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INCREASING INCIDENCE OF ALLERGY IN CROATIA

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Summary

Allergology in Croatia is faced with technological and civilization challenges at the time of approaching full membership to European Union. Continuous, 55 year long tradition, of successful, scientific and clinic work, several generations of organ-based specialists in allergy, is the cornerstone for the constructive integration of Croatian allergology in the Europe. The incidence of allergy is increasing, according to the epidemiological data collected from 1978 till 2004 year. Current prevalence of children asthma, allergic rhinoconjunctivitis and eczema symptoms, in the continental region is 6 %, 12.1% and 7.8%, respectively. Children prevalence in the costal region of Croatia is 8.4% , 17.50% and 3.4%, at the same order. The incidence of positive skin test to inhalant allergens in children of the continental region is 52,34%. High percentage of 51.74% subjects has skin sensitivity to three or more allergens, 29.35% to one and 18.90% to two allergens. House dust mite is the most dominant allergen, equally to most of the European countries. Second rates of sensitization were observed for grasses, followed by dog and cat epithelium, Ambrosia and tree pollens. In Croatian adults, results of prevalence of atopy markers (IgE, skin test to aeroallergens and symptoms), collected for the period of 15-years (1985-1999), showed increasing trend in elevated total IgE and atopic symptoms in male, but not in the female population. In Croatian population of adult, allergic patients, pyroglyphid mites could be considered work-related allergens for fishermen. Non-pyroglyphid mites are occupational risk factors in various rural environments of Croatia. The most common and relevant contact allergens in Croatia, are nickel sulfate, cobalt chloride and carba mix, according to the results in 3293 patients from Clinic for Dermatovenerology, Clinical Hospital Centre, Zagreb.

Keywords: Prevalence of allergic diseases; rhinitis; asthma; eczema; atopy markers; *Dermatophagoides pteronyssinus*

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INTRODUCTION

Clinical allergology is discipline, whose importance, in contemporary medicine, in Croatia is rising, along with numerous tasks, resulting from continuous rise in prevalence of various clinical forms of hypersensitivity.

Rational approach to the organization of clinical allergology in Croatia include implementation of standardized diagnostic and therapeutic protocols, either transferred from international initiatives or originally created, together with recognition of advances in basic sciences and its importance for routine clinic work.

Prevention, diagnosis and treatment of allergic diseases in Croatia until nowadays, was in competence of various medical professionals, like specialists in internal medicine, pediatricians, Ear, Nose and Throat (ENT) specialists, pulmologists and dermatologists who collaborated through clinical praxis, scientific meetings and educational activities. Although organ-based specialists will continue to play an important role in the medical care of allergic patients, the Section of Allergology and Clinical Immunology of the Union of European Medical Specialists (UEMS), recommended that, national organizations work toward establishment and maintenance a core service of care, provided by allergists with a training, based on internal medicine and/or pediatrics [1].

According to this recommendations, working group in Croatia is developing specific core curriculum, and educational and training programs for allergy specialists. Logbook for evaluation of competence and progression in the learning process, are required to qualify as an allergy specialist. Specialized centres are required, for many area of expertise, and special training should be undertaken, at institutions where appropriate training is available.

Working group is consisted of representatives of Croatian Society of Allergology and Clinical Immunology, Medical School University of Zagreb, Ministry of Health Republic of Croatia and Croatian Medical Chamber.

Accepting basic recommendations of UEMS, Croatia will ensure and maintain professional competence of allergologists, improve standards of clinical practice, and contribute to making mobility of allergy specialists, between different European countries, a real possibility.

Given the very high prevalence of allergic diseases and the different medical systems throughout the world, the World Allergy Organization, an alliance of 74 national and regional allergy societies, also created consensus document to establish educational guidelines for worldwide application, to identify and correct allergy training deficiencies, and to define appropriate training goals [2].



EPIDEMIOLOGY OF ALLERGIC DISEASES IN CROATIA

Comparing the results of the studies done from 1978 until 2002, in paediatric population, the prevalence of allergic asthma in Croatia is showing continuous rise (Table 1) [3,4,5,6]. Similar trend could be seen in studies of the prevalence of allergic rhinitis and pollinosis (Table 2) [7].

Table 1. Studies on prevalence of allergic asthma in paediatric population of Croatia

Kolbas V. i sur. (Arhiv ZMD 1979;23:351-63)	1978/79.	1,30 %
Restović-Sirotković M. (Paediatr Croat 1993;37:75-81)	1982/83.	2,80 %
Banac S. (Paediatr Croat 1994;38:7-13)	1988/89.	5,90 %
Aberle N. i sur. (Paediatr Croat 1998;42:9-14)	1990.	3,60 %
Stipić-Marković A. i sur. (Acta Med Croatica 2003;57:281-5)	2000/01.	6,02 %
Banac S. i sur. (Croat Med J 2004;45:721-726)	2001/02.	8,40 %

Table 2. Studies on prevalence of allergic rhinitis and pollinosis in paediatric population of Croatia

Author	Rhinitis	Pollinosis
Restović-Sirotković M. (Paediatr Croat 1993;37:75-81)	2,94%	1,37%
Kavurić-Hafner C. i sur. (Pediater Croat 1996;40:29-34)		1,17%
Stipić-Marković A. i sur. (Acta Med Croatica 2003;57:281-5)	12,13%	7,55%
Banac S. i sur. (Croat Med J, 2004;45:721-726)	17,50%	6,70%

Two research centers (Department of Clinical Immunology, Pulmology and Rheumatology, General Hospital "Sveti Duh", Zagreb and Department of Pediatrics, Clinical Hospital Center, Rijeka), where the most recent epidemiological studies were done, used standardized methodology, developed by the International Study of Asthma and Allergies in Childhood (ISAAC) [8,9]. Due to that, Croatian results on 12-month prevalence of asthma, allergic rhinitis and atopic eczema symptoms, are comparable to the



results obtained in 155 centers worldwide [10,11]. The results showed marked difference in the prevalence of these disorders, between continental and coastal regions, being low in continental and moderate in the coastal region.

In 10 year old children, 12-month prevalence, of asthma symptoms was 6.02%, allergic rhinitis symptoms 12.13%, and atopic eczema 7.83% in the "continental study" (Figure 1).

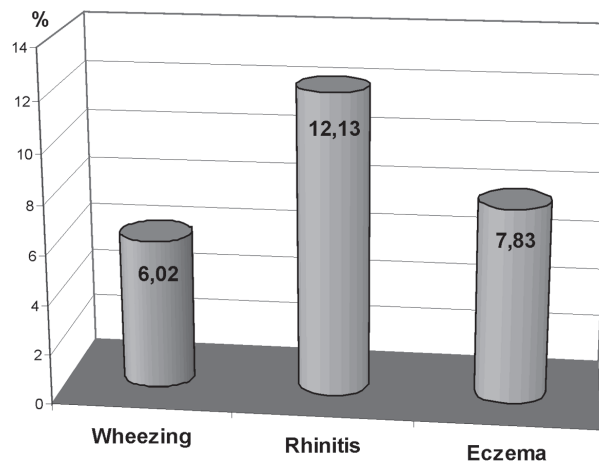


Figure 1. 12-month prevalence rates of symptoms of asthma, rhinoconjunctivitis and eczema, in 10 year old, Zagreb school children (Stipić-Marković A, Pevec B, Radulović-Pevac M, Acta Med Croat, 2004)

Estimated 12-month prevalence rates, of symptoms, in 6-7 year old children, from the coastal region of Croatia were: wheezing 9.7%, allergic rhinitis symptoms 16.9%, allergic rhinoconjunctivitis symptoms 5.6% and atopic dermatitis symptoms 5.4% (Figure 2).

In the 13-14 age group, from the coastal region, 12-month prevalences were: wheezing 8.4%, allergic rhinitis symptoms 17.5%, allergic rhinoconjunctivitis symptoms 6.7%, and atopic dermatitis symptoms 3.4% (Figure 3).

Prevalence rates of allergic symptoms were not similar with positive skin test response rates to inhalant allergens, in children population of the "continental study". The percentage of 52.34% positive skin prick test in 384 children, was much higher results than the prevalence of any of symptoms registered [12]. 29.35% of positive skin reactors were sensitized to only one of ten used allergens, 18.90% to two allergens, and a high percentage of 51.74% children with skin sensitivity were sensitized to three or

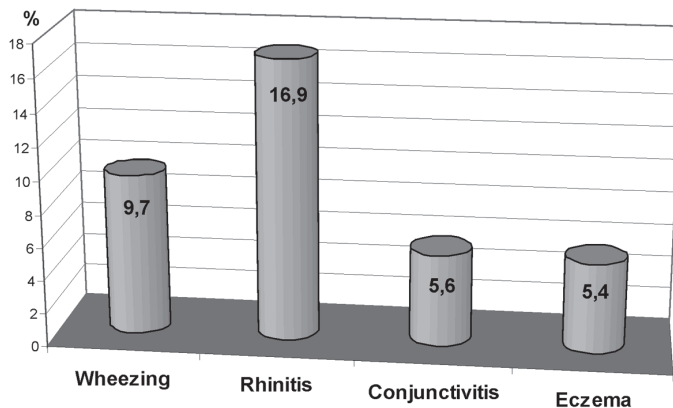


Figure 2. Estimated 12-month prevalence rates, of symptoms, in 6-7 year old children, from the coastal region of Croatia (Banac S, Lah Tomulic K, Ahel V, et al., Croat Med J, 2004)

more allergens. The most common allergen was *Dermatophagoides pteronyssinus* (56.2%), followed by grass pollen (40.3%) and *Dermatophagoides farinae* (39.8%). In addition, a high prevalence of positive SPTs to dog and cat, *Ambrosia trifida*, and tree pollen were found, while cockroach and moulds were causing sensitization in fewer number of subjects (Figure 4). Prevalence rate of sensitization to cockroach is the first report for Croatian children population, what is similar to some Mediteranian countries (13).

Although population in this study was not representative of the general children population it nevertheless, may reflect that prevalence of allergic sensitization to one or

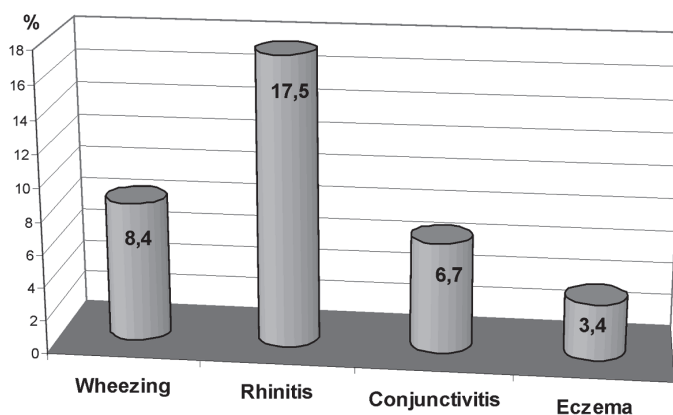


Figure 3. Estimated 12-month prevalence rates, of symptoms, in the 13-14 age group, from the coastal region of Croatia (Banac S, Lah Tomulic K, Ahel V, et al., Croat Med J, 2004)





more inhalant allergens was high. Similar prevalence of sensitization was reported amongst American school children [14].

According to a literature data, some living environmental factors are associated with an increased incidence of allergic diseases. However, the impact of environmental factors and allergic diseases is not so clear. Until recently, genetic and environmental factors have generally been studied independently. To increase the probability of identifying causative factors for complex diseases, it is necessary to study the genes and the environment to determine their interactions.

Regarding relationship between environmental factors and allergic diseases in Croatia, one investigation showed some correlations, similar with the observation of the authors from other countries [15]. Allergic and non-allergic groups of children showed statistically significant differences in attendance of kindergarten, vaccination against pertussis, pertussis infection and parasite infestation. Higher prevalence of allergy positively correlated with attendance of kindergarten without previous attendance of child care facility, correlated with male sex and with previous pertussis infection. Lower prevalence of allergy was found in children with previous parasite infestation and children who received pertussis vaccine. Exposure to tobacco smoke and damp environment with moulds and fungi were identify as risk factor for allergy in Croatia.

Prevalence of adult patients sensitivity to inhalant allergens on the Adriatic coast, was determined by the group of authors from Split [16]. In the group of 3500 patients with symptoms of rhinitis or asthma, prevalence rate was 34,2% for *Dermatophagoides pteronyssinus*, 30,7% for pollens (grass, trees, P.officinals or P.tobira), 8,5 % for animal hair, and 2,5% for molds.

Research by the same group of authors indicated that in coastal region of Croatia, *Ambrosia elatior* is an important cause of seasonal allergic rhinitis and asthma. They suggested that this allergen extract should be included in the routine diagnostic procedures in southern Croatia [17].

Exposure to *Ambrosia elatior* is important cause of allergic symptoms in Osijek-Baranja County too. In the last few years an increase in the number of people hypersensitive to ragweed has been observed. It correlated with the increase of air pollen concentration measured by use of Burkard volumetric apparatus and expressed as counts of pollen grains in mm² of air collected [18].

Authors from Institute for Medical Research and Occupational Health, Zagreb for more than fifteen years are investigating epidemiology of allergic diseases and monitoring exposure to indoor allergens in rural and urban, coastal and continental regions of Croatia.

The most recent epidemiologic study from this group of authors evaluated a 15-year trend in the prevalence of atopy markers (elevated total IgE, positive skin prick test to

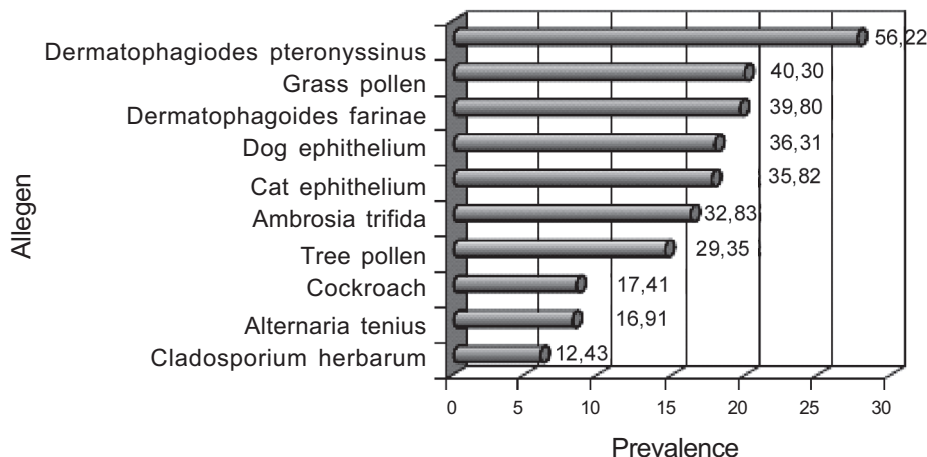


Figure 4. Distribution of different allergens inducing skin reactivity, in 10-year old, Zagreb school children, who were positive in skin prick test (n=201)

common aeroallergens and positive atopic symptoms) in Croatian adults, separately for women and men. The study included 721 subjects (445 men and 276 women), 18-45 years old, examined for allergies within pre-employment preventive examination. Results showed the increasing trend in the prevalence of concurrently elevated total IgE and positive atopic symptoms in Croatian adult male population between 1985 and 1999 (OR 2.44, 95% CI 1.39-4.29, $p=0.002$), but not in the female population. Women showed an increased prevalence of positive SPT only, with borderline significance. In women, rural residence was found as the predictor of elevated total IgE (OR 5.36, 95% CI 2.41-11.93, $p=0.000$) and smoking as the predictor of concurrently elevated total IgE and positive SPT (OR 6.20, 95% CI 1.67-23.07, $p=0.006$). [19].

Difference between the mite fauna in the inland and coastal Croatia was evaluated analyzing floor house dust samples collected from the coastal, inland rural and inland urban area. More than 70% of mites identified in all areas were pyroglyphid. Non-pyroglyphid mites participated with 20-25% of all identified mites in the coastal areas (*Blomia*, *Lepidoglyphus* and *Glycyphagus*) and with 15% in the inland areas (*Lepidoglyphus* and *Acarus*). Significantly the highest Der p 1 median levels were found in the coastal area. The highest Der f 1 median levels were found in the inland urban area, with significantly lower levels in the inland rural and coastal areas. The levels of Der f 1 were significantly higher in samples taken from households with central heating than from those with traditional heating. Compared to traditional heating, central heating significantly increases the risk of exposure to Der f 1 levels >2 mcg/g of dust (odds ratio, 7.35;



95% confidence interval, 1.43- 37.87; $P=0.01$). The results encourage the implementation of separate diagnostic dust mite lists for the coastal and inland areas due to climatic and dwelling differences [20].

Exposure to dust mites was also estimated in various occupational environments in Croatia. In total, 29 occupational dust samples were collected: 10 from urban areas (offices, archive of an insurance company, tobacco, paper-recycling, fish-processing and textile plants, animal unit for experimental rats, winery), 9 from rural areas (barley, hay, animal food and flour warehouses, tailor's shops, wood-processing plant, swine confinement house, grocer's storeroom), and 10 samples from cabins of five fishing boats (five floor and five bed samples). Microscopy showed no mites in urban areas. Pyroglyphid mites (*D.pteronysinus*) were found in all bed samples from fishing boats. Non-pyroglyphid mites were found in samples from barley, hay and animal food warehouses, the swine confinement house, grocer's storeroom, and fishing-boats. Pyroglyphid mite allergens were detected in eight of 10 dust samples from the fishing-boats. Median levels of Der p 1, Der f 1, and Der 2 in cabin bed samples were $10\mu\text{g/g}$, $0.2\mu\text{g/g}$, and $3.5\mu\text{g/g}$, respectively. Findings on fishing boats suggest that pyroglyphid mites could be considered work-related allergens for fishermen. The results of this study confirmed non-pyroglyphid mites as occupational risk factors in various rural environments [21].

The accuracy of common criterion for positive skin prick test (SPT) reaction to dust mites (the mean wheal diameter above or equal than 3 mm) was evaluated with respect to specific IgE values of above 0.35 kUA/L (+sIgE). Specific IgE and standard SPT to *Dermatophagoides pteronyssinus* (DP) and *farinae*, *Lepidoglyphus destructor* (LD) and *Tyrophagus putrescentiae* (TP) were performed in a random sample of 457 subjects, of whom 273 men and 184 women. Where the mean wheal diameter of equal or above 3mm was considered positive (+SPT), the correlation between +SPT and +sIgE was 0.47 for DP ($p<0.001$), 0.43 for DF ($p=0.004$), 0.35 for LD ($p=0.03$) and 0.37 for TP ($p=0.014$). Regarding +sIgE, this SPT criterion has a specificity of 92.2% for DP, 82.3% for DF, 80.8% for LD and 70.1% for TP. When the value 4.5 mm was taken as the threshold for the positive SPT reaction to TP, specificity increased significantly from 70.1% to 86.4%. It was concluded that the 3mm SPT threshold criterion is not reliable in evaluating sensitisation to TP due to an insufficient specificity of the allergen extract to this mite [22].

German cockroach (*Blattella germanica*) allergen levels in house dust and skin reactivity were evaluated in adult atopic and non-atopic subjects from inland areas of Croatia. *Blattella germanica* group 2 allergen was measured in 94 house dust samples collected from living room and bedroom floors. Skin prick testing with common inhalant allergens, *Blattella germanica*, storage mites *Lepidoglyphus destructor* and *Tyrophagus putrescentiae* and total IgE measurement were performed in 187 adult outpatients, 131 from urban and 56 from rural areas. Positive skin prick test to cockroach was observed in 9.6%.



subjects. The frequency of subjects positive to cockroach was higher in atopic than in non-atopic subjects, but not significantly (12.2% vs.4.7%). Positive skin test to storage mites was the only factor which significantly increased the risk of skin positivity to cockroach. *Blattella germanica* allergen was not detectable in house dust samples. These results suggest that there is no relevant exposure to cockroach allergen in house dust samples from inland areas of Croatia. Positive skin prick test to cockroach in atopics is in the majority of cases related to positive skin prick test to storage mites, probably due to cross-reactivity [23].

For evaluation of hypersensitivity to different contact allergens in Croatia, patch test is performing by the standard technique proposed by the International Contact Dermatitis Research Group. The most common and relevant allergens are nickel sulfate, cobalt chloride and carba mix according to the results of the authors from Zagreb Dermatovenerology Clinic. In the group of 3293 patients with allergic contact dermatitis, contact irritant dermatitis, atopic dermatitis, psoriasis vulgaris, seborrhoeic dermatitis and other inflammatory dermatoses results showed statistically significant differences in patch test response according to sex and age for three allergens (cobalt chloride, nickel sulfate and thiomersal decreased with age); according to occupation for nine allergens (cobalt chloride, nickel sulfate, balsam of Peru, fragrance mix, thiuram mix, wood tars, neomycin sulfate, thiomersal and detergents), and clinical diagnosis for two allergens (nickel sulfate, and wood tars). Nickel sulfate, cobalt chloride and carba mix were found in all examinees regardless of age, sex, occupation and diagnoses [24].

CONCLUSION

The data presented in this article reflect current trends in the prevalence of allergic diseases in Croatia in crucial years of negotiations and EU accession. That could serve for the strategy of development of basic and clinical allergology.

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Sažetak

Povećana incidencija alergija u Hrvatskoj

Suvremena alergološka znanost i praksa u Republici Hrvatskoj nalazi se pred izazovima koje donosi civilizacijski i tehnološki razvoj a jedan od vidljivih znakova tih izazova je predstojeći ulazak države Hrvatske u zajednicu Europskih naroda. Zahvaljujući dugom, 55-godišnjem znanstvenom i stručnom radu alergologa iz svih specijalističkih područja medicine, hrvatska alergologija integrirat će se u Europu kao njen ravnopravni dio. Radna grupa za izradu plana i programa specijalizacije iz alergologije i kliničke imunologije izradila je prijedlog koji je u potpunosti usklađen sa preporukama Udruženja medicinskih specijalnosti Europe. Važnost suvremene kliničke alergologije u Hrvatskoj proizlazi iz zadataka koje joj nameće trend porasta prevalencije svih oblika bolesti preosjetljivosti. Prema rezultatima epidemioloških studija učinjenih po međunarodno dogovorenoj metodologiji prevalencija simptoma astme, alergijskog rinitisa i ekcema u populaciji školske djece kontinentalnog dijela zemlje iznosi redom 6%, 12.1% i 7.8%.

Prevalencije u primorskoj Hrvatskoj dio iznose 8,4%, 17,5% i 3,4%, istim redom. Prevalencija pozitivnog kožnog testa u «kontinentalnoj» studiji je 52,3%. Zapažen je visoki postotak kožne reaktivnosti na tri i više alergena (51,74%). Dominantni alergeni su grinje kućne prašine a slijede ih alergeni trava, epitel mačke i psa, korov Ambrozije te poleni stabala.

U populaciji odraslih, rezultati ispitivanja trenda prevalencije markera atopije u 15-godišnjem razdoblju (1985-1999), pokazuju uzlaznu krivulju razine IgE i simptoma alergijskih bolesti, za muškarce ali ne i za žene. Mjerenje koncentracije grinja u uzorcima prašine, dokazane i razlike u vrstama grinja, kontinentalnog i priobalnog područja, što upućuje na potrebu različitog odabira alergena za testiranje u pojedinim regijama.



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A. Stipić-Marković, B. Čvorišćec, B. Pevec, M. Radulović-Pevec: *Increasing incidence of allergy in Croatia*

Specifično za našu alergologiju je, dokaz da se piroglifidne grinje mogu smatrati profesionalnim alergenom u ribara, a nepiroglifidne grinje, profesionalni rizični čimbenik u ruralnim područjima Hrvatske.

Najčešći kontaktni alergeni našeg područja su nikal sulfat, kobalt klorid i mješavina mirisa, prema rezultatima istraživanja provedenih na 3293 pacijenta Klinike za dermatovenerologiju Kliničkog bolničkog centra Zagreb.

Ključne riječi: Prevalencija alergijskih bolesti; rinitis; astma; ekcem; markeri atopije;
Dermatophagoides pteronyssinus