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Is mold sensitization associated with severe asthma exacerbation in children?

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Abstract

Background: Mold sensitization has been reported as a factor associated with severe asthma exacerbation (SAE).

Objective: To identify the factors associated with SAE in asthmatic children, particularly mold sensitization.

Methods: The asthmatic children recruited into this case-control study were classified into an SAE and an outpatient (OPD) group, based on their histories of asthma exacerbation with hospitalization in the preceding year. A skin prick test to common aeroallergens was performed. Possible SAE risk factors were analyzed.

Results: A total of 102 patients were enrolled. The 51 patients in the SAE group were significantly younger than the 51 in the OPD group (mean ages of 6.8 ± 3.3 vs 8.7 ± 3.2 years, $p = 0.005$). Higher proportions of patients with partly controlled or uncontrolled asthma were found in the SAE group (41.2% vs 17.6%, $p = 0.009$). The incidences of a paternal history of atopy, an emergency department visit, and a history of systemic corticosteroid administration in the preceding year were significantly higher for the SAE group (35.3% vs 15.7%, $p = 0.023$; 100% vs 43.5%, $p < 0.001$; and 100% vs 31.4%, $p < 0.001$; respectively). The multivariate logistic regression analysis showed that risk factors for SAE were *Alternaria* sensitization (adjusted odds ratio [AOR] 3.00; 95%CI 1.09–8.3; $p = 0.033$), patients who were younger than 6 years (AOR 3.28; 95%CI 1.17–9.18; $p = 0.024$), and a paternal history of atopy (AOR 2.94; 95%CI 1.05–8.25; $p = 0.040$).

Conclusions: *Alternaria* sensitization, an age younger than 6 years, and a paternal history of atopy were associated with SAE in asthmatic children.

Key words: *Alternaria*, asthma exacerbation, children, mold sensitization, severe asthma

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Introduction

Asthma is the most common chronic respiratory disease in children. In 2001, the International Study of Asthma and Allergies (ISAAC) Phase III reported that asthma affected 15% of children in Bangkok.[1] The most recent study in Thailand in 2019, the Global Asthma Network (GAN) phase I, showed that prevalence of current wheezing in children was 13.5%.[2] Asthma exacerbation remains a major health problem for patients of any age. It also affects patients' families and their community. In 2016, nearly 54% of children with asthma in the USA were reported to have had at least 1 asthma attack in the preceding year, with 4.7% being hospitalized and 16.7% involving emergency department (ED) visits.[2] Similarly, a survey of poorly controlled asthmatic children in 12 geographic areas of Asia-Pacific showed that 43% had had at least one asthmatic exacerbation, 17% had needed hospitalization, and 19% had had an ED visit.[3]

Severe asthma exacerbation (SAE) is defined as a hospitalization or ED visit because of worsening asthma, or the need for systemic corticosteroids to control asthma.[4] SAEs are one of the most common causes of critical illness in children, accounting for approximately 10,000 intensive care unit (ICU) admissions per year in the USA. Children admitted to the ICU are significantly more likely to have an allergy or irritant-triggered exacerbation than those admitted to a general ward (OR 3.9; 95%CI 1.9–8.2; $p = 0.0003$).[5] Most children hospitalized for asthma exacerbations are sensitized to multiple indoor allergens. More than 50% are sensitized to any of *Alternaria*, *Aspergillus*, dust mite, cat dander, and dog dander.[6]

Our previous study showed a significant increase in *Alternaria* sensitization had occurred after the major flooding in Bangkok in 2010.[7] Mold, especially *Alternaria* sensitization, has been reported as a factor associated with SAE.[8,9] Other reported factors are obesity, second-hand smoke, viral infections (particularly rhinovirus), and poor adherence.[10,11,12] Elucidating the roles of these factors in SAE may assist with SAE prevention.

The aim of this study was to identify the factors associated with SAE requiring the hospitalization of Thai children, particularly mold sensitization.

Materials and methods

Participant recruitment

The children in this case-control study were recruited from the Pediatric Allergy Clinic, Faculty of Medicine, Siriraj Hospital. Aged 1–15 years and clinically diagnosed as having asthma, their level of asthma control was defined according to the Global Initiative for Asthma criteria. The study was conducted from 2016 to 2018. Its protocol was approved by the Siriraj Institutional Review Board and registered with ClinicalTrials.gov (NCT03690349). Written informed consent and/or assent was obtained from patients and/or guardians prior to inclusion.

Excluded were patients who were pregnant, lactating, or had a chronic illness (such as heart disease, genetic diseases, and chronic pulmonary diseases). Patients were classified into 2 groups: a severe asthma exacerbation (SAE) group, and an outpatient department (OPD) group. The SAE group was defined as patients who had been hospitalized due to severe asthma exacerbation in the preceding year, whereas the OPD group was defined as patients who had not been hospitalized due to severe asthma exacerbation in a preceding year. The flow of the participants in the study is illustrated in **Figure 1**.

The following patient data were evaluated: age, sex, body weight, height, family history of atopy, parental income and education, severity of asthma, level of asthma control, asthma medication, adherence to the treatment, comorbidities, environment exposure, and past history of asthma treatment.

Skin prick tests (SPT) were evaluated for 16 common aeroallergen extracts (ALK-Abelló A/S, Hørsholm, Denmark). They included *Dermatophagoides pteronyssinus* (Dp), *Dermatophagoides farinae* (Df), American cockroach, German cockroach, cat dander, dog epithelia, mouse epithelium, Bermuda grass, Johnson grass, careless weeds, acacia, *Alternaria* spp., *Cladosporium* spp., *Penicillium* spp., *Aspergillus* spp. and *Curvularia* spp.

SPTs were performed with metal lancets by a trained health professional. Histamine dihydrochloride (10 mg/mL) and normal saline solution were used as positive and negative controls, respectively. The SPT results were recorded 10 and 15 minutes after pricking with histamine and the allergens, respectively. The SPT result was defined as positive if the mean wheal diameter (sum of the widest wheal diameter and the perpendicular diameter, divided by two) was at least 3 mm larger than that of the negative control.

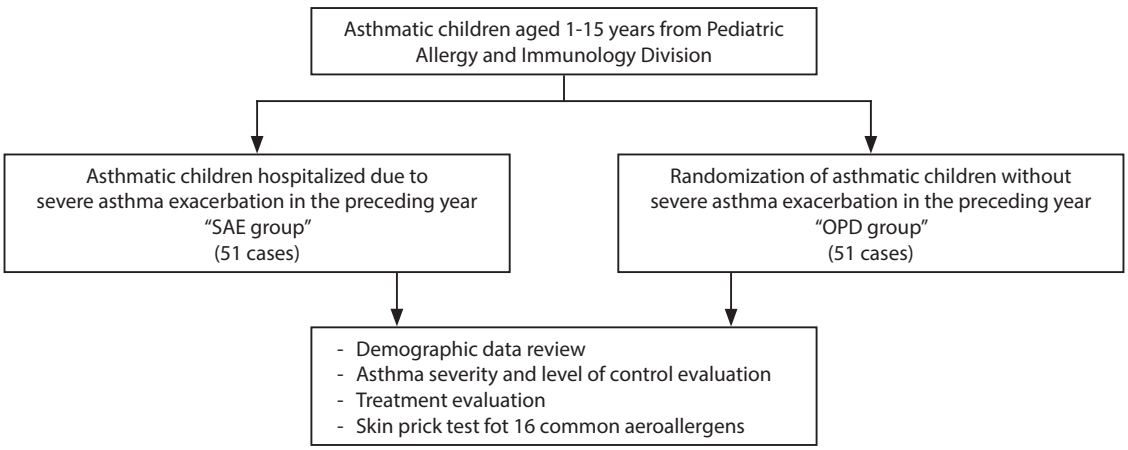

Figure 1. Flow of the participants in the study.

Statistical analysis

The sample size and power were calculated based on data reported by a previous study on adult asthma.[13] We determined that a case-control study with 50 SAE cases and 50 OPD cases would have sufficient statistical power to detect significant ($p < 0.05$) differences in at least one mold sensitization in the SAE group.

The demographic data were summarized using descriptive statistics. The categorical data are presented as number and percentage, and the continuous data are presented as either mean ± standard deviation or median and range. The factors associated with SAE were analyzed using the chi-square test, Fisher's exact test, and unpaired t-test. Multiple logistic regression analysis was used to determine the effect of each independent factor after controlling for the confounding influence of the other factors. The odds ratios and 95% confidence intervals (CI) for the two groups were calculated. A *p*-value of less than 0.05 was regarded as being statistically significant. All statistical analyses were performed using PASW Statistics, version 18.0 (SPSS Inc., Chicago, IL, USA).

Results

This study enrolled 102 patients, with 51 in the SAE group and 51 in the OPD group. There were 68 males (66.7%). The mean ages of the SAE and OPD groups were significantly different (6.8 ± 3.3 years for the SAE group vs. 8.7 ± 3.2 years for the OPD group, $p = 0.005$; **Table 1**). Nine patients in the SAE group were admitted to an intensive care unit for continuous nebulization due to unresponsiveness to conventional asthma therapy.

The possible factors for SAE requiring hospitalization in the previous year compared to those of the OPD group are shown in **Tables 1 and 2**. The proportion of patients with allergic rhinitis was significantly higher for the OPD group (100% vs 86.3%, $p = 0.013$). However, a paternal history of atopy was significantly higher for the SAE group (35.3% vs 15.7%, $p = 0.023$). The proportion of patients with partly controlled or uncontrolled asthma was also higher for the SAE group than the OPD group (41.2% vs 17.6%, $p = 0.009$). Similarly, both the incidence of an ED visit and a history of systemic corticosteroid administration in the preceding year were significantly higher for the SAE group (100% vs 62.7%, $p < 0.001$; and 100% vs 31.4%, $p < 0.001$, respectively). Moreover, the incidence of hospitalization for asthma prior to enrollment in this study was significantly higher for the SAE group (100% vs 66.7%, $p < 0.001$). On the other hand, the two groups were not significantly different prior to study recruitment in terms of age at onset of asthma, obesity, atopic dermatitis, food allergy, sinusitis, maternal history of atopy, passive smoker, pet, damp house, low parental income (< 20,000 Baht/month), severity of asthma, asthma medication, poor adherence, incorrect device method, and history of intensive care unit admission.

A nasopharyngeal wash was performed for common respiratory viruses (influenza A virus, influenza B virus, parainfluenza virus, adenovirus, and respiratory syncytial virus) during asthma exacerbation in 20 patients of the SAE group. Four patients had positive nasopharyngeal wash results: two for respiratory syncytial virus, one for adenovirus, and one for parainfluenza virus.

Table 1. Demographic data of the severe asthma exacerbation (SAE) and outpatient (OPD) groups.

Data	SAE (N = 51)	OPD (N = 51)	*p*-value
Current age; years (mean ± SD)	6.8 ± 3.3	8.7 ± 3.2	0.005
Age of onset; years (mean ± SD)	3.5 ± 2.4	3.2 ± 2.5	0.512
Sex; male	33 (64.7%)	35 (68.6%)	0.834
Obesity	13 (25.5%)	14 (27.5%)	1.000
Allergic rhinitis	44 (86.3%)	51 (100%)	0.013
Atopic dermatitis	7 (13.7%)	9 (17.6%)	0.786
Food allergy	4 (7.8%)	8 (15.7%)	0.357
Sinusitis	13 (25.5%)	8 (15.7%)	0.221
Paternal history of atopy	18 (35.3%)	8 (15.7%)	0.023
Maternal history of atopy	12 (23.5%)	21 (41.2%)	0.057
Passive smoker	23 (44.2%)	15 (30%)	0.137
Pet in house	20 (38.5%)	20 (40%)	0.874
Damp house	22 (42.3%)	22 (44%)	0.863
Parental income < 20,000 Baht/month	37 (72.5%)	37 (72.5%)	1.000

Table 2. Severity of asthma, level of control, and the treatment of the severe asthma exacerbation (SAE) and outpatient (OPD) groups.

Data	SAE (N = 51)	OPD (N = 51)	*p*-value
Severity of asthma			0.054
Mild asthma	17 (33.3%)	29 (56.9%)	
Moderate asthma	30 (58.8%)	19 (37.3%)	
Severe asthma	4 (7.8%)	3 (5.9%)	
Level of control			0.015
Controlled	30 (58.8%)	42 (82.4%)	
Partly controlled	17 (33.3%)	9 (17.6%)	
Uncontrolled	4 (7.8%)	0 (0%)	
Medication			
ICS	37 (72.5%)	40 (78.4%)	0.490
ICS + LABA	14 (27.5%)	10 (19.6%)	0.350
LTRA	9 (17.6%)	7 (13.7%)	0.586
Doxofylline (Puroxan)	3 (5.9%)	0 (0%)	0.243
ED visit in the preceding year			< 0.001
0 times/year	0 (0%)	19 (37.3%)	
1–3 times/year	33 (64.7)	27 (52.9%)	
> 3 times/year	18 (35.3%)	5 (9.8%)	
Systemic corticosteroid ≥ 1 time/year	51 (100%)	16 (31.4%)	< 0.001
Poor adherence	17 (33.3%)	10 (19.6%)	0.116
Incorrect device method	15 (29.4%)	7 (13.7%)	0.054
ICU admission for asthma*	9 (17.6%)	4 (7.8%)	0.138
Hospitalization for asthma*	51 (100%)	34 (66.7%)	< 0.001

*prior to enrolling in this study

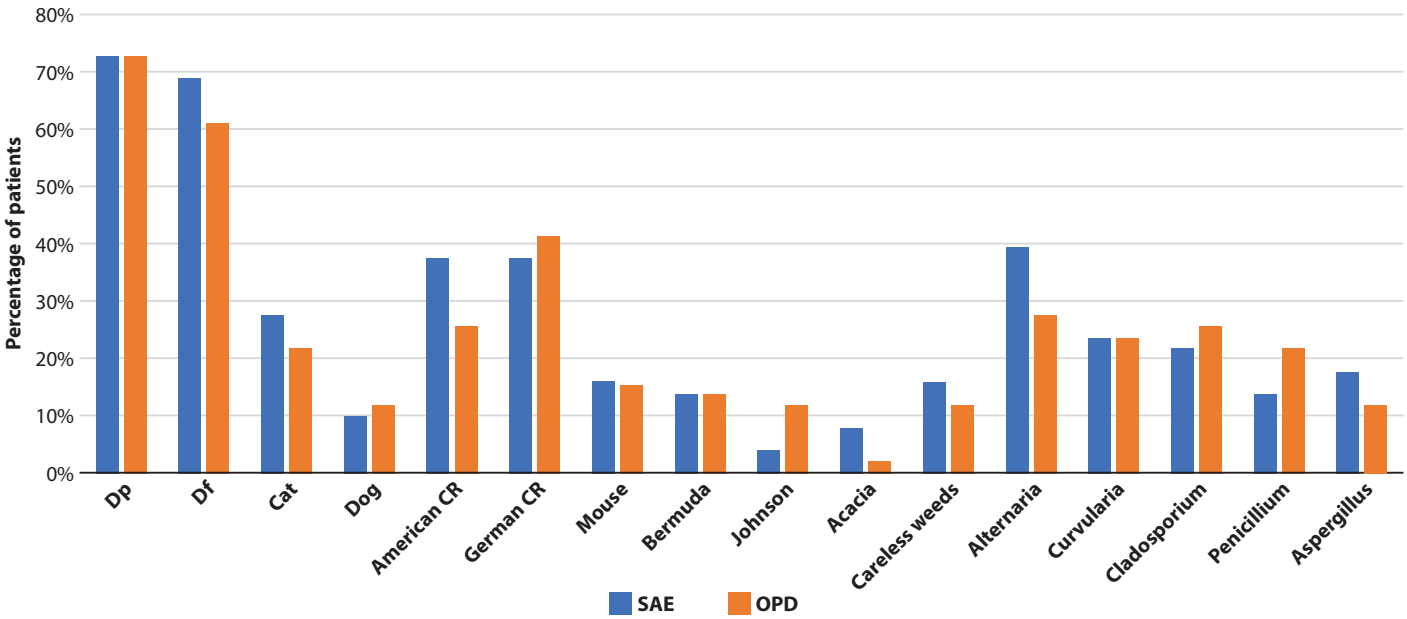

Figure 2. Allergen sensitization in the severe asthma exacerbation (SAE) and outpatient (OPD) groups.
Dp, *Dermatophagoides ptronyssinus*; Df, *Dermatophagoides farinae*; CR, cockroach

Table 3. Multivariate logistic regression analysis of factors associated with severe asthma exacerbation.

Factor	Adjusted odds ratio	95% CI	*p*-value
Alternaria sensitization	3.00	1.09–8.3	0.033
Age < 6 years	3.28	1.17–9.18	0.024
Paternal history of atopy	2.94	1.05–8.25	0.040
Partly-controlled/uncontrolled asthma	2.55	0.94–6.89	0.065

The 4 most common aeroallergens sensitized in the asthmatic patients were house dust mite (*D. pteronyssinus* and *D. farinae*; 74.5%), cockroach (American and German cockroach; 43.1%), *Alternaria* (33.3%), and cat (24.5%). There were no statistical differences in the types of allergen sensitization evidenced by the SAE and OPD groups (**Figure 2**). Of the positive aeroallergen SPTs, poly-sensitization and mono-sensitization were found in 79.4% and 20.6% of cases, respectively. As to the mono-sensitized cases, house dust mite was the most common allergen (90.5%), followed by American cockroach (9.5%). Non-atopic asthma (negative SPT) was found in 19.6% of the patients in each group.

The multivariate logistic regression analysis of the factors associated with SAE that required hospitalization (**Table 3**) showed that *Alternaria* sensitization, an age younger than 6 years, and a paternal history of atopy were risk factors for SAE. The adjusted odds ratio (AOR) of *Alternaria* sensitization was 3.00, with a 95%CI 1.09–8.3, $p = 0.033$. The AOR of an age younger than 6 years was 3.28 (95%CI 1.17–9.18, $p = 0.024$), while that of a paternal history of atopy was 2.94 (95% CI 1.05–8.25, $p = 0.040$).

Discussion

Alternaria alternata is one of the most common saprophytes worldwide and has been clinically associated with asthma. The prevalence of sensitization to *Alternaria* has proven difficult to estimate. The Global Asthma and Allergy European network (GA(2)LEN) study of 3,034 subjects with suspected inhalant allergy showed an approximately 9% prevalence of *Alternaria* sensitization.[14] In a study of more than 17,000 US citizens, positive skin test responses to *Alternaria* occurred in 3.6% of the population, and up to 70% of patients with fungal allergy had skin test reactivity to *Alternaria*.[15] In another study of US inner cities, 38.3% of 12,086 asthmatic children had positive skin test results to *Alternaria* species.[16] Sensitization to *Alternaria* species has been more frequently associated with persistent and severe asthma in both children and adults.[17,18] Children with *Alternaria* sensitivity have also been shown to have heightened airway responsiveness to metacholine.[19]

In this case-control study, we found that patients who had been admitted because of SAE were significantly more sensitized to *Alternaria* than those in the OPD group. Our finding of sensitization to fungal allergens, especially *Alternaria*, is consistent with previous reports. Beck *et al.* found that children aged 4–16 years who had been hospitalized for an asthma exacerbation had an *Alternaria* sensitization of 58.8%.[6] In addition, Black *et al.* reported that 54% of patients aged 18–50 years who had been admitted to an ICU with an asthma attack had a positive skin test to one or more fungal allergens, compared with 30% for patients who had not been admitted to the ICU ($p = 0.005$).[9] The same study showed no differences in the degree of positive skin test results to grasses, cat dander, or house dust mites for cases with and without ICU admission.[9]

Our study showed that asthmatic children who had a paternal history of atopy were more likely (2.94 times) to have SAE. The result is similar to a birth cohort study of 476 families in the USA, in which it was found that the father's disease history, particularly his asthma history, was more strongly related to the pediatric outcomes than the mother's history.[20] Previous studies have also found that persistent asthma in fathers conferred a higher risk of atopy in their children[20] and that a paternal history of asthma was strongly associated with airway hyperresponsiveness in offspring.[21] However, in a contrasting meta-analysis, Lim *et al.* showed that both a paternal and maternal history of asthma increased the offspring risk of asthma, with the effect of maternal asthma having a greater extent than paternal disease.[22]

In the present study, the mean age of the participants in the SAE group was significantly lower than the corresponding figure for the OPD group. This result contrasts with the findings of a study by Lyell *et al.*, which found that asthmatic patients in an ICU group were older than those in a non-ICU group (mean age ± SD: 6.7 ± 5.3 vs. 4.4 ± 3.5 years, $p = 0.01$).[23] In addition, our study did not demonstrate a correlation between SAE and other factors that had been found by earlier studies to be associated with SAE, namely, passive smoking,[24,25] viral infection,[26] obesity,[27] low parental incomes,[28] and poor adherence.[29]

Our study may shed some light on the risk factors for severe asthma exacerbation in the Southeast Asian population, which could be used to advise patients and prioritize care for pediatric asthmatic patients. The limitations of this study were that the nasopharyngeal wash to detect respiratory viruses was performed in some SAE patients only, and the wash did not include rhinovirus, which commonly triggers asthma exacerbation.[10,26] Other limitations were that there was a small number of participants, and that no evaluation was made of air pollution, which has been reported to affect SAE.[30]

Conclusion

Alternaria sensitization, an age younger than 6 years, and a paternal history of atopy were associated with SAE in Thai asthmatic children.

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Conflicts of interest

The authors declare that there are no conflicts of interest related to this study.

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