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Bronchodilator responsiveness in children with cystic fibrosis and allergic bronchopulmonary aspergillosis

To the Editor:

Allergic bronchopulmonary aspergillosis (ABPA) is a hypersensitivity lung disease that occurs in approximately 9% of children with cystic fibrosis (CF) [1]. While ABPA is commonly associated with worsening lung function, differentiating ABPA from other causes of pulmonary function decline often poses a clinical challenge. This is reflected by major differences among the various diagnostic criteria for ABPA that have been suggested to date [2–5]. A positive bronchodilator response (BDR) is characteristic for asthma which is a common co-morbidity in CF patients, but whether this is helpful in differentiating ABPA from other causes of deterioration in lung function is currently unclear. A recent observational study of paediatric CF patients found a significant higher BDR in ABPA compared to patients not sensitised to *Aspergillus fumigatus* [6]; this stands in contrast to the CF Foundation consensus that did not identify airway obstruction reversibility as a characteristic of CF-related ABPA [5]. We therefore aimed to evaluate the clinical utility of BDR for diagnosis of ABPA in CF by comparing rates of positive BDR prior to a diagnosis of ABPA to CF patients experiencing acute lung function deteriorations for other causes.

This was a retrospective review of all paediatric CF patients diagnosed and treated for ABPA between 2002 and 2018 at The Hospital for Sick Children, Toronto, in whom BDR testing was performed up to 14 days prior to diagnosis of ABPA. The diagnosis was based on CF Foundation consensus criteria: clinical deterioration, elevated IgE, immediate cutaneous reactivity to *Aspergillus* and recent abnormalities on chest radiograph or computed tomography [5]. We compared those with ABPA to a cohort of CF patients not diagnosed with ABPA, who experienced a drop in forced expiratory volume in 1 s (FEV_1) of 10% or more from baseline, matched 3:1 for age, gender and best FEV_1 in the previous 6 months. Since our aim was to compare ABPA to all other causes of lung function deterioration, any CF patient with a decline of 10% FEV_1 from baseline could be included in the control group. Most of these patients (67 patients; 62%) were diagnosed with a CF pulmonary exacerbation and started on oral (32/67), intravenous (33/67) or inhaled (2/67) antibiotics. From the remaining, 10/41 patients were experiencing symptoms that were interpreted as an acute viral infection, 11/41 were having asthma like symptoms and were treated either by introducing, or encouraging use or stepping up the dose of ICS. The remaining patients were either encouraged to enhance adherence with closer follow-up or introduction of adding mucolytic therapy. BDR was defined as the percent change between pre- and post-inhaled bronchodilator FEV_1 % predicted, as calculated using the Global Lung Function Initiative reference equations [7]. A significant BDR was defined as a 12% change or greater from pre- to post-bronchodilator FEV_1 [8]. Our standard practise is to ask patients to restrain from any short-acting β-agonist use for at least 4 h and from any long-acting β-agonist (LABA) use for at least 12 h prior to BDR testing.

Clinical characteristics of both groups are summarised in table 1. The ABPA group included 36 patients, of whom 85% had a drop of at least 10% in their FEV_1 at the time of diagnosis. Compared to the control group, CF patients with ABPA tended to have a lower FEV_1 at baseline and significantly larger drop from baseline on the day of diagnosis (median (interquartile range (IQR)) −23% (−35 to −16%), −18% (−25 to −14%); p=0.05). A higher rate of wheezing was present on examination, and a significantly larger proportion of patients were on inhaled corticosteroids (ICS) (table 1). Two patients in the ABPA group and four in the control group were prescribed a combination of ICS and LABA. There was no significant

TABLE 1 Clinical characteristics of patients with allergic bronchopulmonary aspergillosis (ABPA) compared to controls

Characteristic	ABPA	Control	p-value
Subjects n	36	108	
Age at time of BDR	11.4 (8.3 to 14.5)	11.0 (8.2 to 13.9)	0.77
Female patients	17/36 (47%)	51/108 (47%)	0.99
Pancreatic insufficient	32/36 (89%)	98/108 (91%)	0.74
Class I–III mutation	32/36 (89%)	104/108 (96%)	0.11
BMI z-score	−0.68 (−1.23 to 0.08)	−0.59 (−1.13 to −0.14)	0.68
ICS prior to BDR testing	27/36 (75%)	42/108 (39%)	<0.001
Baseline FEV_1	80% (73 to 92%)	84% (65 to 95%)	0.50
FEV_1 % pred on day of BDR testing	58% (44 to 72%)	68% (51 to 77%)	0.06
FEV_1 change from baseline	−23% (−35 to −16%)	−18% (−25 to −14%)	0.05
Wheeze on day of BDR testing[#]	21/36 (58%)	12/106 (11%)	<0.001
BDR	4.7% (2.8 to 11.7%)	5.2% (−1.2 to 10.5%)	0.48
Patients with BDR ⩾12%	9/36 (25%)	22/108 (20%)	0.56

All continuous variables presented as median (interquartile range). Controls were matched 1:3 for age, gender and baseline forced expiratory volume in 1 s (FEV_1). FEV_1 values are the per cent values of those predicted by Global Lung Function Initiative equations. BDR: bronchodilator response; BMI: body mass index; ICS: inhaled corticosteroids; % pred: % predicted. [#]: physical examination not documented for two control patients.

difference in median (IQR) BDR (4.7% (2.8 to 11.7%) *versus* 5.2% (−1.2 to 10.5%); p=0.48) or in the proportion of patients with a significant BDR (9/36 (25%), 22/108 (20%); p=0.56) between groups.

Since the higher proportion of ICS prior to diagnosis in ABPA patients could potentially mask the BDR response, we compared those prescribed ICS to those who were not. Comparing all patients prescribed ICS, regardless of having ABPA or not, to those without ICS, the proportion of patients with significant BDR was similar (18/69 (26%), 15/75 (20%); p=0.38). Within each group, the proportion of patients with significant BDR was not significantly different having been treated with ICS or not.

These results indicate that paediatric patients with CF initially presenting with ABPA do not differ in their BDR response to CF patients experiencing a fall of 10% from their baseline FEV_1, regardless of the cause of deterioration. Overall, the role of BDR testing in CF patients remains not well defined. LEVINE *et al.* [9] showed that positivity of BDR testing varies over time and that there was no association with family history of asthma, serum IgE or blood eosinophils. We recently showed that a significant BDR is rare in children with CF treated for pulmonary exacerbations and usually does not lead to immediate change in clinical management [10]. The current study also questions the yield of BDR testing for differentiating ABPA from other causes of lung function deterioration, indicating that the role for routine BDR testing in the care of CF patients seems to be limited.

While ICS are not recommended routinely in CF, a large proportion of the control group (39%) was receiving this medication. This is strikingly similar to the 39% for patients age 6 years and above receiving ICS reported in the 2018 American CF Registry [11]. Reduction of ICS use in CF could potentially have beneficial effects on bacterial and fungal infection rates; further studies are needed to clarify this.

To conclude, in this analysis, paediatric patients with CF initially presenting with ABPA were not more likely to have a BDR greater than seen in patients with other causes of deterioration in their lung function. Thus, we did not find evidence to support the utility of BDR testing in differentiating ABPA from other causes of acute CF exacerbations.

Mordechai Pollak [1], **Michelle Shaw**[2], **David Wilson**[1], **Hartmut Grasemann**[1,2] **and Felix Ratjen**[1,2]
[1]Division of Respiratory Medicine, Hospital for Sick Children, Toronto, ON, Canada. [2]Translational Medicine, Sickkids Research Institute, Toronto, ON, Canada.

Correspondence: Mordechai Pollak, Hospital for Sick Children, SickKids Learning Institute, Respiratory Medicine, 555 University Ave, Toronto, ON M5G 1X8, Canada. E-mail: morduchp@gmail.com

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