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New Coronavirus Infection (Covid-19): Clinical and Epidemiological Aspects

Abstract

Environmental change, climate warming, population density increase, high migration activity of the population and other factors provoke the emergence and spread of new infections around the world.

The emergence in December 2019 of diseases caused by the new coronavirus («coronavirus disease 2019») has already gone down in history as an emergency of international importance. It is known that the most common clinical manifestation of a new infection is pneumonia, and also in a significant part of patients — respiratory distress syndrome. Our article provides a brief analytical review of these temporary guidelines Ministry of Health of the Russian Federation «Prevention, Diagnosis and Treatment of a New Coronavirus Infection (COVID-19)», version 3 (03.03.20) and other published sources. The team of authors expresses the hope that these data will be useful to doctors in providing medical care to patients with a new coronary virus infection, as well as to teachers in preparing students and residents.

Source: Ministry of Health of the Russian Federation. Temporary guidelines «Prevention, diagnosis and treatment of new coronavirus infection (COVID-19)», version 3 (03.03.20). Available on: https://static-0.rosminzdrav.ru/system/attachments/attaches/000/049/629/original/Временные_MP_COVID-19_03.03.2020_%28версия_3%29_6-6.pdf?1583255386.

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CT — computed tomography, ARF — acute respiratory failure, ARDS — acute respiratory distress syndrome, SARS — severe acute respiratory syndrome

Introduction

In the new millennium, humanity is faced with unknown infectious diseases. Dangerous viruses have replaced the plague and typhoid. Environmental changes, global warming, population density increase and other factors trigger their emergence, while global migration contributes to their spread around the world. Indeed, infections know no boundaries.

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According to UN forecasts, the world's population will reach 10 billion people by 2050. This means that the processes of migration and urbanization will accelerate [1].

The COVID-19 ("coronavirus disease 2019") epidemic has already gone down in history as an emergency of international concern. To date, the number of infected people in the world has exceeded 470,000 [2]. We have yet to study the features of this epidemic, to draw lessons, to analyze the shortcomings of ensuring the biological safety of the population. One thing is clear: new viruses will appear; it is an integral part of our world. Humanity must learn to counter these threats.

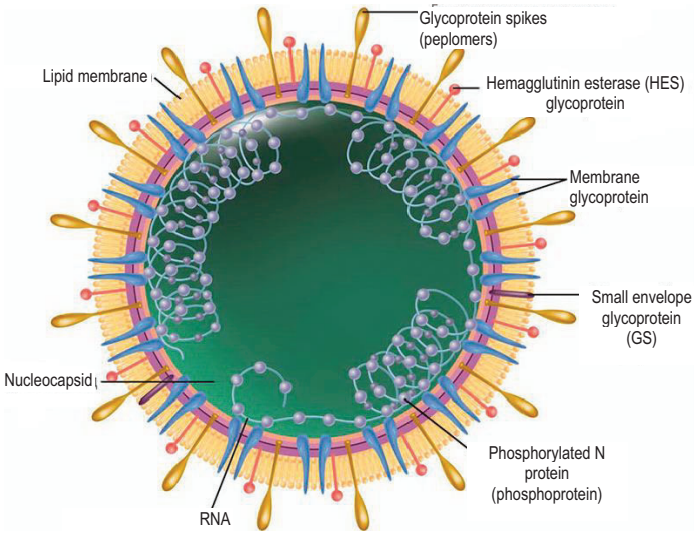

Figure 1. *The structure of coronavirus*

Etiology and Pathogenesis

Coronavirus disease is an acute viral disease with a primary lesion of the upper respiratory tract caused by the RNA virus of the genus Betacoronavirus of the family Coronaviridae.

Coronaviruses (lat. Coronaviridae) are a family of 40 species (as of January 2020) of complex enveloped RNA viruses. They are grouped into two subfamilies that affect humans and animals. The name is associated with the structure of the virus: large spikes protrude from the envelope in the form of a mace, which resemble the crown.

Virions measure 80–220 nm. A nucleocapsid is a flexible helix consisting of a positive RNA strand and a large number of N nucleoprotein molecules. It has the largest genome among RNA viruses. The virus has an envelope, in which glycoprotein trimeric spikes (peplomers), membrane glycoprotein, small envelope glycoprotein, and hemagglutinin esterase are embedded (Fig. 1).

The "crown" of coronaviruses is associated with a specific mechanism of penetrating the cell membrane by simulating the molecules to which transmembrane receptors respond (Fig. 2).

Currently, four coronaviruses (HCoV-229E, -OC43, -NL63, -HKU1) that circulate among the population are known. They are present in the structure of acute respiratory viral infections all year round and normally affect the upper respiratory tract with mild or moderate disease.

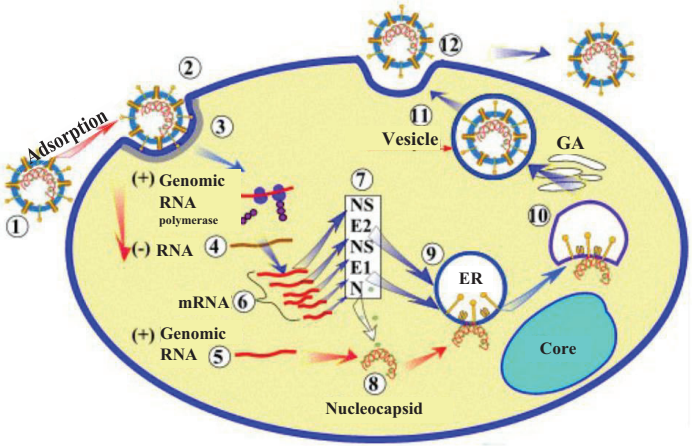

Figure 2. *Coronavirus replication (A.A. Vorobyov. Atlas of Medical Microbiology, Virology and Immunology. 2nd ed., revised. and expanded Medicine. 2003; 236 p. [In Russian].)*

The virus is adsorbed on the target cell (1) via S glycoprotein and penetrates the cell by fusion of the viral and cellular cytoplasmic membrane or receptor-mediated endocytosis (2).

Genomic RNA binds to ribosomes and acts as mRNA in the synthesis of RNA-dependent RNA polymerase (3), which then reads genomic RNA. As a result, a full-length negative strand is synthesized (4). Upon transcription of the negative strand, a new genomic positive-strand RNA (5) and a set of 5–7 subgenomic mRNAs are synthesized (6). Upon translation of each subgenomic mRNA, one protein is synthesized (7). N protein binds to the genomic RNA in the cell cytoplasm, as a result of which a spiral nucleocapsid is synthesized (8). S and M, or E1, E2, glycoproteins are transferred (9, 10) to the endoplasmic reticulum and Golgi apparatus. The nucleocapsid is budded through the membranes into the endoplasmic reticulum, which contains S and M glycoproteins. Virions are transported to the membrane of the host cell (10) and exit the cell via endocytosis (11).

Until 2002, coronaviruses were considered as agents that cause mild diseases of the upper respiratory tract (with extremely rare lethal outcomes). At the end of 2002, coronavirus (SARS-CoV) appeared that became the causative agent of SARS (severe acute respiratory syndrome) in human. This virus belongs to the genus Betacoronavirus. The natural reservoir of SARS-CoV is bats, and camels and masked palm civets are the intermediate hosts. In total, more than 8,000 cases were reported in 37 countries during the epidemic, of which 774 were fatal. Since 2004, no new cases of SARS-CoV-associated disease have been reported.

In 2012, the world faced a new coronavirus (MERS-CoV), a causative agent of the Middle East respiratory syndrome, belonging to the genus Betacoronavirus. The main natural reservoir of MERS-CoV is bats and dromedaries. Since 2012, 2,519 cases of MERS-CoV infection have been reported, of which 866 have been fatal. All cases are geographically associated with the Arabian Peninsula (82% of cases are reported in Saudi Arabia). MERS-CoV continues to circulate and cause new cases of the disease [3].

On February 11, 2020, the World Health Organization assigned the official name to the infection caused by the new coronavirus, COVID-19 ("Coronavirus disease 2019") [1]. The International Committee on Taxonomy of Viruses on February 11, 2020, assigned its own name to the causative agent of COVID-19 — **SARS-CoV-2**.

The new SARS-CoV-2 is a single-stranded RNA virus, and belongs to the Coronaviridae family, to the Beta-CoV of the B lineage.

The virus is assigned to the pathogenicity group II, as well as some other representatives of this family (SARS-CoV virus, MERS-CoV virus).

SARS-CoV-2 is believed to be a recombinant virus between bat coronavirus and coronavirus of unknown origin. The genetic sequence of SARS-CoV-2 is similar to the sequence of SARS-CoV by at least 79% [4].

The main target cells for coronaviruses are cells of the alveolar epithelium, in the cytoplasm of which the virus replicates. After the assembly of virions, they pass into cytoplasmic vacuoles, which migrate to the cell membrane and exit into the extracellular space by exocytosis. Virus antigens are not expressed on the cell surface until virions exit the cell; therefore, antibody formation and interferon synthesis are stimulated relatively late. Virus-driven formation of syncytia facilitates its rapid spread into the tissues. Virus causes an increase in the permeability of cell membranes and enhanced transport of albumin-rich fluid into the interstitium and the lumen of the alveoli. In this case, the surfactant is destroyed, which leads to the collapse of the alveoli. Acute violation of gas exchange causes acute respiratory distress syndrome (ARDS). Immunosuppression contributes to the development of opportunistic bacterial and mycotic infections of the respiratory tract.

The pathogenesis of novel coronavirus disease has not been adequately studied. There are no available data on the duration and intensity of immunity against SARS-CoV-2. Immunity in infections caused by other members of the coronavirus family is not persistent and re-infection is possible.

Epidemiology

The natural reservoir of the SARS-CoV-2 virus is bats. An additional reservoir can be mammals that eat bats, with further spread among humans. Phylogenetic studies of the isolated strains showed that the genomic sequences of viruses found in bats are 99 percent identical to those isolated in patients with COVID-19.

Currently, the main source of infection is an infected person, including those at the end of the incubation period, prodromal period (the beginning of virus isolation from target cells) and during clinical manifestations.

The transmission mechanism is aspiration. Ways of transmission: airborne (release of the virus when coughing, sneezing, talking) during close contact.

The contact way is realized through transmission factors: water, food and objects (door handles, smartphone screens) contaminated with the pathogen. The risk of transmission of the virus from the hands to the mucous membranes of the eyes, nasal and oral cavity and infection is proven. The fecal-oral mechanism is possible (the causative agent was detected in the feces from patients infected with SARS-CoV-2).

The iatrogenic transmission of SARS-CoV-2 has been established. In China, there were more than

1,700 confirmed cases among healthcare providers who worked with COVID-19 patients [4].

Susceptibility to the pathogen is high in all population groups. The groups at risk of severe disease and death include people older than 60 years, patients with chronic diseases (diseases of the respiratory system, cardiovascular system, diabetes mellitus, cancer). Mortality varies from 2 to 4%.

SARS-CoV-2 is characterized by low environmental resistance. It dies under UV radiation, disinfectants, when heated to 40 °C for 1 hour, to 56 °C in 30 minutes. On the surface of objects at 18–25 °C it remains viable for 2 to 48 hours.

Clinical Picture

The incubation period of COVID-19 is 2 to 14 days, 5–7 days on average. In comparison, the incubation period for seasonal flu is about 2 days.

Among the first symptoms of COVID-19, fever (90%), cough — dry or with a small amount of sputum (80%), shortness of breath (55%), myalgia and fatigue (44%), chest tightness (20%), as well as headaches (8%), hemoptysis (5%), diarrhea and nausea (3%) were reported. At the onset, these symptoms can be observed without fever [5].

Clinical patterns and signs of COVID-19:

1. Mild acute respiratory viral infection
2. Pneumonia without signs of respiratory failure
3. Pneumonia with acute respiratory failure (ARF)
4. Acute respiratory distress syndrome
5. Sepsis
6. Septic (toxic) shock

Hypoxemia (SpO_2 decrease below 88%) develops in more than 30% of patients.

There are mild, moderate and severe forms of COVID-19.

Most patients with severe COVID-19 develop pneumonia in the first week of the disease. Dull percussive sound is determined. In the lungs, bilateral crepitant, small-bubbling rales are auscultated. At the maximum of inhalation, the rales become more intense; they do not disappear after coughing, do not change depending on the position of the patient's body (sitting, standing, lying). X-ray shows infiltration in the periphery of the lung fields. As the disease progresses, infiltration increases, the affected areas become larger, and ARDS develops. Sepsis and toxic shock develop.

Diagnosis

The diagnosis is established based on epidemiological history, clinical examination and laboratory test results.

When collecting epidemiological history, it is necessary to take into account the patient's visit to countries and regions affected by COVID-19 during the previous 14 days, the presence of close contacts during this time with people who arrived from endemic areas, as well as contacts with people with diagnosis confirmed by laboratory tests.

Standard laboratory tests:

- Complete blood count with determination of red blood cells, hematocrit, white blood cells, platelets, leukocyte formula;
- Biochemical analysis (urea, creatinine, electrolytes, liver enzymes, bilirubin, albumin, glucose). Biochemical analysis does not provide any specific information, but detected abnormalities can indicate the presence of organ dysfunction, decompensation of concomitant diseases and the development of complications, have a certain prognostic value, and influence the choice of drugs and/or the dosage regimen;
- Serum C-reactive protein (CRP). The level of CRP correlates with the severity of the course, the prevalence of inflammatory infiltration and the prognosis of pneumonia;
- Pulse oximetry with SpO_2 measurement to detect respiratory failure and assess the severity of hypoxemia. Pulse oximetry is a screening method that allows to identify patients with hypoxemia who need respiratory support and to evaluate its effectiveness;
- Arterial-blood gas test with PaO_2, $PaCO_2$, pH, bicarbonates and lactate is indicated to patients with signs of ARF (SpO_2 below 90% according to pulse oximetry);
- Coagulation test with the determination of prothrombin time, international normalized ratio and activated partial thromboplastin time is recommended in patients with signs of ARF.

Investigations:

- Computed tomography (CT) of the chest is recommended for all patients with suspected pneumonia. Chest CT is a more sensitive method for the diagnosis of viral pneumonia. The main

findings in pneumonia are bilateral infiltrates in the form of "ground-glass" or consolidation, which are predominant in the lower and middle areas of the lungs.

- If chest CT is not available, a panoramic chest X-ray is performed in the direct anterior and lateral projections (if the localization of the inflammatory process is unknown, it is advisable to take a picture in the right lateral projection). Chest X-ray shows bilateral confluent infiltrative shadowing. Most often, the most pronounced changes are localized in the basal parts of the lungs. A small pleural effusion may also be present.
- Standard-lead electrocardiography is recommended for all patients. This investigation does not provide any specific information, but viral infection and pneumonia in addition to decompensation of chronic concomitant diseases is currently known to increase the risk of rhythm disturbances and acute coronary syndrome, the timely detection of which significantly affects the prognosis. In addition, certain ECG changes (for example, prolongation of the QT interval) require attention when assessing the cardiotoxicity of a number of antibacterial drugs.

Deciding on the need for hospitalization:

a) with medical history data indicating the likelihood of SARS-CoV-2 infection, regardless of the severity of the patient's condition, hospitalization in an infectious disease hospital/ward in compliance with all anti-epidemic measures is indicated;
b) in the absence of suspicion of SARS-CoV-2 infection, the decision on hospitalization depends on the severity of the condition and another probable diagnosis.

Specific laboratory tests:

- SARS-CoV-2 RNA detection by PCR

The main type of biomaterial for laboratory testing is a nasal, nasopharyngeal and/or oropharyngeal swab, as well as bronchial lavage fluid obtained by fibrobronchoscopy, sputum, lung biopsy or autopsy material, whole blood, serum, and urine.

All samples obtained for laboratory testing are potentially dangerous and the requirements of SP 1.3.3118-13 "Safety of work with microorganisms of I–II pathogenicity groups" should be met. Healthcare workers who collect and/or transport clinical samples to the laboratory should be trained in the safe handling of biomaterial, strictly observe safety precautions and use personal protective equipment.

Samples of biological materials are sent to the research organization of Rospotrebnadzor or the Center for Hygiene and Epidemiology in the constituent entity of the Russian Federation (Appendix 2 of the Temporary Recommendations of Rospotrebnadzor of January 21, 2020, for Laboratory Diagnosis of Novel Coronavirus Infection Caused by SARS-CoV-2) taking into account the convenience of the transport scheme.

For differential diagnosis, PCR studies are carried out for the causative agents of respiratory infections: type A and B influenza viruses, rhinoviruses, respiratory syncytial viruses, parainfluenza viruses, adenoviruses, human metapneumoviruses, and MERS-CoV. Diagnostic microbiology of Haemophilus influenzae type B, Streptococcus pneumoniae, Legionella pneumophila, and Mycoplasma pneumoniae is also mandatory.

Treatment

To date, there is no evidence of the effectiveness of the use of any drugs with COVID-19.

During patient management, for timely treatment, it is necessary to monitor the patient's condition to detect signs of clinical deterioration, such as rapidly progressive ARF and sepsis.

Patients infected with SARS-CoV-2 should receive supportive symptomatic therapy.

Analysis of the literature data on the clinical experience of managing patients with SARS associated with SARS-CoV and MERS-CoV allows us to identify several causative agents that are usually used in combination. These include ribavirin, lopinavir/ritonavir [6] and interferons.

However, the results of the use of these drugs do not allow to make a definitive conclusion about their effectiveness/inefficiency, and therefore their use is permissible by decision of the medical commission in the appropriate manner if the possible benefit to the patient exceeds the risk.

The use of causative agents is justified in the case of moderate and severe infection, when the intended benefit exceeds the potential risk of adverse events.

The list of drugs that can be prescribed for the causal treatment of SARS-CoV-2 infection is indicated in the Interim Guidelines of the Ministry of Health of the Russian Federation (version 4).

According to the WHO recommendations, off-label drugs with the supposed etiotropic efficacy may be prescribed, and their use should comply with ethical standards recommended by WHO and should be carried out on the basis of Federal Law of November 21, 2011, No. 323-FZ "On the Fundamentals of Public Health Protection in the Russian Federation", Federal Law of April 12, 2010, No. 61-FZ "On Circulation of Medicines", National Standard of the Russian Federation GOST R ISO 14155-2014 "Good Clinical Practice", Order of the Ministry of Health of the Russian Federation of April 1, 2016, No. 200n "On the Approval of the Rules of Good Clinical Practice" (registered by the Ministry of Justice of the Russian Federation on August 23, 2016, registration No. 43357), the Helsinki Declaration of the World Medical Association (WMA) on Ethical Principles For Medical Research Involving Human Subjects declared at the 64th General Assembly of the World Medical Academy, Fortaleza, Brazil, 2013.

In February 2020, in a joint project, Chinese and German scientists synthesized a special group of drugs (alpha-ketoamides) that have the ability to inhibit the basic proteases of various viruses, including SARS-CoV-2.

The researchers determined the three-dimensional crystal structure of the main SARS-CoV-2 protease and modified the alpha-ketoamide molecule through the P3-P2 amide bond, which is included in the pyridone ring, which contributed to the specific inhibition of coronaviruses. As a result, the half-life of alpha-ketoamide increased three-fold, and the solubility — 19-fold which, however, led to some decrease in efficiency. In an experimental study in mice, alpha-ketoamide, administered by inhalation, showed pronounced pulmonary tropism and lack of side effects [7].

In addition, umifenovir, remdesivir, and favipiravir are among the studied drugs for COVID-19 treatment.

Pathogenetic therapy involves the intake of a sufficient amount of fluid (up to 3.5 liters per day) in the absence of contraindications, enterosorbents (colloidal silicon dioxide, polymethylsiloxane polyhydrate and others).

In severe patients, infusion therapy is carried out while monitoring blood pressure, chest auscultation pattern, urine output, and other parameters. In order to prevent cerebral and pulmonary edema, it is advisable to carry out infusion therapy combined with forced diuresis. In order to improve sputum discharge during a productive cough, acetylcysteine, ambroxol, carbocysteine and other combined drugs are prescribed.

In the presence of bronchial obstructive syndrome, inhaled bronchodilator therapy (via a nebulizer) with the use of salbutamol, fenoterol and combined agents is actively used.

Symptomatic therapy includes the use of ibuprofen and paracetamol at fever above 38.0 °C. For the treatment of rhinitis, pharyngitis, in case of nasal congestion and/or discharge from the nose, salt preparations for topical administration based on seawater (isotonic, and in case of congestion — hypertonic), various antiseptic solutions are used.

Patients with clinical and laboratory signs of coronavirus pneumonia are prescribed antimicrobial agents (respiratory fluoroquinolones, 3rd and 4th generation cephalosporins, carbapenems, linezolid, etc.) due to the high risk of bacterial superinfection. The choice of antibiotic and method of administration is based on the severity of the patient's condition, the presence of concomitant diseases and the results of diagnostic microbiology.

ARF is one of the most common complications of severe viral pneumonia. ARF management is based on the general principles of respiratory therapy. The optimal level of effectiveness of oxygen therapy is to increase oxygen saturation above 90%, or its steady increase. If primary respiratory therapy (oxygen therapy using a face mask or nasal cannula) is ineffective, mechanical ventilation should be considered.

Prevention

Specific prophylaxis (vaccine) against COVID-19 has not yet been developed.

For drug prevention of COVID-19 in adults, intranasal administration of recombinant interferon alfa is possible.

For drug prevention of COVID-19 in pregnant women, only intranasal administration of recombinant interferon alfa-2b is possible.

Measures to prevent the introduction and spread of COVID-19 in the Russian Federation are regulated by the Decrees of the Government of the Russian Federation of January 30, 2020, No. 140-r, of January 31, 2020, No. 154-r, of February 3, 2020,

No. 194-r, of February 18, 2020, No. 338-r, and Directives of the Chief State Sanitary Doctor of the Russian Federation of January 24, 2020, No. 2, of January 31, 2020, No. 3, etc.

Nonspecific prevention is an activity aimed at preventing the spread of infection and is carried out in relation to the source of infection (sick person), the mechanism of transmission of the causative agent, as well as the potentially susceptible population (protection of persons who are and/or were in contact with a sick person).

Measures regarding the source of infection: isolation of patients in isolation wards / wards in an infectious disease hospital; care and treatment; discharge after a double negative result of laboratory test for SARS-CoV-2.

Measures aimed at the pathogen transmission mechanism [8]:

- observance of personal hygiene (washing hands with soap, using disposable wipes when sneezing and coughing, touching the face only with clean wipes or washed hands);
- use of disposable face masks, which should be replaced every 2 hours;
- use of protective clothing for health workers;
- carrying out disinfection measures;
- disposal of medical waste class B;
- evacuation of patients with special-purpose transport.

Timely visit to healthcare institutions in case of symptoms of acute respiratory viral infection is one of the key factors in the prevention of complications.

Conclusion

Environmental changes, global warming, an increase in population density, the development of biotechnology and other factors trigger the emergence of new infections, and the ever-increasing global migration and economic globalization contribute to their spread.

Biological threats associated with epidemics of infectious diseases are global in nature. The COVID-19 epidemic is not the last threat in the 21st century.

All countries should be prepared for concerted actions to prevent the occurrence and spread of infections, for their timely diagnosis, the development of treatment and prevention methods, and the creation of vaccines.

Author Contribution:

All the authors contributed significantly to the article, read and approved the final version of the article before publication.

T. G. Suranova: collection and analysis of manuscript materials, text editing

T. Ya. Chernobrovkina, Ya. D. Yankovskaya, S. V. Burova: text writing and editing

V. V. Nikiforov: review concept and design, text editing, approval of the final version of the manuscript

References:

1. World Health Organization. Clinical guidelines for the management of patients with severe acute respiratory infections with suspected infection with a new coronavirus (2019-nCoV). Temporary recommendations. Publication Date: January 25, 2020. [Electronic resource]. URL: http://www.euro.who.int/__data/assets/pdf_file/0020/426206/RUS-Clinical-Management-ofNovel_CoV_Final_without-watermark.pdf?ua=1. (date of the application: 23.03.2020) [In Russian]
2. Coronavirus (Covid-19). [Electronic resource]. URL: https://coronavirus-monitor.ru. (date of the application: 23.03.2020) [In Russian]
3. Alserehi H., Wali G., Alshukairi A., Alraddadi B. Impact of Middle East respiratory syndrome coronavirus (MERS-CoV) on pregnancy and perinatal outcome. BMC Infect Dis. 2016; 16: 105–108.
4. Bassetti M. The Novel Chinese Coronavirus (2019-nCoV) Infections: challenges for fighting the storm. https://doi.org/10.1111/eci.13209 URL: https://onlinelibrary.wiley.com/doi/abs/10.1111/eci.13209
5. Gu J., Han B., Jian Wang J. COVID-19: Gastrointestinal manifestations and potential fecal-oral transmission. Gastroenterology. 2020. https://doi.org/10.1053/j.gastro.2020.02.054
6. Cao B., Wang Y., Wen D. et al. A Trial of Lopinavir–Ritonavir in Adults Hospitalized with Severe Covid-19. New England Jurnal Medicine. 2020; DOI: 10.1056/NEJMoa2001282.
7. Zhang L., Lin D., Sun X. et al. Crystal structure of SARS-CoV-2 main protease provides a basis for design of improved α-ketoamide inhibitors. Science. 2020. doi. 10.1126/science.abb3405.
8. Federal Service for Supervision of Consumer Rights Protection and Human Well-Being. About a new coronavirus infection. [Electronic resource]. URL: https://rospotrebnadzor.ru/region/korono_virus/punkt.php. (date of the application: 23.03.2020) [In Russian]