

## COVID-19: НЕКОТОРЫЕ СООБРАЖЕНИЯ О СТАНДАРТНЫХ АЛГОРИТМАХ ЛЕЧЕНИЯ

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**Резюме.** В данной статье проведен ретроспективный анализ историй болезни с целью выработки индивидуализированного подхода к лечению COVID-19. Поставлены вопросы о целесообразности всеобщего проведения иммуносупрессивной терапии, о необходимости назначения глюкокортикостероидов только с учетом цитокинового профиля больных, взаимосвязи глюкокортикостероидной терапии и нарушений углеводного обмена, как одних из наиболее часто встречающихся осложнений фармакотерапии COVID-19 у изученных нами больных. Неоправданная иммуносупрессия в стадии активной борьбы с инфекционным агентом как фактор хронизации процесса и снижения реактивности организма, а также нейтрализация иммуносупрессивной терапией мобилизованных на борьбу с возбудителем факторов защиты врожденного неспецифического иммунитета. Важность учета вероятности тромбообразования с рассмотрением показателей коагулограммы и маркеров тромбообразования (D-димер, продукты деградации фибрина) не исключает риск геморрагических осложнений при назначении высоких доз антикоагулянтов. Антибактериальная терапия при неосложненных вирусных инфекциях не является ни этиологическим, ни патогенетическим вариантом лечения, однако зачастую приводит к появлению резистентных штаммов микроорганизмов в результате мутационной изменчивости и эволюционных адаптаций бактерий, что усложняет выбор эффективного антибактериального препарата. Антитромботическая, глюкокортикостероидная и антибактериальная терапия должны быть клинически и лабораторно оправданы в каждом отдельно взятом случае. В статье описывается безопасность назначения противовоспалительных средств в лечении COVID-19 как противовоспалительных. В обзоре рассмотрены все вышеперечисленные аспекты терапии COVID-19 с ссылкой на зарубежные исследования, описаны варианты патофизиологического развития инфекции. Учитывая масштаб коронавирусной инфекции и тяжелые социально-экономические последствия пандемии, изучение основных этиопатогенетических аспектов, корреляции проводимого лечения с главными звеньями патогенеза, эффективности различных вариантов фармакотерапии COVID-19, поиск наиболее безопасной в отдаленной перспективе терапии – основная задача медицинского сообщества, так как вирусы имеют множество стратегий обхода защитных механизмов иммунной системы. Гарантом эффективности проводимого лечения является воздействие на основные патогенетические звенья, соответственно, проводимая терапия должна быть основана не только на клинических данных, но и подкреплена изменениями лабораторных показателей и соотноситься со степенью тяжести

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рентгенологической картины. Отмечаем необходимость разработки систематизированных данных о коронавирусе, изменениях, которые возбудитель индуцирует в организме. Это позволит выработать инновационные и эффективные терапевтические стратегии для лечения коронавирусной инфекции.

*Ключевые слова:* коронавирусная инфекция, пандемия, инфекционное заболевание COVID-19, цитокиновый шторм, острый респираторный дистресс-синдром, патогенетическая терапия

## COVID-19: OBSERVATIONS ON STANDARD TREATMENT ALGORITHMS

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**Abstract.** In this article, a retrospective analysis of the medical histories was carried out in order to develop an individualized approach to treating COVID-19. Questions were raised about the advisability of the universal immunosuppressive therapy, the need to prescribe glucocorticosteroids only taking into account the cytokine profile of patients, the relationship of glucocorticosteroid therapy and carbohydrate metabolism disorders, as one of the most common complications of pharmacotherapy COVID-19 in the patients we studied. Unjustified immunosuppression in the stage of active fight against the infectious agent as a factor of chronization of the process and decrease of the body reactivity, as well as neutralization by immunosuppressive therapy of factors of protection of innate non-specific immunity mobilized to fight the causative agent. The importance of taking into account the probability of thrombosis with consideration of coagulogram indices and thrombosis markers (D-dimer, fibrin degradation products) does not exclude the risk of the hemorrhagic complications when prescribing high doses of anticoagulants. Antibacterial therapy for uncomplicated viral infections is neither an etiologic nor a pathogenetic treatment option. In addition, it leads to the emergence of resistant strains of microorganisms as a result of mutational variability and evolutionary adaptations of bacteria, which greatly complicates the choice of an effective antibacterial drug in some cases. Antithrombotic, glucocorticosteroid and antibacterial therapy should be clinically and laboratory justified in each individual case. The article focuses on the safety of prescribing antipodagric agents in the treatment of COVID-19 as anti-inflammatory. The review considers all the above-mentioned aspects of COVID-19 therapy with reference to foreign studies, describes options for the pathophysiological development of infection. We note the need to develop systematic data on coronavirus, changes that the pathogen induces in the body. This will allow the development of innovative and effective therapeutic strategies for the treatment of the new coronavirus infection.

*Keywords:* coronavirus infection, pandemic, infectious disease COVID-19, immunity, cytokine storm, acute respiratory distress syndrome, pathogenetic therapy

### Introduction

The causative agent of the infectious disease COVID-19, the SARS-CoV-2 virus, spreads through the respiratory tract after infection, provoking the release of cytokines and the body immune response with decreased number of peripheral blood lymphocytes particularly T-lymphocytes. The initial stage of infection is bound to the penetration of SARS-CoV-2 into target cells that have type II angiotensin-converting enzyme receptors (ACE2). Cellular transmembrane serine protease type 2 (TSP2) promotes the binding of the virus to ACE-2, activating its S-protein, which is necessary for the penetration of

SARS-CoV-2 into the cell. According to the current understanding, ACE2 and TSP2 are expressed on the surface of various cells of the respiratory organs, esophagus, intestines, heart, adrenal glands, urinary bladder, brain (hypothalamus) and pituitary gland, as well as endothelium and macrophages. A large number of lymphocytes are consumed to fight the virus, which reduces the protective capabilities of the immune system and often leads to exacerbation of various chronic diseases. For most patients, severity of COVID-19 syndromes ranges from mild to moderate, but in some cases (about 20%) SARS-CoV-2 it causes intense inflammation, known as the “cytokine

storm”, which can lead to fatal pneumonia and acute respiratory distress-syndrome (ARDS). At the same time, the profiles of the “cytokine storm” may differ in various patients. Inflammatory cytokines are a type of signaling molecule that is secreted by immune cells such as helper T-cells (Th) and macrophages.

In case of COVID-19, severe illness was characterized by lymphopenia with decreased levels of CD4<sup>+</sup>, CD8<sup>+</sup>T-lymphocytes, B-lymphocytes and NK-cells, leukocytosis due to an increase in the number of neutrophilic lymphocytes against the background of a decrease in the content of monocytes, eosinophils and basophils. At the same time, the patients had high levels of the main proinflammatory cytokines in the peripheral blood plasma: tumor necrosis factor alpha (TNF- $\alpha$ ), interferon gamma (IFN $\gamma$ ), IL-1, IL-2, IL-6, IL-8, IL-12, IL-18, which cause the “cytokine storm”, which in turn leads to a hyperinflammatory reaction in the lungs, multiple organ failure and death of patients [8]. Cytokine release syndrome is a potentially life-threatening host systemic inflammatory response to SARS-CoV-2. In this case, the increase in the level of interleukin 6 (IL-6), which correlates with respiratory failure, ARDS and subsequent complications, is of the greatest importance. In addition, new data has surfaced on the participation of mitochondria in activating immune response and the chronicity of inflammation. Damage of organ tissues and cells causes the release of mitochondrial proteins (n-FP, cardiolipin, etc.) and mitochondrial DNA (mtDNA). These products of degradation contribute to the formation of damage-associated molecular patterns (DAMP) that stimulate the innate immune response, by activating Toll-like receptors (TLR), NOD-like receptors (NLRP) and cGAS-STING signaling pathway. As a result, the production of proinflammatory cytokines, type I interferons and chemokines increases [6]. Thus, mitochondrial dysfunction aggravates the pathophysiological situation. In addition, novel coronavirus infection is coupled to the significantly increased D-dimer level, with a wide range of triggered damage to the cell membrane and endothelium, disrupted processes of coagulation and fibrinolysis, plasma being released from the blood vessels, and the progression of these symptoms provokes blood clotting.

At this stage of the COVID-19 treatment, the main goal of the medical community is to reduce the level of complications caused by the release of cytokines and clotting disorders. Glucocorticosteroid drugs (GCS) and monoclonal antibodies (mAb) used for this purpose, are pathophysiologically justified only in the case where characteristic changes in the leukocyte formula and cytokine profile are revealed in the patient laboratory data. This is due to the main

pharmacological drug effects. So, administration of GCS also correlates with disorders of carbohydrate, fat, protein, water-salt metabolism, calcium metabolism, and side effects of GCS targeting the cardiovascular system, musculoskeletal system, hematopoiesis, gastrointestinal tract. The prescription of GCS is associated with high stress for all organ systems and, therefore, requires a careful investigation of any clinical case for each individual patient.

According to the data published by Chinese researchers from Wuhan, one of the major markers associated with increased mortality risk is a high level of D-dimer and fibrinogen degradation products [7]. Thus, early anticoagulant and antiplatelet therapy to prevent the development of acute respiratory distress syndrome and chronic disseminated intravascular coagulation, to protect erythrocyte membranes and endothelium, in patients with a high risk of adverse outcomes, and antithrombotic therapy in maximum doses in patients with D-dimer concentration higher than 1000 ng/ml is associated with decreased frequency of deaths caused by intra-erythrocyte and microcirculatory disorders, intravascular coagulation disorders, erythrocyte hemolysis, microclot formation in the pulmonary vessels and intra-alveolar fibrin formation. However, both GCS therapy and antithrombotic therapy should have a strictly individualized approach, taking into account the side effects of the treatment.

Some hospitals in Russia began to use colchicine, a drug registered in the Russian Federation (P N014955/01) for the treatment of acute gouty attacks to prevent their recurrence. The anti-gout effect of colchicine is associated with a decrease in the migration of leukocytes to the site of inflammation and inhibited phagocytosis of uric acid salt microcrystals. It also prevents neutrophil degranulation, and has a pronounced antimitotic effect, completely or partially suppressing cell division in the anaphase and metaphase stages [2]. Currently, colchicine is not included in the Russian, American, Canadian, Australian, Italian [1, 3, 4] guidelines for the treatment of COVID-19. A retrospective analysis of a study of 14,520 people tested for SARS-CoV-2 in Israel showed no difference in the frequency of colchicine use among infected and uninfected individuals, which casts doubt on the prophylactic efficacy of this drug [5].

## Materials and methods

A retrospective analysis of 80 case histories of patients who received treatment at the Hospital of Especially Dangerous Infections of the Kabardino-Balkaria Republican Children's Clinical Hospital, aged 18 to 86 years, from October to December 2020, was carried out. The following indicators were analyzed: the level of serum interleukin-6 measured

by electrochemiluminescence immunoassay (ECLIA) in the venous blood samples as the biomaterial, the INR value (“international normalized ratio”) using appropriate formulas, taking into account patient prothrombin time and the thromboplastin ISI (international sensitivity index), ferritin level by immunoturbidimetry (a quantitative measurement of concentration of specific proteins by changing the turbidity of the solution during the antigen-antibody reaction, this method is characterized by high sensitivity), the level of C-reactive protein (CRP) by the method of precipitation in a capillary, during which we observe a haze formed due to complexing between soluble molecular antigen and antibodies. All patients underwent MPR (multiplanar reconstruction) CT scans of the chest cavity organs to identify the degree of damage to the lung tissue using the Siemens “Somatom perspective” 64 apparatus.

## Results and discussion

Medical history analysis showed that 77 patients who underwent glucocorticosteroid therapy had no indication for this, because the level of serum interleukin-6 did not exceed 7 pg/ml, which does not correspond to the level observed in cytokine storm syndrome. The prescription of glucocorticosteroid therapy without changes in the cytokine profile could lead to severe immunosuppression and inability to mount proper immune response to invading virus, which led to aggravated patient condition and the appearance of complications. It should also be noted that taking glucocorticosteroids at high doses (16-24 mg/day) leads to hyperglycemia up to 30 mmol/L or more, which increases the risk of hyperglycemic coma. In confirmation of our results, in the Interim Guidelines of the Ministry of Health of the Russian Federation on the prevention, diagnosis and treatment of the new coronavirus infection (covid-19) (Version 10 (02/08/2021), we find that “it is not recommended to use GCS for the treatment of mild and moderate severity of COVID-19”. Only in 3 patients, interleukin-6 level exceeded the reference values 82 pg/ml, 102 pg/ml, 168 pg/ml) so that it justified administered glucocorticosteroid therapy. This category of patients also showed significantly increased serum CRP and ferritin, severe lymphopenia (6% of lymphocytes), and increased ESR (erythrocyte sedimentation rate). Analysis of the chest CT examination data revealed more than 50% of lung damage (CT-3).

According to the recommendations of the Ministry of Health of the Russian Federation, the prescription of low molecular weight heparin (LMWH) at prophylactic doses is indicated for all hospitalized patients and should be continued at least until discharge. However, the choice of the heparin dose

below the intermediate or therapeutic dose is based on the content of D-dimer and detected additional risk factors for venous thromboembolic complications, as well as severe manifestations of COVID-19. The analysis of medical histories revealed that D-dimer was not detected in 76 patients after receiving high doses of anticoagulants, due to the lack of reagents in the laboratory at the time of examination. However, hospitalized patients with moderate COVID-19 require to measure the D-dimer once every two days, in severe patients – daily. Exceptional urgent analysis of the above indicators is conducted for patients in case of deteriorated condition. In these patients, the INR value was determined, which was normal in all patients. This increased the risk of bleeding, as patients received high doses of heparin (5,000 U 5-8 times a day) without D-dimer control.

Antibiotic therapy was received by 76 patients, of which 73 patients showed no signs of bacterial inflammation according to the general blood test, thereby accounting for inappropriate prescription of antibiotics. This is confirmed by the recommendations of the Ministry of Health of the Russian Federation, which states that “COVID-19, like any other viral infection is not an indication for the use of antibiotics”. Antibiotic therapy is prescribed only if there are convincing signs of bacterial infection (increased PCT of more than 0.5 ng/ml, the appearance of purulent sputum, leukocytosis more than  $12 \times 10^9/L$  (in the absence of previous use of glucocorticoids), an increase in the number of stab neutrophils by more than 10%). Bacterial infections rarely complicate the course of COVID-19. Therefore, the vast majority of patients with COVID-19, especially with mild to moderate course, do not require antibiotic therapy». The analysis of the data obtained showed that the patients received ceftriaxone 2 g per day, meropenem, ciprofloxacin 200 mg 2 times per day, buckperazone 2 g per day with no signs of bacterial infection.

The ferritin level in 45 out of 50 women was within the reference values (10-120 µg/l); similar indicators were also observed in male patients, where in 28 out of 30 patients the indicator was also within the reference values (20-250 µg/l), and that is also not an indicator of severe inflammatory process in the upper and lower respiratory tract, which requires administration of a glucocorticosteroid and antibacterial therapy.

The only justification for applying glucocorticosteroid therapy can be considered in case of increased serum CRP in patients, however, high doses of glucocorticosteroids were prescribed to patients with both mildly increased CRP (6.6-7.1 mg/L) and high CRP (80 mg/L) and more). No correlation was found between the degree of increased serum CRP and the dose of glucocorticosteroids administered.

Colchicine was taken by 36 patients with moderate to severe symptoms at a dose of 1 g with an interval of 12 hours, then 1 g per day until the 3rd day of stable normothermia. The same patients received glucocorticosteroid, antibacterial and antithrombotic therapy, complicating drawing specific conclusions about the effectiveness of colchicine in the treatment of patients. Taking into account the recommendations of the British Medicines Agency, the following dose adjustments are necessary: reduction of the colchicine dose by 4 times while used together with ritonavir, ketoconazole, clarithromycin, cyclosporine; 2 times – while used with diltiazem and verapamil. These guidelines appear to be particularly relevant for patients with COVID-19.

## Conclusion

The retrospective analysis of medical histories showed that in most cases the prescription of high doses of anticoagulants, glucocorticosteroid and antibacterial drugs is not justified, since the analysis of laboratory parameters revealed no direct indications

for applying such an aggressive therapy. The lack of data from clinical studies confirming the efficacy and safety of colchicine in COVID-19 and allowing it to be recommended for widespread practice requires a collegial decision on the medical board for its prescription, with consideration of all safety aspects of its use (clinical and hematological control, monitoring of potential interactions with other drugs). We consider it advisable to proceed by a case-by-case approach to the treatment of each individual patient, taking into account the recommendations of the Ministry of Health of the Russian Federation for the prevention, diagnosis and treatment of a new coronavirus infection (COVID-19).

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## References

1. Caring for people with COVID-19. Supporting Australia's healthcare professionals with continually updated, evidence-based clinical guidelines. Available at: <https://covid19evidence.net.au/>.
2. Chia E.W., Grainger R., Harper J.L. Colchicine suppresses neutrophil superoxide production in a murine model of gouty arthritis: a rationale for use of low-dose colchicine. *Br. J. Pharmacol.*, 2008, Vol. 153, no. 6, pp. 1288-1295.
3. Clinical management of patients with COVID-19: Second interim guidance. Available at: <https://www.canada.ca/en/public-health/services/diseases/2019-novelcoronavirus-infection/clinical-management-covid-19.html>.
4. COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. National Institutes of Health. Available at: <https://www.covid19treatmentguidelines.nih.gov/>.
5. Gendelman O., Amital H., Bragazzi N.L. Continuous hydroxychloroquine or colchicine therapy does not prevent infection with SARS-CoV-2: Insights from a large healthcare database analysis. *Autoimmun. Rev.*, 2020, Vol. 19, no. 7, pp. 102566-102588.
6. Mohanty A., Tiwari-Pandey R., Pandey N.R. Mitochondria: the in-dispensable players in innate immunity and guardians of the inflammatory response. *J. Cell Commun. Signal.*, 2019, Vol. 13, no. 3, pp. 303-318.
7. Zhou F., Yu T., Du R. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet*, 2020, Vol. 20, pp. 30566-30569.
8. Zhou P., Yang X., Wang X. A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature*, 2020, Vol. 579, pp. 270-273.

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