

Therapeutic apheresis in allergy

VA Voinov^{1*}, KS Karchevsky², OV Isaulov³

¹Head of the therapeutic apheresis department of I.P.Pavlov First Saint-Petersburg State Medical University, 4/6 Leo Tolstoy Str. 197022 Saint-Petersburg, Russia.

² I.P.Pavlov First Saint-Petersburg State Medical University, Saint-Petersburg, Russia

³ I.P.Pavlov First Saint-Petersburg State Medical University, Saint-Petersburg, Russia

**Corresponding author:* VA Voinov, Head of the therapeutic apheresis department of I.P.Pavlov First Saint-Petersburg State Medical University, 4/6 Leo Tolstoy Str. 197022 Saint-Petersburg, Russia. E-mail: voinof@mail.ru; Tel. +7-911-912-65-02.

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Abstract

Allergic diseases are among the most common in the world, covering up to 20% of the population. This is facilitated by environmental problems with an increasing number of different allergens and immune disorders with the accumulation of specific autoantibodies and cytokines. Unfortunately, the generally accepted therapeutic measures for these various manifestations of allergies are mainly symptomatic for the removal of specific symptoms. All this determines the difficulties in treatment with the transition to chronic forms of disease, and in some cases accompanied by a fatal outcome. Truly pathogenetic treatment is apheresis therapy aimed at removing allergens, tissue degradation products, inflammatory mediators, leukotrienes, autoantibodies and immune complexes from the body.

Key words: allergy; atopic dermatitis; urticaria; toxic epidermal necrolysis; anaphylaxis; rhino-sinusitis; asthma; plasmapheresis

Introduction

In recent years, there has been a worldwide increase in incidence of allergic diseases, involving up to 20% of population. The frequency of such reactions is increasing in the world, reaching 50-112 episodes per 100.000 population per year [1]. In the US, up to 5% of the population suffers from anaphylaxis, and over the years 1992-2012, the frequency of hospitalizations increased by 615% [2, 3]. Industrialization and environmental problems in recent years have contributed to a significant increase in allergic reactions, especially in children [4, 5].

The increase in the frequency of allergic diseases is the result of human contact with an increasing number of allergens: industrial (turpentine, nickel, chromium, tar, tannin, varnishes, resins, tannins, etc.), food (eggs, citrus, tomatoes, chemical additives), plant (ambrosia pollen, phleum, etc.), household (household dust, perfumes, detergents, synthetic textile), agricultural (insecticides, pesticides, defoliants, fertilizers), medicinal (penicillin, sulfonamides, acetylsalicylic acid, etc.) [6- 8]. Often severe allergies are caused by mold fungi *Aspergillus* [9].

Allergy Pathogenesis

The occurrence of allergic diseases is associated with the imperfection of allergen biotransformation in the microsomal apparatus of the liver (the appearance of secondary reactive compounds) and with defects in the immune response (atopic forms), the system of biotransformation and elimination of immune complexes.

Atopy appears to be a hyperreaction of the immune system against normal and harmless environmental substances. Allergic antibodies are immunoglobulins E (IgE). IgE production by B-lymphocytes is stimulated by cytokines IL-4, IL-5 and IL-13 secreted by T-helper lymphocytes under the influence of allergens [10, 11]. Correlation of IgE antibodies with allergens (antigens), involving complement, forms stable immune complexes, elimination of which is difficult in allergy. Part of them remains in the circulation (circulating immune complexes or CIC), and the rest is captured in the interstices of the target organs, causing immune or allergic inflammation there. Among these target organs, the most common sites are the bronchial tree, skin and mucous membranes of the nasal cavity.

Allergy is characterized by a disorder of the immune system such as hypersensitivity type I (immediate), which develops when the IgE response is directed against normally harmless environmental antigens such as pollen, house dust mites or animal dandruff. The IgE-sensitized mast cells, in this case, produce biologically active mediators, which cause an acute inflammatory reaction with the symptoms of asthma or rhinitis [12].

Triggers or provoking factors exacerbating allergic reactions are the above mentioned allergens, among which the most common are pollen of trees such as birch, alder, hazel, oak, and hornbeam. The leading role among them belongs to the pollen of white birch (*Betula verrucosa*), containing the major allergen Bet v 1, which can be detected in 60% of patients with IgE reactions [13]. In atopic forms of dermatitis and bronchial asthma there may be a link of IgE-antibodies and autoantigens with activation of allergic effector cells – mast cells and basophils. IgE-autoimmune reactions thus explain exacerbations in severe forms of atopy, even in the absence of exogenous allergens [14]. In this case, sensitization may also occur against autoantigens. Special studies have shown that *Aspergillus fumigatus* antigens may be affined to antigenic structure of human proteins; therefore, when sensitized to this microorganism, and even in its absence, auto reactivity and allergic manifestations may be maintained [15].

IgE-dependent activation of mast cells plays the leading role in development of an immediate allergic reaction [16]. In this case, mast cells can produce various mediators, including tumor necrosis factor (TNF α) and many other cytokines (interleukins IL-1, IL-2, etc.). Moreover, mast cells stimulate formation of a large number of high-activity surface receptors for IgE and increase the level of IgE-dependent secretion mediators in response to an increase in IgE concentration. Mast cells (and in some cases the cytokines released from them) can play an important role in the initiation of acute, subacute and chronic components of IgE-dependent allergic inflammations, which can influence the development of important functional consequences of these reactions – hyper reactivity of the respiratory tract [17]. In allergic inflammation eosinophils also play its role, increased release of which is stimulated by cytokines IL-4

and IL-5 of T-helper cells. Eosinophils, in turn, release an increased amount of enzymes with high proteolytic activity, and contribute to eosinophilic infiltrates appearance. The basic proteins of eosinophils promote release of histamine by mastocytes, which indicates their close cooperation [18, 19]. A significant frequency of allergic diseases in young children and even newborns suggests the possibility of their perinatal sensitization, especially in the presence of allergies in their mothers. The contributing factors are disorders of pregnancy (toxycosis, threats of premature birth) and when drugs are used in large quantities. In such cases, elevated concentrations of immunoglobulins, including IgE, are also found in newborns within a few months after birth [20]. In industrial countries, up to 20% of the population suffers from allergic symptoms of type I – rhinitis, conjunctivitis, bronchial asthma, and in children of 5 years old they are observed in 30% of cases [21]. The earliest (literally from the first days of life) manifestations of allergies are often on the skin, which is a so-called diathesis (scrofula), with a wave-like course, further converting to a common, persistent, and continuously recurrent neurodermatitis.

Atopic dermatitis

It often accompanies bronchial asthma and allergic rhinitis. Studies show activation of cytokines IL-3, IL-4, IL-5, IL-15. Clinical manifestations largely depend on the body's reactions to exogenous allergens. However, not only products of external origin can play the role of antigens, but also of bacterial origin, in particular – *Staphylococcus aureus*, which can be isolated from 95% of patients with atopic dermatitis. Such bacterial superantigen can activate T-cell local mechanisms and production of IgE [22]. Neurodermatitis course duration indirectly indicates the ineffectiveness of traditional methods of treatment aimed, as a rule, to treat local sites of the skin lesions. Even hormonal ointments lead only to a temporary effect. The most pathogenetically justified approach to treat the affected skin localized lesions is apheresis therapy aimed at elimination of allergens, autoantibodies, immune complexes and other pathological metabolites that create a number of vicious circles, which neither the body itself nor any drugs are able to break down. That is, the treatment should be mostly directed not the localized areas of lesions, but to the elimination of their occurrence

conditions and chronization, which can best be achieved by plasmapheresis. So, I.V. Andozhskaya et al. [23], summarizing the seven-year experience of plasmapheresis use in treatment of 100 patients with neurodermatitis, pointed to the high efficiency (87%) of this method, although in our experience the best results are achieved by adding hemosorption to the course of 4 plasmapheresis procedures with simultaneous irradiation of the blood with ultraviolet or laser rays and subsequent enterosorption. The same results were also achieved in combination of plasmapheresis with subsequent biospecific hemosorption with sorbents that bind IgE [24]. In genesis of so-called photodermatitis or solar dermatitis, urticaria it is not always possible to identify the allergic components, but in these cases the use of plasmapheresis may be helpful [25, 26].

Allergic dermatitis is also dangerous in pregnancy, when many anti-allergic drugs are dangerous for the fetus development and in such cases plasmapheresis courses are also preferred [27].

Local eczema-like dermatitis also has an allergic nature. In particular, periorbital eczema and eyelid dermatitis is a type of contact allergic dermatitis. The reasons may be eye ointments, creams for the face, eye shadow and makeup products, shampoos and nail polish [28].

Urticaria

Urticaria is an episodic and transient allergic skin lesion, although chronic urticaria is also described, when IgG antibodies against highly active IgE receptors are found in the blood of such patients. Removing them by plasmapheresis leads to clinical remission [29, 30]. Combined use of plasmapheresis with polyoxidonium immunopharmacotherapy in vitro is reported [31]. Immunosorption of IgG antibodies ensured almost complete disappearance of autoantibodies followed by the disease regression in 8 months [32].

However, omalizumab usually recommended in such cases sometimes has a limited effect or side effects and it may be difficult to get or too expensive. In such cases, plasmapheresis can also be used [33]. In chronic urticaria resistant to treatment with dexamethasone and gamma globulin a significant success was also achieved, using cascade plasmapheresis [34]. This was confirmed by further

research [35, 36]. Given the greater frequency of the parasites detection in these patients (giardiasis, opisthorchiasis, toxocariasis), it is advisable to conduct an additional examination to detect parasites and prescribe an appropriate therapy (tiberall, glaygl, biltricid, dekaris) [37]. Chronic urticaria can accompany diseases caused by hepatitis B and C viruses, HIV, Epstein-Barr, Coxsackie A and B, and infectious mononucleosis. Acute urticaria can become chronic. Chronic urticaria often develops on the background of other autoimmune diseases such as chronic hepatitis C, and autoimmune thyroiditis [38].

Toxic epidermal necrolysis

Idiosyncratic systemic syndrome of Lyell or Stevens-Johnson is of a toxic and allergic nature with extensive damage not only to the skin, but also to the mucous membranes, which occurs as a reaction to the intake of a number of medications (sulfonamides, antibiotics) [39]. Sometimes viral infections and even graft-versus-host reactions play its role in stem cell transplantation. The death rate at the same time reaches 25-75%. In particular, the death rate in a patient with Lyell's syndrome after administration of ciprofloxacin is described. Most of the hypotheses are based on autoimmune processes with skin infiltration by cytotoxic T-cells (CD8+), monocytes and macrophages, the deposition of a number of cytokines (TNF- α), contributing to extensive apoptosis of keratinocytes [40].

Therapeutic apheresis is able fairly quickly, sometimes already after the first plasmapheresis procedure, to interrupt the reaction and lead to permanent cure [41- 49]. A massive membrane plasma exchange with removal of 2-4 liters of plasma during 2 - 5 sessions was held every other day or daily, with fresh frozen plasma and albumin compensation [50]. In Japan they successfully use not only usual but also cascade plasmapheresis [51].

Isolated use of corticosteroids is fraught with increased septic manifestations, but in combination with plasmapheresis it provides better results [52-54]. Plasmapheresis has been successfully used in such cases in children [46, 55, 56].]. Extremely severe and often fatal toxic epidermal necrolysis occurs in children after allogeneic stem cell transplantation (graft-versus-host reaction), which is also an indication to use plasmapheresis [57]. Plasmapheresis is also necessary in cases when the process spreads to the

eyeballs, which is fraught with sight loss [58, 59].

Anaphylaxis

An even greater danger is posed by acute anaphylactic reactions, the symptoms of which increase very quickly and death may occur within a few minutes [60, 61]. At the same time, 65% of patients come to a state of shock with multiple organ failure within 6-11 minutes from the beginning of anaphylaxis [62]. The frequency of such reactions in the world is increasing, and in the US, up to 5% of the population suffers from anaphylaxis [2, 3]. Often, the factors causing anaphylaxis are insect bites (wasps, bees), snakes (vipers) and even medicines such as antibiotics (Ceftriaxone), nonsteroidal anti-inflammatory drugs, radio-opaque substances [63-67]. Injections of adrenaline, corticosteroids, antihistamines, and plasmapheresis are used as emergency measures [68]. Anaphylaxis sometimes is caused by life-saving drugs, such as factor IX, the only necessary in patients with hemophilia B. In such cases, plasmapheresis can reduce sensitivity to this drug [69].

Quincke's edema

The same episodic angioedema or clearly self-limited angioedema of the skin and subcutaneous tissue usually affects the lips, tongue, larynx, eye tissue. However, it is sometimes life-threatening with edema spreading to the larynx followed by severe suffocation [70]. This edema is usually idiopathic, but can be triggered by a number of medications, including non-steroidal anti-inflammatory drugs. The pathogenetic mechanism may be the isolation of vasoactive mediators (bradykinin) by the mast cells with suppression of mechanisms of its degradation [71].

Another factor in such edema pathogenesis is appearance of autoantibodies to a special protein that inhibits the complement C1 component (C1 inhibitor), the deficiency of which contributes to increased vascular permeability of some local areas of the vascular bed, most often on the face, abdomen, limbs. Until recently, such a sudden swelling associated with the upper respiratory tract obstruction was able to have result in death in up to 50% of patients. The increase of vascular-active peptides of the kinin cascade, in particular the above-mentioned bradykinin in allergic reactions, may be a trigger for such reaction [72]. Emergency therapy includes corticosteroids and antihistamines, but in order to prevent such episodes, plasmapheresis is also of

benefit [73].

Rhino-sinusitis

Vasomotor rhino-sinusitis has persistent course, often accompanied with allergic conjunctivitis. In allergic rhinitis, inflammatory infiltrates are formed from various cells with release of inflammatory mediators (histamine, leukotrienes, cytokines), which attract cells and promote their trans endothelial migration, which creates vicious circles that the body itself is no longer able to break. At first gaze harmless "runny nose" can last for many years, often associated with bronchial asthma. This contributes to nasal breathing limitation. Inhalation of cold air without its moistening and retention of microbes in the nasal cavity contributes to development and maintenance of catarrhal inflammation in the tracheobronchial tree, which also triggers and fixes allergic inflammation in the respiratory tract. The causes of chronic rhinosinusitis can be both immunosuppressive and allergic conditions [74, 75]. Therefore, the attitude to such rhinitis should be no less serious than to bronchial asthma.

Eosinophilic esophagitis.

Intestinal forms of allergy are characterized by sudden dyskinesia of the intestine and biliary tract. In dentistry orthopedic or medical stomatitis is common [76]. Eosinophilic esophagitis is distinguished separately, characterized by transient dysphagic disorders. Esophagoscopy shows local narrowing of the esophagus and biopsy demonstrates a high content of eosinophils in the mucosa. In this case, eosinophilia in the blood as well as other manifestations of allergy, in particular bronchial asthma, are often detected [77, 78].

Bronchial asthma

Asthma is the most serious manifestation of allergy, which is the most dangerous and most difficult to treat. According to American statistics, about 15 million people suffer from asthma in the United States, with a loss of 100 million school days or working days per year [79]. However, even in such country with advanced medical care, where the total cost of treating patients with bronchial asthma is up to \$ 6.2 billion a year, deaths from bronchial asthma increased from 13.4 per 1 million in 1982 to 18.8 per 1 million in 1992. Asthma is also an important cause of disability, loss

of earning capacity in adults, and learning days in children. For a long period of time asthma is often preceded by other manifestations of allergy, in particular, by allergic rhinitis [80, 81]. 78% of patients with asthma have symptoms of rhinitis and 38% of patients with rhinitis have asthma [82]. Atopic sensitization is a leading risk factor of asthma and its exacerbations. In this case, allergic asthma in childhood is often combined with severe course of asthma in adults. In asthma, there are persisting clones of activated T-helpers (CD-4) sensitized by allergens such as environmental antigens or viruses retained in the lungs. Cytokines of these cells (IL-3, IL-5, as well as granulocyte-colony-stimulating factor) activate eosinophils, which excite eosinophilic inflammation of the mucous membranes and secrete IL-4, stimulating, in turn, the production of IgE. This leads to the epithelium damage, hypersecretion of mucus and muscle contraction of the bronchi (bronchospasm) [83]. In addition, as asthma develops and aggravates other homeostasis disorders occur, in particular, activity of the antioxidant system becomes depleted accompanied by lipid peroxidation products increase and high levels of free radicals. This further supports allergic chronic inflammation and also requires special measures to correct such disorders [84]. Unfortunately, the generally accepted therapeutic measures taken in these various manifestations of allergies are mainly symptomatic – various ointments to relieve unbearable skin itching, vasoconstricting drops (galazolin, sanorin) in rhinitis, mucolytics and bronchodilators in bronchial asthma. At best, the effect is achieved by hormonal drugs administration. The potential dangers of hormone therapy are to be considered. At first glance, harmless nasal drops with betamethasone can lead to growth retardation in children, even before the clinical manifestations of Cushing's syndrome appear [85]. In addition, glucocorticoids, in particular, are diabetogenic hormones due to their suppression of glucose consumption by the tissues and its liver production increase. In addition, they may directly inhibit insulin secretion, indicating that the pancreatic islets b-cells are one of their targets [86]. Another complication of long-term glucocorticoid therapy is osteoporosis. These hormones are believed to inhibit proliferation and differentiation of osteoblasts and stimulate their apoptosis. There is also an

indirect mechanism of bone resorption as a result of secondary hyperparathyroidism due to reduced calcium resorption in the bowel. The glucocorticoids effect on the hypothalamus and gonads contributes to hypogonadism [87]. Development of chronic inflammatory polyneuropathy is described [88]. In addition, there is evidence that such an intensive and prolonged immunosuppressive therapy is associated with tumors growth [89,90].

For a long time specific immunotherapy is practiced, which is increasing doses of allergens administered subcutaneously, orally, sublingually or intranasal. This process is also called hyposensitization or desensitization, because it aims to reduce the target organ sensitivity to these allergens. As a rule, these are inhaled allergens such as house dust mites or tiny Hymenoptera ticks. Although this therapy has been used for about 80 years, the mechanisms of its action are still not clear and its effectiveness is not constant [91]. There are doubts concerning the effectiveness of extracorporeal selective immunosorption, in particular to the house dust antigen. And it is not only because of the risk to cause anaphylactic reactions in the result of massive degranulation of basophils, carriers of specific IgE, with release of serotonin, histamine, slowly reacting substance A, up to the development of anaphylactic shock. The main objections are instances of polyvalent allergies. There are practically no patients with bronchial asthma who would be sensitized to only one allergen. Over time, the number of allergens expands to several dozens. In some cases, such immunotherapy is accompanied by complications such as urticaria, arthralgia, myalgia, fever, lymphadenopathy and even anaphylactic reactions that require plasmapheresis to remove them [91-94,]. In recent years, the use of monoclonal antibodies such as omalizumab has become widespread, which inhibits IgE activity [95], but the accumulated allergens, secondary metabolites and autoantibodies still remain in the body. In addition, omalizumab treatment is not possible in case of an excessively high IgE level (over 700 U/l) when preliminary courses of plasmapheresis are required to reduce this level [96].

Despite the fact that the works of numerous researchers have already proved the effectiveness of apheresis therapy introduction in the therapeutic measures

complex, this tactic is still not widely used. In some cases, the diagnosis of bronchial asthma is established only after several years of the disease development as asthmatic bronchitis, bronchitis with an asthmatic component, then pre-asthma, and the final diagnosis is made only before a hormonal therapy started. Often, bronchial asthma emerges on the background of present long-lasting skin manifestations or rhinosinusopathy. Nevertheless, in all these types of allergies the real pathogenetic treatment is apheresis therapy aimed at removing antigens from the body, i.e. allergens that block the receptors of antibodies, inhibitors, tissue degradation products, inflammatory mediators, leukotrienes and immune complexes. The biologically active substances concentration decrease leads to restoration of b-adrenergic reception, and reduces resistance to bronchodilators [97]. The receptors release and removal of T-suppressor activity inhibitors in plasmapheresis leads to T-lymphocytes activity restoration, which contributes to alveolar macrophages activation. Unblocking of phagocytes receptors contributes to a more efficient natural elimination of allergens. In general, it provides a more stable remission. Related photochemotherapy also helps to normalize differentiation of T-lymphocytes with increased activity of T-suppressor cells and reduced production of IgE, and elimination of biochemical disorders [98]. Photochemotherapy using red light even in monotherapy mode had a favorable effect on bronchial asthma course [99]. Plasma removal by plasmapheresis stimulates release of fresh components into the circulation and contributes to normalization of metabolism, in particular, lipid peroxidation processes with increased activity of the antioxidant system. Reducing the level of biologically active substances contributes to the normalization of membrane phospholipid metabolism. All this leads to elimination of allergic inflammation with restoration of sensitivity and reactivity of the bronchi and elimination of broncho-obstructive syndrome. The effect of apheresis therapy continues in a more prospective period. All the new components of homeostasis entering the circulation, young forms of cells, which replace the old ones, retain their genetically predetermined properties and functions in a refreshed environment for a longer period of time, which breaks many formed pathological circles, resulting in

a more stable remission. In particular, the positive effect following courses of plasmapheresis is noted to occur on 5-7 day after the treatment started and it lasts from several months to two years [100]. Combination of bronchial asthma with obstructive pulmonary disease is not uncommon, when plasmapheresis is applied [101]. It has been validated in our clinical practice [73]. In recent years, hemosorption is being replaced by plasmapheresis more often, being the most effective method to remove all pathological products, regardless of their ability to adhere and adsorb to the activated surface of sorbents. The exception is the so-called "aspirin" or "prostacycline" form of asthma [102]. Here-with the sorption methods are effective enough. However, the two methods are still successfully used in the treatment of bronchial asthma, including at the stage of latent preclinical course or pre-asthma [103]. Moreover, there were also selective hemosorbents binding IgE [104]. Plasmapheresis, which promotes elimination of pathological products, can remove the causes, triggering immune disorders and create conditions for their gradual reverse development. Plasmapheresis can be carried out in combination with methylprednisolone pulse therapy. After removal of 1500-1800 ml of plasma, 1000 mg of metipred was injected intravenously during 20 minutes, which allowed significantly reducing the depressive effect of pulse therapy and achieving a good clinical effect with remission up to 6-8 months [105]. Membrane plasmapheresis in conjunction with diucifon immunomodulator has given a favorable result [106]. Combination of plasmapheresis with subsequent plasmadsorption is possible using specific immunosorbent to remove IgE [107]. Plasmapheresis has also been successfully used as a life-saving operation in asthmatic status on the background of thyrotoxic crisis, rhabdomyolysis and acute kidney injury [108]. Bronchial asthma has an adverse effect on the course of pregnancy, contributing to toxicosis with the threat of pregnancy termination and premature birth, labor abnormalities, and fetal hypoxia. All this makes plasmapheresis indicated for this kind of patients [109].

Biochemical homeostasis disorders study shows significant disturbances of lipid peroxidation system with accumulation of toxic end-products and inhibition of antioxidant protection; there are high concentrations of hista-

mine, serotonin, medium-molecular oligopeptides found. Therefore, it is important not only to remove pathological immunoglobulins, antibodies and immune complexes, but also to improve biochemical homeostasis.

In almost all of these types of allergies both not marked with rhinitis or skin lesions and severe asthma, it is advisable to conduct a full course of therapeutic apheresis and immunocorrection, because there is no guarantee that the lighter manifestations of allergies will not transform into severe ones. From this point of view, unjustified delay in recognition of bronchial asthma diagnosis as a fact, registering only the asthmatic components of bronchitis and pre-asthma, does not make it possible to eliminate the cause of homeostasis disorders in time, contributing to pathological allergic reactions consolidation. It is much easier to prevent the progression of primary, yet functional disorders than to achieve the reverse development of organic disorders – severe purulent obstructive endobronchitis, emphysema with destruction of the elastic framework of the lung parenchyma.

Plasmapheresis in initial phases of bronchial asthma formation is often rejected by clinicians who consider prescription of drugs to be quite sufficient. However, quite good results have been achieved in patients with "pre-asthma" using plasmapheresis for elimination of inflammatory mediators stimulates the macrophage system and complement. With all the invasiveness of the technique, plasmapheresis in such patients may well be applied even in outpatient settings. This was confirmed by our own experience of using plasmapheresis in the early stages of asthma, including in children, when it was possible to almost completely interrupt the pathological process.

The apheresis therapy measures complex, in addition to the actual plasmapheresis, included removal of about 1/3 circulating lymphocytes, including those with "pathological memory", i.e. producers of autoantibodies, which allowed achieving more stable remission. In addition, the blood was irradiated in the extracorporeal circuit by helium-neon laser with radiation power at the end of the light guide up to 15-20 mW, it is sufficient to penetrate through the walls of the blood stream, located in a special spherical chamber. Given a common concomitant allergic rhinosinu-

sopathy, additional irradiation of the nasal cavities was performed by the same optical waveguide apparatus, as well as the maxillary, frontal and nasal sinuses irradiated by infrared laser, that penetrate into the tissues up to 8 cm. The latter is feasible to eliminate chronic infection sites, which is considered to be one of the possible triggers for initiation of allergic reactions. Even in the absence of any symptoms in the rhino-sinus zone, it can be considered one of the affecting reflexogenic zones that contribute to allergization, the zone of the first contact with inhaled allergens. Therefore, sanitation of the nasal cavities and sinuses is pathogenetically justified, as well as a reflex impact on this sensitive area. In addition, the upper respiratory tract improvement contributes to greater warming and humidification of the inhaled air, the delay of allergens, and the block of the nasal-bronchial reflex. Moreover, given the significant risk of asthma in patients with allergic rhinitis, more intensive treatment of the latter may be one of the methods of asthma prevention. Enterosorption complements this complex of apheresis therapy, which allows to limit the flow of enterogenic toxins that can support allergic reactions, as well as to remove medium-molecular endotoxins from the circulation. Enterosorption courses may also be repeated periodically after plasmapheresis every 2-3 months for 2 weeks. Unfortunately, it should be recognized that it is almost impossible to completely cure patients with allergies and such patients will need repeated courses of apheresis therapy in later life, which is confirmed by clinical practice. Thus, S.V. Varlamova et al. reported 8 courses of plasmapheresis (4 procedures each) for 10 years in a patient with atopic syndrome while maintaining a fairly stable level of remission for an average of 1.6 years [111].

Wissler-Fanconi subsepsis

Somewhat apart is a fairly rare disease – Wissler-Fanconi subsepsis (“allergosepsis”), characterized by joint syndrome (edema, stiffness of movements), hectic fever, ephemeral roseolus rash on the body, high leukocytosis with a shift “to the left”, thrombocytosis (from 400-600-109/l to 1000-109/l), headaches and an increase in the level of IgE 3-4 times. In such cases frequent repeated procedures of plasmapheresis are of benefit for a long time period [112]. In a patient with this disease, treated in our

Department, there was a picture of advanced infiltrates in the lungs with rapid reverse development during the course of plasmapheresis.

Churg-Straus Syndrome

In the same row is allergic vasculitis (angiitis) and Churg-Straus granulomatosis. It often develops on the background of steroid therapy of bronchial asthma. There is eosinophilic lymphadenopathy occurring on the background of blood eosinophilia with severe vasculitis, up to a fatal outcome. High doses of steroids, and sometimes cyclophosphamide is not always successful. That is why one is to be cautious to administer steroids to patients with bronchial asthma [113]. Plasmapheresis in such cases also provides more stable remission [114]. This is also confirmed by plasmapheresis results in our practice.

Conclusion

Thus, allergies are a fairly large group of diseases, united by common pathogenetic mechanisms, including both exogenous allergeoactive substances together with products of their biotransformation in the body and immune disorders with accumulation of specific autoantibodies and a number of cytokines. All this makes it difficult to treat when there can be a transition to chronic forms of disease and in some cases with a fatal outcome.

Unfortunately, the generally accepted therapeutic measures for these various manifestations of allergies are mainly symptomatic aimed at removal of specific symptoms. In the best case, the effect is achieved by hormonal drugs administration, desensitization, and selective immunosorption, use of monoclonal antibodies such as omalizumab, which suppresses IgE activity, while the accumulated allergens, secondary metabolites and autoantibodies remain in the body. In addition, many types of such drug treatment are not without side effects. Nevertheless, in all these types of allergies, the real pathogenetic treatment is apheresis therapy aimed at removing antigens from the body – allergens that block the receptors of antibodies, inhibitors, tissue degradation products, inflammatory mediators, leukotrienes and immune complexes. This does not exclude, of course, a drug therapy, but in less dangerous doses, and such complex therapy provides more stable remission.

References

1. Tjedor Alonso MA, Moro Moro M, Múgica García MV. Epidemiology of anaphylaxis. *Clin Exp Allergy*.2015; 45: 1027-1039.
2. Turner PJ, Gowland MH, Sharma V et al. Increase in anaphylaxis-related hospitalization but no increase in fatalities: an analysis of United Kingdom national anaphylaxis data, 1992-2012. *J Allergy Clin Immunol*.2015; 135: 956-963.
3. Turner PJ, Jerschow E, Umasunthar T et al. Fatal anaphylaxis: mortality rate and risk factors. *J Allergy Clin Immunol Pract*.2017; 5: 1169-1178.
4. Ebisawa M, Nishima S, Ohnishi H, Kondo N. Pediatric allergy and immunology in Japan. *Pediatr Allergy Immunol*.2013; 24: 704-714.
5. Wong GWK, Li J, Bao YX et al. Pediatric allergy and immunology in China. *Pediatr Allergy Immunol*.2018;29: 127-132.
6. Thomas P, Summer B et al. Diagnosis and management of patients with allergy to metal implants. *Expert Rev Clin Immunol*.2015; 11: 501-509.
7. Esposito S, Castellazzi L, Tagliabue C, Principi N. Allergy to antibiotics in children: an overestimated problem. *Int J Antimicrob Agents*.2016; 48: 361-366.
8. Nishizawa A et al. Dyshidrotic eczema and its relationship to metal allergy. *Curr Probl Dermatol*.2016; 51:80-85.
- 9.Greenberger PA, Bush RK, Demain JG et al. Allergic bronchopulmonary aspergillosis. *J Allergy Clin Immunol Pract*.2014; 2:703-798.
10. Bonyadi MR, Hassanzadeh D, Seyfizadeh N, Borzoueisileh S. Assessment of allergen-specific IgE by immunoblotting method in atopic dermatitis. *Eur Ann Allergy Clin Immunol*.2017; 49(5): 213-219.
11. Wassmann-Otto A, Heratizadeh A, Wichmann K, Werfel T. Birch pollen-related foods can cause late eczematous reactions in patients with atopic dermatitis. *Allergy*.2018; 73: 2046-2054
12. Delves PJ, Martins SJ, Burton DR, Roitt IM. Roitt's essential immunology. Wiley-Blackwell.2017
13. Osborne NJ, Alcock I, Wheeler BW et al. Pollen exposure and hospitalization due to asthma exacerbations: daily time series in a European city. *Int J Biometeorol*.2017; 61:1837-1848.
14. Patel TR, Sur S et al. IgE and eosinophils as therapeutic targets in asthma. *Curr Opin Allergy Clin Immunol*.2017; 17: 42-49.
15. Ghosh S, Hoselton SA, Schuh JM. Allergic Inflammation in *Aspergillus fumigatus*-Induced Fungal Asthma. *Curr Allergy Asthma Rep*.2015; 15(10): 59.
16. Morita H, Saito H, Matsumoto K, Nakae S. Regulatory roles of mast cells in immune responses. *Semin Immunopathol*.2016; 38: 623-629.
17. Galli SJ, Tsai M. et al. IgE and mast cells in allergic disease. *Nat Med*.2012; 18: 693-704.
18. Fulkerson PC, Rothenberg ME. Targeting eosinophils in allergy, inflammation and beyond. *Nat Rev Drug Discov*.2013; 12: 117-129.
19. Kuruvilla M, Khan DA et al. Eosinophilic drug allergy. *Clin Rev Allergy Immunol*.2016; 50: 228-239.
20. Gavalov SM et al. At sources of a sensitization, bronchial asthma and other allergic diseases. *Allergy Immunol (Rus)*.2001; 2(2):10.
21. Henriksen L, Simonsen J, Haerskjold A et al. Incidence rates of atopic dermatitis, asthma, and allergic rhinoconjunctivitis in Danish and Swedish children. *J Allergy Clin Immunol*.2016; 136: 360-366.
22. David Boothe W, Tarbox JA, Tarbox MB. Atopic Dermatitis: Pathophysiology. *Adv Exp Med Biol*.2017; 1027: 21-37
- 23.Andozhskaya IV, Danilova AV, Denisova SA. The choice of plasmapheresis method in the treatment of patients with psoriasis and neurodermatitis in the day hospital. *Proc conf Moscow society of hemapheresis, Moscow*. 1998;63.
24. Rovdo IM, Poplavskaya NB, Kirkovsky VV, Pankratov VG. Innovative technologies in complex treatment of IgE-mediated atopic dermatitis. *Proc XVI conf Moscow society of hemapheresis, Moscow* 2008; 82.
25. Nitiyarom R, Wongpraparut C. Hydroa vacciniforme and solar urticaria. *Dermatol Clin*.2014; 32: 345-353.
26. Gaetze S, Elsner P et al. Solar urticaria. *J Dtsch Dermatol Ges*.2015; 13: 1250-1253.
27. Demina TN, Dzoshua TV, Chermnykh SV, Hanja FA. Allergic reaction as the cause of critical conditions in obstetrics and gynecology. *Medical-social problemi sem'i*. 2009; 14(2): 9-12

28. Park ME, Zippin JH. Allergic contact dermatitis to cosmetics. *Dermatol Clin.*2014; 32: 1-11.
29. Jurakić TR, Lipozencić J, Marinović B. Treatment of chronic urticaria. *Acta Dermatovenerol Croat.*2009; 17: 305-322.
30. Kartal O, Gulec M, Caliskaner Z et al. Plasmapheresis in a patient with "refractory" urticarial vasculitis. *Allergy Asthma Immunol Res.* 2012; 4: 245-247.
31. Efendieva NUh, Navruzov IU, Safaralieva ES. Plasma- pheresis and extracorporeal immunopharmacotherapy in patients with recurrent urticaria. *Allergia Immunologia (Rus).*2001; 2(2) 86.
32. Konovalov GA et al. Immunosorbition treatment – a new concept in medicine]. *Bulletin of MEDSI (Rus).*2009; 3: 56-63.
33. Holm JG, Ivyanskiy I, Thomsen SF. Use of nonbiologic treatments in antihistamine-refractory chronic urticaria: a review of published evidence. *J Dermatolog Treat.*2018;29: 80-97.
34. Jiang X, Lu M, Ying Y, Feng J, Ye Y. A case report of double-filtration plasmapheresis for the resolution of refractory chronic urticaria. *Ther Apher Dia.*2008; 12:505-508.
35. Kim JY, Park JS, Park JC et al. Double-filtration plasma- pheresis for the treatment of patients with recalcitrant atopic dermatitis. *Ther Apher Dial.*2013; 17: 631-637.
36. Chirucuzzi A, Faleri S, Lanti A et al. Apheresis in the treatment of recalcitrant atopic dermatitis: case series and review of the literature. *Eur J Dermatol.* 2014; 24: 545-550.
37. Kolkhir P, Balakirski G, Merk HF, Olisova O, Maurer M. Chronic spontaneous urticaria and internal parasites – a systematic review. *Allergy.* 2016; 71: 308-322.
38. Yadav S, Kanvar AJ, Parsad D, Minz RW. Chronic idiopathic urticaria and thyroid autoimmunity: perplexing association. *Indian J Dermatol.*2013; 58: 325.
39. Ardern-Jones MR, Friedmann PS. Skin manifestation of drug allergy. *Br J Clin Pharmacol.*2011; 71: 672-683.
40. Yang Y, Li F, Du J et al. Variable levels of apoptotic signal-associated cytokines in the disease course of patients with Stevens-Johnson syndrome and toxic epidermal necrolysis. *Australas J Dermatol.*2017; 58: e61-e67.
41. Koh MJ, Tay YK et al. An update on Stevens-Johnson syndrome and toxic epidermal necrolysis in children. *Curr Opin Pediatr.*2009; 21: 505-510.
42. Lissia M, Mulas P, Bulla A, Rubino C. Toxic epidermal necrolysis (Lyell's disease). *Burns.*2010; 36: 152-163.
43. Paulsen KM, Pedersen BN, Soleng A et al. Prevalence of tick-borne encephalitis virus in Ixodes ricinus ticks from three islands in north-western Norway. *APMIS.*2015; 123: 759-764.
44. Seczynska B, Nowak I, Segal A et al. Supportive therapy for a patient with toxic epidermal necrolysis undergoing plasmapheresis. *Crit Care Nurse.*2013; 33(4): 26-38.
45. Wang YM, Tao YH, Feng T, Li H. Beneficial therapeutic effects of hemoperfusion in the treatment of severe Stevens-Johnson syndrome/toxic epidermal necrolysis: preliminary results. *Eur Rev Med Pharmacol Sci.*2014; 18: 3696-3701.
46. Hinc-Kasprzyk J, Polak-Krzemińska A, Glowacka M, Ożóg-Zabolska I. The use of plasmapheresis in a 4-year-old boy with toxic epidermal necrosis. *Anaesthesiol Intensive Ther.*2015; 47: 210-213.
47. Mawson AR, Eriator I, Karre S. Stevens-Johnson syndrome and toxic epidermal necrolysis (SJS/TEN): could retinoids play a causative role? *Med Sci Monit.*2015; 12: 133-143.
48. Han F, Zhang J, Guo Q et al. Successful treatment of toxic epidermal necrolysis using plasmapheresis: a prospective observational study. *J Crit Care.*2017; 42: 65-68.
49. Kinoshita Y, Saeki H. A review of toxic epidermal necrolysis management in Japan. *Allergol Int.*2017; 66: 36-41.
50. Bamichas G, Natse T, Christidou F et al. Plasma exchange in patients with toxic epidermal necrolysis. *Ther Apher Dial.*2002; 6: 225-228.
51. Yamada H, Takamori K. Status of plasmapheresis for the treatment of toxic epidermal necrolysis in Japan. *Ther Apher Dial.*2008; 12: 355-359.
52. Szczeklik W, Nowak I, Seczynska B et al. Beneficial therapeutic effect of plasmapheresis after unsuccessful treatment with corticosteroids in two patients with severe toxic epidermal necrolysis. *Ther Apher Dial.*2010; 14: 354-357.
53. Yamane Y, Matukura S, Watanabe Y et al. Retrospective analysis of Stevens-Johnson syndrome and toxic epidermal necrolysis in 87 Japanese patients – treatment and outcome. *Allergol Int.*2016; 65: 74-81.
54. Velasco-Tirado V, Alonso-Sardón M, Cosano-Quero A

- et al. Life-threatening dermatoses: Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis. Impact on the Spanish public health system (2010-2015). *PLoS One*.2018; 13(6):e0198582.
55. Hung PC, Wang HS, Hsia SH, Wong AM. Plasmapheresis as adjuvant therapy in Stevens-Johnson syndrome and hepatic encephalopathy. *Brain Dev*.2014; 36: 356-358.
56. Yu J, Brandling-Bennett H, Co DO et al. (2016) Toxic epidermal necrolysis-like cutaneous lupus in pediatric patients: a case series and review. *Pediatr*. 137(6): e20154497.
57. Faraci M, Giardino S, Lanino E et al. Toxic epidermal necrolysis-like reaction after hematopoietic stem cell transplantation in children. *J Pediatr Hematol Oncol*.2017;39: 254-258.
58. Hansen MS, Klefter ON, Julian HO et al. Management of patients with ocular manifestations in vesiculobullous disorders affecting the mouth. *Oral Dis*.2017; 23: 849-853.
59. Pinna A, Nuvoli E, Blasetti F et al. Plasmapheresis, intravenous immunoglobulins, and autologous serum eyedrops in the acute eye complications of toxic epidermal necrolysis. *Eur J Ophthalmol*.2017; 27: 658-663.
60. Zilberstein J, McCurdy MT, Winters ME. Anaphylaxis. *J Emerg Med*.2014; 47: 182-187.
61. Castells M. (2017) Diagnosis and management of anaphylaxis in precision medicine. *J Allergy Clin Med* 140: 321-333.
62. Kim SM, Ko BS, Kim JY et al. Clinical factors for developing shock in radio contrast media induced anaphylaxis. *Shock*.2016; 45: 315-319.
63. Malina T, Krecsák L, Korsós Z, Takács Z. Snakebites in Hungary – epidemiological and clinical aspects over the past 36 years. *Toxicon*.2008; 51: 943-951.
64. Park HJ, Kim SH et al. Factors associated with shock in anaphylaxis. *Am J Emerg Med*. 2012; 30: 1674-1678.
65. Shaker MS, Hsu D, Gruenberg DA. (2013) An update on venom allergy. *Curr Opin Pediatr* 25: 629-634.
66. Del Caprio-Orantes L, Azuara-Trujillo HA. Anaphylactic shock associated with ceftriaxone, case report and literature review. *Rev Med Inst Mex Seguro Soc*.2015; 53: 736-741.
67. Elieh Ali Komi D, Shafaghat F, Zwiener RD. Immunology of bee venom. *Clin Rev Allergy Immunol*.2018; 54: 386-396.
68. Bilgir O, Calan M, Bilgir F, Cagliyan G, Arslan O. An experience with plasma exchange treatment of acute lymphoblastic leukemia in a case with fulminant hepatitis related to L-asparaginase. *Transfus Apher Sci*.2013; 49: 328-330.
69. Barnes C, Rudzki Z, Ekert H et al. Induction of immune tolerance and suppression of anaphylaxis in a child with haemophilia B by simple plasmapheresis and antigen exposure. *Haemophilia*.2000; 6:693-695.
70. Stelter K, Lübbers CW, Andratschke M, Leunig A. Quincke's edema: diagnosis and management of 102 patients with sudden upper airway obstruction. *Laryngorhinootologie*.2007;86: 416-419.
71. Károlyi Z et al. Urticaria and Quincke's edema. *Orv Hetil*.2006; 147: 1923-1929. (Hungarian)
72. Valsecchi R, Reseghetti A, Pansera B, Di Landro A. Autoimmune C1 inhibitor deficiency and angioedema. *Dermatology*.1997; 195: 169-172.
73. Voinov VA. (2016) Therapeutic apheresis, Constanța: Celebris.
74. Chiarella SE, Grammer LC et al. Immune deficiency in chronic rhinosinusitis: screening and treatment. *Expert Rev Clin Immunol*.2017; 13:117-123
75. Cheng KJ, Xu YY, Zhou ML, Zhou SH, Wang SQ. Role of local allergic inflammation and *Staphylococcus aureus* enterotoxins in Chinese patients with chronic rhinosinusitis with nasal polyps. *J Laryngol Otol*.2017; 131: 707-713.
76. Salvi GE, Cosgarea R, Sculean A et al. Prevalence and mechanisms of peri-implant diseases. *J Dent Res*.2017; 96: 31-37.
77. Merves J, Muir A, Modayur Chadramouleeswaran P et al. Eosinophilic esophagitis. *Ann Allergy Asthma Immunol*.2014; 112: 397-403.
78. O'Shea KM, Aceves SS, Dellon ES et al. Pathophysiology of eosinophilic esophagitis. *Gastroenterology*.2018; 154: 333-345.
79. Hartert TV, Peebles RS. Epidemiology of asthma: the year in review. *Curr Opin Pulm Med*.2000; 6: 4-9.
80. Khan DA et al. Allergic rhinitis and asthma: epidemiology and common pathophysiology. *Allergy Asthma Proc*.2014; 35: 357-361.
81. Tsiakiris G, Neely G, Lind N, Nordin S. Comorbidity in allergic asthma and allergic rhinitis: functional somatic syn-

- dromes. Psychol Health Med.2017; 22: 1163-1168.
82. O'Hollaren MT et al. Update in allergy and immunology. Ann Intern Med.1998; 129: 1036-1037.
83. Fedoseev GB et al. Bronchial asthma. In "Allergologia", ed. by G.B. Fedoseev, St. Petersburg, Russia. 2001; 2: 64-138.
84. Bogomolova IK, Basharova GI, Maslova NI, Ogneva EY. Estimation of lipid peroxidation in children with bronchial asthma. Allergologia Immunologia (Rus).2006; 7: 311-312.
85. Xu J, Sabarinath SN, Derendorf H et al. Cortisol suppression as a surrogate marker for inhaled corticosteroid-induced growth retardation in children. Eur J Pharm Sci.2009; 36: 110-121.
86. Delaunay F, Khan A, Cintra A et al. Pancreatic cells are important targets for the diabetogenic effects of glucocorticoids. J Clin Invest.1197; 100:2094-2098.
87. Lokaj-Berisha V, Gacaferri-Lumezi B, Berisha N, Gashi-Hoxha S. A Pilot Study on BMI, Serum Testosterone and Estradiol Levels in Allergic Male Patients. Open Access Maced J Med Sci.2015; 3:595-600.
88. Chroni E, Veltsista D, Gavanozi E et al. Pure sensory chronic inflammatory polyneuropathy: rapid deterioration after steroid treatment. BMC Neurol. 2015; 15: 27.
89. Pasquet F, Pavic M, Ninet J, Hot A. Autoimmune diseases and cancers. Part I: cancers complicating autoimmune diseases and their treatment. Rev Med Interne (French).2014; 35(5): 310-316.
90. Giat E, Ehrenfeld M, Shoenfeld Y et al. Cancer and autoimmune diseases. Autoimmun Rev.2017; 16: 1049-1057.
91. Dhimi S, Kakouru A, Asamoah F et al. Allergen immunotherapy for allergic asthma: a systemic review and meta-analysis. Allergy.2017; 72: 1825-1848.
92. Cruz NV, Bahna SL. Fever, urticaria, lymphadenopathy, and protracted arthralgia and myalgia resistant to corticosteroid therapy. Allergy Asthma Proc.2011; 32: 395-398.
93. Dai L, Huang Y, Wang Y et al. Serious systemic adverse events associated with allergen-specific immunotherapy in children with asthma. Zhonnuo Dang Dai Er Ke Za Zhi (China).2014; 16: P. 58-61.
94. Hunci D, Şahin E, Muluk NB, Cingi C. Immunotherapy in all aspects. Eur Arch Otorhinolaringol.2016; 273: 1347-1355.
95. El-Qutob D et al. Off-labeled uses of omalizumab. Clin Rev Allergy Immunol.2016; 50: 84-96.
96. Kerzel S, Zemlin M, Rodosch T et al. Plasmapheresis prior to omalizumab administration in a 15-year-old boy with severe asthma and very high IgE levels: sustained effect over 2 years. Klin Padiatr.2011; 223: 356-359.
97. Shelyagina ED et al. Plasmapheresis in complex treatment of patients with bronchial asthma. Prognostic criteria of efficiency. These masters dissert, Ekaterinburg. (Rus).1999
98. Ishina TI, Kakhnovskii IM, Makarova OV et al. Evaluation of clinical effectiveness of intravenous laser irradiation of blood, plasmapheresis and their combination in patients with bronchial asthma]. Ter Arkh (Rus). 2001; 73(3): 15-19.
99. Paleev NR, Karandashov VI, Ostrovsky EI. Application of photochemotherapy red light in the treatment of bronchial asthma. Proc XVI confer Moscow society of hemapheresis, Moscow. 2008;124.
100. Chemeris AN, Dmitriev AA. The use of plasmapheresis in the complex treatment of bronchial asthma. Proc confer "Actual problems of hemapheresis, surgical hemocorrection and dialysis", Moscow. 2009;89.
101. Provotorov VM, Gaikovich AA. A comparative assessment of the clinical efficacy of standard and low-volume plasmapheresis in treating patients with bronchial asthma and chronic bronchitis. Ter Arch (Rus).1996; 68(12): 28-30.
102. Kacprzak D, Pawliczak R. Does aspirin-induced oxidative stress cause asthma exacerbation? Arch Med Sci.2015; 11: P. 494-504.
103. Komov VV et al. Hemosorption in bronchial asthma. Proc XII confer Moscow society of hemapheresis, Moscow, 2004: 27.
104. Komov VV et al. Application of hemosorption in Allergy and immunology. Efferentnaia Terapiia (Rus).2013; 19(1): 68-69.
105. Tatarskii AR, Cheglecova TA, Bobkov EV. Pulse therapy with methylprednisolone in combination with plasmapheresis in the treatment of patients with bronchial asthma. Ther Arkh (Rus).1995; 67(6): 30-32.
106. Meshcheryakova GM et al. Features of immunometabolic disorders and methods of their correction in the combination of some autoimmune diseases. Thes masters diss,

- Voronezh. 1999.
107. Altynova EV, Afanasyeva OI, Efremov EE et al. Immunosorbent for removal of IgE from plasma of patients with allergic diseases. *Allergologia Immunologia (Rus)*.2006; 7(3): 283.
108. Gong D, Ji D, Xu B, Liu Z et al. More selective removal of myeloperoxidase-anti-neutrophil cytoplasmic antibody from the circulation of patients with vasculitides using a novel double-filtration plasmapheresis therapy. *Ther Apher Dial*.2013; 17: 93-98.
109. Dorogov RA, Sokolova MY, Fedorova TA. Plasmapheresis in the complex therapy of bronchial asthma during pregnancy. Proc confer "Current issues of in vitro treatment", Moscow. 2007: 60-62.
110. Samotokin AK et al. The results of clinical application of plasmapheresis in patients in a state of "predasthma". *Klin Med (Rus)*.1996; 74(2): 64.
111. Varlamova SV, Petrov MM, Fedorova LN, Kalinin NN. Long-term use of therapeutic plasmapheresis in a patient with atopic syndrome. Proc XI confer Moscow society of hemapheresis, Moscow.2003: 12.
112. Vasilyev SA, Belinin GY. Plasmapheresis in the therapy of allergosis (subsepsis of Wissler-Fanconi). Proc VI confer Moscow society of hemapheresis, Moscow.1998;107.
113. Churg A, Churg J et al. Steroids and Churg-Strauss syndrome. *Lancet*.1998; 352(121): 32-33.
114. Homma S, Suzuki A, Sato K. Pulmonary involvement in ANCA-associated vasculitis from the view of the pulmonologist. *Clin Exp Nephrol*.2013; 17: 667-671.