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**НАСЛІДКИ ПАНДЕМІЇ: LONG-COVID.
ТРАГЕДІЯ «ДАЛЕКОБІЙНИКІВ»**

**RESOLUTION OF
Teleconference «Pandemic Consequences: Long COVID.
The Tragedy of «Long-haulers»»**

June 17, 2021

Almost 7 000 health care specialists have registered to participate in Teleconference «Pandemic Consequences: the Tragedy of «Long-haulers»».

Interdisciplinary format of the Teleconference was assured by speakers from different special fields: anesthesiologists, neurologists, cardiologists, endocrinologists, infectious disease specialists, family doctors, pulmonary specialists, and allergologists.

Eleven main reports were offered to the participants for review and discussion and they were dealing with the following issues:

- Medical care standards: rehabilitation of patients with COVID and convalescents.
- Post-COVID immunopathological syndromes.
- Drug rehabilitation options for patients after COVID-19.
- An experience of drug rehabilitation of patients with Long COVID using pathogenic and syndromic approach to treatment.
- Long COVID as viewed by different specialists.

Conclusions and decisions based on discussion of reports:

1. The tragedy of «Long-haulers» or Long COVID has presented new important challenges to health professional. They are related to delivery of high quality health care services including rehabilitative measures after and during COVID-19. The effectiveness of the methods employed depends directly on the early initiation of rehabilitation activities at all stages of medical care: pre-hospital, hospital or outpatient.

There are the following principal directions of rehabilitation of patients with Long COVID:

- Rehabilitation of respiratory function;
- Rehabilitation of neurological, psychological and cognitive functions;
- Rehabilitation of cardio-vascular disorders;
- Rehabilitation of comorbid conditions.

The critical need to develop drug rehabilitation of patients with Long COVID remains a cornerstone today as far as it is not included into the current Medical Care Standards.

2. The signs of immunodeficiency syndromes develop in patients after COVID-19, especially in patients with severe and very severe disease. The following immunodeficiency syndromes should be mentioned: activated infections syndrome related to immune deficiency, autoimmune and allergic (reaginic) syndrome related to hyperimmune response. Quite often the doctors noted increased allergic reactions, especially drug allergy. Reduction of immunological reactivity is an important factor in patient recovery. According to different data, Long COVID may last from several months to half a year or even

longer, as some specialists say. Any patient who had COVID-19 needs an individual approach to drug correction of Long COVID to prevent development of further delayed negative consequences.

3. Pathophysiological syndromes we have never seen before are characteristic feature of Long COVID: systemic background inflammation formed by circulating cytokines, endotheliitis, pneumonitis and asthenic syndrome. Drug rehabilitation that will help to overcome consequences of disease, to get back to normal life and to prevent development of complications is the only solution. Non-drug rehabilitation methods have to be combined with drug ones to achieve significant clinical results and full functional recovery especially of working age patients. Today, in addition to the current Medical Care Standards «Rehabilitation of Patients with COVID-19 and Convalescents», a Project on drug rehabilitation is being developed.
4. A study of efficiency of syndromic and pathogenic approach to drug rehabilitation of patients with Long COVID was conducted at the Department of Neurology, Psychiatry, Addictology and Medical Psychology of the V.N. Karamzin Kharkiv National University. The purpose of the study was to assess the effect of drug combinations of edaravone, L-arginine hydrochloride + L-carnitine and infusion solution based on xylitol and electrolytes on development of complications in patients with Long COVID under the conditions of the neurological department. The study results have demonstrated that the active treatment group had better indicators in comparison to the control group: reduction of neurological symptoms (headache, faintness, depleted state, memory impairment); improvement of cognitive functions proved with MoCA scale; reduction of asthenia signs in asthenic scale research; improvement of the quality of life estimated with SF-36 scale and decreasing of the number of patients with neurological syndromes (cephalgic, vestibulo-ataxic, asthenic, cognitive ones).
5. Cardio-vascular system is one of the targets in patients suffering from Long COVID. The systemic smoldering inflammation, endotheliitis and asthenia are continuation of activity of virus SARS-CoV-2 in a body. The acute coronary syndrome on the background of Long COVID is dangerous because of lack of ST segment elevation, high risk of thrombosis and coronary artery ischemia that is accompanied with depression of NO synthesis. The levorotatory arginine is the only substrate for NO-synthesis, an enzyme that catalyzes the synthesis of nitrogen oxide in endotheliocytes. The effectiveness of cardioprotective effect of L-arginine is proved with an example of treatment of iatrogenic ischemia. Combination of L-arginine and L-carnitine allows resuming of the process of fatty acids beta-oxidation in myocardium to provide it with the necessary energy. It takes two months to restore the endothelium of vessels through treatment with L-arginine in combination with parenteral and peroral forms (sequential therapy). The ischemic cascade blocker – an infusion edaravone – should be used to recover after systemic background inflammation.
6. In average 5% of patients with Long COVID have residual lung tissue damages but if we consider patients with severe COVID-19, it will be 62%. In cases of severe COVID-19 we observe mostly the following changes in lungs: induration of parenchyma in the form of «matt glass» symptom, more rarely cords in parenchyma, reticulation and fractional bronchiectasis, 35% of patients have «fibrosis-like» changes. Molecular basis is formed as a result of COVID-19 (AT2 level increase) and treatment-induced factors (lung injury, pneumotoxicity of oxygen) create conditions for pulmonary fibrosis. Beside of CT changes the patients with Long COVID usually have continuation of respiratory symptoms, reduction of forced vital lung capacity, shorter distance in walking test. Administration of systemic glucocorticosteroids, oxygen-therapy, anticoagulant therapy and pulmonary rehabilitation are usually considered for treatment of patients with Long COVID and pulmonary tissue fibrotic changes. Use of inhaled budesonide in patients with Long COVID is one of promising trends. According to conducted studies the inhaled budesonide has accelerated recovery of patients with Long COVID.
7. Most of toxic substances are got out through kidneys, so nephron is the main detoxification unit. The affinity of SARS-CoV-2 to ACE-2 receptors, a large number of which is located in kidney glomerulus and proximal kidney tubules, has been proved. The most frequent kidney damages are associated with vessel regulation disorders: COVID- nephropathy. That is why it is the kidney vascular apparatus that

has to be properly protected against damaging. The solution is to use nitrogen oxide donor – L-arginine. It will help to prevent vasoconstriction, parietal thrombus formation and pathologic remodeling of vascular wall. An increased level of creatinine in blood is an indicator of kidney damage in patients with Long COVID. Hyperosmolar well-balanced solution improves microcirculation of kidney, promotes elimination of toxins and relieves edemas. So the treatment scheme with administration of the well-balanced hyperosmolar solution and L-arginine protects nephron against ischemia and we may observe it through rapid decreasing of the level of creatinine in blood. Thus a comprehensive approach should be used to protect the main detoxification unit, such as L-arginine and well-balanced hyperosmolar solution that will help to decrease the level of creatinine in blood and to increase glomerular filtration rate.

8. According to the international research data every other patient with COVID-19 has pancreas damage. Virus SARS-CoV-2 is able to induce diabetes mellitus and to increase glucose level in blood, this creates a false circle between the virus and diabetes mellitus. Additional use of corticosteroids, being actually anti-insular hormones, further exacerbates insulin resistance and narrows the false circle. The patients suffering with Long COVID and having diabetes mellitus have to control blood glucose level. They need vascular protection and energetic support. In most cases the heart suffers: the diabetic cardiomyopathy develops. Reduction of nitrogen oxide causes vascular ageing syndrome. Treatment requires a comprehensive approach. An infusion solution based on xylitol and electrolytes penetrates into the cell without insulin and provides nutriment as glucose does. Combination of L-arginine and L-carnitine let us protect the heart muscle and restore physiological endothelium-dependant vasodilatation. It takes 60 days to restore endothelium completely, so the patients are recommended to use L-arginine in the amount of 8.4 g per day during the whole period.
9. The patients who had severe COVID-19 may have different pulmonary ventilation function disorders and restrictive or obstructive type of ventilation disorders may develop and it is often associated with disturbance of diffusing capacity of lungs. Any patient who has respiratory symptoms (cough, labored breathing) after recovery has to go through spirographic study to identify the type of ventilation disorders. If there is bronchial obstruction on the background of clinical symptoms it is recommended to use short- or long-acting bronchodilators. Besides, it is advisable to use inhaled glucocorticosteroids during post-COVID period to remove autoimmune inflammation, especially for those who were taking systemic corticosteroids in high dose during the acute period. If there is a need nebulizer therapy should be used to deliver medication directly to the respiratory tract.
10. Many countries of the world have noticed lack of high incidence of COVID-19 among patients with asthma. Such phenomenon is explained by permanent use of inhaled corticosteroids by such patients. It was proved that inhaled steroids have 3 effects:
 - Reduced enrichment of membrane proteins of ACE-2 receptors, ACE-2 and TMPPSS2, directly participating in entry of SARS-CoV-2 virus into the cells.
 - Inhibiting of SARS-CoV-2 replication in infected epithelium cells.
 - Reduced production of cytokines, including IL-6 and IL-8.

The protective action of inhaled glucocorticosteroids in case of COVID-19 decreasing the viral load and hyperinflammatory immune reaction is considered. The study conducted in Great Britain with participation of 146 patients demonstrated high efficiency of use of dry powder budesonide 1600 mcg in case of mild COVID-19. Good clinical effect was proved: reduction of hospital admissions by 90%, higher level of saturation in patients using budesonide, reduction of symptoms and fever, 3 days faster recovering of patients, reduction of residual effects of COVID-19 on the 14th and 28th day. Use of inhaled glucocorticosteroids during COVID-19 for reduced risk of hospital admission and alleviation of symptoms has demonstrated first positive results and is a promising method for reduction of hospital admission and COVID-19 severity. Dry powder budesonide is represented by Easyhaler inhaler in Ukraine.

11. The patients with Long COVID need obligatory monitoring of respiratory function, cardiac symptoms, nervous system condition and psychical functions, monitoring and correction of disorders along with coexisting diseases (such as diabetes mellitus, arterial hypertension); as well as syndromic and pathogenic approach to rehabilitation of patients. And first of all it should be focused on removal of the systemic background inflammation with edaravone, improvement of the endothelial function with combination of L-carnitine and L-arginine. The infusion solutions based on xylitol and electrolytes are used to decrease asthenia signs as far as they are sources of energy with insulin independent metabolism and provide efficient energetic support. A multidisciplinary rehabilitation in a hospital setting is recommended for better recovery of patients with mild or severe post-COVID symptoms.

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