

## Wheezing Infant

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### 1. Introduction

Symptoms of Gastroesophageal Reflux Disease (GERD) are both esophageal and extraesophageal symptoms. The consensus statements on the definition of GERD in the pediatric population were reported that respiratory symptoms might be occurred by gastroesophageal acid reflux (Sherman et al.,2009). But, the definition of GERD used by gastroenterologists are much different from that used by allergists (Colombo, 2004).

Usually, the diagnosis of GERD is based on the reflux index (percentage of total recording time with a pH below 4) during 24-hour pH monitoring (pH monitoring) (Working group of the European society of pediatric gastroenterology and nutrition, 1992). But, this baseline of the reflux index was defined by gastroenterologists. In our previous study in asthmatic children with GERD, we showed that respiratory symptoms tended to worse not only at night but also in the daytime, and the index of the mean hourly number of acid refluxes (the mean number of acid reflux/h) which we defined parameters as the frequency of acid refluxes during upright position during pH monitoring was important for the diagnosis of GERD when associated with asthma (Yoshida et al., 2009).

In some previous reports, the frequency of GERD in children with respiratory symptoms was comparatively high (Saglani et al., 2006). But, at the present situation, it has not been cleared sufficiently when GERD should be considered in children with episodes of recurrent wheezing. In clinically, when episodes of recurrent wheezing are intractable regardless of doing medications, we suspect that GERD is associated with episodes of recurrent wheezing. So, in the present study, we investigated the difference of characteristics for diagnosis and treatment of GERD more appropriately in children with episodes of recurrent wheezing associated with GERD.

Proton pump inhibitors (PPIs) and histamine-2 receptor antagonists (H<sub>2</sub>RAs) are widely used as acid suppression therapy of GERD (Scarupa et al.,2005). In recent years, not only H<sub>2</sub>RAs but also PPIs were reported for treatment of GERD (Gustafsson et al.,1992; Harper et al., 1987; Khoshoo et al.,2003; Sopo et al.,2009; Stordal et al.,2005; The American lung association asthma clinical research center,2009). However, in Japan, we can only use the enteric-coated tablet-type PPIs. Therefore, PPIs are difficult to use for preschool children especially those under 5 years of age. So, we have no choice but to use the powdered-type H<sub>2</sub>RAs in children under 5 years of age. In our country, the powdered-type H<sub>2</sub>RAs we can use is famotidine. So, in the present study, we used famotidine as acid suppression therapy.

And, in our previous study, the mean number of acid reflux/h during the upright position exceeded 7 in all the children with GERD associated asthma (Yoshida, et al., 2009). So, in the present study, we diagnosed of GERD by the mean number of acid reflux/h which baseline was defined as exceeded 7 and response of acid suppression therapy.

## 2. Materials and methods

We performed pH monitoring between June 2007 and December 2008 in 52 preschool children with episodes of recurrent wheezing. All participant's chest radiograph were normal. They had no other respiratory disorders, for example, bronchiectasis, recurrent pneumonia, aspiration, intestinal lung disease and airway abnormality. And they had no neurological disorders, cardiac disease and gastrointestinal symptoms.

All patients received inhaled corticosteroid (ICS) for more than 3 months. The ICS used was fluticasone or hydrofluoroalkane-beclomethasone dipropionate more than 200  $\mu$ g/day. But, their respiratory symptomatic days during one month were more than 5 days. Their respiratory symptoms were uncontrolled. So, we suspected that GERD was associated with their respiratory symptoms, and we performed the pH monitoring.

When the mean number of acid refluxes/h during upright position exceeded 7, by the result of pH monitoring, we started famotidine therapy (0.5mg/kg twice daily). And, we followed up the children who started famotidine therapy for one month. So, we counted respiratory symptomatic days for one month before and after starting the famotidine therapy. And we compared them before and after starting the famotidine therapy.

So, in the case that symptomatic days were decreased less than half days, we defined that famotidine therapy was effective. When famotidine therapy was effective, children formed the effective group. On the other hand, in the case that symptomatic days were not decreased less than half days, we defined that famotidine therapy was not effective. When famotidine therapy was not effective, children formed the no effective group. Then, we compared the patient's characteristics between the two groups. We investigated the patient's age, onset age of wheezing episodes, level of serum IgE, amount of ICS and results of pH monitoring as patient's characteristics. And we investigated modified asthma predictive index (mAPI) as the risk factors for the development of asthma (Panettieri et al., 2008).

The pH monitoring was performed using a Synectics Digitrapper MKIII (Synectics Medical Stockholm Sweden). The catheter had 4 probes that sensed acid reflux. The most upper probe (the first probe) was 20 cm above the bottom probe. The third probe of the catheter was placed 3-4 cm above the gastroesophageal junction, and its position was checked by chest radiography. We examined the mean number of acid refluxes/h during upright position and the reflux index at the third probe. The asthma medication was continued as usual during pH monitoring.

In our hospital, respiratory symptoms are recorded in a diary in order to acquire the precise clinical manifestation. At every patient's visit, each physician checked the diary.

## 3. Data analysis

Normal distributed data were presented as mean  $\pm$  SD. Nonparametric data were expressed as median. The differences were assessed by the Mann-Whitney U-test. A p-value  $<0.05$  was considered to be statistically significant for all tests.

#### 4. Results

Patient profiles were summarized in Table 1. 27 children showed the results that the mean number of acid reflux/h during upright position exceeded 7. In 18 of the 27 children, the reflux index exceeded 4%. In the remaining 25 children with the mean number of acid reflux/h during upright position being below 7, the reflux index was below 4%.

Gender	
- Male,n	35
- Female,n	17
Age,years*	3.1 (1.8)
Amount of ICS, µg/day*	219 (59.4)
Results of 24-hour pH monitoring	
- Reflux index,%*	6.2 (9.5)
- The mean number of acid reflux/h during upright position, times*	12.4 (13.6)
- The number of children with reflux index over 4 %, n	18
- The number of children with the mean number of acid reflux/h during upright position over seven, n	27

\*Data are presented as mean (SD). n:number. ICS; inhaled corticosteroid

Table 1. Patient profiles (n=52)

19 of the 27 children profiles with the mean number of acid reflux/h during upright position being over 7 were summarized in Table 2. The remaining 8 children did not record respiratory symptoms in the diary or did not visit our hospital. Among the 19 children, 8 were included in the effective group and 11 were included in the no effective group.

Gender	
- Male,n	12
- Female,n	7
Age,year*	3.1 (1.33)
Amount of ICS, µg/day*	235 (236)
Results of 24-hour pH monitoring	
- The mean number of acid reflux/h during upright position, times*	19.5 (19.9)
- Reflux index,%*	9.0 (9.3)
The effective group	8
The no effective group	11

\*Data are presented as mean (SD). n:number. ICS; inhaled corticosteroid

Table 2. Patient profiles with the mean number of acid reflux/h during upright position over 7 (n=19)

A comparison of patient's characteristics between the effective group and the no effective group was summarized in Table 3. The mean (SD) age was 2.4 (1.0) years old in the effective group, and 3.5 (1.3) years old in the no effective group ( $p < 0.05$ ). And, the mean (SD) onset

	Effective group n=8	No effective group n=11	p vale
Age, year	2.4(1.0)	3.5(1.3)	p<0.05
Onset age of episodes of wheezing, year	1.0(1.1)	3.0(1.0)	p<0.05
Serum IgE, IU/ml	209(201)	150(237)	n.s.
Amount of ICS, µg/day	237(106)	236(80)	n.s.
Results of 24-hour pH monitoring			
- reflux index, %	11.4(10.8)	7.6(9.8)	n.s.
- The mean number of acid reflux/h during upright position, times	20.9(9.5)	19.0(19.6)	n.s.
Respiratory symptomatic days			
- Before famotidine	16.0(7.2)	14.1(5.8)	n.s.
- After famotidine	5.6(5.4)	13.9(4.5)	p<0.05

Data are presented as mean(SD).

Table 3. Comparison of the effective group and the no effective group

age of wheezing was 1.0 (1.1) years old in the effective group, and 3.0 (1.0) years old in the no effective group (p<0.05). The mean (SD) respiratory symptomatic days before famotidine were 16.0 (7.2) in the effective group, and 14.1 (5.8) in the no effective group. The mean (SD) respiratory symptomatic days were 5.6 (5.4) in the effective group, and 13.9(4.5) in the no effective group (p<0.05). There was no significant difference between the two groups before famotidine tehapy. But, there was difference between the two groups after famotidine therapy. The changes of the respiratory symptomatic days between before and after famotidine therapy in each group were showed in figure 1. In the effective group, there was singinificant difference (p<0.05). There was no singinificant difference between the two groups about level of serum IgE, amount of ICS and the results of pH monitoring in Table 3. A comparison of modified asthma predictive index between the effective group the no effective group was summarized in Table 4. There was no singinificant difference about each index between the two groups.

Modified Asthma Prediction Index	Effective group (n=8)	No effective group (n=11)	p value
• Major criteria, n			
Parental history of asthma	3	5	n.s.
Physician-diagnosed atopic dermatitis	2	3	n.s.
Allergic sensitization to $\geq 1$ aeroallergen	5	6	n.s.
• Minor criteria, n			
Allergic sensitization to milk, egg, or peanuts	3	3	n.s.
Wheezing unrelated to colds	8	11	n.s.
Blood eosinophils $\geq 4\%$	5	5	n.s.
The presence of 1 of the major criteria or 2 minor criteria, n	8 (100%)	11 (100%)	

Table 4. Comparison of Modified Asthma Prediction Index between the effective group and the no effective group

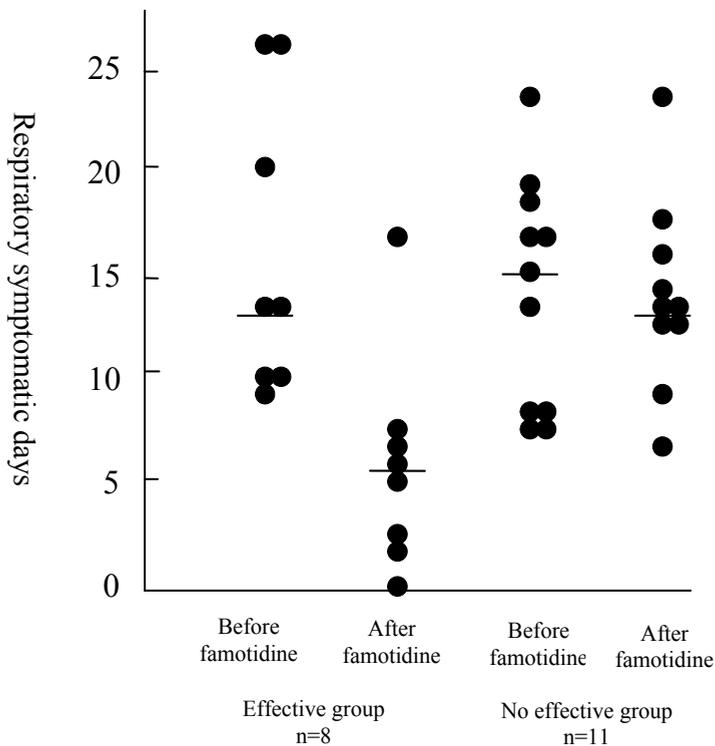


Fig. 1. The difference of the effective group and the no effective group of respiratory symptomatic days between before and after famotidine therapy

## 5. Discussion

The incidence of GERD was comparatively high in children with episodes of recurrent wheezing. The previous report had shown that the incidence of asthma in children with episodes of recurrent wheezing was 40.4%, and that of GERD was 23.4%. In particular, 57% children with asthma also had GERD (Saglani et al., 2006). But, the efficacy of acid suppression therapy was not cleared sufficiently for children with episodes of recurrent wheezing (Brand et al., 2008). For example, in the treatment of asthma, there was a report that PPIs did not improve asthma control (The American lung association asthma clinical research center, 2009). So, in the present study, we prescribed for famotidine based on result of pH monitoring in the lower age preschool children with episodes of recurrent wheezing, and compared between children with effective and ineffective of famotidine therapy. And, we showed that famotidine therapy could be more effective in the lower age preschool children with episodes of recurrent wheezing with associated GERD.

In the present study, 8 out of 19 (42%) children who received the famotidine therapy were included the effective group. And, in the effective group, the mean age and the onset age of first wheezing episode were significantly lower than that of the no effective group. Namely, in preschool children with episodes of recurrent wheezing associated with GERD, the lower

age of and the lower onset age of first wheezing episodes were, the more effective famotidine therapy was. In clinically, a diagnosis of GERD is made by the efficacy of acid suppression therapy in addition to the results of pH monitoring. So, in the effective group, their respiratory symptoms could be defined that GERD was associated with episodes of recurrent wheezing. About relationship of gastroesophageal acid reflux (GER) and age, the other previous report had shown that GER occurs easily below one year of age (Nelson et al., 1997). From the present results and previous reports, we suggested that respiratory symptoms of lower age could be much associated with GERD with symptoms were improved by famotidine in children with episodes of recurrent wheezing.

Some previous reports had shown the efficacy of PPIs for children with episodes of recurrent wheezing (Sopo et al., 2009; Stordal et al., 2005). PPIs were more effective than H<sub>2</sub>RAs such as famotidine. But, PPIs available in Japan are difficult to use for preschool children. So, in the no effective group in the present study, there might be improved respiratory symptoms if PPIs were used. But, unfortunately, this problem could not be cleared in the present situation in Japan.

But, there are two treatment regimens of GERD. One treatment regimen which is called the no effective therapy is to begin with H<sub>2</sub>RAs. When symptoms are not improved by H<sub>2</sub>RAs, then PPIs are used. The other medication which is called step-down therapy is to begin with PPIs. But, in treatment of GERD, cost-effectiveness considerations must be needed when which medication is used (Hassall, 2008). In general, PPIs are superior to H<sub>2</sub>RAs for erosive esophagitis (Vandenplas et al., 2009). So, PPIs were capable of being a cost-effective diagnostic test in adult (Ofman et al., 1999). But, in children, there was no study comparing these two medications (Hassall, 2008). In pediatric gastroesophageal reflux clinical practice guidelines, there needs special concern to prescription of PPIs in infants (Vandenplas et al., 2009). In previous report, PPIs were used over the age of 2 years old or those with moderate symptoms of GERD. But, under the age of 12 month, H<sub>2</sub>RAs were better starting medication (Hassall, 2008; Vandenplas et al., 2009). So, in clinical cases, the medication is selected by considering age and severity of symptoms.

About symptoms of GERD, the presence of esophageal erosions or ulcers is one of the factors that determine the severity of GERD (Armstrong et al., 2005). But, the previous study showed that the presence of esophagitis did not always exist in children with refractory respiratory symptoms of GERD (Ravelli et al., 2006). So, the severity of GERD with episodes of recurrent wheezing could be defined "mild"

Another previous report showed that H<sub>2</sub>RAs were safe and effective for the management of mild GERD symptoms (Vandenplas et al., 2009). So, we suggested that H<sub>2</sub>RAs might be prescribed first for children with episodes of recurrent wheezing. H<sub>2</sub>RAs include cimetidine, famotidine and ranitidine. There was no previous study about the effective of famotidine for respiratory symptoms. So, our present study is valuable.

Asthma is the most common cause in diseases with episodes of recurrent wheezing (Weinberger & Abu-Hasan, 2007). Recurrent wheezing during first 3 years is one of the established risk factor for the development of asthma in childhood (Panettieri et al., 2008). But, we must take careful of asthma like symptoms caused by other causes (Weinberger & Abu-Hasan, 2007). Diagnosis of asthma in preschool children with episodes of recurrent wheezing is difficult (Brand et al., 2008). The previous report had shown that the incidence of asthma in children with episodes of recurrent wheezing was 41%, and that of GERD was 23%, and that of predominantly infection was 13% (Saglani et al., 2006). One of the common diagnosis in the diseases of predominantly infection is protracted bacterial bronchitis (Gibson et al., 2010). Children with protracted bacterial bronchitis are sometimes erroneous

labeled as having severe asthma (Chang et al., 2008). So, the other previous report had shown that the differential diagnosis should be considered when young children with recurrent respiratory symptoms had a negative mAPI (Chipps, 2010).

The mAPI is a clinical index of asthma for 2 years of age and older (Panettieri et al., 2008). When the child has the presence of 1 the major criteria or 2 minor criteria in the mAPI, the recurrent respiratory symptoms of child might be developed persistent asthma (Chipps, 2010). So, we investigated mAPI whether there were differences about risk factor for asthma development between the effective group and the no effective group. As a result, there was no significant difference on each subject. And all children of each groups had the presence of 1 of the major criteria or 2 minor criteria. So, there was no significant difference about risk factor for asthma development according to the mAPI. But, in the no effective group, amount of ICS was increased within 3 months after famotidine therapy for controlling of respiratory symptoms. The mean (SD) amount of ICS was 308 (78)  $\mu\text{g}/\text{day}$ . (data not shown). We speculated that children in the no effective group had more progressive airway inflammation and had more risk for asthma development than children in the effective group. But, it is not cleared sufficiently in the present study.

## 6. Conclusion

It is not cleared sufficiently that we must consider what kind of preschool children with episodes of recurrent wheezing are prescribed for the acid suppression therapy. In our present study, in preschool children with episodes of recurrent wheezing associated with GERD, the lower age of and the lower onset age of first wheezing episodes were, the more effective famotidine therapy was. We suggest that lower age preschool children with episodes of recurrent wheezing whose symptoms are suspected associating with GERD from the result of pH monitoring might be prescribed acid suppression therapy actively. And, famotidien is inferior to PPIs as the acid suppression therapy. But, we suggest that famotidine might be useful as primary medication for "mild" GERD which main symptom is recurrent wheezing.

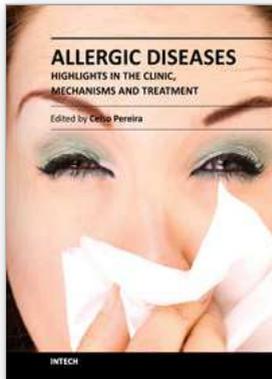
## 7. Acknowledgment

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