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Immunologic Parallels: Infectious Burden and Markers of Atopic Response Type

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Abstract
The relationship between serological markers of infections and the atopic status of patients with allergy symptoms (rhinorrhea, nasal congestion, recurrent cough, asthma attacks, recurrent skin rashes combined with skin itching) and an increased total Ig E level was investigated. The determination of an infectious burden included screening for bacterial pathogens, protozoa, and helminths. All patients also had specific—food and inhalation—Ig E testing done. The relationship between the infectious burden and a specific atopic status is ambiguous—different pathogens have different types of effects such as opposite, synergistic, or no effect in mono-exposure. In addition, it has been shown that the pattern of pathogen influence on specific IgE response can vary in different age periods. This is due to both cumulative effects associated with a prolonged antigen burden and "switching" of the immune response that forms a hyperimmune IgE response as a protective phenomenon against helminths.

Keywords Infectious burden · Pathogens · Specific Ig E · Immunology

1 Introduction

Many atopic diseases develop with underlying gastrointestinal pathology and changes in a normal intestinal microbiota composition, often associated with helicobacteriosis, protozoal invasions and helminthiases. The infectious burden is shown to promote an immune response that is opposite to the formation of an atopic phenotype [1–3]. Infectious pathogens are involved in the development of allergic disorders such as atopic dermatitis, bronchial asthma, allergic rhinitis, and chronic recurrent urticaria. A number of studies underlie the opinion that infectious pathogens (some viral and bacterial pathogens, helminths, *Helicobacter pylori*) stimulate the Th1-targeted immune response, preventing the development of immunological reactions towards the Th2 profile responsible for the formation of atopic disorders [4–6]. Within the framework of a "hygenic theory" accepted by leading specialists, an infectious process can determine the polarization of an immune response, with some viruses and atypical causative agents activating lymphocyte Th2-clones that facilitates an atopy clinical manifestation. At the same time, some causative agents such as mycobacteria, hepatitis A virus, measles virus, some specific respiratory infections occurred in the early childhood, polarize an immune response towards the Th1 profile preventing the formation of atopic pathology [4]. That a light microbial burden causes the poliarization of an immune response and an increased production of Th1-polarizing cytokines due to an increased activity of regulatory T cells is an alternative view [7–9]. Thus, further research of complex relationships between allergic disorders and pathogens may contribute to the understanding of the current tendency of atopic diseases epidemics.

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2 The Study Objective

The study objective is to investigate relationships between serological markers of infections and the patient's atopic status.

3 Materials and Methods

The study enrolled patients with symptoms of atopic diseases (rhinorrhea, nasal congestion, recurrent cough, asthma attacks, recurrent skin rashes combined with skin itching) who underwent assessment in a diagnostic polyclinic. The study population involved residents of Kazan, a large industrial city. All the patients had laboratory tests for allergy done, total Ig E and specific Ig E (sIg E) levels were measured and an infectious burden evaluated. sIgE was detected using an immunoassay kit for qualitative determination of allergen-specific Ig E (asIgE) in blood serum "Allergo-ELISA speicific Ig E" (Alkor-Bio, Russia) and the ImmunoCAP technology, "Phadia 100." The results were expressed in classes according to the manufacturers' instructions. Total Ig E was detected using a test-system of Xema-Medica Co. Ltd. (Russia). A test for allergy included the detection of the most common specific IgE - digested in group 1 (cow's milk, egg white, wheat flour, apple, soybean), digested and inhaled in group 2 (home dust mites such as dermatofagoideus pteronissimus and dermatofagoideus farina, mixed grass, birch and wormwood pollen, mixed molds, cow's milk, egg white, wheat flour, apple, soybeans), inhaled in group 3 (dermatofagoideus pteronissimus, dermatofagoideus farina, mixed grass, birch and wormwood pollen, mixed molds. Patients with an elevated blood serum total Ig E level (1.5-fold above the normal) that is > 70 IU/ml for children and > 150 IU/ml for adults were selected for analysis. The results of specific testing for allergy were interpreted as negative when the specific Ig E level in all tests was within the range of 0.5 IU/ml for the "Allergo-ELISA specific Ig E" test system and 0.35 ku/l for the Immunocap, "Phadia 100," and as positive when sIgE for at least one allergen exceeded 0.5 IU/ml and 0.35 ku/l, respectively. Also a positivity index (PI)—the sum of positive sIg E results in classes divided by 100, characterizing the patient's atopic status was calculated for every patient with positive results of the test for allergy in vitro. The patients examined were divided into three age groups such as children under 6 years old (early—preschool age), children up to 17 years old (school age), and adult patients (over 17 years old). All patients underwent a complex screening for the infectious burden. A level of Ig G antibodies to Cag A *H. pylori* antigen ("Helico-Cag A-Ig G"), total and Ig M antibodies to giardia antigens ("Lamblia-total- EIA- Best, "Lamblia Ig M- EIA-Best"), total antibodies to opisthorchis, toxocara, and echinococcus antigens (an enzyme-immunoassay kit for the detection of antibodies to helminths antigens "Helminths- Ig G-Best", Novosibirsk, Russia), Ig G antibodies to ascaris antigens "Ascaris-Ig G-Best," and Ig G antibodies to anisakis antigens ("Anisakis-Ig G-Best") were determined. These pathogens were selected for the study due to their high prevalence and a chronic recurrent course of infection they cause. That infection manifestations form clinical "masks" of atopic diseases was also the basis to study these pathogens. Positive results with the subsequent calculation of positivity indices or antibody titers (under the manufacturer's instructions) and negative results of pathogen testing were used in the analysis. Statistical processing of the results was carried out using the Statistica 6.0 software. A correlation analysis and methods of variation statistics with the calculation of arithmetic mean (M), standard error of the mean (m) were applied; the results were considered significant at $p < 0.05$. Assay quantitative results were processed with the use of a Student's t test for dependent samples as the Kolmogorov-Smirnov test of the distribution pattern revealed no differences from the normal distribution.

4 Results

The age-related dynamics of infection with pathogens is presented in Table 1. Patterns of pathogen effects on a patient atopic status are shown in Table 2. To characterize pathogen effects, we have introduced a coefficient of opposite balance (COB) calculated as a ratio of %negative to %positive sIgE test results. The pathogen opposite effect was detected with the COB > 1.2, that characterized the prevalence of negative results of the specific test for allergy. The COB ranged from − 0.8 to − 1 indicates no pathogen effect on the patient's atopic status, that corresponds approximately the same number of negative and positive test results for allergy. With the COB < 0.8, the ratio of negative and positive test results is shifted towards the prevalence of positive results that is representative of a pathogen synergistic effect on the atopic status parameters. The analysis of 879 patients with an increased Ig E level and atopic symptoms showed 31.5% of blood serum samples were seropositive to the antigen *Cag A H .pylori* ($n = 277$). When studying the age-related dynamics of infection in this category of patients, it was demonstrated that the number of seropositive sera increased in groups of school-age children (group 2) and adult patients (group 3). The COB was 2.8 in group 1, it decreased in groups 2 and 3 (0.6–0.2. $p < 0.05$, $p < 0.001$ respectively). There was a relationship between the PI value and the presence of antibodies to *Cag A H .pylori* antigen in group 1 ($r = -0.67$, $p < 0.05$), that characterizes an opposite effect of *H. pylori* on the formation of an atopic status in patients of early and preschool age. In groups 2 and 3 there also were relationships between the PI values and the presence of antibodies to *Cag A H. pylori* antigen ($r = -0.55$, $r = -0.73$,

Table 1 Infection with pathogens in groups of patients with increased serum total IgE level and symptoms of atopy

Groups of patients pathogen-number of patients studied; number of seropositive sera; % of seropositive sera	Number of patients/% (M ± m) with seropositive sera in Group 1 (1–6 years old)	Number of patients/% (M ± m) with seropositive sera in Group 2 (6–17 years old)	Number of patients/% (M ± m) with seropositive sera in Group 3 (≥ 17 years old)	Intergroup *p* value
Helicobacter pylori- 879; 277; 35.1	45/5.1 ± 0.4	97/11.0 ± 0.9	135 /15.3 ± 1.1	1–2 < 0.05 2–3 < 0.001
Lamblia Ig G-4320; 607; 14.1	287/6.6 ± 0.5	130/3.0 ± 0.2	190/4.4 ± 0.3	1–2 < 0.05 2–3 < 0.05
Lamblia Ig M-4320; 66; 1.5	18/0.4 ± 0.03	23/0.5 ± 0.05	25/0.6 ± 0.05	
Opisthorch-1689; 165; 9.8	48/2.8 ± 0.3	58/3.4 ± 0.4	59/3.5 ± 0.2	
Toxocara - 1689; 437; 25.8	160/9.5 ± 0.7	127/7.5 ± 0.8	150/8.9 ± 0.8	
Echinococcus – 1689; 48; 2.8	18/1.1 ± 0.1	14/0.8 ± 0.08	16/0.9 ± 0.08	
Ascaris- 1689; 179; 10.6	38/2.2 ± 0.3	59/3.5 ± 0.5	79/4.7 ± 0.3	1–2 < 0.05 2–3 < 0.001
Anisakis-1689; 51; 3.0	15/0.88 ± 0.08	14/0.82 ± 0.08	22/1.3 ± 0.12	

$p < 0.05$ and $p < 0.05$ in groups 2 and 3 respectively) that indicated a synergistic pathogen effect in groups of school-age children and adult patients.

14.1% of 4320 examined patients with an increased total Ig E level and symptoms of atopy had total antibodies, with 1.5% having class Ig M antibodies to lamblia antigens. The number of seropositive sera containing total antibodies was highest in the group of early and preschool age children (6.6%), decreased in the group of school-age children (3.0%, $p < 0.05$) and again increased in adult patients (4.4%, $p < 0.05$). Unlike adults, there were differences between positive and negative test results for allergy in children (groups 1 and 2). The COB was lowest in group 1 (0.5), slightly elevated in group 2 (0.6), and increased to 1.0 in group 3. The COB values less than 0.8 in children are associated with the synergism of Giardiasis invasion impact on the atopic status parameters, these effects not detected in the group of adults. In groups 1 and 2, there were correlations between the PI and the total level of antibodies to lamblia antigens. The correlations were strong in group 1, $r = 0.77$ ($p < 0.05$) and moderate in group 2, $-r = 0.54$ ($p < 0.07$). The number of sera seropositive to lamblia IgM class antigens was approximately the same in the age groups studied (0.41-0.53-0.53%%). The COB also demonstrated similar values in all age groups and was characterized by the prevalence of negative sIg E test results (COB − 5.0-4.7-4.0, respectively). In contrast to total antibodies, class Ig M antibodies characterizing acute invasion, might have an opposite effect on atopic status parameters. There were no correlations between the PI level and the number of sera seropositive for class Ig M antibodies to lamblia antigens that might be related to a small number of positive test results.

Out of 1689 examined patients with an increased total Ig E level and symptoms of atopic diseases, 9.8% were seropositive to opisthorchis antigens, 25.9%—to toxocara antigens, 10.6 and 1.5% were seropositive to ascaris and anisakis antigens respectively. There was a highest number of seropositive sera to toxocara antigens, with no significant differences between groups observed (9.5-7.5-8.8%, respectively). In all age groups, there were significant differences between positive and negative test results with the negative results prevalence. The COB was 11.3–1.5, which indicates the pathogen opposite effect on atopic status parameters. The highest COB level was detected in group 1 (11.3%), then it significantly decreased to 1.5 in group 2 ($p < 0.001$) and to 1.7 in group 3 ($p < 0.001$). In all groups, there were positive correlations between the PI and the presence of antibodies to toxocara antigens; they were strong in group 1 $r = -0.71$ ($p < 0.05$), and moderate in groups 2 and 3—$r = -0.54$ ($p < 0.05$), $r = 0.44$ ($p < 0.05$) respectively. Thus, the opposite effect of toxocara infection on the patients' atopic status was age-related and most pronounced in the groups of early and preschool age children. 10.4% of 1689 patients examined were seropositive to ascaris antigens. The study of age-related dynamics of infection in this category of patients demonstrated that the number of seropositive sera increased in groups of school-age children (group 2) and adult patients (group 3). Most of seropositive sera were detected in adults (4.7%). In all groups of patients, the COB was higher than 1, which characterized the pathogen opposite effect on the atopic status. The COB increased in group 2 versus group 1 ($p < 0.05$), and in group 3 versus group 2 ($p < 0.001$). There were correlations between the PI and the presence of antibodies to ascarid antigens: they were moderate in group 2—$r = -0.55$ ($p < 0.05$) and strong in group 3—$r = 0.78$ ($p < 0.05$). The number of seropositive sera to opisthorchis antigens was 9.8% among 1689 patients examined and was almost the same in the age groups. In all groups of patients, the COB was higher than 1 (2.8-3.4-3.5%%), which characterized the pathogen opposite effect on the atopic

Table 2 Pathogen effects on atopic status of patients with increased serum total IgE level and symptoms of atopy

Pathogen; sIgE-positive; sIgE-negative; PI for sIgE = positive (M ± m) in group as a whole	Group 1 (under 6 years old) Number of patients/% (M ± m) PI in Group 1(M ± m)	Group 2 (6–17 years old) Number of patients/% (M ± m) PI in Group 2 (M ± m)	Group 3 (17 and older) Number of patients/% (M ± m) PI in Group 3 (M ± m)	Intergroup *p* value
Helicobacter pylori positive; sIgE positive; PI = 0.8 ± 0.03	12/26.7 ± 0.4 0.3 ± 0.02	61/62.9 ± 4.2 0.9 ± 0.03	110/81.5 ± 6.7 1.1 ± 0.2	1–2 < 0.001 2–3 < 0.001
Helicobacter pylori positive; sIgE negative	33 /73.3 ± 6.4	36/37.1 ± 0.8	25 /18.5 ± 1.4	1–2 < 0.05 2–3 < 0.001
COB for *Helicobacter pylori*	2.8 ± 0.3	0.6 ± 0.12	0.2 ± 0.6	1–2 < 0.05 2–3 < 0.001
Lamblia Ig G positive; sIgE positive; PI = 1.1 ± 0.2	57/65.5 ± 5.4 1.2 ± 0.1	79/60.7 ± 4.6 0.9 ± 0.1	97/51.0 ± 3.7 1.1 ± 0.1	2–3 < 0.05
Lamblia Ig G positive; sIgE negative	30/34.5 ± 2.9	51/39.2 ± 4.9	93/51.0 ± 4.9	2–3 < 0.05
COB for Lamblia Ig G	0.5 ± 0.04	0.6 ± 0.04	1.0 ± 0.1	2–3 < 0.05
Lamblia Ig M positive; sIgE positive; PI = 0.8 ± 0.06	3/16.6 ± 1.7 0.9 ± 0.06	4/17.4 ± 1.8 0.7 ± 0.04	5/20.0 ± 1.7 0.8 ± 0.07	
Lamblia Ig M positive; sIgE negative	15/83.4 ± 7.8	19/82.6 ± 7.9	20/80.0 ± 6/8	
COB for Lamblia Ig M	5.01 ± 0.5	4.7 ± 0.5	4.0 ± 0.3	
Opisthorch positive; sIgE positive; PI = 1.0 ± 0.1	15/31.2 ± 3.7 0.9 ± 0.08	18/31.1 ± 3.4 1.1 ± 0.1	20/33.8 ± 2.5 1.1 ± 0.1	
Opisthorch positive; sIgE negative	33/69.8 ± 4.6	40/68.9 ± 6.4	39/66.2 ± 5.7	
COB for Opisthorch	2.2 ± 0.2	2.2 ± 0.2	2.0 ± 0.2	
Toxocara positive; sIgE positive; PI = 1.8 ± 0.2	13/8.1 ± 0.6 1.9 ± 0.2	46/44.1 ± 3.8 2.1 ± 0.3	55/36.6 ± 3.9 1.3 ± 0.2	1–2 < 0.001
Toxocara positive; sIgE negative	147/91.9 ± 8.7	81/63.8 ± 5.4	95/63.3 ± 6.2	1–2 < 0.001
COB for Toxocara	11.3 ± 1.7	1.5 ± 0.1	1.7 ± 0.2	1–2 < 0.001
Echinococcus positive; sIgE positive; PI = 1.3 ± 0.1	3/16.6 ± 5.6 0.9 ± 0.1	2/14.3 ± 1.3 1.3 ± 0.2	4/25.0 ± 2.6 1.8 ± 0.3	
Echinococcus positive; sIgE negative	15/83.4 ± 7.8	12/85.7 ± 9.7	12/75.5 ± 7.6	
COB for Echinococcus	5.0 ± 0.8	6.0 ± 0.2	3.5 ± 0.2	
Ascaris positive; sIgE positive; PI = 1.2 ± 0.03	14/42.2 ± 3.8 1.3 ± 0.1	18/30.5 ± 3.0 1.6 ± 0.1	9/11.4 ± 1.3 0.6 ± 0.1	1–2 < 0.05 2–3 < 0.001
Ascaris positive; sIgE negative	24/63.8 ± 5.6	41/69.5 ± 6.7	70/88.6 ± 6.9	1–2 < 0.05 2–3 < 0.001
COB for Ascaris	1.5 ± 0.1	2.2 ± 0.2	7.8 ± 0.9	1–2 < 0.05 2–3 < 0.001
Anisakis positive; sIgE positive; PI = 1.5 ± 0.1	8/53.3 ± 3.8 0.8 ± 0.1	7/50.0 ± 3.4 1.8 ± 0.1	11/50.0 ± 5.0 1.9 ± 0.1	
Anisakis positive; sIgE negative	7/46.7 ± 4.3	7/50.0 ± 4.8	11/50.5 ± 4.2	
COB for Anisakis	0.9 ± 0.08	1.0 ± 0.08	0.9 ± 0.08	

status. 3.0% of 1689 patients examined were seropositive to anisakis antigens, being almost the same in all groups of patients (0.88-0.82-1.3%%). The COB was 1–1.2 in all age groups of patients demonstrating that the pathogen did not affect parameters of the atopic status.

5 Discussion

Our study has demonstrated that the relationship between the infectious burden and a specific atopic status is ambiguous—different pathogens have different types of effects such as opposite, synergistic or no effect in mono-exposure. Chronic infections promote the development of secondary immunodeficiency states, when a specific IgE response occurs under certain conditions. In early childhood, the immune response of the Th2 profile is primarily formed, which underlies the development of an atopic phenotype. However, in adulthood, such "switching" of the immune response can provide a hyperimmune IgE response as a protective phenomenon against a pathogen rather than contribute to the development of atopy [2, 3]. This is likely to determine different types of pathogen

effects on the patients' atopic status. Moreover, it was shown that a pattern of pathogen effects on the specific Ig E response can vary in different age periods. In particular, we have detected this effect for *H. pylori*, which demonstrates an opposite type of effects in early and preschool age when atopy is primarily associated with manifestation of food allergy, and a synergistic type in patients of school age and adults. We suppose that contradictory literature data on the protective effect of *H. pylori* infection on the prevalence of atopic diseases, or vice versa, on the enhancement of atopic mechanisms affected by the pathogen, can be due to insufficient consideration of age aspects of the pathogen effect. Our findings on the protective effect of *H. pylori* infection on the sIg E level to digested allergens are consistent with results obtained by other authors [10]. The synergistic effect of lamblia invasion on atopic status parameters is determined by chronic endogenous intoxication due to dysmetabolic products accumulation, impaired abdominal and membrane digestion, entry of partial digest products into the body that have an allergic effect. Age-related aspects of the synergistic effect manifest themselves primarily in children, due to intensive processes of membrane digestion [11, 12]. There is still no consensus on the relationship between allergic diseases and helminthiases, that is due to complex and diverse mechanisms of parasite interactions with the host's immune system. [13, 14]. We have shown that helminthiases have a predominantly opposite type of effect on parameters of a specific atopic status. Based on the literature, there are two forms of IgE response to helminthic invasion. One of them involves the production of specific antiparasitic antibodies to defend the host organism, while the second involving the synthesis of polyclonal antibodies provoked by a parasite to ensure its survival [15]. Polyclonal IgE can suppress an allergic response, reducing the production of specific antibodies, which manifests as an inversely proportional relationship between total and specific Ig E levels. A number of studies have shown that the production of polyclonal IgE, stimulated by a helminth infection, suppresses an allergic response to other allergens [14, 15]. In some cases, these data are compatible with a more severe course of atopic disease clinical manifestations, which is determined by effects of polyclonal nonspecific total Ig E and specific Ig E to helminth antigen in the setting of helminthiases. We have also identified the age-related dynamics of opposite effects of helminthiases for toxocara in the group of early and preschool age children, and for ascarids in adult patients, which is determined by both cumulative effects associated with a prolonged antigen burden and "switching" of the immune response that forms the hyperimmune IgE response as a protective phenomenon against helminths [13–15].

6 Conclusion

Our study has demonstrated that the relationship between the infectious burden and a specific atopic status is ambiguous—there are different types of effects such as opposite, synergistic and no effect in mono-exposure. *H. pylori* can exert an opposite impact on the formation of an atopic status in patients of early and preschool age and be synergistic in school-age children and adults. Unlike adults, a chronic giardiasis invasion has a synergistic effect in children. The results obtained in our study also confirm the opinion of most specialists that there are opposite relationships between helminthiases and the specific atopic status of patients.

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Compliance with Ethical Standards

The study was approved by the Bioethics Committee at the Kazan Research Institute of Epidemiology and Microbiology (the minutes No. 31 dated on 02.12.2016).

Conflict of Interest The authors declare that they have no conflict of interest.

References

1. Cruz, A. A., Cooper, P. J., Figueiredo, C. A., Alcantara-Neves, N. M., Rodrigues, L. C., & Barreto, M. L. (2017). Global issues in allergy and immunology: Parasitic infections and allergy. *The Journal of Allergy and Clinical Immunology, 140*(5), 1217–1228.
2. Arnold, I. C., Hitzler, I., & Müller, A. (2012). The immunomodulatory properties of Helicobacter pylori confer protection against allergic and chronic inflammatory disorders. *Frontiers in Cellular and Infection Microbiology, 2*(10), 3389–3330.
3. Taye, B., Enquselassie, F., Amberbir, A., Medhin, G., Fogarty, A., Robinson, K., & Davey, G. (2017). Association between infection with Helicobacter pylori and atopy in young Ethiopian children: A longitudinal study. *Clinical and Experimental Allergy, 47*(10), 1299–1308.
4. Alcantara-Neves, N. M., Veiga, R. V., Dattoli, V. C., Fiaccone, R. L., Esquivel, R., Cruz, Á. A., Cooper, P. J., Rodrigues, L. C., & Barreto, M. L. (2012). The effect of single and multiple infections on atopy and wheezing in children. *The Journal of Allergy and Clinical Immunology, 129*, 359–367.
5. Wang, Y. C., Lin, T. Y., Shang, S. T., Chen, H. J., Kao, C. H., Wu, C. C., & Yang, T. Y. (2017). Helicobacter pylori infection increases the risk of adult-onset asthma: a nationwide cohort study. *European Journal of Clinical Microbiology & Infectious Diseases, 36*(9), 1587–1594.

6. Figura, N., Perrone, A., Gennari, C., Orlandini, G., Giannace, R., Lenzi, C., Vagliasindi, M., Bianciardi, L., & Rottoli, P. (2009). CagA-positive Helicobacter pylori infection may increase the risk of food allergy development. *Journal of Physiology and Pharmacology, 50*, 827–831.
7. Ma, Z. F., Majid, N. A., Yamaoka, Y., & Lee, Y. Y. (2016). Food allergy and helicobacter pylori infection: a systematic review. *Frontiers in Microbiology, 23*(7), 368.
8. van Wijck, Y., de Kleijn, S., John-Schuster, G., TCJ, M., Hiemstra, P. S., Müller, A., Smits, H. H., & Taube, C. (2018). Therapeutic application of an extract of Helicobacter pylori ameliorates the development of allergic airway disease. *Journal of Immunology, 200*(5), 1570–1579.
9. Costa, R. D., Figueiredo, C. A., Barreto, M. L., Alcantara-Neves, N. M., Rodrigues, L. C., Cruz, A. A., Vergara, C., Rafaels, N., Foster, C., Potee, J., Campbell, M., Mathias, R. A., & Barnes, K. C. (2017). Effect of polymorphisms on TGFB1 on allergic asthma and helminth infection in an African admixed population. *Annals of Allergy, Asthma & Immunology, 118*(4), 483–488.
10. Matricardi, P. M., Rosmini, F., Riondino, S., Fortini, M., et al. (2000). Exposure to foodborne and orofecal microbes versus airborne viruses in relation to atopy and allergic asthma: epidemiological study. *BMJ, 320*, 412–417.
11. Belmer SV Giardiasis in children (2004) Pediatric Gastroenterology and Nutriciology. 12(3): P.141–143 (In Rus).
12. Agafonova, E. V., YuA, T., Dolbin, D. A., & Kulikov, S. N. (2008). Modern aspects of diagnosis of giardiasis in humans. *Russian Medical Journal, 17*, 112011 (In Rus).
13. Daschner, A., & Pascual, C. Y. (2005). Anisakis simplex: Sensitization and clinical allergy. *Current Opinion in Allergy and Clinical Immunology, 5*(3), 281–285.
14. Pritchard, D. I., Shakib, F., Walsh, E. A., & Smith, S. J. (2013). Measurement of hookworm infection intensity and circulation levels of IgE and antybodies to IgE in atopics and nonatopic living in a parasitized community in Papua New Guinea. *Journal of Investigational Allergology & Clinical Immunology, 4*(5), 238–241.
15. Hagel, I., Lynch, N. R., & Perez, M. P. (2003). Modulation of the allergic reactivity of slum children by helminthic infection. *Parasite Immunology, 15*(6), 311–315.