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ORIGINAL ARTICLE

Response to budesonide among atopic and non-atopic infants/preschoolers with recurrent wheezing

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Abstract
Background: The treatment in non-atopic young children with recurrent wheezing remains controversial.
Objective: The aim of the study was to compare the response of inhaled budesonide in atopic versus non-atopic infants/preschoolers with recurrent wheezing (more than three episodes in the last year or one episode per month in the last three months).
Methods: One hundred and seventy three infants/preschoolers (mean age 1.58 ± 0.9 yrs) with recurrent wheezing without previous use of inhaled corticosteroids were enrolled and divided into two categories: atopics (eosinophils in peripheral blood $\geq 4\%$) and non-atopics ($<4\%$). Both groups were treated with budesonide (200 mcg bid delivered by MDI and spacer) for three months. The primary outcome was the prevalence of wheezing exacerbation episodes at the end of the treatment.
Results: Thirty-seven out of 173 (21.4%) were atopics and they were significantly younger, more frequently with a father with asthma, maternal grandparents with asthma and rhinitis, paternal and maternal grandparents with eczema, and higher number of wheezing episodes in the last year than non-atopics. At the end of the study, among those with good compliance ($>70\%$ of the weekly doses), the proportion of wheezing episodes were similar among atopics and non-atopics (57.7% vs. 44.1%, $p = 0.25$, respectively); the number of exacerbations requiring emergency department (ED) visits and hospital admission were also similar.
Conclusion: Regular budesonide therapy may decrease the episodes of wheezing in infants/preschoolers with recurrent wheezing, independently of atopy.
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Introduction

Even though asthma starts (nearly 80% of the cases) during the first years of life,[1,2] its diagnosis in infants/preschoolers can be difficult, as episodic wheezing and cough are also common in those who do not have asthma -particularly under the age of 3. However, most current international guidelines state that some clinical features can help to identify the risk of asthma at this age (e.g. recurrent wheezing, wheezing occurring in the absence of the common cold, and wheezing in response to exercise or other triggers, atopy, family history of atopic disorder and/or asthma).[3–5]

Peripheral blood eosinophilia is widely observed in asthmatics and has been found to be related to FEV_1, symptom scores and bronchial responsiveness.[6–8] Whether high eosinophil levels are simple markers of general immunologic derangement, or are involved directly in the pathogenesis of asthma is unclear. However, apparently, persistence of eosinophilia with time is linearly associated with increased risk of developing chronic asthma.[9] Furthermore, it has been demonstrated that, in asthmatic children, blood eosinophils correlated well with symptoms and sensitisation; moreover eosinophils discriminate better than serum eosinophil cationic protein in those atopic vs. non-atopic asthmatics.[10]

Current guidelines consider the use of low-doses of inhaled corticosteroids (ICS) as the preferred controller therapy for the management of infants/preschoolers with recurrent wheezing and high probability of asthma, and leukotriene modifiers as an alternative.[3–5] However, the treatment in children with recurrent wheeze but low or intermediate probability of asthma remains controversial.[3] Two large long-term randomised clinical trials (RCT) in preschoolers with a high risk of asthma showed that while regular ICS therapy controls persistent/severe wheezing episodes and improves lung function, it does not alter the progression/underlying state of the disease.[11,12] Recent guidelines[3–5] and a task force expert panel[13] suggest to give a trial of ICS for a period of approximately three months, especially in those preschoolers with high or intermediate risk of asthma.

The aim of the study was to compare the response of three months of regular inhaled budesonide in atopic vs. non-atopic (defined by peripheral eosinophilia) infants/preschoolers with recurrent wheezing. We hypothesise that atopics might have a better response to ICS.

Material and methods

This study was performed in a primary care setting in a suburban area in Antofagasta, Chile. As a pre-requisite to working in that place, physicians must have participated in the National Acute Respiratory Disease Training Programme. The protocol of this programme states that young children with "recurrent wheezing" should be treated with inhaled budesonide 200 mcg bid for at least three months.[14] During two years, all the infants/preschoolers less than four years of age with a diagnosis of recurrent wheezing (more than three episodes of wheezing in the last year or one episode per month in the last three months) were referred to our programme by five primary care paediatricians. Exclusion criteria included: previous use of ICS, pulmonary or cardiac congenital malformations; chronic pulmonary disease (bronchopulmonary dysplasia, cystic fibrosis, bronchiolitis obliterans post viral infection), prematurity, small for gestational age, concurrent stridor, foreign body aspiration, neurological alteration, contact with tuberculosis and laryngomalacia.

The infants/preschoolers were seen by two study paediatricians (LC and MP) and a demographic and environmental questionnaire was completed by the mother at the enrolment. The questionnaire contained data about the delivery; tobacco consumption during pregnancy and at home; anthropometric measures at birth; breastfeeding; characteristics of wheezing (age of onset, duration, frequency, use of systemic corticosteroids, ED and hospitalisation utilisation); cough with exercise and at night; other respiratory illnesses (pneumonia, sinusitis, acute otitis media); immunisation status; pets; home characteristics; maternal age and schooling; mother's employment status; and history of asthma and allergies (rhinitis and dermatitis) in parents and grandparents. A total peripheral blood sample for eosinophil determination was taken at enrolment.

All the infants/preschoolers started a regular therapy with 200 mcg twice daily of budesonide (Inflamide®, Boehringer Ingelheim International, Argentina) delivered by metered inhaler dose (MDI) and with a spacer device (450 ml) for three months. Parents received a training course on the correct use of inhaler therapy according to international guidelines.[4,5] The doses of ICS and the three months of follow-up were in accordance with the National Programme.[14] At the end of the third month, the children were seen again by the same study paediatricians and data on wheezing exacerbation (frequency of exacerbation, ED visits, and hospital admission) and ICS compliance were collected from the parents and recorded on a standard form. Good compliance to treatment was defined as an average of $>70\%$ of the weekly doses.[15]

For the purpose of the study, we divided the population into two groups: atopics ($\geq 4\%$ eosinophils on peripheral blood) or non-atopics ($<4\%$ eosinophils). The primary outcome was prevalence of wheezing exacerbation episodes (defined as increase of respiratory symptoms such as cough and audible wheeze, tachypnoea or laborious breathing during three or more consecutive days) during the three months of the study; secondary outcomes were ED visits and hospital admissions due to wheezing exacerbations during this period.

The Ethics Committee of the Universidad de Antofagasta approved the protocol as part of the National Programme. Informed consent for participation in the study was obtained from the parents.

Statistical analysis of the differences between atopics and non-atopics was performed using the χ^2 test for categorical variables and the t test for continuous variables; a p value of <0.05 using a 2 tailed test was taken as being of significance. Odds ratio (ORs) and 95% confidence intervals (CIs) were also calculated. All analyses were performed with the Stata statistical software, version 7.0 (Stata Corp, College Station, TX, USA).

Results

Of the 187 infants/preschoolers with recurrent wheezing initially enrolled in the study, 14 were misclassified (13 were

small for gestational age or one had had medical complication in the newborn period). Therefore, 173 infants/preschoolers (92.5% of the sample) were included in the study (56.6% males and 1.60±0.9 years of age); 37 (21.4%) were atopics and 136 (78.6%) were non-atopics.

No significant differences in gender, maternal age and schooling, mother's employment status, type of delivery, weight and height at birth, and duration of exclusive breastfeeding were found between atopics vs. non-atopics. However, non-atopics were significantly younger compared with atopics (Table 1). The proportion of lean was similar (83.1% for non-atopics and 86.5% for atopics, $p = 0.34$). Also, the proportion of tobacco during pregnancy and exposure to tobacco at home were similar between non-atopics vs. atopics (11.8% vs. 19.0%, $p = 0.26$; and 58.1 vs. 59.5%, $p = 0.88$, respectively).

The prevalence of eczema and rhinitis was similar between non-atopics and atopics. However, atopics had significantly higher prevalence of father with asthma, maternal grandparents with asthma and rhinitis, and paternal and maternal grandparents with eczema than non-atopics (Table 1).

The number of episodes of pneumonia, sinusitis, and acute otitis were not significantly different between non-atopics vs. atopics (35.3% vs. 51%, $p = 0.08$; 8.8% vs. 18%, $p = 0.08$; and 1.5% vs. 5.4%, $p = 0.16$, respectively). The vast majority of infants/preschoolers had a complete vaccination schedule for their age (92.7% among non-atopics and 97.3% among atopics, $p = 0.30$). The housing conditions were also similar between non-atopics vs. atopics (solid material: 72.2% vs. 75.8%, $p = 0.95$; mould stains on the household walls: 2.9% vs. 8.1%, $p = 0.16$; pets at home: 44.1% vs. 48.7%, $p = 0.62$; number of people living at home: 6.4±2.6 vs. 6.2±1.7, $p = 0.71$; and number of bedrooms at home: 3.1±1.6 vs. 3.3±1.9, $p = 0.61$, respectively).

At baseline, the age of wheezing onset, duration of wheezing episodes, and the use of systemic corticosteroids, number of episodes requiring ED visits, hospital admission and intensive care in the last year were similar between atopics and non-atopics. However, atopics had a significantly higher number of wheezing episodes in the last year than non-atopics (Table 1). Cough at night and with exercise in the last year was similar between groups (Table 1).

Table 1 Baseline demographic characteristics between atopics and non-atopics with recurrent wheezing

Characteristics	Non-atopics n = 136	Atopics n = 37	P value
Male (%)	59.1	47.1	0.21
Age (years)	1.51±0.9	1.89±0.8	**0.028**
Maternal age (years)	27.0±6.3	28.5±6.5	0.22
Maternal schooling (years)	10.3±2.3	10.6±2.5	0.55
Mother job out of home (%)	5.9	13.5	0.10
Delivery by C-section	33.3	27.8	0.53
Birth weight (g)	3,471±469	3,452±432	0.83
Birth height (cm)	49.9±2.6	49.9±2.0	0.97
Exclusive breastfeeding (months)	4.1±2.5	4.9±2.0	0.10
Eczema	35.1	42.7	0.41
Rhinitis	43.2	50.7	0.42
Paternal asthma	9.6	24.3	**0.02**
Maternal asthma	10.3	13.5	0.58
Paternal grandparents with asthma	4.4	5.4	0.80
Maternal grandparents with asthma	12.5	27.0	**0.03**
Paternal eczema	5.2	5.4	0.95
Maternal eczema	8.8	13.5	0.40
Paternal grandparents with eczema	0.74	8.1	**0.008**
Maternal grandparents with eczema	2.2	10.8	**0.019**
Paternal rhinitis	8.8	5.4	0.50
Maternal rhinitis	25.0	16.2	0.26
Paternal grandparents with rhinitis	0.0	2.7	0.06
Maternal grandparents with rhinitis	0.0	8.1	**0.001**
Cough with exercise	22.8	18.9	0.61
Cough at night	19.9	16.6	0.62
Wheezing exacerbations history			
Age of onset (months)	0.48±0.6	0.42±0.4	0.59
Duration of exacerbations (weeks)	2.0±1.1	1.6±0.7	0.12
No. of exacerbations in the last year	5.0±2.5	6.0±2.0	**0.04**
Exacerbations requiring ED visits in the last year	38.2	37.8	0.97
No. of exacerbations requiring hospitalisation(last year)	0.80±1.3	1.1±1.7	0.28
Exacerbations requiring ICU admissions (last year)	2.2	0	0.36
Systemic corticosteroids used for exacerbations (last year)	25.7	18.9	0.39

ED = emergency department; ICU = intensive care unit; IM = intramuscular; IV = intravenous.Numbers were expressed as percentage or mean±SD.

Table 2 Characteristics of infants/preschoolers who completed vs. did not complete the three months of follow-up

Characteristics	Complete n = 108	Did not complete n = 65	P value
Male (%)	56.3	57.1	0.92
Age (years)	1.68±0.9	1.47±0.8	0.18
Maternal age (years)	28.0±6.2	26.1±6.5	0.08
Maternal schooling (years)	10.4±2.5	10.5±2.1	0.79
Mother job out of home (%)	8.3	6.2	0.60
Exclusive breastfeeding (months)	4.2±2.4	4.3±2.5	0.9
Cough with exercise (%)	22.2	21.5	0.92
Cough at night (%)	16.7	23.1	0.30
Wheezing exacerbations history			
Age of onset (months)	0.42±0.3	0.53±0.8	0.22
Duration of exacerbation (weeks)	1.8±0.9	2.1±1.2	0.13
No. of exacerbation in the last year	5.1±2.3	5.5±2.5	0.34
% requiring ED visits in the last year	32.4	47.7	**0.045**
No. of requiring hospital admissions in the last year	0.77±1.4	1.0±1.4	0.26
% requiring ICU admissions in the last year	1.7	1.8	1.0
% systemic corticosteroids used in the last year	24.1	24.6	0.94

ED = emergency department; ICU = intensive care unit.Numbers were expressed as percentage or mean±SD.

Table 3 Characteristics of wheezing exacerbations between atopics and non-atopics after three months of good compliance therapy

	Non-atopics n = 59	Atopics n = 26	p value
Wheezing exacerbations (%)	44.1	57.7	0.25
Number of wheezing exacerbations	0.57±0.8	0.92±1.2	0.11
Wheezing exacerbations requiring ED visits (%)*	1.7	0	0.50
Wheezing exacerbations requiring hospitalisations (%)†	0	3.9	0.13

ED: emergency department.
*One non-atopic child had three ED visits;
†one atopic child had two hospital admissions.

At the end of the study, 108 of the 173 (62.4%) infants/preschoolers completed the three months of follow-up. As a group, there were no differences among those who completed the follow-up and those who did not complete it in terms of gender, age, maternal education and job, exclusive breastfeeding, age of wheezing onset, duration of wheezing episodes, use of systemic corticosteroids and hospital admission. However, those who did not complete the follow-up had a significantly higher proportion of ED visits and had slightly younger mothers than those who completed it (Table 2). A significantly higher proportion of atopics than non-atopics completed the follow-up (94.6% vs. 53.7%, $p = 0.0001$, respectively).

Eighty-five out of 108 (78.7%) infants/preschoolers who completed the follow-up had a good compliance of therapy. The proportion of good compliance was similar between groups (76.5% for atopics vs. 81.9% for non-atopics, $p = 0.51$, respectively). Among infants/preschoolers with good compliance the prevalence of wheezing exacerbation (primary outcome) was not significantly different between atopics and non-atopics (57.7% and 44.1%, $p = 0.25$). In addition, the prevalence of exacerbations requiring ED visits and hospital admission (secondary outcomes) was similar between groups (Table 3).

Discussion

This prospective study, undertaken in a suburban area in a developing country, shows that during three months of regular inhaled budesonide therapy (200 mcg bid delivered by MDI) the proportion of wheezing exacerbation episodes between infants/preschoolers with and without atopy was not significantly different (57.7% and 44.1%, respectively), as was the proportion of exacerbations requiring ED visits and hospital admission.

This similar response to budesonide among atopics and non-atopics (defined by peripheral eosinophilia) found in the present study is in accordance with a recent meta-analysis carried out on the base of 29 RCT (3592 infant/preschoolers with recurrent wheezing) where the efficacy of ICS was independent of the atopy.[16] However, among asthmatic schoolchildren the response of ICS differs due to their atopy condition. One RCT showed that those mild-moderate asthmatics (aged 6–17 yrs) who respond to ICS had significantly more atopic characteristics (e.g. higher blood eosinophils, serum eosinophilic cationic protein and serum IgE levels) than the antileukotreine responders.[17] These findings could suggest that ICS response could be an age response problem. Unfortunately, the two largest long-term RCT[11,12] included in

the above-mentioned meta-analysis were done exclusively in infant/preschoolers with atopy characteristics. Therefore, more studies to test the efficacy of ICS on these two groups (atopic and non-atopic) of infants/preschoolers with recurrent wheezing need to be carried out, including the comparison with leukotriene modifiers. Furthermore, this issue is important since a recent study showed that atopic (increase in total or specific IgE) and non-atopic preschoolers with multitrigger wheeze had similar airway pathology.[18]

That issue is crucial, especially in developing countries like Chile,[19] Perú,[20] or Brazil,[21] where nearly 40%[19] or 79%[20,21] of asthmatic children are non-atopic. A recent study reported high prevalence of recurrent wheezing (43.1%) during the first year of life in Chilean infants;[22] and where the presence of recurrent wheezing during the first three months was the main risk factor for pneumonia, independently of atopy.[23] In the present study the vast majority of infants/preschoolers with recurrent wheezing were non-atopics, which is in accordance with longitudinal birth cohort studies, which showed that under the age of six, mainly two phenotypes of wheezing can coexist: "transients" and "persistents", this latter group can be divided into two sub-groups: "IgE-associated wheezers" who almost certainly have eosinophilic airway inflammation, the counterpart of adult atopic asthma, and "non-atopic wheezers" who also have persistent symptoms and in whom viral infection will be implicated.[24] However, it is important to stress that many of our children are too young for atopy to have completely manifested, as was seen by the lack of different proportions of rhinitis and eczema between groups.

In the present study the response of budesonide (51.8%) for preventing wheezing exacerbation episodes among the atopic and non-atopics as a group was similar to previous RCT (50%) done on recurrent wheezing infants/preschoolers (regardless of the risk of asthma)[13] and higher than the recent meta-analysis (40%).[16] The dose of budesonide (200 mcg bid) and the duration of therapy used in the present study is according to current guidelines.[3–5] As stated above, the dose-response relationship of ICS in preschoolers is not clearly established with apparently no benefit obtained with daily doses higher than 100 mcg bid of inhaled MDI-fluticasone with spacer or equivalent (200 mcg bid of budesonide or beclomethasone).[25]

In our study, peripheral blood eosinophils count $\geq$ 4% was used for defined atopy. This was done because it is more feasible in infants/preschoolers from suburban area in developing countries to have peripheral blood than skin prick test or other more sophisticated atopic markers (e.g. serum eosinophil cationic protein, total or specific IgE). This cut-off of eosinophilia $\geq$4% used in the present study was the same cut-off used as one of the minor criteria of the asthma predictive index.[26] Indeed, previous studies found an association between elevated eosinophil counts in peripheral blood at 3 months of age -but not at age of 6- with subsequent diagnosis of atopic disease up to 18 months[27] and to 6 years of age.[28] This might indicate that the first two years of life are particularly important for the development of allergy.[28] Moreover, a large longitudinal study demonstrated a significant relation between eosinophilic count in peripheral blood and atopy (positive skin test) in children.[9] However, the combination of skin test reactivity and eosinophilia was more associated with increased BHR and respiratory symptoms than with each one alone.[29] The persistence of eosinophilia with time among asthmatics with positive skin test is linearly associated with increased risk of developing chronic asthma.[9]

In the present study, atopics had more severe diseases at admission (e.g. significant higher wheezing exacerbations) than non-atopics. This finding is in accordance with another cross-sectional study done in Brazil[30] and from our group in Chile[19]; whereas atopic asthmatics (by positive skin test) had more uncontrolled asthma; and also similar to longitudinal studies done in Melbourne[31] and Tucson.[32] It is important to stress that atopy was reported as an independent risk factor for persistent asthma in adolescents;[33] and conversely, non-atopic asthmatics were more likely to outgrow their asthma by the age of 11 years than atopics.[34] A recent cohort showed that the lack of eosinophilia in wheezy infants could predict future remission in a large majority of cases; even more eosinophilia was a better variable than allergic sensitisation for discriminated persistent wheezing.[35]

The present study has limitations. First, we have not been able to perform a double-blind placebo controlled study because our National Programme[14] considers it unethical to give placebo to preschoolers with recurrent wheezing, and antileukotrienes was not considered in that programme. Secondly, around only 62.4% of the children finished the study, however, no differences in demographic characteristics were found between those who completed and did not complete the follow-up, with the exception that those who completed have a history of less wheezing exacerbations and there were more atopics (an intention to treat analysis cannot be performed since this study was not a RCT). Thirdly, unfortunately it was not possible to perform other atopic biomarkers (e.g. serum ECP, total or specific IgE, or skin prick test) or lung function on our population; but, as was stated above, blood peripheral eosinophils correlated well with atopy. Fourthly, there is always the possibility of differences appearing by increasing the sample size. Therefore, further RCT including large sample sizes and for longer periods need to be done to elucidate the efficacy of ICS on atopic and non-atopic infants/preschoolers with recurrent wheezing.

Conclusions

In conclusion, a regular inhaled budesonide therapy (200 mcg bid) delivered by MDI and spacer could decrease the wheezing exacerbation episodes in infants/preschoolers with recurrent wheezing, independently of atopy (blood peripheral eosinophilia).

Conflict of interest

Drs. Campusano, Pastenes, Fontecilla, Escalona and Salazar have no conflict of interest to declare.

Dr. Castro-Rodriguez has participated as a lecturer and speaker in scientific meetings and courses under the sponsorship of Merck Sharp & Dohme, GlaxoSmithKline and Grünenthal; and as member of advisory board for GlaxoSmithKline. No sponsorship from institutions or pharmaceutical industry was provided to conduct this study. No pharmaceutical company sponsored this study or had any role in the study design, data collection, data analysis, data interpretation or writing of the manuscript.

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References

1. Barbee RA, Dodge R, Lebowitz ML, Burrows B. The epidemiology of asthma. Chest. 1985;87:21S–5S.
2. Yunginger JW, Reed CE, O'Connell EJ, Melton 3rd LJ, O'Fallon WM, Silverstein MD. A community-based study of the epidemiology of asthma. Incidence rates, 1964–1983. Am Rev Respir Dis. 1992;146:888–94.
3. British guideline on the management of asthma. British Thoracic Society Scottish Intercollegiate Guidelines Network. Thorax. 2008;63:1–121.
4. Global strategy for asthma management and prevention. GINA. (Up date 2007). http://www.ginasthma.com/Guidelineitem.asp?l1=2&l2=1&intId=60.
5. Guidelines for the diagnosis and management of asthma. National Asthma Education and Prevention Program. Expert Panel Report 3. NIH-NHLBI, 2007. http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.htm.
6. Bousquet J, Chanez P, Lacoste JY, Barnéon G, Ghavanian N, Enander I, et al. Eosinophilic inflammation in asthma. N Engl J Med. 1990;323:1033–9.
7. Mensinga TT, Schouten JP, Weiss ST, Van der Lende R. Relationship of skin test reactivity and eosinophilia to level of pulmonary function in a community-based population study. Am Rev Respir Dis. 1992;146:638–43.
8. Ulrik CS. Eosinophils and pulmonary function: an epidemiologic study of adolescents and young adults. Ann Allergy Asthma Immunol. 1998;80:487–93.
9. Karakoc F, Remes ST, Martinez FD, Wright AL. The association between persistent eosinophilia and asthma in childhood is independent of atopic status. Clin Exp Allergy. 2002;32:51–6.
10. Prehn A, Seger RA, Faber J, Torresani T, Molinari L, Gerber A, et al. The relationship of serum-eosinophil cationic protein and eosinophil count to disease activity in children with bronchial asthma. Pediatr Allergy Immunol. 1998;9:197–203.
11. Guilbert TW, Morgan WJ, Zeiger RS, et al. Long-term inhaled corticosteroids in preschool children at high risk of asthma. N Engl J Med. 2006;354:1985–97.
12. Murray CS, Woodcock A, Langley SJ, Morris J, Custovic A, IFWIN study team. Secondary prevention of asthma by the use of Inhaled Fluticasone propionate in Wheezy INfants (IFWIN): double-blind, randomised, controlled study. Lancet. 2006;368:754–62.
13. Brand PL, Baraldi E, Bisgaard H, et al. Definition, assessment and treatment of wheezing disorders in preschool children–an evidence based approach. European Respiratory Society Task Force Report. Eur Resp J. 2008;32 (October, in press)..
14. Ministerio de Salud-Chile. Guía clínica infección respiratoria aguda baja de manejo ambulatorio en menores de 5 años. 1st Ed. Santiago. MINSAL. 2005. http://www.minsal.cl/ici/guiasclinicas/IRABaja.pdf.
15. Carter ER, Ananthakrishnan M. Adherence to montelukast versus inhaled corticosteroids in children with asthma. Pediatr Pulmonol. 2003;36:301–4.
16. Castro-Rodriguez JA, Rodrigo GJ. Efficacy of inhaled corticosteroids in infants and preschoolers with recurrent wheezing and asthma: a systematic review with meta-analysis. Pediatrics. 2009;123:e519–25.
17. Szefler SJ, Phillips BR, Martinez FD, et al. Characterization of within-subject responses to fluticasone and montelukast in childhood asthma. J Allergy Clin Immunol. 2005;115:233–42.
18. Saglani S, Payne DN, Zhu J, et al. Early detection of airway wall remodeling and eosinophilic inflammation in preschool wheezers. Am J Respir Crit Care Med. 2007;176:858–64.
19. Castro-Rodriguez JA, Ramirez AM, Toche P, et al. Clinical, functional, and epidemiological differences between atopic and nonatopic asthmatic children from a tertiary care hospital in a developing country. Ann Allergy Asthma Immunol. 2007;98:239–244.
20. Penny ME, Murad S, Madrid SS, Herrera TS, Piñeiro A, Caceres DE, et al. Respiratory symptoms, asthma, exercise test spirometry, and atopy in schoolchildren from a Lima shanty town. Thorax. 2001;56:607–12.
21. Pereira MU, Sly PD, Pitrez PM, Jones MH, Escouto D, Dias AC, et al. Nonatopic asthma is associated with helminth infections and bronchiolitis in poor children. Eur Respir J. 2007;29:1154–60.
22. Mallol J, Andrade R, Auger F, Rodriguez J, Alvarado R, Figueroa L. Wheezing during the first year of life in infants from low-income population: a descriptive study. Allergol Immunopathol (Madr). 2005;33:257–63.
23. Castro-Rodriguez JA, Mallol J, Rodriguez J, Auger F, Andrade R. Risk factors for X-ray pneumonia in the first year of life and its relation to wheezing: a longitudinal study in a socioeconomic disadvantaged population. Allergol Immunopathol. 2008;36:3–8.
24. Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ. Asthma and wheezing in the first six years of life. The Group Health Medical Associates. N Engl J Med. 1995;332:133–8.
25. Bisgaard H, Gillies J, Groenewald M, Maden C, International Study Group. The effect of inhaled fluticasone propionate in the treatment of young asthmatic children. A dose comparison study. Am.J.Respir.Crit.Care.Med. 1999;160:126–31.
26. Castro-Rodríguez JA, Holberg CJ, Wright AL, Martinez FD. A clinical index to define risk of asthma in young children with recurrent wheezing. Am J Respir Crit Care Med. 2000;162:1403–6.
27. Borres MP, Odelram H, Irander K, Kjellman NI, Björkstén B. Peripheral blood eosinophilia in infants at 3 months of age is associated with subsequent development of atopic disease in early childhood. J Allergy Clin Immunol. 1995;95:694–8.
28. Borres MP, Björkstén B. Peripheral blood eosinophils and IL-4 in infancy in relation to the appearance of allergic disease during the first 6 years of life. Pediatr Allergy Immunol. 2004;15:216–20.
29. Mensinga TT, Schouten JP, Rijcken B, Weiss ST, Speizer FE, van der Lende R. The relationship of eosinophilia and positive skin test reactivity to respiratory symptom prevalence in a community-based population study. J Allergy Clin Immunol. 1990;86:99–107.
30. Drews AC, Pizzichini MM, Pizzichini E, Pereira MU, Pitrez PM, Jones MH, et al. Neutrophilic airway inflammation is a main feature of induced sputum in nonatopic asthmatic children. Allergy. 2009 [Epub ahead of print] PubMed PMID: 19392986.
31. Kelly WJ, Hudson I, Phelan PD, Pain MC, Olinsky A. Atopy in subjects with asthma followed to the age of 28 years. J Allergy Clin Immunol. 1990;85:548–57.
32. Morgan WJ, Stern DA, Sherrill DL, Guerra S, Holberg CJ, Guilbert TW, et al. Outcome of asthma and wheezing in the first 6 years of life: follow-up through adolescence. Am J Respir Crit Care Med. 2005;172:1253–8.
33. Guerra S, Wright AL, Morgan WJ, Sherrill DL, Holberg CJ, Martinez FD. Persistence of asthma symptoms during adolescence: role of obesity and age at the onset of puberty. Am J Respir Crit Care Med. 2004;170:78–85.
34. Halonen M, Stern DA, Lohman C, Wright AL, Brown MA, Martinez FD. Two subphenotypes of childhood asthma that differ in maternal and paternal influences on asthma risk. Am J Respir Crit Care Med. 1999;160:564–70.
35. Just J, Nicoloyanis N, Chauvin M, Pribil C, Grimfeld A, Duru G. Lack of eosinophilia can predict remission in wheezy infants? Clin Exp Allergy. 2008;38:767–73.