

Original Article

Increasing Total Serum IgE, Allergic Bronchopulmonary Aspergillosis, and Lung Function in Cystic Fibrosis

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What is already known about this topic? Allergic bronchopulmonary aspergillosis (ABPA) is a hypersensitivity disorder complicating cystic fibrosis (CF) lung disease but also occurring in asthmatics. ABPA diagnosis is still challenging and relies on a combination of clinical, radiological, and immunological criteria.

What does this article add to our knowledge? Monitoring changes in total IgE (Δ IgE) levels facilitates clinical diagnosis of CF-related ABPA. A Δ IgE-based treatment decision seems to promote a favorable long-term pulmonary outcome in sensitized patients.

How does this study impact current management guidelines? Current total IgE cutoff values might be too high especially in children and provoke underestimation of ABPA. In *Aspergillus fumigatus*-sensitized patients, doubling of total IgE levels within 3 months exceeding normal range may indicate treatment requiring ABPA.

BACKGROUND: Allergic bronchopulmonary aspergillosis (ABPA) is a hypersensitivity disorder contributing to lung disease in cystic fibrosis (CF) and challenging to diagnose.

OBJECTIVE: This study analyzed the predictive value of increasing total IgE (t-IgE) levels in a CF cohort alongside with clinical and serologic data.

METHODS: A total of 387 children and young adults were followed from 2000 to 2006 and retrospectively classified into 6 groups. Patients with t-IgE levels < 95th percentile and without specific *Aspergillus fumigatus* (Af)-IgE were classified as “Naïve,” those with Af-specific IgE (Af-sIgE) as “Sensitized.” Patients with elevated t-IgE at entrance and Af-sIgE were labeled “Former ABPA,” and those without, as “High t-IgE.” Patients whose t-IgE values started normal and exceeded the 95th percentile during the study were labeled either “ABPA at risk” if Af-sIgE-positive or “Rising t-IgE” if not. Courses of t-IgE over time were divided into episodes with increasing IgE (Δ IgE) and related to pulmonary outcome.

RESULTS: A total of 125 patients were classified Naïve (32%), 64 Sensitized (17%), 49 ABPA at risk (13%), 32 Rising t-IgE

(8%), 102 Former ABPA (26%), and 15 High t-IgE (4%). A total of 874 Δ IgE episodes were accompanied by forced expiratory volume in 1 second (FEV₁) declines ($r = -0.21$, $P < .0001$). Steroid treatment of severest Δ IgE episodes resulted in improved long-term pulmonary outcomes ($P < .01$). This FEV₁ preservation effect was only detectable if t-IgE levels at least doubled within 3 months and exceeded the 95th age-specific percentile ($P < .05$).

CONCLUSIONS: Δ IgE obtained from the course of t-IgE levels may be helpful in diagnosing treatment requiring ABPA and predicts the effect of systemic steroid treatment on pulmonary outcome. © 2017 Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2017;■:■-■)

Key words: Allergic bronchopulmonary aspergillosis; ABPA; *Aspergillus fumigatus*; Cystic fibrosis; CF; IgE; Lung function

Cystic fibrosis (CF) is a systemic disease resulting from mutations in the cystic fibrosis transmembrane conductance regulator gene.¹ Although chronic infection with bacteria like *Pseudomonas aeruginosa* (Pa) is known to cause chronic lung disease with tissue damage,² the role of fungi including *Aspergillus fumigatus* (Af) is less well understood. The prevalence of allergic sensitization against Af differs between studies and is around 40% in cystic fibrosis patients.³ Allergic bronchopulmonary aspergillosis (ABPA) is a hypersensitivity disorder observed in patients with CF at a frequency of approximately 9% in pediatric and 10% in adult patients.³ Often the course may be relapsing and ABPA substantially contributes to progressive lung damage and formation of bronchiectasis.⁴ Despite progress in understanding the underlying immunologic mechanisms and novel diagnostic options like basophil activation in the blood or sputum galactomannan, the diagnosis of ABPA in the clinical setting is still challenging.^{5,6} This is reflected by the

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Abbreviations used

ABPA- Allergic bronchopulmonary aspergillosis
Af- *Aspergillus fumigatus*
Af-sIgE- *Af*-specific IgE
 BMI- Body mass index
 CF- Cystic fibrosis
 FEV₁- Forced expiratory volume in 1 second
Pa- *Pseudomonas aeruginosa*
 RAST- Radioallergosorbent test
 t-IgE- Total IgE

evolution of different diagnostic criteria over the years, the earliest being proposed by Rosenberg et al in 1977 and Nelson et al in 1979.^{7,8} Several modifications were made by Greenberger and Patterson⁹ as well as the CF Foundation Consensus Conference.¹⁰ All published criteria rely on a combination of different parameters. These include wheezing, obstructive deterioration of lung function, the presence of infiltrates or central bronchiectasis in chest imaging, increased total IgE (t-IgE) value as well as elevated *Af*-specific IgE (*Af*-sIgE) and IgG (*Af*-sIgG), evidence of immediate skin test reactivity, serum precipitins or peripheral eosinophilia, the detection of *Af* in sputum, and the physicians suspicion.¹¹ All these variables are difficult to define. For example, the proposed threshold for t-IgE varies between 417 IU/mL and 1000 IU/mL.^{9,10,12}

Nevertheless, changes in t-IgE values have already been suggested to indicate ABPA.¹³ Being easily accessible and observable over time in clinical routine makes them a very promising diagnostic tool. Here we report the longitudinal course of t-IgE levels in a large and well-defined cohort of patients.

METHODS**Study design**

This was a single-center, retrospective cohort study on all patients treated at the Cystic Fibrosis-Center of the Munich University Children's Hospital. The study was approved by the local research ethics board (EK 16/5/2008).

Subjects

The study included patients of all age seen at least once in the CF outpatient service from January 1, 2000, to December 31, 2006. The diagnosis of CF was confirmed by the typical phenotype, a pathologic sweat test result, and frequently the presence of 2 disease causing mutations. All patients were followed in our outpatient CF service at 3-month intervals. Usually blood was withdrawn (half-annually in patients below 10 years) and lung function tested.

Children started lung function measurements between the ages of 4 and 6 years. Normal values in children were those of Zapletal and Samanek¹⁴ and for adults those of Quanjer et al.¹⁵ For the overall change in lung function, the first and the last forced expiratory volume in 1 second (FEV₁) value (% predicted) of the study period were compared and adjusted for the time of study (Δ FEV₁(%)/years) in patients who were followed for at least 1 year.

Body mass index (BMI) was obtained at study entrance and exit. BMI percentiles were calculated using the data of Hemmelmann et al for adults¹⁶ and Neuhauser et al for children.¹⁷ Changes in BMI percentiles were adjusted for the time of study (Δ BMI-Perc/year) in all patients followed for more than 1 year.

Routinely the diagnosis of ABPA was made by the physician during clinical care and treated by systemic steroids. Their first

administration during the study period was evaluated separately. Criteria for the routine diagnosis of ABPA included worsening of clinical status (shortness of breath, changes in sputum production, brown crumbles in sputum, weight loss), airway obstruction in lung function testing, new weak infiltrates on chest X-ray, laboratory (t-IgE as well as *Af*-sIgE, eosinophilia), and sputum test results. The diagnosis of asthma was made according to national guidelines.¹⁸

Serum determinations

t-IgE levels were measured routinely on every blood sampling done (N Latex IgE mono, BN ProSpec System, Siemens AG, Munich, Germany). An age-dependent 95th percentile of t-IgE levels was determined by summarizing different reference values¹⁹⁻²⁴ obtained in various European or Northern American populations (Table E1, available in this article's Online Repository at www.jaci-inpractice.org). Specific IgE levels against *Af* antigen were obtained at least once a year by the department of clinical chemistry using different commercial kits (CLA-1 Luminometer, Hitachi Chemical Diagnostics Inc., Tokyo, Japan; Allercoat 6 Mikrotiter-ELISA, Euroimmun AG, Lübeck, Germany; RA-Allergen-Panel, ADL-Matritech GmbH, Freiburg, Germany). Specific IgG levels against *Af* were not measured routinely, but to explore classic ABPA criteria, we analyzed *Af*-sIgG in all patients at first ABPA treatment from stored serum samples (Pharmacia UNICAP 100 System, Peapack, NJ). Skin prick tests were not performed routinely.

Cross-sectional assessment of clinical conditions

The impact of different CF-related conditions known to affect the long-term outcome were analyzed in a cross-sectional design for the last year of observation (Table E2, available in this article's Online Repository at www.jaci-inpractice.org).

Classification of patients according to t-IgE and *Af*-sIgE

Patients were divided into 1 of 6 groups retrospectively: (1) "Naïve" patients were defined as those who neither had elevated t-IgE levels during the study period nor *Af*-sIgE. (2) "Sensitized" were patients with detectable *Af*-sIgE, but whose t-IgE levels never exceeded the 95th percentile. (3) "ABPA at risk" patients had t-IgE levels below the 95th percentile at study entrance, which increased above the 95th percentile during the study period in the presence of *Af*-sIgE. (4) "Rising t-IgE" patients showed the same increase in t-IgE but lacked *Af*-sIgE. (5) "Former ABPA" patients were subjects who had detectable *Af*-sIgE and entered the study already with a t-IgE level above the 95th age-related percentile. (6) Patients with elevated t-IgE values at study entrance not being sensitized to *Af* were grouped as "High t-IgE" (Figure 1).

Definition of Δ IgE episodes

Next we analyzed the individual courses of t-IgE levels in patients whose values exceeded the 95th percentile at least once during study period (groups "ABPA at risk," "Rising t-IgE," "Former ABPA," and "High t-IgE"). The patient's individual t-IgE course was retrospectively assessed for periods of increasing levels. These periods were defined by a minimum relative change between the t-IgE baseline and peak levels of 5%, and called Δ IgE episodes. Additionally, associated FEV₁ measurements were recorded for each Δ IgE episode. There was no minimum or maximum duration of a Δ IgE episode. To standardize episodes, the whole episode length was divided into regular follow-up periods of 90 days. Three months' changes in t-IgE and FEV₁ were calculated as proportions from total episode changes.

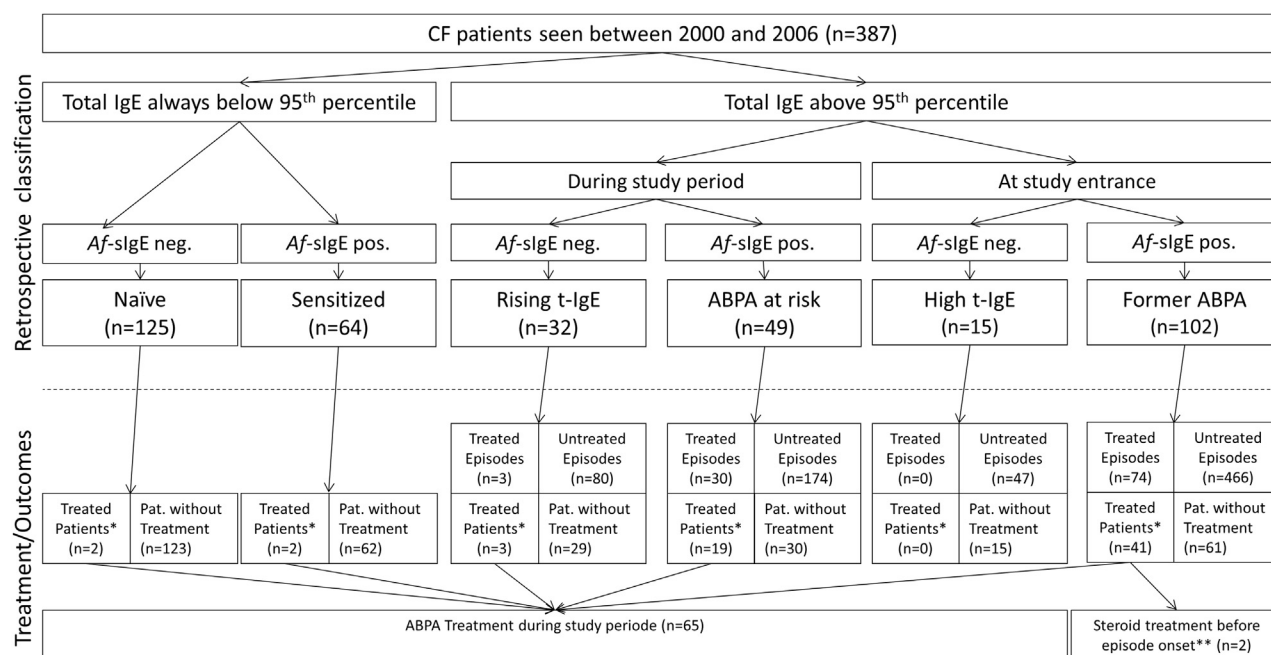


FIGURE 1. Classification of patients into different groups according to their t-IgE levels and specific IgE against *Af*. A total of 12 patients had a non-ABPA-directed systemic steroid therapy that was excluded from the analysis: 7 had acute obstructive episodes suggested to be virus-induced and treated for up to 3 days, and 4 patients took oral steroids for 5 days to treat CF-related arthropathy or arthritis. One patient was on an oral steroid regimen due to a leukocytoclastic vasculitis. The concomitant diagnosis of asthma was made in 10 patients with CF. None of them received oral steroids, but all had intermittent inhaled corticosteroid treatment courses. *Patients with unexplained worsening of lung function, no improvement after iv-antibiotic course. **Patients treated with steroids because of other reasons than ABPA within a Δ IgE episode (leukocytoclastic vasculitis, arthritis). ABPA, Allergic bronchopulmonary aspergillosis; *Af*, *Aspergillus fumigatus*; CF, cystic fibrosis; *sIgE*, specific IgE.

Because numbers and durations of Δ IgE episodes varied between subjects, each patient's episode bearing the greatest change in t-IgE levels was identified and used for comparisons. All patient records were screened for systemic steroid intake and the time points were linked to Δ IgE episodes.

Statistics

Data were expressed as median and range unless otherwise stated using Graph Pad Prism 6 (GraphPad Software, La Jolla, Calif). *P* values lower than .05 were considered statistically significant. Correlation was determined using Spearman's correlation coefficient. Differences in between groups were analyzed by the Mann-Whitney *U*-test or analysis of variance/Kruskal-Wallis test with Dunn's *post hoc* testing. Group differences in the cross-sectional analyses were evaluated using Fisher's exact test.

RESULTS

Study cohort

387 patients with CF at a median age of 10.7 years at study entrance (48% males) were analyzed during a longitudinal period of 7 years (Table I, Figure 1). Most patients were followed for the entire 7-year study period (Figure E1, available in this article's Online Repository at www.jaci-inpractice.org). During the study, the overall relative decline in FEV₁ (% predicted) was $-0.4\%/year$. A slight increase in t-IgE levels was seen ($+1.4$ IU/mL/year). Further clinical and demographic characteristics are detailed in

Table I as well as in Tables E3 and E4 (available in this article's Online Repository at www.jaci-inpractice.org).

Classification of patients according to t-IgE and Af-sIgE

Thirty-two percent of the study cohort (125/387) were classified Naïve and 64 subjects (17%) were Sensitized. Increasing t-IgE levels were observed in 81 patients (21%), with *Af*-sIgE being detectable in 49 of 81. In 117 patients (30%), t-IgE values were increased at study entrance. Those were further separated into 102 Former ABPA (26%) and 15 High t-IgE (4%) (Figure 1). The *Af*Naïve, ABPA at risk, and Rising t-IgE groups were younger at study entry (median age 6.4, 7.3, and 4.8 years, respectively) than *Af*Sensitized, Former ABPA, and High t-IgE patients (13.1, 14.1, and 14.9 years, respectively) ($P < .0001$) (Figure E2 and Table E4, available in this article's Online Repository at www.jaci-inpractice.org).

t-IgE courses

The t-IgE levels were nearly stable over time in the *Af*Naïve, *Af*Sensitized, and Former ABPA groups (median $+1$ IU/mL/year, $+0$ IU/mL/year, and -1 IU/mL/year, respectively) (Figure 2). Although a clear increase in t-IgE values was seen in ABPA at risk and Rising t-IgE patients (25 and 19 IU/mL/year, respectively), a decrease was observed in the High t-IgE subjects (-15 IU/mL/year).

TABLE I. Baseline characteristics of subjects and median change over 7-year study period

Clinical characteristic (n = 387)	At study entrance	Change per year studied
Age (y)	10.7 [0; 41.6]	
Male	186 (48%)	n.a.
F508 del homozygous	205 (53%)	n.a.
F508 del heterozygous	133 (34%)	n.a.
FEV ₁ (% predicted)	87 [14; 147]	−0.4 [−12; +28]
BMI percentile	29 [0; 100]	−0.3 [−31; +50]
t-IgE (IU/mL)	49 [0; 3849]	+1.4 [−372; 1828]

BMI, Body mass index; FEV₁, forced expiratory volume in 1 s; n.a., not applicable; t-IgE, total IgE.

Data are expressed as median [range]. In the longitudinal calculations, only those patients were included who had repeated measurements for at least 1 year (n = 359). An overall decline in FEV₁ (% predicted) of 0.6% per year was seen when only analyzing the patients observed for the whole study period.

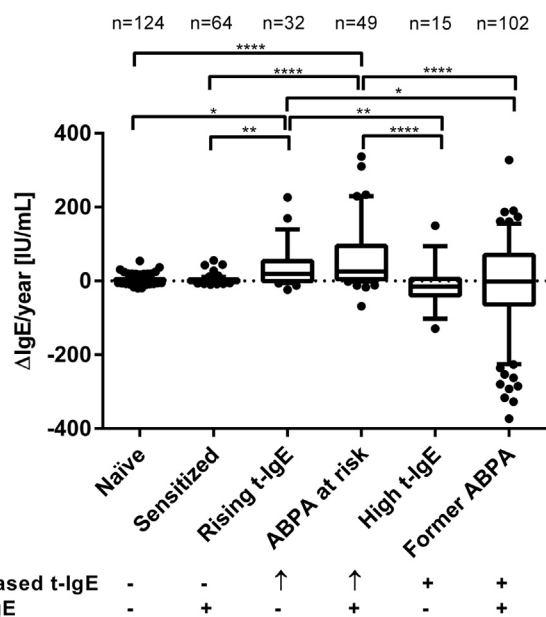


FIGURE 2. Changes of t-IgE levels according to different groups. Boxes show median and interquartile range; whiskers highlight 10th and 90th percentile. Differences were calculated based on the first and the last measurement during the study period. Kruskal-Wallis test: $P < .0001$. * $P < .05$, ** $P < .01$, *** $P < .001$, **** $P < .0001$. ABPA, Allergic bronchopulmonary aspergillosis; Af, *Aspergillus fumigatus*; sIgE, specific IgE; t-IgE, total IgE.

ΔIgE episodes

Patient groups having a least a single t-IgE value above the 95th percentile, that is, ABPA at risk, Rising t-IgE, Former ABPA patients, and High t-IgE, were investigated in detail for their individual t-IgE courses to identify ΔIgE episodes, whereas the patient groups always exhibiting t-IgE levels below the 95th percentile were not further studied. Overall t-IgE elevations during episodes were correlated with deteriorations of FEV₁ (% predicted) ($r = -0.20$; $P < .0001$) (Figure 3). During

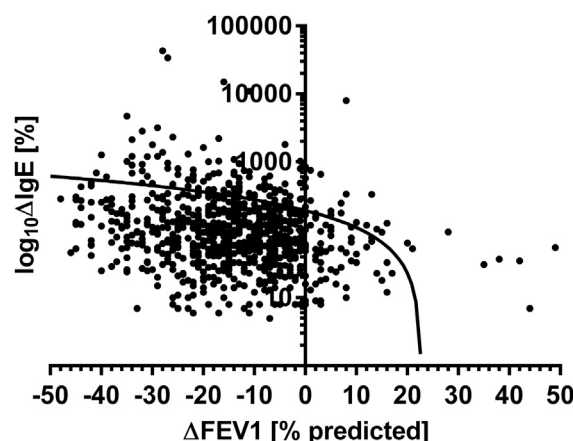


FIGURE 3. Episode-specific changes of t-IgE levels and FEV₁ (n = 824). Spearman correlation coefficient: $r = -0.20$ ($P < .0001$; 95% confidence interval: -0.27 to -0.14). FEV₁, Forced expiratory volume in 1 s.

the 874 ΔIgE episodes identified, median ΔIgE was +93% associated with a ΔFEV₁ of −14%. The median episode length was 160 days (Table II).

ΔIgE episodes were divided into those not associated with any ABPA directed treatment and those during which patients were treated with systemic steroids (Table II). Episodes treated with systemic steroids (n = 107) differed significantly from nontreated episodes (n = 767) in terms of ΔIgE and ΔFEV₁ ($P < .0001$ for each). ABPA treatment was initiated with a median starting dose of 1.3 mg/kg prednisone per day (range 0.2–17.4 mg/kg/day). The median duration of corticosteroid treatment was 20 days (range 2–224 days). Looking at the possible side effects of steroid treatment, we observed a significant difference in diabetes prevalence between treated and untreated patients of the ABPA at risk and Former ABPA groups ($P = .017$) (Table E2, available in this article's Online Repository at www.jaci-inpractice.org). This effect was completely abolished when looking at age-range-matched subgroups (data not shown). No differences were found in chronic *Pa* infection prevalence when looking at age-matched patient groups ($P = .4192$). Height *z* scores did not differ ($P = .1882$) and there was one case of cataract in a patient who underwent multiple courses of steroids. Additional treatment with itraconazole was used in 85% of cases at a dosage of 5 to 10 mg/kg/day continued for 3 months without drug level monitoring on a regular basis. ABPA at risk and Rising t-IgE patients had a median increase in t-IgE values of 289% during their first treated ΔIgE episode, accompanied by a decline in FEV₁ of 32% (n = 22). Similar but less pronounced changes were observed in Former ABPA patients during their first treated episode during the study period, that is, t-IgE was +173% and ΔFEV₁ −25% (n = 39), whereas the median episode duration was somewhat shorter (217 days vs 145 days, not significant).

The Consensus Criteria published in 2003 were retrospectively applied to the treated patients.¹⁰ Only 3 of 18 ABPA at risk and Rising t-IgE patients fulfilled the Consensus Full Criteria, and 8 of 20 met the Consensus Minimal Criteria (data were lacking in 4 and 2 patients, respectively). In the group of Former ABPA patients, Consensus Minimal Criteria were

TABLE II. Characteristics of Δ IgE episodes

	No treatment		Treatment			
	All episodes	All untreated episodes	All treated episodes	All first treated episodes	ABPA at risk + Rising t-IgE First treated episodes	Former ABPA First treated episodes
Number	874	767	107	61	22	39
Δ IgE (%)	93% [5; 43,333]	90% [5; 43,333]	131% [6; 15,030] $P < .0001$	187% [6; 2,841]	289% [25; 1,557] n.s.	173% [6; 2,841]
Duration of episode (d)	160 [2; 940]	161 [2; 940]	146 [12; 749] n.s.	160 [12; 749]	217 [12; 728] n.s.	145 [37; 749]
Δ IgE/3 mo	57% [0; 13,007]	54% [0; 10,598]	91% [4; 13,007] $P < .0001$	97% [4; 2,503]	109% [15; 2,503] n.s.	97% [4; 1,710]
Δ FEV ₁ (% predicted)	-14% [-73; +53]	-13% [-65; +53]	-25% [-73; +21] $P < .0001$	-26% [-73; +21]	-32% [-73; -3] n.s.	-25% [-57; +21]
Fulfilling Consensus Minimal Criteria	ND	ND	ND	38/57 (4)	8/20 (2)	30/37 (2)
Fulfilling Consensus Full Criteria	ND	ND	ND	12/42 (19)	3/18 (4)	9/24 (15)
Missing Consensus Minimal Criteria due to total IgE < 500 IU/mL			ND	ND	12/12	7/7

ABPA, Allergic bronchopulmonary aspergillosis; FEV₁, forced expiratory volume in 1 s; ND, not determined; n.s., not significant; t-IgE, total IgE.

Data are shown as median [range]. Number of subjects for whom data are lacking is shown in parentheses. Consensus Criteria were used according to Stevens et al.¹⁰ Comparisons were made between first treated episodes of ABPA at risk + Rising t-IgE and Former ABPA patients as well as between all treated vs all untreated episodes using the Mann-Whitney U-test.

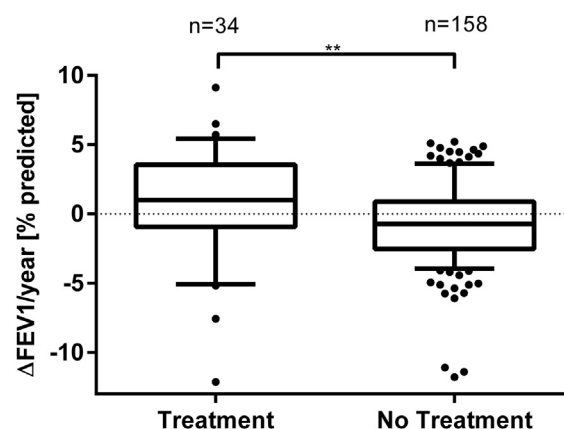


FIGURE 4. Effect of treatment of the most severe Δ IgE episode during the study period on long-term pulmonary outcome. Patients from the ABPA at risk group, Rising t-IgE group, and the Former ABPA group were analyzed with respect to ABPA treatment of the severest Δ IgE episode. Boxes show median and interquartile range; whiskers highlight 10th and 90th percentile. Mann-Whitney U-test: $P = .0049$ (**). Showing comparable age, the *Pa* status in both groups was similar (Fisher's exact test: $P = .4192$). ABPA, Allergic bronchopulmonary aspergillosis; FEV₁, forced expiratory volume in 1 s; *Pa*, *Pseudomonas aeruginosa*.

achieved in 30 of 37 patients but only 9 of 24 met the Full-Criteria (data were lacking in 2 and 15 patients, respectively). Of 63 treated patients, 60 (95%) had detectable *Af*-sIgE. The 3 patients who were *Af*-sIgE-negative at the time of treatment later on developed *Af*-sIgE. The clinical characteristics of these patients are depicted in Table E5 (available in this article's Online Repository at www.jaci-inpractice.org).

Effect of steroid treatment on long-term outcome

Long-term FEV₁ courses of the 6 different groups varied significantly ($P = .04$) (Figure E3, available in this article's Online Repository at www.jaci-inpractice.org), whereas BMI percentiles presented comparably (Figure E4, available in this article's Online Repository at www.jaci-inpractice.org). To assess the long-term impact of steroid treatment on FEV₁ courses, treated and untreated groups had to be compared. Because patients displayed variable numbers of Δ IgE episodes and treatment courses, we focused on the patient's episode with the largest impact on t-IgE levels. Among these patients, a distinct beneficial effect of steroid treatment was detectable ($P = .0049$; Figure 4).

Changes of t-IgE levels during 3-month periods and doubling of t-IgE level (Δ IgE/3 months $\geq 100\%$) as a diagnostic tool

Because the length of the Δ IgE episodes was variable between subjects, we focused on 3 months' intervals (Table II). The median Δ IgE within 3 months (Δ IgE/3 months) was different between treated and untreated episodes (91% vs 54%, $P < .0001$, Table II). A total of 264 Δ IgE episodes with at least a 100% increase of t-IgE levels within 3 months, that is, Δ IgE/3 months $\geq 100\%$, were recorded. Each patient's episode with the greatest change in t-IgE levels was analyzed with respect to the Δ IgE/3 months $\geq 100\%$ criterion and possible treatment

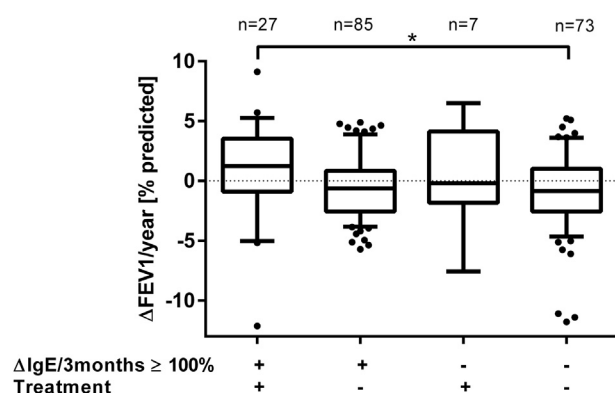


FIGURE 5. Treatment effect of the most severe Δ IgE episode on long-term pulmonary outcome depending on at least doubling of Δ IgE within 3 months. In the groups having Δ IgE episodes with Δ IgE/3 months $\geq 100\%$, 27 of 27 (100%) treated patients and 64 of 87 untreated patients (74%) were specific *Af*-IgE-positive. Kruskal-Wallis test: $P = .033$. * $P < .05$. *Af*, *Aspergillus fumigatus*; FEV₁, forced expiratory volume in 1 s.

intervention (Figure 5, Figure E5, available in this article's Online Repository at www.jaci-inpractice.org). The patients with Δ IgE/3 months $\geq 100\%$ derived a significant benefit from steroid treatment (FEV₁/year +1.2%/year, $n = 27$, $P = .008$). This positive effect of treatment could not be observed in patients with less than a 100% increase in t-IgE (−0.2%/year, $n = 7$). However, a stronger deterioration was seen in patients without treatment (−0.6%/year and −0.9%/year, respectively). Additional consideration of accompanying FEV₁ changes did not augment the discriminatory power of Δ IgE-based treatment decision making (Figure E6, available in this article's Online Repository at www.jaci-inpractice.org).

DISCUSSION

This study demonstrates the benefit of observing the course of t-IgE values to identify treatment requiring ABPA.

First, the treatment of the patient's severest Δ IgE episodes by systemic steroids resulted in a favorable long-term pulmonary outcome and was well tolerated. The median starting dose of prednisone in our cohort was higher than in recent recommendations.^{25,26} The duration of corticosteroid treatment was rather short but displayed high variability. Significant differences in diabetes prevalence, height z scores, or *Pa* infection rates due to steroid treatment could not be observed when looking at age-range-matched subgroups. However, it must be kept in mind that this analysis was retrospective and may have missed such effects.

Looking at long-term FEV₁ courses regardless of steroid treatment, different trends are visible. The negative impact of *Af* sensitization observed in our cohort has already been described by several authors. Nicolai et al reported independent negative correlations between *Af*-radioallergosorbent test results and flow-volume curves.²⁷ Baxter et al observed lung function deteriorations in adult patients with CF with elevated *Af*-sIgE,²⁸ whereas others found worse lung functions in children with repeated *Af* detection in sputum cultures.²⁹ Additionally, Wojnarowski et al found an adverse effect of

Af sensitization on the lung function of children with CF.³⁰ Interestingly, it was observed only in patients with additional elevated t-IgE levels, whereas those with normal t-IgE values despite *Af* sensitization performed like *Af* Naïve CF controls. However, the observation period of 2.2 years was rather short in this cohort. A surprisingly adverse FEV₁ course was seen in our youngest patients with rising t-IgE levels but negative *Af*-sIgE. Although specific IgE are undoubtedly useful and relevant for the diagnosis of ABPA,³¹ they show marked variability over time³² and limited sensitivity.³³ We therefore wondered if we may have missed a present sensitization in a relevant proportion of Rising t-IgE patients especially because we took blood less frequently in patients below 10 years of age. All 3 patients who took steroids without *Af* sensitization at the time of treatment showed *Af*-sIgE later, and 2 of them were highly sensitized to other molds, favoring the retrospective diagnosis of ABPA or allergic bronchopulmonary mycosis in case of *Alternaria species* sensitization²⁵ (Table E5, available in this article's Online Repository at www.jaci-inpractice.org). Therefore, we decided to analyze treated episodes of ABPA at risk and Rising t-IgE patients together. The good long-term pulmonary outcome of patients with high t-IgE from the beginning of the study onwards without evidence of sensitization to *Af* at any time sheds light on other etiologic mechanisms associated with elevated t-IgE levels. t-IgE increases may reflect a broader type 2 helper T-cell activation as a pathogenic pathway in CF also evident in chronic *Pa* infection.^{34,35} Furthermore, asthma, allergic rhinitis, atopic dermatitis, and various allergic sensitizations among others can lead to high t-IgE levels. In fact, 12 of 13 (92%) of the High t-IgE patients showed sensitization to other aeroallergens than *Af*, 3 suffered from chronic rhinitis and 11 (78%) were chronically *Pa* infected (Table E2, available in this article's Online Repository at www.jaci-inpractice.org).

On the basis of the observation of beneficial outcomes in treated patients, we hypothesize that the published threshold values for t-IgE levels might be too high especially in children and provoke underestimation of ABPA cases. The analysis of first treated Δ IgE episodes in ABPA at risk and Rising t-IgE patients revealed a nearly triplication of the baseline t-IgE value accompanied by an FEV₁ loss of more than 30%. Although these changes were considerably severe, the accordance to the Consensus Conference criteria was surprisingly low. Only 3 of 18 episodes met the full criteria and even the minimal requirements were missed in 12 of 20 subjects. A less pronounced observation was also made in Former ABPA patients first treated during the study period. An absolute t-IgE level below 500 IU/mL was observed to be the cause for not meeting the minimal criteria in all 19 cases. The suggestion made by the Consensus Conference to frequently retest patients suspicious for ABPA showing t-IgE levels between 200 and 500 IU/mL seems to be of value in that perspective.¹⁰

The third major finding of our study is the superiority of observing the t-IgE course in clinical treatment decision making. Previous studies have already demonstrated the relationship between rising t-IgE levels and ABPA flares.³⁶⁻³⁸ To facilitate comparisons between episodes of different durations changes in t-IgE values were adjusted to 3 months' periods because this was the regular interval of outpatient contacts. First treated episodes showed mean t-IgE level elevations of 109% in ABPA at risk and

Rising t-IgE patients and 97% in Former ABPA patients, respectively. The distinctive feature of a 100% increase in t-IgE levels within 3 months exceeding the age-specific 95th percentile was further evaluated because of its merit of being rapidly available and easy to calculate in daily clinical practice. A significant benefit of long-term pulmonary outcome was seen in patients with at least a doubling of t-IgE levels within 3 months treated for ABPA. Interestingly, this positive effect of treatment effect was not present in patients with less than 100% change, thus indicating the discriminating potential of Δ IgE/3 months $\geq$ 100%. The power of the Δ IgE/3 months threshold could also  not be improved by adding distinct requirements for FEV₁ deterioration. However, it is important to note that 60 of 63 patients (95%) treated in this study were *Af*sIgE-positive. Among the untreated patients bearing episodes with Δ IgE/3 months $\geq$ 100%, 63 of 85 (74%) were *Af*sIgE-positive. We can only speculate if the lung function preservation effect observed can also be expected in patients without sensitization to *Af*. Interestingly, only 3 of 15 High t-IgE patients, who did very well without steroid treatment, had Δ gE episodes with more than doubling of t-IgE levels within 3 months.

A doubling of t-IgE levels was already described to indicate an ABPA relapse by Greenberger in 1988,³⁹ whereas Marchant et al suggested a 4-fold increase in pediatric patients with CF¹³ for the diagnosis of ABPA. In that study, 10 of 12 pediatric patients treated for ABPA had t-IgE levels above 1000 IU/mL and all showed at least 6 major criteria according to Rosenberg et al.⁷

We used the mean increase during a Δ gE episode as a simplification not analyzing differences between every single t-IgE measurement retrospectively. We adjusted the mean t-IgE increase to our regular 3 months' interval of blood withdrawal. The hypothesis to start treating an ongoing Δ gE episode if t-IgE levels double within a 3-month period has to be evaluated prospectively.

The overall long-term course of FEV₁ and BMI percentiles in our cohort indicates a high quality of care.¹¹ Even when considering only those patients followed for the entire 7-year period, the decline in FEV₁ of -0.6% per year is rather modest. The study period from 2000 to 2006 was chosen because no patient was on long-term triazole treatment at this time. Because most pediatric patients are not able to expectorate even induced sputum, newer diagnostic tools such as *Af* real time-polymerase chain reaction or *galactomannan* measurements in sputum were not included. Given the fact that *Pa* status affects long-term pulmonary outcomes in CF, we assessed the patient's individual *Pa* infection status by analyzing the last year of observation.⁴⁰ We found infection rates in the different groups mainly depending on the patient's age that is consistent with the literature.⁴¹

An important limitation of the study is its retrospective classification of patients. Moreover, the coadministration of itraconazole to the majority of patients complicates the analysis of treatment benefits because the specific contributions of anti-inflammatory and anti-infective treatment cannot be distinguished.

Further prospective studies are needed to prove the concept of treating an ABPA episode based on a $\geq 100\%$ increase of t-IgE levels within 3 months exceeding the age-specific 95th percentile in the presence of specific IgE against *Af*. This diagnostic approach holds promise in terms of facilitating the diagnosis of ABPA in clinical routine.

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ONLINE REPOSITORY MATERIAL

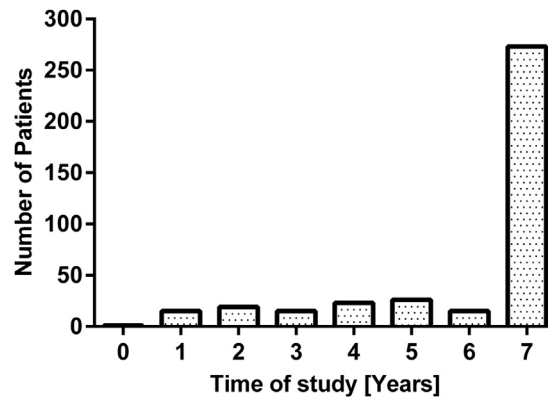
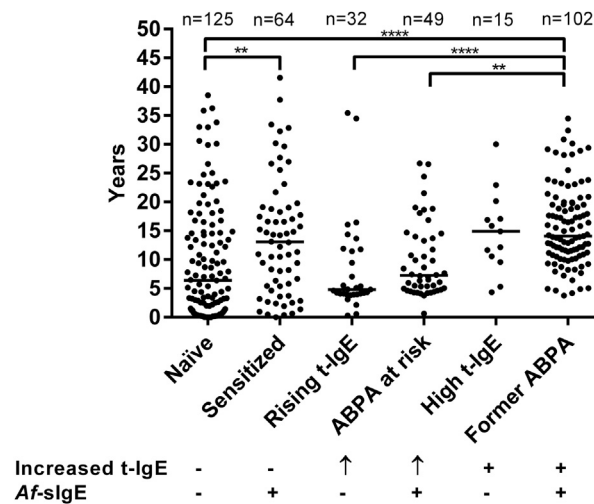


FIGURE E1. Time of follow-up in the cystic fibrosis clinic depicted in yearly intervals.

FIGURE E2. Age at study entrance in different groups. Horizontal lines indicate medians. Kruskal-Wallis test: $P < .0001$. $**P < .01$, $***P < .0001$. ABPA, Allergic bronchopulmonary aspergillosis; Af, *Aspergillus fumigatus*; sIgE, specific IgE; t-IgE, total IgE.

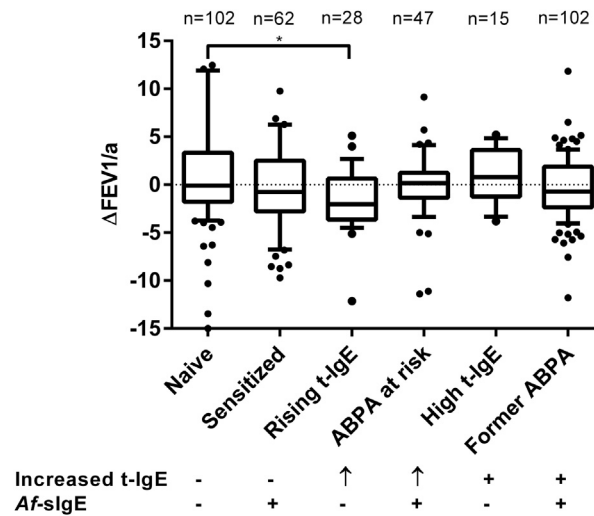


FIGURE E3. Long-term pulmonary outcome of different groups. Boxes represent median and interquartile range; whiskers highlight 10th and 90th percentile. Kruskal-Wallis test: $P = .04$. * $P < .05$. ABPA, Allergic bronchopulmonary aspergillosis; Af, *Aspergillus fumigatus*; sIgE, specific IgE; t-IgE, total IgE.

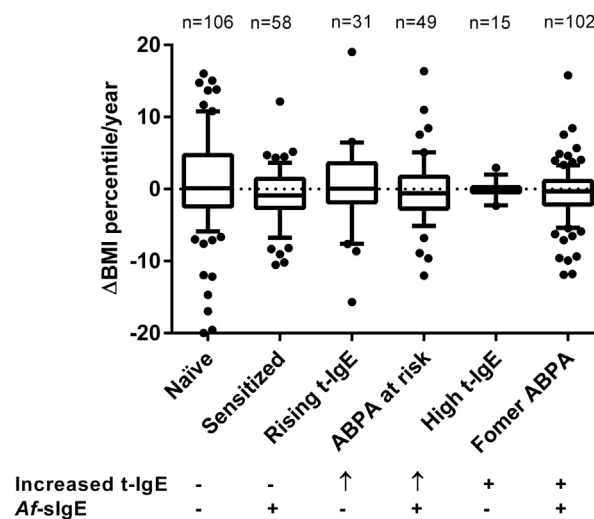


FIGURE E4. Long-term nutritional outcome of different groups. Boxes represent median and interquartile range; whiskers highlight 10th and 90th percentile. Kruskal-Wallis test: not significant. ABPA, Allergic bronchopulmonary aspergillosis; Af, *Aspergillus fumigatus*; sIgE, specific IgE; t-IgE, total IgE.

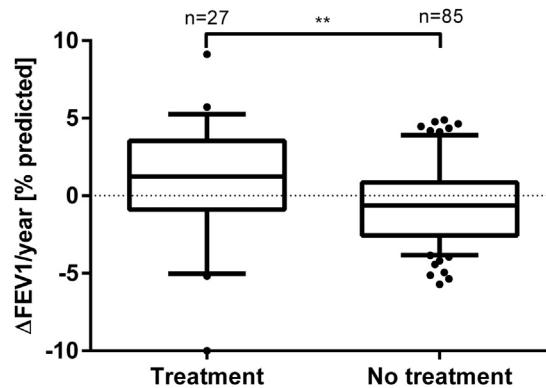


FIGURE E5. Effect of steroid treatment in episodes with $\Delta\text{IgE} \geq 100\%$ within 3 months exceeding the 95th age-dependent percentile. Boxes represent median and interquartile range; whiskers highlight 10th and 90th percentile. Mann-Whitney test: $P = .008$ (**).

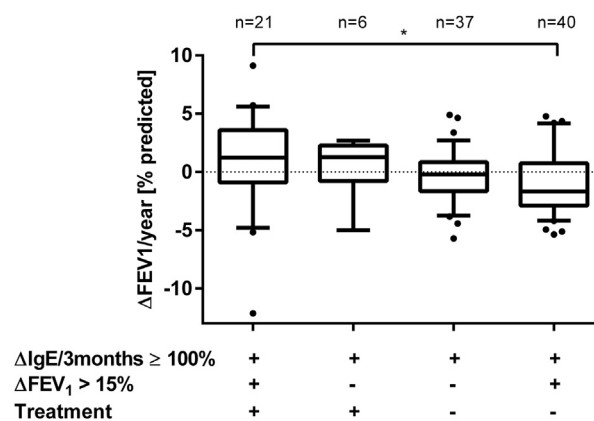


FIGURE E6. Additional consideration of a cutoff value for FEV_1 being greater than 1 standard deviation (-15%). Episodes were all characterized by $\Delta\text{IgE}/3\text{ months} \geq 100\%$. Groups are divided depending on FEV_1 decline and treatment status. Boxes show median plus interquartile ranges. Whiskers indicate 10th and 90th percentiles. Dunn's *post hoc* testing was applied to the groups with $\Delta\text{IgE}/3\text{ months} \geq 100\%$ and FEV_1 changes greater than -15% who differed in terms of steroid treatment. Kruskal-Wallis test: $P = .032$ (*). FEV_1 , forced expiratory volume in 1 s.

TABLE E1. Age-dependent upper limit of t-IgE levels

Age (y)	t-IgE (IU/mL)
0	2
1	40
2	100
3-4	150
5	190
6-17	150
≥18	180

t-IgE, Total IgE.

TABLE E2. Cross-sectional analysis of clinical features of all patients with CF attending the outpatient clinic in 2006 (n = 387)

	All patients	Naive	Sensitized	Rising t-IgE		ABPA at risk		High t-IgE§	Former ABPA	
				Treated	Untreated	Treated	Untreated	Untreated	Treated	Untreated
N	387	125	64	3	29	19	30	15	41	61
Age (y)	17.6 [1-49]	12.0 [1-46]	19.3 [1-49]	5.4 [3-8]	10.5 [2-23]	12.1 [6-42]	15.4 [4-33]	19.0 [9-36]	19.6 [10-39]	17.7 [9-42]
<i>Pa</i> pos.*	207/362 (57%)	50/115 (44%)	39/61 (64%)	0/3	13/29 (45%)	8/19 (42%)	18/30 (60%)	11/14 (78%)	28/39 (72%)	40/55 (73%)
Diabetes†	42/387 (11%)	10/125 (8%)	8/64 (13%)	0/3	1/29 (3%)	2/19 (10%)	0/30 (0%)	3/15 (20%)	11/41 (27%)	7/61 (11%)
Hepatopathy‡	61/387 (16%)	20/125 (16%)	15/64 (23%)	0/3	5/29 (17%)	3/19 (16%)	4/30 (13%)	4/15 (26%)	7/41 (17%)	10/61 (16%)
Meconium ileus‡	56/387 (14%)	23/125 (18%)	9/64 (14%)	0/3	5/29 (17%)	3/19 (16%)	6/30 (20%)	2/15 (13%)	5/41 (12%)	8/61 (13%)

ABPA, Allergic bronchopulmonary aspergillosis; *Af*, *Aspergillus fumigatus*; CF, cystic fibrosis; *Pa*, *Pseudomonas aeruginosa*; t-IgE, total IgE.

Data are expressed as median [range].

*Analysis of 1467 microbiological results (mean 4.1/patient, 48% sputum, 52% deep oropharyngeal swab). Patients were included if at least 2 specimens were collected. Considered positive if any *Pa* was detected in 2006.†Defined as diabetes mellitus requiring treatment. Occurrence of diabetes in treated patients of the ABPA at risk and the Former ABPA groups is more common than in the untreated groups ($P = .017$).‡Defined according to Kappler et al.^{E1,E2}§In the group of High t-IgE patients, we found a sensitization to other common inhaled allergens than *Af* in 12/13 (92%, no radioallergosorbent test available in 2 patients). Three patients suffered from nasal polyposis.

TABLE E3. Demographic characteristics of the study population

Number of patients	387
Median follow-up (y)	7 [0.3; 7]
Follow-up > 6 y	73% (282/387)
Follow-up = 7 y	65% (252/387)
Median age at study entrance (y)	10.7 [0; 41.6]
Median age at study end (y)	17.2 [1.2; 48.6]
Patients < 18 y at study entrance	78% (300/387)
Patients < 18 y at study exit	53% (207/387)

Data are shown as median [range].

TABLE E4. Clinical details of the different groups at study entrance

Clinical characteristic (n = 387)	Naïve (n = 125)	Sensitized (n = 64)	Rising t-IgE (n = 32)	ABPA at risk (n = 49)	High t-IgE (n = 15)	Former ABPA (n = 102)
Age (y)	6.4 [0; 39]	13.1 [0; 42]	4.8 [0; 35]	7.3 [0; 26]	14.9 [4; 30]	14.1 [4; 35]
Male	53 (42%)	26 (41%)	17 (53%)	23 (47%)	10 (67%)	57 (56%)
F508 del homozygous	61 (49%)	32 (50%)	13 (41%)	32 (65%)	7 (53%)	59 (58%)
F508 del heterozygous	54 (43%)	22 (34%)	12 (38%)	12 (25%)	5 (33%)	28 (27%)
FEV ₁ % predicted (%)	90% [30; 145]	86% [25; 147]	101% [59; 128]	88% [35; 130]	89% [34; 108]	80% [14; 146]
BMI percentile	31 [0; 96]	28 [0; 89]	39 [0; 95]	28 [0; 100]	42 [0; 83]	21 [0; 96]
Total-IgE (IU/mL)	11 [0; 146]	19 [1; 135]	41 [6; 124]	65 [2; 505]	248 [89; 549]	366 [39; 3849]

ABPA, Allergic bronchopulmonary aspergillosis; BMI, body mass index; FEV₁, forced expiratory volume in 1 s; t-IgE, total IgE.

Data are shown as median [range].

TABLE E5. Characteristics of the 3 patients who were *Af*-sIgE-negative and treated with systemic steroids and itraconazole

	Patient 1	Patient 2	Patient 3
Age at treatment start (sex)	7 (male)	3 (male)	5 (male)
Δ IgE (%)	66%	99%	1557%
Duration of episode (d)	12	202	56
Δ IgE/3 mo	496%	44%	2503%
Δ FEV ₁ (% predicted)	−32%	Too young	−62%
Classification	Rising t-IgE	Rising t-IgE	Rising t-IgE
Fulfilling Consensus Minimal Criteria	No	No	No
Fulfilling Consensus Full Criteria	No	No	No
<i>Pa</i> status	Negative	Negative	Negative
Sputum/Swab culture	<i>C. albicans</i>	<i>Af, C. albicans</i>	—
RAST abnormalities	<i>Alternaria sp.</i>	<i>Alternaria sp.</i>	—
Specific <i>Af</i> -IgE-positive later on?	Yes	Yes	Yes
Retrospective diagnosis	ABPM	ABPM/ABPA	ABPA?
Long-term outcomes:			
Δ FEV ₁ /y (%)	+4.0	Too young	−12.1
Δ BMI percentile/y	+2.9	−7.6	−7.5
Δ IgE/y (IU/mL)	+32.9	+67.2	+7.4

ABPA, Allergic bronchopulmonary aspergillosis; ABPM, allergic bronchopulmonary mycosis; *Af*, *Aspergillus fumigatus*; *Alternaria sp.*: *Alternaria species*; BMI, body mass index; *C. albicans*, *Candida albicans*; FEV₁, forced expiratory volume in 1 s; *Pa*, *Pseudomonas aeruginosa*; RAST, radioallergosorbent test.

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