Asthma during infection with particular attention to the COVID-19 pandemic

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Abstract:
For almost a year now, we have been living during the COVID-19 pandemic. In November 2019, an increasing number of patients were diagnosed with severe interstitial pneumonia in Wuhan (China). A new coronavirus, previously unknown in humans, SARS-CoV-2, turned out to be an etiological factor. The new virus called SARS-CoV-2 is closely related to the β-coronavirus found in bats. The first cases of the new disease have highlighted a similar clinical course of interstitial pneumonias previously found in China and the Middle East (SARS and MERS). The SARS-CoV and MERS-CoV viruses turned out to be etiological factors. Man has no natural immunity against these newly discovered viruses. As soon as the virus has passed from its natural environment (animals) to man, the transmission rate of the infection has accelerated. Most often the infection occurs in tightly closed, poorly ventilated rooms, which are clusters of large groups of people. With the exhaled aerosol formed in the airways of the infected person (sneezing, talking, singing, laughing, coughing) the virus enters the airways of subsequent people. This observation allowed to develop methods to reduce subsequent infections to a minimum. Pandemic COVID-19 raised many questions about the treatment of asthma/COPD patients and the need to modify their treatment. Due to the similarity of symptoms, questions arose about the diagnosis and differentiation of COVID-19 from asthma/COPD. It is unclear whether patients with asthma/COPD are at increased risk of SARS-CoV-2 infection. It has not been shown in previous analyses that allergic diseases, asthma or COPD are factors in the development of infection caused by SARS-CoV-2. However, the turbulent course of SARS-CoV-2 infection and the cytokine storm syndrome (CSS) caused by this infection, which is characterized by elevated inflammatory markers (e.g., CRP, ferritin) and acquired immunodeficiency (lymphopenia with T-cell reduction) raise concerns about exacerbation of allergic inflammation in the airways. Moreover, disruption of the coagulation cascade in CSS may lead to coagulopathy with elevated D-dimers and fibrin metabolism disorders (generalized severe endovascular disease), which is reflected in the analyzed hematological parameters of COVID-19 patients. Increased lesions in the lung parenchyma may be caused by progressive disorders of the coagulation system, but also changes in small vessels occurring not only in the lungs, but also in the vessels of the kidneys, heart and brain. Older age and coexisting diseases for patients in this age group – heart disease, hypertension, chronic obstructive pulmonary disease (COPD), asthma, diabetes mellitus and obesity are risk factors for the more severe course of COVID-19. However, there is controversy about the influence of asthma and COPD on the course of COVID-19. Current recommendations of the CDC (Centers for Disease Control and Prevention – USA) state that patients with moderate to severe asthma may be more likely to develop a more severe disease if they are infected with SARS-CoV-2. It should be remembered that children are the least exposed to SARS-CoV-2 infection due to lower ACE-2 and TMPRSS2 receptor expression in the airways compared to adults. The basis of control therapy for asthma is inhalation steroids. Steroids interact directly with the respiratory epithelium, contributing to the reduction of inflammatory reactions through the growth of anti-inflammatory cytokines. An important element in SARS-CoV-2 infection are ACE-2 receptors present on the surface of respiratory epithelial cells. There are fewer of these receptors in allergic asthma, which means that SARS-CoV-2 viruses have less ability to connect to these cells. Preclinical studies have also shown that some substances used to treat asthma reduce the replication of SARS-CoV-2 in respiratory epithelial cells. Inhalational steroids reduce the severity of SARS-CoV-2 infection in COPD patients. It has also been shown that medications – glycopyronium, formoterol and triple combination drug containing budesonide, formoterol and glycopyronium inhibit coronavirus replication and reduce the synthesis of proinflammatory cytokines. Similar observations have been made in the case of rhinovirus infections. Not only asthma patients but also COPD patients should not interrupt their treatment with inhalation drugs, especially steroids during the SARS-CoV-2 pandemic. In COPD long-acting bronchodilators (β-mimetics – formoterol, salmeterol, cholinolytics – glycopyronium, tiotropium) are the first line of therapy. The addition of inhalation glucocorticosteroid in patients with frequent exacerbations during these exacerbations,

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followed by the introduction of oral corticosteroids and antibiotics, should be a natural effect in the course of SARS-CoV-2 infection. All safety rules should be observed when using drugs in nebulization. There are no indications to replace nebulization with pMDI. In patients treated with DPI, multi-dose inhalers should be used, safer than single dose (capsule) ones.

Key words: asthma, inhalation therapy, COVID-19

Introduction

The COVID-19 pandemic has been with us for almost a year. In November 2019, in the city of Wuhan, China, cases of severe interstitial pneumonia were diagnosed in a growing number of patients. The aetiological factor behind it transpired to be a new coronavirus, so far unseen in people, which came to be called SARS-CoV-2 [1]. By November 29th 2020, 62 882 389 cases of infection with that virus were diagnosed across the world.

In November 2020, over 600 thousand cases were diagnosed world-wide every day, with ca. 10 thousand daily deaths at the time [2]. SARS-CoV-2 is closely related to the β-coronavirus observed in bats [3]. The first cases of the new disease pointed the attention of the medical world towards a similar clinical course observed in interstitial pneumonia diagnosed earlier in China and in the Middle East (SARS and MERS). Previously, the aetiology involved viruses SARS-CoV and MERS-CoV [1].

People do not have a natural immunity against those newly discovered viruses. Once the virus was transmitted from its natural environment (animals) to humans, the speed of infection transmission accelerated. Infection usually occurs in closed, small and poorly ventilated spaces, with a large number of people inside. That observation has made it possible to implement methods that reduce further infections to a minimum. Hence, limits have been introduced regarding the number of persons staying in the same room at a given time, participating in mass events, and any other gathering held within an enclosed space.

The infection is transmitted through droplets, when we inhale the aerosol of an infected person, generated in the course of speaking, singing, laughing, crying, sneezing or coughing. Wearing a barrier (mask) for the exhaled aerosol, and thorough hand washing remain the main methods of preventing the transmission of infection [4]. One should remember that the effectiveness of facial barriers is not identical in all cases, with the highest efficacy attributed to medical masks, and negligible efficacy attributed to visors [4].

When people speak loudly, cough or sneeze, the aerosol generated by the infected person travels over a distance of 1–5 metres. As has been indicated in simulation studies, it may even be transmitted over a distance of 6 metres. Therefore, keeping a distance of > 1.5 m from other people around is by all means well-founded [4].

COVID-19 and Asthma and Chronic Obstructive Pulmonary Disease

The COVID-19 pandemic has triggered a lot of questions related to the treatment of patients diagnosed with asthma and chronic obstructive pulmonary disease (COPD), and to the necessity to modify their therapies. Due to the similarity of symptoms, questions were raised on how to diagnose COVID-19, and how to differentiate the new disease from asthma and COPD. It is not clear, whether patients who suffer from asthma/COPD are exposed to a higher risk of SARS-CoV-2 infection.

The first cases of COVID-19 in Europe were unequivocally associated with the infection transmitted from people travelling from China, who were asymptomatic. Presently, we observe cases of infection transmitted not only from people travelling from high-incidence areas, but also from those who have never been in those areas, and have only been in contact with asymptomatic or poorly symptomatic persons [5].

It has not been indicated in the analyses conducted to date that allergic diseases, including asthma or COPD are risk factors for the development of infection caused by the SARS-CoV-2 virus [6]. The severe course of SARS-CoV-2 infection and the cytokine storm syndrome (CSS) it triggers, which is characterized by elevated inflammation markers (e.g.,

CRP and ferritin) and acquired immunity deficiency (lymphopenia with T-cell depletion), raise concerns related to the exacerbation of allergic inflammation in the airways [7]. Moreover, disturbance of the coagulation cascade in CSS may lead to a coagulopathy with high D-dimer levels and disturbed fibrin metabolism (a severe systemic intravascular disease), which is reflected in the analysed haematological parameters of COVID-19 patients [8]. The exacerbation of lesions within lung parenchyma may be caused by progressive disorders within the coagulation system, and lesions within small vessels, found not only in the lungs, but also in the kidneys as well as in the heart and brain [9].

Older age and co-morbidities characteristic of that age group, including cardiac diseases, arterial hypertension, COPD, asthma, diabetes and obesity, are risk factors for a more severe course of COVID-19 [10]. However, there are controversies regarding the impact of asthma and COPD on the course of COVID--19. The present recommendations of CDC (Center for Diseases Control and Prevention, US) demonstrate that patients with moderate/severe course of asthma may be more exposed to a severe disease resulting from SARS--CoV-2. One should remember that children have the lowest risk of SARS-CoV-2 infection due to a lower expression of the ACE-2 receptor and TMPRSS2 in their airways as compared to adults [11].

Asthma is amongst the most common allergic diseases. It is estimated that 8–9% of the population suffer from the condition [12], and it would appear that obstructive diseases (asthma, COPD) might be associated with a significant risk of SARS-CoV-2 infection. However, the number of patients suffering from asthma and COPD, presented in the papers published by Chinese and Italian centres, was much lower than expected, considering the incidence of the conditions, and ranged between 1.5% and 4% [6, 13–16]. Entirely different data came from New York and the UK. Among COVID-19 patients in New York, 9% were diagnosed with asthma, and 5.4% with COPD, whereas in the UK, as many as 14% of patients were reported to be suffering from those conditions [16].

Recently, more information has come out indicative of the fact that asthma is not a risk factor for a more severe clinical course of SARS-CoV-2 infection, and does not involve a higher risk of death [17]. In their analysis, Barroso et. al demonstrated that the length of hospital stay due to SARS-CoV-2 infection is not different in patients diagnosed with asthma from those without asthma as concomitant disease (9.72 ± 8.14 days vs. 10.9 ± 9.67 days) [18]. Chhiba et al. indicated that asthma does not contribute to a higher risk of hospitalization due to COVID-19 [19]. It has also been demonstrated that asthma does not prolong the length of hospital stay for COVID-19, and that it is not associated with a higher risk of being hospitalized at an intensive care unit [20]. Moreover, asthma as a concomitant condition does not contribute to a higher risk of intubation, prolonged time of intubation or development of acute respiratory distress syndrome (ARDS) in the course of SARS-CoV-2 infection in asthmatic patients [20].

Therefore, we know that asthma alone is not associated with a higher risk of COVID-19, and concomitant asthma has no impact on the severity of SARS-CoV-2 infection [21]. It has even been indicated that type 2 inflammatory cytokines (IL-4, IL-5), and the accumulation of eosinophils prevent the development of SARS-CoV-2 infection [22–24]. Additionally, it has been demonstrated that expression of ACE-2 receptors, essential for the binding of the virus with the airway epithelium, is reduced in patients who suffer from asthma [21]. However, that finding does not apply to patients who suffer from non-allergic asthma [25].

It has not been demonstrated that severe asthma, which qualifies for biological treatment, is a risk factor for a severe course of COVID-19, or that there is a need for preventative hospitalization of patients with asthma exacerbation in intensive care units [26, 27]. One of the factors which reduce the risk hospitalization of asthma patients in the course of SARS--CoV-2 infection is the use of inhaled glucocorticosteroids (IGCS) [28].

A factor which may contribute to a more severe course of SARS-CoV-2 infection in asthma patients is a poor control of asthma. Reduction of the daily dose of IGCS results in a poorer gas exchange in pulmonary alveoli. An excessive mucus secretion and reduced airflow into the gas exchange units may increase the hypoxemia caused by the diffused damage of pulmonary alveoli in the course of SARS-CoV-2 infection [21, 24, 29].

It is known that coronavirus infections may trigger asthma exacerbation, and thus, SARS-CoV-2 infection may also lead to intensified inflammatory lesions and mucus hyper-secretion [21]. It has been demonstrated, however, that SARS and MERS viruses do not cause such exacerbations [30]. Moreover, Grandbastien et al. did not find SARS-CoV-2 infections to be conducive to asthma exacerbations [20]. Those contradictory observations highlight the need to maintain control therapy in the case of all patients with an obstructive lung disease.

The foundation for asthma control therapy involves inhaled glucocorticosteroids. Glucocorticosteroids directly affect the respiratory epithelium, and contribute to a reduction in the inflammatory reactions by increasing the levels of anti-inflammatory cytokines [21]. An important part in SARS-CoV-2 infection is played by ACE-2 receptors that are present on the surface of the airway epithelium. In allergic asthma the number of receptors is smaller, which means that SARS-CoV-2 viruses have a smaller capacity to bind with the epithelial cells [21]. In pre-clinical studies it has also been demonstrated that some substances used in the treatment of asthma reduce the SARS-CoV-2 virus replication in the cells of the respiratory epithelium [1]. Matsuyama et al. found that one of the inhaled glucocorticosteroids commonly used in the treatment of asthma reduced SARS-CoV-2 replication in the cells of the airway epithelium [31]. Inhaled glucocorticosteroids reduce the severity of SARS-CoV-2 infection in COPD patients as well [32]. It has been demonstrated that glycopyrronium, formoterol and a triple medication including budesonide, formoterol and glycopyrronium all inhibit the replication of coronavirus, and reduce the synthesis of pro-inflammatory cytokines [1, 21, 33]. Similar observations were made with reference to rhinovirus infections [34].

Therefore, it is generally known that in the case of SARS-CoV-2 infection in asthma and COPD patients, one should not discontinue the treatment with inhaled glucocorticosteroids. There is evidence indicative of the fact that the pandemic may lead to a better adherence to inhaled therapies, applied both in asthma and in COPD [16]. Paradoxically, it may transpire that the pandemic has improved the clinical efficacy of treating obstructive diseases, mainly due to an increased discipline in that group of patients (e.g., wearing facial masks, keeping social distance), and improved adherence to inhaled medications [16].

Will the pandemic have an impact on the life of patients with obstructive pulmonary diseases (asthma and COPD)? There are conflicting findings on the subject. In Spain, it has been demonstrated that the pandemic has had a marginal impact on the quality of COPD treatment [35]. Due to the pandemic and lockdown, the number of patients seen by GPs has decreased there, as has the number of patients admitted to hospital emergency departments for exacerbation of obstructive diseases. Perhaps, it is due to the introduced lockdown that exposure to viruses and bacteria has been smaller, leading to a lower number of cases of exacerbation of obstructive conditions, and COPD in particular. Smog has also been reduced in large European cities in the period of the pandemic, and that fact has also contributed to those positive effects [36]. As has been mentioned, the pandemic has a marginal impact on the clinical course of COPD. What about COVID-19 and the impact it has on the course of severe COPD?

The mechanism of interaction has not been fully explained to date. We know that the first site of contact with SARS-CoV-2 in humans is the nasal epithelium. There are lots of ACE-2 receptors in the nose, and they are the site of binding of the SARS-CoV-2 glycoprotein S with the cells of the airway epithelium, thanks to which to virus enters inside the cells. Once the virus has entered inside the cells, it replicates, and hundreds of new virions are generated. The virions released from the infected cells into the intercellular space and the fluid that lines our airways further infect the surrounding cells, and are transported to the peripheral respiratory system. It has already been confirmed that in COPD patients the expression of ACE-2 receptors is higher, especially in the peripheral airways [11, 37]. COPD patients may thus be more exposed to SARS-CoV-2 infection, and may be at a higher risk of its more severe course.

An interesting finding was reported in a study carried out by Attaway et al. The authors demonstrated that in COPD patients treated with IGCS, the risk of COVID-19 development is lower. The diagnosis of SARS-CoV-2 infection was less likely (2.4 times less so) in patients who received IGCS as compared with those patients who were not treated with IGCS (18.3% vs. 44.8%; $p < 0.001$) [38]. Therefore, there is a reason to conclude that also in the population of COPD patients, IGCS have a protective quality, reducing the intensity of SARS-CoV-2 replication in the airways [39]. It goes to show that not only asthma patients, but also COPD patients cannot discontinue inhaled therapies during the SARS-CoV-2 pandemic. In COPD, long-acting bronchodilators (β-mimetics: formoterol, salmeterol; and cholinolytics – glycopyrronium, tiotropium) constitute first-line therapy. Adding IGCS in patients who suffer from frequent episodes of exacerbation (during the exacerbation events), and introduction of oral glucocorticosteroids and antibiotics in the course of SARS-CoV-2 infection should be a recommended management algorithm [40].

Inhalations at the time of COVID-19 pandemic

We know that inhalation treatment should not be discontinued in asthma/COPD patients during the COVID-19 pandemic. Can all inhalation methods be

applied, though? During the previous epidemics caused by coronaviruses, SARS and MERS, bans on inhalation therapies were introduced, primarily in hospitals and healthcare centres [41]. Those guidelines were based on the observations that intubation and forced ventilation contributed to an increased risk of infection (6.6- and 3.3-fold, respectively) among healthcare professionals [42]. Based on that, it was concluded that if intubation and/or forced ventilation contributed to an increased emission of the infected particles from the airways, then nebulization must increase the risk of infection as well, by introducing aerosol into the respiratory system. What was left out, though, was the fact that in the very same analysis, having assessed the increased risk of infection in persons who monitored nebulization, it was demonstrated that the risk was only 0.9. In other words, nebulization itself was not found to contribute to an increased risk of infection among healthcare professionals. However, once it had been established that nebulization carried along an increased risk of contracting infectious diseases (e.g., SARS, MERS, COVID-19), numerous organizations indicated in their analyses that it should be replaced with other techniques, using pressurised metered dose inhalers (pMDI), and dry powder inhalers (DPI). At the same time, no evidence was offered for the legitimacy of such management [41]. It was believed that the greatest potential danger involved pneumatic nebulizers. The structure of those nebulizers promotes the deposition of the medical solution/suspension in the nebulization chamber during the patient's expiration, which may cause contamination of the inhaled solution/suspension. The exhaled solution is also conducive to spreading the bioaerosols outside, constituting a risk both for the patients and their caregivers [43]. Those opinions are impacted by the manufacturing process of inhalers as single enclosed containers (pMDI) with a sterile solution. The precisely measured dose only contains a sterile solution. The generated low-volume and short-lasting aerosol has a very low risk of secondary contamination. However, addition of the inhalation chamber increases the risk of infection, especially when the chamber is inappropriately prepared for use (not cleaned or disinfected) [41, 43]. The nebulization chamber, on the other hand, needs to be cleaned, disinfected and stored in a closed packaging at all times.

Let us return to nebulization. Should it really be abandoned at the time of pandemic? Many people have voiced their opinions on the issue, claiming that there is no evidence in favour of such an approach. Provided we adhere to the appropriate procedures, nebulization is completely safe both in healthcare facilities as well as at home [44, 45]. The World Health Organization (WHO) has also withdrawn from the opinions expressed earlier.

Only in a situation where the medication poured into the nebulizer has been contaminated can we be exposed to the inhalation of a contaminated solution. Therefore, one has to remain particularly cautious, when pouring the solution/suspension into the nebulizer cup. One should never administer a medication that was prepared for use at an earlier time. The drug should be prepared immediately before inhalation.

At the time of COVID-19 pandemic, multidose dry powder inhalers (mdDPI) are by all means the safest inhalers available. Contrary to dry powder inhalers (DPI), the patient does not touch the medication that is to be inhaled, which is why the risk of contamination is reduced to a minimum.

Drugs available in mdDPIs (budesonide, salbutamol, formoterol, and others) rarely provoke fits of coughing immediately after inhalation, thus reducing the risk of sudden emission of bioaerosols from the airways of an infected person [1].

Summary

At the time of COVID-19 pandemic, one should not discontinue inhalation therapy in asthma and COPD patients. Using nebulization, one should adhere to all safety measures. There are no indications for the replacement of nebulization with pMDI therapy. In patients treated with DPIs, multi-dose inhalers should be used, as they are safer than capsule-based DPIs. Treatment with inhaled glucocorticosteroids should not be discontinued either, as they reduce the replication of viruses (coronaviruses and rhinoviruses) in the airways.

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