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ANALYSIS OF THE DYNAMICS OF CLINICAL INDICATORS IN PATIENTS WITH ALLERGIC RHINITIS WITH SENSITIZATION TO POLLEN AND HOUSEHOLD ALLERGENS WHEN USING COMBINED ALLERGEN-SPECIFIC IMMUNOTHERAPY

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Abstract. Analysis of the dynamics of clinical indicators in patients with allergic rhinitis with sensitization to pollen and household allergens when using combined allergen-specific immunotherapy. Biletska S.V., Dytyatkovska E.M., Nikolaychuk M.A. The *aim of this study was to evaluate the clinical efficacy of combined allergen-specific immunotherapy (ASIT) in patients with allergic rhinitis (AR) with combined sensitization to pollen and household allergens. To achieve this goal there were examined 49 patients of working age – 35.5±1.5 years with AR with clinical manifestations of seasonal rhinoconjunctival syndrome with a long period of 9.2±1.1 years, among which there were 25 (51.0%) males and 24 (49%) females. All patients were divided into 2 homogeneous groups by age, sex, duration of the disease, the average number of etiologically significant allergens: the main one – 31 patients who received combined ASIT with solutions of pollen and household allergens and a comparison group – 18 patients in whom only pollen allergens were used. Allergological examination included anamnesis, skin tests with pollen (wormwood, ragweed, quinoa, corn, etc.) and household allergens (house dust, mites, epidermal agents) and/or molecular research methods using the ALEX technology. The quantitative integral assessment of the intensity of AR clinical symptoms was calculated as a total score for the main symptoms. The maximum score for the severity of nasal symptoms – 12, eye - 6, total – 18. The results obtained and their analysis indicate that under the influence of ASIT with pollen and household allergens there is a significant and reliable decrease in the intensity of clinical manifestations of seasonal rhinoconjunctive syndrome: nasal manifestations – by 52,2%, conjunctival – by 60%, integral – by 54.3% and a 2.2 times increase in the percentage of patients in the main group with the disappearance or minimization of clinical symptoms of the disease after treatment compared with patients from the comparison group, which convincingly proves and confirms high efficiency of the selected type of therapy in patients with AR in combination with sensitization to pollen and household allergens.*

Реферат. Анализ динамики клинических показателей у больных с аллергическим ринитом с сенсибилизацией к пыльцевым и бытовым аллергенам при применении комбинированной аллерген-специфической иммунотерапии. Белецкая С.В., Дитятковская Е.М., Николайчук М.А. Целью *данного исследования была оценка клинической эффективности комбинированной аллерген-специфической иммунотерапии (АСИТ) у больных с аллергическим ринитом (АР) с сочетанной сенсибилизацией к пыльцевым и бытовым аллергенам. Для достижения поставленной цели было проведено обследование 49 пациентов с АР трудоспособного возраста – 35,5±1,5 года с клиническими проявлениями сезонного риноконъюнктивального*

синдрома с длительным периодом – 9,2±1,1 года, среди которых было 25 (51,0%) лиц мужского и 24 (49%) женского пола. Все пациенты были разделены на 2 однородные группы по возрасту, полу, длительности заболевания, среднему количеству этиологически значимых аллергенов: основную – 31 больной, которые получали комбинированную АСИТ с растворами пыльцевых и бытовых аллергенов, и группу сравнения – 18 больных, для которых применяли только пыльцевые аллергены. Аллергологическое обследование включало сбор анамнеза, кожные пробы с пыльцевыми аллергенами (полынь, амброзия, лебеда, кукуруза и др.) и бытовыми (домашняя пыль, клещи, эпидермальные агенты) и/или молекулярные методы исследований по технологии ALEX. Количественная интегральная оценка интенсивности клинической симптоматики АР вычислялась как суммарный балл по основным симптомам. Максимальный балл выраженности назальных симптомов – 12, глазных – 6, общий – 18. Полученные результаты и их анализ свидетельствуют, что под воздействием АСИТ пыльцевыми и бытовыми аллергенами у больных наблюдается существенное и достоверное снижение интенсивности клинических проявлений сезонного риноконъюнктивного синдрома: назальных проявлений – на 52,2%, конъюнктивальных – на 60%, интегральных – на 54,3% и повышение в 2,2 раза процента пациентов основной группы с исчезновением или минимизацией клинических симптомов заболевания после лечения по сравнению с больными из группы сравнения, что убедительно доказывает и подтверждает высокую эффективность применения выбранного вида терапии у больных с АР в сочетании с сенсибилизацией к пыльцевым и бытовым аллергенам.

Allergic rhinitis (AR), which includes pollen disease in the form of seasonal or intermittent allergic rhinitis, is a major medical and social problem [5, 7, 9,]. AR is defined as a chronic inflammatory disease of the nasal mucosa caused by IgE-mediated early and late phase of the allergic response. According to ARIA (Allergic Rhinitis and its Impact on Asthma), 10% to 40% of the world's population suffers from AR, which impairs the quality of life, education, work performance of patients and is accompanied by significant economic costs [8].

The epidemiological situation with allergic diseases in Ukraine, in particular with allergic rhinitis, fully corresponds to global trends in the prevalence of diseases, but many questions remain about the diagnosis and treatment of these diseases, especially in industrial cities [2, 4].

Not only pollen aeroallergens of plant origin, but also household allergens (house dust mites, pet epidermis, molds) and their combinations play an important role in increasing the sensitization of the population [6]. In patients with combined sensitization by pollen allergens of III dust wave and house dust, the production of interleukins 4 (IL-4) decreases more slowly and the synthesis of IL-12 increases against patients in the absence of an allergic reaction to household allergens [3].

Among the most scientifically justified methods of treating AR, the leading place belongs to allergen-specific immunotherapy (ASIT) with causative allergens, the advantage of which is a direct effect on the pathogenesis of the disease, reducing symptoms, prolonged remission, prevention of severe disease [4, 10, 11]. According to modern notions, ASIT leads to the transition from IgE-immune response to IgG-response, i.e. to the initiation and maintenance of production of IgG-antibodies (blocking) or the formation of T-lymphocyte tolerance. Most researchers associate the effect of ASIT with an increase in the concentration of IgG4, IgG1 and a decrease in IgE synthesis [4]. It is generally accepted that ASIT should be started as early as possible, and in order to achieve the best switching of the immune response from Th-2 type to Th-1 type, it should be performed with all allergens to which hypersensitivity has been detected [3].

In view of the above, the aim of this study was to evaluate the clinical efficacy of combined allergen-specific immunotherapy in patients with allergic rhinitis with combined sensitization to pollen and household allergens.

MATERIALS AND METHODS OF RESEARCH

The study was conducted among 49 patients with AR of working age (mean age 35.5±1.5 years), with clinical manifestations of seasonal rhinoconjunctival syndrome and perennial allergic rhinitis (with less pronounced clinical symptoms) for a long time (on average 9.2±1.1 years). Among them there were 25 (51.0%) males and 24 (49.0%) females. All patients were treated on the basis of the consultative-diagnostic center and allergy department of the Municipal Non-Profit Enterprise "Clinical Ambulance Hospital" of the Dnipro City Council, Dnipro.

The study was conducted in accordance with the principles of bioethics set out in the Helsinki Declaration on Ethical Principles for Human-Based Medical Research and the Universal Declaration on Bioethics and Human Rights (UNESCO).

Allergological examination of patients included history taking, diagnostic skin tests (prick test) with pollen (wormwood, ragweed, quinoa, corn, cyclamen, sunflower, spring and summer grasses) and household allergens (house dust, mites, epidermal agents) produced by Vinnytsia LLC "Immunologist"

(Ukraine) and / or molecular methods of blood testing using ALEX technology. According to the results of tests in all patients (100%) polyvalent sensitization to pollen and household allergens was revealed, among which allergens of the third wave of pollination prevailed: ragweed pollen (93.9%), wormwood (65.3%), sunflower 63.3%), cyclohanes (63.3%). The number of pollen allergens in one patient ranged from 1 to 11 and averaged 4.6±0.4 allergens per patient.

The diagnosis of the examined persons was established on the basis of "Domestic protocols of medical care for patients with allergic diseases", which were approved at the II Congress of Allergists of Ukraine, and then updated at the III Congress of Allergists of Ukraine.

All patients in the phase of stable remission of the disease received 1 course of pre-season ASIT with etiologically significant allergens in accordance with the express scheme with aqueous saline solutions of allergens (in 1 ml of solution – 10000 PNU of allergen), produced by Vinnytsia LLC "Immunologist" (Ukraine). Patients received the ASIT course parenterally (allergen solution was injected subcutaneously into the upper third of the shoulder) at the Regional Allergology Center in Dnipro under the constant supervision of nurses for 30 minutes after injections.

Depending on the used ASIT, all patients were divided into 2 groups: the main group consisted of 31 patients who received a combined ASIT with solutions of pollen and household allergens. The comparison group consisted of 18 patients who received ASIT only with pollen allergens, despite the detected sensitization to household allergens. Among the main reasons for ASIT only with pollen allergens in the second group, absence of significant complaints related to symptoms of persistent (perennial) rhinitis (55.6%), and rejection of ASIT with household allergens for various reasons (38.9%) dominated. Clinical groups were compared by age, sex of patients, disease duration, the average number of etiologically significant pollen allergens ($p>0.05$) (Table 1).

Table 1

General characteristics of groups of patients under study

Groups under study	Age, years	Sex, abs.	Disease duration, years	Average number of allergens
	M±m	male/female	M±m	M±m
Total (n=49)	35.5±1.5	25/24	9.2±1.1	4.6±0.4
Main (n=31)	35.3±2.0	17/14	10.3±1.5	4.9±0.5
Comparison (n=18)	36.0±2.3	8/10	7.2±1.1	3.9±0.5
Difference between groups, p (criterion)	0.813 (t)	0.483 (χ^2)	0.107 (t)	0.169 (t)

Evaluation of ASIT effectiveness in relation to the main clinical manifestations of AR (nasal and conjunctival) was performed in accordance with the recommendations of the European Association of Allergists and Clinical Immunologists (EAACI) during the pollination season of causative allergens before ASIT and one year after one course [12]. The severity of the main nasal symptoms of seasonal AR (sneezing, itchy nose, nasal congestion, rhinorrhea) was determined by a 4-points' scale TNSS (Total nasal symptom score): 0 points – no symptom (no manifestations), 1 – mild symptom (mild manifestations that are easily tolerated), 2 – moderate (manifestations of moderate severity that do not interfere with daily activities), 3 – severe (manifestations that are difficult to tolerate, significantly impair quality of life and/or sleep). The severity of ocular symptoms of TOSS (Total ocule symptom score) (itching / redness of the conjunctiva and sclera, lacrimation) was also assessed by a 4-points' scale. Integral estimates of the intensity of clinical symptoms of AR were calculated as the total score for the main symptoms. The maximum score of nasal symptoms – 12, ocular – 6, total – 18.

For statistical analysis of the results of the study the licensed program STATISTICA v.6.1 (Statsoft Inc., USA), serial number AGAR909E415822FA) was used. Taking into account the deviations of the distribution of quantitative indicators from the normal law according to the Shapiro-Wilk test, only in some groups or at certain stages of the study, both parametric and nonparametric methods were used: arithmetic mean (M), its standard error (m) and 95% confidence interval (95% CI), Student's criteria for

unrelated samples (t), Mann-Whitney (U) and Wilcoxon (W) [1]. Pearson's Chi-square test ($\chi 2$) was used to compare relative values. Correlation relationships were studied by Spearman's rank correlation coefficient (r) [1]. The results of statistical analysis were considered statistically significant at $p \leq 0.05$, and a trend was determined at $p \leq 0.10$.

RESULTS AND DISCUSSION

Analysis of the clinical picture of AR in the season of pollination of causative allergens before the start of ASIT showed the presence of nasal symptoms in all patients (100%), with the most pronounced manifestations (3 points by the TOSS scale) sneezing (24 – 49.0%), rhinorrhea (15 – 30.6%), nasal itching (12 – 24.5%), nasal breathing difficulties (7 – 14.3% of patients). The appearance of conjunctivitis symptoms was also noted by almost all examined patients (47 – 95.9%), including moderate and severe manifestations (2-3 points by the TOSS scale) of itching, burning in the eyes, conjunctival hyperemia. and sclera were observed in 40 (81.6%) patients, lacrimation – in 23 (46.9%). The total score of nasal symptoms ranged from 6 to 12 points (average – 9.00±0.20 points), ocular – from 0 to 6 points (average – 3.41±0.18 points).

Comparing the severity of the main clinical symptoms of seasonal AR in selected groups, it should be noted statistical comparability of indicators at the onset of the study ($p>0.05$ in all comparisons), but with a tendency to more pronounced symptoms of sneezing, nasal congestion and itching / redness in the main group relative to the comparison group – 2.58±0.09 against 2.33±0.11 points ($p=0.098$), 2.13±0.09 against 1.89±0.11 points ($p=0.098$) and 2.13±0.10 against 1.72±0.21 points ($p=0.1$), respectively (Table 2).

Table 2

Degree of manifestation of the main clinical symptoms of AR in patients under study before ACIT, points (M±m)

Symptoms	Groups under study		Difference between groups (p)
	main (n=31)	comparison (n=18)	
Nasal:	**9.23±0.24**	**8.61±0.36**	**0.183**
- sneezing	**2.58±0.09**	**2.33±0.11**	**0.098**
- nasal itching	**2.26±0.08**	**2.06±0.15**	**0.253**
- nasal congestion	**2.13±0.09**	**1.89±0.11**	**0.098**
- rhinorrhea	**2.26±0.09**	**2.33±0.11**	**0.647**
Conjunctival:	**3.48±0.18**	**3.28±0.39**	**0.974**
- itching / redness of the eyes	**2.13±0.10**	**1.72±0.21**	**0.100**
- lacrimation	**1.35±0.10**	**1.56±0.18**	**0.221**
Total score	**12.71±0.31**	**11.89±0.66**	**0.299**

Note. p - the level of significance of differences between groups (Mann-Whitney U-test).

When evaluating the effectiveness of one course of combined ASIT relative to the symptoms of seasonal AR in patients with sensitization to pollen and household allergens, there was found a significant decrease ($p<0.001$) in the intensity of their manifestations (Table 3) including nasal symptoms – by 52.2% (from 9.23±0.24 points to 4.39±0.14 points), conjunctival – by 60.0% (from 3.48±0.18 points to 1.42±0.12 points), the overall assessment of the severity of symptoms – by 54.3% (from 12.71±0.31 points to 5.81±0.18 points). The percentage of patients with a significant positive effect of ASIT (disappearance or minimal manifestations of symptoms – 0-1 point) increased to 80.6% for

sneezing attacks, to 93.5% – for nasal itching and difficulty breathing, to 83,9% – for mucous secretions from the nasal cavity. The number of complaints of lacrimation decreased by 1.9 times – from 96.8% to 51.6% of cases, and in other patients (48.4%) such manifestations were mild (1 point by the TOSS scale).

Table 3

Dynamics of degree of manifestation of the main clinical symptoms of AR in patients under study against ASIT, points (M±m)

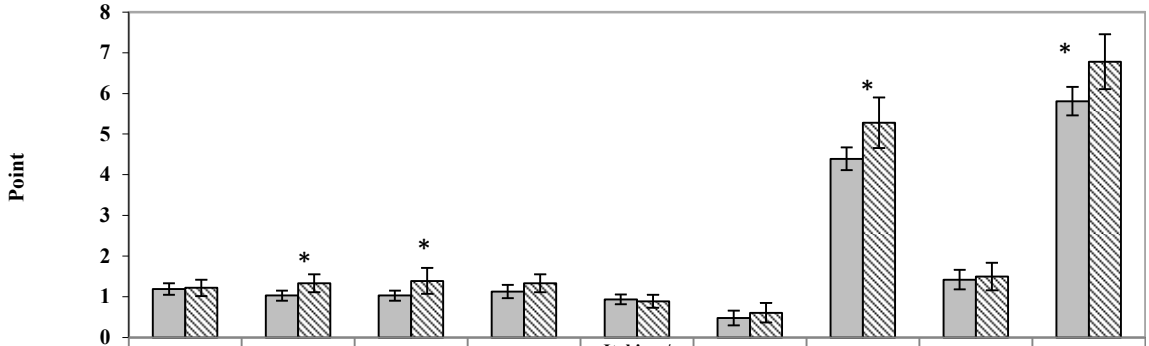
Symptoms	Main group			Comparison group		
	before / after ASIT	Δ, %	Δ1, %	before / after ASIT	Δ, %	Δ1, %
Nasal:	**9.23±0.24 / 4.39±0.14 ***	**-52.2**	**64.5**	**8.61±0.36 / 5.28±0.31 ***	**-38.4**	**27.8**
- sneezing	**2.58±0.09 / 1.19±0.07 ***	**-53.8**	**80.6**	**2.33±0.11 / 1.22±0.10 ***	**-47.8**	**77.8**
- nasal itching	**2.26±0.08 / 1.03±0.06 ***	**-56.5**	**93.5**	**2.06±0.15 / 1.33±0.11 #**	**-38.1**	**66.7**
- nasal congestion	**2.13±0.09 / 1.03±0.06 ***	**-52.4**	**93.5**	**1.89±0.11 / 1.39±0.16 #**	**-26.3**	**50.0**
- rhinorrhea	**2.26±0.09 / 1.13±0.08 ***	**-52.2**	**83.9**	**2.33±0.11 / 1.33±0.11 ***	**-43.5**	**66.7**
Conjunctival:	**3.48±0.18 / 1.42±0.12 ***	**-60.0**	**96.8**	**3.28±0.39 / 1.50±0.17 ***	**-54.5**	**100**
- itching / redness of the eyes	**2.13±0.10 / 0.94±0.06 ***	**-57.1**	**96.8**	**1.72±0.21 / 0.89±0.08 #**	**-47.1**	**100**
- lacrimation	**1.35±0.10 / 0.48±0.09 ***	**-64.3**	**100%**	**1.56±0.18 / 0.61±0.12 ***	**-62.5**	**100**
Total score	**12.71±0.31 / 5.81±0.18 ***	**-54.3**	**61.3**	**11.89±0.66 / 6.78±0.34 ***	**-42.9**	**27.8**

Notes: the numerator shows the data before the start of ASIT / in the denominator – one year after the end of the 1st course of ASIT; * – p<0.001; # – p<0,01 – significance of differences between indicators before and after ASIT in the corresponding group (Wilcoxon W-test); Δ – changes in the average dynamics in percentage; Δ1 – the percentage of patients with disappearance or minimal symptoms (0-1 point) after ASIT.

In the group of patients with AR after preseasonal ASIT only with pollen allergens, a positive dynamics of the main clinical symptoms of the disease (from p<0.01 to p<0.001) (Table 3) was also showed. First, there was noted an increase in the percentage of patients in whom manifestations of such rhinal symptoms as sneezing (from 0% to 77.8%), nasal itching (from 16.7% to 66.7%), rhinorrhea (from 0% to 66.7%) and nasal congestion (from 16.7% to 50.0%) disappeared or decreased to mild ones. Symptoms of itching and redness of the eyes remained in 88.9% of patients, and lacrimation – in 61.1%, but they were mild.

At the same time, treatment of patients with AR with combined sensitization to pollen and household allergens according to the combined scheme of ASIT, against the background of even more intense individual clinical manifestations of the disease before therapy (sneezing, nasal congestion, itching/ redness of the conjunctiva and sclera; p<0.10), led to a more significant decrease in the score of nasal symptoms (by 52.2% vs. 38.4%; p<0.05), including the feeling of itching in the nasal cavity (by 56.5% vs. 38.1%; p<0.05) and difficulty in nasal breathing due to edema and nasal congestion (52.4% vs. 26.3%; p<0.05) than in the comparison group. The total score of the intensity of clinical manifestations of seasonal AR in the main group decreased from 12.71±0.31 to 5.81±0.18 points, i.e. by 54.3%, while in the comparison group the indicator decreased from 11.89±0.66 to 6.78±0.34 points or 42.9% (p<0.05 between groups) (Fig.).

Thus, the obtained results indicate that the combined ASIT with pollen and household allergens in patients with AR with combined sensitization to such allergens contributes to a more significant reduction in the intensity of clinical manifestations of seasonal rhinoconjunctival syndrome. The percentage of patients with a significant positive effect of ASIT (disappearance or minimal symptoms – 0-1 points) in the main group was by 2.2 times higher than in the comparison group – 61.3% vs. 27.8% (p=0.024 by $\chi 2$ criterion).



	Sneezing	Nasal itching	Nasal congestion	Rhinorrhea	Itching / redness of the eyes	Lacrimation	Nasal	Conjuctival	Total score
Main group	1.19	1.03	1.03	1.13	0.94	0.48	4.39	1.42	5.81
Comparison group	1.22	1.33	1.39	1.33	0.89	0.61	5.28	1.50	6.78

Comparison of mean levels (M, 95% CI) of the severity of the main clinical symptoms of AR in patients from the study groups after ASIT: * – p<0.05 between groups (Mann-Whitney U-test)

According to the correlation analysis, it was found that the severity of such key clinical symptoms of seasonal AR as attacks of sneezing and itching in the nasal cavity in thematic patients before ASIT directly correlated with elevated IgE levels (r=+0.412; p=0.003 and r=+0.473; p=0.001) and vice versa – with the level of IgG (r= -0.337; p=0.029 and r= -0.304; p=0.048). After ASIT, the direct correlations between elevated IgE levels and the intensity of clinical symptoms of AR were preserved: the correlation coefficient with the total score of 6 studied symptoms was r=+0.290; p=0.050, with estimated indicators of sneezing attacks – r=+0.505; p<0.001, itching and irritation in the nose – r=+0.452; p=0.001.

CONCLUSIONS

1. It is established that under the influence of preseasonal allergen-specific combined immunotherapy with pollen and household allergens there is a significant decrease (p<0.001) in the intensity of clinical manifestations of seasonal rhinoconjunctival syndrome: nasal symptoms – by 52.2% , conjunctival – by 60.0%, the general symptom complex – by 54.3%.
2. The use of allergen-specific combination immunotherapy in patients with allergic rhinitis with combined sensitization to pollen and household allergens causes a more significant positive effect, manifested by a 2.2-fold increase in the percentage of patients with disappearance or minimal clinical manifestations of symptoms after ASIT than in the comparison group – 61.3% against 27.8% (p = 0.024 according to the criterion $\chi 2$).
3. The positivity of the results of the clinical study convincingly proves the benefits and effectiveness of allergen-specific combined immunotherapy in the treatment of patients with allergic rhinitis with combined sensitization to pollen and household allergens.

Conflict of interest. The authors declare no conflict of interest.

REFERENCES

1. Antomonov MYu. [Mathematical processing and analysis of biomedical data]. Kyiv: Medinform; 2018. p. 579. Russian.
2. Hohunskaia IV, Naumova OA, Kholodenko TYu. [New directions in the diagnosis and treatment of allergic diseases of the upper respiratory tract]. Ukrainskyi pulmonolohichnyi zhurnal. 2016;2:66-67. Russian.
3. Dytyatkovska EM. [Dynamics of cytokines in patients with hay fever under the influence of ASIT depending on the spectrum of sensitization]. Imunolohiia ta alerholohiia: nauka i praktyka. 2011;3:80-83. Ukrainian.
4. Dytyatkovska EM, Hohunska IV, Dytiatkovskyi VO. [Allergic rhinitis, epidemiology, pathogenesis, diagnosis, treatment]. Kyiv: Vistka; 2014. p. 208. Ukrainian.
5. Pukhlyk BM. [Pollinosis: a monograph]. Vinnytsia; 2017 p. 60. Ukrainian.
6. Pukhlyk BM., Bobelo OL, Dziubenko SP. [House dust mites are the most important allergens in the human environment]. Klinichna imunologhiia. Alerholohiia. Infektolohiia. 2018;108(3):22-26. Russian.
7. Bousquet J, Khaltaev N, Cruz AA, Denburg J, et al. Allergic Rhinitis and its impacts on asthma (ARIA) 2008 update (in collaboration with the World Health Organization,

GA(2)LEN and AllerGen). Allergy. 2008 Apr;63:8-160. doi: https://doi.org/10.1111/j.1398-9995.2007.01620.x

8. Brożek JL, Bousquet J, Agache I, Agarwal A, Bachert C, Bosnic-Anticevich S, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines-2016 revision. J Allergy Clin Immunol. 2017 Oct;140(4):950-58.

9. Dytyatkovska E, Gashynova K, Panov V. Patters of molecular sensitization in adults in Dnipro region (Ukraine). Allergy. 2019;74:831-2.

10. Pfaar O, Bachert C, Bufe A, Buhl R, et al. Guideline on allergen-specific immunotherapy in IgE-mediated allergic diseases. Allergy J Int. 2014;23(8):282-319. doi: https://doi.org/10.1007/s40629-014-0032-2

11. Jutel M, Agache I, Bonini S, Burks AW, Calderon M, Canonica W, et al. International Consensus on Allergen Immunotherapy II: Mechanisms, standardization, and pharmacoeconomics. J Allergy Clin Immunol. 2016 Feb:137(2):358-68.
doi: https://doi.org/10.1016/j.jaci.2015.12.1300

12. Pfaar O, Demoly P, Gerth R, et al. Recommendations for the standardization of clinical outcomes used in allergen immunotherapy trials for allergic rhinoconjunctivitis: an EAACI Position Paper. Allergy. 2014;69(7):854-67. doi: https://doi.org/10.1111/all.12383

СПИСОК ЛІТЕРАТУРИ

1. Антомонов М. Ю. Математическая обработка и анализ медико-биологических данных. Киев: Мединформ, 2018. 579 с.

2. Гогунская И. В., Наумова О. А., Холоденко Т. Ю. Новые направления в диагностике и лечении аллергических заболеваний верхних дыхательных путей. *Український пульмонологічний журнал*. 2016. № 2. С. 66-67.

3. Дитятковська Є. М. Динаміка цитокинів у хворих на поліноз під впливом АСІТ залежно від спектру сенсибілізації. *Імунологія та алергологія: наука і практика*. 2011. № 3. С. 80-83.

4. Дитятковська Є. М. Гогунська І. В., Дитятковський В. О. Алергічний риніт, епідеміологія, патогенез, діагностика, лікування. Київ: Вістка, 2014. 208с.

5. Пухлик Б. М. Поллиноз: монографія. Вінниця, 2017. 60 с.

6. Пухлик Б. М., Бобело О. Л., Дзюбенко С. П. Клещи домашней пыли – найболее важные аллергены из окружения человека. *Клінічна імунологія. Алергологія. Інфектологія.* 2018. Т. 108, № 3. С. 22-26.

7. Allergic Rhinitis and its impacts on asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA(2)LEN and AllerGen) / J. Bousquet et al. *Allergy*. 2008. Apr. (Vol. 63, Suppl 86). P. 8-160. DOI: https://doi.org/10.1111/j.1398-9995.2007.01620.x

8. Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines-2016 revision / J. L. Brożek et al. *J Allergy Clin Immunol*. 2017 Oct. (Vol. 140, No. 4). P. 950-958.

9. Dytyatkovska E., Gashynova K., Panov V. Patters of molecular sensitization in adults in Dnipro region (Ukraine). *Allergy*. 2019. No. 74. P.831-832.

10. Guideline on allergen-specific immunotherapy in IgE-mediated allergic diseases / O. Pfaar et al. *Allergy J Int.* 2014. Vol. 23, No. 8. P. 282-319.
DOI: 10.1007/s40629-014-0032-2.

11. International Consensus on Allergen Immunotherapy II: Mechanisms, standardization, and pharmacoeconomics / M. Jutel et al. *J Allergy Clin Immunol*. 2016. Feb. (Vol. 137, No. 2). P. 358-368.
DOI: https://doi.org/10.1016/j.jaci.2015.12.1300

12. Recommendations for the standardization of clinical outcomes used in allergen immunotherapy trials for allergic rhinoconjunctivitis: an EAACI Position Paper / O. Pfaar et al. *Allergy*. 2014. Vol. 69, No. 7. P. 854-867. DOI: https://doi.org/10.1111/all.12383

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