https://doi.org/10.18093/0869-0189-2020-30-5-599-608

Check for updates

Chronic obstructive pulmonary disease and COVID-19: topical issues

Aleksey M. Shchikota [1, ✉], Irena V. Pogonchenkova [1], Elena A. Turova [1], Marina A. Rassulova [1], Sergey A. Gumenyuk [2]

[1] Moscow Centre for Research and Practice in Medical Rehabilitation, Restorative and Sports Medicine: Zemlyanoy Val 53, Moscow, 105120, Russia

[2] Scientific Center of Emergency of Moscow Healthcare Department: Bol'shaya Sukharevskaya pl. 5/1, Moscow, 129090, Russia

Abstract

The problem of comorbidity of new coronaviral infection (COVID-19) and chronic obstructive pulmonary disease (COPD) is acute, considering similarity of clinical manifestations, diagnostic difficulties, the potential severe disease course. Patients with COPD represent a vulnerable group of infected SARS-CoV-2, with a complicated disease course and frequent adverse outcome. Features of the spread of the virus limit treatment and diagnosis for patients with COPD, making it difficult to provide medical care during the pandemic. The negative results of some clinical studies of antiviral drugs for patients with COVID-19 indicate the need for a search for new drugs; for this reason, analysis of the anti-inflammatory effect on the lungs in infection COVID-19 of drugs of basic COPD therapy is promising.

Key words: COVID-19, chronic obstructive pulmonary disease, SARS-CoV-2, smoking.

Conflict of interests. The authors declare the absence of conflict of interests.

For citation: Shchikota A.M., Pogonchenkova I.V., Turova E.A., Rassulova M.A., Gumenyuk S.A. Chronic obstructive pulmonary disease and COVID-19: topical issues. *Pul'monologiya*. 2020; 30 (5): 599–608 (in Russian). DOI: 10.18093/0869-0189-2020-30-5-599-608

Хроническая обструктивная болезнь легких и COVID-19: актуальные вопросы

А.М.Щикота [1, ✉], И.В.Погонченкова [1], Е.А.Турова [1], М.А.Рассулова [1], С.А.Гуменюк [2]

[1] Государственное автономное учреждение здравоохранения города Москвы «Московский научно-практический центр медицинской реабилитации, восстановительной и спортивной медицины Департамента здравоохранения города Москвы»: 105120, Россия, Москва, ул. Земляной Вал, 53

[2] Государственное бюджетное учреждение здравоохранения города Москвы «Научно-практический центр экстренной медицинской помощи Департамента здравоохранения города Москвы»: 129010, Россия, Москва, Б. Сухаревская пл., 5 / 1

Резюме

Актуальность проблемы коморбидности новой коронавирусной инфекции COVID-19 и хронической обструктивной болезни легких (ХОБЛ) обусловлена схожестью клинических проявлений, сложностью диагностики, потенциальной тяжестью течения и взаимоотягощением этих патологий. Больные ХОБЛ, инфицированные SARS-CoV-2, представляют собой уязвимую группу лиц с осложненным течением и часто неблагоприятным исходом болезни. Особенности распространения вируса накладывают значительные ограничения на многочисленные диагностические и лечебные мероприятия при ХОБЛ, затрудняя оказание медицинской помощи больным данной категории в период пандемии на всех ее этапах. Необходимость поиска новых терапевтических решений продиктована отрицательными результатами текущих клинических исследований по изучению эффективности применения ряда препаратов у больных COVID-19; перспективным представляется изучение действия на SARS-CoV-2 препаратов базовой терапии ХОБЛ с доказанным противовоспалительным действием на бронхолегочную систему.

Ключевые слова: COVID-19, хроническая обструктивная болезнь легких, SARS-CoV-2, курение.

Конфликт интересов. Авторы заявляют об отсутствии конфликта интересов.

Для цитирования: Щикота А.М., Погонченкова И.В., Турова Е.А., Рассулова М.А., Гуменюк С.А. Хроническая обструктивная болезнь легких и COVID-19: актуальные вопросы. *Пульмонология*. 2020; 30 (5): 599–608. DOI: 10.18093/0869-0189-2020-30-5-599-608

A new strain of coronavirus emerged in December 2019 in the Chinese city of Wuhan (Hubei province), spread rapidly across the world until the COVID-19 pandemic was officially announced by the World Health Organization (WHO) on March 11, 2020. It is a global challenge for healthcare that forced to consider strategic issues of diagnosis, treatment, and rehabilitation of other noncommunicable diseases exclusively in the context of the pandemic. The coronavirus was named SARS-CoV-2 on February 11, 2020. It enters the human body through the receptors of the angiotensin converting enzyme type 2 (ACE-2). It can infect type 2 alveolar cells, leading to diffuse alveolar damage to the lungs which is clinically seen as viral bilateral pneumonia and acute respiratory distress syndrome [1].

[1] Ministry of Health of the Russian Federation. [Temporary guidelines: Prevention, diagnostics, and treatment of the of novel coronavirus infection (COVID-19). Version 8 (03.09.2020)]. Available at: *https://static-0.minzdrav.gov.ru/system/attachments/attaches/000/051/777/original/030902020_COVID-19_v8.pdf* (in Russian).

Chronic obstructive pulmonary disease (COPD) remains one of the leading reasons for the decline in the quality and duration of life. It is an unresolved medical and social problem, and the urgency has been growing over the years. According to various authors, the prevalence of COPD among the adult population ranges from 4 to 10%, which equals to about 210 million people around the world [1]. According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD), COPD is "a disease that can be prevented and treated". However, the choice of therapeutic strategies for patients with COPD remains challenging, and the ability to influence the endpoints and prognosis of the disease remains limited [2].

Given that both COPD and COVID-19 cause potentially severe lung damage, it is important to study the impact of SARS-CoV-2 infection on the course, complications, and outcomes of COPD, as well as the impact of the pandemic on the organization of medical care for chronic pulmonary patients. The similarities in the pathogenesis of COVID-19 and COPD make it possible to consider a number of drugs for basic COPD therapy as a potential treatment for the new coronavirus infection.

Impact of COPD and smoking on the risk of COVID-19 infection: the relevant pathogenetic features of SARS-CoV-2. *J.M.Leung et al.* conducted one of the first studies on the mutual influence of COVID-19, COPD, and smoking. Their article in the *European Respiratory Journal* highlighted the problem and caused a discussion in the scientific medical press. Professor *J.M.Leung et al.* examined smokers with COPD at St. Paul's Hospital (Vancouver, Canada) and assessed the expression of ACE-2 in the bronchial epithelial cells. The patients with COPD and smokers had increased expression of the ACE-2 gene in the respiratory tract as compared with the non-smokers and former smokers. The greatest changes were observed in the patients with COPD. Based on these data, the authors suggested an increased risk of SARS-CoV-2 infection in COPD patients and active smokers and presented immediate smoking cessation as one of the ways to reduce the risk of infection [2].

This position was also confirmed by the article of *P.Russo et al.* in the same print edition [3]. The researchers have found a significant increase in nicotine expression of ACE-2 via the α_7-nicotine-acetylcholine receptor (α_7-nAChR) of human bronchial epithelial cells. They suggested that exposure to nicotine increases the risk of SARS-CoV-2 entering lung cells; α_7-nicotinic receptors are found in nerve cells, vascular endothelium, and lymphocytes, so smoking can potentially negatively affect the pathophysiology of COVID-19 in many systems and organs, including the brain, as well as the clinical outcomes. In a response article, Professor *J.M.Leung* agreed that nicotine could act via α_7-nAChR receptors and that smokers with COPD can have increased expression of ACE-2 receptors and be prone to severe COVID-19 infection. In this light, he suggested considering selective antagonists of α_7-nicotine-acetylcholine receptors, such as methyllycaconitine and α-conotoxin, as potential antiviral drugs [4].

S.Sharif-Askari et al. indicate transmembrane serine protease 2 (TMPRSS2) as an entry gate for the virus, along with ACE-2. They also pointed out a low level of expression of these receptors in the upper and lower respiratory tract in children, and the increased expression in smokers and patients with COPD, which explains the different course of the disease in these groups and their different susceptibility to infection [5]. A significant decrease in the level of ACE-2 with an unchanged level of expression of TMPRSS2 was also found after infection with COVID-19. This prompted the authors to suggest serine protease inhibitor (camostat) for treatment of COVID-19.

On the other hand, a number of publications provide other data on the effect of smoking, nicotine, and COPD on the risk of infection with SARS-CoV-2 virus. Several Chinese studies and their meta-analyzes indicate an unusually low prevalence of COPD and tobacco smoking among COVID-19 patients. *J.J.Zhang et al.* studied comorbidities and allergic status in 140 patients with an average age of 57 (25 – 87) years old, with verified COVID-19, who were hospitalized at Hospital No.7 in Wuhan in January–February 2020. The study sample included only 2 active smokers and another 7 people with a history of tobacco smoking (6.4% of the sample). Active smoking and COPD were reported in only 1.4% of patients [6], which is lower than the prevalence of COPD and tobacco smoking in China (COPD occurs in 13.7% among adults over 40; 27.3% of the population are active smokers). These findings correlate with a wider study of the clinical status of COVID-19 patients in China by *W.J.Guan et al.* [7]. An analysis of 1,099 inpatient case histories (552 hospitals in 30 provinces) showed that only 1.1% of the patients had COPD as a comorbidity, and 12.6% of patients were active smokers.

According to a meta-analysis by *A.Emami et al.* that was also based on pooled data from Chinese researchers as of March 2020, the prevalence of COPD among those infected with SARS-CoV-2 was 0.95%. 7.6% of the patients were active smokers [8]. Nevertheless, the authors of the meta-analysis name COPD and smoking among the "common comorbidities" in patients with COVID-19 but, obviously, the incidence of these conditions is less than in the general population. Similar data on the relatively low prevalence of smoking and COPD among COVID-19 patients were obtained in the United States. Only 5.1% of 393 patients were active smokers with COPD [9]. In June 2020, the *European Respiratory Journal* published an article by *M.Rossato et al.* which emphasizes that all epidemiological data published to date show an extremely low prevalence of tobacco smoking among COVID-19 patients [10]. The authors cite their own analysis of hospitalizations at the University Hospital of Padua in March-April 2020. None of 132 patients with COVID-19 were smoking, 15.2% of patients had a history of smoking, and the latter did not correlate with the severity of the infection. At the same time, the percentage of active smokers in Italy in general and in the Veneto region, to which the

[2] Global Initiative for Chronic Obstructive Lung Disease. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease. Revised 2020. Available at: *www.goldcopd.com*

hospital belongs, is high and amounts to 25.7 and 22.7%, respectively.

T.Lupia et al. from Italy performed a meta-analysis of the data from China. They also showed a low prevalence of COPD in patients with COVID-19 1 – 2.9%, with a total prevalence of COPD in China equal to 1.2 – 8.9%. The results of the meta-analysis did not allow to attribute COPD to the common comorbidities in patients with the new coronavirus infection [11]. An article by Chinese authors from Zhejiang University indicates a higher prevalence of COPD among 136 elderly patients (⩾ 60 years old) with COVID-19 as compared with the younger population. However, the incidence of COPD in the elderly was 2.21% and cannot be considered high [12].

Professor *F.Polverino* of the Center for Asthma and Respiratory Diseases at the University of Arizona (USA) calls the relationship between tobacco smoking and COVID-19 a «complex interaction». The epidemiological data clearly put in question active smoking as a risk factor for COVID-19. At the same time, the author emphasizes the delicacy and complexity of the topic of the possible protective effect of nicotine in COVID-19, taking into account the proven unconditional and diverse negative effects of cigarette smoke on the lungs [13].

Greek authors *K.Farsalinos et al.* also argue with *J.M.Leung* and *P.Russo* say that additional research on the role of nicotine in the pathogenesis of COVID-19 is required. Their meta-analysis of the prevalence of active smoking in patients with COVID-19 in China and the United States showed that nicotine as an agonist of the cholinergic system can potentially limit the manifestation of the cytokine storm through α_7-nicotine-acetylcholine receptors. Taking this into account, the authors consider the use of α_7-nAChR (methyllycaconitine, α-conotoxin) receptor antagonists dangerous in patients with COVID-19 because of the possible growth of the systemic inflammation. They did not question the general harm of tobacco smoking, but still proposed to consider using pharmacological nicotine-containing drugs in the complex therapy of COVID-19 [14].

J.M.Leung et al. criticized the position of *K.Farsalinos et al.* The latter published a response letter in the *European Respiratory Journal* and admitted that they were also surprised by the small number of smokers among patients with new coronavirus infection. The authors suggest such possible reasons as the underestimated prevalence of smoking, the potential protective effect of inhalers, and a lower prevalence of tobacco smoking among the elderly – the main target population of COVID-19. In any case, Professor *J.M.Leung* urges to approach the epidemiological data with caution and not to consider smoking as a "protection" against COVID-19. He emphasizes that COPD still remains a factor associated with the severe disease and high mortality, despite the low prevalence of smoking and COPD in the infected population [15].

Impact of COPD on COVID-19 severity and outcomes. In the active discussion of the impact of COPD on the risk of infection with SARS-CoV-2, most experts agree on one thing – COPD is an undoubted risk factor for severe COVID-19 and increases the likelihood of an unfavorable outcome of the disease. Changes in the local and systemic inflammatory response in patients with COPD, a decrease in the immune status, an imbalance in the microbiota of the respiratory tract, impaired mucociliary clearance and bronchial architecture, and the consequences of prolonged use of inhaled glucocorticoids are considered the main pathogenetic grounds for this risk, along with increased expression of ACE-2 receptors in COPD patients and tobacco smokers [16].

One of the first meta-analyzes by Chinese authors included 6 studies (n = 1,558) of patients with COVID-19 and showed that the risk of severe infection in the patients with COPD is 5.9 times higher than in the patients without COPD. COPD was recognized to be an independent risk factor for the severe course of the new coronavirus infection along with arterial hypertension, diabetes mellitus, cardiovascular and cerebrovascular diseases [17].

Naturally, a similar small meta-analysis by Italian authors based on clinical information from China showed a similar result: COPD increases the risk of a severe course of COVID-19 by more than 5 times [16]. The authors of the review conclude that patients with COPD should be isolated to avoid contact with the virus and should be monitored carefully if infected.

A nationwide analysis from the People's Republic of China [18] assessed the effect of comorbidities on serious adverse outcomes (death, admission to the intensive care unit (ICU), the need for mechanical ventilation) in 1,590 patients COVID-19. 50% patients with COPD reached the endpoints. If the patient had two or more comorbidities, the prognosis became even worse. Thus, COPD can largely determine the unfavorable outcome of the coronavirus infection, which once again emphasizes the vulnerability of chronic pulmonary patients to COVID-19.

The meta-analysis by *V.Jain et al.* also confirms this conclusion. This meta-analysis assessed the prognostic factors of severe new coronavirus infection and hospitalization in the ICU. They analyzed the influence of various comorbidities on the prognosis in 1,813 patients in 7 studies that were conducted in China. Despite the generally relatively low prevalence of COPD among those infected with SARS-CoV-2, the concomitant COPD had the strongest prognostic value in relation to the severe course of COVID-19 (OR 6.42, 95% CI 2.44 – 16.9) and hospitalization in ICU (OR 17.8, 95% CI 6.56 – 48.2) [19].

Patients with COVID-19 who required repeated hospitalization after discharge had COPD as a comorbidity much more often than those who were hospitalized only once (6.8% *vs* 2.9%) [20]. *S.Shi et al.* studied myocardial injury in COVID-19 and revealed a more frequent increase in markers of myocardial necrosis in patients with several comorbidities, including COPD [21].

Finally, a systematic review of studies and a meta-analysis on the impact of COPD on mortality in COVID-19 patients was performed. *M.Parohan et al.* reviewed the histories of 29,909 patients with confirmed SARS-CoV-2 infection in 14 studies. A total of 1445 deaths were recorded. According to the review, concomitant COPD is associated with a high risk of mortality in COVID-19 patients (OR = 3.53, 95% CI = 1.79 – 6.96, p < 001). The other risk fac-

tors were arterial hypertension, cardiovascular diseases, diabetes mellitus, and age ⩾ 65 years [22].

A meta-analysis by *Q.Zhao et al.*, included a large number of studies (11) and assessed the impact of COPD and smoking history on the severity of COVID-19 [23]. The presence of COPD was associated with an almost four times higher risk of severe COVID-19. The conclusions regarding the active smoking status were contradictory. A meta-analysis showed a twofold increase in the risk of severe COVID-19 in active smokers. At the same time, the effect of smoking history on the severity of the infection became insignificant after one study [24] was excluded from the analysis.

A few other publications illustrate the impact of tobacco smoking on the severity and outcomes of COVID-19 and are largely contradictory to each other. A team of authors from Tiantan Hospital in Beijing published the results of a meta-analysis that investigated the relationship between clinical features and outcomes of COVID pneumonia. The authors reviewed data from 12 cohort studies that included 2,445 patients with COVID-19 and made an unambiguous conclusion that the severe course of infection is associated with a history of smoking. Also, they confirmed a strong relationship between severe COVID pneumonia and concomitant COPD (OR = 5.08, $p < 0.001$) [25]. Several other cohort Chinese studies have confirmed the severe course of the coronavirus infection in smokers. These studies have showed that current and former smokers have more pronounced symptoms, are admitted to ICU, and need mechanical ventilation more frequently [7]. The studies have also confirmed the relationship between smoking and the progression of COVID-19 [26].

At the same time, a large cohort study (1,007 patients) in several hospitals in China confirmed that COPD but not smoking is a risk factor for progression of mild or moderate COVID-19 to a severe disease. Moreover, the proportion of smokers was insignificantly ($p = 0.08$) lower in the COVID-19 progression group as compared to the group of stable patients [27]. Such conflicting data undoubtedly indicate the need for further research of the effect of nicotine and its analogs on the risk of infection with SARS-CoV-2, the severity and outcomes of the infection.

COVID-19 course in the selected groups of patients with COPD. A number of publications discuss the course of the new coronavirus infection in selected cohorts of patients with COPD. In particular, *L.Wang et al.* studied the course and prognosis of COVID-19 in elderly patients. They followed up 339 patients over 60 years old in Wuhan and showed that COPD was a predictor of an unfavorable outcome of the disease, among other comorbidities [28].

Authors of an article on the increased expression of ACE-2 receptors in overweight patients with COPD conclude that there is a risk of a more severe course of COVID-19 in these patients [29].

The Thoracic Surgery Department of Tongji Hospital in Wuhan City studied the features of COVID-19 in patients after thoracic surgery. The highest mortality was recorded in the group of patients with concomitant COPD [30].

In general, COVID-19 patients with lung cancer have a severe course of infection. The authors note that the markers of an unfavorable outcome of the disease were not specific features of cancer and its therapy, but the presence of certain comorbidities, including COPD [30].

Difficulties in diagnosing COVID-19 in patients with COPD. Several publications point out that diagnosing the new coronavirus infections in patients with COPD is challenging. First, there is an obvious similarity between the clinical symptoms of an exacerbation of COPD and COPD-19. The most common signs of SARS-CoV-2 infection are cough (up to 80% of cases), fever and intoxication (> 90% of cases), and shortness of breath (up to 30% of cases). These same symptoms often accompany an exacerbation of COPD [23, 31]. Thus, the infection with SARS-CoV-2 may be clinically unnoticeable and masked by manifestations of chronic lung pathology in patients with a relapsed or symptomatic COPD. The experts [32] recommend using clinical symptoms such as high fever, anorexia, myalgia, and signs of gastrointestinal tract damage for the differential diagnosis, because they are not pathognomonic for an exacerbation of COPD.

COPD Foundation experts warn that COPD patients may experience a sharp deterioration in 6 – 7 days and develop respiratory failure associated with the suppressed COVID-19 symptoms. The authors of the publication propose mandatory testing for SARS-CoV-2 in all patients with an exacerbation of COPD to avoid delayed diagnosis of COVID-19 in COPD [31].

An interesting clinical case was presented in the journal *American Family Physician* in May 2020 [33]. A 67-year-old patient with long-term COPD and a number of other chronic diseases (ischemic heart disease, diabetes mellitus) had watery diarrhea for 4 days. The patient did not report an increase in shortness of breath and cough, did not have a fever, and had stable hemodynamic parameters. Saturation was 92% against the oxygen therapy at home, which was typical for him. The stool analysis for *C. difficile* was negative. On the first day of the hospital stay, his cough intensified, and his body temperature rose to 38.9 °C, the oxygen saturation of the blood dropped to 88%, and bilateral interstitial changes were revealed by a CT scan. The COVID-19 test upon admission was positive. Mechanical ventilation was started because the patient deteriorated. This clinical example clearly illustrates the difficulties of diagnosing the new coronavirus infection against the underlying severe chronic lung pathology, especially with an atypical clinical form of COVID-19.

The difficulties in detecting COVID-19 in COPD patients are not limited to the clinical picture. Interpretation of computed tomography (CT) data in these patients is often also hard. Both false-positive and false-negative diagnoses are possible [34, 35]. Usually, the typical ground-glass opacities occur in patients with COPD against the background of a strongly altered X-ray picture: pulmonary emphysema, bullae, areas of fibrosis [34].

S.Salehi et al., who studied the features of CT in COVID-19 patients with various chronic bronchopulmonary pathologies, also noted that the CT signs

of COVID pneumonia in COPD patients are atypical. In particular, the formation of cavities is not typical for SARS-CoV-2 lung damage. However, small centrilobular emphysematous bullae are characteristic of a long-term COPD, and ground-glass interstitial changes around them create a picture of "pseudocavities" [35]. The authors note that the overlapping of coronavirus pneumonia (interstitial changes and areas of air space consolidation) and the underlying COPD can also mimic the CT picture of aspiration pneumonia or lung atelectasis.

Japanese authors described CT changes in a 78-year-old smoker with a long history of COPD and confirmed COVID-19. They noted multiple peripheral round and irregular ground-glass opacities against the background of emphysematous changes, which they figuratively call "Swiss cheese" [36].

Managing patients with COPD during the COVID-19 pandemic. The COVID-19 pandemic has made significant adjustments to the provision of health care across a range of noncommunicable diseases, and COPD is no exception. The period of self-isolation, the need to comply with restrictive measures during outpatient visits and inpatient treatment, mutual aggravation of COVID and COPD altogether have significantly changed the strategies for managing chronic pulmonary patients at all stages, i.e. prevention, diagnosis, treatment, and rehabilitation. In addition, the similarities in pathogenetic mechanisms of these two diseases require studying the effect of basic bronchodilator therapy for COPD on the course of COVID-19 and, vice versa, studying the effect of antiviral therapy on the clinical status of patients with COPD. Most of the authoritative national and international pulmonary communities have presented their guidelines and strategies for managing COPD during the COVID-19 pandemic.

The Global COPD Initiative (GOLD) responded to the pandemic with a short, patient-centered guide recommending to comply with all restrictive measures to prevent infection with SARS-CoV-2, continue the basic bronchodilator therapy during the pandemic, including the use of inhaled glucocorticosteroids, use oxygen therapy for standard indications, follow the national guidelines for COVID-19, and use the information provided by WHO [37].

Most national guidelines and medical publications repeat the basic principles for the management of patients with COPD listed above [32, 37, 38]. Swiss authors stressed the need to adhere to standard therapy for COPD and bronchial asthma during the COVID-19 pandemic. They also warned of the dangers of spirometry studies and the use of nebulizer therapy in the infected patients due to the increased risk of SARS-CoV-2 infection [32].

Experts from the *Canadian Thoracic Society* (CTS) have formulated general guidelines for COPD patients during the pandemic:

- stay at home as much as possible, including working remotely at home;
- follow national guidelines for the sanitary and hygienic rules, as well as the distance and isolation when going out;
- provide for a minimum 30-day supply of necessary medicines or a reliable channel for their delivery;
- foresee and, if possible, document the plans for hospitalization and resuscitation in case of severe COPD, and, accordingly, the potential risk of severe COVID-19 [38].

General principles of COPD therapy during the pandemic. All national and international guidelines do not recommend changing previously prescribed COPD drug therapy during the COVID-19 pandemic [31, 32, 37–39].

The article by *A.Attaway* (USA) discusses the possible challenges in the treatment of acute respiratory failure during an exacerbation of COPD. The standard methods such as nebulizer therapy, high-flow oxygen therapy through a nasal cannula, and positive pressure non-invasive ventilation (NIV) are associated with a high risk of SARS-CoV-2 infection. The following solutions are proposed: the use of individual metered dose inhalers, dry powder inhalers, and spacers instead of nebulizers; the personnel should use personal protective equipment (PPE) that provides maximum protection and use viral filters if nebulizer therapy and NIV are required; limiting oxygen consumption during oxygen therapy to 30 L/min. At the same time, a complete rejection of NIV is not recommended, given its proven efficacy in the treatment of respiratory failure in COPD [40]. High-flow oxygen therapy should not be used in patients with hypercapnia [32]. Therefore, the analysis of the gas composition of arterial blood is recommended for all patients with COPD and signs of respiratory failure [39].

The need for prophylactic therapy with anticoagulants in patients with a combination of COPD and COVID-19 is emphasized because the coronavirus infection causes coagulopathy while exacerbations and severe course of chronic obstructive pulmonary disease increase the risk of venous thromboembolism [41, 42]. Careful monitoring of the patient's clinical status, laboratory and instrumental parameters is required to exclude any thromboembolic complications [39].

If a patient with COPD uses low-flow oxygen therapy at home, it should be continued. The mode can be changed only after consultation (including remote) with the attending physician [38, 39].

Elements of rehabilitation are essential in the management of clinically severe patients with COPD and COVID-19. The rehabilitation can take the form of physical therapy and active nutritional support to correct the malnutrition and sarcopenia typical for COPD. Weaning from mechanical ventilation is a complex multistep process for the patient and his family because the ventilation can be still required for COPD.

The COPD Foundation experts emphasize that pulmonary rehabilitation is essential for patients with COPD [31]. Given the limited availability of rehabilitation facilities during the pandemic, a number of national and international pulmonary organizations offer web-based platforms for counseling on physical therapy and other methods of medical rehabilitation at home. When treating COPD at home, it is advisable to isolate the patient in his room, ideally, for him/her to have his/her own bathroom. The door to the room should be closed when the patient

uses a nebulizer and remain closed for several hours after the procedure [32].

The overall psychological climate deteriorated during the pandemic and COPD patients are susceptible to anxiety and depression, so the COPD Foundation has released a guide to maintaining the emotional well-being of COPD patients during the COVID-19 pandemic. The guide explains how to monitor and prevent negative thoughts, feelings, and reactions – the triggers of anxiety-depressive states. They also gave the recommendations to improve the psycho-emotional background during a pandemic [43]. CTS also offers an online resource for educating COPD patients and self-managing strategies for disease control and pulmonary rehabilitation during the pandemic (*https://cts-sct.ca/covid-19/*). Experts emphasize the importance of telemedicine technologies for monitoring and education, the importance of maintaining physical activity and strict implementation of the drug treatment plan [38].

Experts from the *Francophonie Pulmonary Society* (SPLF) believe that the huge harm from the COVID-19 pandemic lies in the suspension of most of the current clinical research on COPD. This could delay the introduction of innovative treatments for the disease by several years. In addition, lung transplantation is strictly limited during the pandemic, including for terminal COPD, except for the urgent cases. This may also have delayed adverse effects [39].

Inhaled and systemic glucocorticoids in the treatment of COPD during the COVID-19 pandemic. The problem of using both inhaled and systemic glucocorticoids (GCs) in COPD and COVID-19 is still largely the subject of scientific discussion. Most medical publications like the GOLD guidelines state no proven negative effect of GCs on the course of COVID-19. Therefore, infection with SARS-CoV-2 is not a reason to not prescribe or cancel these drugs in COPD patients [32, 37–39].

D.M.G.Halpin et al. suggest in their systematic review that the relatively low prevalence of COPD in those infected with SARS-CoV-2, which was mentioned above, can be explained, among other things, by the constant use of inhaled GCs. The analysis of a large number of literature sources (771 publications in international databases) regarding the impact of inhaled GCs on the course and outcomes of COVID-19, SARS, and MERS led to the conclusion that there is not enough data at the time [44]. A low evidence level study in Japan provides data on several cases of a positive effect of inhaled ciclesonide on the clinical course of COVID-19 in patients receiving oxygen therapy [45].

At the same time, American authors remind that GCs increase the viral shedding in MERS-CoV and SARS-CoV infections. Therefore, it is advisable to limit the dose of the drug and the duration of GCs therapy in COVID-19 if possible [32]. A number of previous studies indicate a higher prevalence of pneumonia and changes in the airway microbiome in COPD against the use of inhaled GCs, in particular, fluticasone [46, 47]. Glucocorticoids are believed to suppress the production of the antibacterial protective peptide cathelicidin in the lung epithelium [48]. Experts from the CTS believe that the benefit of prescribing prednisolone for an exacerbation of COPD outweighs the potential risk of increased viral shedding. At the same time, the effect of the drug on the course of COVID-19 is still questioned [38, 39]. The latest WHO Interim Guidance for the Clinical Management of COVID-19 advise against the use of systemic corticosteroids outside of clinical trials and the previously approved indications.

Most of the experts interviewed by the COPD Foundation confirmed that systemic glucocorticoids should be prescribed to patients with an exacerbation of COPD and suspected or confirmed COVID-19. A small number of experts said that the minimum doses should be used or that GCs should not be used at all. The question of whether systemic glucocorticoids are recommended for hospitalized COPD patients with COVID pneumonia and inflammatory infiltration of lung tissue has become more complex and controversial. The expert opinions were divided approximately 50/50 [49].

COPD medications with potential benefits for COVID-19. A large number of drugs of various groups are used for the complex treatment of COPD. Many of these medications have systemic and topical anti-inflammatory effects. Given the need to limit the massive systemic inflammation in SARS-CoV-2 infected individuals and to target the interstitial lung damage, many of the treatments for COPD are reviewed in the scientific literature in light of their potential beneficial effects in COVID-19.

As noted earlier, information on the effect of inhaled and systemic GCS in COVID-19 is ambiguous. *S.Matsuyama et al.* reported in a preprint the potential inhibitory effect of ciclesonide on replication of SARS-CoV-2 RNA *in vitro* and its cytopathic activity. A similar effect was found for mometasone [50]. Ciclesonide inhibits viral replication by targeting the non-structural protein NSP15. At the same time, budesonide, beclomethasone, or fluticasone do not have a similar effect [45]. According to another laboratory study, budesonide and formoterol can independently suppress the systemic activation of interleukin IL-6 in the acute lung injury in a mouse model [51]. *B.Lipworth et al.* assessed the general prospects for the use of inhaled GCS against the cytokine storm in patients infected with SARS-CoV-2. The researchers concluded that these drugs influence pro-inflammatory mediators via "crude" non-specific effects. Also, one should not forget that GCs suppress immune mechanisms and might increase the viral replication [47]. Several ongoing studies evaluate the effect of ciclesonide on the rate of eradication of SARS-CoV-2 in patients with mild COVID-19 infection (conducted in South Korea) and on the course of severe forms of COVID-19 pneumonia (conducted in Japan).

In addition, the literature mentions a possible positive effect of bromhexine on the course of COVID-19, given that it inhibits penetration of respiratory viruses via the transmembrane protease TMPRSS2. Also, the use of both agonists and antagonists of nicotine in the new coronavirus infection is discussed. The theoretical prerequisites for this treatment are set out in the previous chapter.

A joint publication by authors from the United Kingdom, Italy, Israel and Canada explores the possibility of using another group of drugs that are prescribed for COPD, i.e. phosphodiesterase-4 (PDE4) inhibitors. These drugs are assumed to have an anticytokine effect in patients with COVID-19, given their pronounced anti-inflammatory effect, which is successfully used in the treatment of skin and articular manifestations of psoriasis and other dermatoses, as well as in severe COPD. The authors discuss the possible positive clinical effect of apremilast, cilomilast, and roflumilast on COVID-19-associated pneumonitis and the associated immunothrombosis in elderly patients with the coronavirus infection. The presumed biochemical mechanism is the ability of PDE4 inhibitors to reduce the activity of key inflammatory mediators, such as tumor necrosis factor, interleukin-12, interleukin-17, and a number of chemokines, as well as to influence alveolar macrophages and neutrophil-mediated reactions. Roflumilast inhibits the interaction of leukocytes and platelets, as well as the prothrombotic functions of leukocytes. This antithrombotic effect is especially important to treat the COVID-19-associated coagulopathy.

The authors highlight that the use of roflumilast and apremilast is not associated with an increase in the incidence of upper respiratory tract infections in patients with COPD and patients with psoriasis. On the contrary, numerous animal studies showed the anti-inflammatory effect of PDE4 inhibitors in respiratory viral infections (not the coronavirus infection). All this suggests a favorable effect of PDE4 inhibitors in COVID-19, especially in the elderly patients, severe cases, and patients with the thromboembolic complications. Of course, the hypothesis must be proven by clinical trials [52].

The article by *B.L. Yen et al.* is also notable. They assessed the potential use of mesenchymal stem cells in COVID-19 therapy, based on a study on the use of stem cells in chronic lung pathology – COPD, bronchial asthma, and idiopathic pulmonary fibrosis. Currently, the use of mesenchymal stem cells in patients with COPD is being studied in 10 clinical trials at different stages. The authors reviewed the theoretical basis for the use of stem cells and the findings of the *in vitro* and animal preclinical studies. They suggested that this therapy might limit the systemic inflammatory response to the coronavirus infection by decreasing the level of the most active pro-inflammatory cytokines – interleukin-6 and tumor necrosis factor-α. At the moment, 31 studies have been initiated on the use of mesenchymal stem cells in patients with the new coronavirus infection COVID-19. A potential clinical target for this treatment method will be severe COVID-19 with ARDS and cytokine storm [53].

Conclusion

Thus, the need to search for new therapeutic solutions comes from negative results of the current clinical studies of the efficacy of several drugs in patients with COVID-19. It seems promising to study the anti-SARS-CoV-2 therapeutic effect of the basic COPD therapeutics with a proven bronchopulmonary anti-inflammatory effect.

References / Литература

1. Pogonchenkova I.V., Zadionchenko V.S. [Pulmonogenic hypertension and systemic inflammation]. *Kardiologiya*. 2012; (6): 51 (in Russian). / Погонченкова И.В., Задионченко В.С. Пульмоногенная гипертензия и системное воспаление. *Кардиология*. 2012; (6): 51.
2. Leung J.M., Yang C.X., Tam A. et al. ACE-2 expression in the small airway epithelia of smokers and COPD patients: implications for COVID-19. *Eur. Respir. J.* 2020; 55 (5): 2000688. DOI: 10.1183/13993003.00688-2020.
3. Russo P., Bonassi S., Giacconi R. et al. COVID-19 and smoking: is nicotine the hidden link? *Eur. Respir. J.* 2020; 55 (6): 2001116. DOI: 10.1183/13993003.01116-2020.
4. Leung J.M., Yang C.X., Sin D.D. COVID-19 and nicotine as a mediator of ACE-2. *Eur. Respir. J.* 2020; 55 (6): 2001261. DOI: 10.1183/13993003.01261-2020.
5. Saheb Sharif-Askari N., Saheb Sharif-Askari F., Alabed M. et al. Airways expression of SARS-CoV-2 receptor, АПФ-2, and TMPRSS2 is lower in children than adults and increases with smoking and COPD. Version 2. *Mol. Ther. Methods Clin. Dev*. 2020; 18: 1–6. DOI: 10.1016/j.omtm.2020.05.013.
6. Zhang J.J., Dong X., Cao Y.Y. et al. Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China. *Allergy*. 2020; 75 (7): 1730–1741. DOI: 10.1111/all.14238.
7. Guan W.J., Ni Z.Y., Hu Y. et al. Clinical characteristics of coronavirus disease 2019 in China. *N. Engl. J. Med*. 2020; 382 (18): 1708–1720. DOI: 10.1056/NEJMoa2002032.
8. Emami A., Javanmardi F., Pirbonyeh N., Akbari A. Prevalence of underlying diseases in hospitalized patients with COVID-19: a systematic review and meta-analysis. *Arch. Acad. Emerg. Med*. 2020; 8 (1): e35.
9. Goyal P., Choi J.J., Pinheiro L.C. et al. Clinical characteristics of COVID-19 in New York city: Multicenter study. *N. Engl. J. Med*. 2020; 382 (24): 2372–2374. DOI: 10.1056/NEJMc2010419.
10. Rossato M., Russo L., Mazzocut S. et al. Current smoking is not associated with COVID-19. *Eur. Respir. J.* 2020; 55 (6): 2001290. DOI: 10.1183/13993003.01290-2020.
11. Lupia T., Scabini S., Mornese Pinna S. et al. 2019 novel coronavirus (2019-nCoV) outbreak: A new challenge.

J. Glob. Antimicrob. Resist. 2020; 21: 22–27. DOI: 10.1016/j.jgar.2020.02.021.
12. Lian J., Jin X., Hao S. et al. Analysis of epidemiological and clinical features in older patients with corona virus disease 2019 (COVID-19) out of Wuhan. *Clin. Infect. Dis*. 2020; 71 (15): 740–747. DOI: 10.1093/cid/ciaa242.
13. Polverino F. Cigarette smoking and COVID-19: A complex interaction. *Am. J. Respir. Crit. Care Med*. 2020; 202 (3): 471–472. DOI: 10.1164/rccm.202005-1646LE.
14. Farsalinos K., Angelopoulou A., Alexandris N., Poulas K. COVID-19 and the nicotinic cholinergic system. *Eur. Respir. J*. 2020; 56 (1): 2001589. DOI: 10.1183/13993003.01589-2020.
15. Leung J.M., Yang C.X., Sin D.D. Reply to: "Current smoking is not associated with COVID-19". *Eur. Respir. J*. 2020; 55 (6): 2001340. DOI: 10.1183/13993003.01340-2020.
16. Lippi G., Henry B.M. Chronic obstructive pulmonary disease is associated with severe coronavirus disease 2019 (COVID-19). *Respir. Med*. 2020; 167: 105941. DOI: 10.1016/j.rmed.2020.105941.
17. Wang B., Li R., Lu Z., Huang Y. Does comorbidity increase the risk of patients with COVID-19: evidence from meta-analysis. *Aging (Albany NY)*. 2020; 12 (7): 6049–6057. DOI: 10.18632/aging.103000.
18. Guan W.J., Liang W.H., Zhao Y. et al. Comorbidity and its impact on 1590 patients with COVID-19 in China: a nationwide analysis. *Eur. Respir. J*. 2020; 55 (5): 2000547. DOI: 10.1183/13993003.00547-2020.
19. Jain V., Yuan J.M. Predictive symptoms and comorbidities for severe COVID-19 and intensive care unit admission: a systematic review and meta-analysis. *Int. J. Public. Health*. 2020; 65 (5): 533–546. DOI: 10.1007/s00038-020-01390-7.
20. Somani S., Richter F., Fuster V. et al. Characterization of patients who return to hospital following discharge from hospitalization for COVID-19. *medRxiv* [Preprint. Posted: 2020, May 22]. DOI: 10.1101/2020.05.17.20104604.
21. Shi S., Qin M., Cai Y. et al. Characteristics and clinical significance of myocardial injury in patients with severe coronavirus disease 2019. *Eur. Heart. J*. 2020; 41 (22): 2070–2079. DOI: 10.1093/eurheartj/ehaa408.
22. Parohan M., Yaghoubi S., Seraji A. et al. Risk factors for mortality in patients with Coronavirus disease 2019 (COVID-19) infection: a systematic review and meta-analysis of observational studies. *Aging Male*. 2020, Jun. 8. DOI: 10.1080/13685538.2020.1774748.
23. Zhao Q., Meng M., Kumar R. et al. The impact of COPD and smoking history on the severity of COVID-19: A systemic review and meta-analysis. *J. Med. Virol*. 2020; 92 (10): 1915–1921. DOI: 10.1002/jmv.25889.
24. Guan W.J., Ni Z.Y., Hu Y. et al. Clinical characteristics of coronavirus disease 2019 in China. *N. Engl. J. Med*. 2020; 382 (18): 1708–1720. DOI: 10.1056/NEJMoa2002032.
25. Li J., He X., Yuanyuan et al. Meta-analysis investigating the relationship between clinical features, outcomes, and severity of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) pneumonia. *Am. J. Infect. Control*. [Preprint. Posted: 2020, Jun. 12]. DOI: 10.1016/j.ajic.2020.06.008.
26. Liu W., Tao Z.W., Wang L. et al. Analysis of factors associated with disease outcomes in hospitalized patients with 2019 novel coronavirus disease. *Chin. Med. J. (Engl.)*. 2020; 133 (9): 1032–1038. DOI: 10.1097/CM9.0000000000000775.
27. Cen Y., Chen X., Shen Y. et al. Risk factors for disease progression in mild to moderate COVID-19 patients – a multi-center observational study. *Clin. Microbiol. Infect*. 2020; 26 (9): 1242–1247. DOI: 10.1016/j.cmi.2020.05.041.
28. Wang L., He W., Yu X. et al. Coronavirus disease 2019 in elderly patients: Characteristics and prognostic factors based on 4-week follow-up. *J. Infect*. 2020; 80 (6): 639–645. DOI: 10.1016/j.jinf.2020.03.019.
29. Higham A., Singh D. Increased ACE2 expression in the bronchial epithelium of COPD patients who are overweight. *Obesity (Silver Spring)*. 2020; 28 (9): 1586–1589. DOI: 10.1002/oby.22907.
30. Luo J., Rizvi H., Preeshagul I.R. et al. COVID-19 in patients with lung cancer. *Ann. Oncol*. 2020; 31 (10): 1386–1396. DOI: 10.1016/j.annonc.2020.06.007.
31. Tal-Singer R., Crapo J.D. COPD at the time of COVID-19: A COPD foundation perspective. *Chronic Obstr. Pulm. Dis*. 2020; 7 (2): 73–75. DOI: 10.15326/jcopdf.7.2.2020.0149.
32. Daccord C., Touilloux B., Von Garnier C. [Asthma and COPD management during the COVID-19 pandemic]. *Rev. Med. Suisse*. 2020; 16 (692): 933–938 (in French).
33. Meyers M.H. A case of COVID-19 infection: Chief symptom, diarrhea. *Am. Fam. Physician*. 2020; 101 (10): 580.
34. Dong X., Cao Y.Y., Lu X.X. et al. Eleven faces of coronavirus disease 2019. *Allergy*. 2020; 75 (7): 1699–1709. DOI: 10.1111/all.14289.
35. Salehi S., Abedi A., Radmard A.R. et al. Chest computed tomography manifestation of coronavirus disease 2019 (COVID-19) in patients with cardiothoracic conditions. *J. Thorac. Imaging*. 2020; 35 (4): W90–96. DOI: 10.1097/RTI.0000000000000531.
36. Miwa M., Nakajima M., Goto H. Peripheral "Swiss Cheese" appearance in a COVID-19 patient with chronic obstructive pulmonary disease. *Am. J. Trop. Med. Hyg*. 2020; 103 (2): 546. DOI: 10.4269/ajtmh.20-0605.
37. Global Initiative for Chronic Obstructive Lung Disease. GOLD COVID-19 Guidance. Available at: *https://goldcopd.org/gold-covid-19-guidance/*
38. Bhutani M., Hernandez P., Bourbeau J. et al. Key highlights of the Canadian Thoracic Society's position statement on the optimization of COPD management during the COVID-19 pandemic. *Chest*. 2020; 158 (3): 869–872. DOI: 10.1016/j.chest.2020.05.530.

39. Deslée G., Zysman M., Burgel P.R. et al. Chronic obstructive pulmonary disease and the COVID-19 pandemic: Reciprocal challenges. *Respir. Med. Res*. 2020; 78: 100764. DOI: 10.1016/j.resmer.2020.100764.
40. Attaway A., Hatipoğlu U. Management of patients with COPD during the COVID-19 pandemic. *Cleve. Clin. J. Med.* [Preprint. Posted: 2020, Jul. 17]. DOI: 10.3949/ccjm.87a.ccc007.
41. Edler C., Schröder A.S., Aepfelbacher M. et al. Dying with SARS-CoV-2 infection-an autopsy study of the first consecutive 80 cases in Hamburg, Germany. *Int. J. Legal. Med*. 2020; 134 (4): 1275–1284. DOI: 10.1007/s00414-020-02317-w.
42. Børvik T., Brækkan S.K., Enga K. et al. COPD and risk of venous thromboembolism and mortality in a general population. *Eur. Respir. J*. 2016; 47 (2): 473–481. DOI: 10.1183/13993003.00402-2015.
43. Latham S., Sullivan J., Williams S., Eakin M.N. Maintaining emotional well-being during the COVID-19 pandemic: A resource for your patients. *Chronic Obstr. Pulm. Dis*. 2020; 7 (2): 76–78. DOI: 10.15326/jcopdf.7.2.2020.0150.
44. Halpin D.M.G., Singh D., Hadfield R.M. Inhaled corticosteroids and COVID-19: a systematic review and clinical perspective. *Eur. Respir. J*. 2020; 55 (5): 2001009. DOI: 10.1183/13993003.01009-2020.
45. Iwabuchi K., Yoshie K., Kurakami Y. et al. [COVID-19 three cases improved with inhaled ciclesonide in the early to middle stages of pneumonia]. Available at: *www.kansensho.or.jp/uploads/files/topics/2019ncov/covid19_casereport_200310.pdf* (in Chinese).
46. Yang I.A., Clarke M.S., Sim E.H. et al. Inhaled corticosteroids for stable chronic obstructive pulmonary disease. *Cochrane Database Syst. Rev*. 2012; (7): CD002991. DOI: 10.1002/14651858.CD002991.pub3.
47. Lipworth B., Chan R., Lipworth S., Rui Wen Kuo C. Weathering the cytokine storm in susceptible patients with severe SARS-CoV-2 infection. *J. Allergy Clin. Immunol. Pract*. 2020; 8 (6): 1798–1801. DOI: 10.1016/j.jaip.2020.04.014.
48. Singanayagam A., Glanville N., Cuthbertson L. et al. Inhaled corticosteroid suppression of cathelicidin drives dysbiosis and bacterial infection in chronic obstructive pulmonary disease. *Sci. Transl. Med*. 2019; 11 (507): eaav3879. DOI: 10.1126/scitranslmed.aav3879.
49. Tal-Singer R., Yawn B.P., Wise R. et al. The COPD foundation coronavirus disease 2019 international medical experts survey: results. *Chronic Obstr. Pulm. Dis*. 2020; 7 (3): 139–146. DOI: 10.15326/jcopdf.7.3.2020.0164.
50. Matsuyama S., Kawase M., Nao N. et al. The inhaled corticosteroid ciclesonide blocks coronavirus RNA replication by targeting viral NSP15. *bioRxiv* [Preprint. Posted: 2020, Mar. 12]. DOI: 10.1101/2020.03.11.987016.
51. Suda K., Tsuruta M., Eom J. et al. Acute lung injury induces cardiovascular dysfunction: effects of IL-6 and budesonide/formoterol. *Am. J. Respir. Cell. Mol. Biol*. 2011; 45 (3): 510–516. DOI: 10.1165/rcmb.2010-0169OC.
52. Bridgewood C., Damiani G., Sharif K. et al. Rationale for evaluating PDE4 inhibition for mitigating against severe inflammation in COVID-19 pneumonia and beyond. *Isr. Med. Assoc. J*. 2020; 22 (6): 335–339.
53. Yen B.L., Yen M.L., Wang L.T. Current status of mesenchymal stem cell therapy for immune/inflammatory lung disorders: Gleaning insights for possible use in COVID-19. *Stem Cells Transl. Med*. 2020; 9 (10): 1163–1173. DOI: 10.1002/sctm.20-0186.

Поступила 18.09.20
Received: September 18, 2020

Author Information / Информация об авторах

Aleksey M. Shchikota – Candidate of Medicine, Leading Researcher of Moscow Centre for Research and Practice in Medical Rehabilitation, Restorative and Sports Medicine; tel.: (916) 544-96-27; e-mail: alexmschikota@mail.ru (ORCID: *https://orcid.org/orcid.org/0000-0001-8643-1829*)

Щикота Алексей Михайлович – к. м. н., ведущий научный сотрудник Государственного автономного учреждения здравоохранения города Москвы «Московский научно-практический центр медицинской реабилитации, восстановительной и спортивной медицины Департамента здравоохранения города Москвы»; тел.: (916) 544-96-27; e-mail: alexmschikota@mail.ru (ORCID: *https://orcid.org/orcid.org/0000-0001-8643-1829*)

Irena V. Pogonchenkova – Doctor of Medicine, Director of Moscow Centre for Research and Practice in Medical Rehabilitation, Restorative and Sports Medicine; tel.: (495) 917-11-64; e-mail: PogonchenkovaIV@zdrav.mos.ru (ORCID: *https://orcid.org/0000-0001-5123-5991*)

Погонченкова Ирэна Владимировна – д. м. н., директор Государственного автономного учреждения здравоохранения города Москвы «Московский научно-практический центр медицинской реабилитации, восстановительной и спортивной медицины Департамента здравоохранения города Москвы»; тел.: (495) 917-11-64; e-mail: PogonchenkovaIV@zdrav.mos.ru (ORCID: *https://orcid.org/0000-0001-5123-5991*)

Elena A. Turova – Doctor of Medicine, Deputy Director on Scientific Research of Moscow Centre for Research and Practice in Medical Rehabilitation, Restorative and Sports Medicine; tel.: (495) 616-81-06; e-mail: TurovaEA1@zdrav.mos.ru (ORCID: *https://orcid.org/0000-0002-4397-3270*)

Турова Елена Арнольдовна – д. м. н., заместитель директора по научной работе Государственного автономного учреждения здравоохранения города Москвы «Московский научно-практический центр медицинской реабилитации, восстановительной и спортивной медицины Департамента здравоохранения города Москвы»; тел.: (495) 616-81-06; e-mail: TurovaEA1@zdrav.mos.ru (ORCID: *https://orcid.org/0000-0002-4397-3270*)

Marina A. Rassulova – Doctor of Medicine, First deputy Director of Moscow Centre for Research and Practice in Medical Rehabilitation, Restorative and Sports Medicine; tel.: (495) 916-45-62; e-mail: RassulovaMA@zdrav.mos.ru (ORCID: *https://orcid.org/0000-0002-9566-9799*)

Рассулова Марина Анатольевна – д. м. н., первый заместитель директора Государственного автономного учреждения здравоохранения города Москвы «Московский научно-практический центр медицинской реабилитации, восстановительной и спортивной медицины Департамента здравоохранения города Москвы»; тел.: (495) 916-45-62; e-mail: RassulovaMA@zdrav.mos.ru (ORCID: *https://orcid.org/0000-0002-9566-9799*)

Sergey A. Gumenyuk – Candidate of Medicine, Deputy Director for Medical Work of Scientific Center of Emergency of Moscow Healthcare Department; tel.: (495) 608-75-55; e-mail: npcemp@zdrav.mos.ru

Гуменюк Сергей Андреевич – к. м. н., заместитель директора по медицинской части Государственного бюджетного учреждения здравоохранения города Москвы «Научно-практический центр экстренной медицинской помощи Департамента здравоохранения города Москвы»; тел.: (495) 608-75-55; e-mail: npcemp@zdrav.mos.ru