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Clinical Course and Factors Associated with Asthma Control in Children under Control-based Asthma Management: A Prospective Study

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ABSTRACT

In the current study, we sought to track the clinical course of children under control-based asthma management and focused on respiratory pathogens monitoring. We prospectively explored influencing factors for asthma control.

121 children with uncontrolled asthma between 3-14 years of age were recruited. Common respiratory pathogens were detected with pharyngeal swabs and serum aeroallergen-specific IgE was measured. Numeric asthma control scores, airway resistance and fractional concentrations of exhaled nitric oxide (FENO) were evaluated. A proper control-based asthma management plan was established by the study physician. Regular reviews were performed, with the above measurements retested at set time intervals.

The proportion of patients achieving asthma control at 1 month and 3 months were 59% and 76%; respectively (p=0.013). These patients exhibited significant improvement in numeric scores and lung function parameters. The prevalence of common respiratory pathogens did not significantly differ between reviews. The number of sensitized aeroallergens significantly increased with age (r=0.235, p=0.010). Children with a high visual analogue scale (VAS) score for asthma at baseline were less likely to achieve asthma control after 1 month, while those sensitized to more aeroallergens were more likely to achieve asthma control after 1 month (p=0.016 and 0.012).

In summary, children with asthma showed significant improvements in control rates and lung function during control-based asthma management, independent of respiratory pathogens testing

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results. Patients with high VAS scores and fewer sensitizations to aeroallergens had difficulty achieving short-term asthma control.

Keywords: Asthma; Pediatrics respiratory function tests; Respiratory pathogen; Sensitization; Visual analogue scale

INTRODUCTION

Asthma affects an estimated 300 million individuals worldwide.[1] Its prevalence is increasing in many countries, especially among children.[2] The Global Initiative for Asthma (GINA) set the goal of asthma management to achieve control of the disease and to maintain control for long periods of time.[2] The asthma control level refers to the extent to which asthma symptoms can be observed in the patients, or have been alleviated or removed through management. Asthma control involves both the assessment of clinical symptoms and future risks.[2]Unfortunately, the ideal level of asthma control has not been accomplished in certain areas of the world. A previous large-scale, cross-sectional study across China found that about 20% of pediatric patients with asthma had the disease uncontrolled. Adherence to treatment and comorbid allergic rhinitis significantly influenced the control status.[3] Meanwhile, both the patients and their parents often overestimated their level of asthma control.[4] Hence, there is an ongoing need for control-based asthma management in a continuous cycle of assessment, treatment and review.[2]

The role of respiratory pathogens in wheezing illnesses, including asthma, has been acknowledged for some time.[5] It has been reported that up to 80% of asthma flare-ups in pediatric patients manifest in combination with a respiratory virus, with human rhinovirus (HRV) consistently accounting for 60-70% of these virus-associated exacerbations.[6-8] However, there is a lack of data about the prevalence of respiratory pathogens in children with uncontrolled asthma symptoms, not necessarily with an exacerbation. Whether the prevalence of respiratory pathogens varies during the aforementioned control-based asthma management and its association with clinical outcomes are unclear.

As asthma can be divided into several phenotypes, one of the most common phenotype seen in pediatric patients is allergic asthma. It is acknowledged that the presence of atopy, including allergen sensitization identified through skin prick test or serum specific IgE level, increases the probability of a patient with respiratory symptoms to be diagnosed with allergic asthma.[2] A 14-year follow-up study of a birth cohort from Australian community demonstrated that the proportion of asthma related with atopy was 52% overall.[9] However, the relationship between allergen sensitization and pediatric asthma control is not clear.

In this study, we investigated the clinical course of children with asthma under control-based asthma management, focusing on respiratory pathogens dynamic monitoring as well as aeroallergen sensitization. We also analyzed the associated factors for achieving asthma control, after standard management for comorbid allergic rhinitis and assuring patients' adherence to treatment.[3] The current results present the short-term outcomes after 3 months.

PATIENTS AND METHODS

Patients

Patients were recruited from an outpatient clinic from April 2015 to January 2016. The criteria for inclusion were patients between the ages of 3 and 14 years diagnosed with asthma classified as uncontrolled or partly controlled according to the guidelines established by the Chinese Medical Association[10,11] who were amenable to accept control-based asthma management and regular follow-ups. Patients with newly diagnosed asthma who were undergoing related symptoms and those unable to acquire standardized asthma management before were also included. Written informed consent from the guardian as well as the patient (8 years and older) was obtained. Exclusion criteria included patients who received or completed specific immunotherapy or had comorbidity of acute or chronic respiratory conditions, such as pneumonia, bronchiectasis or complications related to ENT system other than allergic rhinitis like otitis media or acute tonsillitis, and/or other comorbid systemic disorders. All of the inclusion criteria had to be met to be eligible, while any one of the exclusion criteria was sufficient to

exclude the patient. This study was approved by the Ethics Committee of the University (No. 2013-90).

Study Protocol

At study entry, proper asthma management plans were set by the study physician for all the participants based on the GINA guidelines.[2] For the participants who were comorbid with allergic rhinitis, appropriate treatments were also taken.[12] Regular reviews of asthma control were performed in the clinic every 2 weeks in the first month and then once a month the next 2 months. Regular reviews continued after 3 months, which were not included in the current results. Numeric asthma control scores were used to help with the assessment, including a monthly (Childhood) Asthma Control Test ((c-)ACT), if available based on patient age,[13-15] and a visual analogue scale (VAS)[16,17] for asthma and allergic rhinitis symptoms at each follow-up visit. The scores ranged from 6-27 for c-ACT and 5-25 for ACT (higher scores indicated better outcomes).[2,13] For the VAS, we asked the parents or patients themselves to think about the last 2 weeks or last 3 months when first attending, and mark along a 100mm line to indicate the child's symptoms. Anchor statements were written on each side of the line; "no symptoms" on the left at 0, and "very bad symptoms" on the right at 10. The distance between 0 and the placement of the child's marker was measured to provide a numeric interpretation of their responses.[16] Patients were given a daily symptom diary and were instructed on how to record asthma and/or allergic rhinitis related symptoms and medication use, which helped to promote and reflect patients' adherence to the treatment.

At the study baseline, the patients were also measured for lung function as well as fractional concentrations of exhaled nitric oxide (FENO) (NIOX®, Sweden) if they could cooperate with the test, and were retested upon follow-up after 1 and 3 months. For children aged 6 years and older, we chose to use spirometry for lung function testing, while for younger children, the method of impulse oscillometry (IOS) was preferred (MasterScreen, Jaeger, Germany). All tests were performed by skilled technicians. For spirometry, we defined the parameters within normal ranges as follows: the measured values of forced expiratory volume in first second (FEV1), forced vital capacity (FVC), the peak expiratory flow (PEF) being no less than 80% of the predictive values, the FEV1/FVC ratio being ≥80%, the forced expiratory flow of 25% of FVC (FEF_{25}) being no less than 70%, and the FEF at 50% and 75% of FVC (FEF_{50}, FEF_{75}) being no less than 65% of the predictive values(18). For IOS, the normal range was defined as resistance at 5 Hz /20Hz (R5/R20) ≤120% of the predictive value, and reactance at 5 Hz (X5) if the measured value minus 0.2 was less than the predictive value.[19] Any measurements outside of the above ranges were identified as abnormal.

Also at the study baseline, patient blood was drawn for the serum sIgE test, and pharyngeal swabs were obtained for respiratory pathogens detection. After enrollment, upon the follow-ups at 2 and 4 weeks, pharyngeal swabs were again obtained for respiratory pathogen monitoring.

Laboratory Data

Serum sIgE for a panel of 10 common aeroallergens as well as total IgE were analyzed using the ImmunoCAP system (Thermofisher Scientific/Phadia, Uppsala, Sweden). The tested aeroallergens included house dust mites (HDM) [Dermatophagoide spteronyssinus, (Dpt), and Dermatophagoides farinae, (Df)], dust, cat and dog dander, cockroaches, mixed molds, *alternaria*, and tree and grass pollen. A sIgE level of ≥0.35 kU/L was identified as positive. As sIgE concentrations increased, they were further divided into classes 1 to 6. Classes 1 to 6 were defined by serum sIgE levels of 0.35-0.7, 0.7-3.5, 3.5-17.5, 17.5-50, 50-100 and >100 kU/L. [20]

Pharyngeal swabs were separately kept in the storage medium at -70℃ until they were analyzed for viruses, bacteria, *mycoplasma pneumoniae* (*MP*) and *chlamydia pneumoniae* (*CP*), within the following 6 months using real-time PCR tests (LightMix Roche, Germany and in-house PCR). The following viruses and bacteria were monitored: HRV, respiratory syncytial virus (RSV) and human metapneumovirus (hMPV), *Streptococcus* (*S. pneumoniae*), *Haemophilus* (*H. influenza*) and, and *Moraxella catarrhalis* (*M. catarrhalis*).

Statistical Analyses

This study employed standard statistical methods such as the rank sum test, analysis of variance (ANOVA) and the Chi-square test in basic analyses. The relationship between patient age and number of sensitizations was analyzed using the Spearman rank

correlation test. The associations between the different factors and the asthma control status reviewed 4 weeks and 3 months after the initial visit were analyzed using logistic regression analysis. Logistic regression results were expressed as odds ratio (OR) and 95% confidence intervals (CI). Statistical significance was established at the level of $p<0.05$. Data were analyzed using SPSS 20.0 software (IBM Corp., Armonk, N.Y., USA).

RESULTS

Patient Characteristics

A total of 121 eligible children were recruited for the study, with a mean age of 6.55±2.45 years. Seventy-seven (64%) of them were boys and 71 (59%) of the subjects enrolled had the comorbidity of allergic rhinitis (Table 1). We also included season of recruitment, since respiratory pathogens detection as well as allergic symptoms were all related with season characteristics. Follow up rate of the patients were high within the first one month and remained at about 70% until three months (Figure 1).

Clinical Outcome of Asthma Control Status

The symptoms of asthma in the patients, as well as allergic rhinitis, tended to be controlled over the followed time period under control-based asthma management and treatment for rhinitis. Patients followed were with good adherence, with ≥80% medication use of the prescribed controller therapies according to their diary card record. The proportion of patients achieving asthma control at the 1 month and 3 month follow-ups were 59% (63/107) and 76% (65/85) (χ^2=6.597, p=0.013), respectively. Meanwhile,

Table 1. Asthma patients' characteristics at the study baseline

Factors	Enrolled (n=121)
Age (y)	6.55 (2.45)
Male sex	77 (64%)
With family history of allergies	84 (69%)
Season of recruitment	
Spring (March-May)	26 (21%)
Summer (June-August)	73 (60%)
Fall (September-November)	9 (7%)
Winter (December-February)	13 (11%)
Comorbidity with allergic rhinitis	71 (59%)
At study entry	
Asthma stages	
Acute exacerbation	36 (30%)
Mild	31 (26%)
Moderate	5 (4%)
Chronic persistent	85 (70%)
Asthma control status	
Uncontrolled	69 (57%)
Partly controlled	52 (43%)

Values are presented as mean (stand deviation) for the factor of age and number of cases (proportion in all the enrolled participants) for all other factors.

Table 2. Changes in numeric scores related to disease after initial treatment for asthma

Items	Mean/median scores at each time point			*p* value
	At enrollment	2 weeks	4 weeks	
(c-)ACT	19 (4)	NA	24 (23, 27)	0.000
VAS for asthma	4.2 (2.3)	2.1 (0.7, 3.9)	1.3 (0.3, 3.1)	0.000
VAS for allergic rhinitis	4.5 (2.1)	2.7 (1.8)	1.8 (1.6)	0.000

Scores are presented as mean (standard deviation) or median (interquartile range).
Each item was analyzed longitudinally, making comparisons between different time points.
(c-)ACT = (childhood-) Asthma Control Test VAS = visual analogue scale NA = not applicable

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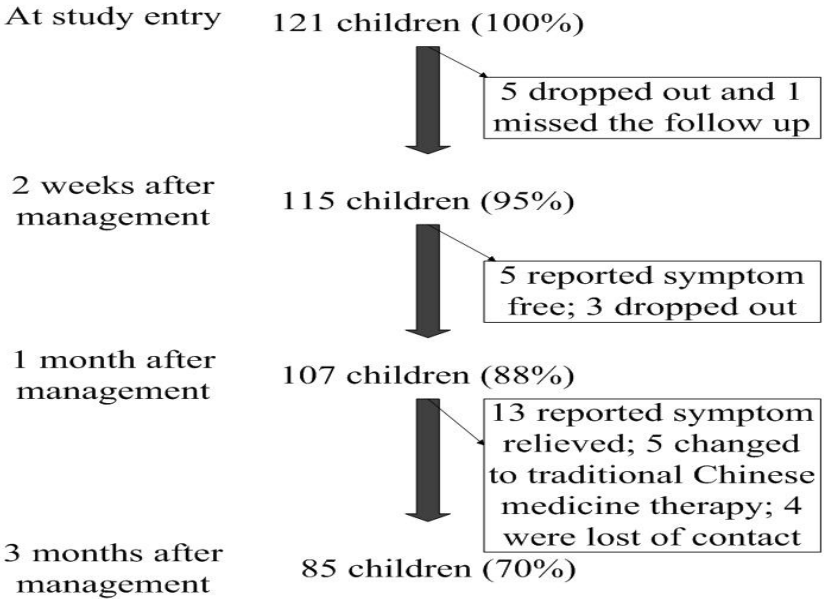

Figure 1. Follow-up rates during the study period of control-based asthma management

significant improvement in the (c-) ACT and VAS scores were also observed over the first month of management (Table 2). At study baseline, the mean level of participants' FEV1% (ratio of measured value to predictive value) was 95.56±16.20%, and significantly increased to 103.67±10.68% and 106.28±12.16% at the 1- and 3-month review (p=0.001). However, no significant differences were found for the FENO values at these 3 follow-ups.

Serum Aeroallergen sIgE Profiles

Serum sIgE for common aeroallergens tested positive in the majority of the asthmatic participants (100/121; 83%), with *alternaria* being the most common. Almost all of the sensitized children, except 3, were sensitized to 2 or more kinds of aeroallergens concomitantly (Table 3). The number of sensitized aeroallergens tended to increase with age, although the correlation was weak (r=0.235, p=0.010).

Detection of Respiratory Pathogens and Its Association with Other Parameters

At each visit, more than 70% of the participants were positive for 1 or more types of common respiratory pathogens in the pharyngeal swabs, although some may have been normal carriers of certain bacterial species (Table 4). Among the detected respiratory pathogens, *haemophilus influenza*, *streptococcus pneumoniae* and *MP* were the 3 predominant species, while *HRV* was the main virus species. Across the 3 consecutive clinic visits, there were no significant differences in the detection rates for each single respiratory pathogen, although some decreasing tendency was observed as the control-based asthma management progressed (p>0.05). We did not find any significant differences when comparing the detection rates of each respiratory pathogen between the patients with comorbid allergic rhinitis and those without at each review (p>0.05).

At the study baseline, patients without any respiratory pathogens detected had an abnormal lung function rate of 38% (10/26), while for those detected positive for 1 or more pathogens, 42% (38/90) showed abnormal lung function results to a different extent (χ^2=0.118, p=0.823). At the 1-month review, abnormal lung function results were found in 20% (4/20) of the patients negative for all included respiratory pathogens at baseline. However, for patients with pathogens detected positive at the first visit, 37% (29/78) had abnormal lung function results at the1 month follow-up assessment (χ^2=2.104, p=0.189).

Influencing Factors of the Outcome of Asthma Control

The chance of achieving asthma control in 1 month after standardized management was negatively

Table 3. Aeroallergen sensitization profile in the enrolled asthma patients at baseline

Aeroallergen	Number of sensitized cases						
	Class 1	Class 2	Class 3	Class 4	Class 5	Class 6	Total (%)
Alternaria	5	5	27	20	4	0	61 (50)
Mixed molds	4	6	37	13	0	0	60 (50)
Df	8	10	9	12	7	3	49 (40)
Dust	5	19	16	6	1	0	47 (39)
Dpt	8	8	11	9	4	5	45 (37)
Tree pollen[a]	13	16	11	0	0	0	40 (33)
Grasses pollen[b]	8	8	9	3	0	0	28 (23)
Dog dander	6	5	3	4	0	0	18 (15)
Cat dander	3	3	4	1	4	2	17 (14)
Cockroach	4	7	1	0	0	0	12 (10)
1 aeroallergen							3 (2.5)
2 aeroallergens							27 (22)
3 aeroallergens							29 (24)
4 aeroallergens							14 (12)
5 aeroallergens							10 (8.3)
6 aeroallergens							2 (1.7)
7 aeroallergens							9 (7.4)
8 aeroallergens							3 (2.5)
9 aeroallergens							2 (1.7)
10 aeroallergens							1 (0.8)

Df:dermatophagoides farina Dpt: dermatophagoides pteronyssinus

a: oak, elm, Chinese parasol, alamo pollen b: ragweed, Artemisia, chrysanthemum, pollen

The last column "total (%)" was presented as total cases for each item and the proportion of these cases in all the participants.

Table 4. Changes in positive rates of respiratory pathogens as control-based asthma management continued

Pathogens	Positive rate/n (%)		
	Baseline (N=121)	2 weeks (N=110[a])	4 weeks (N=103[a])
HRV	20 (17)	12 (11)	11 (11)
RSV	1 (0.8)	1 (0.9)	1 (1.0)
hMPV	2 (1.7)	0 (0.0)	3 (2.9)
Haemophilus influenza	58 (48)	50 (45)	39 (38)
Streptococcus pneumoniae	22 (18)	34 (31)	30 (29)
Moraxella catarrhalis	11 (9)	9 (8.2)	5 (4.9)
MP	37 (31)	31 (28)	27 (26)
CP	8 (6.6)	6 (5.5)	7 (6.8)
None detected	27 (22)	29 (26)	27 (26)
1 pathogen	47 (39)	43 (39)	45 (44)
2 pathogens	31 (26)	19 (17)	20 (19)
3 pathogens	13(11)	17 (15)	6(5.8)
4 pathogens	3 (2.5)	2 (1.8)	4 (3.9)
5 pathogens	0 (0.0)	0 (0.0)	1 (1.0)

HRV: human rhinovirus RSV: respiratory syncytial virus

hMPV: human metapneumovirus MP: mycoplasma pneumonia CP: chlamydiapneumoniae

a: number of patients with available pharyngeal swabs, which is not exactly the same as the numbers in the flow chart, since some of the participants did not comply with the consecutive specimen taking.

There were no significant differences in the positive rates for each single respiratory pathogen within the 3 time points.

Table 5. Possible factors influencing asthma control after initial management in the study participants

Factor	Asthma control at 1 month	Asthma control at 3 months
Age	0.998 (0.983 - 1.013)	1.01 (0.99 - 1.03)
Male sex	0.89 （0.35 - 2.30)	0.38 (0.11 - 1.33)
Family history of allergies	0.67 （0.25 - 1.80)	1.17 (0.32 - 4.26)
Total IgE	1.0 (0.999 - 1.001)	0.999 (0.998 - 1.000)
Positive MP on 1 month's review	0.61 (0.24 - 1.54)	1.07 (0.29 - 4.03)
Positive HRV on 1 month's review	0.51 (0.12 - 2.07)	0.46 (0.06 - 3.36)
Comorbidy with allergic rhinitis	0.51 (0.18 - 1.43)	1.06 (0.23 - 4.82)
Sensitization to HDM	1.49 (0.41 - 5.33)	3.17 (0.93 - 10.85)
Sensitization to molds	0.77 (0.30 - 1.98)	0.56 (0.17 - 1.81)
Exacerbation of asthma at study entry	0.86 (0.26 - 2.81)	0.93 (0.27 - 3.18)
Baseline FEV1	1.03 (0.99 - 1.07)	0.98 (0.94 - 1.03)
Positive bronchial dilation test result at study entry	0.45 (0.16 - 1.24)	0.52 (0.14 - 1.96)
Baseline FENO	1.00 (0.98 - 1.02)	0.996 (0.974 - 1.018)
Baseline VAS for allergic rhinitis	0.81 (0.62 - 1.05)	1.07 (0.79 - 1.46)
Baseline VAS for asthma	***0.75 (0.59 - 0.95)***[a]	0.88 (0.63 - 1.23)
Baseline (c-)ACT score	1.10 (0.92 - 1.31)	0.94 (0.79 - 1.11)
Number of positive respiratory pathogens at study entry	1.07 (0.62 - 1.85)	0.558 (0.311 - 1.002)
Number of sensitized aeroallergens	***1.40 (1.08 - 1.81)***[b]	1.20 (0.90 - 1.61)

Data expressed as OR (95% confidence interval). Bold and italic face indicates a significant result

a: p=0.016 b: p=0.012 MP: mycoplasma pneumoniae

HRV: human rhinovirus HDM: house dust mite

FEV1: forced expiratory volume in 1st second FENO: fractional concentrations of exhaled nitric oxide

VAS = visual analogue scale (c-)ACT = (childhood-) Asthma Control Test

associated with the VAS score of asthma at the study baseline. (p=0.016) Interestingly, the chance of achieving asthma control was positively associated with the number of aeroallergens that the patient was sensitized to (p=0.012, Table 5). However, we did not find any significant influencing factors of asthma control status at the 3-month review.

DISCUSSION

In this current study, the proportion of children achieving asthma control tended to increase over management time. As such, asthmatic outcomes improved after implementing control-based asthma management strategies in different studies, and control-based asthma management is feasible and useful in both developed and developing countries.[21,22] From this point of view, control-based asthma management should be generalized in different hospital settings around the world.

In the present study, we explored the role of common respiratory pathogens in children with asthma. With the cooperation of patients in clinic, we chose to use pharyngeal swabs. We found that the prevalence of these pathogens did not differ between each visit, although the asthma symptoms showed improvement. For certain species of pathogens, like *H. influenza*, *M. catarrhalis* and *MP*, there was a decreasing trend on the positive rate as the management continued, but without significant differences. Our study will continue to monitor on the prevalence of respiratory pathogens through subsequent follow-ups. *H. influenza* was the most commonly detected pathogen, followed by *MP*. The roles of respiratory pathogens, especially viruses,

in asthma exacerbation have been frequently reported.[5] However, our study focused not only on children with asthma exacerbation, but also patients with chronic persistent stage or partially controlled asthma, which accounted for a large proportion of pediatric asthma patients in regular clinics. A previous study from Turkey reported that, in children undergoing asthma exacerbations, 53.8% were positive for a pathogenic respiratory virus, but that the clinical course of asthma flare-up was independent from the positive detection for the pathogen.[23] Similar results from the Asian population in Hong Kong showed that respiratory virus infections were an important trigger for asthma exacerbation, but were not associated with its severity.[24] A recent cross-sectional study from another institute of Beijing, China screened for 8 kinds of respiratory viruses in asthmatic children with nasopharyngeal aspirate, which found that *HRV* was the most prevalent virus with a positive rate of 25.8%. But in the above research, the recruited children with asthma had a mean age of 2.7 years, compared with that in this study of 6.5 years. Additionally, different methods of sample collection might contribute to the variance of prevalence as well.[25]

When compared to viruses, bacteria seem to play a less important role in asthma, at least in exacerbations.[5] The high prevalence of *H. influenza* in the current study may partly due to normal colonization. But another retrospective study from Belgium, which analyzed the bacteria in persistent wheezing children, showed that *H. influenza* was the most predominant, followed by *streptococcus pneumoniae* and *M. catarrhalis*. Our study found the same prevalence order of these three kinds of bacteria. An early survey on nasopharyngeal bacteria in healthy preschool aged children in Beijing area, China demonstrated that, the isolation rate of *S. pneumoniae* and *H. influenza* were 30% and 13% respectively.[26] Another study investigated the throat flora in patients with asthma and showed no significant distribution differences in the throat flora between patients with asthma and the healthy controls. Furthermore, bacteria flora in the pharynx did not change significantly after short term and 12 months of inhaled corticosteroids treatment, which is in accordance with part of the results of our study.[27] However, more research and data are needed to make any recommendation on antibiotic use for asthma.[28] Lieberman et al reported that acute *MP* infections were more common in patients hospitalized for asthma exacerbation than in the control group, and other research suggested that *MP* infections were related to the mechanism of asthma, which may partially explain our relatively high *MP* detection rate in the current study.[5,29]

Lung function should be evaluated upon diagnosis of asthma or at the beginning of treatment and measured periodically to assist in the assessment of asthma control.[2] In our study, we showed that FEV1% significantly increased within the first 3 months of control-based asthma management. It has been reported that low FEV1 is considered to be an important independent predictor of exacerbation risk, even after adjusting the frequency of symptoms.[2] Early research demonstrated that with standardized asthma treatment, FEV1 began to improve just in days, and achieved a plateau about 2 months later.[30] Recent studies from the U.S.A. proved that the Regional Asthma Disease Management Program, which was designed to address the need of asthmatic children living in low-income areas, resulted in decreased emergency department visits and improved lung function.[31] Children with asthma treated with budesonide showed a significantly higher FEV1 in a prospective study than the placebo group.[32] Although FEV1, one of the most important parameters of lung function, was commonly reported to respond to standardized asthma management, we still regularly recorded lung functions to further explore their trajectory. However, we did not find any significant changes in their FENO levels during the asthma management period. Although FENO is one of the parameters that help in diagnosing and assessing asthma, it has been suggested that asthma treatment guided by FENO is ineffective.[33,34]

With respect to the serum sIgE to aeroallergens, one of the important factors to be considered in asthma, *alternaria*, was the most prevalent aeroallergen in our participants, followed by mixed molds. These results were interesting because it had commonly been reported that HDM acted as the predominant aeroallergen in children with atopic asthma.[35,36] One of the factors to be considered is that 60% of our patients were recruited through summer season (Table 1), during which time molds are more common to trigger allergic symptoms in previously sensitized patients, leading those patients to visit clinic. It is acknowledged that exposure to fungi may result in atopic sensitization, and increasing evidence shows that if children with asthma are exposed to outdoor fungal spores, which include *alternaria*, they are at higher risks of having asthma exacerbation.[37] Studies in the U.S.A. also found that sensitization to

indoor allergens, including molds, is a risk factor for wheezing and emergency visits of asthma.[38] Another finding regarding aeroallergens was that, as the participant age increased, the number of sensitized aeroallergens also tended to increase. In accord with our findings, a recent Italian study also determined that multiple sensitization was more common than mono-sensitization in children with allergic symptoms, and that a patient's age correlated with the number of sensitizations.[39] Similarly, results from another multi-center study in Spain showed that number of sensitizations as well as sensitization to certain major allergens tended to increase with age.[40] All of these findings provide more insight into allergen exposure avoidance, which is a modifiable risk factor for asthma.

Considering all above findings, we investigated the factors that influence asthma control after treating comorbid allergic rhinitis and promoting patients' adherence to the treatments based on previous study findings.[3] Our results demonstrated that after 1 month of control-based asthma management, children with a higher baseline VAS scores for asthma were less likely to achieve short-term asthma control. Interestingly, we also found that as children were sensitized to more kinds of aeroallergens, they were more likely to achieve to asthma control status within 1 month. Since VAS is considered a subjective unstructured assessment of asthma severity,[16] our findings were consistent with those from other studies. One cross-sectional study in the U.S.A. enrolled 2429 children aged 4-17 years, and found that self-reported severity of asthma significantly predicted uncontrolled asthma.[41] Studies from Turkey and Thailand also showed that moderate/severe asthma were risk factors for poorly controlled asthma.[42,43] Research from Spain suggested that it was necessary to evaluate aeroallergens sensitization, including aeroallergens from outdoors and indoors, regardless of the severity of asthma at the baseline, because intermittent asthmatic children who were sensitized to trees and weeds pollens were less likely to maintain good asthma control at follow-ups. However, sensitization to pet dander was a protective factor for well-controlled asthma in patients with persistent asthma.[44] Juan et al claimed in a study performed in the USA. that, although sensitization and exposure to indoor allergens was a risk factor for asthma morbidity in children, it did not show a significant association with asthma morbidity in adults in the inner city.[45] Our results may be explained by the satisfactory response to inhaled corticosteroid treatment of patients with allergic asthma phenotypes.[2] However, parents of children with poly-sensitization often are more attentive to asthma control, since aeroallergens sensitization is a modifiable risk factor for asthma, thus helping with a short-term asthma control status. These findings imply that aeroallergens sensitization is not necessarily related to unexpected asthma outcomes, whereas the mechanism for non-atopic asthma needs to be further explored to improve asthma control in children without sensitization.

Study Limitations

First, since this was an observational study, we did not include healthy controls. The clinical outcome of 1 or 3 months may be short, but we are still continuing with the study. Second, considering the acceptance of pediatric patients in outpatient clinics, we used pharyngeal swabs for respiratory pathogens detection, which may have limited positivity. Thirdly, 60% of the participants were recruited during summer season, which together with the recruiting ages of the patients, may partly explain the relatively low detection rate of the respiratory viruses included. Furthermore, data on exposure to environmental tobacco smoke was not available in our study, which might be a potential confounder.

In conclusion, Children with asthma show significant improvements in control rate and lung function during control-based asthma management, regardless of the presence of respiratory pathogens.Given standard treatment for comorbid allergic rhinitis and promoting patients' adhearence, patients with high VAS score for asthma at baseline are difficult to get asthma controlled in short term, while those with poly-sensitization to aeroallergens are prone to achieve short term asthma control.From this perspective, further research into mechanisms of non-allergic asthma are warranted.

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