

IgE Sensitization to *Aspergillus fumigatus* Is Not a Bystander Phenomenon in Cystic Fibrosis Lung Disease

To the Editor:

We have read with great interest the article by Baxter et al¹ in *CHEST* (May 2013) highlighting the importance of sensitization to *Aspergillus fumigatus* (Af) in progression of cystic fibrosis (CF) lung disease. We and many others have previously reported that sensitization to Af is frequent in patients with CF: It was observed in 31% of the patient cohort (n = 153) who were followed up at the Leuven CF referral center.² We also confirmed significantly impaired lung function parameters in Af-sensitized compared with Af-nonsensitized patients, with an average difference in FEV₁ of 19 ± 4% predicted. In a multivariate analysis with age, sex, BMI, *Pseudomonas aeruginosa* colonization, pancreatic insufficiency, and gastroesophageal reflux disease as covariates, a significantly lower FEV₁ and vital capacity ($P < .001$) was associated with Af sensitization, as well as an increased airway resistance ($P < .05$) and hyperinflation (higher residual volume, $P < .001$) (e-Table 1). Interestingly, no significant differences in lung function parameters were found between patients with serologic criteria for allergic bronchopulmonary aspergillosis (ABPA) (n = 17) and patients with sensitization to Af without ABPA. Similar to the data presented by Baxter et al¹ and others,³ we observed, in a 3-year period, more exacerbations in Af-sensitized patients with CF compared with patients without sensitization to Af (5.30 ± 4.54 vs 1.69 ± 2.78 hospital admissions for IV antibiotic therapy, respectively; $P < .005$).

The group of Baxter and Dunn has recently proposed a novel classification of *Aspergillus* disease in patients with CF.⁴ However, interesting from a pathophysiologic point of view and to guide further therapeutic trials, our data on pulmonary function and exacerbation rate show significant differences only for Af-sensitized vs nonsensitized patients. If we reclassified the nonsensitized patients in two groups taking into account the absence or presence of Af IgG, no significant differences were seen between “nondiseased” and “Af-bronchitis” patients.

To date, most evidence has, thus, emerged for the role of Af sensitization, which raises the question if treatment of Af-sensitized patients, even before ABPA is present, could result in better outcomes. The rationale would be to lower Af allergenic burden and/or to inhibit the resulting hypersensitivity response, before pulmonary function decline or ABPA develop. Whether such a treatment should consist of antifungal therapy, as in the pivotal Fungal Asthma Sensitization Trial (FAST) in severe asthma⁵ or should aim to prevent the IgE-mediated hypersensitivity remains to be elucidated. A placebo-controlled intervention study evaluating monitored antifungal treatment (itraconazole, voriconazole), early treatment with anti-IgE therapies such as omalizumab, or perhaps a combination of both seems indicated in Af-sensitized patients with CF.

Marijke Peetermans, MD
Pieter Goeminne, MD, PhD
Christiane De Boeck, MD, PhD
Lieven J. Dupont, MD, PhD
Leuven, Belgium

AFFILIATIONS: From the Department of Internal Medicine (Dr Peetermans), the Department of Respiratory Medicine (Drs Goeminne and Dupont), and the Department of Pediatrics (Dr De Boeck), University Hospital Leuven, Katholieke Universiteit Leuven.

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CORRESPONDENCE TO: Lieven J. Dupont, MD, PhD, Respiratory Medicine, Herestraat 49, B-3000 Leuven, Belgium; e-mail: lieven.dupont@uzleuven.be

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Additional information: The e-Table can be found in the Supplemental Materials section of the online article.

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e-Table 1. Comparison of pulmonary function test results between *Af*-IgE-sensitized and non-IgE-sensitized patients. Results are represented as mean $\pm$ SD, except for Raw %pred, where median (IQR) is used. p-values for multivariate analysis with age, gender, BMI, *P. aeruginosa* colonization, pancreatic insufficiency and gastro-esophageal reflux disease as covariates are given. n = number of patients in each group, %pred = % of predicted value, NS = no significant difference between groups.

*Statistically significant difference between groups.

		<i>Af</i> -sensitized n = 47	<i>Af</i> -nonsensitized n = 106	p-value
FEV ₁ *	% pred	62 $\pm$ 19	82 $\pm$ 23	< 0.001
FVC *	% pred	80 $\pm$ 16	90 $\pm$ 17	0.010
PEF	% pred	77 $\pm$ 18	86 $\pm$ 23	0.093
Raw *	% pred	216 (172-289)	175 (137-222)	0.033
VC *	% pred	79 $\pm$ 14	89 $\pm$ 16	< 0.001
RV *	% pred	167 $\pm$ 50	127 $\pm$ 44	< 0.001
TLC	% pred	101 $\pm$ 14	100 $\pm$ 14	NS

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