Original paper

Polish statement on food allergy in children and adolescents

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Abstract

An adverse food reaction is defined as clinical symptoms occurring in children, adolescents or adults after ingestion of a food or chemical food additives. This reaction does not occur in healthy subjects. In certain individuals is a manifestation of the body hypersensitivity, i.e. qualitatively altered response to the consumed food. The disease symptoms observed after ingestion of the food can be triggered by two pathogenetic mechanisms; this allows adverse food reactions to be divided into allergic and non-allergic food hypersensitivity (food intolerance). Food allergy is defined as an abnormal immune response to ingested food (humoral, cellular or mixed). Non-immunological mechanisms (metabolic, pharmacological, microbiological or other) are responsible for clinical symptoms after food ingestion which occur in non-allergic hypersensitivity (food intolerance).

Food allergy is considered a serious health problem in modern society. The prevalence of this disorder is varied and depends, among other factors, on the study population, its age, dietary habits, ethnic differences, and the degree of economic development of a given country. It is estimated that food allergy occurs most often among the youngest children (about 6-8% in infancy); the prevalence is lower among adolescents (approximately 3-4%) and adults (about 1-3%).

The most common, age-dependent cause of hypersensitivity, expressed as sensitization or allergic disease (food allergy), are food allergens (trophoallergens). These are glycoproteins of animal or plant origine contained in: cow's milk, chicken egg, soybean, cereals, meat and fish, nuts, fruits, vegetables, molluscs, shellfish and other food products. Some of these allergens can cause cross-reactions, occurring as a result of concurrent hypersensitivity to food, inhaled or contact allergens.

The development of an allergic process is a consequence of adverse health effects on the human body of different factors: genetic, environmental and supportive. In people predisposed (genetically) to atopy or allergy, the development of food allergy is determined by four allergic-immunological mechanisms, which were classified and described by Gell-Coombs. It is estimated that in approximately 48-50% of patients, allergic symptoms are caused only by type I reaction, the IgEmediated (immediate) mechanism. In the remaining patients, symptoms of food hypersensitivity are the result of other pathogenetic mechanisms, non-IgE mediated (delayed, late) or mixed (IgE mediated, non-IgE mediated).

Clinical symptomatology of food allergy varies individually and depends on the type of food induced pathogenetic mechanism responsible for their occurrence. They relate to the organ or system in which the allergic reaction has occurred (the effector organ). Most commonly the symptoms involve many systems (gastrointestinal tract, skin, respiratory system, other organs), and approximately 10% of patients have isolated symptoms. The time of symptoms onset after eating the causative food is varied and determined by the pathogenetic mechanism of the allergic immune reaction (immediate, delayed or late symptoms).

In the youngest patients, the main cause of food reactions is allergy to cow's milk. In developmental age, the clinical picture of food allergy can change, as reflected in the so-called allergic march, which is the result of anatomical and functional maturation of the effector organs, affected by various harmful allergens (ingested, inhaled, contact allergens and allergic cross-reactions).

The diagnosis of food allergy is a complex, long-term and time-consuming process, involving analysis of the allergic history (personal and in the family), a thorough evaluation of clinical signs, as well as correctly planned allergic and immune tests. The underlying cause of diagnostic difficulties in food allergy is the lack of a single universal laboratory test to identify both IgE-mediated and non-IgE mediated as well as mixed pathogenetic mechanisms of allergic reactions triggered by harmful food allergens. In food allergy diagnostics is only possible to identify an IgE-mediated allergic process (skin prick tests with food allergens, levels of specific IgE antibodies to food allergens). This allows one to confirm the diagnosis in patients whose symptoms are triggered in this pathogenetic mechanism (about 50% of patients). The method allowing one to conclude on the presence or absence of food hypersensitivity and its cause is a food challenge test (open, blinded, placebo-controlled). The occurrence of clinical symptoms after the administration of food allergen confirms the cause of food allergy (positive test) whereas the time elapsing between the triggering dose ingestion and the occurrence of clinical symptoms indicate the pathogenetic mechanisms of food allergy (immediate, delayed, late).

The mainstay of causal treatment is temporary removal of harmful food from the patient's diet, with the introduction of substitute ingredients with the nutritional value equivalent to the eliminated food. The duration of dietary treatment should be determined individually, and the measures of the effectiveness of the therapeutic elimination diet should include the absence or relief of allergic symptoms as well as normal physical and psychomotor development of the treated child.

A variant alternative for dietary treatment of food allergy is specific induction of food tolerance by intended contact of the patient with the native or thermally processed harmful allergen (oral immunotherapy). This method has been used in the treatment of IgE-mediated allergy (to cow's milk protein, egg protein, peanut allergens). The obtained effect of tolerance is usually temporary.

In order to avoid unnecessary prolongation of treatment in a child treated with an elimination diet, it is recommended to perform a food challenge test at least once a year. This test allows one to assess the body's current abil-

ity to acquire immune or clinical tolerance. A negative result of the test makes it possible to return to a normal diet, whereas a positive test is an indication for continued dietary treatment (persistent food allergy).
Approximately 80% of children diagnosed with food allergy in infancy "grow out" of the disease before the age of 4-5 years. In children with non-IgE mediated food allergy the acquisition of food tolerance is faster and occurs in a higher percentage of treated patients compared to children with IgE-mediated food allergy.
Pharmacological treatment is a necessary adjunct to dietary treatment in food allergy. It is used to control the rapidly increasing allergic symptoms (temporarily) or to achieve remission and to prevent relapses (long-term treatment).
Preventive measures (primary prevention of allergies) are recommended for children born in a "high risk" group for the disease. These are comprehensive measures aimed at preventing sensitization of the body (an appropriate way of feeding the child, avoiding exposure to some allergens and adverse environmental factors). First of all, the infants should be breast-fed during the first 4-6 months of life, and solid foods (non milk products, including those containing gluten) should be introduced no earlier than 4 months of age, but no later than 6 months of age. An elimination diet is not recommended for pregnant women (prevention of intrauterine sensitization of the fetus and unborn child). The merits of introducing an elimination diet in mothers of exclusively breast-fed infants, when the child responds with allergic symptoms to the specific diet of the mother, are disputable. Secondary prevention focuses on preventing the recurrence of already diagnosed allergic disease; tertiary prevention is the fight against organ disability resulting from the chronicity and recurrences of an allergic disease process.
Food allergy can adversely affect the physical development and the psycho-emotional condition of a sick child, and significantly interfere with his social contacts with peers. A long-term disease process, recurrence of clinical symptoms, and difficult course of elimination diet therapy are factors that impair the quality of life of a sick child and his family. The economic costs generated by food allergies affect both the patient's family budget (in the household), and the overall financial resources allocated to health care (at the state level). The adverse socio-economic effects of food allergy can be reduced by educational activities in the patient's environment and dissemination of knowledge about the disease in the society.

Key words: food hypersensitivity, food allergy, children, adolescence, statement.

Introduction

The "Food Allergy" Working Group of the Polish Society of Paediatric Gastroenterology, Hepatology and Nutrition (PTGHiŻDz) presents to the Polish medical community its position on food allergy in children and adolescents.

Hypersensitivity to consumed food or group of foods, in infants, children and adolescents as well as adults, is becoming an increasingly common cause of many individually different, recurrent or chronic clinical symptoms. This global health problem, which is becoming increasingly important in today's society, has been addressed in extensive medical literature and reports of scientific societies and institutions involved in health care. In Poland, this problem is still underestimated, and the only position of a group of Polish experts was published in 1997. The works of the editorial team on this document included an analysis of global literature dedicated to the causal and pathogenetic role of food hypersensitivity in triggering and sustaining symptoms in sensitive individuals, as well as health effects and the socioeconomic impact of this hypersensitivity.

The main purpose of this document was to help the medical community in understanding the appropriate scale of the phenomenon, and to assist physicians of various specialties in taking diagnostic and therapeutic decisions as well as preventive measures concerning food allergy in our country.

The authors are convinced that the information contained in this document will be helpful for parents of the affected children, as well as for adults with this disorder.

Members of the Working Group held two meetings devoted to discussion of the theses of the document (April 2006, May 2009). The draft version was also discussed at a meeting of the Commission for the prevention of Civilisation Diseases, the Human Development Committee, Polish Academy of Sciences (February 2010), and during the 6th Symposium of the Polish Society of Paediatric Gastroenterology, Hepatology and Nutrition, at a session dedicated to food allergy (May 2010).

As chairman of the "Food Allergy" Working Group of the Polish Society of Paediatric Gastroenterology, Hepatology and Nutrition, I give special thanks to all those who contributed, through their valuable comments, to the drafting of the final version of this Statement.

Prof. Maciej Kaczmarski MD, PhD

Definition

Clinical symptoms which occur in some people (children, adolescents, adults) during eating or after eating particular food(s) and/or various food additives are referred to as an adverse food reaction [1].

An adverse food reaction only occurs in people with signs of individual hypersensitivity. These characteristics qualitatively change the nature of the body's biological response to the consumed food or compounds (substances) added to food [2].

Food intake (regardless of the type or dose) by persons to whom it is harmful leads to triggering of pathogenetic mechanisms responsible for the occurrence and

dynamics of specific symptoms. This abnormal reaction to consumed food distinguishes people with hypersensitivity (sick) from healthy subjects [1, 2].

The classification of **adverse food reactions** of the European Academy of Allergy and Clinical Immunology (EAACI) of 1995 was presented in the publication of Bruijnzeel-Koomen *et al.* [1]. In this classification, responses of the human body to consumed food are divided into two categories: **toxic and non-toxic**.

Toxic reactions are always associated with the same kind of clinical symptoms occurring in all people exposed to the same consumed food (e.g. contaminated food = food poisoning).

Non-toxic reactions are attributed to patients with a qualitatively different response to a food, a specific nutrient or food additive. The pathogenetic mechanisms triggered by undesirable, non-toxic reaction of the body to consumed food are the basis for classifying these patients into two groups: those with food allergy and those with food intolerance [1].

According to the proposed definitions:

– **food allergy is a form of adverse food reaction in which clinical symptoms are triggered and/or modified by the immune pathogenetic mechanism (IgE-mediated or non-IgE mediated),**
– **food intolerance is a form of adverse food reaction in which clinical symptoms are triggered and/or modified by non-immune pathogenetic mechanisms (enzymatic, pharmacological or undefined)** [1].

In 2001, members of the European Academy of Allergy and Clinical Immunology (EAACI) and the World Allergy Organization (WAO) proposed a change of the nomenclature of allergic diseases [2]. The aim of these changes was to harmonise the language for allergic diseases used both in scientific research and medical care for patients, as well as education. A glossary of the key concepts in allergy was then developed to optimise their unambiguous understanding by scientists, physicians, patients and anyone interested in the problems of allergy. The glossary is available in 24 languages on the website of EAACI. The proposed allergological terminology has been used in educational materials dedicated to asthma and allergy, posted on the websites of the WAO and the World Health Organization (WHO) [2].

The new nomenclature introduced the concept of **hypersensitivity, i.e. reaction of the body to the effect of a harmful (pathogenic) factor at a dose which produces no reaction in healthy subjects**. Based on this concept, the originally used term food allergy was replaced by the term allergic hypersensitivity (IgE-mediated, non-IgE mediated), and food intolerance was replaced by the term nonallergic hypersensitivity (Table 1) [2].

In 2003, members of the EAACI and the WAO introduced further changes to the allergological nomenclature. According to this nomenclature, the term "food allergy" should be used only in the case of IgE-mediated food allergy, whereas the term "non-allergic food hypersensitivity" should be used for all responses from the subgroup of non-IgE mediated immune mechanisms (Fig. 1) [3].

At the end of 2010, a team of experts appointed by the US National Institute of Allergy and Infectious Diseases (NIAID), in collaboration with 34 professional organizations, federal agencies and patients' associations, published guidelines for diagnosing and treating food allergies in the United States. The NIAID report described the current classification of adverse food reactions. The term "adverse food reaction" is here a broader concept and includes all pathogenetic mechanisms (immune and non-immune) responsible for the occurrence of food-induced symptoms. Depending on the type of immune mechanisms involved in the response to consumed food, a distinction was made between "food allergy" and "coeliac disease", whereas food reaction with involvement of non-immune mechanisms was named "food intolerance" (Fig. 2) [4].

The transparency of this classification makes it the most useful in everyday clinical practice [4]. **According to US guidelines, food allergy is an adverse, reproducible and repeatable reaction resulting from the body's immune response specific to a particular food**.

Table 1. Hypersensitivity classification according to modified terminology of atopic and allergic diseases (EAACI, 2001) [2]

Hypersensitivity			
Immunologic mechanisms defined or strongly suspected = allergic hypersensitivity			Immunologic mechanisms excluded = non-allergic hypersensitivity
Pathogenetic mechanisms IgE-mediated		Pathogenetic mechanisms non-IgE-mediated	
Non-atopic hypersensitivity: • Insects stings • Helmints • Drugs • Others	Atopic hypersensitivity	• T cell-mediated, e.g. contact dermatitis, coeliac disease • Eosinophil-mediated, e.g. eosinophilic gastroenteropathy • IgG-mediated, e.g. allergic alveolitis • Other	

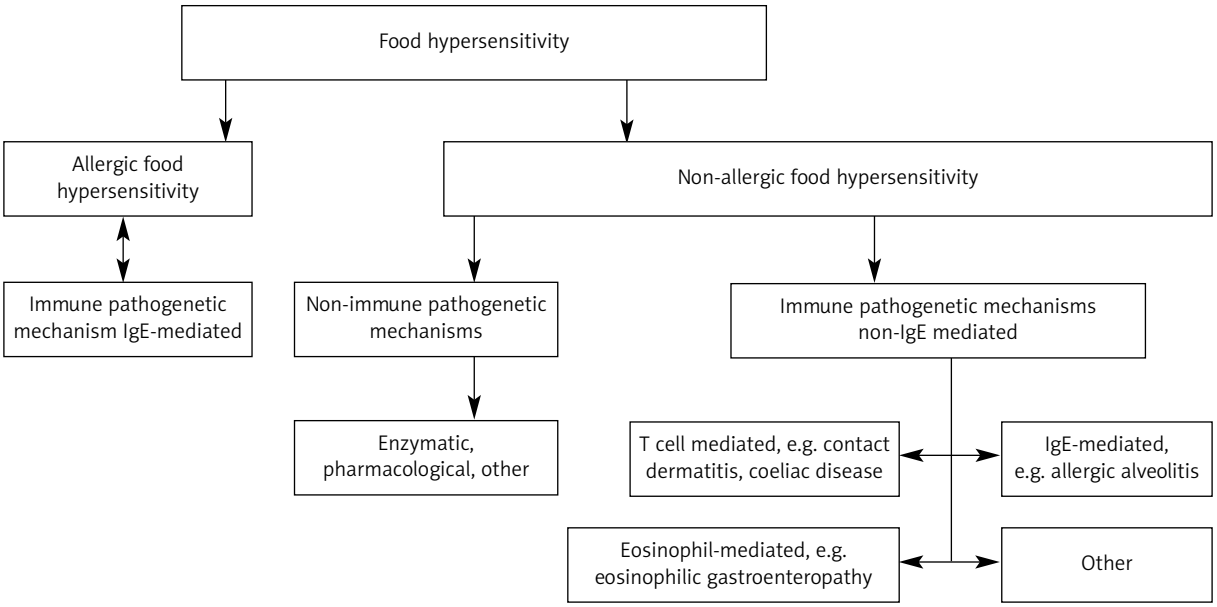

Fig. 1. Food hypersensitivity (WAO revised nomenclature, 2003) [3]

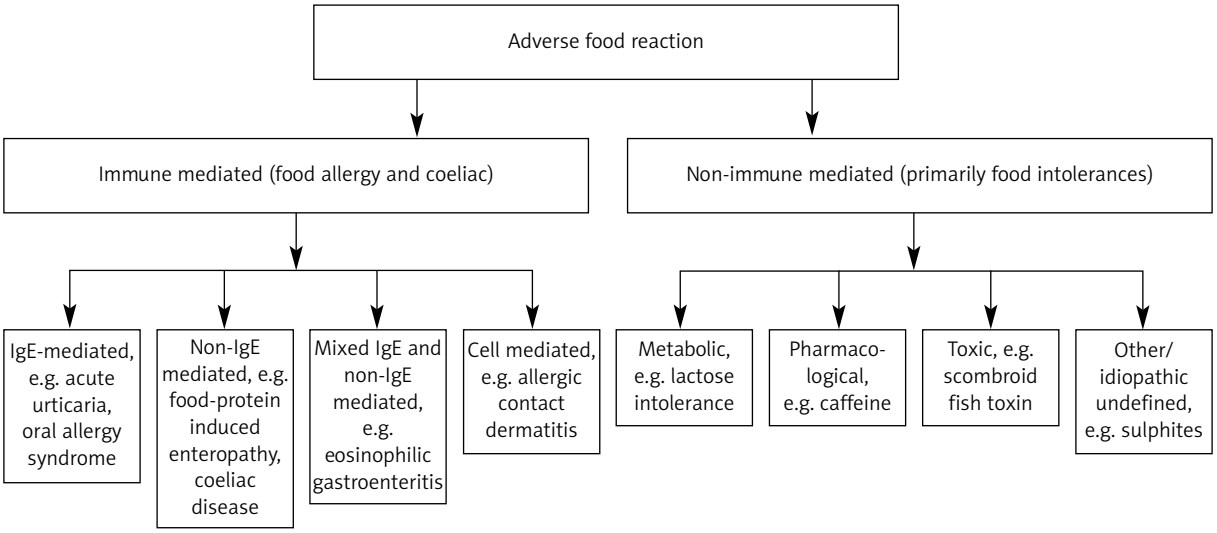

Fig. 2. Types of adverse reactions to food (NIAID classification, 2010) [4]

In this terminology, allergy and allergic diseases mean all medical conditions resulting from the modified immune response to a specific allergen. **Disease symptoms are the result of pathogenetic mechanisms which are divided into four groups: IgE-mediated, non-IgE mediated, mixed (IgE-mediated and non-IgE mediated), and cellular** [4].

According to the guidelines, this group of symptoms includes: 1) food-induced anaphylaxis (systemic symptoms), 2) food-induced gastrointestinal allergy (immediate gastrointestinal response, eosinophilic oesophagitis, eosinophilic gastroenteritis, food-induced proctocolitis, food-induced enterocolitis, allergy of the oral mucosa), 3) food-induced skin reactions (acute urticaria, angioneurotic oedema, atopic dermatitis, contact dermatitis, contact urticaria), 4) respiratory symptoms (from the upper and lower respiratory tract, Heiner syndrome).

These symptoms from various systems may be combined or, more rarely, they can be isolated. Symptoms from the respiratory system, and in particular Heiner syn-

drome, are associated with cellular infiltrates in the lungs and they are often associated with systemic symptoms such as abnormal weight gain and iron deficiency anaemia [4].

In the US classification, the term "food hypersensitivity" was used only to determine the immediate IgE-mediated gastrointestinal (GI) hypersensitivity [4].

Summary 1

Repeatable and reproducible clinical symptoms, which occur in some people (children and/or adults) after eating specific food(s) and various chemical food additives, are referred to as adverse food reactions.

Adverse food reactions only occur in people with signs of individual hypersensitivity. These characteristics qualitatively change the nature of the body's biological response to the consumed food or food additives.

In the terminology currently used in Europe, it has been suggested to define food allergy as a body's response to consumed food, for which an "IgE-mediated" pathogenetic immune mechanism has been shown. Food reactions caused by "non-IgE mediated" immune mechanisms are referred to as non-allergic food hypersensitivity.

According to the US terminology, allergic diseases, including food allergy, are the result of the body's abnormal immune response to a specific allergen, where the pathogenetic mechanisms can be divided into four groups: IgE-mediated, non-IgE mediated, mixed and cellular. According to this terminology, adverse food reaction is a term for reactions with involvement of immune mechanisms (including food allergy and coeliac disease) as well as reactions resulting from various pathogenetic mechanisms of non-immune origin (most often food intolerance).

Epidemiology of food allergy and non-allergic food hypersensitivity

The World Health Organization (WHO) has recognized food allergy as a health problem affecting 1-3% of adults and 4-6% of children, and eight food allergens (called the "big eight") were declared the most common cause of hypersensitivity or allergy and the resulting clinical symptoms of food allergy (Table 2) [5, 6].

This was reflected in the guidelines for food safety contained in the *Codex Alimentarius* [7]. According to Sampson, the prevalence of food allergy varies depending on the allergens present in various food products (Table 3) [8].

It is estimated that food allergy is most commonly diagnosed among the youngest children (6-8%) and adolescents (about 3-4%); it also occurs among adults (1-3%). Allergy to cow's milk proteins affects approximately 2-3% of infants and is the most common cause of allergic symptoms resulting from food intake in this age group [8-10]. In the last decade, 5 studies have been published evaluating the prevalence of this allergy in the first year of life based on the results of a food challenge test. The prevalence was as follows: Finland – 1.9%, the Isle of Wight – 2.16%, Denmark – 2.22%, the Netherlands – 2.24%, Norway – 4.9% [11].

Data on the prevalence of food hypersensitivity and food allergy in the population of children-adolescents and adults in different countries are therefore heterogeneous [11-18]. These differences, and the resulting problems in comparing the results of epidemiological studies conducted in the world, are caused by the methodological criteria. The most important of these is the selection criterion for the study population, for example, the choice of the population of a certain age (children, adolescents, adults), health (population of healthy or sick people, or those at risk of developing allergies – for example, with or without positive allergy history), or the use of other criteria, e.g. taking into account the dietary habits of the study group, and cultural or ethnic differences. In the methodology of epidemiological studies it is important to use a specific research tool (e.g. a survey), and methods allowing one to obtain objective results (such as skin prick tests, sIgE, patch tests, challenge test) [11, 12].

The first epidemiological study in Poland dedicated to these issues was conducted at the Bialystok centre and involved a group of infants from the north-eastern region of Poland [16]. The prevalence of food hypersensi-

Table 2. Foods containing most common allergens sensitizing people according to the FAO Report, 1995 [5]

Cow's milk
Egg
Fish
Shellfish, molluscs
Nuts
Peanuts
Soy
Wheat

Table 3. Prevalence of allergy to various food products in children and adults [8]

Food	Young children [%]	Adults [%]
Milk	2.5	0.3
Egg	1.3	0.2
Peanuts	0.8	0.6
Tree nuts	0.2	0.5
Fish	0.1	0.4
Shellfish/molluscs	0.1	2.0
Overall	**6.0**	**3.7**

tivity among infants who received mixed or artificial feeding, verified by immune assays, was estimated at 4.5%, and the most common foods allergens were cow's milk proteins, egg protein and citrus fruits. Among infants who were exclusively breast-fed, food hypersensitivity was diagnosed in 0.5% of subjects [16].

In 10 European countries, a randomised telephone survey was performed in numerically representative groups of parents, asking about the occurrence of allergies in their children. Based on the responses concerning 8825 children, the prevalence of food allergy was evaluated at 4.7% (90% CI 4.2-5.2). According to the parents' responses, the largest age group affected by this allergy was that of children aged 2-3 years (7.2%). The most commonly indicated sources of food allergens were milk (38.5%), fruits (29.5%), eggs (19%) and vegetables (13%). The prevalence of food allergy varied depending on the country; it was the lowest in Austria (1.7%) and the highest in Finland (11.7%) (Tables 4 and 5) [19].

Surveys concerning the prevalence of food hypersensitivity were also carried out in Poland, among children and adults at the centre of Lodz [20, 21] and among adults in Silesia [22]. The results indicated a high prevalence of food hypersensitivity reporting by the respondents [20-22].

Multicentre and longitudinal, and not cross-sectional, studies are considered the most valuable in the epidemiology of allergic diseases. Examples of such studies are multicentre, international epidemiological studies on asthma and other allergic diseases in children (Interna-

Table 4. Prevalence of hypersensitivity to selected food allergens* in children in different European countries (reported by parents) [19]

	Austria	Belgium	Denmark	Finland	Germany	Greece	Italy	Poland	Slovenia	Switzerland
Prevalence [%]	1.7	4.9	2.5	11.7	3.0	4.8	3.9	8.3	4.6	3.1
Fish	0.0	4.7	0.0	19.8	4.8	8.3	6.1	1.1	7.0	17.4
Seafood	0.0	2.3	4.5	2.1	4.8	0.0	3.0	2.3	4.7	13.0
Wheat	28.6	9.3	4.5	12.5	19.0	0.0	15.2	6.8	23.3	13.0
Meat	0.0	4.7	4.5	1.0	4.8	10.4	15.2	10.2	9.3	8.7
Eggs	7.1	14.0	0.0	14.6	9.5	27.1	15.2	27.3	27.9	21.7
Milk	28.6	55.8	22.7	41.7	23.8	16.7	33.3	55.7	27.9	34.8
Fruits	50.0	23.3	22.7	35.4	66.7	14.6	27.3	26.1	27.9	26.1
Legumes	7.1	11.6	9.1	7.3	4.8	8.3	0.0	1.1	14.0	8.7
Vegetables	28.6	7.0	27.3	24.0	14.3	8.3	9.1	8.0	4.7	13.0
Nuts	7.1	9.3	13.6	13.5	19.0	2.1	9.1	6.8	9.3	13.0
Others	50.0	18.6	18.2	11.5	23.8	27.1	12.1	18.2	18.6	8.7

**Food reported as elicitors (multiple answers allowed)*

Table 5. Prevalence of clinical symptoms of food hypersensitivity in children in different European countries (reported by parents) [19]

Country	Skin	Respiratory system	Gastrointestinal system	Cardiovascular system	Other organs
Austria	71.4	14.3	7.1	14.3	21.4
Belgium	68.9	31.1	33.3	0.0	0.0
Denmark	63.6	9.1	27.3	0.0	9.1
Finland	56.3	21.9	49.0	0.0	6.3
Germany	77.3	9.1	27.3	4.5	9.1
Greece	81.3	10.4	20.8	4.2	10.4
Italy	65.6	9.4	28.1	0.0	6.3
Poland	84.6	20.9	15.4	0.0	0.0
Slovenia	79.5	15.9	13.6	0.0	4.5
Switzerland	62.5	25.0	29.2	8.3	4.2

tional Study of Asthma and Allergies in Childhood – ISAAC), which have also been carried out at selected allergology centres in Poland [23].

Until 2005, no multicentre study had been conducted using the same methodology (including the use of blind placebo-controlled food challenge test), assessing the epidemiology of food allergy. Such wide-scale research, both for children and adolescents and the adult population, have been started in various countries of Europe and in the world as part of the European multicentre research project EuroPrevall (6th EU Framework Programme). One of the main objectives of this programme is to determine the prevalence of food allergy in infants, children and adults in various countries of Europe and the world, and to identify the appropriate research tools for the detection of food hypersensitivity in people of all ages, to provide information on the economic and social costs of this disease (including the quality of life of patients and their families), and to develop regulations necessary for the implementation of an appropriate strategy to help patients suffering from this clinical problem, by the policy workers [24].

The centre of Lodz has been enrolled in the EuroPrevall project; at this centre, 1260 children aged up to 3 years have been included. It was shown that the prevalence of IgE-mediated food allergy in children aged 1-3 years is 2.8%. The diagnosis was made based on medical history, clinical examination, skin prick tests with food allergens, measurement of specific IgE and the results of double-blind placebo-controlled food challenge (DBPCFC). Positive skin tests with food allergens were found in 27% of subjects; specific IgE antibodies against food allergens (sIgE) were detected in 26% of these children, while 55% of the parents of these children reported allergic symptoms after eating certain foods. The most common foods responsible for the reported symptoms were egg protein (1.7%), cow's milk proteins (0.9%), peanuts (0.4%) and fruits (0.4%) (in the following order: oranges, apples, strawberries, kiwifruits) [24]. The reported prevalence of allergy to cow's milk proteins was lower compared to other epidemiological studies involving the youngest age group, including the Polish studies cited below. These results were explained by the authors with the fact that allergy tests were not performed in children in infancy (< 1 year old), where the prevalence of allergy to cow's milk proteins is the highest [12-18, 24].

In the same year, a study was also undertaken to evaluate the prevalence of food allergy in infants and young children in the agglomeration of Lodz. Data obtained from a survey were verified by individual personal history, physical examination, and in some of the surveyed children also by determination of specific IgE antibodies against food allergens (sIgE) or skin prick tests. It was found that 11.7% of the children were affected by food allergy. This percentage decreased with age, and at 3 years of age only 6% of patients were affected [25, 26].

Summary 2

Allergic diseases, including food allergy, are a major health problem throughout the human population in the world. Food allergy deserves particular attention because clinical symptoms may occur already at the youngest age, even in children fed only naturally (breast-fed). These symptoms may be predictive of a specific allergic disease in adulthood.

The prevalence of food allergy varies from country to country. These differences are conditioned, among other factors, by the subjects' age, dietary habits in the evaluated population, cultural or ethnic differences, as well as the degree of economic development of a given country.

The choice of methodology for epidemiological research significantly affects the obtained results. The prevalence of food allergy is higher in surveys than confirmed in an objective manner using food challenge tests or other accepted diagnostic methods.

So far, the few epidemiological studies on the prevalence of food allergy carried out in Poland were cross-sectional and involved a specific population or region. Current epidemiological and clinical information was collected in the studies conducted as part of the European research programme (EuroPrevall), in which the Polish group also participated; the reported results indicate that the prevalence of food allergy in our country among children aged 1 years to 3 years is 2.8%, and the prevalence of food hypersensitivity in children in infancy is 4.5%. The major food allergens causally associated with food hypersensitivity in Polish children include allergens from egg protein, cow's milk proteins, citrus fruits and peanuts.

In various European countries, the prevalence of allergy to cow's milk proteins in infancy has been estimated at 1.9-4.9%.

Type and nature of certain food allergens

Food allergens (trophoallergens) are biological compounds of animal or vegetable origin, mostly water-soluble glycoproteins with a molecular weight of 3-160 kDa (average 20-40 kDa), which are a part of our daily diet. Food allergens are divided into two classes based on their structure and physicochemical properties: class I food allergens are resistant to high temperatures and to the action of proteolytic enzymes or hydrochloric acid; class II food allergens are homologous with the glycoproteins of fruits, vegetables and pollens, and cooking or freezing changes their allergenicity by destroying their conformational epitopes. In the case of some allergens, exposure to high temperatures may increase their allergenicity, e.g. roasting peanuts, or cooking cow's milk (Maillard reaction) [27-34].

Consumed food products (theoretically all) or food additives are a common cause of allergy and/or the

occurrence of various clinical symptoms (allergic disease) in children and adults with hypersensitivity [33, 34]. Clinical experience shows that in the same individual, the process of allergisation and/or symptoms of allergic disease are often caused by not one but more food allergens [27, 30-34].

Cow's milk and dairy products, veal, beef

Two groups of cow's milk proteins are of clinical relevance: casein protein (Bos d8) and whey proteins (α-lactalbumin – Bos d4, β-lactoglobulin – Bos d5, bovine serum albumin – Bos d6, bovine immunoglobulin – Bos d7). Cow's milk casein differs from milk casein of other related mammals more than whey proteins. Cow's milk casein contains 4 fractions: α_{s1}, α_{s2}, β, κ. Patients are often allergic to the fractions of α-casein (100%) and κ-casein (approx. 91.7%). Among patients with allergy to cow's milk protein, in approximately 80% the allergic reactions are associated with α-lactalbumin. The percentage of patients who are allergic to cow's milk bovine serum albumin (a protein also found in veal and beef meat) is estimated at 0-88%, but clinical symptoms after ingestion of a beef or veal meal occur in about 20% of allergic people [11, 27, 31].

The largest biological and immunological similarities exist between the proteins of cow's, goat's and sheep's milk. Compared to cow's milk proteins, the composition of proteins in the milk of mare, donkey and camel is more varied. Camel's milk, like human milk, contains no β-lactoglobulin, a fraction present in the milk of other ruminant mammals. This protein is the cause of allergies and/or allergic symptoms in about 13% to 76% of patients [11, 27, 31].

People allergic to cow's milk may therefore experience cross-reactions after consuming milk or meat of other ruminants.

Allergy to cow's milk proteins is clearly more common than allergy to beef, assessed at 10-20% among those allergic to milk. Therefore, total elimination of beef from the diet of children with allergy to cow's milk proteins is not justified in all cases; however, all patients allergic to beef should temporarily eliminate cow's milk and its products from the diet [11, 27, 31].

Hen's egg protein – proteins of other birds

Egg protein allergens are among the most common food allergens. This allergy occurs more commonly in children than in adults, and the egg white causes more allergies than the yolk. Egg white is a protein complex containing 23 fractions of possible allergen properties. The main allergens include ovomucoid (Gal d1), ovalbumin (Gal d2), ovotransferrin (conalbumin) (Gal d3) and lysozyme (Gal d4).

The main allergen in the yolk is α-livetin, also present in blood and feathers of birds. This protein is responsible for cross-reactions to feather, manure and meat albumin, not just from chickens but also many other birds. In children under 2 years of age with clinically overt sensitivity to hen's egg proteins, sIgE antibodies are directed mainly against ovalbumin, ovomucoid and yolk proteins. Allergens in hen's egg white give cross-reactions to similar allergens from other birds proteins (hen, turkey, goose, duck, quail, gull, and others), resulting in the bird-egg syndrome. Quail egg ovomucoid is also a potent allergen and proteinase inhibitor; despite this, quail eggs are often incorrectly recommended in Poland for children allergic to hen's egg allergens [27, 32].

Contact with masked allergens (f.e. proteins of hen's egg, cow's milk, soy, peanuts), hidden in deli and bakery goods, confectionery and others products, also creates a potential possibility of sensitization in individuals predisposed to allergy [28, 34].

In the case of class II allergens, body sensitization and/or allergic disease occur as a result of their penetration into the digestive tract or respiratory system, leading to the development of an allergic cross-reaction [28].

Many natural substances or chemicals (food additives) used in the production, processing and storage of food, or added to the final product, become the cause of individual hypersensitivity. Their purpose is to improve the organoleptic quality, aesthetics or stability of food products. As an unintended consequence, they may trigger the pathogenetic mechanisms of non-allergic hypersensitivity (intolerance) and the occurrence of disease symptoms [34].

Cross-reactivity cannot be ignored in the aetiopathogenesis of food allergy. The basis for this phenomenon is widely understood similarity of allergens, especially food and airborne antigens, and above all common epitopes. Cross-allergy means the coexistence of clinical symptoms in a person with simultaneous hypersensitivity to at least two allergens (oral, inhaled and/or contact allergens) showing homology of the amino acid sequence, especially within the epitopes (primary structure of the peptide chain), or when the three-dimensional conformation of the two protein molecules can bind with their specific antibody [11].

Recent achievements, mainly in the fields of molecular biology and immunology, allowed us to understand that cross-reactions do not result merely from the nature of allergens (food, inhalation), but the nature of the construction of the main antigens, recognized by the host immune system, stimulating it to the synthesis of specific antibodies (mainly IgE). Taking into account the immune mechanisms of cross-allergy, it can be described as a phenomenon that only occurs when IgE antibodies, produced as a result of contact with one allergen, recognize and bind to a protein of similar structure, which originates from a different allergenic source. The effect of such reactions leads to individually diverse clinical manifestations of cross-allergy [35, 36]. The phenomenon of cross-allergy is also illustrated by data contained in Tables 6 and 7 [37, 38].

Table 6. Clinical cross-reactivity among animal and plant allergens [37]

Allergen origin	Food product	Cross-reaction	Percentage*
Animal	Egg	Chicken meat	< 5
	Cow's milk	Beef/veal	Approx. 10
	Cow milk	Goat milk	Approx. 90
	Beef/veal	Lamb	Approx. 50
	Fish	Other fish species	> 50
Plant	Peanuts	Legumes (except lentil)	< 10
	Soybean	Legumes	< 5
	Wheat	Other cereal grains	Approx. 25
	Peanuts	Tree nuts	Approx. 35
	Tree nuts	Other nuts	> 50

**It should be noted that patients frequently have positive PST or RAST results to other members of a plant family or animal species (approx. 80%), but this does not correlate with clinical reactivity. Clinical reactivity is typically very food-allergen specific*

Table 7. Risk of clinical symptoms during an allergic cross-reaction [38]

Allergy to:	Risk of reaction to:	% risk
Cow's milk	Goat's milk	92.0
Molluscs/shellfish	Other seafood	75.0
Fish (salmon)	Other fish	50.0
Tree nut (walnut)	Other tree nuts (Brazil, cashew, hazelnut)	37.0
Peanuts	Other legumes (peas, lentils, beans)	Approx. 5.0
Grain (wheat)	Other grains (barley, rye)	20.0
Latex (latex glow)	Fruits (kiwi, banana, avocado)	35.0

Genetically modified foods can be a source of food (hypoallergenic) with reduced or altered potential to cause allergy in humans. Such products include rice, tomato, lettuce and soybeans. However, their therapeutic-nutritional use in allergic people needs further research [39, 40].

Summary 3

Food allergens (trophoallergens) are biological compounds of animal or vegetable origin, mostly glycoproteins with a molecular weight of 3-160 kDa (average 20-40 kDa), which are contained in the basic food products ingested by humans.

Both food allergens from selected food products (cow's milk proteins, chicken egg proteins, meat, fish, grain products, vegetables and fruits), and chemicals which are added to them, are a common cause of various clinical symptoms in hypersensitive people, more frequently in children than in adults.

In older children and adults, so-called cross-allergy may occur, which causes allergic symptoms due to concurrent hypersensitivity to food, inhaled and/or contact allergens.

Conditioning factors and pathomechanism of food allergy

Food allergy arises with "failing" tolerance, which is a kind of immune hyporeactivity of the human body "to contact" with food allergen(s). In this case, a pathological phenomenon contrary to tolerance develops, namely "food hypersensitivity". The development of allergic food hypersensitivity (food allergy), as well as other allergic diseases, is conditioned by combined genetic factors, environmental exposure to allergens (environmental factors) and additional nonspecific factors (adjuvant factors), such as exposure to tobacco smoke, air pollution, or infection (Fig. 3) [41-43].

Food sensitization is most common in children in the youngest age groups (0-3 years). This period of life is characterised by anatomical and functional immaturity of the protective barriers of the body (especially in the digestive tract) and the immaturity of many immune mechanisms. These conditions may predispose to increased absorption of food allergens in the body [11]. The above biological predispositions, along with additional contribution of "supporting" factors (constitutional, infective and related to environmental hygiene conditions) may represent the triggering mechanism for the development of food allergy at any age, especially in childhood [30, 33, 41-43].

The development of food allergy, like any allergic reaction, occurs in two phases [30, 33, 41-43]. When a person is predisposed to atopy or allergy (due to genetic factors), the first step of this process is the primary contact of the immune system with an environ-

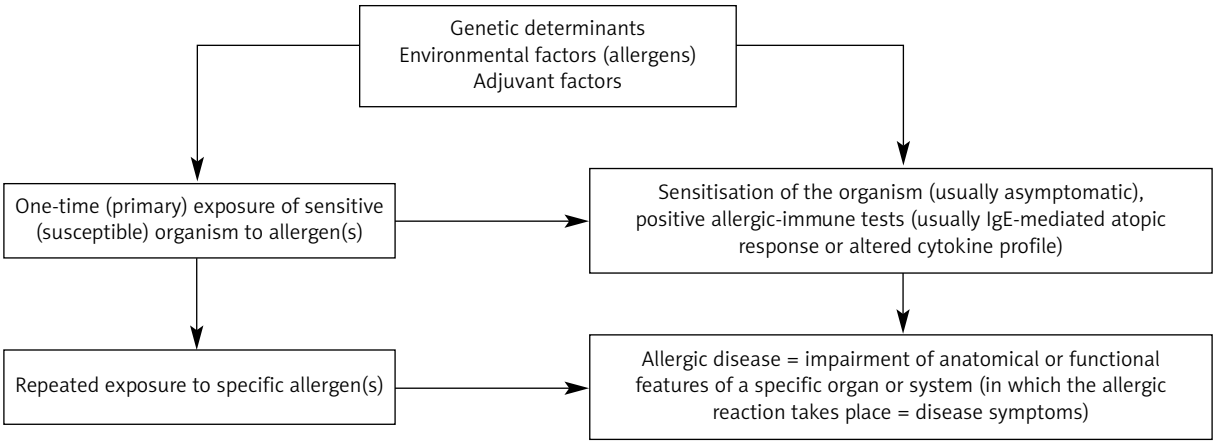

Fig. 3. Induction and expression of allergic disease (modification based on [41, 42])

mental allergen (food). This contact is "saved" in the person's immune memory as sensitization (priming). This phenomenon is usually clinically asymptomatic. Repeated exposure to the same allergen in people with a genetic predisposition to atopy leads to excessive synthesis of sIgE, and in patients with a predisposition to allergy it causes synthesis of pro-allergic cytokines [30, 33, 41-43]. Sensitization of the body (atopic or allergic) is a prerequisite for the development of food allergy or other allergic disease in the case of repeated exposure to the same allergen. The phenomenon of body sensitization does not mean, however, that every sensitized person must become allergic. Some sensitised people do not suffer from allergy; beyond the existing process of sensitization an allergic reaction is also determined by other factors (individual and environmental) [30, 33, 41-43].

Immune and allergic pathogenetic mechanisms of the development of hypersensitivity were described by Gell and Coombs in 1963 [30, 33, 44, 45]. The frequency of immune response in patients with allergy to cow's milk proteins, taking into account the above pathogenetic mechanisms, was examined by Chandra *et al.* The results of these studies are presented in Table 8 [46].

Studies have shown that the estimated percentage of IgE-mediated immediate mechanism (type I allergic reaction) is about 48%. Also other non-IgE mediated pathogenetic mechanisms play an important role in triggering disease symptoms. In approximately 18-20%, sensitised T-cells were involved in the disease process (type IV reaction), reactions with the participation of immune complexes (type III reaction) accounted for about 10%, and cytotoxic reactions (type II reaction) approximately 6%. Mixed IgE-mediated/non-IgE mediated mechanisms were responsible for clinical symptoms in about 18% of examined patients [46].

Hypersensitivity reactions to food additives may involve various non-immune pathogenetic mechanisms (enzymatic disorders, pharmacological effects, conduction disturbances in the central and peripheral nervous system, release of allergic reaction mediators without the involvement of a specific allergen, and others) [33, 34].

In older children and adults, cross-allergy may occur due to simultaneous hypersensitivity to food, airborne and/or contact allergens [35, 36].

The child can also become sensitized *in utero* by allergens from foods eaten by the pregnant woman. Similarly, breast-feeding may cause sensitization of the child with food allergens consumed by the mother and passing into the breast, and thence into breast milk. This should explain hypersensitivity symptoms which appear shortly after birth in some children who are fed only naturally (approx. 0.5%) [11, 47, 48].

Table 8. Type and prevalence of pathogenetic mechanisms in hypersensitivity to cow's milk proteins in children [33, 44, 46]

Mechanism of immune response sensitized to foods according to Gell and Coombs [44]		Percentage of patients in the studies of Chandra *et al.* [46]
Type I	Immediate hypersensitivity	48
Type II	Antibody-mediated cytotoxicity	6
Type III	Immune complex	10
Type IV	Delayed hypersensitivity	18
Mixed type	More than one type of reaction	28

Summary 4

The development of food allergy, like other allergic diseases, is due to the adverse impact on the human body of genetic, environmental and adjuvant factors.

The more common occurrence of food allergy symptoms in the youngest age is associated with physiological immaturity of immune mechanisms (delayed immunological maturation), and the specific morphological-immune condition of the gastrointestinal system (anatomical-physiological immaturity, immaturity of the body's protective barriers). These conditions increase the risk of the child gastrointestinal mucosa damage by infection, what promotes the increased absorption of food allergens from the intestinal lumen into the blood.

The development of food allergy is determined by four different allergic-immune mechanisms, classified and described by Gell and Coombs.

It is estimated that the IgE-mediated mechanism (food allergy) is responsible for about 48-50% of food hypersensitivity symptoms. In the remaining patients, food hypersensitivity symptoms are the result of other pathogenetic mechanisms, non-IgE mediated, mixed (IgE-mediated/non-IgE mediated) or cellular.

During pregnancy the fetus may become sensitized *in utero* to allergens contained in foods consumed by the pregnant woman. There is also the possibility of sensitization of the child after birth, in the period of exclusive breast-feeding. As a result of migration of allergens from the gastrointestinal tract to the mother's breast, they can pass with breast milk to the breastfed infant's gastrointestinal tract. These processes may explain hypersensitivity symptoms seen in a group of children who are fed only naturally.

Clinical course of food hypersensitivity

Isolated clinical symptoms, or a syndrome of a variety of symptoms, found in patients with food allergy are the end result of a specific pathogenetic mechanism, started by eating harmful food or food additives [8, 49-51].

Clinical symptomatology of food allergy in children and adults is rich and varied [8, 10, 14, 28, 33, 42, 49-51]. Subjective and objective symptoms can involve only one organ or system, but much more frequently two or more organs are involved, and the respective symptoms occur simultaneously [8, 14, 42, 50].

Clinical symptoms of food allergy are non-specific. Consumption of the same harmful food by different patients can trigger different clinical symptoms. The time to the onset of symptoms caused by the same food can also vary. These differences result, among other factors, from individual variability of the effector organ for the allergic reaction, and the type of pathogenic mechanisms involved in the allergic reaction (immediate, late or mixed) [44-46]. The consumed food should be considered the sole cause of the disease only when there is a relationship between its consumption and the reported symptoms, ie when its elimination from the diet causes complete or significant relief of clinical symptoms, and its reintroduction causes the recurrence of the same symptoms [8, 10, 14, 33, 50, 51].

The severity of an allergic disease is determined, among other factors, by the location of the disease process (single- or multi-organ), and the clinical course of the disease can be individually varied in different patients, even if the site of the allergic process is the same organ or system [10, 14, 51, 52].

At developmental age, the clinical picture of food allergy may change. Anatomical and functional improvement of the organs and systems involved in allergic reactions leads to recovery, i.e. "growing out" of food allergy in some patients. For others there may be changes in clinical symptoms and new symptoms of allergic disease may occur (so-called allergic march or allergic marathon) [11, 53, 54]. Contact with other allergens (airborne or contact), and also changes in the current target organ of the allergic reaction may play an important role in the unfavourable dynamics of the disease [8, 41, 50-55].

Hypersensitivity to cow's milk proteins is a "model" example of the most common allergic disease in children, causatively related to the harmful effects of food on the child's body. It occurs in about 2-3% of infants and it is the most common cause of post-feeding discomfort in this age group [10]. It may cause symptoms of immediate (IgE-mediated), delayed and late (non-IgE mediated), or mixed (IgE-mediated and non-IgE mediated) reactions [8, 14, 18, 46, 48-50, 56-60]. Clinical symptoms of allergy to cow's milk proteins are characterized by significant diversity [10, 11, 14, 59]. The first classification of the clinical picture of allergy to cow's milk in infants was performed by Clein (Table 9) [56].

Since then, the classic clinical picture of allergy to cow's milk and other foods has changed worldwide. Currently the cutaneous form dominates, with a variety of allergic disorders, including atopic dermatitis (AD), often with severe clinical course. The incidence of acute diarrhoea with subsequent enteropathy, leading to chronic malnutrition in young children, has significantly decreased. Besides of skin manifestations, other common disorders related to the food hypersensitivity are observed, including: impaired motility of the upper and lower gastrointestinal tract (gastroesophageal reflux, constipation), food-induced inflammation of the small intestine and the colon (enterocolitis, proctitis, enteropathy), mucosal eosinophilic infiltration in various organs of gastrointestinal tract. These disorders often manifest themselves as chronic or recurrent abdominal pain, especially in older children [8, 10, 11, 14, 50, 59, 60].

Children with a respiratory response to the harmful food may present with wheezing, recurrent symptoms from the throat, tonsils, larynx, and/or ears, with enlargement of regional lymph nodes. These disorders are usu-

Table 9. Clinical forms of allergy to cow's milk proteins [56]

Gastrointestinal
Skin
Respiratory system/ears
Constitutional
Anaphylactic shock
Other forms (less common)

Table 10. Differential diagnosis of allergy to cow's milk proteins [10]

• Metabolic disorders	• Allergy to other foods (e.g. hen's eggs, soy, wheat, fish)
• Anatomical abnormalities	
• Coeliac disease	• Allergy to other substances (dust, animal dander, moulds)
• Enteropathies	
• Pancreatic insufficiency	• Malignancy
• Non-allergic adverse reactions to food (e.g. lactose or fructoseintolerance)	• Infections
	• Sepsis

ally not associated with fever. The systemic form of food hypersensitivity may also manifest as chronic malnutrition, an isolated, temporary rise in body temperature, or iron deficiency anaemia. There are also less common clinical forms such as bedwetting, proteinuria, allergic vasculitis, hypertransaminasaemia, neurological symptoms (migraine) or other psycho-emotional symptoms, and joint ailments (probably related to food hypersensitivity). This requires a careful differential diagnosis (Table 10) [8, 10, 59, 61-63].

New proposals for classification of clinical allergy to cow's milk proteins take into account the severity of the disease (Table 11), or the pathogenetic mechanisms (Table 12) [8, 11, 14, 50, 59].

In terms of the time between exposure to food and the onset of allergic reactions, they can be divided into immediate, delayed and late reactions. Food induced immediate allergic reactions usually occur within a few minutes to about 4-6 h after food consumption and are IgE-mediated reactions. In the European nomenclature, they meet the definition of food allergy; clinical examples include anaphylactic shock, gastrointestinal anaphylaxis, urticaria, Quincke's oedema, cross-reactions (allergy to latex and foods), and oral allergy syndrome [8, 18, 28, 50, 64, 65, 66].

Delayed or late food hypersensitivity reactions occur within a few to several hours after eating the food; these are non-IgE mediated immune reactions [28, 42, 67-71]. These reactions are mainly mediated by T-cells, and they

Table 11. Clinical forms of allergy to cow's milk proteins (modification based on [59])

Clinical form CMPA	One or more of the following symptoms
Mild or moderate	Gastrointestinal symptoms: • Frequent regurgitation, vomiting • Diarrhoea, constipation (presence or lack of skin lesions around the anus) • Blood in the stool • Iron deficiency anaemia
	Dermatological symptoms – atopic dermatitis
	General symptoms (anxiety or abdominal colic)
	Other symptoms (rare)
Severe*	Gastrointestinal symptoms: • Failure to thrive due to diarrhoea or regurgitation/vomiting • Loss of appetite/refusal to feed • Moderate to high loss of blood in the stool
	Dermatological symptoms: • Severe form of atopic dermatitis • Impaired growth
	Respiratory: • Acute laryngoedema, bronchial obstruction
	Other: • Anaphylactic shock • Severe anaemia (iron deficiency) • Hypoalbuminaemia

**ALARMING SYMPTOMS!!! immediate referral to a specialist*

Table 12. Clinical manifestation of food hypersensitivity based on the pathogenetic mechanism of the disease [8]

IgE-mediated pathogenetic mechanism	
Gastrointestinal tract	Oral allergy syndrome
	Gastrointestinal anaphylaxis
Cutaneous	Urticaria
	Angioedema
	Morbilliform rashes and flushing
Respiratory system	Acute rhinoconjunctivitis
	Bronchospasm (wheezing)
Systemic reaction	Anaphylactic shock
Mixed pathogenetic mechanism IgE and cell mediated	
Gastrointestinal	Allergic eosinophilic oesophagitis
	Allergic eosinophilic gastroenteritis
Cutaneous	Atopic dermatitis
Respiratory	Asthma
Cell-mediated pathogenetic mechanism	
Gastrointestinal tract	Food protein-induced enterocolitis
	Food protein-induced proctocolitis
	Food protein-induced enteropathy syndromes
	Coeliac disease
Cutaneous	Contact dermatitis
	Dermatitis herpetiformis
Respiratory	Food-induced pulmonary hemosiderosis (Heiner syndrome)

are manifested by clinical syndromes with symptoms from the gastrointestinal tract, often occurring in infants and young children.

Food protein induced proctocolitis

Proctocolitis is the most common and the mildest type of non-IgE mediated clinical reaction induced by harmful foods.

This clinical problem mainly affects infants with food hypersensitivity, who appear to be healthy, and the only noticeable abnormality is stools which may contain mucus and/or blood streaks, with a tendency to anaemia and reddening of the skin around the anus (perianal intertrigo, typical of this syndrome). These symptoms occur in the first months of life. The lack of systemic symptoms such as vomiting, diarrhoea, or inhibition of weight gain, is helpful in differential diagnosis from other causes (e.g. infection, anal fissure). These symptoms are most commonly caused by hypersensitivity to cow's milk, less commonly to soy products, and particularly to formula containing hydrolysates of cow's milk proteins. Identical symptoms can occur in infants exclusively breast-fed by mothers eating a general diet. If the child's symptoms persist, then they become an indication for the elimination of (most commonly) cow's milk, egg white or soy from the breast-feeding mother's diet. Continued lack of clinical improvement, despite the use of such a dietary intervention in the mother, may indicate the need to consider the appropriateness of continued breast feeding, and replace it with casein fraction hydrolysate, and in an extreme situation (persistent bleeding, anaemia), even an elementary formula (amino acid formula – AAF).

In children fed with milk or soy formula who manifest persistent symptoms of proctocolitis, leading to anaemia, cow's milk protein hydrolysates should be first used therapeutically, and in the case of anaemia and/or dyspeptic symptoms, an elementary formula should be considered.

These symptoms usually disappear by 2 years of age. After this period of dietary and pharmacological management, an attempt should be made to gradually introduce the eliminated foods. During the expansion of the child's diet it is recommended to test the stool for blood content.

Endoscopy of the lower gastrointestinal tract is helpful in the diagnosis of this syndrome, as it allows one to confirm (or rule out) the presence of localised or diffuse oedematous and erosive lesions of the mucosa, and in histological examination, eosinophilic infiltration and overgrown lymphoid follicles. Allergic and immune assays (skin tests, sIgE to food allergens) tend to produce negative results because the bowel lesions are caused by underlying pathogenic mechanisms of food hypersensitivity which are non-IgE mediated [8, 10, 28, 49, 50, 66, 72].

Food protein induced enterocolitis syndrome

Clinical manifestation of this syndrome can occur at any age, but usually the youngest children (in the first months of life) are affected. The typical symptoms of inflammation of the small intestine and the colon include irritability, recurrent vomiting after feeding (within 1 h to 3 h), profuse sweating during or immediately after a meal, and prolonged diarrhoea. Common symptoms also include abdominal distension, bloody stools or heavier bleeding from the lower gastrointestinal tract, and inhibited growth of the child. Microcytic anaemia has been reported; it may be a manifestation of iron losses as a result of gastrointestinal bleeding (occult or overt). Iron treatment does not improve blood cell counts, as long as the causal factor (harmful food) is not eliminated from the child's diet. Hypersensitivity to cow's milk proteins is believed to be the main cause of these symptoms. In about 50% of cases these problems are associated with the consumption of other foods, containing e.g. soy proteins, cereal proteins, rice, peas, poultry meat. Intake of harmful foods can cause acute crisis with collapse of the

child's general condition (in about 20% of affected children) as a consequence of vomiting, diarrhoea, dehydration, and acidosis. The child's clinical condition and appearance suggest a septic process, and an increased peripheral blood leucocyte count may lead to misdiagnosis. Prolonged diarrhoea and vomiting, along with impaired absorption and digestive functions of the intestine, can lead to symptoms of malabsorption with intestinal protein loss.

Endoscopy of the lower gastrointestinal tract reveals generalised inflammatory and oedematous lesions of the mucosa, which in exceptional cases may resemble the morphology of ulcerative colitis. Biopsy of the large intestine shows diffuse inflammatory lesions with infiltration of mononuclear cells and crypt abscesses of the mucosa. The underlying cause of the intestinal lesions is non-IgE mediated pathogenetic mechanisms of food hypersensitivity [10, 28, 49, 66, 67].

Food protein-induced enteropathy

This pathology is a consequence of the two abovementioned syndromes being unrecognized and inadequately treated. Persistent diarrhoea, poor appetite, frequent vomiting, bloating and anaemia lead to disturbances in body weight gain. Laboratory signs such as anaemia, hypoproteinaemia, hypocalcaemia, and others, form the whole clinical picture of a child with chronic disorders of digestion and absorption [8, 28, 49, 50, 66, 68, 69].

Allergic eosinophilic oesophagitis; allergic eosinophilic gastroenteritis

The clinical picture of food hypersensitivity in children and adolescents may also include syndromes in which mixed pathogenetic mechanisms (IgE-mediated and non-IgE mediated), induced by harmful food, produce symptoms overlapping with each other. This group of pathologies in children includes atopic dermatitis, allergic eosinophilic oesophagitis and allergic eosinophilic gastroenteritis. Since the problem of atopic dermatitis seems to be widely known, the authors focused on the characteristics of the two other syndromes of this group [8, 10, 28, 49, 50, 66].

Both diseases occur in patients from early childhood to the age of youth. The disease consists in eosinophilic infiltration of different layers of the wall of the oesophagus, stomach and intestines. The depth of this infiltration (mucosa, submucosa, serous membrane) correlates with the severity of the disease [8, 10, 49, 50, 66, 70-72].

Allergic eosinophilic oesophagitis manifests as chronic persistent symptoms of gastroesophageal reflux (nausea, vomiting with blood), dysphagia and epigastric pain in the absence of improvement after conventional antireflux therapy [66, 70, 71, 73].

With a negative result of pH-metry, the diagnostic process consists in taking sections from the oesophageal mucosa and finding eosinophilic infiltration in these samples (10-20 eosinophils per high-power field). The treatment involves a comprehensive approach: elimination of the harmful food and the use of anti-inflammatory drugs (steroid therapy, antileukotriene drugs) [66, 70, 71, 73].

Allergic eosinophilic gastroenteritis can also occur in infancy and may be a significant cause of weight gain and growth disturbances. Abdominal pain, vomiting with blood, blood in stool and intestinal protein loss syndrome are typical symptoms of this disease in older children. Atopic mechanisms of the disease (positive tests for IgE antibodies) are found in approximately 50% of these patients. It must be noted, however, that the pathogenesis of this disease is mixed and also involves non-IgE mediated and cellular (T-cell) mechanisms. The correlation of positive allergy tests with the effects of elimination of potentially harmful foods, which include milk protein, soy, cereals, egg white, and others, is usually low [10, 66, 73].

The lack of clinical improvement after 3 to 8 weeks of using an elimination diet is a basis for introducing an elementary diet in patients of both groups; this diet should continue for several months. After this period it is recommended to perform follow-up organ biopsy to evaluate the severity of eosinophilic infiltration. An improvement in the morphology of the intestinal mucosa allows one to continue treatment with an elementary diet, with the introduction of one new food every 2 weeks, starting with fruits or vegetables [66].

Some (naturally) breast-fed babies may also exhibit symptoms of food hypersensitivity as early as in the first hours or days of life after birth. These reactions may have a violent clinical course. As mentioned above, the cause triggering the disease symptoms are allergens penetrating through blood and lymph vessels from the gastrointestinal tract of the nursing mother to her breast, and then into the infant's body, along with the consumed milk. Clinical manifestation of allergy in these children is individually varied and it does not differ in the nature of symptoms from symptoms reported in artificially fed children with food hypersensitivity [47, 48].

Summary 5

The clinical picture of food hypersensitivity in children and adults represents the great variety of the symptoms that may affect a single organ (system) or multiple organs (systems). Simultaneous multi-organ (multi-system) manifestations are more common.

In food hypersensitivity, both the group of associated clinical symptoms and each symptom in isolation are the end result of IgE-mediated, non-IgE mediated, mixed or cellular pathogenetic mechanisms, triggered by the consumption of harmful food, cross-allergy or food additives.

The variety of symptoms triggered by the sensitising food, as well as their potential number, became the basis for classification into specific "clinical forms of food hypersensitivity". As with allergy to cow's milk protein, hyper-

sensitivity to other foods can also be divided into classic and less common clinical syndromes associated with this disease.

At developmental age the clinical picture of food allergy can vary with age (so-called allergic march), which results from anatomical and functional improvement of vital organs affected by the harmful allergen (food).

Food allergy diagnostics

The diagnosis of food allergy is a complex, long-term and time-consuming process, involving analysis of the atopic/allergic personal and family history, a thorough analysis of clinical signs, as well as correctly planned additional tests [79-96].

The underlying causes of difficulties in diagnosing food hypersensitivity include complex pathogenetic mechanisms (immune, non-immune, mixed) responsible for disease symptoms, and biological characteristics of antigens, which, after digestion in the gastrointestinal tract, may become a source of new antigens (neoantigens). Due to these causes, there is so far no simple, inexpensive and sensitive laboratory test which would allow clear identification of the main causative factor of food allergy [74, 76-78].

The commonly used methods and laboratory tests are mainly intended for diagnosing the cases of food hypersensitivity in which IgE-mediated pathogenetic mechanisms are involved; they represent about 50% of patients. For the diagnosis of other pathogenetic mechanisms of food hypersensitivity, more complex, technically difficult and time-consuming techniques and methods are used, available primarily in specialised clinical centres and research laboratories [8, 33, 42, 50, 66, 79-96].

The first stage of diagnostics is to collect the patient's history in order to determine the beginning and type of complaints, their organ location, evolution and dynamics associated with the growing process of the affected child. To complete the history, a physical examination is performed, including an assessment of the general condition, organ abnormalities, as well as the presence or absence of constitutional features of allergy [8, 28, 42, 50, 74, 84].

Allergological-immune assays are used in the diagnostics of food allergy to confirm or rule out atopic (IgE-mediated) mechanisms as the cause of the clinical symptoms. In this regard, we have the ability to determine specific IgE (sIgE) in the serum. We also use skin tests with food allergens (commercial, native), and airborne allergens [8, 11, 18, 28, 42, 50, 60, 77, 84-88, 93, 96].

Prick skin tests (PST) are typically performed using the commercial extracts of antigens; they are a rapid, inexpensive method for detecting IgE antibodies on the surface of the mast cells of the skin. A negative result indicates the lack of participation of these antibodies in the IgE-mediated pathogenetic mechanism of food-induced allergy in the diagnosed patient. The negative predictive value of these tests is 90%. A positive result of the test (wheal diameter of > 3 mm, compared to a negative control test) does not clearly confirm the diagnosis of food allergy (30-40% positive predictive value); however, it confirms sensitization to the allergen (food) tested. In fact, a positive result of the test is not an equivalent of the clinical reactivity of the body, and the wheal diameter does not correlate with the severity of the disease [50]. Such a result must be confirmed in a food challenge test [50, 66]. Often the definitive diagnosis is made by correlating the positive results of the tests with information from the patient's history and analysis of the disease symptoms. The authors at various centres assessed the correlation between wheal diameter and the likelihood of the occurrence of clinical symptoms after ingestion of a sensitising food [28, 59, 77, 85, 96]. According to Sporik *et al.*, wheal diameters are as follows: for cow's milk proteins > 8 mm; for egg white protein > 7 mm; for peanuts > 8 mm [85]. The following issues were discussed in the commentary on these studies: the varying wheal diameter for commercial allergens depends on allergens' different sources, and relates on the study population dietary habits, place of residence, and race. Skin tests with commercial allergens and fresh products (native tests) may be the cause of an extremely rare adverse reaction during the test; the risk of its occurrence increases when native allergens are used [92].

The second method for determining the IgE-mediated pathogenetic mechanism in food allergy is the determination of specific antibodies (sIgE) in the serum, directed against specific allergens (foods) – Immuno CAP system. This test is more expensive than SPT [74, 77, 84, 86-88, 92-96].

A positive result of the sIgE test, falling within the range of values for class 2 of e.g. a CAP assay (0.7-3.5 kU/l) in a person without clinical symptoms, also only proves sensitization [74, 77, 84, 93]. In this case, the procedure is the same as for the interpretation of skin tests – a food challenge test determines the diagnosis. Also for this test were established the positive predictive values of specific antibodies (sIgE) for which there is 95% likelihood of clinical response after ingestion of a specific food (Table 13) [77, 86-88, 96].

A new method for detecting allergen-specific IgE antibodies is the ISAC assay (Immuno Solid-phase Allergen Chip). It is a combination of the latest achievements in the research on the structure of allergens and biochip technologies and is based on the use of allergens of a defined molecular structure (pure allergens). This allows the determination of sensitization to individual allergenic proteins contained in the mixture of allergens (allergen extract), as well as precise identification of molecules that cause allergic reactions (component-resolved diagnosis, CRD). The advantage of this test method over the other assays previously used in food allergy diagnosis has not been documented until now. There are also no studies

comparing the sensitivity and specificity of this method compared to the food challenge test [11, 88].

It seems that the described method will be applied primarily in the diagnosis of cross-allergy where it is important to determine the profile of cross-reacting sensitizing allergens. The previously used extracts show allergen instability and contain trace amounts of specific allergens, which affects the diagnostic effectiveness of these methods. The currently introduced methods will allow one to detect more accurately which of the allergens contained in the consumed food causes the patient's allergy, considering that each patient responds with an individual clinical response to allergens contained in the same food product [88, 94].

In conclusion, a negative result of these tests in a person presenting with symptoms is a basis to conclude that the disease symptoms are not the result of an IgE-mediated response induced by the harmful food. They are probably a result of triggered non-IgE mediated pathogenetic mechanisms, and possibly other coexisting causes of the disease (see Table 10) [10, 28, 33, 50, 77, 84].

In some conditions (atopic dermatitis, eczematous lesions, gastroesophageal reflux, eosinophilic oesophagitis, food-induced enterocolitis), when a food hypersensitivity reaction triggered by a cellular, non-IgE mediated pathogenetic mechanism is suspected, then diagnostic patch skin tests (PST) are performed [11, 89, 90, 92, 95, 96]. This test, which involves occlusive application of a food allergen to the skin (ideally for 48 h), allows one to detect or rule out a late cellular response, assessing skin reaction (the number of follicles, not erythema) 48 h and 72 h after the application of the allergen. Patch skin tests in conjunction with specific IgE antibody concentration assay can detect most cases of sensitization to food allergens, especially milk and egg white. A weakness of this test is the lack of standardisation of this test method and the divergent opinions of allergists, which makes the predictive value of PTS a subject of dispute [94]. Other laboratory tests to confirm or rule out allergic-immune reactions type II, III and IV according to Gell-Coombs, due to the required effort and high cost, are performed in highly specialised immunology and allergology laboratories [4, 11, 18, 33, 42, 66, 75, 84, 89, 90, 92, 95, 96]. According to the authors of the EAACI and WAO document, the presence of specific food antibodies in the IgG class (sIgG) in the patient's serum has no diagnostic significance in food allergy, but only indicates previous exposure of the body to a given allergen (food) [3, 11]. Elevated sIgG4 concentrations may indicate the ongoing process of acquiring tolerance to previously harmful food in patients with IgE-mediated food allergy [11].

A method allowing one to clearly determine the existence of food hypersensitivity, or lack thereof, as well as to confirm the reliability of the tests described above, is the result of bioassay challenge with the suspected food (Tables 14 and 15) [74, 79-83, 96].

Table 13. Food-specific IgE levels that give 95% likelihood of reaction [8, 9, 77]

Allergen	sIgE level [kIU/l]
Cow's milk (< 2 years of age)	≥ 5.0
Cow's milk (> 2 years of age)	≥ 15.0
Eggs (< 1 year of age)	≥ 10.9
Eggs (> 1 year of age)	≥ 13.2
Peanuts	≥ 14.0
Nuts	≥ 15.0

This test is crucial in demonstrating the relationship between a consumed food and clinical symptoms that occur as a result of a specific pathogenetic mechanism of the allergic reaction. These mechanisms determine the approximate time of occurrence of symptoms, and the time elapsing after the intake of the harmful food (immediate, delayed, late symptoms) [8, 50, 66, 77, 84]. This test, depending on the patient's age, is done in two ways: an open challenge test (up to 3 years old), or a blind food challenge test, using placebo (single-blind placebo controlled food challenge test – SBPCFC; double-blind placebo-controlled food challenge – DBPCFC). Patients receiving anti-allergic drugs or antihistamines should eliminate them for at least 72 h (or more, depending on the type of drug) before the food challenge test. In a blind challenge test, the patient receives the food suspected to cause the adverse effects, in a masked form, alternately with placebo. It is started from the initial dose for a given food and continues in increasing doses to the amount normally consumed. In order to avoid a shock reaction, a lip test is performed before oral administration of the tested food [91, 96]. If the patient has a shock reaction or there is a risk of such a reaction during the challenge (e.g. in patients with Quincke's oedema and oral allergy syndrome [OAS]), the test should always be performed in a hospital ward (specialist office), in the presence of a doctor and a nurse, in a room where lifesaving equipment and drugs are readily available (intubation kit, oxygen, auto-syringe with epinephrine) [66, 77, 84]. The estimated time of reaction after food ingestion, and thus the time of observation of the patient during a challenge test, depends on the clinical manifestations of allergic disease and is longer in gastrointestinal disorders (e.g. eosinophilic oesophagitis, eosinophilic gastroenteritis). According to Nowak-Wegrzyn, patients with symptoms of allergic inflammation of the gastrointestinal tract, after determining the challenging ingested dose, equal to 0.15-0.3 g/kg body weight (the dose should not exceed 3 g of protein or 10 g of the tested food), receive the prepared food sample over 45 min, in 3 portions [66]. If the patient does not experience any symptoms within 4 h after the first administration of the food, he/she should receive

Table 14. Types of oral food challenge [96]

Type of challenge	Food administration method	Comment
Open-label	Food in the natural form	Recommended in infants
		Positive result in 50% confirmed by DBPCFC
Single-blind placebo-controlled food challenge (SBPCFC)	Hidden food, masked appearance, colour, taste and smell (in capsules, in liquid or solid form, in other foods)	Usually sufficient for clinical purposes
	The patient is not informed about the type of food fed	
Double-blind placebo-controlled food challenge (DBPCFC)	Food hidden, masked appearance, colour, taste and smell (as above)	Diagnostic "gold standard"
	The patient, nurse and doctor are blinded to the tested food	A technique recommended for research purposes, enables results from different centres to be compared
	The food and placebo are prepared and coded by a third person	

Table 15. Indications after double blind placebo controlled food challenge [80, 83]

Recommendations	Food challenge result	
Elimination diet reccommended	Allergen/positive result (+)	Placebo/negative result (–)
Challenge repeat reccomendation	Allergen/positive result (+)	Placebo/positive result (+)
No indications for a diet	Allergen/negative result (–)	Placebo/negative result (–)
No indications for a diet	Allergen/negative result (–)	Placebo/positive result (+)

a second dose, and observation is continued for 2-3 h. The challenge test is performed in a hospital, under medical supervision, with readily available rescue facilities in case of an anaphylactic reaction. According to Nowak-Wegrzyn, due to the possible occurrence of delayed or insidious symptoms, this observation may have to be extended up to a few days. An open food challenge test should be discontinued immediately when any allergic symptom occurs (sneezing, runny nose, cough, vomiting, etc.), and the patient should be observed for a few hours [66].

In the initial diagnosis of atopic dermatitis, when food hypersensitivity is suspected to be a contributing factor in the aetiopathogenesis, it is proposed to eliminate the harmful food for a period of 2 weeks. After this period, the food should be re-introduced under medical supervision. Skin symptoms, which commonly occur in a positive challenge test, may be associated with gastrointestinal or respiratory symptoms [66].

For procedural reasons, double-blind, placebo-controlled tests should be performed in a hospital ward, in a diagnostic laboratory specialising in the preparation and masking of the samples. This rule also applies to open-label trials if there is a likelihood of an anaphylactic reaction in a child with mild to moderately severe clinical hypersensitivity (positive results of immunological tests for the presence of specific IgE antibodies). These tests should always be performed in a hospital, until the results of PTS and/or sIgE indicate a reduced responsiveness of the body to an initially harmful allergen [10].

Open-label tests can also be performed in a doctor's office, provided that the patient is not at risk of shock reaction (negative results of allergic-immune tests in IgE class with certain environmental allergens). This test can then be continued at home [59, 79-83].

The likelihood of a reaction in the challenged child can be predicted based on serum sIgE levels. According to previous studies, there is a high probability of such reaction and thus no indications for a challenge test in children with the following levels of serum sIgE against proteins: cow's milk > 15 kIU/l, chicken egg > 7 kIU/l, peanuts > 14 kIU/l. In the youngest children (up to 2 years of age) serum sIgE concentration thresholds are different: chicken egg white > 2 kIU/l, cow's milk proteins > 5 kIU/l [8, 9, 50, 66, 77, 85-88].

In order to facilitate and streamline the diagnostic process of food hypersensitivity, various clinical centres have developed many procedures (diagnostic algorithms) including a food challenge test. The differences in food challenge tests mainly concern the choice of food, selection of the initial dose and subsequent doses, food masking, and methodological procedure [79-84].

Niggemann proposed a diagnostic algorithm for food hypersensitivity with an open and a blind challenge tests interpretation, and Vandenplas developed diagnostic and dietary guidelines for children with allergy to cow's milk proteins, artificially or naturally fed (Table 16 [80], Tables 17-20 [10]).

In various informational materials, available mostly on the Internet, patients with food hypersensitivity are encouraged to use other diagnostic tests, such as the following: determining the concentrations of specific IgG antibodies (sIgG), microscopic evaluation of blood cells after exposure to the food, chemical analysis of hair, kine-

Table 16. Interpretation of the results of food challenge tests [80]

Open food challenge	Open food challenge		Open food challenge
Positive challenge result (+) Immediate type of allergic reaction (IgE-mediated)	Positive challenge result (+) Delayed and late phase of allergic reaction		Negative challenge result (–)
Recommended an elimination diet	Double-blind placebo-controlled food challenge (DBPCFC)		No indications for a diet
	Positive challenge result (+)	Negative challenge result (–)	
	Recommended an elimination diet	No indications for a diet	

Table 17. Diagnosis and management of cow's milk allergy in formula-fed infants, mild or moderately severe symptoms (modification based on [10])

Suspected allergy to cow's milk protein (CMP)			
Formula-fed children/mild or moderately severe symptoms			
Stage 1	Clinical assessment and family history		
	Consider performing skin tests or patch tests to cow's milk protein		
	Blood tests – total IgE, specific IgE		
Stage 2	Elimination diet		
Stage 3	Improvement		No improvement
	Open-label challenge test based on the results of IgE assay. Administration of milk formula under supervision of a physician		Elimination diet with an AAF formula or return to the supply of milk in the diet
Stage 4	Recurrence of symptoms	No symptoms	
	Use the elimination diet until 9-12 months of age, for at least 6 months	Return to cow's milk supply in the diet	
Stage 5	Repeat the challenge test	Follow-up	

Table 18. Diagnosis and management of cow's milk allergy in formula-fed infants, severe symptoms (modification based on [10])

Suspected allergy to cow's milk protein (CMP)		
Formula-fed children/severe symptoms		
Stage 1	Clinical assessment and family history	
	Consider performing skin tests or patch tests to cow's milk protein	
	Blood tests – total IgE, specific IgE	
Stage 2	Refer the child to a specialist	
	In the meantime an elimination diet with AAF formula for 2–4 weeks	
Stage 3	Improvement	No improvement
	Challenge test at a specialist clinic	Further diagnostics at a specialist clinic

Table 19. Diagnosis and management of cow's milk allergy in breast-fed infants, mild/moderately severe symptoms (modification based on [10])

Suspected allergy to cow's milk protein (CMP)			
Breast-fed children/mild or moderately severe symptoms			
Stage 1	Clinical assessment and family history		
Stage 2	Continue breast-feeding		
	Eliminate cow's milk (and eggs) from the mother's diet for 2-4 weeks		
	Administer calcium supplementation		
Stage 3	Improvement		No improvement
	Re-introduce cow's milk to the mother's diet		Return to normal diet in the mother and consider other causes (differential diagnosis)
Stage 4	Symptoms	No symptoms	
	Maintain the elimination diet in the mother plus calcium supplementation	Re-introduce eggs to the mother's diet	
Stage 5	After breast feeding, introduce an eHF formula in place of the mother's milk. CMP free solid foods until 9-12 months and for at least 6 months	Follow-up	

Table 20. Diagnosis and management of cow's milk allergy in breast-fed infants, severe symptoms (modification based on [10])

Suspected allergy to cow's milk protein (CMP)	
Breast-fed children/severe symptoms	
Stage 1	Clinical assessment and family history
Stage 2	Refer the child to a specialist for diagnostic tests and treatment
	In the meantime, eliminate cow's milk from the mother's diet and use calcium supplementation

siology, iridology, electrodermal tests (BICOM) and others. These methods have no scientifically proven diagnostic value and are not recommended by scientific societies and other competent scientific and clinical organisations, dealing with the problems of food hypersensitivity [3, 94, 96].

Summary 6

The diagnosis of food allergy is a complex, multistep and time-consuming process. It includes analysis of the allergic history (personal and in the family), detailed examination of the patient and analysis of the existing clinical symptoms, and interpretation of well-planned allergic immune tests.

The underlying difficulties in the diagnosis of food hypersensitivity include the complex pathogenetic immune mechanisms – IgE-mediated, non-IgE mediated, mixed or cellular – responsible for the observed symptoms.

Due to these mechanisms, so far there is no universal test for diagnosing food hypersensitivity, i.e. a single test, inexpensive, sensitive, easy to perform and clearly identifying the causative agent in food allergy or hypersensitivity.

The commonly used methods for the determination of specific IgE in the blood and skin tests (skin prick tests with food allergens) are used primarily for diagnosing food hypersensitivity, in which solely an IgE-mediated pathogenetic mechanism is involved (food allergy according to the European nomenclature). This is possible in only about 50% of patients with this hypersensitivity, in whom positive results of such tests confirm the causal factor of the

disease (harmful food). In the remaining patients, the results of these tests are usually negative, because their clinical symptoms of food hypersensitivity are triggered by non-IgE mediated pathogenetic mechanisms, which are not detectable using the diagnostic methods described above.

The method allowing definitive confirmation of the presence and type of food hypersensitivity, and the causal relationship between the harmful food and the clinical symptoms (confirmed or ruled out) is a challenge test with the suspected food. The time interval from food administration to the onset of disease symptoms in a positive test indicates the pathogenetic mechanisms responsible for the clinical symptoms in this disease (immediate, delayed, late).

Dietary treatment of food hypersensitivity

Three important issues related to the elimination diet are the subject of scientific and clinical considerations:
- is the elimination diet, when strictly adhered to, the proper method of treating food hypersensitivity?
- does this treatment accelerate the process of recovery ("outgrowing the food allergy") and does it eventually mean restoring or acquiring tolerance to the originally harmful food?
- is the elimination diet useful or can it be useful in the prevention of food hypersensitivity, and in the broader sense, of atopic and allergic diseases?

Food hypersensitivity is a clinical condition in which harmful food is the major cause of the disease. An elimination diet as a causal treatment of food allergy is often the primary, and sometimes the only way to treat this disease [8, 10, 14, 28, 32, 33, 50, 51, 59, 66, 97-105]. Elimination consists in the temporary removal of the harmful food from the patient's diet, with the introduction of nutritionally equivalent substitute ingredients, in place of the eliminated food (group of foods). Infants with mild or moderately severe allergy to cow's milk should first use an elimination diet for two weeks to establish the initial diagnosis. In children with atopic dermatitis or allergic symptoms from the gastrointestinal tract, the initial elimination period should be extended to 4 weeks [10]. The aim of this procedure is to "silence" the allergic immune reaction, to allow regeneration of the gastrointestinal mucosa, and to improve its digestive and absorption functions. The measures of the effectiveness of a therapeutic elimination diet and use of the milk replacement extensively hydrolysed formula (eHF) include the following: complete or partial resolution of clinical symptoms, improved general condition and normal physical development (weight gain, growth) and psychomotor development of the treated child [8, 10, 50, 66, 97-105].

The period of using the elimination diet in the treatment of food hypersensitivity is individually varied. The period of using this diet is determined based on the following: the child's age at the time of the diagnosis, the type of food allergy (primary, secondary), the form of clinical hypersensitivity (single-organ or multi-organ), pathogenetic mechanism (IgE-mediated, non-IgE mediated, mixed, cellular), positive family history of atopy/allergy and previously used treatment of the disease, including dietary measures (any kind of diet/no previous dietary treatment) [33, 95-100].

To meet the expected therapeutic requirements, the individually selected elimination diet must be adjusted for the patient's age (qualitatively and quantitatively balanced). It should take into account the type of eliminated food or group of foods, stage of the disease (severity) and the estimated period of medicinal use of the diet [95, 96, 97-102]. Patients highly sensitive to the causative allergen, e.g. with atopic dermatitis and allergy to cow's milk proteins, should avoid contact with allergens through the skin or by inhalation (e.g. vapours of boiled milk), as well as contact with milk products from other ungulate ruminants [11].

Milk and dairy products, chicken egg proteins, meat and vegetable proteins are basic nutritional products for both children and adults. When we eliminate such products (usually cow's milk and dairy products) from a young child's diet, then milk replacement products containing a highly hydrolyzed fraction of casein or whey proteins of cow's milk (eHF) should be used as a substitute for the eliminated protein. In the case of unacceptable taste of the milk replacement formula, lack of clinical improvement indicating a possibility of sensitization to the therapeutic-nutritional product, or signs of malnutrition, Vandenplas recommends considering the introduction of an elementary formula (AAF), while other authors recommend a soy protein formula (SF) [10, 59, 60, 66, 97-100]. In hypersensitivity to other food proteins (animal, vegetable), a hypoallergenic diet should be used with substitution of the eliminated proteins with other harmless protein products, and with supplementation of macronutrients (especially calcium) as well as trace elements and vitamins [10, 50, 97-100]. WAO guidelines recommend mandatory use of a therapeutic-nutritional milk replacement formula (eHF) in children with allergy to cow's milk proteins to the age of 2 years. In older children the use this type of formula depends on clinical indications and the decision of the treating physician [11].

Soybean formulas, which can be used in the treatment of certain clinical forms of food allergy, may represent a therapeutic-nutritional alternative for some of these patients. Contraindications to these product include age less than 6 months and food-induced enterocolitis or enteropathy in young children. Other reasons for restrictions on the use of such formulas may also be cross-reactions to cow's milk proteins allergens, observed in about 10-14% of patients with primary hypersensitivity to these allergens, as well as the adverse effects of phytates and phytoestrogens contained in soya beans [10, 72, 103, 104].

For the last 20 years, there has been an increasing number of clinical reports, including in Poland, on the pos-

Table 21. Treatment of milk allergy according to the current recommendations in different countries (WAO) [11]

Type of feeding	ESPACI/ESPGHAN 1999	AAP 2000	No. Scientific Society 2007*	Australian Consensus Panel 2008
	Høst A. Dietary products used in infants for treatment and prevention of food allergy. Joint Statement of the ESPACI Committee on hypoallergenic formulas and ESPGHAN Committee on nutrition. Arch Dis Child 1999; 81: 80-4	American Academy of Pediatrics. Committee on Nutrition. Hypoallergenic infant formulas. Pediatrics 2000; 106: 346-9	Vandenplas Y, Koletzko S, Isolauri E, et al. Guidelines for the diagnosis and management of cow's milk protein allergy in infants. Arch Dis Child 2007; 92: 902-8	Kemp AS, Hill DJ, Allen KJ, et al. Guidelines for the use of infant formulas to treat cow's milk protein allergy: an Australian Consensus Panel Opinion. Med J Aust 2008; 188: 109-12
Breastfed	In exclusively breastfed infants, strict elimination of the causal protein from the diet of the lactating mother should be tried	Elimination of cow's milk from the maternal diet may lead to resolution of allergic symptoms in the nursing infant. If symptoms do not improve or mothers are unable to participate in a very restricted diet regimen, alternative formulas can be used to relieve the symptoms	Breast-fed infants with proven CMA should be treated by CM avoidance. Continue breastfeeding but avoid CMP in mother's diet (plus Ca^{2+} supplement)	Breastfeeding may be continued, and recommendations are provided for eliminating maternal intake of CM protein
Formula-fed	Allergen elimination is relatively easy in exclusively formula fed infants	eHF or SF (see infra)	**Mild-to-moderate CMA:** **eHF** When: – The child refuses to drink eHF, but accepts AAF – Symptoms do not improve on eHF after 2-4 weeks – Cost-benefit ratio favours the AAF **AAF** **Severe CMA** Refer to a paediatric specialist. In the meantime, an elimination diet should be started with AAF	–
Partially hydrolyzed formula (pHF)	Not to be used for treatment of CMA	Not intended to be used to treat CMA	–	No place for pHF (known as HA) in treating CM
Extensively hydrolyzed formula (eHF)	Extensively hydrolyzed protein is recommended for the treatment of infants with cows' milk protein allergy	At least 90% of CMA infants tolerate extensively hydrolyzed formulas	Some eHF based on whey and casein met the criteria to be considered a therapeutic formula: tolerated by at least 90% (with 95% confidence) of CMA infants	Appropriate for treating CMA

Table 21. cont.

Soy formula (SF)	Formulas based on intact soy protein isolates are not recommended for the initial treatment of food allergy in infants	Although soy formulas are not hypoallergenic, they can be fed to infants with IgE-associated symptoms of milk allergy, particularly after the age of 6 months	Are not hypoallergenic. Significantly cheaper, better acceptance than eHF and AAF, but high risk of soy allergy particularly < 6 months. High concentration of phytate, aluminium and phyto-oestrogens (isoflavones), possible undesired effects	Appropriate for treating CMA
Other milks	CMA children should not be fed preparations based on unmodified milk of other species (such as goats' or sheep's milk) because of a high rate of cross-reactivity	Milk from goats and other animals or formulas containing large amounts of intact animal protein are inappropriate substitutes for breast milk or cow's milk-based infant formula	The use of unmodified mammalian milk protein, including unmodified cow's, sheep, buffalo, horse or goats' milk, or unmodified soy or rice milk, is not recommended for infants	There is no place for other mammalian milks (such as goats' milk) in treating CMA
Soy hydrolyzed formula (HSF)	Extensively hydrolyzed protein is recommended for the treatment of infants with cows' milk protein allergy (non-specified if also HSF)	–	eHFs based on another protein source met the criteria to be considered a therapeutic formula: tolerated by at least 90% (with 95% CI) of CMA infants (HSF not expressly cited)	–
Rice hydrolyzed formula (HRF)	At the time of recommendations, not extant	At the time of recommendations, not extant	eHFs based on another protein source met the criteria to be considered a therapeutic formula: tolerated by at least 90% (with 95% CI) of CMA infants (HRF not expressly cited)	At the time of recommendations, not available in Australia
Amino acid formula (AAF)	Are considered to be non-allergenic. Highly sensitive patients (i.e., patients reacting to eHF) may require an amino acid based dietary product	Tolerated	AAF met the criteria to be considered a therapeutic formula: tolerated by at least 90% (with 95% CI) of CMA infants	Appropriate for treating CMA

Table 21. cont.

	ESPACI/ESPGHAN 1999	AAP 2000	No. Scientific Society 2007*	Australian Consensus Panel 2008
Differentiation of recommendations by phenotype	No, only IgE mediated vs. non-IgE-mediated, but the recommendations do not differ	Infants with IgE-associated symptoms of allergy may benefit from a soy formula, after 6 months of age (eHF before 6 months). Non-IgE-associated syndromes such as enterocolitis, proctocolitis, malabsorption syndrome, or oesophagitis – eHF	–	**< 6 months:** eHF for immediate CMA (non-anaphylactic), FPIES, atopic eczema, gastrointestinal symptoms and food protein-induced proctocolitis **> 6 months:** SF for immediate reactions, GI symptoms or atopic dermatitis in the absence of failure to thrive AAF 1st choice in anaphylaxis and eosinophilic oesophagitis
Formula to be given during the diagnostic elimination phase	–	–	Mild-to-moderate CMA: eHF or AAF Severe CMA: AAF	–
Anaphylaxis	eHF	SF (no specific indication for anaphylaxis, only for IgE-mediated CMA)	–	AAF
Immediate GI reactions	eHF	SF 1st, eHF 2nd	–	eHF < 6 months, AAF > 6 months
IgE-mediated respiratory reactions	eHF	SF 1st, eHF 2nd	–	eHF < 6 months, AAF > 6 months
IgE-mediated cutaneous reactions	eHF	SF 1st, eHF 2nd	–	eHF < 6 months, AAF > 6 months
Atopic dermatitis	eHF	SF 1st; eHF 2nd? No specific recommendation	–	eHF < 6 months, AAF > 6 months
Delayed GI reactions	eHF	eHF: "In infants with adverse reactions to food proteins and malabsorptive enteropathy, the use of a formula with highly reduced allergenicity (extensively hydrolyzed formula or amino acid mixture) without lactose and with medium chain triglycerides might be useful until normal absorptive function of the mucosa is regained"	–	eHF < 6 months, AAF > 6 months AAF in eosinophilic oesophagitis

Table 21. cont.

Heiner syndrome	eHF	eHF? No specific recommendation	–	eHF? AAF? No specific recommendation
Follow-up	Controlled re-challenges should be performed at regular intervals to avoid unnecessarily prolonged avoidance diets	–	–	–

**Company-supported guidelines intended for general paediatricians and/or GPs. Recommendations valid for mild to moderate CMA. In case of suspicion of severe CMA, refer to a specialist*

sibility of allergy to hydrolysed casein or whey proteins of cow's milk, obtained by extensive hydrolysis and used in milk substitutes (eHF formulas). Allergy to hydrolysates is sometimes the cause of the absence of clinical improvement in patients with atopic dermatitis, refractory gastroesophageal reflux, lack of weight gain, or multiple food allergy, treated with these formulas. These patients should receive an amino acid formula (AAF), in which the protein fraction is replaced by a set of synthetic amino acids. The validity of any such therapeutic-nutritional change is confirmed by a positive result of the test for specific IgE against casein or whey fractions of cow's milk proteins. Where these tests are not available, *ex juvantibus* treatment should be considered [63, 105].

To avoid unnecessary dietary treatment, every treated child with clinical improvement, after a period of using the elimination diet (minimum 6 months), should be assessed for the acquisition of tolerance of the initially harmful food. This is usually achieved by performing a food challenge test with the previously eliminated food [10, 14, 59, 66, 74-84].

It must be remembered that dietary treatment of food hypersensitivity may be associated with some risks. One of them is unjustified, unwise (and therefore unpredictable in its consequences) elimination of a specific food from the previously used diet of the patient. This precaution applies to those persons (children/adults) who used to consume a certain product (products) without any clinical signs of hypersensitivity to this food (e.g. children with atopic dermatitis). Parents of children or adult patients who have positive results of allergy tests (PST, sIgE), showing only "sensitization" of the body (e.g. to allergens contained in chicken egg proteins or fish), which is not causally related to the allergic condition, often take an unjustified decision to temporarily eliminate the products containing these allergens from the patient's diet. The use of an elimination diet for a limited time in these patients can paradoxically result in loss of previously existing tolerance to the allergen tested. A repeated exposure to the eliminated allergen (accidental or deliberate consumption) can trigger serious symptoms of an allergic reaction, including shock [106-109]. Nutritional-therapeutic formulas containing partially hydrolyzed protein fraction of cow's milk (casein, whey proteins) (partially hydrolyzed formula – pHF) are not recommended for the treatment of allergy to cow's milk. They should be used solely for the prevention of the development of allergic processes [10, 59]. The guidelines concerning the application of different nutritional formulas, including milk of certain ungulates (sheep, goat, buffalo, camel) and milks based on vegetable protein (rice, almonds, soy), in the treatment of patients with allergy to cow's milk protein contains Table 21 [11]. The rationale for limited therapeutic use or the lack of indications is the possibility of cross-reactivity with cow's milk proteins; moreover, some of these products used as a single nutrient do not provide a sufficient source of protein coverage for the treated patients (Table 21) [10, 11, 98-100].

Summary 7

Food hypersensitivity is a clinical condition in which harmful food is the major cause of the disease. The basis of treatment is the elimination diet, which consists in temporary removal of the harmful food from the patient's diet, with simultaneous introduction of replacement components with equivalent nutritional value in place of the eliminated food or group of foods.

Measures of the therapeutic efficacy of an elimination diet include complete or partial resolution of clinical symptoms, improvement of the patient's general condition, normal physical development (weight gain, growth) and psychomotor development of the paediatric patient.

To meet the expected therapeutic requirements, an elimination diet should be individually selected with consideration of the type of harmful food, qualitatively and quantitatively adjusted to the patient's age, taking into account the progress of the disease and the necessary time of its therapeutic application.

Careless or reckless use of an elimination diet in patients with laboratory-confirmed allergy to specific antigen(s) who have no symptoms of an allergic disease may result in loss of previously existing immune tolerance to this antigen. The reintroduction of the temporarily eliminated food (allergen) into the diet can trigger symptoms of allergic disease, including anaphylactic reaction.

In everyday clinical practice we meet patients who rapidly "grow out" of food allergies, without using a strict elimination diet, as well as those who do not lose their hypersensitivity to the harmful food, despite using a strict diet.

The extensively hydrolyzed milk replacement products (eHF formulas), the elementary AAF formulas, soybean formulas and nutritional formulas enriched with MCT, probiotics, prebiotics, and LC-PUFA, adjusted for age (both qualitatively and quantitatively balanced), may be used in children with food hypersensitivity. A milk free elimination diet including these products must enable normal physical and psychomotor development of the treated child.

Acquisition of tolerance to initially harmful food ("outgrowing" food allergy)

In accordance with the principle that the therapeutic diet cannot be more troublesome than the primary disease, the patient treated using this method should periodically undergo a food challenge test. This test allows one to assess the ability of the paediatric patient's body to acquire tolerance to the eliminated food [10, 11, 14, 59, 66, 74-92, 110, 111]. Everyday clinical observations show that a significant number of children with allergic reactions to consumed foods begin to tolerate it with time, usually within 2-3 years after diagnosis of the disease and starting the appropriate treatment [11, 14, 112-114]. This phenomenon is also supported by immunological studies. Immune tolerance is antigen-specific suppression of humoral and cellular response of the body, occurring as a result of previous oral exposure to an antigen. In the clinical meaning, it is the lack of response to exposure to the causative antigen, even after a long period without any contact with the antigen [110, 111]. This phenomenon is also referred to as "outgrowing" food allergy; it involves the loss of hyperreactivity of the body to most previously sensitizing allergens (protein of cow's milk, eggs, soybean and others). In approximately 85% of patients this process takes place in the first years of life. Based on observations in selected clinical centres it can be concluded that the appearance of tolerance in hypersensitivity to these commonly consumed food products is more common in people without specific antibodies (sIgE) against these foods in allergy tests [54, 55, 57, 58, 112-114]. They "outgrow" their hypersensitivity faster and in a higher percentage compared to atopic patients who longer maintain IgE against food allergens and the disease process becomes persistent [112-114].

The studies of Høst *et al.*, evaluating the process of tolerance development among children with allergy to cow's milk proteins, showed that it is acquired more rapidly by children whose symptoms were mediated by non-IgE mechanisms, as compared to children with IgE-mediated allergy. Patients with IgE-mediated allergy to cow's milk were characterized by a tendency to a persistent disease process; over time, these children additionally developed other allergy symptoms (respiratory allergy) (Table 22) [14].

In other studies of Høst *et al.*, 56% of children allergic to cow's milk proteins acquired tolerance to milk and dairy products by 1 year of age, 77% by 2 years, 87% by 3 years, 92% between 5 and 10 years, and about 97% by 15 years [112].

The development of tolerance to cow's milk proteins, with consideration of the pathogenetic mechanism of allergy, was the aim of the study conducted by Vanto *et al.* among Finnish children (Table 23) [113].

The results of these studies confirm that the tolerance acquisition process is faster and occurs in a higher proportion of children with allergy to cow's milk proteins when non-IgE mediated mechanisms are involved [113].

Persistent allergy to cow's milk proteins was also confirmed in studies conducted among Portuguese children by Santos *et al.* [114]. In comparison to the overall study group, in the subgroup of children with IgE-mediated allergy to cow's milk proteins, the tolerance acquisition process occurred significantly later. This is depicted by the following data: by 2 years of age, tolerance was acquired by 34.0% of the whole group vs. 0.0% of children with IgE-mediated allergy; by 5 years of age – 55.0% vs. 22.0%; by 10 years of age – 68.0% vs. 43.0%. Most of the children from the group with symptoms of allergy to cow's milk proteins (73%) demonstrated clinically more than one symptom: skin (81%), gastrointestinal tract (55%), respiratory system (16%) or a systemic reaction (shock) (3%). Children with IgE-mediated allergy had higher values of immunological parameters (PST, sIgE) compared to the entire study group. The IgE-mediated pathogenetic mechanism of their hypersensitivity, along with clinical picture of the disease (including asthma) and high values of allergic and immune markers of this process, were considered in these children to be independent and

Table 22. Prognosis of cow's milk protein allergy [14]

Study type	% Recovery	% Allergy to other food	% Inhalant allergy
Prospective unselected (0-3 years)	84-87	54-60	28*
Prospective selected (2-4 years)	33-38	41-75	40-43**

**Among infants with CMA (IgE-mediated reactions) 48% have developed inhalant allergy by 3 years of age, **In one study 80% developed inhalant allergy before puberty*

Table 23. Development of tolerance to cow's milk proteins in children with cow's milk hypersensitivity depending on the pathogenetic mechanism of reaction [113]

Age [years]	Mechanism IgE mediated (immediate reaction)	Mechanism non-IgE mediated (delayed reactions)
2	31.0%	64.0%
3	53.0%	92.0%
4	63.0%	96.0%

negative predictive factors, delaying the process of immunological tolerance acquisition [114, 115].

Three main immune mechanisms are involved in the emergence of food tolerance: clonal anergy, clonal deletion and active suppression. They may occur simultaneously or independently in the same organism, and the main factor determining the type of the leading mechanism is the nature of the antigen (soluble, solid), its dose and the frequency of administration. Using high doses of the antigen results in the development of food tolerance through clonal deletion or anergy; small doses of the antigen generally induce active suppression, associated with the role of regulatory T lymphocytes (Treg) [116-118].

Summary 8

Most children with food hypersensitivity, diagnosed and treated during infancy or early childhood, "outgrow" the disease over time (about 80% by the age of 4-5 years). In the remaining patients, the state of persistent food hypersensitivity is individually varied over time.

The process of "outgrowing" food hypersensitivity is determined by several factors, of which the following should be considered the most important: the child's age at the time of the diagnosis and initiation of treatment (including the elimination diet), severity of disease symptoms and pathogenetic mechanisms that trigger them (IgE-mediated, non-IgE mediated, mixed, cellular), positive family history of atopy and/or allergy.

The ability to acquire tolerance to previously harmful food occurs earlier and in a higher percentage of patients with non-IgE mediated food hypersensitivity compared to patients whose symptoms are triggered by an IgE-mediated (atopic) pathogenetic mechanism.

Drug therapy and other treatment options of food hypersensitivity

Pharmacological treatment is a "complement" of comprehensive therapy of food hypersensitivity states, in cases where dietary measures alone appear to be ineffective or inadequate.

Pharmacological treatment of food hypersensitivity includes both immediate and long-term management. The immediate procedure is to fight short-term clinical symptoms of an ongoing or already developed post-feeding allergic reaction. If the reaction is shock, then this procedure involves the control of life-threatening symptoms, in the first place to administer first aid drugs, including epinephrine (auto-syringe). It is vital to educate the family and caregivers (teachers) of a sick child who is experiencing this type of reaction about the principles of first aid and the nature of allergic disease. In fact, such a reaction may occur both at home and outside the home (kindergarten, school, excursion, restaurant) [119-121].

Long-term pharmacological treatment involves the administration of anti-allergic drugs for prevention. It aims to prevent a recurrence or relapse of allergic disease.

In the pharmacological treatment, various agents are available with a different potency, different mechanisms of receptor interaction, administered in various forms and using various routes to the patient's body. Their proper selection, taking into account the pharmacological and pharmacodynamic properties and clinical manifestations of food allergy (single-organ, multiple-organ) determines the effectiveness of this therapy in hospital and outpatient treatment. However, no drug, even the most effective one, can replace causal treatment of food hypersensitivity, that is, temporary elimination of the harmful food from the patient's diet. The drugs available on the Polish market are widely used to fight symptoms of food hypersensitivity, both in acute and chronic phases of the disease (pharmacological prophylaxis). Drugs with systemic and local action are used for this purpose, using their antihistaminic properties (classical H_1 receptor blockers, 2nd and 3rd generation antihistamines); antihistamines and anti-allergic; anti-inflammatory (steroids); antileukotriene; and others (biological drugs, calcineurin inhibitors).

In the case of life threatening food reactions (anaphylactic shock), the recommended anti-shock procedure should be implemented immediately (auto-syringe with epinephrine) and the patient should be transferred for further treatment to a hospital [8, 10, 11, 28, 33, 50, 66, 92, 100, 119-121].

A better understanding of the allergic process, owing to advances in the fields of molecular biology and clinical immunology, opens up new prospects for treatment of food hypersensitivity. They are based on the principle of causing a change in immune responses, in people sensitive to the harmful food, from the state of "hyperreactivity" to "hyposensitivity". Attempts are made to treat patients with food allergy using methods of broadly understood "immunomodulation". One of these methods is oral immunotherapy (OIT), considered a method alternative to the elimination diet in the treatment of food allergy [122-124]. It involves oral or sublingual administration of allergens (sublingual immunotherapy – SLIT) in increasing doses (for months or years) with simultaneous monitoring of clinical symptoms and immunological markers. This method can only be applied to certain IgE-

mediated allergic conditions such as allergy to cow's milk proteins, chicken egg proteins and nuts (peanuts, hazelnuts). Sublingual immunotherapy has been used to treat cross-allergies in people allergic to birch pollen and responsive to apples. Skripak *et al.* desensitised for 4 months a group of 20 children with IgE-mediated allergy to cow's milk proteins using increasing doses of the allergen, and compared the results to a group of 20 children treated with an elimination diet alone (placebo group). The conclusion of this study was that "compared to placebo, immunotherapy with milk resulted in various degrees of desensitization in the treated group of patients" [123].

A methodological variant of this therapy is specific induction of food tolerance by the patient's contact with a thermally processed harmful allergen (specific oral tolerance induction – SOTI) [125, 126]. This method induces tolerance in allergy to cow's milk proteins or chicken egg proteins. The effect of tolerance is transient and does not necessarily lead to "persistence" of the process. Constant supply of the allergen is required to maintain the obtained status as an interruption in its supply usually results in loss of the therapeutic effect achieved so far [125, 126].

It should be noted that oral immunotherapy is not yet an approved method of treatment for IgE-mediated food allergy, although it appears to be effective in obtaining "desensitization" in a certain group of patients. There is also no clear opinion as to whether this method can lead to long-term tolerance, in which form the allergen should be introduced into the body (soluble or solid), and how safe is this therapeutic method [123-126]. Further research is needed on new opportunities for the treatment of food hypersensitivity and prophylactic and/or therapeutic measures using specific bacterial strains showing probiotic properties, prebiotics, LC-PUFA, and vitamin D, which can create better opportunities than ever to comprehensively help patients with food hypersensitivity [11, 127-130].

Summary 9

Pharmacological treatment is complementary to comprehensive treatment of food allergy and should be used temporarily to control the rapidly increasing allergic symptoms. Long-term pharmacological treatment used along with dietary therapy should be used when dietary treatment alone does not produce the desired effects in the form of clinical improvement.

No drug, even with high temporary efficacy, can substitute causal treatment of food allergy, that is, temporary elimination of the harmful food from the diet of the paediatric or adult patient.

New therapeutic opportunities for IgE-mediated food allergy include oral immunotherapy and sublingual immunotherapy with a native food allergen, or specific "desensitization" of the sensitized organism using thermally processed food allergen.

Preventive actions in food hypersensitivity

Preventive and prophylactic measures in food hypersensitivity consist in protective activities in patients in whom the risk of atopic or allergic disease is possible or highly probable (positive family history, atopic or allergic constitution, exposure to adverse environmental and infectious factors) [33, 41, 130-133].

Preventive actions, carried out in a comprehensive manner, are targeted at the general public or selected groups, which include people with an increased risk of developing allergies, or patients with symptoms of allergic diseases [11, 132, 133]. These activities fall within concepts of primary prevention (preventing the sensitization in a person predisposed to atopy or allergy, who has not yet come into contact with a potentially harmful antigen). Secondary prevention means preventing the allergic disease development in a "sensitized" person, or subsequent relapse of symptoms of an already developed allergic disease. Tertiary prevention means protecting against progressive damage of organs affected by the allergic disease [51, 131-133].

Feeding a child in infancy and early childhood is the primary area of activities involved in primary prevention of food allergy. One of the key activities is to promote natural breast-feeding for at least the first 4-6 months of life. Natural nutrition during this period, as compared to artificially fed infants (with a milk replacement formula), reduces the incidence of atopic dermatitis, and the risk of allergies to milk protein in children during the first 2 years of life. After reccomended breast feeding period, the diet of infants or small children should be gradually enriched in new products, including potentially allergenic foods (meat, egg white, cereals, fish, soy, fruits, vegetables and other products) (Table 24) [134-140].

An inherent part of these activities is also rational nutrition of women during pregnancy and lactation (a qualitatively and energetically balanced diet). In the case of mothers belonging to the so-called group of increased risk of allergy, an individually selected hypoallergenic diet in a breast-feeding mother can be effective as a preventive measure. For pregnant women, the preventive effect of such a diet has not been clearly demonstrated, although there is clinical evidence for the possibility of in utero sensitization of a child by foods consumed by a pregnant woman [136-141]. There is controversy as to intrauterine sensitization, as exemplified by the studies of Rowe *et al.* These authors challenged in their studies the concept of early, prenatal sensitization, as well as providing evidence that sensitization occurs only after birth, during early childhood. These authors observed a group of 200 children born in families with a high risk of allergies; specific IgE and IgG4 antibodies and cytokine profile (IL-4, IL-5) of mononuclear cells against selected food allergens (including chicken egg protein and cow's milk

Table 24. Maternal and infant diets for prevention of allergic diseases – guidelines [140]

Definitions/ interventions	Group/publication			
	AAP 2008 Clinical Report	AAP 2000 Recommendations	ESPACI/ESPGHAN 1999, ESPGHAN 2008 Recommendations	SP-EAACI, 2004, 2008 Recommendations
Risk category: "high risk"	Parent or sibling with documented allergic disease	Biparental or parent plus sibling history of allergy	Parent of sibling affected (1999)	Parent of sibling with documented allergic disease
Pregnancy avoidance	Lack of evidence	Possible peanut	–	No special diet*
Breast feed "exclusively" until	Evidence for 3-4 months (wanting 4-6 months tied to introducing solids)*	6 months	4-6 months*	At least 4 months, prefer 6 months*
Maternal lactation avoidance of allergens	Some evidence for reduced atopic dermatitis	Peanuts, tree nuts and "consider" egg, milk, fish, and "perhaps other foods"	–	No special diet*
Prevention formulas	Compared with whole cow's milk protein, evidence for certain extensive hydrolysates (eHF), partial hydrolysates (pHF), but not soy	"Hypoallergenic formula" (extensive hydrolysate, possible partial hydrolysate); not soy	Confirmed reduced allergenicity (1999)	Extensively hydrolysed until 4 months of age (2004); documented educed allergenicity (2008)
Types of "solids" and complementary foods	Evidence to wait for 4 (to 6) months; lack of convincing evidence for avoiding specific allergenic foods	Solids held to 6 months Diary products, age 1 years Egg, 2 years Peanuts, nuts, fish, age 3 years	Not before 17 weeks and no later than 26 weeks; no convincing evidence for delaying potentially allergenic foods such as fish, egg (2008)*	No evidence of diet effect after 4-6 months

**Advice that is the same for those not "high risk", AAP – American Academy of Pediatrics, ESPACI – European Society for Pediatric Allergology and Clinical Immunology, ESPGHAN – European Society for Paediatric Gastroenterology, Hepatology and Nutrition, SP-EAACI – Section on Pediatrics, European Academy of Allergology and Clinical Immunology*

proteins) and airborne allergens (house dust mite) were determined after birth (cord blood and at 6, 12, 24 months of age). The dynamic behaviour of these antibody titres, with a downward trend in their concentrations in the age range of 0 to 24 months, indicates that this is the period when tolerance develops ("time window"). Contact with allergens in this age range may promote the induction of immune tolerance in a given child [142].

The overall context of prophylactic measures against food allergies also includes the appropriate use of therapeutic-nutritional formulas (cow's milk protein hydrolysates, other hypoallergenic formulas) [136-141, 143-147]. This category of activities also includes the use of anti-allergic drugs and antihistamines [100], probiotics and prebiotics, LC-PUFA, vitamin D, eliminating the risks associated with exposure to tobacco smoke and other airborne and contact allergens, and infections [127-130, 148-151]. These measures should be complemented with broad educational activities for the patient and his environment (family, nursery, kindergarten, school, workplace, etc.) [152-158]. More clinical studies and new data are necessary to assess long-term outcomes of early dietary intervention, and the use of probiotics, prebiotics, omega-3 acid, and vitamin D during infancy, to prevent the development of allergic and infectious diseases later in life (youth and adulthood) [149-152].

Summary 10

Preventive and prophylactic activities in the context of allergy development must be carried out in relation to children belonging to risk groups, i.e. those who have a positive history of atopic or allergic disease in their parents, siblings or other relatives.

Preventive measures (primary prevention of allergy) consist in comprehensive prevention of sensitization of the organism. These relate to the pre-conception, prenatal and postnatal periods. An important role in the postnatal period (infancy and early childhood) can be attributed to the correct nutrition of the child, avoiding exposure to selected allergens, and avoiding exposure to some other harmful environmental factors (e.g. tobacco

smoke). Secondary prevention consists in prevention of recurrence of allergic disease, after the first occurrence of clinical symptoms. Tertiary prevention means protecting against progressive damage of organs affected by the allergic disease resulting from its chronicity and recurrence.

The preventive and prophylactic measures in the group of patients at risk of developing an allergy should be comprehensive and include:

– general promotion of natural breast-feeding of infants during the first 4-6 months of life;
– introduction of solid non-milk products (including gluten products) in the infant's diet no earlier than 4 months and no later than 6 months of age;
– introduction, after 6 months of age, of nutritional products considered highly allergenic (milk, eggs, soy, fish) probably does not increase the incidence of atopic diseases; it is even believed that delaying such a diet may promote the development of these diseases.

There is no evidence that cow's milk protein hydrolysates, used preventively in infants at risk of developing an allergic process, are superior to natural feeding. Protein hydrolysates, used in the prevention, are superior to milk replacement formulas used in infant feeding. They can prevent the occurrence of AD or delay its development; however, the final effect depends on the degree of protein hydrolysis (eHF, pHF formulas).

There is insufficient evidence regarding the preventive value of amino acid formulas (AAF) in the development of atopic diseases.

Dietary restrictions implemented by pregnant women have not yielded satisfactory results in reducing the prevalence of atopic diseases in their children.

The elimination of certain food products from the diet of a breast-feeding woman during lactation (justified by the presence of food allergens in her milk) induced a beneficial effect only among infants with atopic dermatitis.

The assessment of the effectiveness of a diet enriched in probiotics, prebiotics, LC-PUFA, vitamin D and other ingredients (milk or milk replacement formulas), used in infants and young children, in the prevention of allergic and infectious diseases, requires further research and clinical trials.

Social and economic aspects of food allergy*

According to the Allergy White Paper of the WAO (2011), allergic diseases affect about 30-40% of the global population [159]. Due to the increasing prevalence, they occupy a significant place among other chronic diseases and are a public health problem in the developed countries [159-163].

Food allergy, like other allergic diseases, is a chronic disease of children, adolescents and adults, with a prevalence estimated by the WHO to be around 3% to 8% among children and about 1% to 3% in the adult population [7]. The WAO Allergy White Paper indicates that 220 to 520 million people in the world are affected by this condition [159]. In Poland, food allergy is included in the list of chronic, congenital or acquired diseases, for which drugs and medical devices are prescribed free of charge, for a flat or partial payment [164].

Due to the scale of the problem, many countries have started studies aimed at assessing the social and economic effects of food allergy, in terms of both the negative impact of the disease on the quality of life of patients and their families, and the generated costs, including the significant impact of the cost of treating allergies to cow's milk on the overall financial resources allocated to health care in some countries. This issue has been the subject of several publications [154, 165-174].

An international research project, EuroPrevall, is focused on multi-faceted problems of food allergy in the European Union. One of its main topics of research focuses on assessing the socio-economic impact of food allergy [171, 173, 174].

In the opinion of the participants of this project, the social impact of this disease in European society may be much greater than previously thought; it affects the different spheres of life of the patients and their families, reducing their quality of life [171, 173].

The group of researchers implementing the project drew attention to the fact that the economic costs of food allergy are borne at different levels of functioning in society, by both public and private organisations. The researchers pointed to several "stakeholders" incurring the costs of this disease: consumers (mostly patients and their families), food industry (manufacturers and food processors, retail, catering firms and restaurants), health and social care (hospitals, specialist clinics and primary care outlets, diagnostic laboratories, welfare – mostly benefits), carers and care institutions (parents and relatives, schools, kindergartens, nurseries, non-governmental organizations), employers, institutions and agencies dealing with legal regulations and control (local and international) [171]. The direct costs of the disease, borne by individuals (patients or their caregivers) and households (families), are mainly related to special feeding and care of sick children, treatment and transport to the doctor, as well as the search for relevant information about the disease. The direct costs incurred by the public sector are mainly related to the provision of health care to these patients (expenses for health services, including medicines) [165, 171, 174]. The indirect costs borne by patients (parents of sick children) are measured in terms of lost opportunities, including the time necessary for the use of medical care, seeking information about the disease, lost possibility of gainful employment by the patient or his guardians (sick leave or resignation from work), and lost opportunity to rest. In the category of non-quantifi-

able costs of the disease, the quality of life of patients and their families has been assessed [171, 173, 174]. The results of studies on food allergy social impact suggest a number of adverse phenomena, disrupting the daily activities and social contacts of the patient (sick child) and his family (difficulties arising from the recommended elimination diet, and stress associated with the risk of a dietary mistake). The consequence is a significant reduction in the level of quality of life of patients and their families, as well as a negative impact on the psycho-emotional and physical development of children suffering from the disease [154, 167-171, 173].

The need to continue this type of research and to disseminate the results in society involves the requirement for broader educational activities, not only for the patient and his family, but also all those public and private organisations that have a direct and indirect effect on the health of the individual and society [158, 171-173, 175].

In some countries, both state institutions dealing with public health problems, such as scientific societies, and organisations of patients and their families, have taken actions aiming to reduce the negative effects of food allergy. The problems related to food allergy were analysed and educational activities have been started, aimed at both the patients and their families, and the medical community. An example of such activities is the development of uniform guidelines regarding the diagnosis and treatment of food allergy, preceded by a thorough analysis of available studies worldwide. These guidelines are published on public websites, sometimes in two versions – for physicians and health care professionals, and for patients or their parents; there are also many educational websites addressed at sick children and their caregivers [4, 11, 120, 139, 176-179].

These problems seem to be still underestimated in Poland. The only position on allergy and food intolerance available to date, developed by a Polish group of experts, was published in 1997 [180].

Summary 11

Chronic diseases, including allergic diseases, are characterized by long duration, recurrence and disruptive symptoms. In the perspective of health care financing, the situation of the patient, his family and the environment, chronic disease is a serious socio-economic problem.

These diseases include food allergy, which lowers the quality of life of the sick child or adult patient and their families, impacting negatively on the psycho-emotional state of the patient and interfering with his/her social contacts.

Food allergy also generates economic costs incurred by different entities (public and private) participating in social life.

Direct costs of the disease are borne by both patients and their families (expenses related to special feeding and care of sick children, treatment, travel, searching for information about the disease), and by the public sector (expenditure on health services and medicines). The indirect costs incurred by the patients themselves or parents of these children are measured in terms of lost opportunities (time lost for the use of medical care, seeking information about the disease, lost possibility of gainful employment, lost opportunity to rest). The indirect costs borne by the public sector are mainly related to costs of lost productivity and expenditures in the sphere of social security.

An immeasurable cost of the disease is the reduced quality of life of the patients and their families.

To reduce the socio-economic costs of food allergy, it is necessary to implement educational activities to promote knowledge about proper diagnosis of the disease and the principles of treatment (primarily an elimination diet). They should be addressed at: the parents of sick children, adult patients, their families, professional staff involved in health care and education, people and institutions involved in the production and distribution of food and nutrition, as well as the staff of the institutions of care and education.

The relationship between chronic disease, such as food allergy, and the quality of life of patients and the costs generated by the disease, borne by both patients and their families and the economy, should be the subject of prospective studies in our country. It is also advisable to undertake educational activities addressed at various groups of society.

Glossary of terms used in the text

AAF (amino acid formula) – a milk replacement formula in which the protein fractions were replaced by a set of synthetic amino acids.

Active immunosuppression – inhibition of cell activity by interactions with other cells producing suppressive cytokines, or idiotypically specific lymphocytes that recognize the receptors for a specific antigen.

Adverse reaction to foods – repeatable and reproducible clinical symptoms, occurring in some people (regardless of age) after intake of food(s) or food additives.

Allergen – a substance with the characteristics and properties of an antigen, potentially harmful to those persons in whom it induces a state of sensitization.

Allergy – a manifestation of hypersensitivity with a specific immune response to a specific allergen. The nature of allergy is the qualitatively altered reactivity of the tissues of the body, based on the antigen-antibody, or antigen-immunocompetent cell reactions.

Anaphylaxis – antigen-specific immune response, primarily mediated by IgE antibodies. It is a life-threatening reaction due to rapid vasodilation (pressure drop), and smooth muscle contraction (including those in the bronchi).

Antigen – a substance foreign to the body, causing the development of a specific immune response, i.e. antibodies interacting with immunocompetent cells through specific receptors located on these cells.

Antigen presentation – the process by which certain cells of the body (antigen presenting cells) present an antigen on their surface so that it can be recognised by lymphocytes.

Antigen processing – the conversion of an antigen to a form that can be recognised by immunologically competent cells.

Atopy – a genetically determined (individual or familial) immune response, involving the capacity of the body to systematically produce sensitising IgE antibodies, after exposure to an usual dose of an environmental allergen.

Clinical tolerance – lack of the body's response to exposure to the causative antigen, even after long periods of abstinence.

Clonal anergy – the state of non-reactivity of T-cells, which are not capable of an effective immune response despite exposure to the antigen.

Clonal deletion – the elimination of specific clones of lymphocytes at some stage of their maturation.

Cross-allergy – simultaneous hypersensitivity to food, airborne or contact allergens with a homologous amino acid sequence, especially within the epitopes.

Cytokines – a basic term for soluble molecules that mediate reactions between cells.

Cytotoxic effect – the ability to kill cells.

DBPCFC (double-blind, placebo-controlled food challenge) – a double-blind food challenge test with the use of placebo.

eHF (extensively hydrolyzed formula) – a milk replacement formula with a high degree of hydrolysis of the protein fraction.

HRF – rice hydrolyzed formula, a milk replacement formula based on extensively hydrolyzed rice protein.

HSF – soy hydrolyzed formula, a milk replacement formula based on extensively hydrolyzed soy protein.

Epitope – a single antigenic determinant, a defined sequence of amino acids in the polypeptide chain. Functionally it is part of an antigen that combines with the antibody paratope.

Food – a set of biologically active substances (compounds, elements) that are important to human life, having not fully understood physiological and metabolic functions in the body.

Food allergy – a manifestation of hypersensitivity of the body in the form of a broad spectrum of clinical symptoms (single- or multi-organ), caused by eaten food (food allergen), which initiates and/or sustains an immune response of the organism.

Food hypersensitivity – a manifestation of the inability to generate and maintain immune tolerance of ingested food products or a "breach/collapse" of pre-existing tolerance.

GALT (gut-associated lymphoid tissue) – lymphoid tissue associated with the bowels.

Hapten – a small molecule that can act as an epitope, but is not able by itself to elicit an antibody response.

Hypersensitivity – objectively reproducible symptoms caused by exposure to a specific stimulus in a dose tolerated by healthy people.

Immune complex – the product of antigen-antibody reaction, which may also contain components of complement.

Immune specificity and memory – two features of acquired resistance; the immune system responds more effectively to a secondary or further contact with a given antigen.

Immune tolerance – antigen-specific suppression of humoral and cellular response of the body, occurring as a result of previous oral, subcutaneous or mucosal exposure to the antigen.

Immunogenic – having the ability to generate an immune response, which involves, among others, T and B lymphocytes.

Immunomodulation – the possible biological effects on the body's immune system via stimulation (immunostimulation), inhibition (immunosuppression) or actions adjusting the immune reactivity (immunoregulation).

Immunotherapy – the administration of the causal allergen to a sensitized organism, in increasing doses, at appropriate time intervals and via the appropriate route (oral, subcutaneous, sublingual), in order to desensitize the body, which eventually leads to sustained immune and clinical tolerance of a given allergen.

Interleukins – a group of molecules playing a role in transmitting signals between cells of the immune system.

LC-PUFA – long chain poly-unsaturated fatty acids.

Ligand – a binding or joining molecule.

MALT (mucosal-associated lymphoid tissue) – lymphoid tissue associated with mucous membranes.

MCT – medium chain triglycerides.

Multiple food allergy – simultaneous hypersensitivity to two or more food allergens.

OIT (oral immunotherapy) – oral administration of an allergen in order to induce immune tolerance.

Pathogen – the organism that causes a disease.

pHF (partially hydrolyzed formula) – a milk replacement formula with partial hydrolysis of the protein fraction.

Primary immune response – (cellular or humoral), following the body's first contact with a given antigen.

Priming – the primary cause of sensitization of the body to an antigen.

PST (prick skin test) – test to measure specific IgE attached to mastocytes in the skin.

RAST (radioallergosorbent test) – blood test to detect specific IgE antibodies to suspected or known allergens.

Receptor – a cell surface molecule that specifically binds to a particular extracellular molecule.

Secondary immune response – after secondary or further contact of the body with a given antigen.

SF – soy formula, a milk replacement formula based on intact soy protein isolates.

Skin tests – skin reaction to injection or contact with an antigen or allergen.

SLIT (sublingual immunotherapy) – sublingual administration of an allergen in order to induce immune tolerance in the body.

SOTI (specific oral tolerance induction) – the administration of a specific (processed) allergen to induce transient or permanent immune tolerance in the body.

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