

# Outcomes of young children hospitalized with acute wheezing

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## Abstract

**Background:** Wheezing in preschool children is a common symptom.

**Objective:** The study aimed to determine an incidence of recurrent wheezing among young children who had been hospitalized with acute wheezing after 12 months. Factors associated with recurrent wheezing were explored.

**Methods:** A longitudinal study was conducted among 236 children, aged between 6 months and 5 years, who were hospitalized with acute wheezing in 4 hospitals located in Bangkok and adjacent provinces, Thailand. Demographics, house environments and clinical characteristic data were collected at entry. Serum specific IgE levels against common food and inhalant allergens and serum 25-hydroxyvitamin D (25OHD) concentrations were measured.

**Results:** At entry, the mean age was 24.4 months (SD = 15.7 months). Of 236 hospitalized children with acute wheezing, ninety-four cases (39.8%) were the first wheezing episode of life. By laboratory results, 197 (83.5%) and 56 (23.7%) children were atopic and had vitamin D insufficiency respectively. There were 195 cases completely followed for 12 months. One-year risk of emergency visits and hospitalization due to recurrent wheezing were 49.7% and 23.1% respectively. By multivariable analysis, being the second born child or more, vitamin D insufficiency, “ever wheeze”, and allergic rhinitis were significantly associated with recurrent wheezing within 12 months with adjusted odds ratios of 2.5 (95% confidence interval: 1.3-5.3), 2.3 (95% confidence interval: 1.1-4.4), 1.9 (95% confidence interval: 1.2-3.5), and 1.6 (95% confidence interval: 1.3-2.9) respectively.

**Conclusion:** Being the second born child or more, vitamin D insufficiency, ever wheeze, and allergic rhinitis were significant risks of recurrent wheezing.

**Key words:** incidence, recurrent wheeze, preschool, hospitalization, risk factors

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## Introduction

Wheezing is the problem that is often found in children, especially the small ones. It's most often found in the first year of life.<sup>1-2</sup> Approximately one third of children had had wheezing at least once by the time they reached 3 years of age. Half of the children had cumulative wheezing during the first 6 years.<sup>3-4</sup> Recurrent wheeze in preschool children has various prognoses. The management of wheezing in young children is associated with many challenges. The diagnosis could be difficult as wheezing can occur in this age without asthma and confirmatory lung function tests are difficult to perform.<sup>5</sup> Genetic with environmental factors might be responsible for childhood pattern of wheezing. Also, many medications for asthma are poorly studied in very young children. From the birth cohort study,<sup>4</sup> some children had only transient wheezing, which related to viral infection but would not develop into asthma at school. However, the classification of patients by retrospective wheezing phenotype pattern as transient wheeze or persistent wheeze cannot be used in clinical practice, since

it is retrospective categorization. This study aimed to determine the incidence of recurrent wheezing after 12 months among young children who were hospitalized with acute wheezing. Factors associated with recurrent wheezing were explored.

### Material and Methods

A longitudinal study was conducted among 236 preschool children who were hospitalized with acute wheezing in four hospitals including Bhumibol Adulyadej Hospital, King Chulalongkorn Memorial Hospital, Saraburi Hospital, and Thammasat University Hospital. They were recruited during July 2014 to June 2015 with ages of 6 months to 5 years. The first or recurrent wheezing episodes were eligible for the study but would be excluded from the study if they had onset of wheezing in perinatal period or chronic diseases including congenital heart diseases, bronchopulmonary dysplasia, structural airway malformation, acquired immune deficiency syndrome (AIDs), and cerebral palsy. The informed consents were obtained from their caregivers.

At admission, demographic and household characteristic data were collected by parental-administered questionnaire. Serum samples of the participants at entry were measured for specific IgE levels by ImmunoCAP (Phadia, Uppsala, Sweden) to determine sensitization to common allergens including cow's milk, egg white, dust mite, cockroach, dog, cat and Bermuda grass. Atopy was defined as having at least one allergen sensitization by the cutoff value of 0.35 kUA/L. Serum samples at entry were assessed for 25-hydroxy vitamin D (25OHD) concentrations by enzyme-linked immunosorbent assay (ELISA).

Vitamin D insufficiency was defined by the serum 25OHD levels of < 30 ng/ml. Eighty children were available to obtain nasopharyngeal suction to identify influenza virus, respiratory syncytial virus (RSV), rhinovirus and enterovirus68 using realtime polymerase chain reaction (RT-PCR).

The participants were followed every 4 months for 12 months to record the outcomes including hospitalizations and emergency visits due to recurrent wheezing. The study was approved by the human ethics committees of all four hospitals.

The study required the sample size of 236 to determine estimated incidence of recurrent wheezing at 12 months of 30 percent. The margin errors of the estimation of 6 percent with the type one errors of 0.05 were determined. Exploratory analysis by multiple logistic regressions was used to determine independent factors associated with recurrent wheeze during 12 months of follow-up, presented with adjusted odds ratio and 95% confidence interval (95%CI). Subgroup analysis was performed to assess an association between rhinovirus infection and recurrent wheezing during 12 months of follow-up presented with risk ratio.

### Results

At entry, the mean age of the participants was 24.4 months (SD = 15.7 months) with 148 boys (62.7%). Of 236 hospitalized children, ninety-four cases (39.8%) were the first wheezing episode of life. Paternal and maternal history of asthma was 17.4 and 13.6 percent respectively. The highest prevalence of sensitization was to cow's milk (50.8%), followed by egg white (35.6%). Patients' characteristics stratified by history of wheezing at admission were presented in **Table 1**.

**Table 1. Patients' characteristic at entry, stratified by history of wheezing at admission**

Characteristics	Total		"The first wheeze" group		"Ever wheeze" group	
	N = 236	%	N = 94	%	N = 142	%
Parental academic degrees						
Primary school	23	9.7	10	10.6	13	9.2
Secondary school	132	55.9	57	60.6	75	52.8
Bachelor degrees or higher	81	34.3	27	28.8	54	38.0
Paternal asthma	41	17.4	13	13.8	23	16.2
Maternal asthma	32	13.6	10	10.6	18	12.7
Current passive smoking in household	106	44.9	48	51.1	58	40.8
Boys	148	62.7	56	59.6	92	64.8
Age (months)						
6-12	61	25.8	26	27.7	35	24.6
12-24	66	28.0	25	26.6	41	28.9
24-36	48	20.3	18	19.1	30	21.1
36-60	61	25.8	25	26.6	36	25.4
The second born child or more	121	51.3	46	48.9	75	52.8
Allergic rhinitis	48	20.3	16	17.0	32	22.5

Table 1. (Continued)

Characteristics	Total		“The first wheeze” group		“Ever wheeze” group	
	N = 236	%	N = 94	%	N = 142	%
Atopic dermatitis	37	15.7	14	14.9	23	16.2
Allergen sensitization (> 0.35 kUA/L)						
cow's milk	120	50.8	42	44.7	78	54.9
egg white	84	35.6	32	34.0	52	36.6
dog	47	19.9	19	20.2	28	19.7
cat	33	14.0	14	14.9	19	13.4
dust mite	77	32.6	27	28.7	50	35.2
cockroach	45	19.1	15	16.0	30	21.1
Bermuda grass	37	15.7	14	14.9	23	16.2
Atopy (> one allergen sensitization)	197	83.5	75	79.8	122	85.9
Blood Eosinophil > 4%	11	4.7	4	4.3	7	4.9
Vitamin D insufficiency (< 30 ng/ml, N = 225)	56	23.7	19/89	21.3	37/136	27.2
Viral antigen assay* (N = 80)			(N = 33)		(N = 47)	
Not detected	32	40.0	14	42.4	18	38.3
Rhinovirus	36	45.0	15	45.5	21	44.7
RSV	8	10.0	3	9.1	5	10.6
Enterovirus68	4	5.0	1	3.0	3	6.4
Influenza	0	0	0	0	0	0

\*Nasopharyngeal specimen by real-time PCR

Table 2. Patients' characteristics between completed follow-up and loss to follow-up group

Characteristics	Completed follow-up		Loss to follow-up		p-value
	N = 195	%	N = 41	%	
Parental academic degrees					0.564
Primary school	19	9.7	4	9.8	
Secondary school	112	57.4	20	48.8	
Bachelor degrees or higher	64	32.8	17	41.5	
Paternal asthma	33	16.9	8	19.5	0.656
Maternal asthma	26	13.3	6	14.6	0.804
Current passive smoking in household	85	43.6	21	51.2	0.392
Boys	120	61.5	28	68.3	0.480
Mean age at entry (months)	24.8 ± 15.8		24.1 ± 16.9		0.791
The second born child or more	99	50.8	22	53.7	0.864
Allergic rhinitis	40	20.5	8	19.5	0.885
Atopic dermatitis	29	14.9	8	19.5	0.480

**Table 3. Incidence of recurrent wheezing during the follow up period of 12 months**

	Recurrent wheezing within 12-months follow-up			
	Emergency visits		Hospitalization	
	N	Incidence risk (95%CI)	N	Incidence risk (95%CI)
Total (N = 195)	97	49.7% (42.5%-57.0%)	45	23.1% (17.4%-29.6%)
The first wheeze episode (N = 78)	33	42.3% (31.2%-54.0%)	15	19.5% (11.3%-30.1%)
History of “ever wheeze” (N = 117)	64	54.7% (45.2%-64.0%)	30	25.7% (18.0%-34.5%)

There were 195 cases completely followed for 12 months. Characteristics of patients who were loss to follow-up was comparable to the completed follow-up group detailed in **Table 2**. One-year risk of emergency visits and hospitalization due to recurrent wheeze were 49.7% and 23.1% respectively, presented in **Table 3**. Inhaled corticosteroids and leukotriene receptor antagonist (LTRA) were prescribed, at least once from

hospital visits, during follow-up period of 12 months for 33.3% and 23.1% respectively.

By multiple logistic regression model, being the second child or more, history of previous wheezing, allergic rhinitis, vitamin D insufficiency were significantly associated with recurrent wheezing during a follow-up period of 12 months described in **Table 4**.

**Table 4. Risk factors of emergency visits due to recurrent wheezing during 12 months of follow-up**

Risk factors	Adjusted Odds ratio (95% CI)	P-value
The second born child or more	2.5 (1.3-5.3)	0.007*
Vitamin D insufficiency (< 30 ng/ml)	2.3 (1.1-4.4)	0.046*
“Ever wheeze” before admission	1.9 (1.2-3.5)	0.041*
Allergic rhinitis	1.6 (1.3-2.9)	0.035*
Atopic dermatitis	1.7 (0.87-3.47)	0.231
Boy	0.97 (0.33-1.59)	0.471
Age more than 2 years	0.95 (0.71-1.29)	0.740
Atopy**	0.97 (0.24-3.21)	0.819
Paternal asthma	1.04 (0.89-1.33)	0.404
Maternal asthma	1.06 (0.74-1.24)	0.542
Current passive smoking in household	1.31 (0.55 -2.81)	0.649
Blood eosinophilia (> 4%)	0.85 (0.14-4.73)	0.791
Prescribing inhaled corticosteroids	1.2 (0.6-3.1)	0.152
Prescribing LTRA	0.9 (0.3-3.9)	0.481

\* Statistical significance at the level of 0.05 by Wald tests of logistic regression model

\*\* > one allergen sensitization

**Table 5. Association between rhinovirus infection at admission and recurrent wheeze during 12 months of follow-up**

Rhinovirus infection	No recurrent wheezing*	Recurrent wheezing*	Risk ratio (95% Confidence interval)	P-value
“The first wheeze at admission” group				
No Rhinovirus	11 (84.6%)	2 (15.4%)	-	
Rhinovirus	5 (50.0%)	5 (50.0%)	3.3 (0.8-13.4)	0.074
“Ever wheeze at admission” group				
No Rhinovirus	7 (36.8%)	12 (63.2%)	-	
Rhinovirus	6 (35.3%)	11 (64.7%)	1.0 (0.6-1.7)	0.923

\*Emergency visits due to recurrent wheezing

According to nasopharyngeal suction for viral study in 80 children, there were 48 cases (60%) positive for viral PCR and the most prevalent viral infection was rhinovirus (40%). Rhinovirus increased the risk of recurrent wheeze during one-year follow-up period among hospitalized children who had the first wheezing episode at admission with the risk ratio of 3.3 (95% CI: 0.8-13.4), but not reach statistical significant level presented in **Table 5**.

## Discussion

This is a prospective study that justifies the ability to identify associated factors for recurrent wheezing in hospitalized preschool children with acute wheezing. However, there are some limitations. First, the study sample size was relatively small, limiting the ability to identify associated factors of recurrent wheezing during 12 months of follow-up. Secondly, the duration of follow-up was until the patient had a recurrent wheeze, with a maximum duration of one year. Thirdly, only 80 children available for viral study of nasopharyngeal suction specimens at admission. Viral infection variable was not included in the multivariable logistic model due to large missing data. Fourthly, this study was conducted in four centers, three of which were tertiary hospitals. This might limit the generalizability of the results.

More than 60% were boys which are consistent with the epidemiology of general pediatric patients with acute wheezing.<sup>6</sup> The incidence of recurrent wheezing of 49.7% in this study corresponds with the previous results of prospective studies (45.2%-61.8%).<sup>7-9</sup>

In our study, over 80% of children with acute wheezing had atopy with the highest sensitization to cow's milk protein and egg white. This result is consistent with the sensitization pattern of preschool age children in other studies.<sup>10,11</sup> Contribution of sensitization to aeroallergens and food allergens to the risk of recurrent wheezing has been reported.<sup>12,13</sup> But our study did not find an association between allergen sensitization and recurrent wheezing during follow up of 12 months ( $p = 0.870$ ). The effect of atopy on recurrent wheezing might differ depending on phenotype of the study population and the method used determining sensitization. Most participants in our study were preschool children hospitalized with the first wheezing episode or less than 3 wheezing episodes before admission while the Prevention of Asthma in Kids (PEAK) trial<sup>12</sup> and the study of Guo J, et al<sup>13</sup> enrolled preschool children with history of more than 3 wheezing episodes. Sensitization reported in the study of Chantawarangul K, et al<sup>7</sup> was assessed by skin prick tests while specific serum IgE level was used in our study.

Our study identified significant factors associated with recurrent wheezing during 12 months of follow up in preschool children including being the second born child or more in siblings, "ever wheeze" at admission, vitamin D insufficiency, and allergic rhinitis. Rhinitis was reported as a risk of persistent wheezing in young children by Guo Jing, et al<sup>13</sup>, especially with aeroallergen sensitization. Other significant factors have been reported to associate with recurrent wheezing including sensitization to allergens (atopy), atopic dermatitis, and blood eosinophilia.<sup>7,12-15</sup> These factors were not found

to have the association with recurrent wheezing during 12 months of follow up in our study. However, epidemiological results varied depending on the study type, study population, definition of exposures and timeframe of follow up.

The second born children or more in siblings were more likely to expose infections from their siblings, resulting in infection induced wheezing more than the first born children. However, Hygiene hypothesis proposed that the risks of asthma reduced by contact with infection in early life.<sup>16</sup> Reduction of asthma risk was reported with increasing birth order children.<sup>17</sup> Therefore, longer duration of follow up among these young children was required to identify subsequent asthma development.

Passive smoking in household did not significantly increase the risk of recurrent wheezing in our study, similar to the report from Chantawarangul K, et al.<sup>7</sup> However, there were evidences that maternal smoking during pregnancy increased the risk of recurrent wheezing in the first few years of life.<sup>15,18</sup>

Rhinovirus was found to be the most prevalent virus precipitating acute wheezing in hospitalized children with acute wheezing in our study. The finding was consistent with the previous reports.<sup>13,19,20</sup>

Prescription of controllers in our study was counted if inhaled corticosteroids or leukotriene receptor antagonist was prescribed from any hospital visits during follow-up period of 12 months. Prescription of inhaled corticosteroids and leukotriene receptor antagonist was not associated with recurrent wheeze during 12 months of follow-up in our study. There is an evidence from clinical trials that inhaled corticosteroids had beneficial effect on prevention of recurrent wheeze in preschool children,<sup>21</sup> but not for leukotriene receptor antagonist.<sup>22</sup> A course of inhaled steroids after acute bronchiolitis is not effective in preventing recurrent wheeze.<sup>23</sup> Almost half of participants in our study admitted with the first wheezing episode, may suffered from acute bronchiolitis. According to a non-randomized control trial design of our study; there is a risk for bias to determine a treatment effect during follow-up. Indication and contraindication bias occurs because physicians normally prescribe controllers based on clinical findings and guidelines of individual hospital. Some participants were prescribed controllers after ER visits of recurrent wheeze while some of them might be prevented from recurrent wheeze by controllers prescribed earlier. Interpretation the effect of controllers in our study, therefore, should be cautious since causality and reverse causality bias mixed up the observed effect.

In conclusion, recurrent wheezing during 12 months of follow-up among preschool children who were admitted with acute wheezing was common. It is recommended to evaluate and followed preschool children with acute wheezing for a period, especially patients with the risk factors including the second born child or more, vitamin D insufficiency, "ever wheeze", and allergic rhinitis.

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