Sensitization profile in differential diagnosis: Allergic asthma vs. chronic (nonspecific) cough syndrome

Background:
In the subgroup of children with chronic cough, distinguishing children with allergic asthma from those with non-specific respiratory symptoms is difficult. We have focused on determination of diagnostic efficiency of serum total IgE, sIgE, and skin prick test in differentiation of asthmatic children from children with nonspecific respiratory symptoms.

Material/Methods:
A total of 131 children with median age of 7.5 years were enrolled in study and divided into 2 groups; children with allergic asthma (N=71) and children with chronic cough (N=60). Participants underwent the standard allergological examination, including skin prick test and measurement of total IgE, and following 3 allergen-specific IgE antibodies against aeroallergens: Dermatophagoides pteronyssinus, Ambrosia artemisiifolia, and Phleum pratense.

Results:
The percentage of patients with elevated level of total and sIgE was higher in children with allergic asthma than in children with chronic cough syndrome (P=0.0001). In children with asthma, sIgE had a better diagnostic value than total IgE. The best diagnostic efficiency of cut-off values for sIgE was shown for Der p sIgE. Skin prick test to all allergens had 78.82% sensitivity and 91.3% specificity in differentiating the 2 tested groups. The highest sensitivity and specificity in skin prick test was proved for Dermatophagoides pteronyssinus.

Conclusions:
The sensitization profile consisting of total IgE, sIgE levels, and SPT clearly distinguishes children with allergic asthma from children with chronic nonspecific cough, but still with overlap. Therefore, diagnosis should always be confirmed by a thorough allergy investigation.

Key words: asthma • chronic cough • total IgE level • allergen-specific IgE level • diagnostic efficiency

Full-text PDF: http://www.medscimonit.com/download/index/idArt/883925
Background

Among the many different symptoms encountered in everyday practice, cough is the most common symptom in children visiting the pediatrician. Chronic nonspecific cough is defined as a nonproductive cough in the absence of identifiable respiratory disease or known cause persisting for more than 3 to 8 weeks [1,2].

The usual symptom of asthma is chronic coughing [3]. As is well known, atopy and allergic sensitization play important roles in asthma. Routine diagnostic tests, such as total serum IgE determination, allergen-specific serum IgE determination, and skin prick test, can help significantly in diagnosing allergic asthma and distinguishing it from other respiratory diseases as well as from chronic nonspecific cough syndrome [1].

Although sensitization is a major risk factor for asthma development [4], the role of sensitization remains poorly understood and thus is continuously debated in scientific literature [5–7]. The importance of total serum IgE levels in diagnosis of asthma has been verified throughout a number of studies. Asthmatic children have an elevated level of total serum IgE levels [8–10]. It is also reported that asthma below certain levels of total IgE does not exist [10,11]. In addition, increased levels of total serum IgE at birth and in early life have been associated with an increased risk for the development of persistent asthma later in life [12].

While total serum IgE determination is one of the key methods to reveal atopy, the determination of allergen-specific IgE (sIgE) to environmental allergens has diagnostic and therapeutic importance; reveals the patient’s sensitization to a certain allergen and enables monitoring of the success of specific immunotherapy (SIT) [13]. Among specific allergens, high sensitization rate have been reported for the house dust mites *Der p* (*Dermatophagoides pteronyssinus*) and *Der f* (*Dermatophagoides farinae*) [14–16]. Early sensitization and levels of sIgE to perennial respiratory allergens have likewise been associated with increased risk of childhood asthma [17,18]. Yunginger et al. similarly reported that mite sensitization early in infancy (measured by sIgE levels) accounts for an up to 19.7-fold increased risk for allergic asthma [19,20]. Arshad et al. also found house dust mite sensitization to be the most important risk for allergic asthma [21]. Kovac et al. have shown that asthmatic children with higher asthma severity have a higher serum concentration of both total IgE and specific IgE to *Der p* [15,22].

The atopy can also be defined by positive result to skin prick test (SPT) to a standard panel of allergens [23–25]. Investigating the association of skin test reactivity, total serum IgE levels, and peripheral blood eosinophilia with asthma, Khadadah et al. found SPT to be the most effective measure of atopy [26].

Tschopp et al. proved SPT has the best positive predictive value and best efficiency in diagnosing respiratory atopic diseases [27]. Comparing SPT to total serum IgE levels, Fajraoui et al. found that the 2 tests agree in 80% of cases [28].

Because chronic cough is one of the most common presentations of allergic asthma in children and being sensitized does not automatically include diagnosis of asthma, differentiation between allergic asthma and chronic (nonspecific) cough syndrome remains a relevant clinical problem. Even though allergic diseases and diagnostic methods have been investigated during recent years, conclusive guidelines on how to distinguish allergic asthma from chronic (nonspecific) cough in the population of children have not been available.

The aim of this study was to determine the diagnostic value of sensitization profile (including serum total, sIgE determination, and SPT) in children with persistent respiratory symptoms to differentiate between children with allergic asthma and children with chronic (nonspecific) cough.

Materal and Methods

Study subjects

This study is an analysis of data collected from patients at Children’s Hospital Srebrnjak, Department of Allergology and Pulmonology, Zagreb, Croatia, during a 6-month period. A total of 131 children, aged 1–15 years, were included in the study. There were 89 males (67.94%), and 32 females (32.06%). Informed consent was obtained from parents of all participants. The study was approved by the Ethics Committee of Children’s Hospital Srebrnjak.

All of the patients included in the study experienced respiratory symptoms and were sent to our Department for further diagnosis. Participants underwent the standard allergological examination, including SPT to the standard set of inhalatory allergens common for the region, lung function tests, and *in vitro* diagnostic tests. Participants were tested for total IgE and 3 allergen-specific IgE antibodies against the most prevalent aeroallergens in children in continental region in Croatia: house dust mites (*Dermatophagoides pteronyssinus*), common ragweed (*Ambrosia artemisifolia*), and timothy grass (*Phleum pratense*) pollen.

Study participants were divided into 2 groups:
1. Children with clearly diagnosed allergic asthma, ie, having at least 3 episodes of wheezing and/or a positive bronchodilatation test (NIH GINA 2009); N=71, age 2–15 years, X=8 years, 49 (69.01%) males.
2. Children with chronic cough, ie, having less than 3 episodes of wheezing, with persistent cough lasting for more than 6 weeks; N=60, age 1-14 years, x̄=7 years, 40 (66.67%) males.

Total serum IgE concentration was determined by fluorimunochemical method (Abbot, USA) using an automatic analyzer IMx (Abbot, USA). For data comparison, 95% central range was used and serum IgE concentration was compared to in-house reference values [29].

The sIgE to 3 allergens – Der p (Dermatophagoides pteronyssinus), Phl p (timothy grass pollen), and Amb a (short ragweed) – were determined by ImmunoCAP (Pharmacia, Uppsala, Sweden). Analysis was performed using a UniCAP 100 analyzer (Pharmacia, Uppsala, Sweden).

The SPT was performed with standardized allergens produced by Allergopharma, comprising the standard set of inhalatory allergens common for Croatia.

Statistical analysis

Data distribution was assessed by the test of proportion difference and Pearson χ² test. P<0.05 was considered statistically significant. Total and specific IgE concentration showed asymmetric distribution and were presented by range and median, and the statistical significance of the difference between the 2 groups was tested using the Wilcoxon test. The diagnostic efficiency of total IgE and sIgE determination – sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) – were estimated for the groups of patients with allergic asthma and chronic cough. Receiver operating characteristic (ROC) curve analysis was performed using STATISTICA for Windows, version 6.0 (StatSoft, Inc., Tulsa, OK, USA).

Results

The 2 tested groups differed in median total IgE. Median total IgE in the group of children with allergic asthma was significantly higher than in the group of children with chronic cough (495.0 kIU/L in the allergic asthma group; 59.0 kIU/L in the chronic cough group, P<0.05; Table 1)

The percentage of patients with elevated concentration of total and specific IgE was higher in children with allergic asthma than in children with chronic cough (P<0.0001; Table 2).

Comparing the number of patients with elevated total and sIgE level between the 2 groups, we found an elevated total IgE level in 97.2% of children with allergic asthma, whereas elevated IgE level was found in 31.7% children with chronic cough. Level of sIgE was elevated in 100% of children with allergic asthma and in 21.7% children with nonspecific cough (χ²=116.258; df=2; P=0.0000, ** χ²=129.741; df=2; P=0.0000).

Comparing levels of sIgE in sensitized children, we discovered that children sensitized to Der p had a higher concentration of sIgE than children sensitized to Phl p and Amb a (P<0.05) (Table 3).

We established that at a cut-off value of 116.6 kIU/L of total IgE had 96.8% sensitivity and 77.8% specificity in differentiating allergic asthma and chronic cough. When comparing sIgE to Der p in the group of children with allergic asthma and those in group with chronic cough, we found 89% sensitivity and 97% specificity.

Table 1. Concentration of total IgE in children with allergic asthma, children with chronic cough, and healthy children.

| Total IgE (kIU/L) | Allergic asthma (N=71) | Chronic cough (N=60) |
|------------------|------------------------|---------------------|
| Range            | 43.0–2453.8            | 5.0–1000.0          |
| Median           | 495.0                  | 59.0                |

Allergic asthma: chronic cough, P<0.05.

Table 2. Elevated serum concentration of total IgE and sIgE in children with allergic asthma and children with chronic cough.

| Total IgE | Specific IgE |
|-----------|--------------|
| Patients  | Total IgE1 * | sIgE2 **     |
| Allergic asthma (N=71) | 69 (97.2%) | 71 (100%) |
| Chronic cough (N=60) | 19 (31.7%) | 13 (21.7%) |

* χ²=116.258; df=2; P=0.0000. ** χ²=129.741; df=2; P=0.0000.

Table 3. sIgE concentrations in children with allergic asthma and children with chronic cough.

| Specific IgE (kIU/L) | Der p | Amb a | Phl p |
|----------------------|-------|-------|-------|
| Range                | 0.44–0.93 | 1.1–471.0 | 0.35–96.1 |
| AM ±SD               | 206.6±214.3 | 97.7±168.1 | 18.9±28.5 |
| Median               | 94.4 | 21.1 | 6.4 |

AM – arithmetic mean; SD – standard deviation; Der p: Amb a P<0.05; Der p: Phl p P<0.05.
The best diagnostic value of cut-off values for sIgE was found for Der p between children with allergic asthma and children with chronic cough (Table 4).

**Table 4.** ROC curve analysis for the concentration of total and different serum sIgE in children with allergic asthma and children with chronic cough.

|                     | Specific IgE | Total IgE |
|---------------------|--------------|-----------|
|                     | Der p        | Amb a     | Phi p     | Der p        | Amb a     | Phi p     |
| Allergic asthma/chronic cough (N=71/60) | AUC 0.933 | 0.679 | 0.739 | 0.927 |
|                      | Cut-off 0.35 kIU/L | 0.39 kIU/L | 0.35 kIU/L | 116.6 kIU/L |
|                      | Sensitivity 89.0% | 56.0% | 60.5% | 96.8% |
|                      | Specificity 97.0% | 80.5% | 81.3% | 77.8% |
|                      | PPV 84.5% | 100.0% |
|                      | NPV 100.0% | 95.4% |

AUC – Area under the ROC curve; Sensitivity – probability that specific IgE will be positive when allergic asthma is present (true positive rate); Specificity – probability that specific IgE will be negative when allergic asthma is not present (true negative rate). PPV – positive predictive value, probability that disease is present when total/specific IgE is positive; NPV – negative predictive value, probability that disease is not present when total/specific IgE is negative.

Another important diagnostic procedure in estimating sensitization of children is the measure of IgE to specific allergens in blood. Results of our study show that children sensitized to the perennial allergen Der p showed a higher concentration of sIgE than in children sensitized to Amb a and Phi p, which are present only during the blooming season. It is believed that because house dust mites are the most widespread perennial inhalatory allergens, a greater exposure to Der p in comparison with other allergens results in higher sIgE concentration [40].

The concentration of sIgE is not a static variable. Variations between normal and elevated IgE in the same individual may occur, depending on the age, the exposure to the specific allergen, and disease development [13]. Diagnostic efficiency of sIgE to pollen allergens could therefore be influenced by the period during which blood was sampled (during or before vs. after the blooming season). It was also confirmed that exposure and sensitization to certain allergens strongly depend on the region and climate [21]. The allergens tested in this study are the most common inhalatory allergens in Croatia [41].

Sensitization to aeroallergens in correlation to asthma development is currently a world-wide scientific focus. Sensitization is most commonly defined by a positive skin prick test result, along with sIgE in serum. Being sensitized does not imply the diagnosis of allergic asthma or any other atopic disease [42,43]. In 2001, Crimi et al. showed that in a population of children proven to be sensitized, a third of them were without any allergic symptoms.

It is also important to emphasize the correlation between sensitization, especially to the most common aeroallergens, and asthma...
in children [44]. In 2010 Craig used SPT to define sensitization and concluded that about 95% of patients with mild asthma were sensitized, as well as the 90% of those with severe asthma [45]. Craig et al. showed that 81% of children with asthma were polysensitized to at least 3 aeroallergens [46].

One of the most frequent sensitizations in children with asthma is to the house dust mite. As in Croatia, in many other countries around the world this sensitization is the most common among asthmatic children [47–49]. In Florida, 89.6% of asthmatic children had positive sIgE to house dust mites, along with 81.9% of Chinese asthmatic children and children in Zimbabwe [50–52].

Many studies have observed that deteriorating asthma can be related to increased exposure to allergens, particularly allergens from house dust mites, cockroaches, cats, rodents, mold, or pollen [53,54].

Sensitization profile also correlates with asthma severity and chance of asthma remission during childhood. ISAAC, the international study of childhood asthma and allergies, showed that remission of asthma is 10% yearly and was inversely correlated to sensitization. Carroll et al. confirmed that increasing atopic sensitization (estimated by SPT and total IgE level) is associated with increased disease severity in children with asthma [23]. Furthermore, elevated level total serum IgE has also been linked to risk of hospital admission [24,55,56]. In contrast, Jedrychowski et al. related reversibility of asthma with lung function growth [57].

Table 5. ROC curve analysis for a positive SPT for *Dermatophagoides pteronyssinus*, *Ambrosia artemisifolia*, and *Phleum pratense* in children with allergic asthma and children with chronic cough.

| Parameter                  | Der p | Amb a | Phl p |
|----------------------------|-------|-------|-------|
| Sensitivity Estimate       | 83.61%| 66.67%| 66.67%|
| 95% CIs                    | 72.39, 90.84 | 46.71, 82.03 | 48.78, 80.77 |
| Specificity Estimate       | 71.43%| 48.6% | 49.5% |
| 95% CIs                    | 59.95, 80.68 | 39.34, 57.95 | 39.95, 59.09 |
| Positive Predictive Value  | 71.83%| 22.54%| 28.17%|
| 95% CIs                    | 60.46, 80.96 | 14.37, 33.52 | 19.04, 39.54 |
| Negative Predictive Value  | 83.33%| 86.67%| 83.33%|
| 95% CIs                    | 71.97, 90.69 | 75.83, 93.09 | 71.97, 90.69 |
| Diagnostic Accuracy        | 77.1% | 51.91%| 53.44%|
| 95% CIs                    | 69.19, 83.46 | 43.42, 60.29 | 44.92, 61.76 |
| Likelihood ratio of a Positive Test | 2.926 | 1.297 | 1.32 |
| 95% CIs                    | 2.633–3.252 | 1.177–1.429 | 1.21–1.441 |
| Likelihood ratio of a Negative Test | 0.2295 | 0.6859 | 0.6733 |
| 95% CIs                    | 0.1857–0.2836 | 0.5159–0.912 | 0.5318–0.8525 |
| Diagnostic Odds            | 12.75 | 1.891 | 1.961 |
| 95% CIs                    | 5.431–29.93 | 0.7464–4.79 | 0.8352–4.603 |
| Cohen’s kappa (Unweighted) | 0.5446 | 0.08675 | 0.1092 |

Table 6. ROC curve analysis for a positive SPT to 1 or more of all tested allergens in children with allergic asthma and children with chronic cough.

| Parameter                  | Overall data for SPT |
|----------------------------|----------------------|
| Sensitivity Estimate       | 78.82%               |
| Lower–Upper 95% CIs        | 68.99, 86.16         |
| Specificity Estimate       | 91.3%                |
| Lower–Upper 95% CIs        | 79.68, 96.57         |
| Positive Predictive Value  | 94.37%               |
| Lower–Upper 95% CIs        | 86.39, 97.79         |
| Negative Predictive Value  | 70%                  |
| Lower–Upper 95% CIs        | 57.49, 80.1          |
| Diagnostic Accuracy        | 83.21%               |
| Lower–Upper 95% CIs        | 75.88, 88.64         |
| Likelihood ratio of a Positive Test | 9.065 | 5.51–14.91 |
| Likelihood ratio of a Negative Test | 0.2319 | 0.2071–0.2598 |
| Diagnostic Odds            | 39.08                |
| Lower–Upper 95% CIs        | 12.37–123.4          |
| Cohen’s kappa (Unweighted) | 0.6555               |
| Lower–Upper 95% CIs        | 0.4884–0.8226        |

There are a number of factors that can influence sensitization, such as location of residence, sex, and ethnicity. With lower prevalence of sensitization, female sex and residence in a rural environment were proven to be connected [58–60].

A great number of studies have investigated risk factors for allergen sensitization and asthma development. Sporic et al. described a significant relationship between early life exposure...
to dust mite allergen and asthma at the age of 11 years [61]. Nevertheless, most other studies could not reproduce these results. Studies that are still ongoing, such as the Prevention and Incidence of Asthma and Mite Allergy study (PIAMA), the Manchester Asthma and Allergy Study (MAAS), and the Childhood Asthma Prevention study, are expected to reveal new information about asthma prevention through prevention of sensitization to specific aeroallergens.

In conclusion, it is important to emphasize that for a confirmed diagnosis of allergic asthma, determination of serum IgE should always be supplemented with a thorough allergy investigation, including a detailed medical history (especially concerning allergen exposure), the presence of other possible immediate hypersensitivity diseases, skin tests, challenges, examinations for eosinophilia in blood and mucous membrane secretions, and in some cases with excluding the GER as a possible risk for asthma development [62].

The results of our study show that determination of total IgE and sIgE is a good method for differentiating asthmatic children from those with nonspecific chronic cough. sIgE determination in children with clinical asthma symptoms had a better diagnostic value than total IgE determination. The best diagnostic value of cut-off values for sIgE was shown for Der p I.

Conclusions

Although the differentiation between children with non-specific respiratory problems and children with asthma can be difficult, sensitization profile (total and specific IgE levels and SPT) facilitates achieving diagnosis. After analyzing 131 patient aged 1–15 years, we conclude that total IgE, and particularly sIgE, clearly distinguish children with allergic asthma from children with nonspecific chronic cough. The final diagnosis should, however, always be confirmed by a thorough allergy investigation.

Considering the results of our study, as well as the results of other studies of sensitization profile and its correlation to asthma, we conclude that standardized procedures such as SPT, total IgE level, and sIgE should be performed in patients presenting with chronic cough, while it significantly correlates with asthma and can lead the physician to the final diagnosis of asthma vs. nonspecific cough.

References:

1. Chang AB, Asher MI: A review of cough in children. J Asthma, 2001; 38: 299–309
2. Chang AB, Lasserson TJ, Gaffney J et al: Gastro-esophageal reflux treatment for prolonged non-specific cough in children and adults. Cochrane Database Syst Rev, 2011; CD004823
3. Sylvester DC, Karos SD, Vaughan C et al: Chronic cough, reflux, postnasal drip syndrome, and the otorlaryngologist. Int J Otorhinolaryngol, 2012; 564852
4. Simpson BM, Custovic A, Simpson A et al: NAC Manchester Asthma and Allergy Study (NACMAAS): risk factors for asthma and allergic disorders in adults. Clin Exp Allergy, 2001; 31: 391–99
5. Custovic A, Simpson A: Environmental allergen exposure, sensitisation and asthma: from whole populations to individuals at risk. Thorax, 2004; 59: 825–27
6. Pearce N, Pekkanen J, Beasley R: How much asthma is really attributable to atopy? Thorax, 1999; 54: 268–72
7. Pearce N, Douwes J, Beasley R: Is allergen exposure the major primary cause of asthma? Thorax, 2000; 55: 424–31
8. Sinclair D, Peters SA: The predictive value of total serum IgE for a positive allergen specific IgE result. J Clin Pathol, 2004; 57: 956–59
9. Haven J, Amie PA, Hvatum M et al: IgE concentrations in allergic asthma in children. Arch Dis Child, 1973; 48: 850–55
10. Burrows B, Martinez FD, Halonen M et al: Association of asthma with serum IgE levels and skin-test reactivity to allergens. N Engl J Med, 1989; 320: 271–77
11. Sears MR, Burrows B, Flannery EM et al: Relation between airway responsiveness and serum IgE in children with asthma and in apparently normal children. N Engl J Med, 1991; 325: 1067–71
12. Martinez FD, Wright AL, Taussig LM et al: Asthma and wheezing in the first six years of life. The Group Health Medical Associates. N Engl J Med, 1995; 332: 133–38
13. Ahlstedt S: Understanding the usefulness of specific IgE blood tests in allergy. Clin Exp Allergy, 2002; 32: 11–16
14. Chou TY, Wu KY, Shieh CC, Wang YJ: The clinical efficacy of in vitro allergen-specific IgE antibody test in the diagnosis of allergic children with asthma. Acta Paediatr Taiwan, 2002; 43: 35–39
15. Kovac K, Dodig S, Tjesic-Drinkovic D, Raos M: Correlation between asthma severity and serum IgE in asthmatic children sensitized to Dermatophagoides pteronyssinus. Arch Med Res, 2007; 38: 99–105
16. Munivarna H, Vorko-Jovic A, Munivarna S et al: The prevalence of allergic diseases among Croatian school children according to the ISAAC Phase One questionnaire. Med Sci Monit, 2007; 13: CR505–2
17. Simpson A, Soderstrom L, Ahlstedt S et al: IgE antibody quantification and the probability of wheeze in preschool children. J Allergy Clin Immunol, 2005; 116: 744–49
18. Illi S, von Mutius E, Lau S et al: Perennial allergen sensitisation early in life and chronic asthma in children: a birth cohort study. Lancet, 2006; 368: 763–70
19. Yunginger JW, Ahlstedt S, Eggleston PA et al: Quantitative IgE antibody assays in allergic diseases. J Allergy Clin Immunol, 2000; 105: 1077–84
20. Gudej I, Mirkic Kobal I et al: Intraracial differences in asthma prevalence and risk factors for asthma among adolescents in Split-Dalmatia County, Croatia. Med Sci Monit, 2012; 18(A): PH43–50
21. Arshad SH, Tariq SM, Matthews S, Hakim E: Sensitization to common allergens and its association with allergic disorders at age 4 years: a whole population birth cohort study. Pediatrics, 2001; 108: E33
22. Nogalo B, Mirkic M, Maloca I et al: Normal variation of bronchial reactivity in nonasthmatics is associated with the level of mite-specific IgE. J Asthma, 2008; 45: 273–77
23. Carroll WD, Lenney W, Child F et al: Asthma severity and atopy: how clear is the relationship? Arch Dis Child, 2006; 91: 405–9
24. Siuroux V, Orszuczyk MP, Paty E et al: Relationships of allergic sensitization, total immunoglobulin E and blood eosinophils to asthma severity in children of the EGEA Study. Clin Exp Allergy, 2003; 33: 746–51
25. Sears MR, Herbison GP, Holdaway MD et al: The relative risks of sensitivity to grass pollen, house dust mite and cat dander in the development of childhood asthma. Clin Exp Allergy, 1989; 19: 419–24
26. Khadadah M, Onadoko BO, Ezeamuzie CI et al: The association of skin test reactivity, total serum IgE levels, and peripheral blood eosinophilia with asthma in Kuwait. J Asthma, 2000; 37: 481–88

27. Tschopp JM, Sistek D, Schindler C et al: Current allergic asthma and rhinitis: diagnostic efficiency of three commonly used atopic markers (IgE, skin prick tests, and Phadiatop). Results from 8329 randomized adults from the SAPALDIA Study. Swiss Study on Air Pollution and Lung Diseases in Adults. Allergy, 1998; 53: 608–13

28. Fajraoui N, Charfi MR, Khouani H et al: [Contribution of serum total immunoglobulin E measurement in the diagnosis of respiratory allergic diseases]. Tunis Med, 2008; 86: 32–37

29. Dodig S, Richter D, Benko B et al: Cut-off values for total serum immunoglobulin E between non-atopic and atopic children in north-west Croatia. Clin Chem Lab Med, 2006; 44: 639–47

30. Eysink PE, ter Riet G, Balberse RC et al: Accuracy of specific IgE in the prediction of asthma: development of a scoring formula for general practice. Br J Gen Pract, 2005; 55: 125–31

31. Kotaniemi-Syrjanen A, Reijonen TM, Romppanen J et al: Allergen-specific immunoglobulin E antibodies in wheezing infants: the risk for asthma in later childhood. Pediatrics, 2003; 111: e255–61

32. Wever-Hess J, Kouwenberg JM, Duiverman EJ et al: Prognostic characteristics of asthma diagnosis in early childhood in clinical practice. Acta Paediatr, 1999; 88: 827–34

33. Delacourt C, Labbe D, Vassault A et al: Sensitization to inhalant allergens in wheezing infants is predictive of the development of infantile asthma. Allergy, 1994; 49: 843–47

34. Malinowska E, Kaczmarski M: Total IgE levels in children under three years of age. Med Sci Monit, 2002; 8(2): CR113–18

35. Johnson CC, Peterson EL, Oywnb DR: Gender differences in total and allergen-specific immunoglobulin E (IgE) concentrations in a population-based cohort from birth to age four years. Am J Epidemiol, 1998; 147: 1145–52

36. Petridou E, Kanariou M, Liatsis M et al: Factors influencing serum immunoglobulin E levels in Greek children. Allergy, 1995; 50: 210–14

37. Kulig M, Tacke U, Forster J et al: Serum IgE levels during the first 6 years of life. J Pediatr, 1999; 134: 453–58

38. Backer V, Ulrik CS, Wendelboe D et al: Distribution of serum IgE in children and adolescents aged 7 to 16 years in Copenhagen, in relation to factors of importance. Allergy, 1992; 47: 484–89

39. Ma XL, Zhen YF: [Serum levels of 25-(OH)D3 and total IgE in children with asthma]. Zhongguo Dang Dai Er Ke Za Zhi, 2011; 13: 551–53

40. Nahm DH, Park HS, Kang SS, Hong CS: Seasonal variation of skin reactivity and specific IgE antibody to house dust mite. Ann Allergy Asthma Immunol, 1997; 78: 589–93

41. Toth I, Peterem R, Gajnik D, Vojinkovic B: Micro-regional hypersensitivity variations to inhalant allergens in the city of Zagreb and Zagreb County. Coll Antropol, 2011; 35(Suppl 2): 31–37

42. Crem P, Minale P, Tazzer C et al: Asthma and rhinitis in schoolchildren: the impact of allergic sensitization to aeroallergens. J Invest Allergol Clin Immunol, 2001; 11: 103–6

43. Miraglia Del Giudice M, Pedulla M et al: Atopy and house dust mite sensitization as risk factors for asthma in children. Allergy, 2002; 57: 169–72

44. Schmidt WP: Model of the epidemic of childhood atopy. Med Sci Monit, 2004; 10(2): HYS–2

45. Craig T: Aeroallergen sensitization in asthma: prevalence and correlation with severity. Allergy Asthma Proc, 2010; 31: 96–102

46. Craig TJ, King TS, Lemanske RF Jr et al: Aeroallergen sensitization correlates with PC20 and exhaled nitric oxide in subjects with mild-to-moderate asthma. J Allergy Clin Immunol, 2008; 121: 671–77

47. Huss K, Adkinson NF Jr., Eggleston PA et al: House dust mite and cockroach exposure are strong risk factors for positive allergy skin test responses in the Childhood Asthma Management Program. J Allergy Clin Immunol, 2001; 107: 48–54

48. Karabulut AB, Atamam M, Karaman U et al: House dust mites: effect on antioxidant enzyme activities. Med Sci Monit, 2006; 12(9): CR378–81

49. Ercog D, Nenadic N, Plavec D et al: Inhaled corticosteroids used for the control of asthma in a “real-life” setting do not affect linear growth velocity in prepubertal children. Med Sci Monit, 2012; 18(9): CR564–68

50. Kambarani RA, Marecreha F, Sibanda EN, Chitiyo ME: Aero-allergen sensitisation patterns amongst atopic Zimbabwean children. Cent Afr J Med, 1999; 45: 144–47

51. Leung TF, Lam CW, Chan IH et al: Inhalant allergens as risk factors for the development and severity of mild-to-moderate asthma in Hong Kong Chinese children. J Asthma, 2002; 39: 323–30

52. Nelson RP Jr., DiNicolo R, Fernandez-Caldas E et al: Allergen-specific IgE levels and mite allergen exposure in children with acute asthma first seen in an emergency department and in nonasthmatic control subjects. J Allergy Clin Immunol, 1996; 98: 258–63

53. Barnig C, Casset A: [Respiratory allergens and asthma exacerbation]. Rev Mal Respir, 2012; 29: 810–19

54. Custer A, Simpson BM, Simpson A et al: Current mite, cat, and dog allergen exposure, pet ownership, and sensitization to inhalant allergens in adults. J Allergy Clin Immunol, 2003; 111: 402–7

55. Ponsonby AL, Gatenby P, Glasow N et al: Which clinical subgroups within the spectrum of child asthma are attributable to atopy? Chest, 2002; 121: 135–42

56. Wever-Hess J, Kouwenberg JM, Duiverman EJ et al: Risk factors for exacerbations and hospital admissions in asthma of early childhood. Pediatr Pulmonol, 2000; 29: 250–56

57. Jedrychowski W, Maugeri U, Falk E, Bianchi I: Reversibility of asthma-like symptoms and lung function growth over two-year follow-up in preadolescent children. Med Sci Monit, 2001; 7(2): 293–98

58. Majkowska-Wojciechowska B, Pelka J, Korzon L et al: Prevalence of allergy, patterns of allergic sensitization and allergy risk factors in rural and urban children. Allergy, 2007; 62: 1044–50

59. Riedler J, Eder W, Oberfeld G, Schreuer M: Austrian children living on a farm – rural protection or an urban living effect? Pediatr Allergy Immunol, 2007; 18: 209–16

60. Priftis KN, Anthracopoulos MB, Nikolaou-Papagiotou A et al: Increased sensitization in urban vs. rural environment – rural protection or an urban living effect? Pediatr Allergy Immunol, 2007; 18: 209–16

61. Sporik R, Platss-Mills TA, Cogswell JJ: Exposure to house dust mite allergen of children admitted to hospital with asthma. Clin Exp Allergy, 1993; 23: 740–46

62. Wawowska-Krolowska K, Toporowska-Kowalska E, Krogulska A: Asthma and gastroesophageal reflux in children. Med Sci Monit, 2002; B3(1): RA64–71