

COVID-19 from the interdisciplinary standpoint. Round table

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On February 25, 2021, an expert round table was held, which considered the problem of interdisciplinary discussion of a coronavirus disease 2019 (COVID-19) and the development of joint actions for management of patients with chronic noncommunicable diseases during a pandemic.

Keywords: COVID-19, interdisciplinary approach, chronic noncommunicable diseases.

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On February 25, 2021, an online expert round table was held with the presentation of reports and further discussion between each other and the audience on the interdisciplinary problems of coronavirus disease 2019 (COVID-19) and the development of joint actions for management of patients with noncommunicable diseases (NCDs) during a pandemic.

The first to make a report **“COVID-19: the fundamentals of an interdisciplinary approach”** was made by MD, Professor **Mehman N. Mamedov**.



At the moment, in the morbidity and complication patterns, including disability and deaths among adults,

NCDs occupy an important place [1]. According to experts, their prevalence is expected to increase to 56% in the coming decades. At the same time, an increase in the prevalence of acquired immunodeficiency syndrome is predicted, while the incidence of other infectious diseases has stabilized [2]. In 2020, the world is faced with a new problem — COVID-19, which was declared a pandemic by the World Health Organization (WHO) due to high morbidity and mortality. The Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) belongs to RNA virus family that can infect humans and some animals [3]. Until 2002, coronaviruses were considered to cause mild upper respiratory tract infections with extremely mortality rate. At the end of 2019, there was a COVID-19 outbreak with an epicenter in Hubei province (People's Republic of China) [4]. The infected person can spread the virus, including being in the incubation period, and an asymptomatic carrier of SARS-CoV-2. The epidemic situation in different countries is heterogeneous. Cases of the disease were recorded in 185 countries. There are currently >122 million confirmed cases of COVID-19 worldwide, with >2,7 million deaths. The largest numbers of infections have been reported in the United States, India, Brazil and the United Kingdom. In Russia, >4,4 million cases of COVID-19 were detected and >96 thousand people died. One of the serious negative phenomena is the presence of several COVID-19 mutations [3, 5].

The risk group includes persons aged >65 years, mainly men. In addition, the risk is increased in the presence of chronic diseases such as cardiovascular diseases (CVDs), diabetes, obesity, lung diseases,

cancer, and immunosuppression conditions. Smoking is also an important risk factor (RF). It should be emphasized that medical workers are also at risk. The high risk of medical worker infection is due to the high viral load during contact with COVID-19 patients [6].

The combination of NCDs and COVID-19 has a negative prognostic effect, along with this, the quality of life also deteriorates significantly. Preventive measures such as quarantine and self-isolation have in some cases restricted patients from regularly visiting health facilities and receiving care [7].

The cross-sectional multicenter study was carried out to assess the changes in behavioral RFs and psychosomatic status in patients with NCDs during quarantine/self-isolation. The study involved patients from 5 cities of Russia (Moscow, Saransk, Penza, Nizhny Novgorod, Ulyanovsk) and 4 cities of CIS/neighboring countries (Vilnius, Baku, Bishkek, Nur-Sultan). The study involved 260 adults (men, 41%; women, 59%). The age of the subjects was 30–69 years old. Each of the patients had at least one NCD. All patients underwent a standard survey using a questionnaire prepared at the National Medical Research Center for Therapy and Preventive Medicine, which assesses socio-demographic parameters, behavioral RFs, NCDs, and psychosomatic status. Also, blood pressure, heart rate, body weight and body mass index were evaluated. The questionnaire showed that 68% of patients were married, while 14% — widowers; 56% of respondents noted that they worked before the pandemic. Of these, 22% continued to work as before, 15% worked remotely, 20% did not work, and only 2% lost their jobs. During self-isolation and quarantine, 38% of patients reduced their physical activity, while 13% declared an increase in their physical activity. An increase in nutrition was noted by 40% of the surveyed, which was associated with an increase in body weight and body mass index on average up to 15%. Initially, 33% of patients consumed alcohol; during the pandemic, alcohol consumption increased only in 3% of cases. Before the pandemic, 12% of patients smoked; the frequency of smoking during quarantine increased by 1.5 times. During self-isolation, 53% of patients noted mild stress, 40% — moderate stress, and 6.5% — severe stress. Mild anxiety/depression was noted by 46% of patients with NCDs, while severe anxiety/depression was revealed in 5.4% of respondents. Among NCDs, hypertension prevailed (67% of patients). During quarantine, a hypertensive crisis was recorded in 22% of patients, and in 19% of cases an increase in antihypertensives' doses was required. The second place was occupied by class I–III exertional angina (32%), and only in 2% of cases the patient condition was a deteriorated. Also, 25% of patients reported the type 2 diabetes, while every second of them noted an increase in the dose of antihyperglycemic drugs. Chronic

obstructive pulmonary disease (COPD) was reported by 14% of respondents, and cancer — 6.5%. Among them, complications and deterioration were noted in less than 1% of cases. In the surveyed group of patients, COVID-19 was revealed in 18%, while complications were recorded in every second of them.

Thus, the presence of NCDs is a serious risk factor in COVID-19 patients. Quarantine measures in the form of self-isolation influenced behavioral RFs, psychosomatic status and clinical course, which requires additional secondary prevention.

The report “**Russian scientific publications on COVID-19 — the problem of presenting updated information**” by MSD Yulia V. Rodionova focuses on the global problem of high-quality scientific publications on COVID-19 in relation to Russia and reviews significant papers in Russian journals.



The timing of expert round table on COVID-19 at the end of February is also significant by the fact that a year ago, video messages began to arrive from hospitals overcrowded with critically ill patients in Europe, and full quarantine was announced in Italy. In addition, before the editors of scientific journals, the question arose: how much will the WHO call “release data on COVID-19 research as soon as possible” affect the quality of published material? The next question was: how will the types of publications change in a pandemic, when your own research base has not yet been collected? In addition, the natural response of leading journals was the appeal to the authors — not to send review articles, because some scientists instantly decided to take advantage for published “copy-paste”. Therefore, cardiology journals only observed from the outside what was happening in international medical journals.

One can immediately identify the central problem — accelerated peer review or its absence: scientists are joining the campaign to release the study results as early as possible; academic journals publish as

early as possible; the media is trying to bring the most shocking and frightening data to the public as soon as possible, while the so-called “experts” are eager to comment on the situation. The second problem is that this information is often false, distorted or misinterpreted, while the third is the impossibility of verifying the information received, discussing it among experts; there are difficulties in tracking changes in information (erratum, retraction). We should not forget about the conflict of interest: there are cases when the merits of one or another pharmaceutical product are praised without reliable verification of its effectiveness in treating COVID-19 patients.

The tough stance of scientific journals toward papers on COVID-19 has left many creations in sections of preprints and other repositories. There were no massive COVID-19-related publications in leading Russian journals. Scientific materials published this year (from February 2020 to February 2021) can be divided by type:

- Medical registries,
- Recommendations, consensus,
- Clinical observations,
- Case reports,
- Review articles.

By subject:

- Healthcare management,
- Vaccination,
- Epidemiology,
- Rehabilitation.

The “silence” position taken by leading scientific journals made it possible to consider the first official publication in the Russian Federation — “Temporary guidelines for the prevention, diagnosis and treatment of new coronavirus infection (COVID-19) of the Ministry of Health of the Russian Federation, last updated on 08.02.2021, version 10 [8]. The first Russian manual for cardiologists, “9. Guidelines for the diagnosis and treatment of circulatory diseases in the context of the COVID-19 pandemic” reflecting the position of the Russian Society of Cardiology, was also published at the end of March 2020 [9]. In June, a whole cluster of publications appears, starting with the consensus of experts from the two societies [10, 11], which supplement the Ministry of Health guidelines and focus on the prevention of NCDs in the population and their complications. Since COVID-19 poses a particular threat to elderly and senile people, an expert position paper from the Russian Association of Gerontology and Geriatrics is being published [12]. In July 2020, we already saw the national consensus statement on the management of patients with comorbidity during novel coronavirus (COVID-19) pandemic [13]. Such publications are intended for the attention of heads of medical organizations, general practitioners, pediatricians, various medical specialists, to whom patients turn to for outpatient or inpatient care during a pandemic.

It should be noted that at the end of June 2020, a specialized issue of the Cardiovascular Therapy and Prevention journal on COVID-19 was published, where, in addition to the aforementioned expert consensus, articles were published on methodological aspects of assessing the incidence, prevalence, and mortality in COVID-19 [14], the peculiarities of antithrombotic therapy and the use of angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor antagonists in COVID-19 patients [15, 16], nutrition during pandemic and isolation [17] and such RF as smoking [18].

The first publication of the international register “Dynamics analysis of comorbidities in SARS-CoV-2 survivors” (AKTIV SARS-CoV-2) was carried out in November 2020 [19]. The concept of the disease was largely formed on the basis of large registers carried out in the USA, Spain, Italy, China. However, there was no data on the characteristics of clinical course in Eurasian patients. The work brought together specialists from the Russian Federation, the Republic of Armenia, the Republic of Kazakhstan and the Kyrgyz Republic. The first analysis of the register included data from 1003 patients. In March 2021, it is planned to publish the the narrative of already expanded version of the register with the addition of data from second wave patients (AKTIV 2).

During 2020, research work on COVID-19 was carried out in several directions: concomitant diabetes, the clinical course in children, predictors of complications, diagnosis and improvement of instrumental investigations, vaccination (only publications in English-language journals (!)).

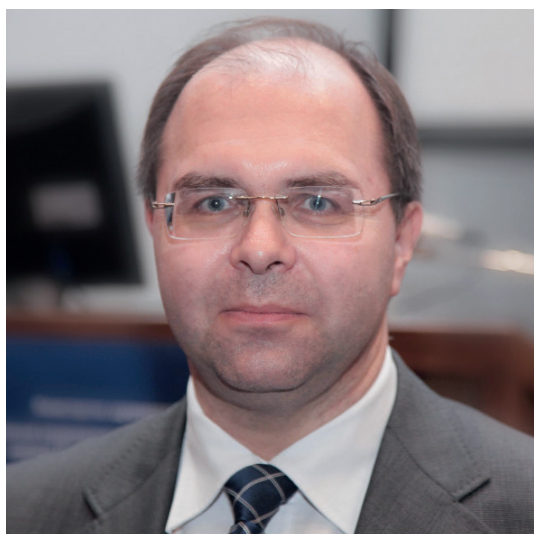
Taking into account global trends, different scenarios for scientific publications on COVID-19 can be predicted. If the pandemic ends and the virus becomes a seasonal disease, then clinical registers on various narrow topics, rehabilitation and vaccination programs, and the study of immunity will be in demand. If the pandemic continues and new virus strains appear, the priority topics will be as follows: novel diagnostic methods, rehabilitation programs, study of new vaccines and their tolerance, new methods of managing infected patients with NCDs.

Of course, we can expect an increase in the number of publications, but the following features are worth noting:

1. Review articles will not be in demand: every month the epidemiological situation changes, new publications appear, so the information is often outdated.
2. Clinical cases will be carefully selected — this material should be of interest to readers.
3. Original retrospective studies will be treated with care: using databases and registers to support the likelihood of an insignificant hypothesis is not a priority for readers. The standards for the requirements for scientific material will remain the same, but the authors

will need to take into account the study limitations: quarantine is already a limitation, the COVID-19 is already a new factor affecting the result.

The report “**COVID-19 and cardiovascular diseases**” of MD **Igor S. Yavelov** focuses on the connection and mutual influence of the incidence of COVID-19 and CVDs.



From the very beginning of the wide incidence of COVID-19, it became clear that this infectious disease adversely affects the cardiovascular system, and the combination of COVID-19 with CVD indicates an increased risk of complications and poor outcomes.

The Chinese meta-analysis showed that CVD was associated with a 3,84-fold increase in the risk of severe COVID-19 (95% confidence intervals (CI), 2,9-5,07) [20]. Further, the meta-analysis of 21 studies with a total of 77314 patients hospitalized with COVID-19 revealed that presence of cardiovascular RFs or CVD is a predictor of cardiovascular events (CVE) and death [21]. At the same time, CVE during inpatient treatment of COVID-19 patients occurred on average in 14% of patients and were also predictors of death. In addition, it turned out that CVDs can occur after discharge from the hospital. So, according to the retrospective analysis of data from 47780 COVID-19 patients, on average 140 days after discharge, major CVEs (composition of heart failure, myocardial infarction (MI), stroke and cardiac arrhythmias) occurred 3 times more often than in the control group, and about half of these events were first noted outside the hospital [22].

There are different reasons for the unfavorable COVID-19 course in cardiovascular patients and CVD occurrence during COVID-19.

Thus, cardiovascular damage during the infectious disease is well documented. This is the direct effect of the virus on endothelial, vascular and myocardial, and the features of immune response, and excessive inflammation, sometimes reaching

the cytokine storm, and increased metabolism with intoxication. As a result, conditions are created for endothelial dysfunction, microcirculation disorders, destabilization of atherosclerotic plaques, myocardial damage, myocarditis, arrhythmias and heart failure. An important role in COVID-19 is played by the blood coagulation system activation, which is largely associated with the severity of vascular damage, immune response and inflammation. This, on the one hand, promotes the formation of small and, as a rule, non-occlusive fibrin microthrombi, on the other hand, the appearance of blood clots in larger vessels with venous and arterial thrombotic and thromboembolic events [23]. Since intravital diagnosis of microthrombosis is difficult, its prevalence in various clinical manifestations of COVID-19 is unknown. The incidence of macrovascular thrombosis in COVID-19 depends on the severity of the disease. Thus, according to the cumulative data of 43 studies with 8271 subjects, lower limb deep vein thrombosis (DVT) was observed on average in 20% of patients, while in those in the intensive care unit — in 28%, and among the deceased — in 35% of cases [24]. The incidence of pulmonary embolism (PE) was 13%, 19%, and 22%, respectively. Arterial thromboembolism was noted much less frequently, on average in 2% of patients and in 5% of those in the intensive care unit. At the same time, the detection of thromboembolic events was associated with an increase in the death risk by 1,74 times ($p=0,04$). In general, it is possible that with the introduction of effective treatment methods, along with a decrease in the severity of clinical manifestations of COVID-19, the incidence of thrombotic events will also decrease.

Therefore, antithrombotic therapy for COVID-19 can help not only prevent DVT/PE, but also be part of the pathogenetic treatment of the disease, reducing the severity of its clinical manifestations and improving the prognosis. At the same time, it should be borne in mind that patients with COVID-19 have high bleeding risk, which also rises with increasing severity of the disease [25]. At the same time, a high blood D-dimer level, traditionally considered a marker of blood coagulation system activation, is associated with a higher frequency of bleeding. The latter does not seem surprising if we consider the D-dimer as one of the markers of COVID-19 severity.

It is now generally accepted that all patients hospitalized with COVID-19 should receive at least prophylactic dose against DVT. The rationale of higher anticoagulant doses (up to therapeutic) in patients without thrombotic/thromboembolic macrovascular events remains unclear and is actively studied in randomized controlled trials. The rationale of anticoagulant therapy in the outpatient treatment of COVID-19, as well as the need for long-term DVT/PE prophylaxis after discharge from the hospital, continues to be clarified. In COVID-19, it is recommended to

give preference to parenteral heparin administration, which have additional properties that are potentially useful in COVID-19 (in particular, they have an anti-inflammatory effect). Direct oral anticoagulants remain an option for patients already receiving them for other indications, or in cases where heparin drugs are not available, or if the main purpose of anticoagulant use is the prevention and treatment of DVT (in particular, after discharge from hospital). Since activated platelets can also participate in the pathogenesis of thrombotic events, the rationale of using antiplatelet agents (acetylsalicylic acid, P2Y₁₂ receptor blockers, dipyridamole) in COVID-19 is being studied [26].

In addition to the increased D-dimer level, the severity and prognosis of COVID-19 are associated with blood concentration of cardiac troponin (correlating with inflammation severity — C-reactive protein level) and N-terminal pro-brain natriuretic peptide (NT-proBNP) (correlating with the severity of myocardial damage — cardiac troponin level) [27]. It has been shown that the prognosis is most unfavorable if CVD is combined with an increased blood concentration of cardiac troponin.

The causes of myocardial damage in COVID-19 are diverse: microangiopathy with thrombosis, inflammation with increased cytokine levels, myocarditis, stress-induced cardiomyopathy, and acute myocardial infarction, which often occurs not due to thrombotic complications of coronary atherosclerosis, but due to hypoxia, microvascular disorders, tachyarrhythmias and other causes leading to myocardial ischemia. Moreover, with an in-depth examination of patients, it turned out that cardiac damage is often observed even in initially healthy individuals with mild COVID-19 manifestations. So, according to the data of magnetic resonance imaging in 48 student-athletes with a positive SARS-CoV-2 polymerase chain reaction with a mild clinical course, data suggestive of pericarditis was noted in 27,1%, while small structural and functional myocardial abnormalities without signs of ongoing myocarditis — in 16,7%, and their combination — in 12,5% of cases [28].

In general, the accumulated data indicate that COVID-19 and cardiovascular diseases exacerbate each other's course: on the one hand, due to additional cardiovascular damage, COVID-19 can contribute to cardiovascular pathology or the aggravation of existing CVDs, which additionally worsens the prognosis, on the other hand, it is possible that the presence of CVD itself adversely affects the course of an infectious disease [20].

Adverse effects in patients with COVID-19 can result from refusal of treatment to control symptoms and prevent complications in patients with CVD, as well as side effects of drugs used to treat COVID-19. An example is concerns about the use of ACE inhibitors and intensive hydroxychloroquine therapy at the onset of the COVID-19 pandemic. Subsequently, concerns about ACE inhibitors were not confirmed [29-31], and

the widespread use of hydroxychloroquine was either actually stopped due to insufficient evidence of its effectiveness, or was limited to patients without severe cardiovascular pathology [8].

An additional contribution to the increase in CVE incidence during the COVID-19 pandemic is made by the overload of healthcare system, when the provision of routine medical care is significantly limited or stopped, as well as the consequences of limited contact and self-isolation. All this can lead to inadequate control of cardiovascular RFs, defects in the diagnosis and treatment of CVD, untimely care provision when the patient's condition worsens. Thus, according to the analysis of hospitalization rate in California during the growing COVID-19 pandemic, the frequency of hospitalizations with acute myocardial infarction decreased [32]. At the peak of the epidemic in Italy, there was also a decrease in MI hospitalization rate, which, along with a higher incidence of complications and mortality, despite the same frequency of coronary angiography, may indicate hospitalization of only the most severe patients [33]. According to information received in 909 hospitals in 108 countries, during the COVID-19 pandemic, the prevalence of heart examinations, both invasive and non-invasive, decreased [34].

Thus, the interaction between COVID-19 and cardiovascular disease seems to be quite complex and multifaceted. Accordingly, to solve the problems arising, it is necessary not only to improve the treatment of an infectious disease, its immediate and long-term consequences, but also timely diagnosis and proper treatment of CVD. It is also important to maintain the current level of medical care for CVD patients.

The report **“Acute respiratory infection and chronic respiratory diseases with COVID-19 aspects”** by MSD **Marina I. Smirnova** was dedicated to the prevention of acute respiratory infections (RI), including COVID-19, in patients with chronic respiratory diseases.



According to the WHO, lower respiratory tract infections (LRTIs) are the leaders in the mortality pattern of the world population — 3rd and 4th places in 2015 and 2016, 2019, respectively [35]. The highest position, 1st place, LRTIs took in 2015 and 2019 in low-income countries. This disease includes COPD, which in recent years took the third place in the world mortality pattern [35]. Mortality from other chronic respiratory diseases (CRDs), asthma, is not so high, but the prevalence of asthma continues to increase [36]. In this regard, as well as taking into account certain difficulties in the diagnosis and control of diseases, LRTIs represent a serious medical and social problem.

LRTIs are primarily represented by community-acquired pneumonia (CAP), the proportion of which among the death causes from infectious diseases in 2016 in the Russian Federation was 54% [37]. Despite the successes achieved in antibiotic therapy, respiratory support and sepsis therapy, mortality among patients with severe CAP ranges from 21 to 58% [38]. At the same time, there are very serious data that CAP in the elderly can be associated with death within a year after recovery. For example, a study by Ramirez JA, et al. (2017) [39] showed that among 7449 patients hospitalized with CAP (mean age, 68 years), the death rate was 6,5% during hospitalization, and 13, 23,4 and 30,6% during 1, 6 and 12 months, respectively. It is known that most patients of older age groups hospitalized with CAP have one or more RFs of unfavorable outcomes (COPD, CVD, chronic renal failure, diabetes, cancer, etc.). According to McLaughlin JM, et al. (n=2034; age, 65-102 years; mean, 76 years) the incidence of COPD in these patients can reach almost 53% [40].

Prevention of LRTIs has always been relevant, but now it is especially important with the advent of a novel RI — COVID-19. COVID-19 is an acute RI caused by SARS-CoV-2. Despite the fact that more often COVID-19 proceeds in a mild form (according to WHO, ~80% of cases), this RI is associated with high CAP risk and severe acute respiratory syndrome (SARS). The RFs for severe COVID-19 course are, in addition to age, male sex and others, various NCDs, including CRDs [41]. These RFs are similar to those previously known for the severe RI. For example, in a Korean study published in 2016 (5459 patients with acute RI, including 52,9% with influenza), there were following independent RFs for pneumonia and SARS in acute RI: age ≥ 65 years (odds ratio (OR), 5,71, 95% CI: 4,10-7,94), autoimmune diseases (OR, 3,35, 95% CI: 1,79-6,27), Immunodeficiency disorders (OR, 3,12, 95% CI: 1,47-6,62), chronic kidney disease (OR, 2,62, 95% CI: 1,73-3,99), COPD (OR, 2,34, 95% CI: 1,48-3,69), asthma (OR, 2,33, 95% CI: 1,62-3,36), coronary artery disease (OR, 1,54, 95% CI: 1,07-2,22); the risk of SARS and pneumonia increased with more chronic diseases in one patient [42].

What is the contribution of respiratory viruses to COPD and asthma? It is known that more than half of asthma exacerbations can be caused by respiratory viruses, that an asthma patient with viral infection has a high risk of secondary bacterial infection (*S. pneumoniae*, *S. aureus*, *H. Influenzae*). In asthma patients >65 years old, primarily, influenza is associated with a high risk of death, secondly, with bacterial pneumonia and CVE [43]. Also, in patients with COPD, $>50\%$ of exacerbations are associated with RI [44]. Of these, 70% have a bacterial infection (*S. pneumoniae*, *H. Influenzae*, *M. Catarrhalis*, less often other microorganisms), while the rest — viral or mixed infection, or a viral infection is a precursor of bacterial one [44]. Using the polymerase chain reaction (PCR), viral infection (according to data published 20 years ago) can be detected in 39% of patients with COPD exacerbation [45]. A large Canadian study published in 2020 showed that among patients seeking emergency care for COPD (817 141 visits over 11 years), ~ one third (31,9%) were hospitalized, while for asthma (649 666 visits over 11 years) — 10,6%, for RI (4 365 578 visits) — 7,4% [46]. At the same time, 66,7% of emergency department visits and 74,4% of hospitalizations is associated with respiratory viruses (type A and B influenza virus, respiratory syncytial virus, rhinovirus, metapneumovirus, adenovirus, parainfluenza virus, previously known coronaviruses), while there were 52,5% of visits and 48,2% of hospitalizations for COPD, and 13,3% of visits and 10,4% of hospitalizations for asthma [46].

Since COVID-19 is a novel RI, which began to be studied from the end of 2019, for now we can rely on data from cross-sectional and relatively short-term prospective studies. However, there are some very large and important ones among them. The OpenSAFELY study carried out in England (February 1, 2020 — April 25, 2020) included a population of 17 278 392 people. The primary endpoint was death associated with COVID-19 (n=10926). In addition to other risk factors for death from COVID-19, they turned out to be severe asthma and other CRDs. Severe asthma required oral glucocorticosteroid therapy has been associated with a 55% increased risk of death from COVID-19; CRDs (COPD, pulmonary fibrosis, bronchiectasis, cystic fibrosis) almost doubled this risk (OR, 1,95, 95% CI: 1,86-2,04); data presented are adjusted for sex and age [41].

I dare to suggest that the problem may be aggravated by the lack of experience in the management of asthma and COPD patients by doctors (of various specialties) who work during the epidemic in hospitals with severe COVID-19 patients. A number of these reasons gave rise to some systematization of management of asthma or COPD patients with signs of RI, in particular COVID-19, which was published in more detail earlier [47]. In that work, it was emphasized that in addition to the differential diagnosis of the causes of the onset/increase of respiratory symptoms in a patient with asthma and COPD, the most important aspects in the management are:

- a) continuation of inhalation therapy of CRDs in any RI, if there is no exacerbation,
- b) correction of CRD therapy in case of exacerbation (in accordance with its severity),
- c) the appointment of basic CRD therapy immediately after the relief of exacerbation.

Of course, both basic therapy and therapy for asthma or COPD exacerbation are prescribed taking into account the approaches published in the current Federal clinical guidelines on asthma and COPD and other documents.

Prevention of RIs, including COVID-19, especially for groups at risk of severe course, is extremely important. No less important is the prevention of exacerbations of CRDs, including the prevention of RI — potential RF of infectious CRD exacerbation and RF of unfavorable outcomes. Experts from the Global Initiative for Asthma (GINA), The Global Initiative for Chronic Obstructive Lung Disease (GOLD), the Russian Respiratory Society and others strongly recommend continuing the treatment of asthma and COPD patients during the COVID-19 pandemic, taking into account the previously developed guidelines [48-50]. It is required to improve the asthma control, reduce the severity of symptoms and risk of COPD exacerbations, as well as follow the generally accepted protective measures from RI (masks/respirators, washing hands and disinfecting, limiting contacts). In addition, they remind about the need for vaccination against influenza and pneumococcal infection. Since December 2020, GINA experts have been recommending vaccination of asthma patients against COVID-19, taking into account the allergological anamnesis and the current condition of a patient.

Discussing the report “**Management of patients with diabetes in the context of COVID-19 pandemic**”, of MSD Ekaterina N. Dudinskaya draws attention to diabetic nephropathy.



Diabetes is one of the main causes of morbidity, disability and mortality both in Russia and around the world. This is due to vascular complications of diabetes, which ultimately contribute to a reduction in the patient's life. The relationship between diabetes and various infectious diseases has been discussed for many years, and in recent years, interest in this topic has only increased. Infections such as seasonal acute respiratory viral infections, herpes infections and pneumonia are quite common in people with diabetes and pose a serious threat to patients, especially in old age. The question of how the very fact of diabetes presence increases the patient's susceptibility to infection and can influence the outcomes is actively discussed by clinicians. Perhaps the main reasons for the high susceptibility to infections are vascular damage due to diabetes or decreased renal function and other related complications.

Carbohydrate metabolism disorders and, in particular, type 1 and 2 diabetes, represent a serious problem in the current epidemiological situation associated with the COVID-19 pandemic around the world.

It was previously known that the presence of diabetes and other carbohydrate metabolism disorders are significant risk factors for the severity and high mortality of patients infected with various viruses, including the 2009 H1N1 flu pandemic, SARS-CoV, and MERS-CoV (Middle East Respiratory Syndrome Coronavirus).

Patients with type 2 diabetes are known to be at increased risk of severe COVID-19. Thus, according to the study by Li S, et al. [52], diabetes as a concomitant disease is detected in 9,7% of patients with COVID-19 pneumonia (95% CI: 6,9-12,5), and ranked third after hypertension and cardiac/cerebrovascular diseases. And in the group of patients with a severe clinical course, patients with diabetes were more often: 11,7% among severe/critical patients compared with 4,0% of non-severe/non-critical patients.

It should be noted that the pathogenetic relationship between COVID-19 and diabetes remains not fully understood. It is possible that COVID-19 in patients with diabetes more intense stress hyperglycemia with the release of glucocorticoids and catecholamines. This, in turn, leads to hyperinsulinemia, hyperglycemia, and abnormally high glucose variability. Several defects in the immune response associated with hyperglycemia have also been described, although the clinical significance of some *in vitro* disorders is still being studied [52-54].

One of the most studied RFs for the severe COVID-19 course in diabetes patients is unsatisfactory control of the disease, which is associated with inhibition of the proliferative response of lymphocytes to various types of pathogens, as well as with dysfunction of monocytes, macrophages and neutrophils.

Experts postulate an important point — the risk of COVID-19 in people with diabetes is not higher than in the general population. However, failure to achieve

target glycemic values and poor glucose control have an undeniable proven relationship with severe infection. Close glycemic control and keeping target glucose levels is key to reducing the infection risk. Therefore, patients with diabetes are advised to continue the selected successful glucose-lowering, antihypertensive and lipid-lowering therapy, and, if necessary, to intensify the treatment.

Glucose-lowering therapy in the case of COVID-19 depends on the general condition of a patient and on the glucose level. So, with an uncomplicated course of COVID-19 and a plasma glucose level <13 mmol/L, in the absence of dehydration, body temperature $<38,5^{\circ}\text{C}$, it is recommended to continue the current selected antihyperglycemic therapy with any classes of drugs: immediate- or extended-release metformin, dipeptidyl peptidase-4 inhibitors (excluding saxagliptin), sulfonylureas with a low hypoglycemia risk, glucagon-like peptide-1 receptor agonists, and sodium/glucose cotransporter 2 (SGLT2) inhibitors under strict urine ketone control.

In cases of an increase in glucose >13 mmol/L and signs of dehydration, body temperature $>38,5^{\circ}\text{C}$, then transfer to an intensified scheme of insulin therapy with short and long-acting insulin is recommended.

In the management of patients with diabetes and COVID-19, it is important to have a team of specialists: infectious disease specialists, endocrinologists, pulmonologists and rehabilitologists, not only during the period of illness, but also at the further stages [55].

It is important to pay special attention to patients with diabetic nephropathy or micro- and macrovascular complications of diabetes, obesity. Increased attention of diabetes patients themselves to their disease, strict adherence to preventive measures, and lower thresholds for hospitalization of such patients can have a positive effect on COVID-19 course.

Raising the relevant issue “**Cardio-oncology during a COVID-19 pandemic**”, MD Vera I. Potievskaya draws attention to patients with combined oncological and cardiological pathology.



Patients with a combination of cancer and CVDs have significantly higher risks of severe COVID-19 [56, 57]. The increased risk of complications from COVID-19 is due to a number of factors common to cancer patients. These factors include immunosuppression against the background of the underlying disease and anticancer therapy, senile age, and the need to visit hospitals frequently. Recent chemotherapy (within the last 3 months), radiation therapy, bone marrow and stem cell transplantation within the last 6 months, oncohematological disease, and leukopenia or low levels of immunoglobulins potentiate the risk.

According to Chinese researchers, the COVID-19 incidence among patients with cancer is 0,79%, which is >2 times higher than that for the general population. At the same time, lung cancer patients predominated among infected cancer patients [58]. Mortality among cancer patients was 35% compared with 8% among patients without cancer [59].

Taking into account the above data, it is recommended to postpone radiation treatment, chemotherapy or surgery if COVID-19 is detected. If the patient is receiving metronomic, targeted, or hormonal therapy, the continuation of treatment should be discussed with the oncologist [60].

A potential danger for cancer patients is the development of COVID-19-related CVE. The heart is the second target for COVID-19 after the lungs, which is due to the expression of ACE receptors both on the membranes of cardiomyocytes and endothelial cells. Total endothelial damage leads to microthrombosis and impaired microcirculation, deterioration of myocardial perfusion. Hypoxia causes the development of oxidative stress, intracellular acidosis, damage to cell membranes and mitochondria. The situation is aggravated by the so-called cytokine storm against the background of a systemic inflammatory response and overproduction of biologically active compounds: interleukin (IL)-1-beta, IL-6, interferon-gamma, IL-1 inhibitors, IL-6 and Janus kinase inhibitors.

Thus, with COVID-19, there is direct viral damage to cardiomyocytes, acute hypoxemia, thrombosis and, ultimately, ischemic myocardial damage develop. The severity of CVE is also determined by secondary immune damage, local myocardial toxemia.

Currently, cases of fulminant myocarditis in COVID-19 patients have been described. At the same time, there is a rapid progression of heart failure, life-threatening arrhythmias. There is an increase in the level of troponin and natriuretic peptide (BNP) or NT-proBNP, a sharp decrease in the left ventricular ejection fraction, myocardial wall thickening due to edema according to echocardiography and cardiac magnetic resonance imaging [61, 62].

In addition to myocarditis, with COVID-19, it is possible to develop acute myocardial infarction of both

the first and second types, as well as stress-induced takotsubo cardiomyopathy.

A number of cancer patients may continue to take targeted drugs, antiestrogens and antiandrogens, antagonists or agonists of luteinizing hormone-releasing hormone. It is known that in some patients the use of vascular endothelial growth factors inhibitors causes endothelial dysfunction, manifested by thrombosis, ischemia and hypertension. Hormone therapy can also lead to the progression of atherosclerosis. Such changes can be potentiated by the endothelial damage characteristic of COVID-19.

The effect of COVID-19 on ACE receptors can lead to blood pressure variations, provoking the development of hypertension or aggravating the course of an already existing hypertension.

Cancer patients with a high risk of cardiotoxic complications and concomitant cardiovascular pathology are recommended to continue cardioprotective therapy previously prescribed: beta-blockers, ACE and angiotensin 2 receptor inhibitors, statins, and trime-tazidine.

As a cardioprotective therapy, including in patients at high risk of myocardial injury, the use of exogenous phosphocreatine may be considered. The main mechanisms of the cardioprotective action of phosphocreatine include improvement of local microcirculation, cardiomyocyte membrane stabilization, and normalization of intracellular metabolism [63].

The study on the effect of phosphocreatine in 175 patients aged 36–67 years during hospitalization with COVID-19 and verified acute myocardial injury, a significant decrease in creatine phosphokinase-MB by 18%, cardiac troponin I by 19%, NT-proBNP by 19% and an increase in left ventricular ejection fraction by 8,4% were revealed [62].

According to our own data, inhalation of xenon-oxygen gas mixtures had a positive effect in patients with moderate and severe COVID-19. Examination of 17 patients in the intensive care unit after xenon therapy showed a significant decrease in NT-proBNP by 47,1% ($p < 0,05$), as well as clinical state stabilization.

The main points of the management of cardio-oncological patients with COVID-19 are as follows:

- COVID-19 screening;

- widespread telemedicine use;
- immune system restoration, including the use of leukopoiesis stimulants;
- considering the postponement of myelosuppressive therapy and immunotherapy in patients with remission;
- reducing the frequency of instrumental investigations' use, as well as the frequency of patient visits to oncology hospital, using abbreviated research protocols (for example, with echocardiography);
- using an outpatient ECG monitoring;
- considering a delay in RF correction (treatment of hyperlipidemia, for example);
- delayed examination of asymptomatic patients who survived after cancer (elective assessment of myocardial function).

In conclusion, it should be noted that patients with cancer, CVDs and COVID-19 are at extremely high risk. Such patients require increased attention and careful monitoring for the timely treatment of complications.

Summing up the current expert round table results it should be noted that:

- the presence of NCDs is a serious risk factor for COVID-19 incidence;
- the combination of COVID-19 and CVDs is a complex and multifaceted problem, therefore, timely diagnosis and proper treatment of the immediate and long-term consequences of an infectious disease is necessary, as well as efforts to maintain the current level of medical care for patients with CVD;
- a constant supportive program for the prevention of RI and CRD exacerbations is required; strict adherence to generally accepted measures of protection against RI and timely vaccination;
- it is important to pay special attention to patients with diabetic nephropathy or micro- and macrovascular complications of diabetes and obesity;
- patients with cancer and CVDs infected with COVID-19 are at extremely high risk;
- priority research issues will be: novel diagnostic methods; rehabilitation programs; the study of novel vaccines and their tolerance; novel methods of managing patients with combination of CNDs and COVID-19.

Relationships and Activities: none.

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