

Allergic rhinitis may impact the recovery of pulmonary function tests after moderate/severe asthma exacerbation in children

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Abstract

Background: During an asthma exacerbation, pulmonary function test parameters (PFTs) return to their baseline values within a few weeks. Factors affecting the recovery of PFTs other than the severity of exacerbation are not well known.

Objective: The primary aim of the study was to determine the risk factors for recovery of PFTs > 7 days after a moderate to severe asthma exacerbation in children.

Methods: Children who had moderate to severe asthma exacerbation performed serial prebronchodilator PFTs on days 1, 3, 7 of the exacerbation and then once weekly until their PFTs reached a plateau. All children received systemic corticosteroid for 3 days and inhaled salbutamol as long as they needed.

Results: Fifty-seven children were recruited. When all PFTs were considered, 42% and 74% of children recovered within 7 and 14 days, respectively. The last recovered PFT parameter was FEF_{25–75}. Allergic rhinitis (AR) ($P = 0.016$), persistent AR ($P = 0.005$), and severe asthma exacerbation ($P = 0.009$) were significantly higher in children whose PFTs recover > 7 days; only severe asthma exacerbation was different for recovery > 14 days ($P = 0.048$). Logistic regression analysis revealed that AR and severe asthma exacerbation increase the recovery of PFTs > 7 days by 4.3 (95% CI: 1.29–14.67) and 8.1 (95% CI: 1.51–44.43), respectively.

Conclusions: Recovery of PFTs during a moderate/severe asthma exacerbation may take up to 4 weeks. Apart from severity of the exacerbation, AR is a significant factor affecting the recovery time of PFTs and therefore may impact asthma management. This issue reinforces the combined treatment of AR and asthma.

Asthma is one of the most prevalent diseases in children (1). Exacerbation of asthma is characterized by mechanical obstruction of the airways that decreases expiratory flow. The severity of obstruction can be quantified objectively by pulmonary function test (PFT) (2). Practice guidelines for the treatment of asthma in the emergency department recommend the use of PFT to assess the response to therapy (3). In addition, monitoring of PFT is very important to estimate the prognosis of asthmatic children (4). Previously, prebronchodilator forced expiratory flow (FEV₁) percent predicted was shown to be related to asthma outcomes in several studies (5, 6). A recent study using data from Childhood Asthma Management Program suggested that even on inhaled corticosteroid treatment, prebronchodilator FEV₁%

predicted was able to predict changes in hospitalizations, emergency department visits, and need for oral corticosteroid therapy (7).

Besides FEV₁, another PFT parameter that is forced expiratory flow at 25–75% of forced vital capacity (FEF_{25–75}) also provides important information for the assessment and management of asthma in children. Rao et al. (8) showed that a low FEF_{25–75} in the setting of a normal FEV₁ was associated with increased asthma severity, systemic steroid use, and asthma exacerbations in children. In another study, among children with normal FEV₁, having a reduced FEF_{25–75} < 60% was found to be strongly associated with asthma-related hospitalizations in the previous year (9). In addition to FEV₁ and FEF_{25–75}, peak expiratory flow (PEF) is widely

used as an objective way to monitor asthma symptoms, to measure airway obstruction, and to guide making therapeutic decisions both at home and at emergency departments (2, 3, 10, 11).

Severe asthma exacerbations are associated with a more rapid decline in lung function (12). Pulmonary function parameters return to their baseline values within 1–2 weeks time during a severe asthma exacerbation (13). Factors other than the severity of exacerbation leading to a longer recovery of PFTs are not well known. Therefore, the primary aim of the study was to determine the risk factors for recovery of PFTs >7 days after a moderate to severe asthma exacerbation in children. Secondary aims were to find the time to recovery of all PFTs and risk factors for recovery of PFTs >14 days.

Methods

Study population

Children with moderate/severe asthma exacerbation according to Global Initiative for Asthma (GINA) were consecutively recruited. Children who were <6 years of age, not able to perform PFT, under systemic corticosteroid treatment or applied to the clinic after short-acting β_2 -agonist treatment, had a diagnosis of chronic suppurative lung disease, bronchiolitis obliterans, bronchopulmonary dysplasia, or congenital heart disease were excluded from the study. Ethics committee of the university approved the study, and written informed consent was obtained from all children and/or their parents.

Study design

Children performed serial prebronchodilator PFTs (FEV_1 , FEF_{25-75} , and PEF) between 8 and 10 a.m just before bronchodilator dose on days 1, 3, 7 of the asthma exacerbation and then once weekly until they reached a plateau with no further improvement. All children received 1 mg/kg/day methylprednisolone (max: 40 mg) for 3 days and inhaled salbutamol as long as they needed. Inhaled corticosteroid prophylaxis with 400 μ g/day budesonide or equivalent was initiated to children who were not under controller medication at the first day of the exacerbation. Children who had allergic rhinitis comorbid with asthma had also given intranasal mometasone furoate treatment 50 mcg/day to each nostril on the first day of asthma exacerbation.

Pulmonary function tests

Pulmonary function tests were performed according to American Thoracic Society Guidelines with a daily calibrated spirometer (Vmax 20C, Sensor Medics Co., Yorba Linda, CA, USA). Standard instruction was given prior to efforts and each effort coached by an experienced technician. Multiple maneuvers obtained from each child and PFT values associated with the best maneuver were assessed. Age, sex, and ethnicity-appropriate prediction equations were used to calculate

percent predicted values for FEV_1 , FEF_{25-75} , and PEF. Personal best percent predicted values for FEV_1 , FEF_{25-75} , and PEF were considered normal.

Skin prick tests

Atopic sensitization was determined with a panel of skin prick tests (SPTs) that included house dust mites, pollens, alternaria, animal dander, and histamine (10 mg/ml of histamine phosphate) as positive and 0.9% sterile saline as negative controls. The SPT was considered positive if the mean wheal diameter was ≥ 3 mm than the negative control.

Definitions

Severity of asthma exacerbation

Classification of asthma exacerbations were made according to GINA 2012 (2).

Allergic Rhinitis (AR)

Allergic rhinitis was diagnosed and classified according to allergic rhinitis and its impact on asthma (ARIA) 2008 (14).

Personal best% predicted PFT values after an asthma exacerbation

The values of PFTs that reached a plateau without further improvement >5% in two consecutive visits during follow-up.

Recovery of PFTs

The time when all PFTs (FEV_1 , FEF_{25-75} and PEF) reach their personal best% predicted after the asthma exacerbation.

Time to recovery of PFTs

The period from initial evaluation (1st day) to the day on which all PFTs (FEV_1 , FEF_{25-75} , and PEF) reached their personal best% predicted after the asthma exacerbation.

Study parameters

The primary study parameter was risk factors for recovery of PFTs >7 days after a moderate to severe asthma exacerbation in children. Secondary study parameters were time to recovery of all PFTs and risk factors for recovery of PFTs >14 days.

Duration of asthma complaints before exacerbation, use of controller treatment for asthma, exacerbations requiring hospitalizations and/or systemic corticosteroid use in the previous year, atopic sensitization, passive smoking, AR, persistent AR, moderate/severe AR, and severity of asthma exacerbation were evaluated as possible risk factors for prolonged recovery of PFTs after a moderate to severe asthma exacerbation in children.

Statistical analysis

Statistical analysis was performed by Statistical Package for Social Sciences (SPSS) 17.0 software (SPSS, Inc., Chicago, IL, USA). A descriptive analysis was used for the characterization

of patients. Data that have a normal distribution were described by using mean $\pm$ SD values; median and interquartile ranges (IQRs) were used otherwise. Pearson's chi-square test or Fischer's exact test was used to compare categorical variables between the groups. Unpaired Student's *t*-test was used for comparisons of normally distributed data, and Mann-Whitney *U*-test was used for nonparametric data. For the multivariate analysis, the possible risk factors for the recovery of PFTs after a moderate to severe asthma exacerbation in children identified as significant ($P < 0.05$) or borderline significant ($P < 0.25$) with univariate analysis were further entered into the logistic regression analysis to determine independent predictors. A two-sided value of $P < 0.05$ was considered statistically significant.

Results

Demographics

Fifty-seven children with moderate/severe acute asthma agreed to participate in the study. Thirty-eight (67%) children had a previous diagnosis of asthma, whereas 19 (33%) patients were newly diagnosed during an asthma exacerbation. The median duration of asthma symptoms before admission was 5 days (IQR: 2–12 days), and the severity of asthma exacerbation was moderate in 42 children (74%) and severe in 15 children (26%). Three children required hospitalization; the others were followed in outpatient clinic. Forty children had atopic sensitization to one or more aeroallergens (70%). The other demographic characteristics of children are presented in Table 1.

Median (IQR) recovery time for FEV₁, FEF_{25–75}, and PEF was 7 (7–14), 14 (7–21), and 7 (3–14) days, respectively. The last recovered PFT parameter was FEF_{25–75}. When all PFTs were considered, 42% and 74% recovered within 7 and

14 days after the exacerbation (Fig. 1). Mean values for % predicted FEV₁, FEF_{25–75}, and PEF during successive days are presented in Table 2.

Recovery of PFTs according to 7 and 14 days

FEV₁

FEV₁ of 23 children (40%) returned to normal in >7 days. FEV₁ of 9 children (16%) returned to normal in >14 days. Persistent AR ($P = 0.031$) and severe asthma exacerbation ($P < 0.001$) were associated with recovery in >7 days. The other parameters were not associated with recovery >7 days ($P > 0.05$ for each). None of the parameters were associated with recovery >14 days ($P > 0.05$ for each).

FEF_{25–75}

FEF_{25–75} of 32 children (56%) returned to normal in >7 days. FEF_{25–75} of 15 children (26%) returned to normal in >14 days. Allergic rhinitis ($P = 0.003$), persistent AR ($P = 0.021$), and severe asthma exacerbation ($P = 0.006$) were associated with recovery in >7 days. Severe asthma exacerbation ($P = 0.048$) was associated with recovery in >14 days. The other parameters were not associated with recovery in >7 days and >14 days ($P > 0.05$ for each).

PEF

PEF of 21 children (37%) returned to normal in >7 days. PEF of 5 children (9%) returned to normal in >14 days. None of the study parameters were associated with recovery in >7 days and >14 days ($P > 0.05$ for each).

All PFTs (FEV₁ + FEF_{25–75} + PEF)

Allergic rhinitis ($P = 0.016$), persistent AR ($P = 0.005$), and severe asthma exacerbation ($P = 0.009$) were significantly higher in children recovering >7 days. Severe asthma exacerbation ($P = 0.048$) was associated with recovery >14 days. Other study parameters were not associated with recovery in >7 days and >14 days ($P > 0.05$ for each) (Table 3).

Table 1 The demographics of children with moderate/severe asthma exacerbation

Characteristics	<i>n</i> (%)
Age	10.7 $\pm$ 2.4
Male gender	41 (72)
Previous diagnosis of asthma	38 (67)
Use of controller treatment for asthma	9 (24)
No controller medication for asthma	29 (76)
Concomitant atopic disease	34 (60)*
Allergic rhinitis	32 (56)
Persistent	17 (53)
Moderate/severe	11 (34)
Atopic eczema	2 (3.5)
Food allergy	2 (3.5)
Passive smoking	22 (39)
Family history of atopic disease	38 (67)
Asthma	27 (47)
Allergic rhinitis	20 (35)

*One child had concomitant allergic rhinitis and atopic eczema; one child had concomitant allergic rhinitis and food allergy.

Factors affecting recovery of PFTs in children with moderate/severe asthma exacerbations

There was no difference in recovery time (median [IQR]) between atopics (14 [7–19]) and nonatopics (median [IQR]: 14 [7–21]) ($P = 0.634$). Logistic regression analysis revealed that AR and severe asthma exacerbation increased the recovery of PFTs >7 days by 4.3 (95% CI: 1.29–14.67) and 8.1 (95% CI: 1.51–44.43), respectively. In univariate analysis, *P* values of all possible risk factors for the recovery of PFTs >14 days were higher than 0.25 except severe asthma exacerbation ($P = 0.048$) and allergic rhinitis ($P = 0.118$). A logistic regression analysis was performed with the two parameters (allergic rhinitis and severe asthma) and found severe asthma as the only significant independent factor that may increase the risk of recovery of PFTs >14 days (risk ratio: 3.7 [95% CI: 1.01–13.97]).

We further compared the children included in the study according to the presence of comorbid AR for any difference

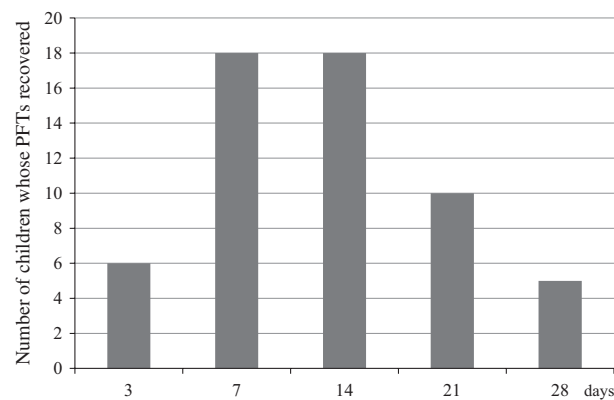


Figure 1 Number of children whose PFTs recovered within days.

in possible risk factors for prolonged recovery of PFTs after a moderate to severe asthma exacerbation. There was no difference between asthmatic children with and without AR considering age ($P = 0.71$), sex ($P = 0.54$), severity of the exacerbation ($P = 0.72$), prebronchodilator% predicted FEV₁ ($P = 0.47$), FEF₂₅₋₇₅ ($P = 0.94$), PEF ($P = 0.35$) on the first day of the exacerbation, duration of asthma complaints preceding exacerbation ($P = 0.18$), use of controller treatment for asthma ($P = 0.16$), exacerbations requiring hospitalizations and/or systemic corticosteroid use in the previous year ($P = 0.84$), and passive smoking ($P = 0.45$).

Discussion

This study documented changes in airflow obstruction after moderate/severe exacerbations of asthma in children. Recovery of PFTs during a moderate/severe asthma exacerbation prolonged to 4 weeks. It took >7 days in two-thirds of children and to >14 days in one-fourth of children. The risk factors for the recovery of acute obstruction >7 days were severe asthma exacerbation, comorbid AR, and persistent AR. Only severe asthma exacerbation was found significant for the recovery of PFTs >14 days. Interestingly, severity of AR, duration of complaints, use of controller medication, atopic sensitization, and exposure to passive smoking at home were not associated with recovery of PFTs either >7 or >14 days.

The time to recovery of PFTs was 14 days at the latest in almost three-quarters of children with moderate to severe asthma exacerbation. This result was compatible with a recently published study by Debley et al. (13). In that study,

Table 3 Comparison of PFT recovery in children with moderate/severe asthma exacerbation according to 7 and 14 days

Recovery of PFT (FEV ₁ + FEF ₂₅₋₇₅ + PEF)	≤7 days (n = 24)	>7 days (n = 33)	≤14 days (n = 42)	>14 days (n = 15)
Age (mean ± SD)	11 ± 2.3	11 ± 2.5	11 ± 2.4	10 ± 1.9
Male gender, n (%)	17 (71)	24 (73)	30 (71)	11 (73)
Duration of complaints, day, median (IQR)	5 (2–10)	5 (2–14)	5 (2–8)	7 (2–14)
Use of controller treatment for asthma, n (%)	5 (21)	4 (12)	7 (17)	2 (13)
History of hospitalization and/or systemic steroid in previous year, median (IQR)	1 (1–2)	1 (1)	1 (1–2)	1 (1)
Severe asthma exacerbation, n (%)	2 (8)	13 (39)*	8 (19)	7 (47)†
Passive smoking, n (%)	9 (38)	13 (39)	16 (38)	6 (40)
Atopic sensitization, n (%)	16 (67)	24 (73)	30 (71)	10 (67)
Allergic rhinitis, n (%)	9 (38)	23 (70)*	21 (50)	11 (73)
Persistent allergic rhinitis, n (%)	1 (11)	16 (70)*	11 (52)	6 (55)
Moderate/severe allergic rhinitis, n (%)	1 (11)	10 (44)	7 (33)	4 (36)

* $P < 0.05$ compared to children that recovers within ≤7 days.

† $P < 0.05$ compared to children that recovers within ≤14 days.

lung function in children who were hospitalized for acute asthma exacerbation reached a plateau in improvement within 1–2 weeks following discharge. In daily practice, PFTs are evaluated as percent predicted values according to reference values for the age, sex, height, and ethnicity. In our study, percent predicted values of FEV₁ and FEF₂₅₋₇₅ of all children returned to >80% and >70% predicted, respectively, in the third day, and PEF reached to >80% predicted on the seventh day. However, National Asthma Education and Prevention Program (NAEPP) states that the use of percentage of personal best values is ideal for the management of asthma exacerbations (3). In our study, improvement to personal best% predicted PFT values after the exacerbation

Table 2 Monitoring of PFTs in children with moderate/severe asthma exacerbations

Days	1	3	7	14	21	28	35
FEV ₁	67 ± 17	87 ± 17	95 ± 15	96 ± 11	97 ± 9	103 ± 10	105 ± 14
FEF ₂₅₋₇₅	48 ± 17	77 ± 19	82 ± 18	86 ± 17	88 ± 15	91 ± 14	90 ± 6
PEF	63 ± 16	77 ± 19	82 ± 18	88 ± 17	88 ± 20	91 ± 14	92 ± 17

All values were presented as percent predicted (mean ± SD).

took much longer until 4 weeks. Therefore, personal best percent predicted values may be more suggestive to determine the time of resolution of PFTs after asthma exacerbations. To our knowledge besides us, only Debley et al. monitored the time of resolution according to personal best PFTs after an asthma exacerbation (13).

In this cohort of children, central airway obstruction improved earlier than small airway obstruction. As an indirect measure of small airway obstruction, FEF_{25-75} was found to be the last to improve according to the personal best predicted even after normalization of FEV_1 . Therefore, FEF_{25-75} may be a better indicator of the recovery of acute obstruction after a moderate/severe exacerbation of asthma in children. This result is consistent with the previous reports that indicated FEF_{25-75} as the most specific and sensitive measure of airway obstruction (8, 15). This may be related to relatively lower drug deposition in these parts of the lung than central airways. Similarly, de Lange et al. (16) indicated that FEF_{25-75} was better correlated with air trapping in asthmatics than $FEV_1\%$ predicted and $FEV_1/FVC\%$ predicted.

In this study population, we found that the severe asthma exacerbation prolonged the recovery of acute obstruction >7 days nearly eight times compared to moderate exacerbation. This is an expected finding. It has been mentioned even two decades ago that the more severe the asthma exacerbation, the more probable the changes involving the peripheral airways and the recovery takes more time (17). However, an interesting and novel finding of this study is the effect of AR on the recovery time of PFTs in children with moderate to severe asthma exacerbation. Comorbidity of AR with asthma prolonged the recovery of PFTs >7 days at least 4 times compared to children with asthma alone. Although we did not design this study to reveal solely the impact of AR on recovery of PFTs, we re-analyzed our data after the logistic regression results to compare other risk factors that may affect the recovery of PFTs after exacerbation between asthmatic children with and without comorbid AR. None of them (prebronchodilator PFTs, severity of the exacerbation, duration of complaints preceding exacerbation, use of controller treatment for asthma, exacerbations requiring hospitalizations and/or systemic corticosteroid use in the previous year, exposure to passive smoking) were different between children with and without AR. Therefore, we think that the impact of AR on recovery of PFTs >7 days is independent of other risk factors. However, this effect lost its significance

2 weeks after the exacerbation. We think that this is due to the initiation of nasal corticosteroid treatment as an add-on treatment to asthmatic children with AR during exacerbation. The effect of intranasal corticosteroids on PFTs in patients with asthma was shown to be effective as short as 1 week after the initiation of treatment and usually ranges between 2–17 weeks in the published studies (18). Previous reports indicated that AR increased the severity of asthma, disrupted the control of the disease, and caused increased ED visits (19–23). To our knowledge, this is the first study that specifically indicates a relationship with AR and prolonged recovery of acute bronchial obstruction in asthma. We think that the extent of inflammation involving both upper and lower airways in case of comorbidity of asthma with AR is greater than that of asthma alone, which may be a reason for prolonged recovery of PFTs (24). Unfortunately, our study was not designed to reveal this hypothesis. Nevertheless, we think that the prolonged recovery of PFTs after an asthma exacerbation is another impact of AR on asthma. Allergic rhinitis and its impact on asthma is an evolving subject, and there are probably many more issues to delineate than what has been revealed until today which needs further investigation.

There are several limitations of our study. Children did not perform PFT daily; therefore, we could not determine the exact recovery period. Parameters such as bronchial hyper-reactivity, airway inflammation such as exhaled nitric oxide level and sputum eosinophilia, viral respiratory pathogens were not studied which might help us to further understand the mechanisms underlying the recovery of PFTs. Also, we were unable to track treatment compliance with a method other than self-report of the patients. Lastly, small number of children included in the study may prevent the generalization of our results.

In conclusion, the recovery of PFTs during a moderate to severe asthma exacerbation may prolong until 4 weeks. Allergic rhinitis is a significant factor affecting the recovery of PFTs in asthmatic children presenting with exacerbation and therefore may impact asthma management in another way. This issue reinforces the combined treatment of AR and asthma. It may also play role considering the duration of asthma treatment during an exacerbation.

Conflicts of interest

The authors declare that there are no conflicts of interest.

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