Heading – Literature Review

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Primary Prevention as an Effective Response to the Epidemic of Allergic Diseases

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Rapid growth of incidence of allergic diseases in the last 40 years allows us naming allergy the pandemic of the XXI century. Allergic diseases harm not only individual patients, but the society in whole in the form of progressive increase in direct and indirect costs. According to the latest estimates, more than 150 mn people suffer from allergies, whereas more than 250 mn patients in Europe are expected to suffer from allergies in the next decade. National and international documents stating rules of preventing and treating allergic diseases must become current guidelines for clinicians everywhere. The article summarizes the latest recommendations of the European Academy of Allergology and Clinical Immunology (2014) and of the National Food Allergy Guidelines. The article presents evidence-based methods of primary allergy prevention in infants.
Modern primary food allergy prevention may consist of exclusively breast feeding for at least 4-6 months; if breast feeding is not feasible, prevention may be attained by means of using preventive hypoallergenic formulas with confirmed low allergenicity and not introducing supplemental feeding before the age of 4 months. Evidence-based studies do not confirm effectiveness of any dietary restrictions of pregnant and nursing women regardless of whether they belong to the risk group or not.
Keywords: *allergy, atopic disease, allergic march, risk of development, allergen, cow milk, breast milk, prevention, infants.*

RELEVANCE

Allergy used to be quite a rare phenomenon at the beginning of the XX century. However, under the influence of different factors its prevalence increased dramatically over the last 40 years. Nowadays, allergy is a great healthcare problem. It is becoming pandemic and affects more than 150 million people in Europe alone [1]; this has a significant impact not only on the healthcare budget, but also on national macroeconomics.
Almost 0.5 billion people suffer allergic rhinitis and ca. 300 million people suffer bronchial asthma worldwide [2]. According to the current evaluations, up to 30% of Europeans suffer allergic rhinitis or conjunctivitis, up to 20% suffer bronchial asthma, and 15% suffer dermal manifestations of atopic disease. The prevalence of allergic diseases tends to increase in many areas [3]. If allergy sets on during a person's childhood, they suffer it over the subsequent years of life due to atopic march and pathogenesis (tb. 1). Food allergy is becoming an increasingly

frequent issue, and its severity tends to increase as well. Given the abovementioned tendencies identified by means of epidemiological studies, the European Academy of Allergy and Clinical Immunology (EAACI) predicts that in 15 years more than a half of the European population will suffer one or another type of allergy (Fig. 1).

FOOD ALLERGY AS THE STARTING POINT OF ATOPIC MARCH

Food allergy is an increasingly significant healthcare issue as it serves as the starting point for several allergic diseases (atopic march). More than 17 million people in Europe suffer food allergy [4]. Every fourth schoolchild suffers an allergic disease, whilst the number of severe and possibly life-threatening allergic responses, or anaphylactic shock, to food is increasing. As of now, no precise social-economic evaluation has been done, and the epidemiological data on the prevalence of food allergy vary significantly [5-7]. A 2014 meta-analysis, the scope whereof included the studies published from January 1, 2000 to September 30, 2012, contains an evaluation of food allergy prevalence and morbidity tendencies in European countries [5]. According to the survey, 17.3% of respondents identify some manifestations of this pathology [95% confidence interval (CI) – 17.0-17.6], and 5.9% of respondents have been diagnosed with food allergy (95% CI – 5.7-6.1). The prevalence of sensitization to food allergens (based on the determination of the specific IgE titers) is 10.1% (95% CI – 9.4-10.8). According to dermal tests, it is 2.7% (95% CI – 2.4-3.0). The provocative tests returned positive results in 0.9 % of all cases (95% CI – 0.8-1.1). No predictive factors of food allergy development risk have been identified. However, there is no doubt that the sex, the age, the area of residence, the hereditary background, and the presence of comorbid allergic diseases are all important factors.

Cow milk protein is the most clinically significant allergen for infants. According to the data of the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition, or ESPGHAN, the morbidity of cow milk protein (CMP) allergy peaks during the infancy and amounts to 2-3% of infants. According to the meta-analysis results, the frequency of allergic responses to cow milk amounts to 6% (95% CI – 5.7-6.4) (according to the survey) [5]. According to the survey, the prevalence of CMP allergy is 2.3% (95% CI – 2.1-2.5), as confirmed by the dermal tests. According to the survey and determination of sIgE titer, it is 4.7% (95% CI – 4.2-5.1). Provocative tests have returned positive results in 0.6% of all cases (95% CI – 0.5-0.8). In Northern Europe, CMP allergy is more frequent than in Southern Europe. In infants, the frequency of milk protein allergy is 4.2%, in 2-5-year-old children, it is 3.75%. In these age groups, sIgE to CMP has been identified in 1.6% and 6.8% of all cases, respectively.

More than 75% of children develop tolerance to CMP by the age of 3 years; 90% of children do so by the age of 6 years [8].

Therefore, pandemic allergic diseases is a significant issue of public healthcare and requires medical societies and communities to take coordinated actions on the development and implementation of preventive measures.

THE PURPOSE OF PRIMARY ALLERGY PREVENTION IS TO FORM FOOD TOLERANCE AND PREVENT SENSITIZATION

The International Association of Allergists and Clinical Immunologists in collaboration with the World Health Organization has proposed a combined multi-level program for prevention of food allergy, including primary, secondary, and tertiary prevention. Primary prevention is, without any doubt, the most interesting aspect when it comes to stopping the pandemic spread of allergic diseases (tb. 2; fig. 2) [9].

Allergy development risk

Several epidemiological studies have shown that both genetic predisposition and environmental factors play a role in allergy development [10]. It has allowed developing an algorithm of evaluation of the potential allergy development risk in children. As of now, it is recommended to implement primary preventive measures on the basis of such evaluation. It has been found out

that if a family includes patients suffering atopic diseases, the risk of food allergy development within the first six years of life is doubled. The more patients the family has, the higher is the risk. Children with no family history of allergies has a 15-20% risk of allergy development. If one or more of family members suffer an allergic disease, the risk that allergy will develop in the child is significantly higher and may reach 33-48%. If both parents are allergic, it amounts to 60% [11]. Increased total IgE level in the cord blood combined with family history of allergies may also indicate a high risk (up to 80%) of allergy development in a child.
It has also been identified that boys [12] and children delivered via caesarean section [13, 14] have a greater predisposition to allergies. There are data on the influence of the family's social-economic status on the frequency of allergies in children, but the influencing factors need to be studied further [15].
Nutrition is the key external factor to impact allergy development [16]. It is currently impossible to change genetic factors, which is why the strategy for primary allergy prevention is focused at the infancy, as it is the time when a child experiences first interactions with proteins that start off the pathogenesis. The scope of the strategy may include prenatal and breast-feeding periods and be either focused at the mother's diet or have a direct impact on the child's nutrition. Nowadays, different nutritional factors that can modulate the immune response are subject to research. Those include prebiotics, probiotics, polyunsaturated fatty acids, vitamins etc.
The primary goal of preventive measures taken in respect of the children at risk is to prevent, on the one hand, sensitization, and, on the other hand, to form oral tolerance.

Role of intestinal microflora

The role of intestinal microflora in the immunity formation has become the subject of multiple hypotheses and experimental studies in recent years. The hygienic hypothesis has so far been replaced by the suggestion of "microbial deprivation" as a risk factor of development of allergic and autoimmune diseases. The intestinal microbiota is a must for the development of food tolerance. The intestinal indigenous flora bacteria are capable of inducing secretion of cytokines Th1 (INF γ in particular), as well as the production of interleukins (IL) 10 and 12 that counter Th2-dependent allergic sensitization. What is more, the protective flora maintains Th1/Th2 balance, which prevails in healthy children of older age [19].
A child "meets" various environmental factors, including microbial antigens impacting the development of the immune system, as early as intrauterine [20]. Nowadays, it is evident that the mother-to-embryo interaction is important for the formation of immune response [21].

Prenatal allergy prevention

Until recently, issues of the preventive measures taken to organize hypoallergenic nutrition of pregnant and nursing women were under discussion. Experimental data have proved that the child's immune system needs to interact with food antigens in order to induce tolerance to food proteins. This has called the justification of pregnant women's elimination diet into question [22]. It is also known that small quantities of food allergens contained in breastmilk may be important for the induction of oral tolerance in children. The diversity of such allergens depends on the mother's diet [20].
As of now, there is no convincing evidence to support recommendations neither to observe a hypoallergenic diet during pregnancy to prevent the development of allergic diseases in children nor to consume supplements, e.g. probiotics (level of evidence B).
A systematic review [22] and two controlled randomized studies have not proved that dietary restrictions imposed on pregnant women with regard to the primary allergens are efficient [23, 24]. Two randomized studies have shown there is an egg sensitization reduction tendency if pregnant women's nutrition is enriched with cod liver oil, but these data need further evidence [25, 26].
Without any doubt, use of functional nutritional components is a promising area of focus when searching for new opportunities of preventing allergies. It has been shown that the prescription of

Lactobacillus GG to pregnant and nursing women reduces the frequency of atopic dermatitis in children, but it does not reduce IgE sensitization [27]. At the same time, a series of randomized studies has not proved the effect of probiotics in relation to prevention of allergy in children at risk [28, 29]. The effectiveness of probiotic use has been proved only in relation to children delivered via caesarean section [30].
X.Y. Kong et al. have conducted a meta-analysis of 2,701 studies carried out in 2007-2012 and concluded that prenatal and postnatal prescription of probiotics does not have a significant impact in relation to food allergy prevention in children (RR – 0.88%, 95% CI – 0.76-1.03). They have also come to a conclusion that there is no evidence base to make recommendations in support of using probiotics. The authors emphasize the need for new well-planned studies to determine the most effective types and strains of probiotics, dosage, and duration of administration. Target patient groups need to be selected [30].

Postnatal allergy prevention. Breastfeeding
Interaction with large amounts of foreign proteins during the neonatal period is apparently important for the development of allergic responses. Such proteins may enter the body both as food allergens, such as whole cow milk proteins, and as aeroallergens. Without any doubt, breastfeeding has many advantages both for mothers and children. There is evidence that breastfeeding wields protective effects in relation to allergy prevention (level of evidence C).
Women's milk contains components of humoral and cellular immunity, and thus provides for immunological protection of the child not only from the impact of food antigens, but also from gastrointestinal and respiratory infections. Breastfeeding of children until the age of 4-6 months provides for a significant reduction of the risk of future development of allergic pathologies in a child. It has been found out that natural feeding has a preventive effect in relation to food allergy in children at risk, i.e. those who have at least one next-of-kin relative with a formally confirmed allergic disease. Children fed only with maternal milk or a combination of breastmilk and hypoallergenic formulas, and receiving supplemental feeding after the age 4 months demonstrated reduced total morbidity of atopic dermatitis, allergy, and cow milk protein intolerance over the first 2-4 years of life [31].
EAACI Guidelines of 2014 state there is no need for mothers both at risk and not at risk to observe a hypoallergenic diet (level of evidence B). Two non-randomized comparative studies have shown that exclusion of food allergens from the diet during lactation does not reduce allergy risks [32, 33]. However, given the histamine release activity of some foods and other mechanisms of possible triggering actions of nutrition, national documents contain recommendations on balanced diet for pregnant and nursing mothers with limited use of foods that may trigger allergic response [34].
Such immunomodulatory components as long-chain polyunsaturated fatty acids and oligosaccharides may quantitatively and qualitatively differ in nursing women, which makes it difficult to evaluate the preventive effect of breastfeeding on allergy development [33, 35, 36].

Postnatal allergy prevention. Hypoallergenic formulas
When breastfeeding is not an option for allergy prevention, child's exposure to cow milk proteins shall be prevented or delayed. To achieve that, specialized hypoallergenic foods based on cow milk protein hydrolysis are used.
Formulas based on extensively hydrolyzed proteins were developed in the early 1950s and were used to treat and, later, to prevent food allergy in children. Extensive protein hydrolysis minimized allergenicity of formulas; however, large amounts of free amino acids and small peptides made them bitter, which would often impede extensive use of such formulas for prevention. Although extensively hydrolyzed formulas (EHF) provide for a stronger protection from allergy during a person's infancy, mechanisms of tolerance formation cannot be induced when such formulas are used.

Preventive effects of formulas based on partially hydrolyzed proteins have been subject to research since the 1980s. Unlike EHF, partially hydrolyzed formulas (PHF) contain larger peptides. On the one hand, they prevent the development of sensitization to whole CMPs; on the other hand, they contain enough tolerogenic epitopes to form food tolerance. Besides, PHFs are more physiological as compared to foods based on extensively hydrolyzed proteins as they contain more lactose, which stimulates growth of bifidum bacteria, facilitates the absorption of calcium, magnesium, and manganese, and is a source of galactose required for the synthesis of cerebral galactocerebrosides, which take part in neuron myelination. The advantages thereof include not only low allergenicity, but also better taste and a relatively lower cost. Unlike EHFs, use of partial hydrolysates ensures that oral tolerance is formed and, probably, that whole formulas administered later on will not provoke allergic sensitization to intact proteins.
Several systematic reviews have shown that unlike standard formulas, PHFs may protect children from food allergy development [37-39]. The discrepancy between serum and casein formulas and between partial and extensively hydrolyzed formulas are not significant in terms of allergy prevention. One of areas of focus in relation to improvement of PHF prophylactic effectiveness is the enrichment of hypoallergenic formulas with prebiotic oligosaccharides that mimic the effect of breastmilk oligosaccharides.
For instance, a meta-analysis of four studies [40] has shown a relevant reduction of atopic eczema frequency in those children who consumed formulas with prebiotic oligosaccharides (1,218 infants: OP – 0.68; 95% CI – 0.48-0.97). At the same time, no data have been acquired in the framework of this meta-analysis that would prove a reduction in the frequency of respiratory allergies and urticaria. Some studies have indicated a significant reduction in the frequency of atopic eczema in children at allergy risk when formulas are enriched with galactooligosaccharides and fructooligosaccharides (9:1, 0.8 g per 100 ml) [41, 42].
It has so far been convincingly proved that soy formulas cannot protect children from allergy development [43].

Implementation of supplemental feeding

EAACI Guidelines of 2014 state absence of sufficient evidence to support any specific recommendations on the introduction of supplemental feeding to prevent food allergy in children (level of evidence C).
Earlier practice of delayed supplemental feeding introduction for children at risk has been reviewed, as evidence has been obtained that delayed introduction of supplemental feeding (i.e. after 4 months) does not feature any preventive impact on allergy development [44, 45]. EAACI experts recommend introducing supplemental feeding from the age of 4-6 months in accordance with the local standards and practices regardless of the presence of allergic family members.
According to the National Program for Infant Feeding [46] and the Russian National Guidelines on Diagnosis and Treatment of Cow Milk Protein Allergy in Infants [47], supplemental feeding ought to be introduced for children at allergy risk from the age of 4.5-6 months. Highly allergenic foods, such as wheat, milk etc., are to be added to the diet after the age of 6 months. Supplemental foods are added one by one, i.e. one kind of vegetables, cereals, fruits, meat etc. (tb. 3).

CONCLUSION

The progradient increase in allergic diseases worldwide and in Europe, as well as the massive social and economic damage caused thereby make it imperative to find new ways to prevent the XXI century's pandemic disease. The effectiveness of initial preventive measures needs to be appraised by means of clinical studies carried out in accordance with principles of the evidence-based medicine. It has so far been proved that contemporary primary food allergy prevention can be achieved by means of exclusive breastfeeding for over 4-6 months, introduction of supplemental feeding at the age of 4 months or later, and use of hypoallergenic formulas with confirmed low allergenicity. As of now, effectiveness of dietary restrictions imposed on pregnant

and nursing women regardless of their risk status has not been proved by studies carried out in accordance with principles of the evidence-based medicine.

CONFLICT OF INTEREST

S.G. Makarova is a nutrition advisor for Nutricia and Mid Johnson.
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E.A. Vishnyova, T.V. Turti, Y.S. Akoyev, and M.I. Petrovskaya have declared absence of reportable financial support / conflict of interest.

Table 1. Allergic disease course peculiarities

• As a rule, allergy sets on during a person's childhood and persists for many years, in many cases, for the entire lifespan. However, allergic diseases may develop at any age. • Patients with one allergic disease are at risk of development of another allergic pathology • In children, allergic diseases usually develop one by one; this is known as atopic march. The first disease to occur is atopic dermatitis identified in more than 10% of European infants. • As a rule, allergic diseases are traced in families, but nowadays, an increasing number of allergy cases is registered in families with no history of allergies.

Table 2. Levels of evidence of the measures for primary prevention of allergy in children (EAACI, 2014).

Preventive measures	**Level of evidence**
Breastfeeding until the age of at least 4-6 months is recommended for all children	II–III
Dietary restrictions are not recommended for pregnant and nursing women	I–II
In case the amount of breastmilk is not sufficient, or breastfeeding is not feasible, • children at risk ought to consume hypoallergenic formulas with confirmed preventive effect over the first 4 months of life • other children may consume standard formulas • after the age of 4 months, standard formulas are recommended regardless of congenital predisposition to atopic disease	I
Regardless of predisposition to atopic disease, it is recommended to introduce supplemental feeding after the age of 4 months in accordance with standard practices and nutritional guidelines	II–III
It is not recommended for children at risk to observe specific dietary restrictions. After supplemental feeding is introduced, it is not recommended to impose restrictions or employ stimulatory effects of strongly allergenic foods, such as cow milk, chicken eggs, or peanuts regardless of the family history of atopic disease	II–III

Table 3. Time of introduction and range of supplemental foods for healthy infants and infants at risk of atopic disease

Foods	**Age in months**	
	Healthy children	**Children at risk of atopic disease development***
Cereals	4-6	4.5-6
Vegetable puree	4-6	4.5-6
Fruit puree	4-6	5.5
Fruit juice	4-6	6
Meat mash	6	6
Quark	6	6-7
Yolk	7	8
Fish puree	8	9-10
Kefir and yoghurt for children	Strictly after 8	Strictly after 8
Rusks and cookies	7	7
Wheat bread	8	8

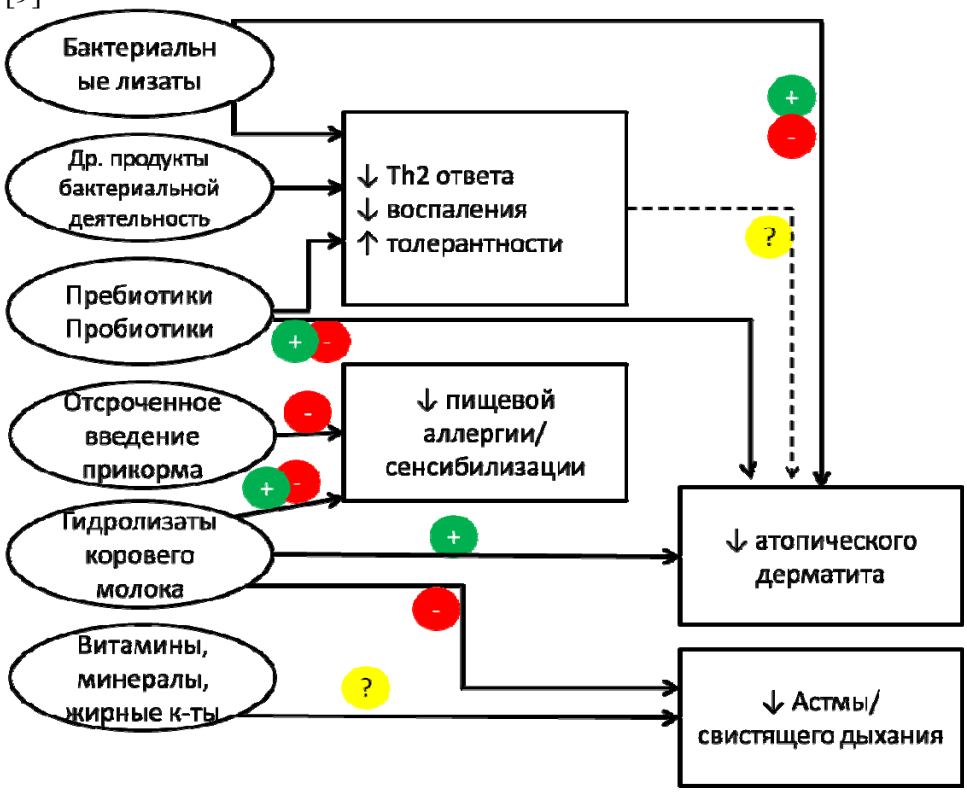
Vegetable oil	4-6	5
Butter	4-6	5.5

Note. * A thorough consideration of individual tolerance to foods introduced to the diet is imperative.

Fig. 1. Prevalence of different socially significant diseases in Europe (EAACI 2014)

RUSSIAN	ENGLISH
Астма и аллергии	Asthma and allergies
Сахарный диабет	Diabetes
Онкологические заболевания	Oncological diseases
Ишемическая болезнь сердца	Ischemic heart disease
Инсульт	Stroke
Болезнь Альцгеймера	Alzheimer’s disease
Болезнь Паркинсона	Parkinson’s disease

Fig. 2. Effectiveness of certain measures of prevention of atopic dermatitis and bronchial asthma [9]



RUSSIAN	ENGLISH
Бактериальный лизаты	Bacterial lysates
Др. продукты бактериальной деятельность	Other products of bacterial activities
Пребиотики Пробиотики	Prebiotics Probiotics
Отсроченное введение прикорма	Delayed introduction of supplemental feeding
Гидролизаты коровьего молока	Cow milk hydrolysates
Витамины, минералы, жирные к-ты	Vitamins, minerals, fatty acids
Th2 ответа	Th2 response
Воспаления	Inflammation
Толерантности	Tolerance
Пищевой аллергии/сенсибилизации	Food allergy/sensitization
Атопического дерматита	Atopic dermatitis
Астмы/свистящего дыхания	Asthma /hissing respiration