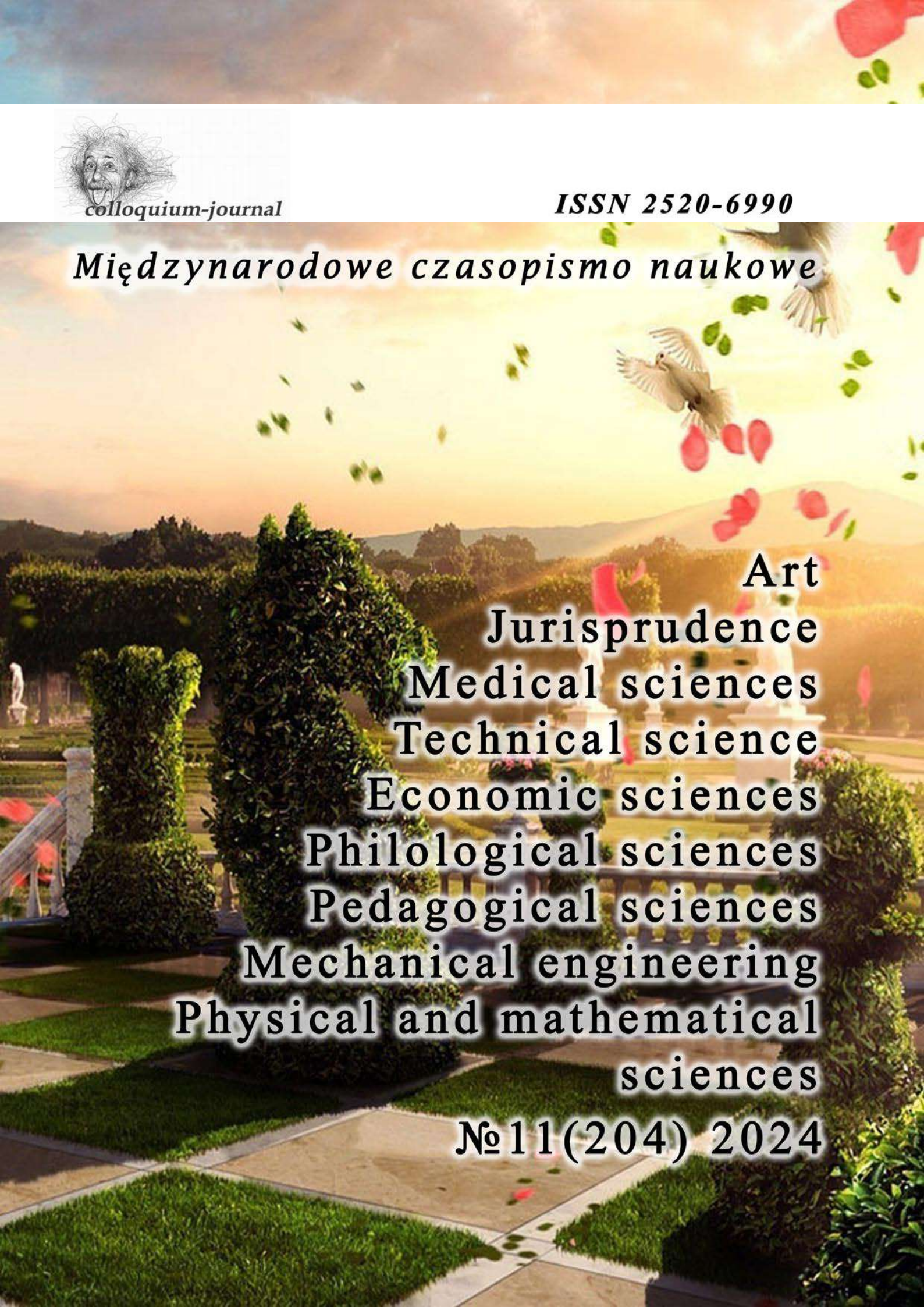
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DIFFICULTIES OF DIAGNOSTIC AND FEATURE TREATMENT OF ALLERGIC RHINITIS IN PATIENTS AFTER CORONAVIRUS INFECTION

Abstract.
The 2020 COVID-19 pandemic coincided with consecutive pollination seasons for trees, grasses, and weeds. The final results of the pandemic will not appear soon, but we can already say that it will influence the course of history no less than the well-known plague and Spanish flu pandemics. At the beginning of the pollen allergy season, many questions arose regarding the difficulty of differential diagnosis of allergic rhinitis (AR) with manifestations of coronavirus and other viral infections. The mutual influence of these pathological conditions on each other was unknown. In the process of monitoring patients, more and more data was accumulated, which highlighted the peculiarities of the clinical characteristics of COVID-19, influenza, acute respiratory infections, and seasonal AR (rhinoconjunctivitis). Some of the symptoms of these respiratory pathologies are similar, but each of these diseases has its own characteristic features that make it possible to carry out a differential diagnosis and choose the correct patient management tactics. Among the numerous respiratory and non-respiratory symptoms (systemic nature of the lesion) of COVID-19, a decrease in the sense of smell and a runny nose deserve attention.

Keywords: *allergic rhinitis, COVID-19, diagnosis, treatment.*

AR is a common disease that affects approximately 20% of the global population and can be triggered by seasonal allergens, year-round allergens, or both. In the atopic march, AR most often manifests for the first time in the age category of teenagers (from 13 to 19 years). With SAD, symptoms can appear in the spring, summer, and early fall and are caused by an allergic sensitivity to grass, tree, weed, or mold pollen. With CAR, symptoms are present throughout the year; caused by dust mites, pet dander, cockroaches, or mold. Several types of effector cells, cytokines, and bioactive mediators are involved in the pathogenesis of AR, which contribute to the formation of the inflammatory process, which leads to the development of a biphasic inflammatory reaction and is clinically characterized as immediate (early) and late-phase symptoms. Patients in most cases have a genetic predisposition to develop AR with hyperproduction of specific immunoglobulin E (sIgE) to the causative allergen (for example, grass pollen), which binds high-affinity IgE receptors on mast cells and basophils.

At the beginning of the pandemic, it was unclear whether patients with allergic diseases, including asthma, developed a more severe course of COVID-19. According to current data, the main target cells for coronaviruses are cells of the alveolar epithelium, in the cytoplasm of which virus replication takes place. The virus causes an increase in the permeability of cell membranes and increased transport of fluid rich in albumin into the interstitial tissue of the lungs and the lumen of the alveoli. At the same time, the surfactant is destroyed, which leads to the collapse of the alveoli. Acute respiratory distress syndrome (ARDS) develops as a result of a sharp violation of gas exchange. SARS-CoV-2 uses angiotensin-converting enzyme 2 (ACE2) as a cellular receptor to enter the airway epithelium. Higher ACE2 expression increases susceptibility to SARS-CoV as shown in in vitro studies.

Studies have shown that increased expression of the ACE2 gene, found in smokers, patients with diabetes and hypertension, causes a more severe course of COVID-19. While the decrease in the expression of the ACE2 gene in the cells of the respiratory tract in patients with asthma and other allergic diseases gives reasons not to consider allergic pathology as a risk factor for the development of COVID-19 and its severe course.

The concept of a single respiratory tract is supported by numerous evidences. A pronounced correlation between allergy symptoms from the upper and lower parts of the respiratory tract was determined. Concomitant uncontrolled AR can negatively affect the course of BA, which may necessitate a change in AR treatment tactics.

In the study of D. Jackson, W. Busse, it was shown that the expression of ACE2 in the nasal epithelium of children with allergic sensitization and allergic asthma is reduced. ACE2 expression decreases in the nasal and bronchial epithelium of allergic patients after allergen provocation. The data obtained show that the expression of ACE2 was the lowest in patients with a high level of allergic sensitization and BA. Importantly, nonatopic asthma was not associated with decreased ACE2 expression.

Given that ACE2 is a receptor for SARS-CoV-2, the obtained results suggest a lower risk of severe COVID-19 in patients with allergic diseases. However, this hypothesis needs additional research to confirm or deny.

AR therapy

The goal of treatment is to achieve full control of AR symptoms, prevention of progression of symptoms, prevention of BA and the development of complications (medicinal rhinitis, sinusitis, postnasal drip syndrome, otitis media, sleep disorders, cognitive functions). The COVID-19 pandemic has made adjustments

to people's everyday lives. Forced self-isolation led to the fact that, as a result of a long stay at home, the contact of patients with pollen allergens significantly decreased, but the contact with household allergens (epidermal allergens of pets, house dust mites) increased. Wearing masks also reduced exposure to pollen allergens.

Modern evidence-based medicine offers:

Elimination of the causative allergen. The degree of severity and the course of AR are mainly determined by the concentration of allergens in the environment, therefore, the elimination of allergens helps not only to reduce the severity of AR symptoms, but also the need for drug treatment. All possible measures to reduce contact with the allergen should be used as the first step in the treatment of AR. Special attention should be paid to elimination measures in cases where there are serious restrictions for pharmacotherapy (pregnant women, breastfeeding women, patients with severe concomitant pathology, athletes).

AR pharmacotherapy.

Allergen-specific immunotherapy (ASIT) is a method of pathogenetic treatment of IgE-mediated allergic diseases, which makes it possible to change the course of the disease. Effective ASIT provides a reduction or complete disappearance of symptoms during the period of natural exposure to the allergen. After ACIT, the duration of the disease decreases, the need for medication decreases. ACIT makes it possible to prevent the development of asthma or delay it, to prevent the expansion of the spectrum of sensitization in the patient.

Educational programs for patients.

In the national protocol on AR (2016) and international clinical recommendations - the WHO document ARIA (Allergic rhinitis and its influence on asthma) 2001-2020, the principle of stepwise therapy is recommended depending on the form and severity of AR.

In the case of a mild course of AR, monotherapy with non-sedating AGPs of the II generation or local AGPs, or cromoglycate drugs, or anti-leukotriene drugs is recommended. In the case of a moderately severe course of AR, as well as in the absence of an effect at the first step of treatment, topical intranasal corticosteroids (InCS) is prescribed. If the effect is incomplete, it is recommended to increase the dose of InKS to the maximum allowed.

In June 2020, Michael C. Peters, Satria Sajuthi reported that CSs used to treat AD may affect the expression of ACE2 or TMPRSS2 genes in sputum cells. TMPRSS2 is a transmembrane protease that modifies the spike proteins of some viruses, including SARS-CoV, SARS-CoV-2, MERS-CoV, and influenza A and B, to promote viral infection and spread. A similar increase in the expression of both genes (ACE2 and TMPRSS2) in the same subgroups of patients provides a mechanism for the double hit of SARS-CoV-2 infection and the incidence of COVID-19.

The data on the expression of ACE2 and TMPRSS2 genes in the samples of induced sputum were analyzed, and three groups of patients were compared: the first group – did not use inhaled CS; the second - used low and medium doses of inhaled CS and the third - used high doses of inhaled CS. Data analysis showed that the expression levels of ACE2 and TMPRSS2 genes were significantly lower in patients with asthma who used inhaled CS, in contrast to patients who did not receive such treatment. ACE2 and TMPRSS2 gene expression mediates SARS-CoV-2 infection of patient lung cells. Thus, the obtained data on the decrease in the expression of the ACE2 and TMPRSS2 genes during therapy with inhaled CSs suggest that the use of topical CSs does not increase the risk of SARS-CoV-2 infection, but this issue requires further study.

Approaches to the treatment of AR after the transferred disease of COVID-19

The AR therapy algorithm is built depending on the intensity of symptoms, the predominance of certain clinical manifestations of rhinitis and the level of disease control. At the current stage, 5 classes of therapeutic drugs are distinguished:

- non-sedating H1-histamine blockers, leukotriene receptor antagonists, cromons;
- inCS;
- inCS + intranasal azelastine;
- oral CS for a short course and as an additional treatment;
- treatment by a narrow specialist, ASIT.

InKS is the most effective group of drugs in achieving AR control. They have a pronounced anti-inflammatory effect, as they affect all mediators of allergic inflammation. InCS are effective against all symptoms of AR, which gives reason to consider them drugs of choice in patients with AR of moderate and severe course, especially in cases of predominance of nasal obstruction.

Requirements for modern InCS:

• rapid development of the effect and duration of action;
• influence on the maximum number of symptoms;
• security;
• absence of systemic side effects (low bioavailability);
• minimal risk of developing local side effects.

One of the main characteristics of InCS is the therapeutic index - the ratio of the total score of effectiveness to the total score of side effects. Despite the fact that safety and effectiveness have been proven in numerous studies for all used ICS, systematic data analysis makes it possible to differentiate drugs according to clinically important features.

In the conducted analysis, the maximum therapeutic index was obtained for mometasone furoate (TIX = 7), which indicates high efficiency and low potential for the development of side effects. The lipophilicity of InCS plays a significant role in achieving the clinical effect. High lipophilicity ensures rapid penetration of the drug into the mucous membrane of the nasal cavity and reaching the CS receptor, which ensures the development of a clinical effect in a minimal period of time. In addition, high lipophilicity contributes to the long-term retention of the drug in the nasal mucosa, which makes it possible to use the drug once a day.

Mometasone furoate has the maximum lipophilicity among all ICS. Unlike other ICS, this compound has high anti-inflammatory activity due to its tropism to the epithelium of the mucous membrane of the nasal cavity, as well as good solubility in nasal secretions, the fastest development of the clinical effect, which is registered already 12 hours after the start of application. At the same time, long-term administration of mometasone furoate is not accompanied by a decrease in its anti-inflammatory effect.

At the cellular level, mometasone furoate inhibits the release of inflammatory mediators, increases the production of lipomodulin, an inhibitor of phospholipase A. Phospholipase A inhibits the release of arachidonic acid and, accordingly, the formation of the products of its metabolism - cyclic endoperoxides, prostaglandins. This compound reduces the formation of inflammatory exudate and the production of lymphokines, inhibits the migration of macrophages, inhibits the processes of infiltration and granulation, reduces inflammation due to the reduction of the formation of a chemotaxis substance (effect on late allergic reactions), inhibits the development of an allergic reaction of the immediate type (due to inhibition of the production of arachidonic acid metabolites and a decrease release of inflammatory mediators from mast cells), which causes anti-inflammatory, anti-edematous and membrane-stabilizing effect.

The high safety profile of mometasone furoate ensures minimal systemic and local side effects due to the lowest bioavailability among ICS, which is 0.1%. In addition, it was established that mometasone furoate reduces the expression of the ICAM-1 molecule, which ensures the adhesion of viruses to the epithelial cell, and also disrupts pre-transcriptional mechanisms in the cycle of the development of a viral infection. The absence of changes in endogenous cortisol secretion is a significant safety criterion for the use of mometasone furoate, which plays an important role in the normal functioning of the hypothalamic-pituitary-adrenal system. The optimal safety profile of mometasone furoate spray is associated with the absence of the development of atrophic changes in the mucous membrane of the nasal cavity and the preservation of the mobility of the ciliated epithelium when using the drug.

InCS are effective not only for AR manifestations, but also for accompanying ocular symptoms. The causes of eye symptoms in AR are the direct impact of allergens on the conjunctiva, as well as the reflex reaction of the conjunctiva in response to irritation of sensitive nerve endings in the nasal cavity. The release of inflammatory mediators during an allergic reaction stimulates the trigeminal ganglion, which leads to vasodilatation, conjunctival erythema, lacrimation, and itching. This reflex is triggered when allergens enter the nasal cavity.

A meta-analysis of the effectiveness of the use of mometasone furoate in the form of a nasal spray for the relief of eye symptoms in patients with RA (seasonal and year-round) was conducted. A significant reduction in the intensity of symptoms such as tearing, itching and redness of the eyes was noted compared to placebo.

Mometasone furoate meets the requirements of modern ICS to a greater extent: rapid onset of clinical effect, duration of action of 24 hours, effect on all symptoms of AR and eye symptoms, high level of safety, which is ensured by low bioavailability, high lipophilicity and minimal local side effects.

The pharmacological market of Ukraine is represented by numerous preparations of mometasone furoate. The drug Momixon manufactured by the Adamed Pharma company deserves special attention.

The suspension of the drug Momikson, compared to other mometasones, penetrates the most deeply into the distal parts of the nasal cavity. Momikson is a physiologically stable suspension that does not change its viscosity under the influence of temperature in the nasal cavity. The nasal dispenser ensures a stable flow of the substance, even after the 10th injection.

Mometasone furoate nasal spray has a wide range of indications among InCS drugs:

• SAR and CAR of adults, adolescents and children from the age of 2;

• acute sinusitis or exacerbation of chronic sinusitis in adults, including the elderly, in adolescents from 12 years of age - as an auxiliary therapeutic agent in antibiotic treatment;

• prophylactic treatment of SAD of medium and severe course in adults and adolescents from 12 years of age (recommended to be used 2–4 weeks before the expected start of the pollination season);

• polyposis of the nose, which is accompanied by impaired nasal breathing and smell, in adults;

• acute rhinosinusitis with mild and moderately pronounced symptoms without signs of severe bacterial infection in patients aged 12 years and older;

• treatment of nasal polyps and associated symptoms, including nasal congestion and loss of smell, in patients aged 18 years and older.

The listed characteristics of mometasone furoate and broad indications for use allow the practitioner to safely use the drug in patients with AR during epidemics of respiratory viral infections, including the new coronavirus infection.

Conclusions. Modern algorithms for diagnosis and therapy of AR have been developed. The course of the disease may change over time (degree of severity, phase of the course, appearance of extranasal symptoms), which requires revision of treatment in accordance with the principles of step-by-step therapy of AR. InCS play an important role in achieving disease control. Mometasone furoate, characterized by the highest therapeutic index among ICS, has a wide range of indications and occupies a special place in the treatment of rhinitis.

Specific recommendations for the treatment of allergic diseases in the era of COVID-19 should take into account the similarities and differences between the clinical manifestations of AR and coronavirus infection. Early mild symptoms of COVID-19 can be confused with AR manifestations, or they can be concomitant. Adequate AR therapy is especially important during this period, as an uncontrolled course of an allergic disease can lead to a severe course of a viral infection.

AR pharmacotherapy is not a factor that aggravates the course of COVID-19, including ICS, and in the case of concomitant BA – also inhaled CSI. Allergic disease of the respiratory tract is probably not a risk factor for a severe course of COVID-19, especially under conditions of control of allergic pathology.

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