus bronchitis was detected in 43.4% (n= 36) of all patients and led to nonsignificant decline in FEV1%, FVC% and FEF25-75%.

**Conclusion.** ABPA is recognized as the most common Aspergillus associated disorder in CF patients and is related to deteriorated pulmonary function tests; however Aspergillus colonization and bronchitis may also be associated with worsening lung function.

**Key words:** cystic fibrosis, aspergillus colonization, aspergillus sensitization, ABPA, aspergillus bronchitis.

Cystic fibrosis (CF) is a systemic chronic disease and abnormalities in CFTR (Cystic fibrosis transmembrane conductance regulator) function affect interactions between the epithelial surface and microorganisms such as fungi. Conidial spores are usually cleared by airway epithelium; however, in CF due to disruption of epithelial barrier and germination of the fungi induce inflammatory response. Increased mucus viscosity and lung injury result in an ongoing cycle of infection, inflammation and pulmonary damage. Aspergillus, the most commonly detected filamentous fungi in CF induces this abnormal pulmonary inflammation. The main Aspergillus- associated clinical manifestations...
in CF are Allergic Bronchopulmonary Aspergillosis (ABPA), *Aspergillus* sensitization, *Aspergillus* colonization, *Aspergillus* bronchitis and, rarely aspergilloma and invasive disease.\(^1\)

ABPA is a hypersensitivity response to *Aspergillus* antigens; the prevalence of ABPA changes from 2 to 8%, and lung function has been shown to deteriorate over time related with ABPA. The increasing prevalence of *Aspergillus* sensitization has also been reported from 20 to 65% recently and separate from CF-ABPA, *Aspergillus* sensitization has significant clinical effects on lung function and patient morbidity.\(^1,3,4\) The term ‘colonization’ defines the presence of a microorganism which causes neither symptoms nor immunologic response. *Aspergillus* bronchitis was first described by Shoseyov et al.\(^5\) for patients with CF who had respiratory exacerbations non-responsive to appropriate antimicrobial therapy, cultured *Aspergillus* from sputum and responded to antifungal therapy. Few studies have addressed the role of *Aspergillus* on lung function in CF. However, the effect of colonization and *Aspergillus* bronchitis on lung function other than ABPA is not clear.\(^1\)

Recommendations for the treatment of ABPA in patients with CF are now clearly described; however, the pathogenic role of *Aspergillus* and the benefit of treatment of an *Aspergillus* bronchial infection remain to be clarified in clinical conditions other than ABPA. There is also no consensus on the antifungal therapies of CF patients presenting with persistent *Aspergillus*-positive cultures or those with sensitization to *Aspergillus*.\(^6,8\)

Here we aimed to review the different clinical phenotypes related with *Aspergillus* growth on the airway culture of patients with CF and we also aimed to evaluate the effect of *Aspergillus* growth on lung function of these patients. Our second aim was to review the risk factors affecting the growth of *Aspergillus* in airway culture of patients with CF.

**Material and Methods**

**Subjects**

In this retrospective cohort study, medical records of children with a diagnosis of CF (two positive sweat chloride tests (≥60 mmol/L) and/or genotype confirmation) treated at our tertiary care centre between April 2001 and June 2016 who had *Aspergillus* growth in sputum culture were evaluated.

Age, gender, symptoms, physical examination findings, pulmonary function tests including Forced expiratory volume in the first second (FEV1), Forced vital capacity (FVC), Forced expiratory flow between 25% and 75% of the FVC (FEF25-75), and airway culture results were recorded for every visit. “Increase in symptoms” were defined as increased cough, sputum, dyspnea or fever; new physical examination findings were also defined newly detected lung sounds like rale or rhonchi that were not defined on clinical follow-up of the patient. Immunological data included total immunoglobulin E (IgE), specific anti-*A. fumigatus* IgE in all patients and specific anti-*A. fumigatus* IgG only in two patients as it is not routinely performed in our hospital. Skin prick test reactivity to *Aspergillus* antigen and treatment modalities were also recorded in all patients. Patients were followed every three months. Spirometric data were recorded for three years.

**Microbiological methods**

Airway cultures were taken at each visit to our centre from all patients. Respiratory cultures of the patients were inoculated onto 5% sheep blood agar, MacConkey agar, chocolate agar with bacitracin, mannitol salt agar and *Burkholderia cepacia* selective agar. Bacterial isolates were identified by conventional methods and automated bacterial identification systems (BD Phoenix, USA; or VITEK 2, bioMerieux, France). Mycological cultures were plated on Sabouraud dextrose agar (SDA) and incubated at 35 ± 2°C and 25 ± 2°C for seven
Identification of *Aspergillus* strains at species complex (SC) level were performed using conventional mycological methods.9

**Definitions**

Patients with *Aspergillus* growth on airway cultures were classified into different groups according to criteria defined by Baxter et al. and Shoseyov et al.5,10,11 As *Aspergillus* specific IgG testing is not available in our hospital, we could not use *Aspergillus* specific IgG for this classification.

1- *Aspergillus* colonization: Two or more *Aspergillus fumigatus* SC positive cultures in any 12 months during the study period without elevation of total IgE and *A. fumigatus* specific IgE.

2- *Aspergillus* sensitization: Elevation of total IgE and *A. fumigatus* specific IgE without fulfilling the diagnostic criteria of ABPA. *A. fumigatus* specific IgG is not elevated. Because of missing data of *Aspergillus* specific IgG in our cohort, we defined sensitization depending on clinical criteria, total IgE and *A. fumigatus* specific IgE.

3- *Aspergillus* bronchitis: Due to missing examinations of sputum galactomannan, *Aspergillus* specific DNA and serum specific IgG in our cohort, *Aspergillus* bronchitis was defined according to these criteria; clinical deterioration with positive sputum cultures for *Aspergillus*, no antibiotic treatment response, total serum IgE level <200 kU/l, no observation of new pulmonary infiltrates and appropriate antifungal treatment response with the exclusion of ABPA.5,12 Because of missing data of *Aspergillus* specific IgG; differential diagnosis with colonization was made depending on clinical deterioration of these patients.

4- ABPA diagnosis was based on the criteria published in the ABPA consensus paper that included five or more of the following: (a) Acute or subacute clinical deterioration not attributable to another etiology; (b) Total serum IgE concentration higher than 500 IU/ml; (c) Skin prick test reactivity to *Aspergillus*; (d) Presence of serum IgE antibodies to *A. fumigatus* (higher than 0.35 kU/l); (e) Precipitins or IgG antibodies to *A. fumigatus*; (f) New or recent pulmonary infiltrates, mucus plugging, or bronchiectasis with no response to antibiotics and physiotherapy.13

This study was approved by the local institutional review board in 2018 with the number GO/18/271-43.

**Statistical analysis**

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 23.0 (SPSS Inc., Chicago, IL, USA). The Kolmogorov-Smirnov test was used to determine whether the variable had a normal distribution. Means and standard deviations (SD) were calculated for continuous and numbers (percentages) for categorical data. More than two independent groups were compared using One-Way Anova and Tukey post-hoc test for normal continuous variables or Kruskal-Wallis test and Bonferroni adjusted Mann-Whitney U test for non-normal continuous variables. Mann-Whitney U test was used to compare continuous variables between independent two groups. Chi squared test was performed to compare proportions between groups. Logistic regression was used to analyse the effects of potential factors on *Aspergillus* growth. Repeated measures of variance analyses were used for yearly lung function test changes of patients. Mean FEV1 and FVC decline were expressed as the annual average change in FEV1% and FVC% during one year period by simple regression analysis. Statistical tests were two-sided and statistical significance was accepted at p <0.05.

**Results**

There were 100 patients with *Aspergillus* growth in airway culture during the study period. From these, medical records of 83 patients and 147 airway cultures of these patients were attained. The mean age of all patients was 17.6 ± 7.7 years and the mean age of the first *Aspergillus* growth
in airway culture was 12.5 ± 6.7 years. Male to female ratio was 47/36. 26.5% (n= 22) of patients have F508 homozygous deletion, 16.8% (n= 14) of patients have F508 heterozygous deletion and 56.4% (n= 47) of patients have other CFTR mutations.

Fifty-three patients had *Aspergillus* growth more than once. Bronchiectasis was detected in 91.6% (n= 76) and pancreatic insufficiency was noticed in 100% (n=83) of the patients. Chronic *Pseudomonas aeruginosa* and chronic *Staphylococcus aureus* colonization were detected in 49.4% (n= 41) and 48.2% (n= 40) of patients, respectively.

At first isolation, *A. fumigatus* SC was the most common SC of *Aspergillus* in airway cultures (76.3%). 25.3% (n= 21) of the patients had *Aspergillus* growth once a time and asymptomatic at first isolation. The remaining 62 patients were classified into different groups. ABPA was diagnosed in 9.6% of patients (n= 8) and totally ABPA was diagnosed 24 times of these eight patients in this period. *Aspergillus* sensitization was detected in three patients and *Aspergillus* colonization was detected in 18.1% (n=15) of the patients. *Aspergillus* bronchitis was detected in 43.4% (n= 36) of the patients. Table I shows the clinical characteristics of patients at first isolation according to diagnosis of ABPA, *Aspergillus* colonization, *Aspergillus* bronchitis and *Aspergillus* sensitization.

In three years of follow up, ABPA led to statistically significant decline in FEV1% (p= 0.02). Although decline in FVC% and FEF25-75% were also present; these findings were not statistically significant.

*Aspergillus* colonization and *Aspergillus* bronchitis also led to decline in FEV1%, FVC% and FEF25-75% which was not statistically significant in these patients furthermore. Table II shows the change of lung function tests within the time in patients with ABPA, *Aspergillus* colonization and *Aspergillus* bronchitis. Figure 1 and Figure 2 also show the graphic of the lung function tests within the groups of ABPA, *Aspergillus* colonization and *Aspergillus* bronchitis. The decline of FEV1% (p= 0.45) and FVC% (p= 0.10) were not statistically significant between the groups furthermore. We did not include the change of lung functions in the group with *Aspergillus* sensitization due to small number of patients in this group. The mean FEV1 decline within the groups of ABPA, *Aspergillus* bronchitis and *Aspergillus* colonization was 5.5%, 3.3%, 2.2% per year and the mean FVC decline within the groups of ABPA, *Aspergillus* bronchitis and *Aspergillus* colonization was 6.2%, 3.8%, 0.3% per year respectively in the following three years.

![Fig. 1. Change of FEV1% in patients with ABPA, *Aspergillus* colonization and *Aspergillus* bronchitis.](image1)

![Fig. 2. Change of FVC% in patients with ABPA, *Aspergillus* colonization and *Aspergillus* bronchitis.](image2)
Table 1. Demographic and clinical characteristics of patients with ABPA, *Aspergillus* colonization, *Aspergillus* bronchitis and *Aspergillus* sensitization.

| ABPA | Aspergillus colonization | Aspergillus bronchitis | Aspergillus sensitization | P  |
|------|--------------------------|------------------------|---------------------------|----|
| Number of patients, n | 8 | 15 | 36 | 3 |
| Age at last visit (years), Mean (±SD) (Min-Max) | 18.6 (± 4.2) | 18.6 (± 4.5) | 18.4 (± 5.5) | 19.7 (± 5) | 0.95 |
| Age at first *Aspergillus* isolation (years), Mean (±SD) (Min-Max) | 13.6 (± 4.1) | 12.3 (± 6.9) | 13.6 (± 5) | 11.2 (± 5.1) | 0.71 |
| CFTR mutation, n | 0.66 |
| F508 del homozygous | 2 | 3 | 10 | 2 |
| F508 del heterozygous | 1 | 5 | 4 | 1 |
| Other | 4 | 7 | 22 | 0 |
| Increase in symptoms at first isolation, n (%) | 7 (87.5%) | 6 (40%) | 23 (63.9%) | 0 | 0.01 |
| New physical examination finding at first isolation, n (%) | 5 (62.5%) | 5 (33.3%) | 20 (55.6%) | 0 | 0.10 |
| Bronchiectasis, n (%) | 8 (100%) | 15 (100%) | 35 (97.2%) | 3 (100%) | 0.70 |
| Chronic *P. aeruginosa* colonization, n (%) | 5 (62.5%) | 9 (60%) | 17 (47.2%) | 3 (100%) | 0.23 |
| Chronic *S. aureus* colonization, n (%) | 4 (50%) | 8 (53.3%) | 15 (41.7%) | 1 (33.3%) | 0.77 |
| Pulmonary function tests at first isolation, Mean (±SD) | 55 (± 24) | 76 (± 10) | 60 (± 19) | 64 (± 45) | 0.22 |
| FEV1% | 59 (± 22) | 87 (± 11) | 68 (± 20) | 64 (± 10) | 0.08 |
| FVC% | 47 (± 24) | 62 (± 25) | 49 (± 23) | 45 (± 13) | 0.68 |
| Aspergillus SC, n | 0.004 |
| *A. fumigatus* | 2 | 13 | 27 | 1 |
| *A. flavus* | 4 | 0 | 3 | 2 |
| *A. terreus* | 1 | 0 | 3 | 0 |
| *A. niger* | 0 | 0 | 2 | 0 |
| *Aspergillus* spp. | 1 | 0 | 1 | 0 |
| Coinfection with other pathogens at first isolation, n | 0.59 |
| No growth | 1 | 2 | 3 | 0 |
| *S. aureus* | 2 | 4 | 12 | 0 |
| *H. influenza* | 0 | 0 | 1 | 0 |
| *S. pneumonia* | 0 | 1 | 0 | 0 |
| *P. aeruginosa* | 3 | 4 | 8 | 3 |
| Acinetobacter | 0 | 0 | 0 | 0 |
| *S. aureus* and *P. aeruginosa* coinfection | 2 | 4 | 12 | 0 |
| Inhaled antibiotic at first isolation, n | 0.90 |
| Inhaled tobramycin | 4 | 5 | 11 | 1 |
| Inhaled colimycin | 0 | 1 | 1 | 0 |
| Treatment at first isolation, n | 0.001 |
| Oral antifungal treatment | 6 | 12 | 32 | 3 |
| Intravenous antifungal treatment | 2 | 0 | 0 | 0 |
| Steroid treatment | 8 | 0 | 0 | 0 |
| Hospitalization, n | 3 | 2 | 7 | 0 | 0.42 |

ABPA: allergic bronchopulmonary aspergillosis, CFTR: cystic fibrosis transmembrane conductance regulator gene, FEV1: forced expiratory volume in the first second, FVC: forced vital capacity.

FEF25-75: forced expiratory flow between 25% and 75% of the FVC.
The risk of *Aspergillus* growth in airway cultures was not affected significantly by the age, CFTR mutation, symptoms, physical examination findings, radiological findings, sputum culture results and inhaled antibiotic treatment in logistic regression analysis.

**Discussion**

*A. fumigatus* SC is one of the main fungal subgroup found in CF airways and results in different clinical states and wide range of host responses affecting the progression of CF lung disease. In this retrospective cohort, we reviewed different clinical phenotypes of *Aspergillus* growth on the airway culture of patients with CF classified as *Aspergillus* colonization, *Aspergillus* bronchitis, *Aspergillus* sensitization and ABPA.7,11

The prevalence of *Aspergillus* colonization ranges from 10 to 57% with increasing age in CF patients.14 de Vrankrijker et al.15 reported a cohort of 259 CF patients and found 61 (23.5%) of these patients had *A. fumigatus* colonization according to the criteria of having more than 50% positive sputum cultures in a given year. The prevalence of *Aspergillus* colonization in pediatric CF patients is not well established yet. In our cohort we reported 18.1% of patients with *Aspergillus* colonization. Saunders et al.16 also reported 22% of children fulfilled the criteria for *A. fumigatus* colonization within eight years of study period. The prevalence of ABPA in patients with CF varied from 3 to 25% and the prevalence of *Aspergillus* sensitization varied from 20 to 65% in a metaanalysis by Maturu et al.17 Our cohort revealed 9.6% of ABPA patients. In our cohort we had three patients with sensitization. Baxter et al.10 and Shoseyov et al.5 defined *Aspergillus* bronchitis as repeatedly *Aspergillus* growth in sputum samples without hypersensitivity to *Aspergillus* and with persistent respiratory symptoms and no response to antibiotics in patients with CF. Baxter et al.10 reported 30% of patients with *Aspergillus* bronchitis in their adult cohort. In our cohort we also reported 43.4% of patients with *Aspergillus* bronchitis similar to these results.

Few studies have reported the association between age and risk of *Aspergillus* isolation. Saunders et al.16 reported that the isolation of *A. fumigatus* was common in children older than 10 years and most of the older children.

### Table II. Lung functions of patients in different groups.

| Lung function test | *Aspergillus* bronchitis (n=12) p | *Aspergillus* colonization (n=6) p | ABPA (n=5) p |
|-------------------|------------------|------------------|----------|
| FEV1%, mean±SD    | 0.41             | 0.09             | 0.02     |
| First year        | 64.1 ± 18.4      | 83 ± 10          | 68 ± 17  |
| Second year       | 63.6 ± 19.4      | 73.6 ± 8         | 53.2 ± 12.5 |
| Third year        | 54.1 ± 23.5      | 76.3 ± 7.7       | 51.5 ± 14.6 |
| FVC%, mean±SD     | 0.31             | 0.14             | 0.22     |
| First year        | 81.3 ± 11.9      | 85.6 ± 0.5       | 67.3 ± 23.5 |
| Second year       | 79 ± 9.9         | 76 ± 7.2         | 53.6 ± 13.2 |
| Third year        | 69.8 ± 21.5      | 84.6 ± 5         | 48.6 ± 17.7 |
| FEF25-75%, mean±SD| 0.41             | 0.26             | 0.12     |
| First year        | 49.8 ± 22.3      | 62.3 ± 10.5      | 56 ± 17  |
| Second year       | 42 ± 18.8        | 47.3 ± 5.5       | 35 ± 7.7 |
| Third year        | 39.8 ± 20.1      | 58.3 ± 10.6      | 40 ± 13.7 |

ABPA: allergic bronchopulmonary aspergillosis, FEV1: forced expiratory volume in the first second, FVC: forced vital capacity, FEF25-75: forced expiratory flow between 25% and 75% of the FVC.
eventually became persistently colonized. We also found that the mean age of the first Aspergillus growth in airway culture was 12 ± 6.6 years similar to this study. In our cohort the risk of Aspergillus colonization was not affected significantly by age, CFTR mutation, symptoms, physical examination findings, radiological findings, sputum culture results and inhaled antibiotic treatment. Colonization of the airways by A. fumigatus usually develops after chronic colonization with P. aeruginosa. Noni et al.18 concluded that their patients with colonization were not found to have significantly higher P. aeruginosa colonization and inhaled antibiotic treatment rates similar to our study. However Bargon et al.19 suggested that prophylactic antibiotics may cause A. fumigatus colonization. Another study by Burns et al.20 concluded the use of inhaled tobramycin increased A. fumigatus isolation in the treatment group, at the end of the study period. According to our findings, it is difficult to say whether there is a causal relationship between the use of inhaled antibiotics and A. fumigatus colonization. However most of our patients were using inhaled tobramycin at first isolation of Aspergillus.

There are few studies investigating the role of A. fumigatus on lung function in CF, and these studies have not shown significant lung function decline in patients colonized with A. fumigatus.21 Bargon et al.19 found no significant association between A. fumigatus colonization and lung function, in their adult CF patients. Although the decline of FEV1, FVC and FEF25-75 in our cohort with Aspergillus colonization, these findings were not statistically significant. Other retrospective cohort analysis on 163 patients with Aspergillus colonization also did not find any differences regarding lung function decline during the study period.22 A causal relationship was not shown, but this study suggests that A. fumigatus may influence lung functions and risk of pulmonary exacerbations. However, in another cross-sectional study with 7010 CF patients from the European Epidemiologic Registry of Cystic Fibrosis, Aspergillus colonization was associated with impaired lung functions.23 In Canada, a retrospective cohort study of pediatric non-ABPA CF patients showed that two or more respiratory samples positive for A. fumigatus in any given year was associated with a significant reduction in FEV1 and a significant increase in pulmonary exacerbations requiring hospitalization compared with pediatric CF patients without A. fumigatus in respiratory samples.22

Noni et al.18 showed that A. fumigatus chronic colonization and lung function decline may have a causal relationship. Patients with A. fumigatus chronic colonization had significantly lower lung function in a seven-year prospective study period. Also baseline FEV1 was statistically different between groups before colonization and this may have led to the chronic colonization in these patients. Saunders et al.16 also reported that A. fumigatus colonization may be associated with worse lung functions.

Aspergillus sensitization and its association with poorer lung function in CF lung disease was investigated by a number of studies.4,8 Baxter et al.10 revealed that CF patients with Aspergillus sensitization showed a significantly higher FEV1 decline over two years compared to the group of patients without sensitization. We could not estimate the effect of Aspergillus sensitization on lung functions, because of the small number of patients in our cohort. Furthermore, Fillaux et al.3 reported that, ABPA, Aspergillus sensitization and persistent carriage have an impact on pulmonary functions in CF patients. Aspergillus bronchitis is also associated with lung function decline in patients with CF.1,5 Aspergillus bronchitis led to decline in FEV1%, FVC% and FEF25-75% in our cohort which is not statistically significant.

Kraemer et al.24 showed a significant negative effect of ABPA on FEV1 in a retrospective study with 122 mostly pediatric CF patients. Baxter et al.10 also reported, CF patients with ABPA had significant FEV1 decline over a two year study period compared to other patients without
ABPA. Our findings also showed that the most prominent lung function decline was in patients with ABPA which was not statistically significant as shown in Figure 1.

Aspergillus colonization and infection are treated with antifungal agents such as azoles, however ABPA is usually treated with corticosteroids additionally with itraconazole or voriconazole.6,25 There is only one published prospective, randomized, controlled study investigating the effect of antifungal therapy on pulmonary outcomes in CF patients.26 Due to the retrospective nature of our study we have limited results about the effect of antifungal therapy on pulmonary outcome.

Our findings are limited by the retrospective nature of data collection and low numbers of the patients and the lack of longitudinal data for Aspergillus classification stages in the relevant subgroups. Also because this is a retrospective study of CF patients with Aspergillus growth, we could not compare the results with other CF patients as a control group. It can be assumed that patients can change within the different classification stages and that the classification status is probably not stable. We could not classify the patients depending on immunological results due to missing examinations of Aspergillus-specific IgG in these patients, we also defined sensitization, Aspergillus bronchitis, and colonization depending on the clinical criteria. Also due to a small number of patients having performed spirometry, evaluation of the lung function tests within years is difficult to estimate the prognosis of colonization, sensitization and ABPA in CF patients.

In conclusion, our study provides evidence for the significant effect of Aspergillus colonization on lung functions and emphasizes that chronic colonization should be considered pathogenic in CF patients. However, the most important question that requires addressing is the clinical significance of the fungi detected in CF and whether eradication needs consideration.

Prospective controlled studies with treatment arms are an important requirement for this field to progress.

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