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MODERN APPROACHES TO THE TREATMENT OF BRONCHIAL ASTHMA IN CHILDREN

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Annotation

Bronchial asthma (BA) is one of the most common chronic diseases worldwide, affecting more than 100 million people. It occurs in all countries regardless of their level of development and represents a significant social problem for both children and adults. Bronchial asthma can develop at any age; however, in almost half of patients it begins in childhood, and in another 30% it develops before the age of 40. Women are more frequently affected by bronchial asthma. The prevalence of BA is associated with environmental deterioration, exposure to household allergens, and infectious diseases. The social significance of this problem and the economic burden caused by the disease are considerable for healthcare systems. One of the most important tasks of modern medicine is the improvement of methods for the diagnosis and treatment of asthma.

KEYWORDS: asthma, wheezing, genes, infections, allergens.

Etiology of Bronchial Asthma

Bronchial asthma is a chronic inflammatory disease of the airways in which many cells and cellular elements are involved. Chronic inflammation leads to the development of bronchial hyperreactivity, which results in recurrent episodes of wheezing, shortness of breath, chest tightness, and coughing, especially at night or in the early morning. These episodes are usually associated with widespread but variable airway obstruction in the lungs, which is often reversible either spontaneously or under the influence of treatment [1].

Both internal and external factors influence the development and manifestations of bronchial asthma. Internal factors include sex, obesity, and genetic predisposition (genes responsible for atopy and genes associated with bronchial hyperreactivity). External factors include allergens, infections (most often viral), occupational hazards, smoking, air pollution, and nutrition. The most important factors responsible for the development of bronchial asthma are allergens that sensitize the airways, trigger the onset of the disease, and subsequently maintain its course. Identification and elimination of allergens are key to the successful treatment of bronchial asthma.

Therapy of Bronchial Asthma

The treatment of bronchial asthma (BA) is комплексный (comprehensive). It includes adherence to an anti-allergic regimen, pharmacological therapy, and non-pharmacological treatment. Great importance is attached to selecting basic therapy depending on the level of control over asthma symptoms. Currently, a classification of bronchial asthma according to the level of control is recommended, reflecting not only the severity of clinical manifestations but also the adequacy of therapy (Table 1). All medications used in treatment are divided into two groups: drugs for basic therapy and drugs for relieving exacerbations.

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The national strategy for the treatment of bronchial asthma recommends a **stepwise approach** to therapy (Table 2), in which treatment becomes more intensive as the severity of the disease increases. This approach takes into account the variability of disease severity both between different patients and within the same patient over time. The goal of the stepwise approach is to achieve asthma control using the smallest possible number of medications. If the course of asthma worsens, the number and frequency of medications increase ("step up"). If asthma remains well controlled for three months, the amount and frequency of therapy are reduced ("step down").

A reduction in the dose of basic therapy is performed only if the patient's condition remains stable for at least three months (monitored using patient diaries, peak flow measurements, and physician examination). Therapy is reduced gradually: the previous drug dose is decreased by 25–50%, or additional medications are discontinued. In combined therapy with inhaled glucocorticosteroids (ICS) and systemic glucocorticoids (GC), systemic hormonal drugs are reduced and discontinued first while maintaining the ICS dose. During dose reduction, asthma symptoms, clinical manifestations, and pulmonary function parameters must be carefully monitored.

Currently, **inhaled glucocorticosteroids (ICS)** are considered the most effective drugs for controlling the disease. Their use is recommended in persistent asthma of any severity. Long-term ICS therapy significantly reduces the frequency and severity of exacerbations. The more severe the asthma, the higher the required doses of inhaled steroids (Table 3).

The anti-inflammatory effect of ICS is related to their inhibitory action on inflammatory cells and mediators, including suppression of cytokine production, interference with arachidonic acid metabolism and leukotriene and prostaglandin synthesis, reduction of microvascular permeability, prevention of migration and activation of inflammatory cells, and increased sensitivity of beta receptors in smooth muscles. ICS also increase apoptosis and reduce the number of eosinophils by inhibiting interleukin-5. Thus, ICS stabilize cell membranes, reduce vascular permeability, improve beta-2 adrenoreceptor function, and stimulate epithelial cells. Because ICS therapy is local, it provides a strong anti-inflammatory effect directly in the bronchial tree with minimal systemic effects.

An important characteristic of ICS is **lipophilicity**, which allows the drug to accumulate in the airways, slows its release from tissues, and increases its affinity for glucocorticoid receptors. These drugs are rapidly absorbed from the bronchial lumen and retained in airway tissues for a long time. This lipophilicity distinguishes ICS from systemic glucocorticoids; therefore inhalation of systemic steroids (such as hydrocortisone, prednisolone, or dexamethasone) is ineffective because they exert only systemic effects regardless of the route of administration.

ICS include: **beclomethasone dipropionate, budesonide, fluticasone propionate, flunisolide, triamcinolone acetonide, and mometasone furoate** (Table 4). These drugs are available as metered-dose aerosols, dry powders, and solutions for nebulizer use.

Pulmonary bioavailability depends on the presence or absence of a propellant. Inhalers without freon have better effectiveness. For example, beclomethasone dipropionate with a freon propellant requires approximately double the dose compared with the freon-free form. The amount of ICS delivered to the airways also depends on the dose, the type of inhaler, and the inhalation technique.

Principles of ICS use include:

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- ICS should be recommended for patients who require short-acting beta-2 agonists two to three times daily or more.
- ICS can reduce the need for systemic glucocorticoids in steroid-dependent asthma.
- Asthma control is achieved faster with higher initial doses of ICS.
- All ICS drugs are sufficiently effective in equivalent doses.
- Administration twice daily has proven effectiveness; increasing to four times daily only slightly improves efficacy at the same dose.
- Standard doses (e.g., 800 µg of beclomethasone) can be increased up to 2000 µg if necessary.
- Dose reduction should be gradual (25–50%) once the condition remains stable for at least three months.

Methods of delivering drugs to the airways include:

- Metered-dose aerosol inhalers (standard, breath-activated, or with a spacer)
- Dry powder inhalers (single-dose, multidose reservoir, multidose blister)
- Nebulizers (ultrasonic or jet)

Each aerosol-generating device has advantages and disadvantages, including portability, the need to coordinate inhalation with actuation, the need for refilling medication, and cost. About 80% of patients have difficulties using metered-dose inhalers. Therefore physicians must teach correct inhalation technique and may recommend nebulizers or spacers. Spacers allow more medication to reach the bronchi while reducing deposition in the mouth, throat, and tongue, thereby lowering the risk of hoarseness, fungal infection, and cough. Patients are advised to rinse their mouth with water after inhalation to prevent fungal infections.

Long-term treatment with high doses of ICS may cause systemic side effects such as hemorrhage, adrenal suppression, osteoporosis, cataracts, and glaucoma. ICS are not contraindicated in patients with tuberculosis. Considering possible side effects, combination therapy is often advisable to achieve asthma control with lower doses of ICS.

Starting from **step 3** of therapy, if asthma control remains insufficient, **long-acting beta-2 agonists (LABA)** should be added to ICS. These drugs are considered an alternative to increasing ICS doses in patients who respond poorly to anti-inflammatory therapy. However, LABAs should not be used as monotherapy because they lack significant anti-inflammatory activity and may increase the risk of death in some patients. Regular use may also lead to drug tolerance.

Combination therapy significantly improves respiratory function, reduces nighttime attacks, and decreases the need for short-acting beta-2 agonists. Adding LABA is often more effective than doubling the dose of ICS. The two most commonly used drugs are **salmeterol** and **formoterol**. Salmeterol has a slow onset of action, with bronchodilation occurring within 10–20 minutes and lasting about 12 hours. It is highly lipophilic and stabilizes mast cell membranes, reduces histamine levels, and decreases pulmonary capillary permeability. Formoterol has similar clinical properties and acts as a full beta-2 receptor agonist with a somewhat stronger dose-dependent effect.

Combination inhaled medications containing both ICS and LABA have become central in asthma therapy. These drugs increase treatment adherence, reduce costs compared with using two separate medications, and improve effectiveness at lower ICS doses. Using one inhaler also simplifies inhalation technique.

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Examples include **Seretide Multidisk** (salmeterol + fluticasone propionate) and **Symbicort Turbuhaler** (budesonide + formoterol fumarate). These allow flexible dosing (1–4 inhalations per day) depending on the patient's condition. Short-acting beta-2 agonists should still be available for acute symptom relief.

The most effective drugs for rapid symptom relief are **fast-acting beta-2 agonists**, which are the bronchodilators of choice for acute asthma symptoms. They are available as aerosols, tablets, and powders. Among long-acting bronchodilators, **theophylline** and **terbutaline** are sometimes used, especially for nocturnal symptoms.

Systemic corticosteroids are usually used during exacerbations, administered orally or intravenously in high doses. Their mechanisms of action are similar to ICS, but they affect additional target cells and can cause systemic complications during long-term use. A typical dose is **40–50 mg of prednisolone daily for 5–10 days** during exacerbations. Long-term control using systemic steroids alone is considered a serious medical error because it requires higher doses and leads to complications such as osteoporosis, diabetes, and obesity.

Patients receiving long-term systemic corticosteroids require monitoring including:

- physical development assessment
- blood pressure monitoring
- slit-lamp eye examination for cataracts
- electrolyte monitoring
- blood glucose testing
- fecal occult blood testing
- evaluation for infections
- measurement of basal cortisol levels

Common systemic corticosteroids used in asthma include **prednisolone** and **methylprednisolone** because they have minimal mineralocorticoid effects and relatively short half-lives. Long-acting depot forms are not recommended.

Some common **medical errors in asthma therapy** include:

- failure to prescribe ICS
- underestimating disease severity
- attempting to control exacerbations with low steroid doses
- using beta-blockers
- incorrect selection of inhalation devices
- continued exposure to allergens

In some cases, respiratory symptoms attributed to asthma may actually result from other diseases, leading to an incorrect diagnosis.

Infections may trigger asthma exacerbations, particularly when asthma coexists with bronchitis or pneumonia. When prescribing antibiotics, allergic history should be carefully evaluated because reactions commonly occur with penicillins and sulfonamides. If penicillin allergy is present, alternative antibiotics such as **doxycycline** or **macrolides** may be used.

Nedocromil or **sodium cromoglycate** may be used as an adjunct to ICS or as an alternative in patients who cannot tolerate steroids. These drugs inhibit the release of allergic mediators and

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prevent bronchoconstriction, though they are less effective than first-line treatments. Therapy usually lasts at least two months with two inhalations twice daily.

Antileukotriene drugs are also used because leukotrienes play a significant role in asthma pathogenesis. These medications reduce symptoms, decrease coughing, and have mild bronchodilator and anti-inflammatory effects. They include two groups: leukotriene synthesis inhibitors and leukotriene receptor blockers. Their main side effect is hepatotoxicity.

Anti-IgE therapy is indicated for patients with elevated serum IgE levels. Clinical studies have shown that **omalizumab** significantly reduces the frequency of severe asthma exacerbations and emergency medical visits, improves quality of life, and decreases the need for oral corticosteroids and rescue medications.

Non-pharmacological treatment of bronchial asthma includes:

- respiratory therapy (breathing training, breathing control, intermittent hypoxic training)
- herbal therapy

Patient education and regular medical follow-up are essential components of asthma management. To evaluate treatment effectiveness, patients should monitor their condition using **peak flowmetry**, which allows objective assessment of disease progression and appropriate adjustment of therapy.

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