

Airway Resistance and Allergic Sensitization in Children With Obstructive Sleep Apnea Hypopnea Syndrome

Jie Zhang, MD,^{1*} Jing Zhao, MD,¹ Min Chen, MD,¹ Shilin Liu, MD,¹ Xuexi Zhang, MD,¹ Fengzhen Zhang, MD,¹ Yamei Zhang, MD,¹ Hui Chen, PhD,² and Xin Ni, MD^{1*}

Summary. Objective: The purpose of this study was to determine the airway resistance in Chinese children with obstructive sleep apnea hypopnea syndrome (OSAHS) by impulse oscillometry (IOS) and investigate the association of the severity of OSAHS with the airway resistance and allergic sensitization. Method: A total of 120 children (92 boys) treated for snoring in Beijing Children's Hospital between October 2010 and March 2011 were included in this study. Ninety-three children were diagnosed with OSAHS and 27 did not show OSAHS. Total airway resistance (R5), proximal airway resistance (R20), and peripheral airway resistance (X5) were determined by IOS. Serum levels of total IgE and allergen-specific IgE (sIgE) were also determined. Results: R5 in the OSAHS group was significantly higher than that in the non-OSAHS group ($P=0.0025$), whereas R20 and X5 were similar in the two groups. R5 was positively correlated with apnea hypopnea index and obstructive apnea index and negatively correlated with the lowest arterial oxygen saturation significantly (all $P<0.05$). The percentage of children with abnormal serum levels of total IgE or abnormal allergen-specific IgEs was comparable in OSAHS and non-OSAHS groups. The proportions of abnormal R5 and of abnormal serum levels of total IgE were significantly higher in children with severe OSAHS compared with children with mild or moderate OSAHS (all $P<0.05$). Conclusions: Total airway resistance was significantly increased in Children with OSAHS. Allergic sensitization might contribute to the exacerbation of existing OSAHS in children. Large scale studies are required to further validate these findings. **Pediatr Pulmonol.** © 2015 Wiley Periodicals, Inc.

Key words: airway resistance; allergen; children; impulse oscillometry; obstructive sleep apnea hypopnea syndrome.

Funding source: Beijing Municipal Science and Technology Project of Children's Health, Number: Z13110006813044; Scientific Research Project of Capital Health Development, Number: 2014-1-2091.

INTRODUCTION

Obstructive sleep apnea hypopnea syndrome (OSAHS), a common sleep-related breathing disorder in adult, is increasingly recognized in children recently. It has been reported that the incidence of OSAHS in children aged 2–8 years is 2–3.5% in western countries.^{1,2} In China, as the economic situation improves substantially for the past 3 decades, childhood OSAHS is becoming increasingly prevalent possibly owing to an increased population of obese children.³ In 2004, a survey on sleeping disorder in children aged 2–12 years in eight cities of China revealed that the prevalence of sleeping disorder was 27.1%, and 5.7% and 0.4% of the children participating in the survey suffered from snoring and sleep apnea, respectively.³

Adenotonsillar hypertrophy has been shown to contribute to the development of childhood OSAHS, and adenotonsillectomy is commonly practiced to relieve OSAHS in children.^{4,5} In addition to adenotonsillar hypertrophy, allergic rhinitis, which often causes nasal

¹Department of Otorhinolaryngology, Beijing Key Laboratory for Pediatric Diseases of Otolaryngology, Beijing Children's Hospital, Head and Neck Surgery Beijing Pediatric Research Institute, Capital Medical University, Beijing, P. R. China.

²School of Biomedical Engineering, Capital Medical University, Beijing, P. R. China.

Conflict of interest: The authors declare none of conflict of interest.

Jie Zhang and Jing Zhao contributed equally to this work.

*Correspondence to: Xin Ni, MD and Jie Zhang, MD, Department of Otorhinolaryngology, Beijing Children's Hospital, Capital Medical University, 56 Nanlishi Road, Xicheng District, Beijing 100045, People's Republic of China. E-mail: nixin@bch.com.cn (X.N.); stzhangj@263.net (J.Z.)

Received 1 February 2015; Revised 23 June 2015; Accepted 25 June 2015.

DOI 10.1002/ppul.23264

Published online in Wiley Online Library (wileyonlinelibrary.com).

mucosal swelling, increases the risk of OSAHS in children by increasing upper airway resistance.^{6,7} Cao et al. compared the airway resistance in adult patients with OSAHS versus health controls and found that the airway resistance in OSAHS patients was significantly higher than that in healthy controls.⁸ However, the association between airway resistance and OSAHS in children remains unknown. Impulse oscillometry (IOS) is a computer-supported method for the measurement of both small and large airway resistance. In this method, a noninvasive superimposition of pressure fluctuations is applied on the airway of the subject's normal, quiet, tidal breathing. This method is convenient, noninvasive, and minimally dependent on patient cooperation. IOS has been tested to evaluate the clinical outcomes in patients with chronic obstructive pulmonary disease (COPD) and to diagnose COPD and asthma in both adults and children.^{9–14} The purpose of this study was to determine the airway resistance in children with snoring by IOS and to investigate the association of the severity of OSAHS with airway resistance and allergic sensitization. The status of airway resistance and allergic sensitization in children with OSAHS might be used as indicators to evaluate the severity of OSAHS so to facilitate early intervention.

MATERIALS AND METHODS

Patients

The study protocol was approved by the Institutional Ethics Committee for Research of Beijing Children's Hospital. Patients' parents signed the informed consent form. In this retrospective study, a total of 120 children treated for snoring in our hospital between October 2010 and March 2011 were included in this study. All the children met the following criteria: (1) aged between 3 and 14 years, (2) with obvious symptoms of snoring. Children with facial deformity, Down syndrome, and Crouzon syndrome were excluded. The diagnosis of OSAHS was based on the 2009 guidelines of Chinese Medical Association for childhood OSAHS, which is consistent with the International Classification of Sleep Disorders-Third Edition.¹⁵ All the children were evaluated for allergic rhinitis according to the Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines for symptoms and clinical diagnosis of allergic rhinitis.¹⁶ All the children had adenotonsillar hypertrophy.

Sleep Index Assessment by Polysomnography (PSG)

All the children underwent at least one standard overnight in-lab PSG (Compumedics E-series, Compumedics Inc, Abbotsford, Australia) provided by trained and certified pediatric sleep technicians. Children

accompanied with one parent were monitored for up to 8 hr in a dedicated observation room. Four-channel electroencephalogram (C3, C4, O1, and O2) with bilateral central and occipital leads, electrooculogram, submental electromyogram, electrocardiogram, and body position were recorded. Respiratory variables included thoracic and abdominal wall movement, nasal airflow, and oxygen saturation were also measured. An obstructive hypopnea was defined as a $\geq 50\%$ reduction in the amplitude of the airflow signal with persistent respiratory effort. It was only quantified if it was longer than two baseline breaths and was associated with oxygen desaturation of $\geq 3\%$ and/or arousals. Apnea hypopnea index (AHI) was defined as the total number of obstructive apneas, mixed apneas, and obstructive hypopneas per hour of total sleep time (TST). Obstructive apnea index (OAI) was defined as the number of obstructive apneas and mixed apneas per hour of TST. The oxygen desaturation index was defined as the number of oxyhemoglobin desaturation events $\geq 3\%$ from baseline per hour of TST. Children diagnosed with OSAHS were divided into mild, moderate, and severe OSAHS subgroups according to AHI value. Mild OSAHS was defined as $1 \leq \text{AHI} < 5$ episodes/hr and $\text{OAI} > 1$; moderate OSAHS was $5 \leq \text{AHI} < 20$ episodes/hr; severe OSAHS was $\text{AHI} \geq 20$ episodes/hr.

Impulse Oscillometry

Impulse oscillometry was performed to evaluate airway resistance of the patients (IOS, Jaeger Viasys, Healthcare GmbH Company, Germany). The following IOS parameters were recorded: airway resistance at 5 Hz (R5) and 20 Hz (R20) representing total and proximal airway resistance. R5 and R20 with values $< 150\%$ of the expected values were considered normal. For healthy people, R5 and R20 values are very similar. The reactance at 5 Hz (X5) representing peripheral airway abnormalities was also recorded. Normal X5 was defined as the difference between the expected and the actual value is $< 0.2 \text{ kPa} / (\text{L} \cdot \text{s})$.

Measurement of Serum Levels of Total IgE and Allergen-Specific IgE (sIgE)

Serum levels of total IgE and sIgE were determined using a sensitive screen and quantitative allergen detection system (Allergy Screen, Mediawiss Analytic GmbH, Germany). A total of 15 environment allergens were tested, including dust mites, dusts, short ragweed, artemisia, humulus, cat and dog hairs, cockroaches, mixed molds (*Penicillium notatum*, *Alternaria*, *Branching neurospora*, and *Aspergillus fumigatus*), and mixed tree pollens (oak, elm, Chinese parasol tree, willow, cottonwood). sIgE $> 0.35 \text{ IU/ml}$ is considered allergen positive and total IgE $> 100 \text{ IU/ml}$ is considered abnormal.

Statistical Analysis

Continuous variables are presented as mean $\pm$ standard deviation (SD). Categorical variables are presented as number or percentage. Data were analyzed using the statistical analysis software SPSS17.0. Comparison between two groups was analyzed by student's *t*-test. Bonferroni correction was used for multiple comparisons. Correlations among variables were examined by χ^2 test. *P* value was 2-sided, and *P* < 0.05 was considered statistically significant.

RESULTS

Total Airway Resistance Was Significantly Higher in the OSAHS Group Than in the Non-OSAHS Group

In the 120 children, 93 (77 boys and 16 girls) were diagnosed with OSAHS; 27 (15 boys and 12 girls) were not. The median age was 5 years for both OSAHS and non-OSAHS groups. The non-OSAHS group was considered as the primary snoring group of this study. The clinical characteristics including age, BMI z-scores, and proportion of children with allergic rhinitis were comparable in the two groups (Table 1). The proportion of children exhibiting abnormal serum levels of total IgE or sIgE was not significantly different between the two groups (Table 1), suggesting that allergic responses to environmental allergens might not contribute to the

development of OSAHS. The total airway resistance (R5) in children with OSAHS was significantly higher compared with that in the primary snoring group (*P* = 0.0025, Table 1), whereas proximal (R20) and peripheral (X5) airway resistances were similar in the two groups. The children with OSAHS showed significantly higher AHI and OAI and lower LSAO₂ than the primary snoring group (all *P* < 0.001, Table 1). Total airway resistance (R5) was positively correlated with AHI (*P* < 0.001) and OAI (*P* < 0.004) significantly, whereas it was negatively associated with LSAO₂ significantly (*P* < 0.001, Table 2).

The Proportions of Abnormal R5 and of Abnormal Serum Levels of Total IgE Were Significantly Associated With the Severity of OSAHS

In this patient cohort, there were 53 cases of mild OSAHS, 29 moderate OSAHS, and 11 severe OSAHS. The proportion of children with abnormal total airway resistance (R5) was correlated with the severity of OSAHS significantly (*P* = 0.001, Table 3). Of the children with severe OSAHS (*n* = 11), eight (72.7%) showed abnormal R5 value. In contrast, 18.9% of mild and 44.8% of moderate OSAHS exhibited abnormal R5. Both R20 and X5 were not associated with the severity of OSAHS (Table 3). In addition, significantly higher proportion of children with severe OSAHS had abnormal serum levels of total IgE compared with children with

TABLE 1—Clinical Characteristics

	OSAHS n = 93	Primary snoring n = 27	<i>P</i> value
Age (year), mean $\pm$ SD (range)	5.2 $\pm$ 1.9 (3.0–11.0)	5.7 $\pm$ 2.3 (3.0–12.5)	0.213
Sex, n (%)			
Male	77 (82.8)	15 (55.6)	0.03
Female	16 (17.2)	12 (44.4)	0.003
BMI z-score, mean $\pm$ SD (range)	0.8 $\pm$ 1.7 (–4.7 to 4.9)	0.5 $\pm$ 1.3 (–1.6 to 2.7)	0.398
Allergic rhinitis n (%)	79 (85.0)	22 (81.5)	0.893
Allergic sensitization, number of cases with abnormal values (%)			
Total IgE	37 (39.8)	13 (48.1)	0.438
sIgE	33 (35.5)	9 (33.3)	0.837
Mixed mold	30 (32.2)	10 (37.0)	0.643
House dusts	8 (8.6)	3 (11.1)	0.985
Mixed tree pollens	5 (5.4)	1 (3.7)	1.000
Single allergen positive	24 (25.8)	7 (25.9)	0.990
Multiple allergen positive	9 (9.7)	2 (7.4)	1.000
IOS parameters (kPa/L/s), mean $\pm$ SD			
Total airway resistance (R5)	105.5 $\pm$ 24.2	93.1 $\pm$ 15.8	0.0025*
Proximal airway resistance (R20)	96.4 $\pm$ 24.9	91.9 $\pm$ 22.2	0.395
Peripheral airway resistance (X5)	83.4 $\pm$ 27.4	77.1 $\pm$ 20.5	0.274
PSG variables			
AHI	13.1 $\pm$ 14.2	2.3 $\pm$ 2.0	<0.001
OAI	7.2 $\pm$ 10.5	0.80 $\pm$ 0.2	<0.001
LSaO ₂	81.5 $\pm$ 11.1	93.4 $\pm$ 1.5	<0.001

IOS, impulse oscillometry; OSAHS, obstructive sleep apnea hypopnea syndrome; PSG, polysomnography; AHI, apnea-hypopnea index; OAI, obstructive apnea index; LSAO₂, the lowest arterial oxygen saturation. Values were compared by Student's *t*-test. *represents significantly different between primary snoring versus OSHAS group, *P* < 0.05.

TABLE 2—Correlation Between PSG Variables and IOS Parameters

	R5	R20	X5
r/P value			
AHI	0.348/<0.001	0.061/0.509	0.088/0.339
OAI	0.258/0.004	−0.027/0.773	0.092/0.317
LSaO ₂	−0.331/<0.001	−0.093/0.374	0.028/0.792

AHI, apnea hypopnea index; OAI, obstructive apnea index; LsaO₂, lowest arterial oxygen saturation. The correlation between IOS parameters and the PSG variables were analyzed by calculating the Pearson product-moment correlation coefficient (r).

mild or moderate OSAHS (72.7% vs. 30.2% and 44.8%, $P = 0.026$, Table 3), whereas the proportion of children with abnormal serum levels of sIgE was not significantly different among children with different severity of OSAHS ($P > 0.05$, Table 3). These results indicated that allergic sensitization might affect the exacerbation of childhood OSAHS.

DISCUSSION

Compared with other approach to estimate airway resistance, IOS appears to be more convenient, less invasive, and less dependent on patient cooperation.^{9–14} Thus, IOS may be easily to be employed on children. In this report, we used IOS to measure airway resistance and found that the total airway resistance (R5) in children with OSAHS was significantly increased compared with that in the children without OSAHS, whereas the proximal (R20) and peripheral (X5) airway resistances were similar between the two groups. These findings are similar to the results from studies on adult patients with OSAHS. Cao

TABLE 3—Correlation Between Severity of OSAHS and the Proportions of Abnormal Airway Resistance and Abnormal Allergic Sensitization

	Mild n = 53	Moderate n = 29	Severe n = 11	P value
Number of cases with abnormal values (%)				
IOS parameters				
Total airway resistance (R5)	10 (18.9)	13 (44.8)	8 (72.7)	0.001
Proximal airway resistance (R20)	10 (18.9)	6 (20.7)	2 (18.2)	0.975
Peripheral airway resistance (X5)	0 (0)	2 (6.9)	0 (0)	0.096
Allergic sensitization				
Total IgE	16 (30.2)	13 (44.8)	8 (72.7)	0.026*
sIgE	24 (45.3)	16 (55.2)	5 (45.4)	0.678

OSAHS, obstructive sleep apnea hypopnea syndrome. Data were analyzed by Pearson's Chi-squared test. *indicates significant different, $P < 0.05$.

et al. demonstrated that the IOS parameter R5, R10, R15, R20, and R25 were significantly higher in adults patients with severe OSAHS than in healthy adults without OSAHS, suggesting that both total airway resistance and proximal airway resistance are increased in adult patients with severe OSAHS compared with healthy controls.⁸ In this study, we also found that total airway resistance (R5) was significantly correlated with AHI, OAI, and LsaO₂ in our patient cohort, indicating that IOS parameter R5 might reflect the severity of OSAHS. Thus, IOS could be used as a method in addition to PSG to diagnose and evaluate OSAHS in children. Although IOS shows obvious advantages over PSG for children in term of convenience and requirement of only passive patient cooperation, whether it can replace PSG as a diagnostic approach remains to be determined by further studies.

Allergic rhinitis often causes nasal mucosal swelling, leading to nasal obstruction and an increase in nasal resistance. In our patient cohort, more than 80% of the children presented allergic rhinitis. Nasal obstruction is thought to contribute substantially to airway resistance and the development of OSAHS. Zang et al. compared the pharyngeal aerodynamic characteristics of patients with OSAHS versus healthy people and found that patient with OSAHS had a greater negative pressure in the pharyngeal cavity compared with healthy people, indicating that nasal airway resistance might play a key role in OSAHS development.¹⁷ Staevska et al. also showed that nasal resistance was an independent predicative factor for OSAHS in non-obese patients.¹⁸ Thus, alleviation of nasal obstruction could effectively relieve OSAHS. In a prospective multicenter randomized clinical trial, Kryger et al. found that a nasal expiratory positive airway pressure device significantly reduced AHI and improved the quality of sleep in patients with OSAHS.¹⁹

Studies investigating the association between allergic rhinitis and OSAHS suggest that allergic rhinitis might affect the progression of existing OSAHS but might not be a risk factor for OSAHS.^{20–24} In a study including 119 adult patients presenting typical symptoms of OSAHS, Kramer et al. found that allergic rhinitis was not a significant risk factor for OSAHS.²² Contrarily, in a systematic review, Ng et al. suggested that allergic rhinitis could increase the risk of OSAHS in children because it induces nasal obstruction, enlarges tonsils and adenoids, and consequently increases upper airway resistance.²³ Allergic rhinitis might affect the development and progression of OSAHS not only by causing nasal obstruction but also by inducing inflammation in the respiratory tract system, including pharynx, larynx, and trachea, resulting in an increased in airway resistance.²⁴ In fact, topical corticosteroid therapy is emerging as a promising therapy to relieve OSAHS, further indicating that inflammation associated with allergic reactions might contribute to the exacerbation of OSAHS.¹⁹ In this study,

we found that the proportion of children with abnormal allergic sensitization was similar in the OSAHS versus non-OSAHS group; however, the proportion of abnormal serum levels total IgE was significantly correlated with the severity of OSAHS. These findings further suggest that allergic rhinitis might not directly cause OSAHS, but might lead to the exacerbation of existing OSAHS in children. Thus, to properly manage OSAHS in children, allergic rhinitis should not be overlooked. In addition to the common therapies such as adenotonsillectomy and continuous positive airway pressure, sufficient management of allergic rhinitis might effectively prevent the exacerbation of OSAHS in children.

There are limitations in this study. Because this was a retrospective study, it was difficult to deduce causal relationship between total airway resistance and the development of OSAHS. The number of children in the primary snoring group was small. The children in the primary snoring group also presented symptoms of snoring. Healthy non-snoring children would be the ideal controls to characterize the IOS parameters in children with OSAHS.

ACKNOWLEDGMENT

The authors thank the staff at the Laboratory of Sleep Assessment Unit and Lung Function for their excellent technical support. This study was funded by the Beijing Municipal Science and Technology Project of Children's Health (Grant No: D131100005313014) and the Scientific Research Project of Capital Health Development (2014-1-2091).

REFERENCES

- Schlaud M, Urschitz MS, Urschitz-Duprat PM, Poets CF. The German study on sleep-disordered breathing in primary school children: epidemiological approach, representativeness of study sample, and preliminary screening results. *Paediatr Perinat Epidemiol* 2004;18:431–440.
- Shine NP, Coates HL, Lannigan FJ. Obstructive sleep apnea, morbid obesity, and adenotonsillar surgery: a review of the literature. *Int J Pediatr Otorhinolaryngol* 2005;69:1475–1482.
- Liu X, Lu X, Cui Z. A survey of sleep disorder in children at 2-12 years of age in 8 cities of China. *J Sleeping Medicine* 2004;1:4–7.
- Carr E, Obholzer R, Caulfield H. A prospective study to determine the incidence of atopy in children undergoing adenotonsillectomy for obstructive sleep apnea. *Int J Pediatr Otorhinolaryngol* 2007;71:19–22.
- Busino RS, Quraishi HA, Aguila HA, Montalvo E, Connelly P. The impact of adenotonsillectomy on asthma in children. *Laryngoscope* 2010;120 suppl 4:S221.
- McColley SA, Carroll JL, Curtis S, Loughlin GM, Sampson HA. High prevalence of allergic sensitization in children with habitual snoring and obstructive sleep apnea. *Chest* 1997;111:170–173.
- Ishman SL, Smith DF, Benke JR, Nguyen MT, Lin SY. The prevalence of sleepiness and the risk of sleep-disordered breathing in children with positive allergy test. *Int Forum Allergy Rhinol* 2012;2:139–143.
- Cao J, Que C, Wang G, He B. Effect of posture on airway resistance in obstructive sleep apnea-hypopnea syndrome by means of impulse oscillation. *Respiration* 2009;77:38–43.
- Winkler J, Hagert-Winkler A, Wirtz H, Hoheisel G. Modern impulse oscillometry in the spectrum of pulmonary function testing methods. *Pneumologie* 2009;63:461–469.
- Winkler J, Hagert-Winkler A, Wirtz H, Schauer J, Kahn T, Hoheisel G. Impulse oscillometry in the diagnosis of the severity of obstructive pulmonary disease. *Pneumologie* 2009;63:266–275.
- Li Y, Chen Y, Wang P. Application of impulse oscillometry and bronchial dilation test for analysis in patients with asthma and chronic obstructive pulmonary disease. *Int J Clin Exp Med* 2009;63:266–275.
- Haruna A, Oga T, Muro S, Ohara T, Sato S, Marumo S, Kinose D, Terada K, Nishioka M, Ogawa E, et al. Relationship between peripheral airway function and patient-reported outcomes in COPD: a cross-sectional study. *BMC Pulm Med* 2010;10:10.
- Reinhold P, Macleod D, Lekeux P. Comparative evaluation of impulse oscillometry and a monofrequency forced oscillation technique in clinically healthy calves undergoing bronchochallenges. *Res Vet Sci* 1996;61:206–213.
- Komarow HD, Myles IA, Uzzaman A, Metcalfe DD. Impulse oscillometry in the evaluation of diseases of the airways in children. *Ann Allergy Asthma Immunol* 2011;106:191–199.
- Sateia MJ. International classification of sleep disorders-third edition: highlights and modifications. *Chest* 2014;146:1387–1394.
- Brozek JL, Bousquet J, Baena-Cagnani CE, Bonini S, Canonica GW, Casale TB, van Wijk RG, Ohta K, Zuberbier T, Schunemann HJ. Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines: 2010 Revision. *J Allergy Clin Immunol* 2010;126:466–476.
- Zang HR, Li LF, Zhou B, Li YC, Wang T, Han DM. Pharyngeal aerodynamic characteristics of obstructive sleep apnea/hypopnea syndrome patients. *Chin Med J (Engl)* 2012;125:3039–3043.
- Staevska MT, Mandajieva MA, Dimitrov VD. Rhinitis and sleep apnea. *Curr Allergy Asthma Rep* 2004;4:193–199.
- Kryger MH, Berry RB, Massie CA. Long-term use of a nasal expiratory positive airway pressure (EPAP) device as a treatment for obstructive sleep apnea (OSA). *J Clin Sleep Med* 2011;7:53B–449.
- Kalpaklıoğlu AF, Kavut AB, Ekici M. Allergic and nonallergic rhinitis: the threat for obstructive sleep apnea. *Ann Allergy Asthma Immunol* 2009;103:20–25.
- Alkhalil M, Schulman E, Gatsy J. Obstructive sleep apnea syndrome and asthma: what are the links? *J Clin Sleep Med* 2009;5:71–78.
- Kramer MF, De La Chaux R, Dreher A, Pfrogner E, Rasp G. Allergic rhinitis does not constitute a risk factor for obstructive sleep apnea syndrome. *Acta Otolaryngol* 2001;121:494–499.
- Ng DK, Chan CH, Hwang GY, Chow PY, Kwok KL. A review of the roles of allergic rhinitis in childhood obstructive sleep apnea syndrome. *Allergy Asthma Proc* 2006;27:240–242.
- Farabollini B, Braschi MC, Bonifazi F. Allergic rhinitis and associated pathologies: the rationale for steroid options. *Eur Ann Allergy Clin Immunol* 2009;41:67–79.