

## **Allergic Rhinitis in Childhood. A Look at Pathogenesis and Comparison of Treatment Methods (Literature Review)**

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**Abstract:** Allergic conjunctivitis is a common disease in children, often occurring with allergic rhinitis, and occurring, according to various sources, in 18% of children. Symptoms such as itchy eyes, lacrimation associated with symptoms of allergic rhinitis, difficulty in nasal breathing, rhinorrhea - often cause severe physical and emotional suffering, discomfort, and reduce the quality of life of patients.

**Keywords:** allergic conjunctivitis, childhood, immunoglobulin E, interleukin, antihistamines.

The pathogenetic basis of allergic conjunctivitis, like rhinitis, is IgE-mediated reactions that lead to the formation of allergic inflammation. A significant role in the occurrence of these diseases is played by hereditary predisposition to allergic conditions, as well as exposure to exogenous allergens. Risk factors for allergic rhinitis include maternal smoking during pregnancy, passive smoking in children, and living in ecologically unfavorable regions [2, 3]. Unfavorable social and living conditions, as well as previous food, epidermal or household sensitization, play a major role in the development of allergic conjunctivitis [1].

In the pathogenesis of the above diseases, a special role belongs to T-helpers of the 2nd type, the proliferation and activation of which leads to increased production of interleukins (IL) 4 and 13. These cytokines contribute to the activation of B lymphocytes and increased production of IgE by plasma cells. The interaction of causative allergens with IgE fixed on the surface of mast cells leads to their activation and subsequent secretion of mediators and cytokines, which contribute to the involvement of other cells in the allergic process with the development of inflammation in the nasal mucosa and conjunctiva. All this constitutes the pathogenetic basis of allergic rhinitis and allergic conjunctivitis, often combined within the definition of "allergic rhinoconjunctivitis" [18].

The main effector cells that secrete mediators that cause the clinical manifestations of allergic conjunctivitis and allergic rhinitis are mast cells, basophils and eosinophils [4, 5]. The early phase of the allergic response is caused by preformed (histamine, etc.) and newly synthesized (PGD2) biologically active substances of mast cells. These substances, through interaction with receptors of nerve endings and vessels, cause clinical manifestations of the disease. Histamine released by mast cells in the early phase of the allergic response causes vasodilation, itching of the mucous membranes, hyperreactivity of the nasal mucosa and conjunctiva [12].

Leukotrienes are more important than histamine in the development of nasal congestion. Eosinophils play a key role in the development of allergic inflammation. Under the influence of proinflammatory cytokines (IL 3, IL 5) secreted by mast cells, the synthesis of adhesive molecules by epithelial and endothelial cells is activated, with subsequent accumulation and activation of eosinophils in the nasal mucosa. Activated eosinophils release granules containing

the main eosinophil protein, eosinophil cationic protein, neurotoxin, which have a damaging effect on tissues. Eosinophils also produce IL-8 and granulocyte-macrophage colony-stimulating factor (GM-CSF), which contribute to the accumulation of eosinophils and mast cells in the mucous membrane, the persistence of the resulting allergic inflammation in the nasal mucosa [4,6].

Clinical manifestations of allergic conjunctivitis include burning and pain in the eyes, hyperemia of the mucous membrane of the eyelids, swelling, itching of the eyelids, a sensation of a foreign body in the eyes, as well as lacrimation and photophobia. Allergic conjunctivitis is bilateral and is accompanied by itching, which is a symptom specific to atopy [10].

Diagnosis of allergic conjunctivitis and rhinitis includes collection of allergy history data, skin prick tests, allergy diagnostics (testing of total and specific IgE in the blood), rhinoscopy, ophthalmological examination, peripheral blood test, ultrasound examination of the paranasal sinuses, cytological and immunological examination [15].

Seasonal (intermittent) allergic conjunctivitis is characterized by sensitization to pollen allergens, seasonality of the disease. In year-round (persistent) allergic rhinitis and allergic conjunctivitis, sensitization to aeroallergens of the home, epidermal, food, fungal allergens is revealed, the absence of seasonality of the disease is characteristic [7].

The main therapeutic approaches to the treatment of allergic conjunctivitis are the elimination of causative allergens, reduction of the impact of non-specific trigger factors, pharmacotherapy, and allergen-specific immunotherapy. The pharmacotherapeutic agents used include systemic and topical antihistamines, general and local mast cell membrane stabilizers, topical glucocorticosteroids, and decongestants [9].

The most effective and safest method of preventing an allergic reaction is the complete elimination of the allergens. Elimination of causative allergens is also extremely important in the case of an already developed clinical picture of the disease. However, in reality, this is almost impossible to achieve. In cases of a mild reaction based on the results of skin allergy tests and laboratory research, as well as in the case of polyvalent sensitization, non-specific hyposensitizing immunotherapy is carried out. Histoglobulin injections are most often used (6-10 injections per course). Allergen-specific immunotherapy using causative allergens is carried out in cases where allergens have been identified, but it is impossible to achieve their elimination, and drug symptomatic therapy is not effective enough [14].

In the treatment of children suffering from allergic conjunctivitis in combination with allergic rhinitis, the basic therapy is antihistamines. In 2013, the European Academy of Allergology and Clinical Immunology proposed classifying all antihistamines into drugs of the first and second (new) generation. First generation antihistamines include clemastine (Tavegil), chloropyramine (Suprastin), diphenhydramine (Diphenhydramine), quifenadines (Fenkarol, Bicarfen), and dimethindene (Fenistil). Currently, there are a large number of different antihistamines on the market, but not all antihistamines are equally effective and safe. Therefore, the experts of ARIA (WHO group "Allergic Rhinitis and its Impact on Asthma") have developed the following requirements for antihistamines: the ability to selectively block H1 receptors; the presence of antiallergic action; the rapidity of the onset of the clinical effect; effectiveness within 24 hours, allowing the drug to be taken once a day; safety with long-term use [8].

First-generation antihistamines are characterized by a short-term therapeutic effect, low specificity for H1 receptors, and high permeability through the blood-brain barrier, which causes a sedative effect, manifested by the occurrence of drowsiness after taking the drugs, impaired concentration, memory, and decreased learning ability. First-generation antihistamines may also cause anticholinergic effects (dry mouth, urinary retention, visual impairment). After taking them, side effects may occur in the form of nausea, vomiting, abdominal pain, diarrhea, constipation, and if there are liver dysfunctions, the risk of overdose of this group of antihistamines increases. With prolonged use, tachyphylaxis to these drugs develops and their

therapeutic effectiveness decreases. Sometimes in children, the prescription of first-generation antihistamines can cause severe agitation. In allergic conjunctivitis and allergic rhinitis, first-generation antihistamines can be used only in severe manifestations of the disease that require parenteral administration of these drugs [11].

Modern antihistamines (2nd generation) meet ARIA requirements, although to varying degrees. They are characterized by a rapid onset of action (within the first 30 min - 1 h), effectiveness for 24 h and a minimum number of side effects. In this regard, there is no need to use first-generation antihistamines in outpatient practice, given the safety issues of their use.

In recent years, new (II) generation antihistamines have become widely used in the treatment of allergic conjunctivitis and allergic rhinitis in children: desloratadine, loratadine, cetirizine, etc., which are characterized by high affinity for H1 receptors, the development of a rapid and long-lasting effect, and low permeability through the blood-brain barrier. Crossing the blood-brain barrier results in drowsiness in approximately 10% of patients receiving cetirizine and levocetirizine, while drugs such as desloratadine, loratadine, and fexofenadine do not cause sedation when taken in therapeutic doses. Second-generation antihistamines are characterized by a virtual absence of tachyphylaxis, which allows for their long-term use. Most of them do not have a connection between taking the drug and taking food. The exception is fexofenadine, the bioavailability of which is significantly reduced when taking fatty foods and juices (apple, citrus, including grapefruit). Modern antihistamines are distinguished by the absence of interactions with other pharmacological drugs that are dangerous to the patient's health, and side effects on the cardiovascular system. However, one should remember the risk of developing cardiac arrhythmias when increasing the dose of ebastine to 20 mg and taking erythromycin or ketoconazole at the same time. It is extremely important to have a convenient regimen for taking these drugs (once a day). Given the peculiarities of pharmacokinetics, cetirizine should be used 2 times a day in children under 6 years of age. New generation antihistamines are not metabolized in the liver by cytochrome P 450. Drugs of this series inhibit the release of proinflammatory cytokines (IL 5, 6, 8, 13, GM-CSF, tumor necrosis factor  $\alpha$ , etc.) [13,17].

In terms of suppression of the synthesis of proinflammatory mediators, desloratadine (Erius) exhibits the most pronounced effect in the group of antihistamines, which is associated with its effectiveness in the treatment of nasal congestion in allergic rhinitis. The combination of clinical and pharmacological characteristics: high efficacy in allergic rhinoconjunctivitis, associated with the antihistamine, antiallergic and anti-inflammatory activity of the drug, and a high level of safety (no sedation and no effect on cognitive functions, no clinically significant interactions with other drugs and food, no cardiotoxicity), the presence of a pediatric dosage form and pharmacokinetics that allow the drug to be taken once a day, regardless of age in children from 1 year of age, distinguishes desloratadine as the preferred antihistamine in pediatric practice [16].

The use of second-generation antihistamines helps improve the quality of life of patients with allergic conjunctivitis. Regardless of the causative factor, local antiallergic drug therapy is necessary for seasonal and year-round allergic conjunctivitis to relieve acute manifestations of the disease (itching of the eyelids, photophobia, lacrimation, edema, conjunctival hyperemia). The drugs that have long been used in the treatment of allergic conjunctivitis are 2 groups of eye drops: antihistamines and cromones. They can be used as monotherapy, or combined with each other or with anti-inflammatory drugs that have a different mechanism of pharmacological action [10].

In moderate to severe allergic rhinitis with severe nasal congestion and allergic conjunctivitis, intranasal glucocorticosteroids are indicated. They have a powerful antiallergic and anti-inflammatory effect. The anti-inflammatory action of glucocorticosteroids involves several mechanisms. They suppress the biosynthesis of arachidonic acid, a precursor of prostaglandins, inhibit the release of a number of inflammation mediators and the migration of mast cells, reduce the permeability of capillary walls, and slow down proliferative processes. Thus, glucocorticosteroids block all phases of inflammation.

Often, with severe allergic conjunctivitis, there is a layering of secondary infection, which necessitates the use of local antibacterial drugs. In these cases, it is advisable to use antiallergic, anti-inflammatory and antibacterial drugs together. The use of combined drugs containing glucocorticosteroids (betamethasone, dexamethasone) and antibiotics (gentamicin, tobramycin, framycetin with gramicidin) is effective. In severe cases of allergic conjunctivitis, 1% hydrocortisone ointment can be used [1,7].

**Conclusion.** Thus, treatment of patients with allergic conjunctivitis is based on 3 main principles: elimination of the allergen, allergen-specific immunotherapy and pharmacotherapy. Systemic antihistamines should be prescribed to reduce the severity of acute and subacute manifestations of allergic conjunctivitis, as well as conjunctivitis combined with allergic rhinitis. Individual sensitivity of receptors to antihistamines dictates the need for individual selection of the drug for each patient. Membrane-stabilizing drugs locally retain their relevance in the treatment and prevention of allergic conjunctivitis, as they are highly safe.

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