

# First episode of preschool wheeze requiring hospitalization: a prospective study on the chance of recurrence and associated factors

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## Abstract

**Background:** Although wheezing is very common in preschoolers, epidemiologic studies in Thailand are quite limited. The likelihood of having a second wheezing episode following the first attack remains unclearly established.

**Objectives:** This study aims to investigate the incidence of recurrent wheezing in preschool children presenting with first wheezing episode and identify the associated factors.

**Methods:** The study is an observational prospective study conducted at the inpatient pediatric department. Patients admitted with first episode of wheezing were followed up as an outpatient approximately one week after hospital discharge and subsequently followed up by telephone 3-monthly with a structured questionnaire seeking information concerning recurrent wheezing, defined as having a second wheezing episode requiring bronchodilator within a 1-year period.

**Results:** The total of 97 patients, aged 6 months to 5 years, were recruited from June 2014 to November 2015. Thirty-five patients were excluded because of inaccessibility for telephone follow-up. Amongst the remaining 62 patients, twenty-eight (45.2%) had recurrent wheezing within one year. The mean lapse duration was  $4.7 \pm 3.7$  months after the first episode. Having an allergic sensitization to aeroallergen was a risk factor for recurrent wheezing (OR 2.48, 95%CI 1.81–3.4). Although not statistically significant, having an allergic sensitization to food seems to be another related factor (OR 2.36, 95%CI 1.75–3.18).

**Conclusion:** The recurrent rate of wheezing was 45%, which was considerably significant. Allergic sensitization to aeroallergen might increase the risk. These patients should be followed up, especially within the first year after their first wheezing episode.

**Key words:** First wheezing, Preschool, Hospitalized, Recurrent, Incidence, Associated factors

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## Abbreviations:

EVW, episodic viral wheeze; ER, emergency room; HFNC, high flow nasal cannula; mAPI, modified asthma predictive index; MTW, multiple-trigger wheeze; OPD, outpatient department; PIS, pulmonary index score; RSV, respiratory syncytial virus

## Introduction

Wheezing is very common in infants and young children due to age specific anatomical and physiological properties. One in three children under the age of 3 years have at least one episode of wheezing prior to their third birthday,<sup>1</sup> with a cumulative prevalence of up to 40% during the first 6 years of life.<sup>2</sup>

Various phenotypes of recurrent wheezing have been recognized. It could be classified as transient, late onset, and persistent wheezing according to population based cohort studies<sup>3</sup> or into episodic viral wheeze (EVW) and multiple-trigger wheeze (MTW), categorized by The European Respiratory Society Task Force on Preschool Wheeze.<sup>4</sup> Identification of these patterns of wheeze might allow the clinician to classify children during an office visit, which leads to effective treatment and follow up.<sup>5-7</sup> However, the classifications of episodic and

multiple-trigger wheeze might be unstable over time, with more than half of children switching to the other phenotype over the course of a year.<sup>8</sup>

In patients admitted for the first time with an acute wheezing episode, a commonly asked question from their parents is “Will my child wheeze again?”. However, in Thailand, epidemiologic studies and long-term data are quite limited. A 5-year prospective study at two tertiary hospitals in Khon Kaen revealed the recurrent wheezing of 61.8% in the first three years of follow-up, with the mean duration of  $5.4 \pm 7.2$  months after the first episode of wheezing in children aged 1–24 months.<sup>9</sup>

The current study focused on investigating the incidence of having a second episode of wheezing in preschool children, aged 6 months to 5 years, presenting with a first wheezing episode and identifying its associated factors during a one year follow-up period.

## Methods

This observational prospective study was conducted at the inpatient Pediatric department of King Chulalongkorn Memorial Hospital from June 2014 to November 2015. This study was reviewed and approved by the human rights and ethics committee of the Faculty of Medicine, Chulalongkorn University, Thailand. Written informed consent was obtained from the parents of each patient. In this study, the term “recurrent wheezing” was defined as having a second wheezing episode requiring treatment with nebulized bronchodilator at any hospital within a 1-year follow-up.

### Participants and Procedure

Patients were included in the study if they were admitted with a first episode of wheezing. Other criteria were age (6 months to 5 years old), nationality (Asian), and consent from parents. The subjects were then excluded if they had congenital

or chronic illness (including chronic lung disease, bronchopulmonary dysplasia, cerebral palsy, congenital heart disease, congenital anomalies, structural airway malformation, primary immunodeficiency, gastroesophageal reflux disease, illness that requires steroid use) or clinical of sepsis or septic shock. Data concerning the age of the patients at the initial wheezing episode, sex, gestation age (preterm/term), breast-feeding duration, parental history of asthma, exposure to secondhand smoke, modified asthma predictive index (mAPI), comorbidity (allergic disease, including allergic rhinitis, atopic dermatitis, food allergy, cow’s milk protein allergy, sensitization to aeroallergens) were obtained through an interview questionnaire. The severity of the acute episode was assessed using pulmonary index score. Data regarding the length of stay, treatment needed (high flow nasal cannula (HFNC)), and viral pathogen (RSV or Non-RSV) were collected from the medical records. Viral antigen detection was tested on subjects through nasopharyngeal swabs at the discretion of the primary doctor.

As shown in **figure 1**, at the beginning of the study, there were 97 patients recruited. The patients were followed up as an outpatient approximately one week after being discharged and subsequently received an active follow up by telephone 3-monthly with a structured interview questionnaire seeking information on recurrent wheezing within a one year period. Out of the 97 originally recruited, sixty-two patients completed the follow up. The reason for drop-out was due primarily to the inability to contact their parents who may have changed their telephone number without automatic update.

Amongst the 62 subjects completing the telephone followed up, eight subjects reported having a positive skin prick test. The medical records of these subjects were subsequently reviewed. The skin prick tests were done by allergists in the outpatient allergy clinic at King Chulalongkorn Memorial Hospital. A wheal of 3 mm. or greater is considered a positive result. Types

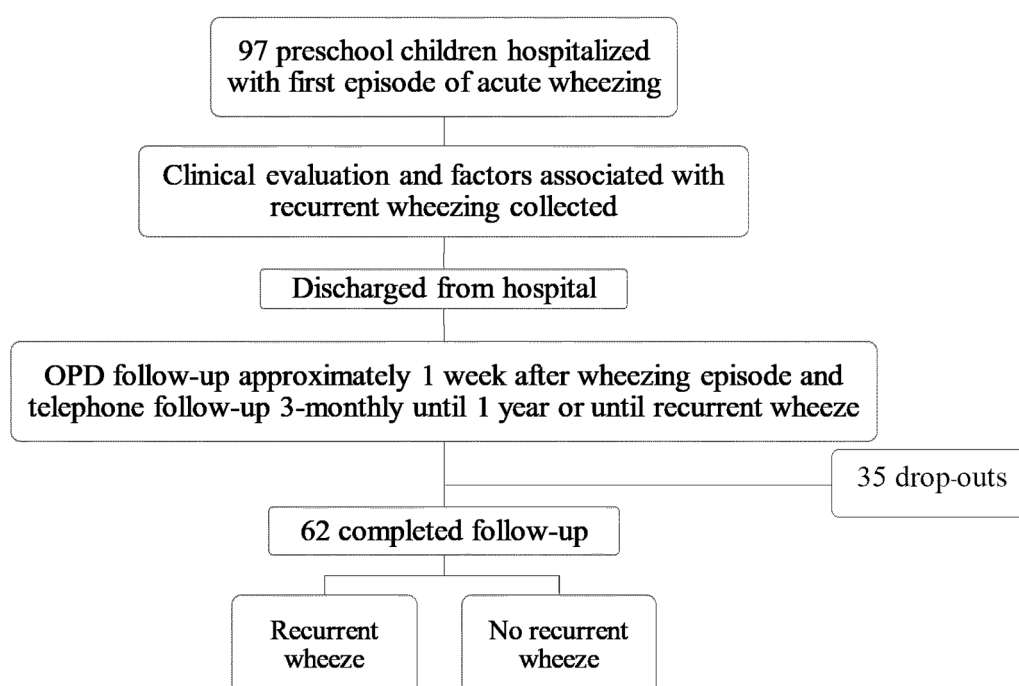


Figure 1. Patient disposition

of food allergens are Cow's milk, Casein, Egg yolk, Egg white, Soy bean, Peanut, Wheat, and Shrimp. Whereas aeroallergens consists of; D.pteronysinus, D.farinae, German cockroach, American cockroach, Cat, Dog, Mold (Aspergillus, Alternaria, Cladosporium, Penicillium), Bermuda grass, and Johnson grass. This covers most of the allergens common in Thai population.<sup>10</sup>

**Statistical Analysis**

Data were analyzed using Statistical Package for Social Sciences (SPSS) version 22. The descriptive analysis included calculating percentages and mean ± SD for demographic variables. Logistic regression models were used to identify clinical variables associated with recurrent wheezing. Results from logistic models described by odds ratios and 95%CI. P-value < 0.05 was considered to indicate statistical significance.

**Results**

**Demographic data**

The total of 97 patients with the age of 6 months to 5 years old were diagnosed with first episode wheezing. Thirty-five patients were excluded because of inaccessibility of the parents for follow-up. Their characteristics are presented in **Table 1**. There were no significant differences in clinical and demographic characteristics between the subjects and dropouts indicating that the sample population was representative of the root population of 97 patients.

Of the completed 62 patients, 28 patients (45.2%) had recurrent wheezing while the remaining of 34 patients (54.8%) did not have it. The mean lapse duration of recurrence was 4.7 ± 3.7 months after the first episode.

Of the 62 patients included in the study, 31 (50%) were male subjects. The mean age of the patients at admission was 23 months (± 14.7 months). The weight and height of the patients are within the normal range for age. The entry points of study population varied, from visiting the emergency room (ER)/out-patient department (OPD) without appointment (88.7% being most of the case) to OPD with appointment and referred.

The record revealed that most of the subjects is of term, while 16.1% is of preterm. More than half (56.5%) were breast fed for over 6 months. About 44% had been exposed to household cigarette smoke. The majority of the subjects (88.7%) did not have co-morbid diseases, while only a few had atopic dermatitis (9.7%) and food allergy (1.6%).

**Factors associated with recurrent wheezing**

**Table 2** shows the demographic and clinical characteristics of children with and without recurrent wheezing. The analysis revealed that demographic features and the severity of the wheezing episode; pulmonary index score, length of stay, and requirement of HFNC were not significant factors contributing to recurrent wheezing.

RSV infection was found positive in 21 subjects, eight (28.6%) in the recurrent wheeze group comparing to 13 (38.2%) in the other. There were 3 subjects tested positive for Rhinovirus, they all had recurrent wheezing. Four subjects were tested positive for other viruses each; Adenovirus, Bocavirus, Human metapneumovirus, and Influenza virus. These subjects did not

**Table 1. Characteristics of study population and drop-outs**

Factors	Subjects (n = 62)	Drop-outs (n = 35)	p-value
<b>Demographic data</b>			
Age at 1 <sup>st</sup> wheezing (months)	23 ± 14.7	23.71 ± 14.05	0.811
Male sex	31 (50%)	17 (48.6%)	0.892
Preterm	10 (16.1%)	2 (6.3%)	0.174
Exposure to cigarette smoke	27 (44.3%)	2 (40%)	0.854
<b>Allergy-related history</b>			
Parental asthma	7 (11.3%)	3 (17.6%)	0.360
Atopic dermatitis	6 (9.7%)	1 (2.9%)	0.213
Allergic sensitization to aeroallergen	5 (8.1%)	0 (0%)	0.085
Eosinophilia > 4%	3 (4.8%)	0 (0%)	0.186
Allergic sensitization to food	3 (4.8%)	0 (0%)	0.186
Allergic rhinitis	2 (3.2%)	1 (2.9%)	0.920
Positive mAPI	13 (23.2%)	4 (11.4%)	0.161
<b>Severity</b>			
PIS before treatment	5.76 ± 2.01	5.95 ± 1.67	0.703
Required HFNC	7 (13.7%)	2 (5.7%)	0.233
Length of stay (days)	3.69 ± 2.85	3.97 ± 2.13	0.617
RSV positive	21 (33.9%)	12 (34.3%)	0.967

Values presented as frequency (%), Mean ± SD. and Odds ratio (95%; Confidence interval). P-value corresponds to Logistic regression analysis HFNC, high flow nasal cannula; mAPI, modified asthma predictive index; PIS, pulmonary index score; RSV, respiratory syncytial virus

have recurrent wheezing. However, some of the subjects were tested with RSV rapid test only, hence did not undergo other viral antigen detection. No significant association between respiratory viruses and recurrent wheezing was demonstrated in this study.

During the follow-up period, eight out of 62 subjects was found to have a positive skin prick test. In one subject, the skin prick test was done after having the wheezing episode, while the other 7 subjects underwent a skin prick test after having a second attack. Five were positive to aeroallergens, two were positive to food allergens, and 1 was positive to both. From the initial interview, three subjects were suspected to have food allergies. They all underwent a skin prick test for food allergens, and the tests were positive. Allergic sensitization to aeroallergen was a factor identified as being of significance (odds ratio 2.48, 95%CI 1.81–3.4) and allergic sensitization to food also contributes to the risk of recurrent wheezing (odds ratio 2.36, 95%CI 1.75–3.18). While, parental asthma, atopic dermatitis, eosinophilia > 4%, allergic rhinitis, and a positive mAPI were not significant factors influencing the recurrence of wheezing.

Table 2. Demographic and clinical characteristics of children with and without recurrent wheezing

Factors	Recurrent wheeze (n = 28)	No recurrent wheeze (n=34)	OR (95%CI)	p-value
<i>Demographic data</i>				
Age at 1st wheezing (months)	20.21 ± 13.06	25.29 ± 14.63	0.97 (0.94, 1.01)	0.161
Male sex	16 (57.1%)	15 (44.1%)	1.33 (0.76, 2.33)	0.444
Preterm	6 (21.4%)	4 (11.8%)	1.42 (0.78, 2.58)	0.326
Breast fed > 6 months	14 (50%)	21 (61.8%)	0.77 (0.45, 1.33)	0.443
Exposure to cigarette smoke	10 (35.7%)	17 (51.5%)	0.72 (0.4, 1.3)	0.31
<i>Allergy-related history</i>				
Parental asthma	1 (3.6%)	5 (14.7%)	0.35 (0.06, 2.11)	0.209
Atopic dermatitis	3 (10.7%)	3 (8.8%)	1.12 (0.48, 2.62)	1
Allergic sensitization to aeroallergen	5 (17.9%)	0 (0%)	2.48 (1.81, 3.4)	0.015*
Eosinophilia > 4%	1 (3.6%)	2 (5.9%)	0.73 (0.14, 3.7)	1
Allergic sensitization to food	3 (10.7%)	0 (0%)	2.36 (1.75, 3.18)	0.087
Allergic rhinitis	1 (3.6%)	1 (2.9%)	1.11 (0.27, 4.57)	1
Positive mAPI	8 (28.6%)	5 (17.9%)	1.51 (0.87, 2.6)	0.22
<i>Severity</i>				
PIS before treatment	5.7 ± 1.59	5.81 ± 2.34	0.97 (0.75, 1.26)	0.845
Required HFNC	4 (15.4%)	3 (12%)	1.31 (0.64, 2.66)	0.691
Length of stay (days)	3 ± 1.47	4.26 ± 3.54	0.77 (0.56, 1.05)	0.095
RSV positive	8 (28.6%)	13 (38.2%)	0.78 (0.42, 1.46)	0.59

Values presented as frequency (%), Mean ± SD. and Odds ratio (95%; Confidence interval). P-value corresponds to Logistic regression analysis HFNC, high flow nasal cannula; mAPI, modified asthma predictive index; PIS, pulmonary index score; RSV, respiratory syncytial virus

## Discussion

Several birth cohort studies have revealed the natural history of wheezing in preschool children.<sup>11-13</sup> In 2008, reclassification of preschool wheezing to EVW and MTW was recommended.<sup>4</sup> This study attempts to investigate the incidence of a second episode wheezing after only the first episode, which all of the subjects had a history of preceding viral upper respiratory tract infection. The incidence of recurrent wheezing of 45% found in this study corresponds with the results of prospective studies reported by Schultz *et al.* in 2010<sup>8</sup> and Kappelle *et al.* in 2012,<sup>14</sup> and in line with the retrospective study of Topal *et al.* in 2013,<sup>15</sup> as well as the results of a study in Thailand carried out by Teeratakulpisarn *et al.* in 2014.<sup>9</sup>

Schultz *et al.*<sup>8</sup> studied 38 cases of EVW for one year and found that 65.8% had recurrent wheezing. Which the phenotype classification remained as EVW in 31.6% of the cases, 34.2% changed to MTW, and the remaining 34.2% recovered. Kappelle *et al.*,<sup>14</sup> who studied 78 patients with severe EVW for 3.9 years, also reported that 66.7% of the patients had recurrent wheezing, while 33.3% recovered. The retrospective study of 236 cases by Topal *et al.* 2013 on short-term changes in phenotype of EVW and MTW concluded that EVW phenotype is not stable and may change over a short-term follow-up period.<sup>15</sup>

A positive mAPI for major criteria, and anti-inflammatory treatment at the time of diagnosis were identified as predictors of persistence of wheeze in preschool children with EVW by Topal *et al.*,<sup>15</sup> this present study did not find these elements to be of statistical significance.

Previous studies have shown the benefit of the mAPI in predicting asthma development in patients having 4 or more episodes of wheezing. Lowering the number of wheezing episodes to 2 (m2API) lowered the predictive value after a positive test.<sup>16</sup> This study used the mAPI to evaluate patients with only a first wheezing episode, and found no significant association between a positive mAPI and recurrent wheezing. Therefore, it could be implied that in patients with a first episode of wheezing, a positive mAPI does not indicate a higher risk of recurrence.

The severity of symptoms in this study, assessed by the Pulmonary Index Score, length of stay, and the requirement of HFNC was not found to have any differences between both groups. This differs from the study of Bessa *et al.* 2014,<sup>17</sup> which found that recurrent wheezers had more severe symptoms, nocturnal symptoms, and visits to emergency rooms and hospitalizations for wheezing and pneumonia, when compared to infants with occasional wheezing. However, all the subjects in

this study were hospitalized. This accounts for already having severe symptoms, which might be the reason for the insignificant differences of these factors between both groups. As for the factor of having an RSV infection, no association with recurrent wheezing was found, similar to previous studies.<sup>18,19</sup>

The present study identified one risk factor for recurrent wheezing in preschool children with first episode wheezing: allergic sensitization to aeroallergen. Allergic sensitization to food also contributes to the risk of recurrent wheezing, although it was not statistically significant. These results are similar to the Prevention of Asthma in Kids (PEAK) trial in 2004.<sup>20</sup> However, it is not a common practice in Thailand to perform skin prick tests in patients with only a first wheezing episode. It is usually done in cases of recurrent wheezing, which asthma is suspected. Although there was a trend for family history of asthma to be associated with recurrent wheezing, it was not conclusive in this study that it is a risk factor for recurrent wheezing. Other factors previously found to have significant association with recurrent wheezing are blood eosinophilia, atopic dermatitis, and a history of earlier episodes of wheezing in infancy.<sup>21</sup> These factors were not found to have an association with recurrent wheezing in this study.

The advantage of this study is that it is a prospective study. This justifies the ability to identify associated factors which are considered as risks for recurrent wheezing. However, the present study is considered to have the following limitations.

First, the study sample size was relatively small, limiting the ability to identify associated factors of recurrent wheezing during the one-year follow-up period. This is because this study only includes children admitted with first episode wheezing and excludes patients with already recurrent wheezing (either from the hospital records or the history suggested by their parents). The study population was representative of the initial population of 97 children positively identified as having a first episode wheezing (**Table 1**) in terms of age, gender, and history of allergic diseases. Further studies in larger prospective hospital-based cohorts of patients presenting with first episode wheezing are needed to confirm the results of the present study.

Secondly, the duration of follow-up was until the patient had a second episode wheezing, with a maximum duration of one-year period. Although recurrent wheezing was reported to occur mostly within the first year, with a mean duration  $5.5 \pm 7.2$  months after the first episode,<sup>9</sup> which bears a resemblance to this study of  $4.7 \pm 3.7$  months, other long-term follow-up cohort studies have shown that a number of patients had recurrent wheezing later in life and were diagnosed with asthma beyond the preschool age.<sup>22-24</sup> By extending the duration of the follow-up, the phenotypes of wheezing could be classified and the natural history of patients presenting with first episode wheezing could be more clarified.

A third limitation is that respiratory virus detection during episodes of wheezing was not performed in every subject. Previous studies have looked in to respiratory viruses in preschool wheeze and suggested that rhinovirus and respiratory syncytial virus may have impact on increasing the likelihood of persistent asthma.<sup>9,25,26</sup> However, viral testing is not necessary in children presenting with wheezing and is not recommended in clinical guidelines for preschool wheeze.<sup>4</sup> Therefore, data collected on respiratory viruses in this study was limited, and so no

association between respiratory viruses and recurrent wheezing could be demonstrated.

The final limitation is that this study was conducted in a single center, which may limit the generalizability of the findings. Nonetheless, King Chulalongkorn Memorial Hospital is a tertiary hospital located at the city center of Bangkok. Hence, a number of patients visit the emergency room and the out-patient department each day, including patients referred from other hospitals. Therefore, it is believed that the subjects in this study are a representative of preschool children with first episode wheezing in a tertiary care center.

In conclusion, the incidence of recurrent wheezing in preschool children, age 6 months – 5 years, presenting with first wheezing is 45% which is of significance, with mean lapse duration of recurrence from the first episode of  $4.7 \pm 3.7$  months. It remains a challenge for the clinicians to differentiate children with transient symptoms from children who will have recurrent wheezing. Having an allergic sensitization to aeroallergen could increase their risks. It is recommended to evaluate and follow up preschool children with first episode wheezing within the first year of their attack, especially patients with the risk factor above, so that clinicians could be able to early detect cases likely to develop recurrence

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