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Prevention of allergies in children

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The article is dedicated to the issue of preventing allergies in children. Increase in the spread of allergic diseases among children and adolescents remains one of the most significant medical and social issues and constitutes a heavy burden for healthcare budgets of many countries around the world. The Federal clinical recommendations must become modern guidelines for practicing clinicians everywhere; these are modern regulatory documents – protocols of medical care rendering to children with various allergic manifestations. The authors substantiate complex approach to the therapy of allergic diseases and determine the role of preventive measures and elimination of trigger effects. The authors traditionally distinguish between primary, secondary and tertiary measures and demonstrate their orientation. They consider the issue of preventing respiratory infections, which often constitute a factor of exacerbation of chronic allergic processes and are one of the frequent causative agents of allergic inflammation. The optimal preventive effect and maximum reduction in the incidence rate of respiratory infections may be achieved by combining vaccination and immune pharmacotherapy.
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Term "allergy" first appeared in the essay by Clemens von Pirquet, a pediatrician from Vienna, in the Münchener Medizinische Wochenschrift on July 24, 1906; it defined specifically altered body responsiveness [1]. Nowadays, allergy is defined as an undesirable specific immune response, "immunological hypersensitivity", realization of multiple pathogenetic mechanisms whereof may lead to various allergic diseases.

Congenital immune system plays the fundamental role in the formation of sensitization reaction to potentially allergenic proteins. Protein becomes an allergen for a specific person by interacting with Toll-like, C-lectin, NOD-like and protease-activated receptors (present on epithelial and dendritic cells) or with surfactant proteins (dissolved). Moreover, immune response may be morphed into allergic response, especially in allergy-predisposed persons, by the lipids directly associated with allergenic proteins or present in the allergen source; the mechanism may also be launched by microbial contamination [2, 3].

Despite the involvement of various pathogenetic mechanisms in the development of allergic inflammation, therapeutic approaches pursue a common goal – attainment of control over the disease [2-6]. The selected drug therapy may feature focus at blocking certain key inflammation mediators and/or broad range of anti-inflammatory effects resulting in blocking activation chain of the key cytokines aggravating and maintaining allergic inflammation. Allergen-specific immune therapy (ASIT) plays a special role in the treatment of allergies: it induces

immunological tolerance to the causative allergen, decreases disease manifestations and improves quality of life and control over the allergic disease [7]. Complex approach to the therapy of allergic diseases consists in adequate baseline therapy, immunological tolerance attainment, preventive measures and suppression of triggers.

Allergy has been one of the most significant medical-social issues for a long time; it puts a heavy burden on the healthcare budget in many countries [2, 3]. Allergic diseases are widespread among children and adolescents, negatively affect physical and psychological condition, social life, school performance and degrade quality of life of both patients and members of their families [2-6, 8, 9].

However, despite high incidence rate, the problem of allergies is often given only little attention: most pediatric patients either do not undergo the necessary therapy or receive only sporadic treatment with symptomatic drugs; self-treatment is widespread along with that [2-6].

One of the reasons of this (not only in Russia) is the absence and/or unavailability (for practicing physicians) of the modern evidence-based recommendations on allergies in children.

Professional Association "Union of Pediatricians of Russia" and the Russian Association of Allergology and Clinical Immunology are developing the Federal clinical recommendations – modern regulatory documents and protocols of medical care rendering to children with various allergic diseases.

Specific attention is given to proven preventive measures. Timely preventive measures help to prevent both the development of allergic process and disease exacerbation in patients with atopic disease, extend remission and diminish adverse consequences of the disease [2-6].

Traditionally, preventive measures are divided into primary, secondary and tertiary prevention; they are directed at different aspects, but have a common objective [3].

Primary prevention is aimed at risk group persons and consists in prevention of allergic sensitization (formation of IgE antibodies). It is known that sensitization may develop *in utero*, in trimester II. That is why allergy prevention in fetuses **in the antenatal period** consists in prevention of pathological course of pregnancy. Placental barrier malfunction results in entry of allergens into amniotic fluid; even small concentrations thereof suffice to develop reagin immune response in the fetus. High antigen loads, such as gestational toxicoses, irrational drug therapy of the pregnant woman, exposure to occupational allergens, unilateral carbohydrate nutrition, excessive consumption of foods with obligate food-borne allergens etc., considerably increase the risk of atopic disease. Elimination of these factors is an important aspect of prevention. Pregnant women with compromised hereditary allergic background must avoid contacts with any (food-borne, domestic, occupational) allergens, especially if they suffer from an allergy.

Neonates must not undergo excessive drug therapy and early artificial feeding **in the postnatal period**, as they lead to IgE synthesis stimulation. Individual diets are indicated not only for children, but also for nursing mothers. Neonates with allergy development risk factors require proper skin care, normalization of the gastrointestinal tract's function, organization of a rational diet with explanation of the need in breast feeding, rational administration of supplemental feeding and observation of recommendations on hypoallergenic regimen. Virtually, the only measure aimed at development of tolerance in the postnatal period is maintenance of natural breast feeding until the age of 4-6 months. However, it ought to be mentioned that breast feeding effect is transitory and lasts for a short period of time only. Primary preventive measures reasonably involve avoidance of tobacco smoke, as exposure thereto both in prenatal and postnatal periods negatively affects development and course of the disease accompanied by bronchial obstruction.

Thus, observation of the following factors is important for allergy prevention:

- no smoking during pregnancy and where the child stays;
- no contacts of the pregnant woman and the infant with pets;
- minimal contacts of children with chemical substances in everyday life;
- prevention of acute respiratory viral and other infectious diseases.

Secondary prevention is aimed at preventing manifestations of an allergic disease or severe course thereof in sensitized children; it consists in the following measures:

- control over the environmental conditions, primarily over the rational feeding of the child (especially during shift from breast feeding to artificial feeding);
- ASIT;
- prevention of respiratory infections as allergy triggers;
- educational programs.

It has been proven that observation of a hypoallergenic diet by the mother of a child with atopic dermatitis in the breastfeeding period may alleviate course of the disease [10]. If entirely breast feeding in the first months of life of allergy-predisposed children is unfeasible, it is advisable to use hypoallergenic formulas (amino acid formulas, later – hydrolysates: first – complete hydrolysates, later – partial hydrolysates) [11].

Tertiary prevention is aimed at improving control over the allergic disease and reducing the need in drug therapy by removing adverse disease course risk factors.

Healthy lifestyle, prevention of respiratory infections, sanitation of ENT organs, rational organization of everyday life, avoidance of active and passive tobacco smoking, contacts with dust, animals and birds, elimination of mold, dampness and cockroaches from the living quarters are important. Caution towards the use of drugs, especially of penicillin antibiotics, aspirin and other non-steroidal anti-inflammatory drugs in children with atopic disease must be exercised. Treatment of the concurrent comorbid conditions may considerably affect control of the allergic disease. These include allergic bronchopulmonary aspergillosis, gastroesophageal reflux disease, obesity and rhinitis/sinusitis.

Condition-adequate regular baseline anti-inflammatory therapy is an important component of tertiary prevention.

Elimination of triggers (domestic, epidermal and other allergens) is an essential aspect of attaining control over the allergic inflammation and reducing the rate of exacerbations [12]. According to the current concepts, elimination measures must be selected on the individual basis for each patient and contain recommendations on reducing exposure to house dust mites, allergens borne by animals, cockroaches, fungi and other non-specific factors. A range of studies demonstrated noncompliance with elimination regimen leads to infeasibility of attaining control over the disease and condition aggravation and causes drug load increase even in the event of adequate baseline therapy.

Prevention of acute respiratory infections (ARIs), such as influenza, which often cause exacerbation of many chronic diseases and initiate allergic inflammations, deserves specific attention [2, 3, 13, 14]. According to the World Health Organization, the ARI rate in under-3 children in all countries is 5-8 cases per year; the primary cause of frequent respiratory infections is abundance of contacts, especially at children's preschool establishments, where a 2-3-year-old child may suffer up to 15-20 ARI episodes [13]. The incident rate becomes lower with age. Specific gravity of ARIs in the primary pediatric morbidity structure may reach 60%; however, the rate of hospitalizations with this pathology is ca. 35%. In the structure of pediatric mortality, infectious diseases constitute the cause of death in 40% of the dead infants [15].

ARIs may trigger exacerbation of bronchial asthma, atopic dermatitis and allergic rhinitis. At the same time, a lot of children with respiratory and skin manifestations of an allergy are predisposed to frequent respiratory infections [3, 13, 14]. Results of immunological examination of such children reveal functional peculiarities of the immune system [13, 14]. Patients with primarily Th2 immune response have a tendency to reduced concentration of immunoglobulins A and G in blood serum, of interferon γ and secretory immunoglobulins as well; to disturbed differentiation of immunocompetent cells; apparently, this results in persistent vulnerability to viruses.

Moreover, recent studies of respiratory tract microbiota have demonstrated that bronchial tree of a virtually healthy person is characterized by low bacterial load (the most characteristic bacteria belong to genera *Pseudomonas*, *Streptococcus*, *Prevotella*, *Fusobacteria* and *Veilonella*;

potentially pathogenic genera *Haemophilus* and *Neisseria* are observed far less often) [16]. In patients with bronchial asthma, lower respiratory tract microbiota undergoes qualitative transformation: amount of *Proteobacteria* increases, of *Bacteroidetes* – decreases (in comparison with healthy persons). Severe bronchial asthma in children is associated with considerably *Staphylococcus spp* load in the respiratory tract. The scientists also revealed an association of higher asthma development risk in infants with such microbes as *Haemophilus*, *Moraxella* and *Neisseria spp*. Respiratory microbiome undoubtedly plays an important role in the development of bronchopulmonary system diseases, its effect on the disease course peculiarities and development of resistance to therapy.

Thus, prevention of acute respiratory infections remains a relevant issue of pediatric allergology. Active specific immunization is considered the optimal method [3]. However, the potential of vaccinal prevention of respiratory infections has its limits. At the moment, there are effective and safe vaccines against only several respiratory pathogens, such as influenza virus, pneumococcus and *H. influenzae* (type b), whereas the etiological range of respiratory infections is rather broad. Still, maximal use must be made of preventive potential of the existing vaccines.

The following aspects must be taken into consideration when providing vaccination to allergic children and children from risk groups [3]:

- vaccination must not be provided during exacerbation of the disease regardless of the severity;
- immunization must be provided only to children in stable condition (preferably at the stage of disease control or remission) and always in the setting of baseline therapy;
- in children undergoing ASIT, vaccination must not be provided at the stage of dosage buildup or on the same day as ASIT injection (at least 7-10 days after the allergen injection; the following allergen injection must be administered at least 3 weeks after the vaccination); in the event of sublingual ASIT, allergen intake is temporarily discontinued at the stage of maintenance therapy (3 days prior to vaccination, on the day of vaccination and for 10-14 days after).

Maximal decrease in the ARI incidence rate may be attained by combining vaccination with immunopharmacotherapy [3, 4].

Under the current conditions, use of immunomodulators is considered one of the promising methods of prevention of respiratory infections [3, 13-15, 17-20]. The primary requirements for drugs of this pharmacotherapeutic group are immunomodulating effect, high clinically proven effectiveness and safety, absence of habituation and adverse effects. Immunomodulators must not cause excessive sensitization and induction of immunopathological reactions and adverse additive effect in the event of concurrent use with other pharmaceuticals. Predictable metabolic pattern and elimination pathways, potential for combination with other drugs used at infectious and inflammatory diseases are essential properties of these drugs. Ease of use and potential for non-parenteral use are preferable properties [14, 17].

Bacterial immunomodulators may activate humoral immune response to bacterial antigens and indirectly affect systemic immune response. Being bacterial vaccines, drugs of this pharmacotherapeutic group stimulate monocyte-macrophage system and phagocytosis and activate humoral and cell-mediated immunity. Bacterial lysates, fractions of microbial cell membranes and bacterial ribosomes are used for manufacturing bacterial immunomodulators. Polyvalent drugs producing immunomodulating effect and activating non-specific resistance have gained widespread circulation.

The only drug with proven effectiveness and safety for preventing recurrent respiratory infections and preventing exacerbations of allergic pathologies in children (according to the foreign clinical studies [21, 22]) is ribosomal immunomodulator Ribomunyl (Pierre Fabre, France). This ribosomal-proteoglycan complex consists of ribosomes of the 4 most relevant causative agents of upper and lower respiratory tract diseases (*Streptococcus pneumoniae*, *Streptococcus pyogenes*, *Haemophilus influenzae*, *Klebsiella pneumoniae*) and *K. pneumoniae* cell wall proteoglycans as an adjuvant. The component ribosomes contain antigens identical to superficial bacterial antigens. They are capable of inducing formation of antibodies against the specific causative agents in the human body. The drug contains *K. pneumoniae* membrane

proteoglycans, which increase intensity of antibody response 5 and more times in comparison with isolated intake of ribosomes; they also stimulate non-specific immunity by improving phagocytic activity of macrophages and polynuclear leukocytes and increasing concentration of non-specific resistance factors. Peroral treatment of children with bronchial asthma and frequent acute respiratory diseases with Ribomunyl [2] demonstrated decrease in the rate of acute respiratory diseases and exacerbations of bronchial asthma associated therewith accompanied by increase in the level of interleukin 2, γ-interferon, CD8+ cells and CD3+ leukocytes, decrease in the amount of CD4+ cells and tumor necrosis factor alpha and reduction of cell activation indices (decrease in the amount of CD25+ and CD23+ lymphocytes, increase in the level of IgA, IgG3 and IgG4 and decrease in the level of IgM, IgG, IgG1 and IgG2) in 93.3% of the patients. Immunomodulator's therapeutic mechanism is associated with activation of natural killers, B lymphocytes, γ-interferon and sIgA production and formation of specific antibodies to vaccinal antigens. High immunogenicity of ribosomal antigens determines vaccinal effect of the drug against the causative agents, ribosomes whereof it contains.

Ribomunyl features high safety profile (almost no contraindications) and no identified interactions with other drugs; it is permitted for use in children over 6 months of age. A sufficient amount of studies both in Russia and abroad have been dedicated to the immunomodulator's immunological and therapeutic effectiveness in the children susceptible to frequent respiratory infections [18, 21-25].

Without any doubt, immunoprophylaxis is one of the crucial components of the complex therapy of patients with allergic diseases. However, only a combination of all the components of such a therapy, i.e. provision of preventive measures, ASIT, adequate baseline therapy of elimination of trigger factors to the full extent and in time, may produce significant progress.

REFERENCES

1. Ring J. Allergy in practice. *Springer, Berlin, Heidelberg, New York*. 2005–01–19.
2. Global atlas of allergy. Editors: Cezmi A. Akdis, Ioana Agache. *Published by the European Academy of Allergy and Clinical Immunology*. 2014. 388 p.
3. Namazova-Baranova L. S., Alexeeva A. A., Altunin V. V., Antonova E. V., Arshba E. A., Akhmedullina D. I., Bakradze M. D., Baranov A. A., Botvin'eva V. V., Vazhnova I. M., Vishneva E. A., Voznesenskaya N. I., Volkov K. S., Galitskaya M. G., Gaivoronskaya A. G., Gevorkyan A. K., Goryachkina L. A., Deev I. A., Dvoryakovskii I. V., Dmitrienko E. G. et al. *Allergiya u detei: ot teorii — k praktike. Pod red. L.S. Namazovoi-Baranovoi. Seriya «Sovremennaya pediatriya: ot teorii — k praktike»* [Allergy in Children: from Theory to Practice. Ed. by L.S. Namazova-Baranova. Edition "Current Pediatrics: from Theory to Practice"]. Moscow, 2011.
4. Papadopoulos N. G., Arakawa H., Carlsen K.-H., Custovic A., Gern J. et al. International consensus on (ICON) pediatric asthma. *Allergy*. 2012; 67: 976–997.
5. Vishneva E. A., Namazova-Baranova L. S., Alekseeva A. A., Efendieva K. E., Levina Yu. G., Voznesenskaya N. I., Tomilova A. Yu., Muradova O. I., Selimzyanova L. R., Promyslova E. A. *Pediatricheskaya farmakologiya – Pediatric pharmacology*. 2014; 11 (1): 6–14.
6. Vishneva E. A., Namazova-Baranova L. S., Alekseeva A. A., Efendieva K. E., Levina Yu. G., Voznesenskaya N. I., Tomilova A. Yu., Selimzyanova L. R., Promyslova E. A. *Pediatricheskaya farmakologiya – Pediatric pharmacology*. 2013; 10 (4): 60–72.
7. Burks A. W., Calderon M. A., Casale T., Cox L., Demoly P., Jutel M. et al. Update on allergy immunotherapy: American Academy of Allergy, Asthma & Immunology/European Academy of Allergy and Clinical Immunology. PRACTALL consensusreport. *J Allergy Clin Immunol.* 2013; 131: 1288–1296.
8. Haahtela T., Holgate S., Pawankar R., Akdis C., Benjaponpitak S., Caraballo L. et al. The biodiversity hypothesis and allergic disease. WAO position paper. *WAO Journal*. 2013; 6: 3.

9. Ring J., Akdis C., Behrendt H., Lauener R. P., Schaeppi G., Akdis M. And participants of the Global Allergy Forum, Davos 2011. Davos Declaration: Allergy as a global problem. *Allergy*. 2012; 67: 141–143.
10. Roduit C., Frei R., Depner M., Schaub B., Loss G., Genuneit J. et al. In creased food diversity in the first year of life is inversely associated with allergic diseases. *J Allergy Clin Immunol.* 2014; 133: 1056–1064.
11. Vishneva E. A., Namazova-Baranova L. S., Turti T. V., Torshkhoeva R. M., Alekseeva A. A., Levina Yu. G. *Voprosy sovremennoi pediatrii – Current pediatrics*. 2012; 11 (3): 65–69.
12. Platts-Mills T. A. Allergen avoidance. *J Allergy Clin Immunol.* 2004; 113: 388–391.
13. Bulgakova V. A. *Voprosy sovremennoi pediatrii – Current pediatrics*. 2013; 12 (5): 74–79.
14. Selimzyanova L. R., Promyslova E. A., Vishneva E. A. *Voprosy sovremennoi pediatrii – Current pediatrics*. 2013; 12 (1): 103–107.
15. Chernikov V. V. *Voprosy sovremennoi pediatrii – Current pediatrics*. 2012; 11 (4): 176–181.
16. Fedosenko S. V., Ogorodova L. M., Karnaushkina M. A., Kulikov E. S., Deev I. A., Kirillova N. A. *Vestnik RAMN – Annals of the Russian Academy of Medical Sciences*. 2014; 3–4: 71–76.
17. Namazova-Baranova L. S., Vishneva E. A. *Voprosy sovremennoi pediatrii – Current pediatrics*. 2012; 11 (1): 143–146.
18. Bocharova K. A. *Voprosy sovremennoi pediatrii – Current pediatrics*. 2012; 11 (3): 126–130.
19. Karaulov A. V., Kalyuzhin O. V. *Terapevticheskii arkhiv – Therapeutic archive*. 2013; 85 (11): 100–108.
20. Karaulov A. V. *Voprosy sovremennoi pediatrii – Current pediatrics*. 2014; 13 (1): 119–123.
21. Bellami J. A., Olivieri D., Seranno E. Ribosomal immunostimulation: assessment of studies evaluating its clinical relevance in the prevention ol upper and lower respiratory tract infections in children and adults. *BioDrugs*. 2003; 17: 355–67.
22. Bousquet J., Fiocchi A. Prevention of recurrent respiratory tract infections in children using a ribosomal immunotherapeutic agent: a clinical review. *Paediatr Drugs*. 2006; 8 (4): 235–43.
23. Namazova L.S. *Patogeneticheskie osnovy differentsirovannogo lecheniya bronkhial'noi astmy u detei. Avtoref. dis. … dokt. med. nauk* [Pathogenetic Principles of Differentiated Treatment of Bronchial Asthma in Children. Author's abstract]. Moscow, 2000. 40 p.
24. Zaplatnikov A. L. *Kliniko-patogeneticheskoe obosnovanie immunoterapii i immunoprofilaktiki virusnykh i bakterial'nykh zabolevanii u detei. Avtoref. dis. … dokt. med. nauk* [Clinical-pathogenetic Substantiation of Immunotherapy and Immunoprophylaxis of Viral and Bacterial Diseases in Children. Author's abstract]. Moscow, 2003.
25. *Opyt primeneniya Ribomunila v Rossiiskoi pediatricheskoi praktike. Sbornik nauchnykh trudov. Pod red. N. A. Korovinoi* [Experience of Use of Ribomunyl in Russian Pediatric Practice. Collection of Scientific Papers. Ed. by N.A. Korovina]. Moscow, 2002.