Covid-19 and Bronchial Asthma
(Clinical and Epidemiological Aspects)

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Annotation: The review article combines modern knowledge about the origin, pathogenesis, epidemiology, clinical and laboratory diagnostics, as well as therapy and prevention of new coronavirus infection; describes the possible relationship of coronavirus infection with bronchial asthma, as well as possible options for the effect of coronavirus infection on the severity of bronchial asthma collected from publications of specialists of the Russian Federation and researchers from various countries.

Keywords: coronavirus infection, coronavirus, COVID-19, bronchial asthma, pandemic.

Bronchial asthma (BA) refers to widespread chronic respiratory diseases (CRD). According to a recent report by the World Health Organization, the number of AD patients in the world is more than 339 million [1]. Experts predict an increase in the number of patients with AD to 400 million by 2025 [2, 3].

March 11, 2020 The World Health Organization (WHO) has announced the beginning of the COVID-19 pandemic. At the Extraordinary Summit of the Heads of State of the Group of 20 on COVID-19 held on March 26, WHO Director-General Dr. TedrosAdhanom Ghebreyesus said: "We have gathered to discuss measures to counter the most severe crisis of our time in the field of health. We are at war with a virus that threatens to destroy our lives if we do not resist it. For the first time, the widespread spread of a new coronavirus in the territory of the People's Republic of China (PRC) was announced at the end of 2019 [4].

By the beginning of 2020, confirmed cases of the disease were registered in all administrative entities of the PRC. More than 80% of cases were detected in the Southeastern part of China, with the epicenter in Hubei Province. The National Health Commission of China reported details of the first 17 deaths before January 22, 2020 [5]. On January 25, 2020, a total of 1975 COVID-19 infections were confirmed in mainland China with a total of 56 deaths. From mid-January 2020 the infection caused by the new virus spread rapidly across the countries of Asia, America, Europe and then was recorded on the territory of the Russian Federation.

Since the first report dated January 7, 2020, according to PubMed [6], in less than 2 months, more than 200 papers on virology, epidemiology, etiology, diagnosis and treatment of COVID-19 have been published.
The causative agent was a new type of virus from the family of RNA-containing coronaviruses. For the first time, this was stated by Xu Jianjiang, a researcher at the Engineering Academy of China, who headed the group for evaluating the results of testing pathogenic microorganisms.

Coronaviridae (CoV) are one of the main pathogens of both humans and vertebrates, having a different host spectrum and a wide tissue tropism. Among this family, there are several groups of infectious agents that cause diseases from mild forms of upper respiratory tract inflammation to severe (in rare cases) in children and are directly dangerous to humans – these are HCoV-229E, HCoV-NL63, HCoV-OC43, HCoV-HKU1 and SARS-CoV virus, the causative agent of atypical pneumonia, the first case of which was registered in 2002.; The MERS-CoV virus, the causative agent of the Middle East Respiratory Syndrome (English Middle East Respiratory Syndrome, - MERS), an outbreak of which occurred in 2012 in Saudi Arabia.

After decoding the genome [7], making it publicly available to the scientific community, the International Committee on the Taxonomy of Viruses on February 11, 2020 assigned an official name to the causative agent of the infection – SARS-CoV-2. On February 11, 2020, WHO officially approved the name of the new infection – COVID-19 (abbreviation from the English COroNaVirus Disease 2019 – severe acute respiratory infection caused by the coronavirus SARS-CoV-2 Coronavirus disease 2019) [8].

Since its discovery, the virus has spread to more than 210 countries around the world, causing thousands of deaths, and has had a huge impact on their health systems and economies.

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]. In a systematic review of 12,760 COVID-19 cases, Khan M. et al. concomitant AD was detected in 1.4% [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 was 8.9% [22, 31]. However, it is not indicated whether AD 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 AD-related inflammation of the second type 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 has been 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].

Is BA a risk factor for severe COVID-19?

To date, there is no evidence that AD itself is a risk factor for infection or the development of severe COVID-19. Initially, all patients with chronic lung diseases were classified as at risk, and, according to current clinical recommendations, patients with AD require hospitalization even with a mild course of COVID-19. However, there are more and more articles, the authors of which suggest that BA not only does not contribute to the severe course of a new coronavirus infection, but can also have a protective effect. In addition to the above pathogenesis features, there are data indicating a decrease in the expression of angiotensin converting enzyme 2 (APF2) receptors, which is a target for the virus, in patients with atopic asthma and in patients receiving Inhaled glucocorticosteroids (IGCS).

The administration of low doses of short-acting IGCS 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 the 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].

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.

Conclusion

The above results of the currently available studies on the problem of the combination of AD 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 AD and, conversely, about the negative impact of COVID-19 on the course and control of AD. 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.
LITERATURE


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