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**ABSTRACT**

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## MODERN APPROACHES TO THE PROBLEM OF IMMUNODEFICIENCIES IN CHILDREN

The course and development of infectious and inflammatory processes is often accompanied by immune system malfunction. A considerable number of lymphotropic viral infections can suppress immune system cells and increase the frequency of immunodeficiencies. This occurs, in particular, due to immunoproliferative, allergic, autoimmune diseases, etc.

**The paper aims** to investigate the problem associated with childhood immunodeficiency diseases as of today.

Immunodeficiencies are divided into two large groups by their origin: 1) phenotypic (secondary), which do not have genetic disorders; 2) genotypic (primary), which have genetic disorders. At the same time, immune disorders that arise during life in an organism with a normally formed immune system and are not associated with genetic abnormalities are diagnosed more often than primary immunodeficiencies. These disorders cannot represent an independent diagnosis because they are not an independent nosology.

Acquired immunodeficiency can have the same clinical manifestations as primary immunodeficiency; in particular, it is manifested by frequent and prolonged infections. The so-called "opportunistic" infections may occur: these are diseases caused by microorganisms that are usually unable to cause a pathological process in a patient with a healthy immune system but can provoke diseases in people with suppressed immunity. Thus, paying special attention to the early diagnosis of congenital immunodeficiencies is necessary.

Even though manifestations of immunodeficiency are not an indication for immediate treatment, doctors should monitor the changes that have been detected in specific immune system parameters.

**Conclusions**. It is necessary to consider that any intervention in the immune system must have serious grounds. Usually, when eliminating

the factors underlying acquired immunodeficiency, this condition resolves on its own.

**Keywords:** children, infection, immunodeficiency, leukocytes, neutropenia, cytokines.

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## СУЧАСНІ ПІДХОДИ ДО ПРОБЛЕМИ ІМУНОДЕФІЦИТНИХ СТАНІВ У ДІТЕЙ

Дуже часто перебіг та розвиток інфекційно-запальних процесів супроводжується порушеннями в роботі імунної системи. Величезна кількість лімфотропних вірусних інфекцій мають здатність пригнічувати клітини імунної системи та збільшувати частоту імунодефіцитів. Це відбувається зокрема за рахунок імунопроліферативних, алергічних, аутоімунних захворювань, тощо.

**Мета роботи –** дослідити проблему, пов'язану з дитячими імунодефіцитними захворюваннями станом на сьогоднішній день.

Імунодефіцитні захворювання за своїм походженням поділяються на дві великі групи: 1) фенотипові (вторинні) – не мають порушень у геномі; 2) генотипові (первинні) – мають генетичні дефекти. Водночас, порушення імунітету, що виникають в процесі життя в організмі з нормально сформованою імунною системою і не пов'язані з генетичними аномаліями, діагностуються частіше, ніж первинні імунодефіцити. Ці порушення не можуть виступати самостійним діагнозом, адже вони не є самостійною нозологією.

Набутий імунодефіцит може мати такі самі клінічні прояви, що і первинний імунодефіцит, зокрема, він проявляється частими та тривалими інфекціями. Можуть виникати так звані «опортуністичні» інфекції – це хвороби, які викликані мікроорганізмами, що зазвичай не здатні викликати патологічний процес в пацієнта зі здоровою імунною системою, але можуть провокувати захворювання в людей з ослабленим імунітетом. Таким чином, необхідно приділяти особливу увагу саме ранній діагностиці вроджених імунодефіцитних станів.

Незважаючи на те, що прояви імунної недостатності не є показанням до негайного лікування, втім, лікарі мають контролювати в динаміці ті зміни, що були виявлені в показниках імунної системи.

**Висновки.** Необхідно зважувати, що будь-яке втручання в імунну систему повинно мати серйозні підстави. Зазвичай, при ліквідації факторів, що лежать в основі набутого імунодефіциту, цей стан минає самостійно.

**Ключові слова:** діти, інфекція, імунодефіцит, лейкоцити, нейтропенія, цитокіни.

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## INTRODUCTION

The course and development of infectious and inflammatory processes is often accompanied by immune system malfunction [1]. It has been established that 8 to 15% of the world's population has immune system disorders, the clinical manifestations of which are recorded in childhood or young adulthood [2]. A considerable number of lymphotropic viral infections can suppress immune system cells and increase the frequency of immunodeficiencies. This occurs, in particular, due to immunoproliferative, allergic, autoimmune diseases, etc.

The term "immunodeficiency" refers exclusively to the laboratory (molecular/cellular) substrate of an immunodeficiency disease. Thus, the latter is a broader concept that encompasses all clinical attributes, from etiology and pathogenesis to prognosis, treatment, and prevention. Immunodeficiencies are divided into two large groups by their origin: 1) phenotypic (secondary), which do not have genetic disorders; 2) genotypic (primary), which have genetic disorders [3].

The **objective of the paper** is to investigate the problem associated with childhood immunodeficiency diseases as of today.

Materials and Methods. To prepare the review, methods of theoretical analysis and synthesis of scientific literature were used, covering the latest achievements in the field of immunology and pediatrics. For this purpose, a systematic search and analysis of publications in international scientific databases was conducted, in particular PubMed, Google Scholar, Scopus and Web of Science, as well as materials containing clinical guidelines and recommendations published by the World Health Organization (WHO) and the European Society for Immunodeficiency (ESID). The literature sample was limited to the period from 2010 to 2024 and included scientific articles that considered primary and secondary immunodeficiencies in children, as well as studies of the clinical manifestations of these diseases, their pathophysiological mechanisms, and methods of diagnosis and treatment. The criteria for selecting literature were high relevance to the topic of childhood immunodeficiencies, the availability of scientifically sound data and evidence base, as well as compliance with international clinical standards. The selection of publications was carried out on the principle of maximum coverage of various aspects of the problem, including etiology, pathogenesis, diagnosis, and treatment of immunodeficiency states. The methodology included a comparative analysis of primary and secondary immunodeficiencies in children, classification of immunodeficiency states by origin, as well as consideration of clinical cases indicating the development of opportunistic infections in patients with immunodeficiencies. To systematize the information obtained, a classification approach based on the recommendations of the International Union of Immunological Societies (IUIS) was used. Immunodeficiencies associated with infectious agents, autoimmune processes, allergic reactions, and oncological diseases were considered separately. Special attention was paid to the issues of early diagnosis of immunodeficiencies and monitoring the dynamics of changes in immunological indicators in children. To analyze the etiology and clinical manifestations, statistical processing of data obtained from epidemiological studies and official statistics was used, which allowed assessing the frequency and prevalence of various types of immunodeficiencies in the child population. In order to ensure academic integrity, scientifically based citation of literature and proper reference to original sources were used in the preparation of the work.

Scientists have divided the immunodeficiency disorders (IDD) into the following groups: hereditary immunodeficiencies (immunodeficiencies that are genetically determined, with mutations/polymorphisms of genes in germ cells), congenital immunodeficiencies (a group of immunodeficiencies acquired antenatally), and acquired immunodeficiencies (disorders that occur postnatally, for example, as a result of the use of cytostatics, or a group of immunodeficiencies due to the transfer of a mutation from a donor to a recipient during allogeneic bone marrow transplantation) [3].

The available literature focuses more intensively on the issues of etiology, clinical picture, and laboratory diagnosis of primary immunodeficiencies (PID) in children [4, 5]. However, the features of detecting a suspected case of PID remain controversial from both scientific and practical points of view, especially since in most cases of PID, clinical symptoms progress over time, numerous clinical manifestations cumulate, worsening the patient's condition and often leading to complications [6, 7, 8, 9].

As for immune system disorders in previously healthy immunocompetent individuals, they are more common than primary immunodeficiencies; they are not considered an independent nosology, and, therefore, cannot be an independent diagnosis [10]. Therefore, there is no code for such conditions in the International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10). They are only mentioned in the section related to other specified immunodeficiencies (infectious, toxic, metabolic, physical, psychogenic, post-traumatic, with a specific diagnosis of the disease that caused it; ICD-10 code D.84.8) and unspecified immunodeficiencies (cryptogenic or essential, or idiopathic, or spontaneous, if there is no etiological factor; ICD-10 code D.84.9) [11].

In recent years, the term "patient with a compromised immune system, or immunocompromised patient" has been increasingly used in the literature as a synonym for secondary (acquired) immunodeficiency. These are transient conditions and usually resolve with the elimination of factors that affect the normal functioning of the immune system [10].

Among the most recognized compromising factors, there are the following:

1. Age of the person (premature and newborn babies, people over 65)
2. Human immunodeficiency virus (HIV)
3. Therapeutic factors with immunosuppressive properties
4. Oncological or hematological diseases
5. Surgical interventions and injuries
6. Long-term dysfunctions of various organs and systems

Thus, functional immunodeficiency of maturation is typical for newborns and young children. Preterm infants with low antibody levels (IgG deficiency, which is transplacentally transmitted mainly in the last months of gestation) are particularly affected [10].

In recent years, the number of immunocompromised patients has increased due to massive immunosuppressive therapy during organ or bone marrow transplantation. At the same time, continuous treatment with immunosuppressive drugs to prevent organ rejection maintains the state of secondary immunodeficiency [10, 12]. Immunosuppressive therapy (corticosteroids) is believed to have an immunosuppressive effect only if they are used systemically in a dose of more than 2 mg/kg or more for at least two weeks. It should be remembered that topical application of corticosteroids, whether in the form of a spray or inhalation, does not lead to immunosuppression. Also, in recent years, monoclonal antibodies have been used as immunosuppressive therapy for the treatment of non-Hodgkin's lymphoma, rheumatoid arthritis, or chronic lymphocytic leukemia [10].

Various oncological processes, especially those involving the bone marrow (leukemia and lymphoma), also interfere with the production of normal white blood cells: T- and B-cells.

Certain surgical interventions, including splenectomy, also lead to immunosuppression by affecting the cellular component of the immune system. This leads to impaired immune system stability and an imbalance between pro- and anti-inflammatory immune responses [10, 13].

The issue of radiotherapy, which is carried out to treat cancer or as a preparation for bone marrow transplantation, is also relevant. It is believed that only radiotherapy aimed at irradiating the bone marrow leads to immunosuppression [10]. The causes of “milder” immunosuppression in children may include malnutrition, diabetes mellitus, renal failure, etc [10]. According to some authors, protein-calorie malnutrition is also considered a significant cause of immunological disorders, which can affect almost half of the population in developing countries. They report a direct correlation between a decrease in the number and function of T-cells and the level of protein deficiency. In this situation, the patient is very susceptible to diarrhea and respiratory tract infections. However, such disorders disappear when the protein balance in the body is restored [10]. However, a child often faces various factors that do not lead to persistent changes in the immune system (acquired immunodeficiency). Such temporary deviations in immunity parameters may be due to peculiarities of situational response [14].

Acquired immunodeficiency is considered as a clinical and immunological syndrome and has its own characteristics:

a) development of disorders in immunocompetent individuals;

b) persistent significant reduction in specific and/or non-specific immunodeficiency parameters;

c) the basis for developing autoimmune pathologies, allergic diseases, chronic processes, and neoplasms [14].

Such changes in the immune system are indeed secondary and occur in previously healthy children, in clinical and laboratory terms. They are persistent and pronounced, which is an important condition for addressing the issue of immunocorrection [14].

The disorders are not only quantitative in nature, but they also represent deviations in the functional activity of immunocompetent cells, with changes in both specific (adaptive) immunity and nonspecific (innate) immunity. They are characterized by damage to one of the immune chains, which leads to immunosuppression. That is why different types of immune system defects are distinguished:

- lymphocytic immunodeficiency: persistent quantitative and/or functional changes in the T-cell component of the immune system;
- humoral immunodeficiency: persistent quantitative and/or functional changes in the B-cell component of the immune system that affect the production of immunoglobulins;
- phagocytic immunodeficiency: persistent quantitative and/or functional changes in phagocytic cells (monocytes/macrophages, granulocytes).
- complementary immunodeficiency: persistent changes in the level and activity of complement components;

- combined immunodeficiency: persistent quantitative and/or functional changes in two or more parts of the immune system [14].

A number of authors, relying on the work of Prof. Kuznetsova L.V. [14], more often consider temporary immune deficiency in infectious diseases.

For example, the following conditions are necessary for the development of an infectious process: a pathogen (dose and virulence of the pathogen), its penetration into the body (condition of the human natural barriers and the place of penetration of the pathogen), and the susceptibility of the macroorganism (activity of the immune system). The development of the infectious process depends on the severity of the above conditions. However, it is believed that the main condition is the degree of deficiency of a person's natural or acquired immunity (the ratio of pathogenicity of the pathogen to the "capabilities of the immune system" at the time of infection) [14].

Opportunistic bacteria and fungi induce an infectious process in immunocompetent individuals only if the infectious dose of bacteria or fungi exceeds the unit of protective factor (phagocyte). Obligate pathogens (especially those classified as dangerous infections, such as plague, anthrax, etc.) are highly virulent and have the factors for neutralizing and overcoming the natural barriers of the immune system in healthy people, but not in an organism that is not immune to them (relative immunodeficiency). Many viruses can overcome the barriers of innate immunity; however, after activation of acquired immunity through vaccination (measles, polio, influenza, etc.), the infection does not develop [14].

The literature also describes the mechanisms of pathogens' protection against immune system factors: mechanisms of microorganisms' protection against complement-dependent cytolysis reactions or monocytes and macrophages; expression of highly immunogenic antigens on their surface and processes of transformation into R- or L-form; antigenic variability of microorganisms; the similarity of some structures of microorganisms to the receptors of the Fc-fragment of immunoglobulins; production of proteases that destroy antibodies; stimulation of the protein formation that reduces the expression of HLA (human leukocyte antigens) class I molecules and blocks the activity of T-cytotoxic lymphocytes; a change in the CD4+/CD8+ ratio towards the activation of the humoral link, etc [1].

Recently, in connection with the SARS-CoV-2 pandemic, there have been studies of the impact of this virus on the human immune system. In some cases, even in immunocompetent individuals, SARS-CoV-2 could cause immunological disorders, which was confirmed by a number of studies; it could also induce secondary lymphopenia, which was usually observed during the acute period of the disease and could last for 3 months after the infection. Under the influence of the virus, the number of CD19+ B-lymphocytes in patients' blood decreased (metabolic disorders in these immunocompetent cells), and CD4+ T-helper cells were deficient, which led to secondary virus-induced combined immunodeficiency; it also led to increased rate of immune disorders and coronavirus disease [15, 16]. It was also proven that a deficit in the number of CD19+ B lymphocytes and non-classical monocytes in patients' blood was a very significant prognostic factor for deaths in coronavirus disease [17, 18, 19].

According to many studies, secondary changes in the immune system occur against the background of vitamin, macro- and micronutrient deficiencies. These deficiency states can cause imbalances between the cellular and humoral components of the immune system. Zinc plays the most important role in the balanced functioning of the immune system. Studies of the zinc effect have confirmed that it has a significant impact on the state of the human immune system. Zinc maintains a balance between different parts of the immune system [20], namely:

- it is a cofactor of thymulin, which is necessary for the conversion of pretimulin to thymulin; it affects the activity of mature peripheral blood T cells and stimulates their maturation;
- it is related to the synthesis of γ-interferon and interleukin-2 production;
- it prevents a decrease in the weight of lymphoid tissue (thymus, lymph nodes, spleen, tonsils), total leukocyte count, and T-lymphocyte count, and supports their functional activity [20].

It has been found that an increase in the amount of zinc in monocytes prevents the negative effects of oxidative processes in the body, and a sufficient amount of this trace element inhibits the synthesis of proinflammatory cytokines (tumor necrosis factor-αand interleukin-1β) [20].

According to B. Korant, zinc has a negative effect on the processes of virus replication. Zinc is a blocker of polypeptide cleavage processes of viruses (rhinoviruses, enteroviruses) [21]. Zinc has a similar effect on the herpes simplex virus (Herpes simplex 1,2), enterovirus 70, and others. Zinc can stimulate T-effectors, and accelerate lymphoblast transformation and interferon release in the acute period of viral infection [20, 22].

Equally important is the role of other micro- and macronutrients, as well as some vitamins, in maintaining sufficient immune system activity due to

their immunotropic and antioxidant properties. Thus, in the studies of S.V. Zaikov (2015), the role of iron, iodine, copper, cobalt, chromium, selenium, manganese, as well as vitamins A, C, D, E, and group B vitamins, which provided an immunomodulatory effect on the body, was proved [23].

Iron provides bactericidal activity of macrophages and myeloperoxidase activity of neutrophils, as well as the number and functional activity of T-lymphocytes. Iodine has bactericidal properties against bacteria, fungi, and viruses, regulating the functioning of immune system cells. Copper is involved in the synthesis of hemoglobin and erythrocyte maturation, provides antioxidant protection, and synergizes with vitamin C in the body's anti-infective defense. Cobalt promotes the phagocytic activity of leukocytes. Chromium activates natural resistance factors, especially during increased physical and mental stress, infectious processes, or trauma. Selenium enhances the activity of nonspecific defense factors, cellular and humoral immunity reactions, regulates the stability of cell membranes, and synergizes with vitamin E in the formation of antibodies, enhancing the body's immune defense. Manganese stimulates hematopoiesis, participates in almost all metabolic processes in the body, is a synergist of copper and calcium, and is involved in the metabolism of other vitamins (C, E, B). Calcium takes an active part in the formation of a normal immune system response, and also protects cells from the penetration of pathogenic microorganisms.

It is also necessary to underline the role of the following vitamins: vitamin A participates in the proliferation of T cells by increasing the secretion of interleukin-2 and, together with vitamin E, promotes the formation of antibodies against infectious pathogens; it also has regulatory properties on the differentiation of immune system cells. Vitamin D helps the proliferation of circulating monocytes. Vitamin C has a positive effect on increasing the content of immunoglobulin A (IgA), IgM, and components of the complement system in the blood plasma; it also enhances the phagocytic activity of macrophages. Vitamin E has an effect on the activity of T-cell proliferation, an increase in CD4 and interleukin-2, and helps to increase the level of antiviral antibodies. Most B vitamins have properties similar to vitamin E [23].

Acquired immunodeficiency can have the same clinical manifestations as primary immunodeficiency; in particular, it is manifested by frequent and prolonged infections. The so-called "opportunistic" infections may occur: these are diseases caused by microorganisms that are usually not able to cause a pathological process in a patient with a healthy immune system, but can provoke diseases in people with suppressed immunity [10]. Thus, it is necessary to pay special attention to the early diagnosis of congenital immunodeficiency disorders. The actions of a physician in managing a patient with suspected primary immunodeficiency are regulated by the current Order [24]; for a basic (screening) immunological examination, or if necessary, special immunological examinations, they should be referred to a pediatric immunologist no later than on the 10th day.

Diagnostic measures should include not only a medical history (including family and vaccination history), but also basic and specific immunological tests.

It should be noted that when making a diagnosis of primary immunodeficiency, practitioners need to refer patients to a pediatric immunologist in a timely manner. Therefore, the European Union of Immunologists and medical experts from the Jeffrey Modell Foundation have developed recommendations that include ten warning signs for primary immunodeficiencies in children as of 2018 [25]:

1) 4 or more new otitis media within one year,
2) 2 or more serious sinus infections within one year,
3) 2 or more months of antibiotic therapy with minimal effect,
4) 2 or more cases of pneumonia within one year,
5) children under one year of age lagging in growth and weight gain,
6) repeated abscesses of internal organs or skin,
7) recurrent oral thrush or fungal infection of the skin,
8) the need for intravenous antibacterial drugs,
9) 2 or more invasive infections, including manifestations of septicemia,
10) primary immunodeficiency in the family.

If two or more of the above signs are present, the child should be referred to a pediatric immunologist for consultation. Immunological laboratory diagnostics is carried out in stages: first, screening methods (their interpretation); then, a pediatric immunologist determines the algorithm for further examination and makes decisions on more in-depth immunological laboratory, instrumental, morphological, microbiological, or genetic methods.

The basic/screening immunological examination includes a complete blood count; measurement of total IgG, IgA, IgM, IgE in the blood serum (taking into account the presence of transient changes); CH50 (total plasma hemolytic activity); isohemagglutinins α and β; HIV testing.

Particular attention should be paid to the detection of leukocytopenia, lymphocytopenia, neutropenia, monocytopenia, eosinophilia, or thrombocytopenia using

the blood test. For example, some studies analyzed cytopenias in newborns and found that leukopenia was detected in 14 (11.86%) infants, neutropenia was observed in 86 children, which was 72.9%, and lymphopenia was detected in 29 children, which was 24.6% (including their combination). Thus, cytopenia in newborns is a laboratory finding (most often mild to moderate neutropenia), followed by lymphopenia, and least often isolated leukopenia, which, according to the authors, is most likely due to the compensatory growth of some cell subpopulations in the absence of others (neutrophilia in lymphopenia and vice versa) [26].

Congenital (primary) neutropenias are PIDs in which the maturation of stem or myeloid cells is impaired [27, 28]. The clinical course depends on the genetic defect and the severity of the neutropenia and can range from subclinical to severe, life-threatening course, with severe manifestations of infectious complications [29]. It is important to measure the absolute neutrophil count (ANC). ANC of <1500 cells per μL in children after the first year of life suggests the diagnosis of neutropenia. There are also degrees of neutropenia severity: 1500-1000 cells per μL – mild; 1000-500 cells per μL – moderate; < 500 cells per μL – severe neutropenia [30]. It is also necessary to measure the levels of IgG, IgA, IgM, IgE immunoglobulins in the blood serum by radial immunodiffusion, turbodimetric and nephelometric methods, and IgE levels – by enzyme-linked immunosorbent assay [31].

For patients who do not have a genetic diagnosis, verification of the clinical diagnosis of PID should be performed according to the ESID criteria "Diagnostic criteria for the clinical diagnosis of PID of the European Society of Immunodeficiency ESID, 2019" (exceptions are atypical severe combined immunodeficiency (ASID) and DiGiorgi syndrome) [32].

It should be remembered that antibody deficiency is defined as a decrease in IgG levels by more than twice the standard deviation (absolute hypogamma-globulinemia) or the absence of specific antibodies with serum IgG within the normal range (functional hypogammaglobulinemia) [33]. In patients with secondary antibody deficiencies, the IgG level is < 4 g/l [34]. In case of changes in the indicators at the baseline diagnostic level, and in case of suspicion of a particular pathogenic variant of PID, a pediatric immunologist orders further general laboratory screening and detailed (special) immunological studies [34].

It is believed that in the era of genomic medicine and the reduction in the cost of genetic testing, in recent years, the possibility of using whole exome sequencing and genome sequencing in the diagnosis of genetic mutations has been increasingly considered, which will allow the identification of a wide range of diseases, although a number of ethical and economic issues of such screening still remain unresolved [35].

The development of an effective, cost-efficient method of newborn screening based on TREC/KREC excision circles determination has improved the survival prospects of patients with severe combined immunodeficiency (SCID) [36]. The experience of foreign countries demonstrates that real-time polymerase chain reaction analysis of TREC/KREC counts is cost-effective and highly sensitive even before the clinical manifestation of SCID [37].

Previously, PID was thought to be a rare disease, but screening programs for newborns revealed real incidence rates that were higher than expected. After pilot screening programs in the United States, the following data were obtained: 1 in 30,000-50,000 babies may be born with SCID, while in Turkey, Saudi Arabia, and Kuwait, these rates were higher [38]. In Ukraine, according to the 2012 registry, the number of diagnosed PID was 1680 cases with a high prevalence of the Slavic mutation of Niemegen syndrome and agammaglobulinemia [36].

Positive international experience, the increase in the number of cases of SCID in recent years, and the development of hematopoietic stem cell transplantation led to the implementation of a neonatal SCID screening program in Ukraine [36, 39]. Thus, the clinical practice guideline on primary immunodeficiencies [40] states that in America, according to studies, the average delay in time from the onset of the first symptoms of primary immunodeficiency to diagnosis was approximately 4.7 years, and the higher the age at diagnosis, the higher the mortality rate.

Thanks to effective measures for primary immunodeficiencies, primarily interdisciplinary guidelines, an increase in the frequency of diagnosis has been observed in developed countries in recent years, as well as a slight reduction in the time between symptom detection and diagnosis. However, immunodeficiencies that manifest themselves in adulthood, such as generalized variable immunodeficiency, are often not recognized until several years later.

**CONCLUSIONS.** Thus, despite the variety of factors and manifestations of immune deficiency, there is no need for immediate treatment of these disorders. It is recommended to monitor certain parameters of the immune system over time.

It should be remembered that interference with the immune system should be well justified. As a rule, these are manifestations of acquired immunodeficiency due to the influence of various known factors, so when the identified factors are eliminated, the manifestations might resolve.

## AUTHOR CONTRIBUTIONS

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## CONFLICT OF INTEREST

The authors declare no conflict of interest.

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