RESOLUTION OF

Eurasian Teleconference «Delta Variant. Experience of International Experts»

September 16, 2021
Kyiv, Ukraine

Almost 12 000 health care specialists from Uzbekistan, Tadzhikistan, Kirghizia, Ukraine, Kazakhstan, Azerbaijan, Georgia, Moldova and other countries have registered to participate in the Teleconference «Delta Variant. Experience of International Experts».

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

13 main speeches were offered to the participants and they were dealing with the following issues:

- Specific features of coronaviral infection caused by new Delta variant;
- Guidelines for the treatment of such patients;
- Algorithms for choice of infusion and antibacterial therapy at different stages of disease;
- Patient surveillance in severe cases of coronaviral infection.

Conclusions and decisions based on discussion of reports:

1. At the beginning of July, 2021 the World Health Organization has registered Delta variant in 98 countries having either high or low level of vaccination among citizens. And it becomes dominant in many countries. It is carried-over within different age groups, even among those who are 12-20 years old. It has a short incubation period, just 1-3 days. There is also an increased viral load (in comparison to other strains). It causes severe cold symptoms including illness, elevated temperature, migraine, throat pain, cough and rhinitis. The risk of hospitalization is 1.85 times higher than the alpha strain.

2. The cytokine storm and uncontrolled inflammation dominate in the pathogenesis of coronaviral pathology development. The latter results in development of blood clots and generalized endothelial dysfunction with diffuse microthrombosis and development of multiple organ failure. The patients require additional measures for treatment of ARDS and toxic shock, as well as for prevention of complications. The therapy should include: anticoagulants – low molecular weight heparin (also taking into account their anti-inflammatory properties on the background of hyperinflammation); anti-inflammatory medicines, being able to «extinguish» cytokine storm; antibacterial agents.

3. The progressing systemic inflammation accompanied with lymphopenia and neutrocytosis play an important role in COVID-19 pathogenesis. Pathological hyperreactivity of the immune system, expressed in uncontrolled activation of immune cells by cytokines in the heart of inflammation and release by the latter of a new portion of cytokines and chemokines, has received the name «cytokine storm». The patients with COVID-19 demonstrate high levels of interleukins 2 and 6, macrophagal inflammatory protein, vascular endothelial growth factor, α tumour necrosis factor and other pro-inflammatory chemokines, cytokines and signalling proteins. «Cytokine storm» raises the risk of development of ARDS and may result in multiple organ failure. The use of edaravone helps to reduce the continuous activation of the links of a systemic inflammatory cascade, to reduce endothelial

damage and increased permeability, and to reduce the probability of development of multiple organ failure syndrome.

4. Delta variant causes severe disease with rapid development of system endotheliitis and high risk of cardiovascular complications. Use of a fixed combination of L-carnitine and L-arginine for patients with Delta variant helps to reduce spasm and vascular disruption, to improve microcirculation, to prevent thrombosis, and use of edaravone decreases release of pro-inflammatory cytokines and results in faster improvement of the patient's condition.

5. In critical patients the frequency of thrombosis remains high even with the use of preventive doses of low molecular weight heparin. Hypovolemia and low cardiac output have an adverse effect on the course of coronavirus disease in patients in intensive care units. It is recommended to prescribe liberal mode of infusion therapy using hyperosmolar crystalloid solution. Pulmonary hypertension, which is often a consequence of pulmonary thrombovasculitis, requires correction, for which a fixed combination of L-carnitine and L-arginine can be used.

6. Bacterial infection is a frequent complication of coronavirus disease. Patients with COVID-19 are at risk of hospital infections due to reduced immunity caused by both the viral infection itself and the use of glucocorticoids, monoclonal antibodies, broad-spectrum antibiotics. It is crucial to choose the method of administration of antibacterial preparations taking into account the peculiarities of their pharmacokinetics and pharmacodynamics. It is recommended to use the 3rd generation cephalosporins (for example, cefoperazone + sulbactam) in combination with macrolide for initial treatment of bacterial complications. It they are not efficient enough the 4th generation fluoroquinolones are prescribed, for example, moxifloxacin as a concentrate, pre-dissolved at 0.9% sodium chloride solution. In heavy patients, a high degree of caution should be exercised regarding the possible occurrence of mycotic candida infection and pulmonary aspergillosis.

7. Due to a shorter incubation period for the Delta variant, the immune system has less time to react and protect. More frequent are the severe course of the disease and the need for intensive care. In case of bacterial infection, it is recommended to use the 4th generation fluoroquinolones: the presence of methoxy ring in the structure thereof increases the permeability of the bacterial wall, inhibits the intensified withdrawal of the preparation from the microorganism and reduces resistance of microorganisms (in comparison to fluoroquinolones of the 2nd and 3rd generations). Moxifloxacin as a concentrate has a wide spectrum of action and has a rapid bactericidal effect.

8. Nervous system disorders occur in every third patient with coronavirus disease. The frequency of occurrence of certain neurological features depends on the severity of COVID-19, and they are more commonly diagnosed in patients with severe illness. Use of edaravone, combination of L-carnitine and L-arginine and hyperosmolar balanced solution in a complex therapy for patients with COVID-19 contributes to definitely faster regression of clinical aspects (fever, headache, sleep disturbances, anxiety and general weakness in comparison to the patients of the control group ($p < 0,01$)) and normalization of lab test values in comparison to the standard pathogenic therapy.

9. The risk of cardiovascular complications in the new Delta variant is higher than that observed in other SARS-CoV-2 strains. COVID-19 can combine various ethiopathogenetic mechanisms for cardiovascular complications: presence of pre-existing cardiovascular diseases, direct (through receptors to ACE-2) and indirect (by cytokines) myocardial injury, endotheliitis and cardiotoxic effects of medicines. Edaravone influences on trigger mechanisms for developing complications in COVID-19: neutralizes a wide range of free radicals, reduces inflammatory cytokines activity (IL-2, IL-6, TNF-α), helps to protect endothelium from damage.

10. Expression of ACE-2 on endothelium and vascular smooth muscle cells when infected with the SARS-CoV-2 virus promotes involvement of cardiovascular system in systemic damage, and development of «endotheliitis», which is promoted by hypercytokinaemia, leads to the main manifestations of the disease and systemic disruption of microcirculation in various organs.

During COVID-19 there is an intensive adhesion of platelets to endothelium, their aggregation and blood platelet thrombus formation. The use of pentoxifylline improves red blood cell elasticity and flexibility, decreases blood viscosity and platelet aggregation, and improves tissue microcirculation and oxygenation. During acute respiratory distress syndrome (ARDS) pro-inflammatory cytokines released by stimulated macrophages in alveoli play a significant role in pathogenesis. Given that pentoxifylline is capable of reducing cytokine inflammatory effect and cell proliferation in lung interstitial tissue, its use in ARDS is justified.

11. Current data indicate that patients infected with SARS-CoV-2 and associated bronchial obstruction are a vulnerable group with a high probability of complications and adverse outcome. Short-range bronchial spasmolytics and inhaled steroids should be considered to eliminate bronchial obstruction in such patients.

12. Patients who have suffered acute COVID-19 may experience various lung ventilation disorders and a restrictive or obstructive type of ventilation disorders may be formed, it is often associated with the impairment of the diffuse capacity of the lungs. Every patient who, after recovery, has respiratory symptoms (cough, shortness of breath) should undergo a spirographic study to determine the type of ventilation disorders. If there is a bronchial obstruction in the background of clinical symptomatology it is recommended to use bronchodilators with a short-term or long-term effect. In addition, it is desirable to use inhaled glucocorticosteroids to eliminate autoimmune inflammation in bronchial regions in the post-COVID period, especially for those who have taken high doses of systemic corticosteroids in the acute period. Where appropriate, it is recommended that preference be given to nebulizer therapy as a way of administering drugs directly into the airways.

13. In Ukraine, methods for the prevention of coronaviral infection have been developed and tested in the department of technology for treatment of non-specific lung diseases of the National Institute of Phthisiology and Pulmonology named after F.G. Yanovskyi NAMS of Ukraine and are being proposed for introduction into the practice of medical and preventive treatment institutions. They are based on use of antiseptic drug decametoxinum. It is a cationic surface-active compound that, in contact with phosphatidic lipid groups of cytoplasmic membranes (CPMs) of microorganisms, causes interference with their permeability, changes in intracellular homeostasis and cell lysis, which has a pronounced anti-bacterial, anti-fungal and antiviral action.

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