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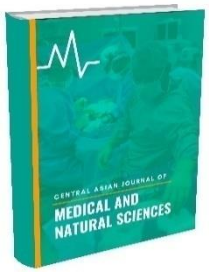

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Issues of Comorbidity of Bronchial Asthma and Covid-19

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Abstract: The literature review presents the results of studies on various aspects of the combination of bronchial asthma and COVID-19. In particular, the issues of the frequency of bronchial asthma among patients with confirmed COVID-19, the influence of bronchial asthma on the risk of developing a new coronavirus infection, the peculiarities of the course of bronchial asthma in patients with COVID-19 are discussed. The features of the use of individual components of basic therapy of bronchial asthma during the pandemic, in particular, inhaled and systemic corticosteroids, antileukotriene medicals, targeted therapy, are considered. Attention is paid to recommendations on the choice of devices for the administration of inhaled medications in the light of prevention of the spread of a new coronavirus infection.

Key words: bronchial asthma, COVID-19, comorbidity.

In the context of the COVID-19 (COronaVIrus Disease 2019) pandemic, doctors faced difficulties in diagnosing and treating diseases of the respiratory system, including bronchial asthma (BA) [1, 14, 16, 36, 37], which affects more than 300 million patients worldwide [32]. In the light of this unique medical problem, clinicians in each case have to make a decision on the choice of components of basic therapy or on-demand therapy in patients with newly diagnosed AD, on the possibility of continuing treatment of patients with an existing diagnosis of AD with recommended medications [2, 4, 5, 37], and also in cases of combination of BA and COVID-19.

The effect of bronchial asthma on the risk of COVID-19

The data obtained in China at the beginning of the pandemic did not indicate a higher risk of developing COVID-19 in patients with AD. Several clinical reviews were conducted on the assessment of concomitant diseases in patients with COVID-19 over 18 years of age who were treated in a hospital, but AD was not included in the list of considered comorbidities, so its relationship with COVID-19 could not be reliably established [26, 62]. Guan W. J. et al. presented data from the national registry, which included 1,590 cases of COVID-19 in China, according to which none of the patients had AD [35]. According to the results of a study conducted by Li H. et al. In Wuhan, among 584 patients with COVID-19, BA as a concomitant disease was significantly less common (0.9%) compared to the general population (6.4%) [45]. In a study involving 290 patients with confirmed COVID-19, Zhang J. J. et al. They also found a very low prevalence of AD, which was 0.3% [62]. In addition, Zhang J. J. et al. 140 clinical cases

of COVID-19 were analyzed, none of the patients were found to have asthma or other allergic diseases. This was the reason to assume that this pathology is not a risk factor for COVID-19 [63]. There are 12,760 COVID-19 cases in the system review

Khan M. et al. concomitant AD was detected in 1.4% (n = 355) [41]. In support of the above results, comorbid BA was not detected in any of the 99 patients with COVID-19 in the study presented by Chen N. et al., as well as among 138 patients examined by Wang D. et al. [19, 59].

However, other studies conducted outside China, the results of which are described below, show a higher prevalence of AD among patients with confirmed COVID-19. Recent studies conducted in the USA and the UK have revealed an increased incidence of AD among hospitalized patients over 18 years of age with COVID-19 [15, 25]. In the work of Chhiba K. D. et al. Concomitant AD was detected in 220 (14%) of 1,526 patients with COVID-19 confirmed by polymerase chain reaction (PCR). At the same time, the presence of AD did not increase the risk of hospitalization of these patients [20]. Published by the Centers for Disease Control and Prevention, the results of a study involving patients with confirmed COVID-19 from several hospitals across the United States showed that 27.3% of COVID-19 patients aged 18 to 49 years had concomitant AD, while the incidence of AD in the general population is 8.9% [22, 31]. However, it is not indicated whether BA was allergic or non-allergic in its etiology [39]. Zhu Z. et al., analyzing data from 492,768 patients of the UK biobank, concluded that patients with AD have a higher risk of severe COVID-19. At the same time, no significant relationship has been established between the presence of allergic asthma and the severe course of COVID-19 [65]. In Strasbourg, France, according to Grandbastien M. et al., out of 106 hospitalized patients with COVID-19 included in the study, 23 suffered from AD [34]. In 9 Seattle hospitals, Bhatraju P. K. et al. 24 clinical cases of COVID-19 were analyzed, of which 3 (14%) patients had concomitant AD [15]. AD was the fourth most common concomitant pathology (14% of cases) among 16,749 hospitalized patients in the UK included in the study presented by Docherty A.V. et al. [25]. In general, 17% of patients hospitalized with COVID-19 suffered from AD, and 27.3% aged 18 to 49 years, according to a study conducted by Garg S. et al. in 14 US states [31].

The low incidence of AD, according to the results of studies in the PRC, can be explained by underdiagnosis and/or insufficient consideration of the entire spectrum of concomitant pathology of the respiratory system in patients with COVID-19. In addition, conflicting data on the occurrence of AD in COVID-19 patients in various studies may be related to general differences in the prevalence of concomitant diseases, including AD, in different countries.

In a retrospective study conducted in 60 regions of the Russian Federation, Avdeev S. N. et al. studied the prevalence of asthma and chronic obstructive pulmonary disease in 1,307 patients with pneumonia caused by SARS-CoV-2 hospitalized in intensive care units. AD occurred in 1.8% of patients. It was assumed that, unlike cardiovascular pathology and diabetes mellitus, chronic respiratory diseases slightly increase the risk of developing a severe form of COVID-19, requiring hospitalization in intensive care units and artificial ventilation. At the same time, patients with chronic obstructive pulmonary disease had a tendency to a more severe course of COVID-19, including a greater need for noninvasive ventilation and a greater incidence of shock [14].

Features of the course of bronchial asthma in patients with COVID-19

Currently, there is no unambiguous opinion on the features of the pathophysiology of AD in patients with confirmed COVID-19. Theoretically, patients with AD have an increased susceptibility to SARS-CoV-2 infection and a tendency to a more severe course of COVID-19 due to a decrease in antiviral immunity and the risk of virus-induced exacerbation [48]. However, it is interesting to suggest that cytokines mediating inflammation of the second type (interleukins -4, -5 and -13) and eosinophilia in

AD can protect against COVID-19. SARS-Cov-2, similar to SARS-Cov and other coronaviruses, uses the angiotensin-converting enzyme receptor 2 (APF2) to enter the cell [39, 53]. Increased expression of APF2 is thought to increase susceptibility to COVID-19. In patients with AD, respiratory epithelial cells have reduced expression of APF2 receptor genes, which may provide protection against SARS-Cov infection-2 [39, 48, 53]. However, in non-allergic AD, the expression of APF2 receptor genes remains at the same level [39]. It was also found that the second type of inflammation is associated with an increased level of transmembrane serine protease 2 (TMPRSS2 – transmembrane Serine Protease 2), which ensures effective binding of the virus to the cell membrane [53]. It is possible that a decrease in the expression of the APF2 gene with a margin compensates for a minimal increase in the expression of TMPRSS2, which potentially makes it possible to consider AD-related inflammation of the second type as a protective factor against COVID-19 [48, 53, 65]. On the contrary, other authors have suggested that the second type of inflammation associated with AD reduces the antiviral immunity of the body [18]. In addition, obstruction of the lower respiratory tract in AD may exacerbate hypoxemia resulting from diffuse alveolar damage in COVID-19 [23, 43]. It was revealed that viral infections, including several types of coronaviruses, cause exacerbation of asthma, contribute to inflammation of the respiratory tract and hypersecretion of mucus [44]. Nevertheless, it was found that SARS pathogens, as well as MERS (Middle East Respiratory Syndrome), similar types of coronaviruses, do not contribute to an increase in the risk of exacerbation of AD, whereas seasonal coronaviruses do increase it [50]. Grandbastien M. et al. It was determined that SARS-Cov-2 infection does not increase the frequency of severe exacerbations of AD [34]. However, it is assumed that, as in the case of other human coronaviruses (HCoV – Human CoronaVirus), SARS-Cov-2 contributes to the development of exacerbation of AD [44]. For these and other reasons, patients with AD are recommended to continue supportive therapy throughout the COVID pandemic-19 [7, 37, 54].

The results of the study Ferastraoaru D. et al. It has been shown that in patients with AD with COVID-19 infection, the phenotype of Th2 asthma, characterized by peripheral blood eosinophilia (≥ 150 cells/ml), is associated with a reduced risk of hospitalization [30]. The development of eosinophilia in patients with AD during hospitalization was associated with a decrease in hospital mortality from COVID-19. Thus, this study demonstrated the potential protective role of eosinophilia in patients with AD and COVID-19. The exact role of eosinophils in SARS-CoV-2 infection has not been studied. Several studies have shown that many hospitalized patients have eosinopenia, which can serve as a prognostic factor for the development of a more severe COVID infection-19 [28, 47, 62]. The results of in vitro and in vivo studies showing the interaction between Th2 inflammation and the expression of the APF2 gene in COVID-19 suggest that this asthma phenotype may be an important predictor of morbidity and mortality from COVID-19.

Treatment of bronchial asthma during the COVID-19 pandemic

Inhaled corticosteroids (ICS) are effective first-line medications for the control of AD with the delivery of the active substance directly to the point of application in the bronchial epithelium, which makes it possible to quickly suppress inflammation by regulating the level of proinflammatory cytokines [4, 8, 60].

In the above-mentioned studies, which demonstrated the suppression of antiviral immune protection of the bronchi in patients with asthma due to the development of type II inflammation, it was suggested that ICS, by reducing the severity of inflammation, may contribute to an increase in the activity of the local antiviral immune response [18, 36, 44]. In addition, the results of studies conducted at the beginning of the COVID-19 pandemic showed that ICS can reduce the expression of APF2 and TMPRSS2 genes in the epithelial cells of the respiratory tract, thereby preventing the penetration of SARS-Cov-2 [3, 8, 36, 51]. It was found that the administration of ICS both in monotherapy and in combination with bronchodilators led to suppression of coronavirus replication and a decrease in the

production of proinflammatory cytokines [7, 38, 49]. In an in vivo study, Matsuyama S. et al. It was found that X cyclesonide selectively suppresses HCoV replication in human cells [49]. In vitro studies have shown that formoterol, glycopyrronium bromide, as well as a combination of formoterol, glycopyrronium bromide and budesonide have an inhibitory effect on seasonal coronavirus replication and cytokine production [61]. Moreover, despite the fact that corticosteroids are not the main means of treating lung damage in COVID-19, they can contribute to the suppression of cytokine release syndrome that develops in some COVID-19 patients [54, 55]. The administration of low doses of short-acting ICS in the first days from the onset of the disease was accompanied by a decrease in the duration of additional oxygen support. In addition, less severity of clinical symptoms and lower mortality were observed in this group of patients [12, 54, 60]. According to Licskai C. et al., taking into account current recommendations, systemic glucocorticosteroids, such as prednisone, can be used in the treatment of severe exacerbation of AD, regardless of whether it is caused by COVID-19 infection or has a different etiology [32, 33, 37]. Leukotriene receptor antagonists, having anti-inflammatory and broncholytic effects, are considered as an addition to the basic therapy of AD. In influenza and acute respiratory distress syndrome, montelukast reduces inflammation in the lung tissue. In inflammatory diseases of the upper respiratory tract, montelukast also reduces eosinophilic infiltration by suppressing the release of cytokines by epithelial cells [24, 40]. Bozek A. et al. It was found that the incidence of COVID-19 was significantly lower among elderly patients with severe asthma who took montelukast compared to those who did not receive it [17]. Among patients with AD hospitalized for COVID-19, patients who used montelukast as a basic therapy, as a rule, did not need respiratory support or multicomponent antiviral treatment. In addition, Khan A. et al. It was shown that in patients with confirmed COVID-19 who took montelukast, the severity of clinical manifestations of coronavirus infection is significantly less in comparison with those who were not prescribed therapy with leukotriene receptor antagonists [40].

In several studies in COVID-19 patients, azithromycin proved to be an effective treatment for AD, insufficiently controlled by standard inhalation therapy, by reducing the frequency of exacerbations and improving the quality of life [52]. In addition, it was shown that the administration of azithromycin in patients with AD contributed to an increase in the production of interferons by respiratory tract cells, therefore, this therapy could hypothetically be effective to reduce the risk of adverse outcomes of COVID-19 in patients with AD. However, routine administration of azithromycin is currently not recommended as a prevention and treatment of COVID-19 [3, 7].

Allergen-specific immunotherapy (ASIT) is the treatment of allergic diseases of the respiratory tract, including asthma, in which immune tolerance to a specific allergen is achieved by repeated administration of it in minimal doses [42, 64]. ASIT in patients with AD leads to desensitization and immune tolerance, which can play a protective role in terms of prevention of cytokine storm that occurs in severe cases of COVID-19 [48]. The initiated ASIT can be continued in patients with AD without clinical symptoms of COVID-19, who have not had contact with SARS-Cov-2 in the recent past. However, in acute respiratory tract infections, including COVID-19, it is recommended to interrupt ASIT until recovery [42].

Biological targeted medications are also used as an adjunct to the basic therapy of AD in order to reduce the frequency of severe exacerbations [6, 29, 32]. According to experts of the Canadian Thoracic Society, during the COVID-19 pandemic, patients with AD should continue therapy with monoclonal antibodies in order to reduce the frequency of emergency treatment and hospitalization. If therapy with biological medications has been discontinued, other medications should be prescribed to prevent exacerbations, such as low doses of prednisone, high doses of ICS in combination with long-acting beta-2-adrenergic receptor agonists or muscarinic cholinergic

receptor antagonists [34]. It is recommended, if possible, to continue self-treatment with a biological targeted medication at home in order to reduce the number of visits to the doctor and prevent the planned administration of the medication from being missed. In order to ensure the transition from hospital treatment to therapy at home and to prevent or timely detect side effects of biological medications, preliminary training of patients and their relatives is necessary, as well as subsequent remote monitoring by medical personnel with the possibility of consulting with the attending physician 24/7. With the development of COVID-19, targeted therapy of AD should be temporarily discontinued until clinical recovery and a negative PCR result for SARS-Cov-2 [57]. The use of metered-dose inhalers plays a crucial role in the effective treatment of respiratory diseases, including asthma. For many patients, they are ideal devices, since their use does not require much time and is characterized by simplicity [13]. The use of individual metered-dose inhalers is characterized by a low risk of virus spread, but they are not suitable for the treatment of patients with acute life-threatening respiratory insufficiency, with cognitive or neuromuscular disorders or insufficient inhalation force [13]. Powder inhalers are activated by inhalation and therefore do not require synchronization of inhalation with inhaler activation. However, their use in some patients may be accompanied by irritation of the respiratory tract, contributing to the appearance of cough and, therefore, potentially increasing the risk of spreading the virus. Nebulizers are the most versatile and effective devices for inhalation therapy of asthma, but their use requires certain time and maintenance costs [11, 13]. There are conflicting data on the high risk of viruses entering the environment when using nebulizers. Wan G.-H.et al. It was shown that the use of nebulizers in medical institutions in patients with SARS did not increase the risk of infection [58]. Nevertheless, medical organizations were forced to revise the rules for the use of nebulizer therapy in order to reduce the risk of the spread of COVID-19 among patients and medical workers [11]. In particular, recommendations are given to avoid the use of nebulizers during a pandemic [37]. Instead, to reduce the spread of the virus, it is preferable to use a metered aerosol inhaler with a spacer or a powder inhaler [9, 46].

Currently published guidelines on the management of patients with AD during the COVID-19 pandemic, prepared by specialists in the field of pulmonology, allergology, clinical immunology, recommend maintaining maintenance therapy and therapy of exacerbations in the same volume [7, 37, 46]. In addition, it is necessary to apply additional precautions, observing a set of anti-epidemic measures (social distancing, hygienic hand treatment), avoid exposure to triggers of exacerbation of asthma, strictly follow the technique of using inhalers [10, 46]. It is not recommended to change the pre-selected tactics of management of patients with AD in the absence of indications for intensification of therapy.

If symptoms appear or they worsen, the patient should contact the attending physician, since shortness of breath, dry cough, while observing BA therapy regimens, may be a manifestation of COVID-19 infection. The introduction of telemedicine and remote consulting technologies during the pandemic allowed monitoring patients, while reducing the number of personal visits to the doctor. A recent meta-analysis showed that remote patient management and teleconsultations were equally effective for improving AD control and improving the quality of life of patients [21, 27]. The action plan developed jointly with the attending physician allows the patient to adjust therapy in a timely manner, reduces the likelihood of hospitalization for an exacerbation of AD. In addition, it has been shown that telemedicine is not inferior to face-to-face consultations in the management of patients with AD.

Conclusion The above results of the currently available studies on the problem of combination of BA and COVID-19 do not allow us to draw an unambiguous conclusion about a greater predisposition to SARS-CoV-2 infection and a more severe course of COVID-19 in patients with

BA and, conversely, about the negative impact of COVID-19 on the course and control of BA. Most specialists are inclined to the need to continue basic therapy and on-demand therapy for the prevention of exacerbations of AD during the COVID-19 pandemic. At the same time, it is recommended to use with caution some components of the complex therapy of AD, in particular antileukotriene and targeted medications, in case of confirmation of COVID-19.

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