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THE IMPACT OF LOCAL AND SYSTEMIC IMMUNE RESPONSES ON CHILDREN'S RESPIRATORY ALLERGIES AND STRATEGIES FOR OPTIMAL TREATMENT

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Annotation

Based on literature data and the results of our own scientific research, the etiology, pathogenesis, and treatment of a number of diseases included in the group of respiratory allergies have been analyzed. Special attention is paid to allergic inflammation and mediators of intercellular interaction—cytokines. Cytokines are secreted glycosylated polypeptides that regulate and determine the nature of immune responses. A key role in the pathogenesis of respiratory allergies in pediatric practice is played by the imbalance of cytokine levels involved in allergic inflammation.

Alterations in indicators related to phagocytic activity, lysozyme, immunoglobulins, and lymphocyte subpopulations indicate pathological reactions in nonspecific defense processes, a decrease in local and systemic immunity, which also determines the severity of the disease course and necessitates the use of additional corrective methods in children.

Pronounced changes in cytokine profile indicators dictate the need to include immunocorrection methods in the scheme of comprehensive therapy and to assess the effectiveness of the treatment provided.

The immunomodulatory effect of drugs is manifested in an increase in T-lymphocyte counts, restoration of leukocyte bactericidal activity, influence on humoral factors (activation of the complement system, increase in total and activated B-lymphocytes), and phagocytosis.

Respiratory allergies remain among the most common allergic diseases in childhood. To develop adequate therapeutic methods, it is necessary to continue detailed studies of pathogenesis, including the cytokine system. The emergence of new knowledge about disease pathogenesis will allow expanding the spectrum of therapeutic options.

KEYWORDS: respiratory allergies, cytokines, allergic inflammation, immunoglobulins, immunocorrection, Ismigen, Derinat, Amiksin

Mediators of Allergic Reactions

Respiratory diseases account for 30–40% of pediatric morbidity in different age groups.

Over the past decade, there has been an increase in the number of patients in dispensary groups of frequently ill children. Among these children, recurrent bronchitis occupies a leading position among respiratory system pathologies. In recent years, there is a tendency toward recurrence of bronchial pathology, an increase in obstructive forms, and prolonged disease course. Due to comorbidities of the respiratory, nervous, cardiovascular, and musculoskeletal systems, the premorbid background of children often deteriorates. The etiological structure of

pathogens changes, and the effectiveness of drug therapy decreases due to increasing pathogen resistance.

Anatomical and physiological characteristics of pediatric patients, increased frequency of secondary immunodeficiencies related to adverse environmental factors, noncompliance with sanitary standards, allergic sensitization from pharmacological agents and allergen-containing products are the main causes of respiratory allergies. Genetic predisposition should also be considered as a cause of respiratory allergies.

Today, specialists pay special attention to the causes of recurrent obstructive syndrome and the progression of local and systemic immune disorders, as well as the induction of chronic forms of bronchial obstruction. Adequate interpretation of immune system abnormalities allows selection of optimal therapy, and timely clinical diagnosis helps prevent complications.

Currently, there is an increase not only in the prevalence of respiratory allergies but also in the number of patients with severe disease and resistance to standard therapy. At the same time, the profile of clinical manifestations of allergy is changing. Some nosological forms are underdiagnosed, indicating the relevance of studying immune system disorders in children with allergic pathology. Confirmation of this is reflected in the growing number of publications on the topic. Both domestic and international studies evaluate laboratory data in children with allergies, including hypersensitivity to specific allergens. It has been established that external factors also influence the prevalence of allergic diseases.

Respiratory allergies are a group of diseases of the respiratory system, including lesions of the nose and paranasal sinuses, larynx, trachea, bronchi, and lungs. Allergic immune mechanisms are involved in disease development. The immunological conflict depends on the action of allergens and the immune response of the organism, determined by genetic and hormonal factors.

Allergens are substances carrying genetically foreign information and causing specific immune responses. Allergens can be complete or incomplete (haptens), and of infectious or non-infectious nature.

The main route of allergen entry into the body is inhalational.

Typically, household dust is the main inhalational allergen in respiratory allergies, due to microscopic mites of the genus *Dermatophagoides*. Respiratory allergies in children can also be caused by plants, especially during flowering periods (e.g., lamb's quarters in autumn, timothy grass in summer), and by animal fur. Poor sanitary conditions, mold, and fungi also contribute to allergy development.

Types of Allergic Reactions

1. **Anaphylactic** – characterized by sensitization of tissue cells, mainly mast cells; antigen-antibody binding triggers the release of biologically active substances, mast cell degranulation, vasodilation, edema, infiltration, and bronchial smooth muscle spasm.
2. **Cytotoxic (immediate)** – involves IgE-mediated humoral reaction (e.g., transfusion reaction), but plays a minor role in respiratory organ lesions.

3. **Cytotoxic (semi-delayed)** – involves IgG-mediated humoral reaction with complement system activation.
4. **Delayed cellular reaction** – humoral antibodies are not involved; characterized by slow onset and gradual resolution.

Often, different reaction types coexist, with one predominating.

In some cases, diagnosing respiratory allergies in children is difficult. Therefore, it is necessary to analyze medical history and consider genetic predisposition. Close relatives of children with bronchial asthma (BA) often also have allergic diseases. Comorbid allergic conditions such as urticaria, atopic dermatitis, or helminthic infections may accompany respiratory allergies. Respiratory allergies in children are characterized by frequent relapses, often one to two times per month. Peripheral blood eosinophilia is also important; it may remain normal or decrease during disease manifestation, increase after symptom relief, and persist during remission.

The diagnostic algorithm may include IgE determination and blast transformation tests with specific allergens.

Specific Respiratory Allergic Diseases

Allergic rhinitis (AR) in children is rarely isolated and usually affects sinuses, pharynx, larynx, bronchi, Eustachian tubes, and middle ear. Symptoms include sneezing, nasal itching, coughing, sometimes urticaria, laryngotracheitis, or Quincke's edema. Fever may occur. Rhinitis can recur.

Allergic rhinosinusitis arises on the background of frequent acute respiratory diseases, leading to polypoid changes in the nasal and sinus mucosa. Symptoms include nasal obstruction, mucous or mucopurulent discharge, headache, and low-grade fever. Post-adenoidectomy, relapses are possible. Eosinophil levels in nasal mucus can reach 80%. Allergy testing is diagnostically important.

Adenoid hypertrophy is often of allergic etiology; surgery alone may not yield the expected results.

Chronic tonsillitis may have an infectious-allergic nature; food allergens are significant triggers. The disease often develops rapidly after allergen exposure.

Allergic laryngitis develops acutely; edema can lead to asphyxia. Food allergens are a common cause, often presenting as false croup, typically requiring hospitalization.

Acute and chronic otitis media may be recurrent; fever can reach 39 °C, ear pain is common, with up to 12 relapses per year.

Allergic tracheitis and bronchitis are most common in children aged 3–6 years. Allergic tracheitis often precedes BA and is associated with sweating, excessive salivation, pupil constriction, and sinusitis; the cough resembles pertussis.

Allergic bronchitis is persistently recurrent; fever is usually absent or subfebrile; nighttime coughing is common. Diagnosis is often missed.

Allergic pneumonia develops independently or on the background of other allergic diseases, particularly BA (3% of BA patients). Lesions are usually in the middle and right lower lobes. Blood eosinophilia and lymphocytosis are present; ESR may be normal or elevated; fever is usually absent. Radiological changes resolve rapidly.

Eosinophilic pulmonary infiltrates are often asymptomatic and found incidentally, frequently in BA patients. Blood eosinophilia is common.

Recent domestic and foreign studies emphasize cytokine profiling in children with respiratory allergies, as cytokine imbalance leads to pronounced inflammatory processes in the respiratory tract. Cytokines regulate nearly every aspect of immunity and inflammation, including antigen presentation, bone marrow cell differentiation, cell recruitment or activation, adhesion molecule expression, and acute-phase responses. They are classified by cellular source (mono- vs. lymphokines) or biological activity (humoral, cellular, allergic reaction mediators, or immunosuppressive).

Cytokines regulate inflammation. Proinflammatory cytokines include:

- Chemotactic cytokines activating inflammatory cells
- Cytokines destroying altered cells and promoting inflammatory cell proliferation and differentiation
- Cytokines stimulating bone marrow precursors of inflammatory cells and their release into blood
- Cytokines suppressing inflammatory cell function, thus inhibiting inflammation

Upon exposure to specific antigens, T-helper cells differentiate into Th1 and Th2 subpopulations. Th1 secrete IL-1, IL-2, IFN-gamma, TNF-alpha and beta, supporting T- and B-cell differentiation, natural killer activity, and antiviral/antibacterial defense. Th2 secrete IL-4, IL-5, IL-10, promoting humoral responses. Th1 predominates in healthy individuals; Th2 predominates in atopic patients.

Severe BA is associated with increased IL-8 in airway secretions. Interleukins regulate IgE synthesis, B-cell maturation, epithelial cell status, lung hyperreactivity, and atopic dermatitis development. Innate immunity, Toll-like receptor polymorphisms, and IL-33 are also implicated in obstructive bronchitis pathogenesis.

BA patients show reduced suppressor T-lymphocytes, Th2-predominant response, cytokine dysregulation, eosinophil activation, and neuroendocrine disturbances. Asthmatic inflammation is driven by Th2 cells secreting IL-4, IL-5, IL-9, IL-13. Th1 function is impaired, with decreased IFN-gamma and overproduction of IL-4 and IL-10. Cytokines thus play a key role in BA pathogenesis, though data on individual cytokines remain contradictory.

Despite advances in pharmacotherapy, severe BA prevalence continues to rise, necessitating new diagnostic and therapeutic strategies.

Immunomodulators in Pediatric Respiratory Allergies

Therapeutic strategies aim to reduce Th2 activity and enhance Th1. Currently, no immunomodulators selectively alter Th1/Th2 balance, but immunomodulators are used in pediatric respiratory allergy therapy.

- **IRS-19**: halved frequency and duration of intercurrent acute respiratory infections; BA exacerbations reduced by 1.3×.
- **Broncho-Vaxom**: clinical improvement in 68% of cases; increased IFN-gamma, reduced IgE and circulating immune complexes.
- **Ismigen**: increases CD3+ T-helper cells; in combination therapy, CD8+ lymphocyte levels normalize; improves phagocytosis, lysozyme activity, and NBT test.
- **IFN and IFN inducers (Amiksin)**: stimulate immunity via NK cells, macrophages, and T-lymphocytes.
- **Polyoxidonium**: immunomodulatory, antioxidant, detoxifying, membrane-protective; reduces ARVI episodes and exacerbations in BA patients.
- **Derinat**: natural polymer immunomodulator from sturgeon milt; antioxidant, membrane-stabilizing; increases T-lymphocytes, leukocyte bactericidal activity, complement activation, total/activated B-lymphocytes, and phagocytosis; shifts Th1/Th2 balance toward Th1.

Inclusion of immunomodulators in comprehensive therapy reduces BA exacerbations, prolongs remission, decreases ARVI frequency, and positively influences immune response. Ongoing research is needed due to the absence of selective Th1/Th2 immunomodulators and rising pediatric respiratory allergy prevalence.

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