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5803 Methodical instructions

for practical lessons
on the discipline ***"Current issues of COVID-19"***

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TOPIC 1. ACUTE RESPIRATORY DISEASES CAUSED BY CORONAVIRUSES. ETIOLOGICAL FEATURES OF SARS-COV-2

Duration – 2 hours.

1 Relevance of the topic.

The COVID-19 pandemic caused by the SARS-CoV-2 virus is still relevant today. Despite the fact that, after a series of mutations, the virus causes a disease characterized by a less aggressive course, numerous cases of severe complications have been recorded, which significantly worsen the condition of patients and even lead to death. The knowledge of the structure of the virus, the peculiarities of its interaction with target cells allows to better understand the pathogenesis of the disease and the pathophysiological features of its course.

2 Specific objectives

2.1 The student should know:

- The main types of agents that cause SARS.
- The types of coronaviruses that cause SARS.
- The main strains of SARS-CoV-2.
- Structure of SARS-CoV-2 and mechanisms of its interaction with target cells.

2.2 The student should be able to:

- Give a clinical description of SARS caused by different types of viruses.
- Navigate the classification of SARS-Cov-2 virus variants.
- Determine which type a particular strain of SARS-CoV-2 belongs to according to the classification.

3 Basic knowledge, skills, and abilities necessary to study the topic (interdisciplinary integration)

Table 1

Previous disciplines	Skills acquired
Histology, cytology and embryology	Knowledge of cell structure, organelle function, concept of epithelial tissue structure and function, and its role in various organs and systems
Microbiology, virology and immunology	Knowledge of the structure and classification of viruses, the variability in viral structure, the concept of viral strains, and the basics of the immune response
Infectious diseases	Differential diagnosis of diseases of various origins. Recognition of an infectious disease, its complications

4 Tasks for independent work in preparationto class

4.1 A list of basic terms, parameters, characteristics that the student must learn in preparation for the lesson

Table 2

Term	Definition
1	2
Acute respiratory viral infection (SARS)	Acute viral infection of the respiratory tract, manifested mainly by catarrhal inflammation of the upper (rarely lower) respiratory tract with varying degrees of impairment of general condition
SARS	Severe acute respiratory syndrome (SARS) is a disease characterized by symptoms of acute respiratory viral infection, fever, respiratory distress, and pneumonia

Continuation of Table 2

1	2
Coronaviruses	The RNA family is a dense virus that infects animals (birds, amphibians and mammals) and humans. They have a characteristic structure with the presence of spiky proteins on the surface that form a structure similar to the sun's corona
COVID-19	Human coronavirus disease caused by coronavirus SARS-CoV-2
SARS-CoV-2	Severe acute respiratory syndrome-associated coronavirus 2
VOI	Coronavirus variant of interest
VOC	Coronavirus variant of concern
VUM	Coronavirus variant under monitoring

The most important viral etiological agents of SARS are ortho- and paramyxoviruses, picornaviruses, coronaviruses and adenoviruses.

Orthomyxoviridae: influenza viruses, divided into four types: A–D. For humans, types A and B are epidemiologically significant, since the others do not cause disease in humans, or cause it very rarely.

Paramyxoviridae: respiratory syncytial virus, parainfluenza virus 1–4, human metapneumovirus. These six human viruses are the most important causes of lower respiratory tract infections, in children worldwide. Respiratory syncytial virus is the single most important cause of bronchiolitis and the leading cause of upper and middle respiratory tract infections requiring hospitalization. Human metapneumovirus (hMPV) causes a similar disease, but less frequently, while parainfluenza viruses are associated with bronchiolitis and croup.

Picornaviridae: enteroviruses and parechoviruses. It is the most common cause of infectious diseases in humans. More than 100 serotypes of rhinoviruses of species A–C (currently classified as enteroviruses) are the most important causative agents of the common cold. Infections are usually mild and confined to the upper respiratory tract, but may be associated with exacerbations of asthma and chronic bronchitis.

Adenoviridae. Adenoviruses are the most common cause of epidemic infectious conjunctivitis in low- and middle-income countries and upper and middle respiratory tract infections in children and young people worldwide. Outbreaks of adenovirus respiratory infections can occur in closed crowded places, such as kindergartens, boarding schools, as well as among the military. Most adenovirus infections remain subclinical.

Coronaviridae. The four major human respiratory coronaviruses (229E, OC43, NL63, and HKU1) are associated with relatively mild upper respiratory tract lesions and may cause 10 to 25 percent of cold, but sometimes cause severe infections requiring hospitalization. In 2002–2003, a new severe form of pneumonia of unknown etiology, known as severe acute respiratory syndrome (SARS), occurred in Guangdong Province, China. The cause of the disease, which spread rapidly around the world, was the *SARS-CoV coronavirus.* The epidemic began in November 2002 and ended in July 2003. Reasons that made it possible to stop the epidemic include SARS being most contagious in its later stages, as well as extraordinary efforts to control the spread of infection worldwide. Ten years later, it was discovered that another novel coronavirus is associated with acute severe pneumonia in Middle Eastern countries, *the Middle East respiratory syndrome virus* (MERS). MERS causes milder and more asymptomatic cases, and mortality is closely related to age and comorbidities.

The 2019 novel human coronavirus disease (COVID-19) was first reported in Wuhan, China, in 2019 and then spread around the world. Severe Acute Respiratory Syndrome (Related Coronavirus 2, SARS-CoV-2) is 79 % genetically similar to the SARS-CoV virus. It

is an enveloped single-stranded RNA, a virus whose genome consists of approximately 30 thousand base pairs of nucleotides, encoding approximately 29 proteins. It belongs to the family Coronaviridae, subfamily Orthocoronavirinae, genus Betacoronavirus, subgenus Sarbecovirus. This subfamily has structural features – spike-like proteins on the surface of the virion, which resemble the solar corona in appearance.

The proteins encoded in the virus genome are divided into 16 non-structural proteins (which are needed for transcription and replication of the virus), 4 structural proteins – nucleocapsid (N), spike protein (S), membrane protein (M), envelope protein (E) and 9 auxiliary proteins.

The target cells for the virus are those that have on their surface the ACE2 receptor (angiotensin-converting enzyme 2, a cell membrane protein that acts as an angiotensin II inhibitor) and a transmembrane protease TMPRSS2. Such cells include neurocytes of the cardiovascular center and motor layers of the cerebral cortex, epithelial cells of the retina and cornea, cells of the mucous membrane of the nasal and oral cavity (including the tongue), follicular cells of the thyroid gland, cells of the endothelium and smooth muscles of blood vessels, epithelial cells of renal corpuscles and tubules, urothelium of the bladder, epithelium of the esophagus and stomach, exocrine and endocrine cells of the pancreas, enterocytes of the small intestine, epithelial cells of the colon, epithelial cells of the female reproductive system and oocytes, Leydig cells and epithelium of the convoluted tubules in men, sebaceous gland cells in the skin. In the upper respiratory tract, the virus infects mainly goblet and ciliary cells, in the lungs – endothelial cells.

The virus penetrates into the cell with the help of receptor-mediated endocytosis. The S protein is made up of two parts – S1, which binds to the ACE2 receptor, and S2, which binds to the cell membrane. Between these parts is the S1/S2 region, which undergoes proteolytic cleavage by transmembrane protease TMPRSS2 and/or cellular cathepsin L. The first enzyme is directly used in the

penetration of the virus in the lungs, cathepsin L helps in the penetration with the endosomes, specifically in cells that do not have TMPRSS2. Due to the cleavage of the S1/S2 region, the virus envelope fuses with the cell membrane. After that, the viral RNA is released into the cytoplasm of the cell, where the RNA-based ribosomes are synthesized by the polymerase proteins pp1a and pp1b. From them, with the help of virus-encoded protease, non-structural proteins are formed, including RNA polymerase. Replication begins in double-membrane vesicles that originate from the endoplasmic reticulum. Here, with the help of viral polymerase based on genomic RNA, genomic RNA replication and subgenomic RNA synthesis occur. The result of the translation of subgenomic RNA is the formation of structural and accessory proteins that are incorporated into the vesicle membrane in the region between the endoplasmic reticulum and the Golgi complex, resulting in the assembly of the virion. In the last step, the genomic RNA is incorporated into the newly created virions, which are released from the cell through exocytosis.

SARS-CoV-2 has a relatively low mutation rate of about 2 per month, and at the beginning of the epidemic it was believed that this would not pose a danger to the emergence of new strains with new characteristics that would be of clinical importance, however, chronic isolation of the virus by immunocompromised carriers led to the rapid emergence of new strains. The WHO recommended the use of Greek letters to refer to new variants of the virus.

The classification of SARS-CoV-2 variants is divided into variant of interest (VOI), variant of concern (VOC), and variant under monitoring (VUM).

VOI is defined as a variant of SARS-CoV-2 with genetic alterations that are predicted or known to affect the characteristics of the virus, such as transmissibility, severity of the disease, decreased effectiveness of the immune response, difficulty in diagnosis or treatment, and an increase in the incidence caused by this variant has been detected, indicating a risk that occurs to global public health.

VOC is defined as a variant of SARS-CoV-2 that meets the definition of VOI and has one or more of the following characteristics:

– increased transmissibility or a change that worsens the epidemiology of COVID-19,

– increased virulence or change in the clinical picture of the disease,

– a decline in the effectiveness of health and social interventions or available diagnostic tools, vaccines and therapeutics.

VUM is a variant of SARS-CoV-2 with genetic changes that are thought to affect the characteristics of the virus, with some indications that it may pose a risk in the future, however, the evidence for phenotypic or epidemiological effects at this time is unclear, requiring increased monitoring and re-evaluation pending new evidence.

As of the end of 2021, 4 variants belonged to the VOC, which, according to the WHO classification, were named Alpha, Beta, Gamma and Delta. The disease caused by these variants was characterized by a severe course with complications, and a significant level of contagiousness. Over time, the Omicron variant began to dominate, which has an even higher level of contagiousness, but causes a disease characterized by a lower rate of severe cases with the development of complications and death. As of early 2023, VOI, VOC, and VUM include different subtypes of the Omicron strain.

4.2 Theoretical questions for the lesson:

1) The main types of viruses that cause SARS and their clinical characteristics.

2) Types of coronaviruses affecting the human respiratory system.

3) Structure of the SARS-CoV-2 virus.

4) SARS-CoV-2 target cells and the mechanism of interaction of the virus with these cells.

5) Classification of SARS-CoV-2 variants according to WHO recommendations.

4.3 Practical tasks to be performed in the classroom

Typical example:

In the children's institution, there was an outbreak of the disease with symptoms of damage to the respiratory system, pharyngitis, keratoconjunctivitis.

Question to consider:

What viruses could have caused this disease?

Answer:

The clinical symptoms of the disease suggest adenoviruses as an etiologic factor.

Task 1

There was an outbreak of the illness in the army team that was accompanied by symptoms of SARS and severe abdominal pain.

Question to consider:

What viruses could have caused this illness?

Task 2

The patient, who returned from Saudi Arabia, has symptoms of SARS, fever and respiratory failure. Instrumental studies confirm the presence of pneumonia.

Question to consider:

What viruses could have caused this illness?

5 Content of the topic

In the laboratory, students will be introduced to the major types of viruses that can cause acute respiratory illness. They will study the clinical features of diseases caused by these viruses and how they differ from those caused by coronaviruses. The structure of the SARS-CoV-2 virus and the mechanisms of its interaction with target cells will be studied. Learn the classification of SARS-CoV-2 virus variants according to WHO recommendations.

6 Self-assessment questions:

1) Define acute respiratory viral infection.
2) What are the major types of SARS pathogens?
3) What organs and systems are affected by Orthomyxoviridae viruses?
4) What organs and systems are affected by Paramyxoviridae viruses?
5) What organs and systems are affected by viruses of the Picornaviridae family?
6) What organs and systems are affected by viruses in the Adenoviridae family?
7) What are the main populations most commonly affected by viruses of the Adenoviridae family?
8) Which viruses in the Coronaviridae family cause disease in humans?
9) Define the term SARS.
10) What virus is referred to by the acronym MERS?
11) How many types of coronaviruses have been associated with SARS?
12) When and where was the SARS-CoV virus identified?
13) Are the SARS-CoV and SARS-CoV-2 viruses identical?
14 What proteins are found on the surface of the SARS-CoV-2 virus?
15) What are the target cells of SARS-CoV-2?
16) How is SARS-CoV-2 classified?
17) What does VOI, VOC, VUM mean?
18) Which strains of SARS-CoV-2 are currently VOCs?

TOPIC 2. EPIDEMIOLOGY AND PATHOGENESIS OF COVID-19 DISEASE

Duration – 2 hours.

1 Relevance of the topic

The SARS-CoV-2 virus, which is the cause of the COVID-19 pandemic, is structurally similar to the SARS-CoV-2 virus, which has been well studied since the SARS epidemic of 2003–2004. But, despite this, the pathogenesis of the disease caused by SARS-CoV-2 has features, the knowledge of which is necessary to understand the pathological processes in the human body that occur during the development of this disease.

2 Specific objectives

2.1 The student should know:

- Epidemiology of the SARS-CoV-2 virus: source of infection, transmission mechanisms, susceptibility of the body to infection.
- Persistence of the virus in the external environment.
- Main anti-epidemic measures.
- Pathogenesis of coronavirus infection.

2.2 The student should be able to:

- Carefully collect an epidemiological history.
- Examine the cell by examining it in detail.
- Identify sources of COVID-19.
- Develop and carry out anti-epidemic measures to eliminate the center.

3 Basic knowledge, skills, and abilities necessary to study the topic (interdisciplinary integration)

Table 3

Previous disciplines	Skills acquired
Epidemiology	Study of the patterns of the spread of the disease over time, over the territory and among different groups of the population. Study of the epidemiological process and its links. Collection of epidemiological anamnesis. Development of anti-epidemic measures
Microbiology, virology, immunology	Knowledge of the structure and classification of viruses, the variability of the structure of the virus, the concept of virus strains, and the basics of the immune response
Infectious diseases	Differential diagnosis of diseases of different origins. Recognition of an infectious disease, its complications

4 Tasks for independent work in preparation for class

4.1 A list of basic terms, parameters, characteristics that the student must learn in preparation for the lesson

Table 4

Term	Definition
1	2
Epidemiology	Medical science about the objective patterns of occurrence and spread of infectious diseases at the population level, measures for their prevention and control
Epidemic process	A complex socio-biological phenomenon that arises as a result of the interaction of micro and macro organisms at the population level, manifests itself in specific infectious conditions among people and ensures the preservation of the pathogen in nature as a biological species

Continuation of Table 4

1	2
Pandemic	An epidemic when a new infectious agent covers the majority of the world's population because there is no immunity to it
Physical or social distancing	Measures to limit contact between people outside their homes
Self-isolation	A more complex form of physical distancing that applies to people who isolate themselves because they belong to a high-risk group that is susceptible to the disease
Quarantine	A state of isolation that is carried out to separate infected patients from the rest of the population

Epidemiology of SARS-Cov-2

The first cases of coronavirus disease, which were recorded in late 2019 and early 2020, indicated a link between the disease and contact with bats, which are the natural reservoir of this type of virus, due to an unidentified intermediate host. But, quite quickly, data on the infection of people who cared for patients and medical workers revealed the anthroponotic nature of the disease. To date, it is known for certain that the source of infection is a person who is infected with the virus.

The incubation period of infection is up to 14 days (average 4–5 days), the affected person spreads the virus during the incubation period and for 8-20 days after the disappearance of symptoms.

Transmission of infection is carried out mainly by airborne droplets in an aerosol that is formed when an infected person (sick or asymptomatic carrier) talks, sneezes or coughs, as well as when in contact with infected surfaces. The fecal-oral route of transmission is theoretically possible, but has not been confirmed in studies. Susceptibility to infection is high regardless of gender, but studies have shown that the vast majority of infected people are aged from

30 to 80 years old, in second place are people over the age of 80, and the lowest incidence is observed in children. The basic R0 (number of people infected by one infected person) reproduction rate at the beginning of the epidemic was 1.5 to 3.5 (average 2.56) for the predominant strains of the virus at that time. The Omicron virus has an R0 of 5.5 to 24 in different countries (highest in Africa) and an average of 9.5.

Hot and humid climates prevent the spread of the virus, while cold and dry climates increase the spread of infection. In addition, the seasonal increase in temperature in spring and summer in temperate countries leads to a decrease in morbidity and mortality from COVID-19, and as temperatures decrease in fall and winter, morbidity and mortality rates increase.

The virus can persist on plastic and stainless steel surfaces for up to 3 days and on paper and cardboard for up to 1 day. The virus is not resistant to disinfectants, so according to CDC recommendations, any disinfectant used in the home can be used to treat surfaces. To disinfect the skin of the hands, solutions of ethyl alcohol (in concentrations from 40 % to 80 %), as well as a solution of isopropyl alcohol (in a concentration of 70 %) are used, which effectively destroy the virus on human skin within 5 seconds. Ultraviolet irradiation causes the destruction of structural proteins and nucleic acids of the RNA of the virus, so artificial UV irradiation can be used to inactivate the virus on surfaces.

Pathogenesis of COVID-19

The pathogenesis of coronavirus disease is associated with the interaction of the virus with target cells and the response of the immune system. The first target cells during natural infection are ciliary cells of the epithelium of the nasopharynx and trachea, and supporting epithelial cells of the olfactory zone of the nasal mucosa. Alternative "gates" of infection may be cells of the lower respiratory tract, namely type 2 alveolocytes. These cells are also affected as the disease progresses. The virus is also able to penetrate other cells that

express the ACE2 receptor. The penetration of the virus into the cell is achieved through its interaction with cells with the help of the structural (spiny) S-protein of the virus and the ACE2 receptor on the cell surface. In response to the penetration of the virus, there is an increase in the synthesis of interferon, which, in turn, increases the level of expression of ACE2 on the cell surface. The S1 subunit of the protein binds to the ACE2 receptor, while the S2 subunit is cleaved by the transmebrane serine protease (TMPSS2), thereby fusing the virus with the cell membrane. This process induces a cascade of immune responses that lead to tissue damage. Combinations of these changes can be divided into three distinct groups based on aberrant interferon-dependent responses, cytokine changes, involvement of functionally altered immune cells, and uncontrolled complement activation with associated extracellular neutrophil traps (NETS) and systemic thrombosis. These groups include:

– Humoral immunodeficiency with defects in B cells.

– Hyperinflammatory state characterized by loss of T-cell subpopulations and high cytokine levels due to IL-6, IL-1β, TNF-α.

– Damage caused by complement.

Neutrophil extracellular traps (NETS) are three-dimensional lattice structures compoced of decondensed chromatin filaments. NETS formation is associated with increased levels of IL-6, IL-8, and platelet factor 4 and can be directly induced by SARS-CoV-2. The NET response is one of several important components of innate immunity, but it can become unregulated and lead to cell damage. Activation of this response promotes platelet aggregation and complement formation. In parallel with this, the vascular endothelium is damaged by the virus, which leads to the formation of microthrombi.

Cell death, caused by viral replication (pyroptosis) or the induction of programmed cell death (apoptosis), results in the release of large amounts of proinflammatory cytokines and impairs macrophage and lymphocyte function, leading to peripheral lymphopenia. At the same time, T lymphocytes produce a significant

amount of pro-inflammatory cytokines, resulting in the so-called “cytokine storm”. The hyperinflammatory state is also caused by the binding of macrophages to the S-protein-anti-S-IgG complex, which leads to the accumulation of immune cells in the lung tissue. This explains the significant increase in IgG antibodies at the onset of severe disease. The mechanisms of the pathological immune response described above can occur not only in lung cells, but also in other cells that express (contain on the surface) ACE2 receptors. These include cells of the heart muscle, liver, pancreas, thyroid gland,and central nervous system.

The mechanisms described above in alveolocytes cause their desquamation in the alveoli, contribute to alveolar dysfunction, edema and bleeding, disrupt gas exchange and lead to respiratory failure. At the same time, the amount of surfactant decreases, and, accordingly, the ability of the lungs to expand and contract during the act of breathing decreases. This process can cause the lungs to collapse during exhalation. As the alveoli fill with fluid, respiratory failure increases. Death occurs when the integrity of the alveolar membrane is violated, which leads to the accumulation of liquid exudates in the alveolar space, mechanical ventilation of the lungs is useless.

Damage to the nervous system occurs due to the direct destructive effect of the virus on nerve cells, due to the toxic effect of cytokines that penetrate the blood-brain barrier, and indirect mechanisms associated with impaired microcirculation due to the formation of microthrombi. Disorders of the functioning of the brain-heart axis due to damage to some brain structures lead to disruption of the cardiovascular system. Areas distributed throughout the nervous system, including the anterior insular cortex, the anterior cingulate cortex, the amygdala, the hypothalamus, the periaqueductal gray matter, the parabrachial nucleus, and several regions of the medulla oblongata, exercise sequential control over cardiac function. These areas are critically involved in emotional behavior, stress responses, and homeostatic reflexes and affect heart rate and heart contractility through the sympathetic and parasympathetic nervous

systems. An imbalance in the work of this system leads to the development of cardiovascular accidents, such as stroke and myocardial infarction, or the development of arrhythmias. Cardiovascular disorders are one of the most common causes of death in patients, especially in the long-term period.

4.2 Theoretical questions for the lesson:

1) Historical information about the emergence of coronavirus infections.

2) What are the causes and conditions for the spread of COVID-19?

3) What is the epidemiological chain of coronavirus infection?

4) What are the types of anti-epidemic measures in the COVID-19 outbreak?

5) How is the epidemiologic investigation carried out at the site of this infection?

6) How is an epidemiologic history taken? What does it include?

7) What measures are being taken against persons who have been in contact with the sick person?

8) Which cells are “target cells” for SARS-CoV-2?

9) How does the coronavirus interact with the target cell?

10) What is a “cytokine storm”?

5 Content of the topic

In the practical lesson, students recall materials from previous disciplines related to the infectious disease COVID-19. They discuss the epidemiologic features of coronavirus infection, collection of epidemiologic anamnesis and pathogenesis (mechanism of disease development), effects of the virus on organs and systems. For better assimilation, common terms related to this infection are repeated. Personal protective equipment is considered. Drawing up an action plan in the epidemic center.

TOPIC 3. CLASSIFICATION AND MAIN CLINICAL SYMPTOMS OF CORONAVIRUS INFECTION

Duration – 2 hours.

1 Relevance of the topic

Coronavirus infection remains an urgent problem at present. With timely detection of clinical symptoms and consultation with a doctor, it is possible to predict and prevent the occurrence of complications that can lead to death, as well as to correctly prescribe the tactics of therapeutic measures for this disease.

2 Specific goals

2.1 The student should know:

- Classification of coronavirus infection depending on genetic properties and the course of the disease.
- The main symptoms of the disease.
- Clinical symptoms of different strains.
- Clinical variants and manifestations of COVID-19.

2.2 The student should be able to:

- Collect medical history.
- Analyze the data of the clinical picture of COVID-19.
- Perform differential diagnosis of coronavirus infection with other respiratory diseases.
- Formulate and make a diagnosis based on the patient's complaints.

3 Basic knowledge, skills, and abilities necessary to study the topic (interdisciplinary integration)

Table 5

Previous disciplines	Skills acquired
1	2
Infectious diseases	Perform differential diagnosis of respiratory diseases based on clinical manifestations

Continuation of Table 5

1	2
Physiology	Possess information about the physiological features of the respiratory system; norms of laboratory parameters and their assessment
Pathological physiology	Describe pathological changes in the respiratory system in respiratory diseases
Propaedeutics of Internal diseases	Possess the method of examining a patient with diseases of the respiratory system. To evaluate clinical studies and the main symptoms of diseases of the respiratory system
Functional diagnostics	Interpret data and evaluate the results of radiological examinations

4 Tasks for independent work in preparation for class

4.1 A list of basic terms, parameters, characteristics that the student must learn in preparation for the lesson

Table 6

Term	Definition
COVID-19	An acute viral disease, with an airborne transmission mechanism, caused by the SARS-CoV-2 coronavirus, characterized by predominant damage to the respiratory system and gastrointestinal tract
Anosmia	Pathology in which there is a complete or partial loss of smell
Dysgeusia	A condition in which there is a distortion of the sense of taste
ARDS	Acuterespiratorydistresssyndrome is a typeoflungfailureof various etiologies, which is characterized by non-cardiac pulmonary edema, impaired external respiration and hypoxia

At present, coronavirus infection is a rather urgent problem of mankind, because constant outbreaks of this disease lead to the incidence of a large number of the population, as well as to the appearance of fatal consequences.

There are several types of coronavirus that cause disease in humans. Depending on the genetic properties of the pathogen, there are 6 groups of coronaviruses:

1 Human virus HCoV-229E (one of the SARS viruses, can be complicated by pneumonia and bronchiolitis).

2 Human HCoV-OC43 virus (10–15 % of SARS cases).

3 Human virus HCoV-HKU1 (one of the SARS viruses, can be complicated by pneumonia and bronchiolitis).

4 Human HCoV-NL63 virus (approximately 4.7 % of SARS cases).

5 Coronaviruses SARS-CoV and MERS-CoV.

6 Coronavirus SARS-CoV-2.

Severe clinical manifestations are observed when infected with pathogens such as:

- SARS-CoV virus, which causes SARS or Severe Acute Respiratory Syndrome.
- The MERS-CoV virus, which causes Middle East Respiratory Syndrome, characterized by the development of acute pneumonia and renal failure.
- The SARS-CoV-2 virus, which causes the development of respiratory distress syndrome.

The symptoms of coronavirus infection are quite typical and do not have specific clinical features, therefore, before prescribing treatment, differential diagnosis with other respiratory diseases should be carried out.

The incubation period for COVID-19 is from 2 to 14 days, with an average of 5 days. Most infected people have mild to moderate symptoms and recover without hospitalization. Clinical manifestations appear about four to five days after infection.

Typical symptoms include:

- Increased body temperature (in 90 %).
- Cough (dry or with a small amount of sputum in 80 %).
- Feeling of tightness, congestion in the chest (in 20 %).
- Shortness of breath (55 %).
- Myalgia and fatigue (44 %).

- Headache (8 %).

Loss of smell and taste was quite common among patients during the 2020–2021 epidemic, but cases caused by the latest variants of the virus cause these changes in fewer cases. In populations of European descent, the incidence of anosmia is approximately 11.7%, while in other populations it can be between 1.9 % and 4.9 %. Disturbances in smell and taste usually disappear within 30 days, but, sometimes, can be observed for up to 60 days.

Atypical symptoms include:

- Symptoms of gastrointestinal damage (diarrhea, nausea, vomiting).
- Skin changes (macular rash or hives, discolored areas of skin on the fingers and/or toes).
- Impaired consciousness (confusion, or delirium, may be the only symptom in the elderly, associated with a severe course and poor prognosis).
- Eye diseases (conjunctivitis, increased sensitivity to light, pain and itching of the eyes).

On days 3–5, pneumonia may follow, which is characterized by fever, dry cough, fatigue, anorexia, myalgia, dyspnea, sputum production, and bilateral infiltrates on chest x-ray.

Depending on the course of the disease, coronavirus infection is classified into the following forms:

- Asymptomatic form (there are no clinical symptoms, but the result of the laboratory test – serologic or PCR – is positive).
- Mild form (clinical symptoms are mild: body temperature below 38 °C, cough, weakness, sore throat, manifestations of pneumonia are not detected on imaging).
- Moderate form (symptoms are: fever above 38 °C, respiratory rate more than 22 min, shortness of breath during physical exertion, manifestations of pneumonia are detected on imaging, $SpO_2 < 95$ %).
- Severe form (respiratory rate ≥ 30 breaths per minute; $SpO_2 < 93$ % at rest; oxygenation index (PaO_2/FiO_2) < 300 mmHg

art., or during chest x-ray – infiltrates in the lungs more than 50 %, decreased level of consciousness, agitation).

– Extremely severe form (acute respiratory failure requiring respiratory support, septic shock, multiple organ failure).

Clinical variants and manifestations of COVID-19:

- Mild acute respiratory viral infection.
- Pneumonia without respiratory failure.
- Pneumonia with acute respiratory failure.
- ARDS.
- Sepsis.
- Septic (infectious-toxic) shock.

Major clinical syndromes associated with COVID-19

Table 7

Pathologic condition	Characteristics
1	**2**
Respiratory syndrome	Clinical symptoms are mild to moderate. CT/chest x-ray shows no evidence of pneumonia
Mild pneumonia	Mild intoxication syndrome, cough without shortness of breath with normal respiratory rate (HR up to 18/min). There are no signs of respiratory failure (SpO_2 > 95%). There are no manifestations of pneumonia on the x-ray of the OGK, according to CT- foci of "frosted glass"
Moderate pneumonia	Moderate intoxication syndrome, cough with dyspnea and heart rate 20–30/min. Manifestations of moderate respiratory failure (pulse oximetry – SpO_2 < 95%). According to CT scan, multifocal shadows or subpleural foci of “ground-glass” type consolidation may be detected, pneumonic infiltrates may be detected on x-ray of the lung

Continuation of Table 7

1	2
Severe pneumonia	There is a cough with dyspnea, respiratory rate >30/min, severe respiratory insufficiency (pulse oximetry – SpO_2 < 93 %).According to CT and x-ray, OGK – multifocal shadows or foci of condensation such as "frosted glass", “cobblestones”, pneumonic infiltrates >50 % of the lung field for 24–48 hours
Acute respiratory distress syndrome (ARDS)	This is a set of symptoms of acute LN against the background of lung damage, which is characterized by non-cardiac pulmonary edema, impaired external respiration, and hypoxia
Sepsis	This is a life-threatening organ dysfunction caused by a patient’s impaired immune response to a suspected or proven infection, accompanied by multiple organ failure. Signs of organ dysfunction include: - Altered mental status. - Difficulty or frequent breathing, low blood oxygen saturation. - Decreased urine output. - Tachycardia, weak pulse, cold extremities, or hypotension, skin discoloration. - Laboratory evidence of coagulopathy, thrombocytopenia, acidosis, high lactate level, or hyperbilirubinemia
Septic shock	Hypotension persists despite volume expansion. For example, in the case of the United States of America, the need for vasopressors to maintain a mean arteria pressure ≥ 65 mm Hg. and serum lactate >2 mmol/L or 2–3 of the following: - Altered mental status. - Tachycardia or bradycardia. - Prolonged capillary filling (>2 seconds). - Tachypnea. - Variegated petechial or purpuric skin rash; increased lactate. - Oliguria. - Hyperthermia or hypothermia

In 80–90 % of cases, the disease ends in recovery. Mortality ranges from 4 to 19.7 % of cases, and in the group of patients on artificial lung ventilation – 57.7 %.

Comorbidities and advanced age increase the risk of severe disease with adverse outcomes.

4.2 Theoretical questions for the lesson:

1) Definition of the term coronavirus infection.
2) Classification of coronavirus infection depending on the course of the disease.
3) Definition of the term ARDS.
4) Provide a clinical picture of a moderate form of coronavirus infection.

4.3 Practical tasks to be performed in the classroom

Typical example:

Patient V., 25 years old, came to the doctor with complaints of an increase in body temperature up to 38.5 °C, general weakness, headache, dry cough with dyspnea, shortness of breath on physical exertion, loss of smell and taste, nasal congestion. Objective examination revealed RR –23/min, SpO_2–94 %. The chest x-ray showed infiltrates in the lower lobe of the right lung, the degree of damage is 15 %. A few days ago, I had contact with a patient with SARS.

Questions to consider:

1) Formulate a probable clinical diagnosis.
2) List the major methods used to diagnose this disease.
3) Prescribe a treatment plan, including doses, route of administration, and duration of use.

Answer:

1) Coronavirus disease caused by the causative agent SARS-CoV-2 (PCR), pneumonia of the lower lobe of the right lung, moderate course. DN I Art.

2) Complete blood count, biochemical blood test, PCR (specific diagnosis), pulse oximetry.

3) Rehydration – 100 ml of fluid every 30 to 40 minutes. Ibuprofen 400 mg – 1 tablet each. 2 times a day. Adjunctive therapy based on laboratory results.

Task 1

Patient M., 25 years old, consulted a doctor with complaints of dry cough, fever up to 38°C, fever, headache, feeling of tightness in the chest. Two days ago, I noticed changes in the taste buds, and loss of smell. During an objective examination: RR – 25/min, blood pressure – 100/70 mm Hg. Art., SpO_2– 93 %.

Questions to consider:

1) Formulate the clinical diagnosis.
2) What changes in laboratory tests can be expected with this disease?
3) Prescribe a treatment plan, including doses, route of administration, and duration of use.

Task 2

An ambulance brought a patient with altered consciousness and signs of respiratory failure to the Infectious Diseases Department. BHR – 40/min, BP – 85/40 mm Hg. Century. He was treated for COVID-19 one week ago.

Questions to consider:

1) Formulate the clinical diagnosis.
2) What changes in laboratory tests can be expected with this disease?
3) Prescribe a treatment plan, indicate the doses, route of administration, and duration of use.

Task 3

A 20-year-old girl went to the family doctor with complaints of loss of smell and taste, fever up to 37.3 °C, general weakness, nasal congestion. After arriving in Ukrainefrom England, a rapid test for COVID-19 was performed at the state border, which confirmed the disease.

Questions to consider:

1) Formulate the clinical diagnosis.
2) Prescribe an investigation plan for this disease.
3) What preventive measures should be taken in this situation?

5 Content of the topic

In the practical part of the course, students will learn the clinical classification of coronavirus diseases according to the genetic characteristics of the pathogen and the severity of the disease. They will receive information on clinical manifestations of the disease and variants of the course of COVID-19. The differential diagnosis of coronavirus infection is made according to the strain that caused the disease.

6 Self-assessment questions:

1) The length of the COVID-19 incubation period.
2) Which strain of coronavirus infection is severe in adolescents and pregnant women?
3) What are the main clinical manifestations of coronavirus disease?
4) What are the main symptoms of ARDS in coronavirus infection?
5) What changes in the lungs do chest x-rays show in severe pneumonia?

TOPIC 4. “RED FLAGS” - SYMPTOMS OF SEVERE COVID-19

Duration – 2 hours.

1 Relevance of the topic

The majority of patients with COVID-19 have mild (40 %) or moderate disease (40 %), approximately 15 % develop severe disease that requires oxygen support, and 5 % have an extremely severe (critical) course with complications such as respiratory failure, ARDS, sepsis and septic shock, thromboembolism, and/or multiple organ failure, including acute kidney and heart damage. Age, smoking, and major noncommunicable diseases such as diabetes, hypertension, heart disease, chronic lung disease, and cancer are identified as risk factors for serious illness and death.

2 Specific goals

2.1 The student should know:

- Pathophysiological mechanisms of severe disease.
- Criteria for the severity of COVID-19.
- Complications of COVID-19.
- Concomitant pathologies that complicate the course of the disease.

2.2 The student should be able to:

- Conduct a detailed collection of complaints, epidemiological anamnesis, medical and life history.
- Conduct a detailed, objective examination of the patient.
- Interpret laboratory and instrumental tests.
- Carry out differential diagnosis of comorbid conditions.

3 **Basic knowledge, skills, and abilities necessary to study the topic (interdisciplinary integration)**

Table 8

Previous disciplines	**Skills acquired**
1	**2**
Microbiology	Properties of the pathogen, methods of specific diagnosis and interpretation of results
Immunology and allergology	Basic concepts about the role of the infectious process in the immune system, the impact on the period of elimination of the pathogen from the human body. Evaluation of immunological data
Physiology	Parameters of the physiological norm of human organs and systems. Evaluation of laboratory examination parameters
Pathophysiology	The mechanism of the course of dysfunction of body systems and individual organs in pathological conditions of various genesis with the interpretation of pathological changes based on the results of clinical and laboratory examination
Epidemiology	Epidemic process (source, mechanism of infection, routes of transmission) in SARS-CoV-2, prevalence of pathology in Ukraine and the world. Methods of collecting epidemiological anamnesis, carrying out anti-epidemiological and preventive measures in the focus of infection
Propaedeutic of internal diseases	Main stages and methods of clinical examination of a patient. Methods of collecting anamnesis, conducting clinical examination of the patient with detection of pathological symptoms or syndromes with obligatory analysis of the obtained data
Clinical disciplines: Internal medicine, surgery, gynecology	Variety of clinical symptoms in patients in the presence of comorbid pathology, comorbid conditions. Differential diagnosis with other pathological conditions and diseases with similar clinical symptoms. Diagnosis of the impact of complications on the patient's body

Continuation of Table 8

1	2
Clinical pharmacology	Pharmacokinetics and pharmacodynamics, side effects of etiotropic, pathogenetic and symptomatic therapies. Prescribing treatment depending on the severity of the course, the individual characteristics of the patient and concomitant pathology

4 Tasks for independent work in preparation for class

4.1 A list of basic terms, parameters, characteristics that the student must learn in preparation for the lesson

Table 9

Term	Definition
1	2
COVID-19	It is an acute severe infectious respiratory disease caused by the new coronavirus SARS-CoV-2 with an airborne transmission mechanism
Clinical symptoms and their frequency	- Fever (99 %). - Dry cough (59 %). - Fatigue (70 %). - Anorexia (40 %). - Myalgias (35 %). - Shortness of breath (31 %). - Sputum production (27 %) and bilateral infiltrates on chest x-rays
Clinical variants of the course of the disease	- Acute respiratory viral infection (damage to the upper respiratory tract only). - Pneumonia without respiratory failure. - Pneumonia with acute respiratory failure. - ARDS. - Sepsis. - Septic (infectious-toxic) shock. - Thrombosis. - Thromboembolism. - Multiple organ failure

Continuation of Table 9

1	2
Signs of severe disease	- Respiratory rate more than 30 / min - $SpO_2 \leq 93$ %. - PaO2/FiO2 ≤ 300 mmHg. - Progression of changes in the lungs typical of pneumonia in COVID-19 (infiltrates in the lungs >50 % of the lung field within 24–48 hours). - Decreased level of consciousness, agitation. - Unstable hemodynamics (systolic blood pressure less than 90 mm Hg or diastolic blood pressure less than 60 mm Hg, urine output less than 20 mL/h). - Arterial blood lactate > 2 mmol/L. - A qSOFA score >2 is suggestive of sepsis –extremely severe. - Acute respiratory failure with the need for respiratory support (invasive ventilation) - ARDS
Complications	Pneumonia, acute respiratory distress syndrome, coagulopathy, heart damage, liver damage, acute renal failure, neurological disorders, and others
Concomitant pathologies that complicate the course	Cardiovascular diseases, hyperlipidemias, chronic pathologies of the respiratory tract, diabetes mellitus, other hormonal disorders, autoimmune diseases, immunodeficiency states, severe concomitant infectious diseases (tuberculosis, HIV/AIDS, chronic hepatitis with cirrhosis of the liver)

Acute respiratory distress syndrome (ARDS) is a symptom complex of acute lung injury secondary to lung injury of various etiologies, characterized by non-cardiac pulmonary edema, impaired external respiration, and hypoxia.

Onset is defined as the onset of new symptoms of lung injury or worsening of existing symptoms within one week of clinical pathology.

Chest imaging (x-ray, CT, or lung ultrasound): bilateral infiltrates not explained by pleural effusion, lobe or whole lungcollapse, or focal lesions.

Clinical diagnostic criteria:

- Severe shortness of breath and cyanosis.
- Cough with pink frothy sputum.
- Tachycardia, tachypnea.
- Auscultation – a large number of wet rales of various calibers in the lungs and pronounced crepitus, which are signs of pulmonary edema.
- Signs of increasing pulmonary hypertension with acute pulmonary heart syndrome.
- Multiple organ failure: renal (oligoanuria, proteinuria, cylindruria, microhaematuria, hypercreatinemia); liver (jaundice, increased activity of AST, ALT, LDH); brain (dizziness, lethargy).

ECG criteria: deviation of the electrical axis of the heart to the right, P-pulmonale.

Radiographic criteria: pulmonary cone burst, signs of increased pulmonary artery pressure <30/15 mmHg, bilateral lung infiltrates, sometimes a "blizzard" symptom is determined.

Laboratory and biochemical criteria:

- Arterial hypoxemia (PaO_2<50 mm Hg) and hypercapnia ($PaCO_2$>45–50 mm Hg).
- Decrease in pH to 7.2 units or less and other signs of respiratory decompensated acidosis.
- Respiratory index $PaO_2/FiO_2 \leq$200 mm Hg (where PaO_2 is the partial pressure of oxygen in arterial blood, FiO_2 is the concentration of oxygen in the inhaled air, expressed in tenths).

The main clinical criterion for the development of ARDS is persistent hypoxemia with an insufficient response to breathing with an oxygen-air mixture.

Severity of oxygenation disorders in adults:

- Mild ARDS: 200 < $PaO_2/FiO_2 \leq 300$.
- Moderate ARDS: 100 < $PaO_2/FiO_2 \leq 200$.
- Severe ARDS: $PaO_2/FiO_2 \leq 100$.

If PaO_2 is not available, SpO_2/FiO_2 is used at SpO_2/FiO_2 ≤315 suspected ARDS (including in unventilated patients).

Clinical signs of sepsis:

Adults: Life-threatening organ dysfunction caused by the body's uncontrollable response to suspected or proven infection.

Signs of organ dysfunction include:

- Altered mental status.
- Shortness of breath or rapid breathing.
- Low oxygen saturation.
- Decreased urine output.
- Fast heart rate.
- Weak pulse or low blood pressure.
- Skin mottling or laboratory evidence for coagulopathy, thrombocytopenia, acidosis, high lactate, or hyperbilirubinemia.

Children: Suspected or confirmed infection and criteria for systemic inflammatory response syndrome (SIRS) at ≥2 years of age, which should include abnormal fever or white blood cell count.

The criteria for the CVS include:

- Abnormal temperature <36 °C or >38.5 °C.
- Heart rate >2 points of standard deviation above normal age, or bradycardia if <1 year of age.
- Respiratory rate >2 points of standard deviation above normal by age.
- Abnormal white blood cell count or >10 % immature neutrophils.

Clinical signs of septic shock:

Adults: Persistent hypotension, despite replenishing the circulating blood volume, requires the use of vasopressors to maintain a mean arterial pressure of ≥65 mm Hg and lactate level in blood serum >2 mmol/L.

Children: Any degree of hypotension (mean arterial pressure below the 5th centile or >2 standard deviation points below normal for age) or any two to three of the following:

- Altered mental status.

- Tachycardia or bradycardia (heart rate <90 bpm or >160 bpm in infants and heart rate <70 bpm or >150 bpm in children).
- Pale patches (>2 sec) or weak pulse.
- Tachypnea.
- Blotchy or cool skin or petechial or purpuric rash.
- Increased lactate.
- Oliguria.
- Hyperthermia or hypothermia.

4.2 Theoretical questions for the lesson:

1) 1 Definition of COVID – 19.
2) Main clinical symptoms of COVID-19.
3) Clinical variants of COVID-19.
4) Key signs of severe COVID-19.
5) What are the complications of severe COVID-19?

4.3 Practical tasks to be performed in the classroom

Typical example:

An 18-year-old girl presents to the emergency department with a 1-week history of chest pain, shortness of breath, and fatigue. The patient reports that 1 week ago she felt a sudden sharp pain along the right side of her chest and ribs. She was initially admitted to another hospital where she was diagnosed with acute obstructive bronchitis and prescribed inhaled Berodual and prednisone tablets. The patient's condition has not improved and she goes to the emergency room where she denies fever, chills, cough, nausea, and pain in her abdomen or legs. Medical history: I started taking oral contraceptives 2 months ago. On treatment: blood pressure – 90/70 mm Hg; respiratory rate – 20 per minute; pulse – 116 beats per minute; temperature – 37.1 °C; oxygen saturation – 93 %; on physical examination: general condition of moderate severity, consciousness is clear, perioral cyanosis is present, pallor of the skin, orthopnea position, auscultation in the lungs fine vesicular rales in the lower parts, in the heart: systolic murmur at the site of the

xiphoid process. Laboratory confirmed (PCR) COVID-19. D-dimer 3.0 μg/mL. Chest x-rayshows low intensity homogeneous ground-glass opacity in the inferior medial area on the right. Contrast CT: Thromboembolism of the small branches of the right pulmonary artery.

Questions to consider:

1) Make a diagnosis.

2) Explain the possible factors that led to the severe course of the underlying disease.

3) 3 Follow-up.

Answer:

1) COVID-19. Communityacquired rightlower lobar pneumonia. Type DN 2 Art. Severe course. Pulmonary embolism.

2) Against the background of taking oral contraceptives, under the influence of an increased amount of sex hormones, homeostasis occurred in the form of hypercoagulability. (COCs have a procoagulant effect).

3) Hospitalization in the intensive care unit (ICU). Anticoagulant therapy and discontinuation of COCs under the supervision of a gynecologist are recommended. After elimination of complications, etiotropic and pathogenetic therapy of the underlying disease.

Task 1

The EMS team arrived at the scene of the call to the apartment, where they found a man almost unconscious on the bed in the room, his skin pale, cold, covered with sticky sweat. According to his wife, the patient has been treated on an outpatient basis for pneumonia for about 2 weeks, a rapid test or PCR for COVID-19 was not performed, both are not vaccinated. When examining the patient: the condition is severe, consciousness is confused, the patient is not oriented in time and space, but orientation in his own personality is preserved. The skin is pale, cyanotic, covered with cold sticky sweat. The blood pressure is 70/30, the peripheralpulse is weak, almost inaudible, more than 120/min. RR 30/min. Saturation is

68%. Body temperature is 39.6 °C. Auscultatory, wet, large-bellied rales in all parts of both lungs. Mixed shortness of breath can be heard in the distance. There is no urine when urinary catheteris placed, there is no urine; according to my wife, I last went to the toilet a day ago.

Questions to consider:

1) Make a clinical diagnosis.
2) Prescribe basic laboratory and instrumental diagnostic procedures with interpretation of results.
3) Follow-up.

Task 2

A 56-year-old male patient was admitted to the Infectious Diseases Clinic with complaints of shortness of breath, nonproductive wet cough, fever, and general weakness. According to the patient, this condition began about a week ago with the appearance of a sore throat and the disappearance of smells and tastes. From the epid.anamnesis - it is known from the anamnesis that several employees at work are on sick leave due to COVID-19. From the anamnesis it is known that the patient has had COPD for about 10 years, constantly takes Symbicort and theophylline tablets. Objectively: the condition is serious, consciousness is clear, the position is orthopnea. The skin is pale, diffuse cyanosis. On auscultation, difficult breathing, crackles of various calibers, weakening of heart sounds. BP – 130/80 mmHg, heart rate – 112/min, pulse is 26/min. Saturation is 84 %. X-ray of the chest: bilateral infiltrates of the lower parts of the lungs, “snow storm” effect on x-ray study.

Questions to consider:

1) Make a clinical diagnosis.
2) Prescribe basic laboratory and instrumental tests to confirm the diagnosis.
3) Follow-up.

Task 3

A 35-year-old male patient was admitted to the hospital with complaints of fever, myalgia, severe fatigue, insomnia, dry cough, shortness of breath at rest, heart failure, low back pain, and acute urinary retention. He reported that he had been ill for 2 weeks, beginning with sore throat and fever. About 3 weeks ago, he had contact with a patient with COVID-19. The patient has not been vaccinated against COVID-19 for personal reasons. The patient lives with his wife and child who have no signs of the disease. He was self-treated with paracetamol, lazolvan. From the anamnesis it is known: the patient has had chronic glomerulonephritis since childhood. Objectively: the condition is severe, consciousness is clear, the position is active lying down, the skin is pale, moist. Auscultatory: labored breathing, wet rales of different calibers in the lower parts of both lungs, weakened heart sounds. Blood pressure is 80/50 mmHg arterial, heart rate more than 120/min, pulse is 24/min, body temperature is 37.6 °C. On palpation the acute abdomen is negative, Pasternatsky's symptom is doubtful on both sides. Labs: creatinine – 330 μmol/L, urea – 23 mmol/L, potassium – 8.4 mmol/L.

Questions to consider:

1) Make a clinical diagnosis.
2) Prescribe basic laboratory and instrumental tests to confirm the diagnosis.
3) Follow-up.

5 Content of the topic

At the practical lesson, students study the signs of threatening conditions that indicate a complicated course of coronavirus disease. They consider practical cases in which decisions are made about further tactics for managing patients.

6 Self-assessment questions:

1) Give a complete definition of the COVID-19 disease.
2) What criteria indicate the risk of severe COVID-19?

3) Describe the main clinical symptoms of severe COVID-19.

4) What are the indicators for the development of acute respiratory failure?

5) What are the indicators for the development of sepsis?

6) What are the indicators for the development of septic shock?

TOPIC 5. PRINCIPLES AND METHODS OF LABORATORY DIAGNOSIS OF THE DISEASE

Duration – 2 hours.

1 Relevance of the topic

In the context of the pandemic, all countries, despite their different political status and economic potential, have focused their efforts on combating COVID-19 caused by the SARS-CoV-2 coronavirus. The issue of diagnosing coronavirus disease is of particular relevance.

2 Specific objectives

2.1 The student should know:

- Basic laboratory research methods.
- Study methodology.

2.2 The student should be able to:

- Formulate a plan for the laboratory examination of the patient.
- Interpret laboratory test results.

3 Basic knowledge, skills, and abilities necessary to study the topic (interdisciplinary integration)

Table 10

Previous disciplines	Skills acquired
Microbiology	Properties of pathogens, methods of specific diagnostics
Physiology	Knowledge of laboratory blood parameters and their norms
Immunology and allergology	Knowledge of the place of the immune system in the infectious process. Evaluation of immunological data

4 Tasks for independent work in preparation for class

4.1 A list of basic terms, parameters, characteristics that the student must learn in preparation for the lesson

Table 11

Term	Definition
PCR	Experimental method of molecular biology, a method of significantly increasing small concentrations of desired DNA or RNA fragments in biological material (sample)
ELISA	An immunological method for determining the presence of certain antigens, by antigen-antibody reaction. It is widely used in research and clinical laboratory diagnostics
Rapid test	A rapid diagnostic test suitable for point-of-care testing that directly detects the presence or absence of an antigen

Usually, the doctor is consulted with cough, difficulty breathing, fever, which are considered typical for this virus.

Laboratory diagnosis of COVID-19 is divided into general and specific.

General includes: clinical blood count with determination of erythrocyte count, hematocrit, leukocytes, platelets, leukocyte formula; biochemical blood count with determination of urea, creatinine, electrolytes, liver enzymes, bilirubin, glucose and albumin; coagulogram, determination of C-reactive protein and D-dimer levels.

General clinical laboratory tests of patients with COVID-19 often reveal leukopenia or leukocytosis, lymphopenia, thrombocytopenia, increased alanine and aspartate aminotransferase activity. A high neutrophil-to-lymphocyte ratio is a useful marker of increased risk of severe disease and poor prognosis.

Specific laboratory diagnostics: polymerase chain reaction (PCR) tests, enzyme-linked immunosorbent assay (ELISA) tests and rapid immunochromatographic assay (RICA).

PCR diagnostics determines the presence of viral RNA in the sample. The ELISA test method detects two types of

immunoglobulins: lgM and lgG. If lgM is detected, then we are talking about an acute process of the disease. If it is lgG, then it means that a person has been ill or infected with the virus and has developed antibodies to this disease. The use of ELISA tests to detect COVID-19 antibodies is regulated by the order of the Ministry of Health dated 20.05.2020 No. 1227. Only the PCR result is recommended for diagnosis.

Currently, polymerase chain reaction (PCR) detection of viral RNA is used to confirm the diagnosis of SARS-CoV-2 coronavirus infection. The PCR method is considered accurate because it records the presence of the virus itself (its RNA, which are carriers of genetic information). The essence of the method is to detect a fragment of the pathogen's RNA, i.e. the virus in the sample. The method is quite complicated, but it allows you to detect the virus even if there is only one molecule of its genome in the sample. Thus, the main advantages of PCR as a diagnostic method are its high sensitivity, direct determination of the presence of the pathogen, ability to diagnose not only acute, but also latent infections. For laboratory diagnostics, respiratory material should be collected from outpatients, nasopharyngeal and oropharyngeal swabs.

Using ELISA test systems, it is possible to detect markers of infection in serum and blood plasma with high sensitivity and specificity, such as antibodies to the infectious agent or its antigens.

Rapid tests determine the presence of antibodies to the virus in the blood, and not the actual presence of the virus. This method is considered not very accurate, since the human body begins to produce antibodies not from the first day of infection with the disease, but in the midst of it – in the case of Covid-19, it is about 7–12 days. The result of the test becomes known in 15 minutes, and it can be done at any medical institution. But in any case, the result of the rapid test must be confirmed by PCR.

Upper respiratory tract (URT) specimens from the nasopharynx and oropharynx followed by reverse transcription-polymerase chain reaction (RT-PCR) are recommended in all suspected cases; if clinical suspicion persists and URT specimens are

negative, lower respiratory tract (LRT) specimens should be obtained if not difficult to obtain (e.g., sputum specimens or endotracheal aspirate/bronchoalveolar lavage in ventilated patients). Additional laboratory testing for other respiratory viruses and bacteria should be performed as clinically indicated.

Depending on local epidemiologic factors and clinical symptoms, testing for other infections (e.g., malaria, Dengue, typhoid fever) should be performed.

Notes:

1) Patients with COVID-19 have had other respiratory infections (viral, bacterial and fungal) in parallel. In other words, a positive test result for another pathogen does not rule out COVID-19 infection and vice versa. At this stage, it is necessary to perform detailed microbiological tests in all suspected cases. For example, it is possible to test material from both URT and LRT for other respiratory viruses, such as influenza A and B viruses (including zoonotic influenza A), respiratory syncytial virus, parainfluenza viruses, rhinoviruses, adenoviruses, enteroviruses (e.g., EVD68), human metapneumovirus, and endemic human coronaviruses (HKU1, OC43, NL63, and 229E). NDS specimens can also be tested for bacterial pathogens, including Legionella pneumophila.

2) In malaria-endemic areas, patients with fever should be screened for malaria or other concomitant infections using certified rapid diagnostic tests (RDTs) or by taking thick and thin blood smears, and appropriate treatment should be given if necessary. In endemic areas, the differential diagnosis of febrile illness, especially in the presence of thrombocytopenia, should also include arbovirus infection (Dengue/Chikungunya). An associated infection with COVID-19 may also be observed. A positive diagnostic test for Dengue (e.g. serological tests for Dengue virus) does not exclude the need for COVID-19 testing. If tuberculosis is suspected, it is necessary to collect a sputum sample, following special rules (collection of the sample in the open air, outside the house and preferably outside the premises of a medical institution, at a distance

from other people). A staff member should not be near the patient when taking the sample.

Table 12 –Other research

Investigations in case of hospitalization of moderate, severe, or critical cases	
Hematological/ biochemical research	Complete blood count, C-reactive protein, renal and liver function tests, ferritin, creatine phosphokinase, troponins, lactate dehydrogenase, coagulogram, D-dimer
In case of clinical deterioration of the patient's condition	
Hematological / biochemical research	C-reactive protein, renal and liver function tests, ferritin, creatine phosphokinase, troponins, lactate dehydrogenase, coagulation tests (prothrombin time (PT), Partial Thromboplastin Time (PTT), D-dimer, fibrinogen)

4.2 Theoretical questions for the lesson:

1) General and specific laboratory diagnostics.
2) Serologic diagnosis of COVID-19.
3) PCR as the main diagnostic method.
4) Express diagnosis of the disease. Advantages and disadvantages of the tests.

4.3 Practical tasks to be performed in the classroom

Typical example:

A woman with signs of acute respiratory viral infections (cough, runny nose, fever) turned to the family doctor, notes that she has been ill for 5 days. Indicates that a colleague has similar symptoms at work. The doctor suspected a coronavirus infection.

Questions to consider:

1) What tests should be performed to confirm the diagnosis?
2) What should be done to prevent the spread of the disease?

Answer:

1) PCR for SARS-Cov-2 is required to confirm the diagnosis.

2) To prevent the spread of infection, contacts should be identified and PCR should be performed on all to rule out the disease.

Task 1

Several laboratory tests are used to diagnose COVID-19. However, the "gold standard" to confirm the diagnosis is PCR.

Questions to consider:

1) Why is PCR used to confirm the diagnosis? Justify your answer.

2) What other methods are used to identify the pathogen?

5 Content of the topic

During the practical part of the course, the students will be introduced to the methods of COVID-19 laboratory diagnostics. They receive information about the most informative and accurate methods. They will master the skills of quick and high quality diagnosis of the disease.

6 Self-assessment questions:

1) What is general laboratory diagnostics?
2) What are the methods of serological diagnosis?
3) What materials are selected for examination?
4) Which test can be used for rapid diagnosis?
5) Do rapid tests confirm the diagnosis? Why not?
6) Which of the laboratory values indicate a previous illness?
7) What can the ELISA detect in SARS-CoV-2?

TOPIC 6. RAPID TESTS IN DIAGNOSING COVID-19

Duration – 2 hours.

1 Relevance of the topic

The topic of coronaviruses is perhaps the most prevalent in society today. During the pandemic, testing for SARS-CoV-2 is an extremely important part of the first line of defense for the population of any country in the world against COVID-19. It is a timely test that allows you to identify and isolate an infected person, slow the transmission of the coronavirus, and provide targeted care to patients.

2 Specific objectives

2.1 The student should know:

- What rapid tests determine COVID-19.
- Indications for rapid tests.
- Algorithm for conducting rapid tests.

2.2 The student should be able to:

- Conduct rapid tests to determine COVID-19.
- Identify patients who need rapid tests.
- Interpret the results.

3 Basic knowledge, skills, and abilities necessary to study the topic (interdisciplinary integration)

Table 13

Previous disciplines	**Skills acquired**
Microbiology	Properties of pathogens, methods of specific diagnostics

4 Tasks for independent work in preparation for classes

4.1 A list of basic terms, parameters, characteristics that the student must learn in preparation for the lesson

Table 14

Term	Definition
Evidence-based medicine	Conscientious, accurate and conscious use of the best results of clinical trials to select the treatment of a particular patient
COVID-19	Human coronavirus disease caused by coronavirus SARS-Cov-2
SARS-CoV-2	Severe Acute Respiratory Syndrome – related coronavirus 2

For diagnostic purposes, antigen and antibody tests are used. PCTs for antigen directly detect the antigen (Ag) of the SARS-COV-2 virus. An antibody test (Ab) detects one or more types of antibodies produced by a sick person's body in response to a viral infection. A number of devices for the etiological diagnosis of COVID-19, influenza and other respiratory viral infections have been registered in Ukraine, the list of which is constantly updated. Their use is important and necessary in the work of a practical or family doctor for etiological and differential diagnosis, especially during the seasonal rise in the incidence and/or pandemic spread of COVID-19 coronavirus infection. To expand testing capabilities, a combination of two or more types of PCTs is usually used. Two types of CTs are used for testing for COVID-19: the first is for the qualitative detection of antigens (Ag) of the SARS-CoV-2 coronavirus and the second is for the qualitative detection of antibodies (Ab) of the IgM and/or IgG classes to the SARS-CoV-2 coronavirus.

The rapid test "CITO TEST COVID-19 Ag" for the qualitative detection of SARS-CoV-2 coronavirus antigens is registered in Ukraine, developed on the principle of immunochromatographic assay (ICA) for the detection of coronavirus antigens in nasopharyngeal swabs of persons suspected of coronavirus infection caused by any strain of the SARS-CoV-2 virus. As a rule, in COVID-19, virus antigens are detected in samples

from the upper respiratory tract during the first 5–7 days of manifestations of acute respiratory disease. The sensitivity and specificity of “CITO TEST COVID-19 Ag” have been determined in numerous clinical studies and are: 90.4 % (sensitivity) and 99.5 % (specificity). “CITO TEST COVID-19 Ag” works on the principle of RICA with visual accounting of test results. During testing, a sample of biological material is applied with a disposable pipette to the nitrocellulose membrane of the test cassette in zone “S” (sample), then migrates through the capillaries of the membrane to zone “C” (control) at the end of the test cassette. In the area of the test line (T), pre-labeled antibodies to SARS-CoV-2 are applied to the membrane, and if there is coronavirus hypertension in the sample, then hypertension interacts with labeled BP to form the immune complex “AH+AT”, as a result of which a colored line appears in the “T” zone, which indicates a positive test result. In cases where there is no hypertension SARS-CoV-2 in the material from the patient (in the sample), then the immune complex is not formed and a colored line does not appear in the “T” zone, which indicates a negative test result, that is, the SARS-CoV-2 virus has not been detected. A colored line that should always appear in the control zone “C” indicates the quality of the test. It is the control of the correct execution of the test procedure, thereby indicating that a sufficient amount of the sample has been used and the filling of the membrane capillaries has occurred. It is important to emphasize that if the result is positive, two colored lines always appear on the membrane of the test cassette. One colored line is in the “C” control zone and the other is in the “T” zone. The intensity of the staining of the lines in the “T” zone may vary depending on the concentration of antigens in the sample. Therefore, the appearance of a colored line of any intensity in the test region should be considered a positive result. If the result is negative, only one colored line will appear in the control region “C”. There is no line in the test region “T”. The complete absence of a control line is considered an invalid result. The reason for such a test result may be an insufficient amount of specimen used, non-compliance with the test procedure, expiration dates, and storage

conditions of the test. If an invalid result is obtained, it is necessary to repeat the study using a different PCT.

The TEST COVID-19 Ag Rapid Screen is a qualitative test and can only be used to detect SARS-CoV-2 viral antigens in nasopharyngeal swabs from individuals with suspected coronavirus infection. The test cannot be used to determine the quantitative content of the pathogen or the concentration of SARS-CoV-2 antigens in the test material. A positive result obtained with SIEVE TEST COVID-19 Ag only indicates the presence of SARS-CoV-2 antigens in the specimen and cannot be the sole criterion for the diagnosis of coronavirus infection. As in all diagnostic cases, the test result must be considered in conjunction with the clinical information available to the clinician. If the test result is negative and symptoms of COVID-19 are present, it is recommended that the test be repeated in a few days or tested by RT-PCR or other NAAT. It is important to remember that a negative test result does not rule out coronavirus infection, especially in contacts. A negative result is also possible if the concentration of hypertension in the test sample is very low. Of course, it is also important that the specimen for the test is taken correctly, as excess mucus or the presence of blood can lead to a false negative result. In general, the recommendations for use of SIEVE TEST COVID-19 Ag meet the criteria of effectiveness and can be used in conditions when molecular genetics research methods are not available to a practitioner or when laboratories belonging to the health care system of Ukraine are overloaded, which leads to prolongation of the time of RT-PCR in real time or other NAATs by 48–72 hours. For best results, SIEVE TEST COVID-19 Ag tests should be performed within the first 5–7 days after the onset of symptoms of coronavirus infection.

The rapid test “CITO TEST COVID-19” for the qualitative detection of IgM and IgG antibodies to the SARS-CoV-2 coronavirus should be used for diagnostic purposes in cases where real-time RT-PCR or any other NAAT was not performed or a negative or uncertain result was obtained. It can be used to establish the presence of specific antibodies to SARS-CoV-2 in medical personnel working

with patients with COVID-19 (determination of IgM, IgG), in epidemiological studies to examine the population in order to determine persons who have been ill and/or have had an infection without pronounced clinical manifestations of the disease. As a result of serological studies using “CITO TEST COVID-19” it is possible to identify potential donors of convalescent plasma (one of the methods of treatment of severe COVID-19 patients) and retrospectively assess the dynamics of formation of population immunity. “CITO TEST COVID-19” is a rapid immunochromatographic test for the qualitative detection of IgM and IgG antibodies against SARS-CoV-2 coronavirus in human whole blood, serum and plasma for the diagnosis of coronavirus infection. It is intended for professional in vitro diagnostic use. It is recommended that the test be used from the second week after the first symptoms of coronavirus infection. The material for testing the presence of antibodies can be capillary blood, venous blood, serum or plasma. Specimen collection, preparation and testing are described in detail in the instructions for use. The principle of the method is as follows: after the introduction of a test specimen containing IgM and IgG class antibodies to the virus and a buffer solution onto the test membrane in the “S” zone, during its passage to the “T” zone, interaction with the antigens of the SARS-CoV-2 virus occurs.SARS-CoV-2 virus adsorbed on the nitrocellulose membrane and labeled with colored particles, resulting in the formation of an immune complex. If the specimen does not contain antibodies to SARS-CoV-2 coronavirus, no colored lines appear in the "T" region and no immune complex is formed, indicating a negative test result. The colored line that always appears in the control region "C" is a control of the procedure, indicating that a sufficient amount of specimen has been used and that filling of the membrane capillaries has occurred. The intensity of the staining of the test lines may vary depending on the concentration of antibodies to the SARS-CoV-2 virus in the sample. Therefore, the appearance of a colored line of any intensity in the area of the test lines should be considered as a positive result. The reason for an invalid test result may be an

insufficient amount of the blood sample being tested, non-compliance with the procedure and expiration dates, storage conditions, etc. If an invalid test result is obtained, it is necessary to repeat the study using another test cassette. The rapid test “CITO TEST COVID-19” should be used only for the detection of IgG and IgM antibodies to the SARS-CoV-2 virus in samples of whole blood, plasma and serum for the purpose of diagnosing coronavirus infection. With the CITO test COVID-19, it is not possible to determine either the quantitative content or the degree of increase in the concentration of IgG and IgM antibodies to SARS-CoV-2. It is important to emphasize that a positive result of the "CITOTEST COVID-19" test, which indicates the presence of antibodies to SARS-CoV-2 in blood samples, should be taken into account in conjunction with other information, including clinical information, available to the doctor. If the test result is negative and symptoms of COVID-19 are present, further testing with other laboratory methods is recommended. A negative result does not rule out infection with SARS-CoV-2 coronavirus. A negative result is also possible if the titer of antibodies to SARS-CoV-2 in the test blood samples is lower than the declared operational characteristics, or if the antibodies have not yet appeared in the body of an infected person at the time of sampling. In general, already developed diagnostic algorithms can be used for the effective use of CITO TEST rapid immunochromatographic tests.

4.2 Theoretical questions for the lesson:

1) Rapid tests for the detection of COVID-19.

2) The difference between antigen and antibody detection in the diagnosis of COVID-19.

3) Advantages and disadvantages of rapid tests.

4.3 Practical tasks to be performed in the classroom

Typical example

The patient consulted a family doctor for cough, headache, and fever up to 37.3 °C. He associates his condition with the outbreak of COVID-19 at work.

Questions to consider:

1) What diagnostic method should be used?

2) What is the procedure in case of a negative result of the rapid test in the presence of characteristic symptoms?

Answer:

1) In this case, a rapid test for SARS-COV-2 viral antigen is recommended.

2) If the test result is negative and symptoms of COVID-19 are present, additional testing with other laboratory methods is recommended. A negative result does not exclude the possibility of SARS-CoV-2 coronavirus infection.

Task 1

A patient with COVID-19 was diagnosed with a rapid test for the determination of the antigen of the SARS-COV-2 virus, which showed a positive result.

Questions to consider:

1) What is the doctor’s plan of action?

2) Is further confirmation by other tests required?

Task 2

A patient who came to the family doctor with complaints of general weakness, cough and fever up to 37.5 °C was diagnosed with a rapid test for the determination of the SARS-COV-2 virusantigen, which gave a negative result.

Questions to consider:

1) What is the doctor's planof action?

2) Is further confirmation by other tests required?

Task 3

The patient consulted his family doctor for cough, headache, and fever to 37.8 °C. According to the patient, it is known that his wife and daughter had similar symptoms 10 days ago.

Questions to consider:

1) Is it appropriate to use rapid tests to diagnose COVID-19 in this case?

2) What is the incubation period for COVID-19?

5 Content of the topic

At the practical lesson, students get acquainted with the modern approach to the early diagnosis of COVID-19 with rapid tests. They receive information about the types of rapid tests, how they are carried out and how to interpret the results of this study.

6 Self-assessment questions:

1) The length of the COVID-19 incubation period.

2) Indications for rapid tests to diagnose COVID-19.

3) What materialsare used for rapid tests to diagnose COVID-19.

4) The difference between antigen and antibody detection in the diagnosis of COVID-19.

TOPIC 7. PRINCIPLES AND APPROACHES TO THE TREATMENT OF PATIENTS WITH COVID-19 ON AN OUTPATIENT BASIS

Duration – 2 hours.

1 Relevance of the topic

The relevance of coronavirus disease is an extremely serious problem in the context of the global pandemic. SARS was called SARS because of its similarity in clinical symptoms to already known atypical pneumonias. The new respiratory disease was called coronavirus disease 2019 – COVID-19. It is caused by the SARS-CoV-2 coronavirus.

Today, the topic of coronavirus is perhaps the most common in society. In particular, the current treatment of patients with COVID-19 on an outpatient basis.

2 Specific objectives

2.1 The student should know:

- Who receives outpatient treatment.
- Drugs and doses used in treatment.
- Basic principles of patient management.
-

2.2 The student should be able to:

- Support the final diagnosis by performing a differential diagnosis.
- Write prescriptions.
- Identify patients who need outpatient treatment.
- Prescribe treatment for outpatients.

3 Basic knowledge, skills, and abilities necessary to study the topic (interdisciplinary integration)

Table 15

Previous disciplines	Skills acquired
Microbiology	Knowledge of the biological properties of the pathogen, methods of specific diagnosis, preventive measures. Evaluation of the results of specific diagnostic methods
Physiology	Knowledge of the physiological norms of the respiratory system; norms of laboratory parameters and their assessment
Pathophysiology	Knowledge of the pathogenesis of impaired function of the respiratory system in pathological lesions
Epidemiology	Knowledge of the links of the epidemic process (source of infection, mechanism of transmission, susceptible organism), prevalence of the disease
Propaedeutic of Internal Diseases	Knowledge of the main stages and methods of clinical examination of the patient. Collection of anamnesis, clinical examination of the patient, identification of pathological symptoms and syndromes, analysis of the data obtained
Pharmacology	Prescribe drugs: antipyretic, antiviral, antibacterial

4 Tasks for independent work in preparation for classes

4.1 A list of basic terms, parameters, characteristics that the student must learn in preparation for the lesson

Table 16

Term	Definition
1	2
Evidence-based medicine	The conscientious, accurate, and informed use of the best clinical trial results to select a treatment for a particular patient

Continuation of Table 16

1	2
Outpatient treatment	This is the care a patient receives without hospitalization
SARS-CoV-2	Severe Acute Coronavirus Coronavirus-2 associated with Severe Acute Respiratory Syndrome

Outpatient care for patients with suspected COVID-19

Patients with a mild form of the disease who do not belong to the risk groups for complications of patients with COVID-19 are recommended to be treated on an outpatient basis (at home). Recovering patients who no longer need round-the-clock supervision should also be transferred to outpatient treatment.

1 It is forbidden to provide medical care and care on an outpatient basis to **patients who are at risk of complications**:

- Severe chronic diseases of the lungs and cardiovascular system.
- Renal failure.
- Immunosuppressive states (primary and secondary immunodeficiencies).
- Severe allergic diseases or conditions.
- Autoimmune diseases, **as well as symptoms characterizing a moderate to severe course, such as**:
- Suffocation.
- Difficulty breathing.
- An increase in the frequency of respiratory movements greater than the physiological norm.
- Hemoptysis.
- Gastrointestinal symptoms (nausea, vomiting, diarrhea).
- Changes in mental status (confusion, lethargy).

2 The decision to provide medical care in an outpatient setting is made by a primary care physician after a clinical evaluation

of the patient's condition and an assessment of the safety of the patient's home environment through a survey.

A mild course of the disease is characterized by:

- Low-grade fever (up to 38 °C), well controlled with antipyretics.
- Runny nose.
- Dry cough without signs of respiratory failure (such as difficulty breathing, increased respiratory rate, hemoptysis).
- Absence of gastrointestinal manifestations (nausea, vomiting and/or diarrhea).
- Absence of status changes (decreased consciousness, lethargy).

Respiratory complications in COVID-19 usually develop in the second week of illness, so patients should be actively monitored, re-evaluation (including physical) is recommended to be carried out during this period:

- If the patient has contacted the family doctor by means of remote communication: the family doctor assesses the patient's condition according to the classification of the severity of the disease;
- If the patient has mild symptoms of the course of the disease, the doctor gives recommendations for self-isolation, treatment in case of aggravation of the condition.
- If the patient has a severe course of the disease, the primary care physician recommends calling emergency medical services by dialing 103.

3 Patients in a state of convalescence who do not require round-the-clock supervision are transferred to outpatient treatment.

4 Justification of the decision on outpatient treatment shall be entered in the form of primary records No. 025/o "Medical Record of Outpatient No. ____", approved by the Order of the Ministry of Health of Ukraine No. 110 of February 14, 2012, registered in the Ministry of Justice of Ukraine on April 28, 2012 under No.

661/20974 (hereinafter referred to as the Medical Card of an Outpatient).

5 Healthcare professionals (physicians/nurses) monitor the current status of patients and contacts. The monitoring method is chosen individually (e.g. daily visits, telephone surveys). Monitoring data are entered into the outpatient's medical record.

6 Patients and co-residents should be informed:

- The need to maintain personal hygiene.
- Basic measures for the prevention of infection.
- Safe approaches to care.
- Restrictions on household contacts.
- Methods of communication with medical personnel (for example, indicate the phone number to call in case of deterioration of the condition).
- Ways of transporting the patient to the outpatient clinic, if necessary (for example, to determine the time and entrance to the institution).

7 Healthcare workers and household members providing medical care at the place of residence/stay must use personal protective equipment.

8 If a contact person has symptoms, health care providers will assess the condition and determine the need for hospitalization or outpatient care. If it is decided that hospitalization is necessary, a series of measures (Appendix 11) will be taken to limit the further spread of the disease.

9 **Hospitalization according to clinical criteria is indicated for patients with suspected/confirmed COVID-19 in the following cases**:

- Moderate to severe condition – signs of pneumonia and/or respiratory failure (increased respiratory rate above the physiologic norm, hemoptysis, $SpO_2$when measured with a pulse oximeter < 93 %) in the presence of radiologically confirmed pneumonia.
- Availability of clinical and instrumental data of acute respiratory distress syndrome (ARDS).

- Presence of clinical and laboratory findings of sepsis and/or septic shock (systemic inflammatory response syndrome).
- Presence of clinical and laboratory findings of organ/systemic insufficiency, other than respiratory.
- Patients, regardless of the severity of the condition, who are at risk of complications: severe arterial hypertension, decompensated diabetes mellitus, immunosuppressive conditions, severe chronic pathology of the respiratory and cardiovascular systems, renal failure, autoimmune diseases, severe allergic diseases, cerebrovascular diseases in the stage of decompensation), oncological diseases.
- Patients, regardless of the severity of the condition, in whom there is an increase in temperature above 38 °C, which is difficult to correct (temporary, no more than 1–1.5 hours decrease against the background of taking antipyretic drugs, followed by its increase).

10 If self-isolation is not possible (e.g. living in a military barracks), according to epidemiological criteria, isolation in a separate facility with individual accommodation (e.g. hotels, dormitories) determined by the decision of local authorities is indicated. Hospitalization according to epidemiological criteria in health care facilities providing 24-hour in-patient medical care is not recommended.

Treatment:

- Provide the patient with information on good nutrition and appropriate rehydration.
- Symptomatic treatment with antipyretics (paracetamol, ibuprofen, etc.) for fever and pain. Disclaimer: Do not take more than 1g of paracetamol per dose or more than 3g per day. Avoid the use of high doses of ibuprofen (≥2400 mg per day) in patients with uncontrolled hypertension, congestive heart failure (NYHA functional class II-III), diagnosed coronary artery disease, peripheral arterial disease and/or cerebrovascular disease, chronic kidney disease stage III-V. Low doses of ibuprofen (up to 1200 mg per day) do not increase the risk of cardiovascular thrombotic events.

- Consider direct-acting antivirals for at-risk groups with mild to moderate disease.

Risk groups: age >65 years and the presence of severe comorbidities in the stage of decompensation - decompensated diabetes mellitus, severe chronic pathology of the respiratory and cardiovascular systems, immunosuppressive conditions, renal failure.

Diagnostic criteria for moderate severity. In addition to the signs characteristic of mild severity:

- Clinical signs of pneumonia (fever, cough, labored and rapid breathing (for age less than 2 months - RR 60, from 2 to 11 months - RR 50, from 1 to 5 years - RR 40).

- Pulse oximeter reading for oxygen saturation is between 93 % and 95 %.

Treatment:

- Provide the patient with information on good nutrition and appropriate rehydration.

- Symptomatic treatment with antipyretics (paracetamol, ibuprofen, etc.) for fever and pain. Disclaimer: Paracetamol. Do not take more than 1g per dose or more than 3g per day. Avoid the use of high doses of ibuprofen (≥2400 mg per day) in patients with uncontrolled hypertension, congestive heart failure (NYHA functional class II-III), diagnosed coronary artery disease, peripheral arterial disease and/or cerebrovascular disease, chronic kidney disease stages III-V. Low-dose ibuprofen (up to 1200 mg per day) does not increase the risk of cardiovascular thrombotic events.

- Do not use corticosteroids to treat COVID-19 in patients who do not require oxygen support.

- Antibacterial agents are contraindicated and prescribed only in the presence of laboratory-confirmed concomitant bacterial infection or in case of reasonable suspicion of it.

- If you have difficulty breathing, it is recommended that you lie on your stomach, as this helps to open up the dormant alveoli and increase the amount of oxygen in the blood.

- Consider favipiravir on the first day - a loading dose of 1600 mg 2 times a day, then 600 mg 2 times a day. According to

epidemiological observations, it is recommended to prescribe favipiravir in the first 5 days after the onset of the first symptoms of the disease. The duration of treatment is 5-14 days. Caution: Favipiravir is teratogenic to the foetus and is contraindicated during pregnancy. It should also not be used during lactation and hypersensitivity to the components that make up this drug. The drug is prohibited for use in women and men without the use of contraception. It is recommended to use reliable contraception for at least 7 days after the last dose of the medication.

- Consider direct-acting antivirals for at-risk groups with mild to moderate disease.

4.2 Theoretical questions for the lesson:

1) Therapeutic tactics for mild severity.

2) Therapeutic tactics for moderate severity.

3) Grades of severity of coronavirus infection and their characteristics.

4) Indications for prescribing antibacterial drugs.

4.3 Practical tasks to be performed in the classroom

Typical example:

A 56-year-old man consulted a doctor with complaints of dry cough, fever up to 38.2°C, headache, joint and muscle pain. On x-ray, pneumonic infiltrates are observed.

Questions to consider:

1) Formulate the clinical diagnosis.

2) Assign an examination plan indicating the expected results.

3) Prescribe a treatment plan, specify doses, route of administration and duration of administration.

Answer:

1) Coronavirus disease caused by the causative agent SARS-CoV-2 (PCR, Omicron strain), community-acquired pneumonia of the lower lobe of the right lung, clinical group II, moderate course, DN 0 Art.

2) PCR is a specific diagnostic method. Complete blood count, blood chemistry, pulse oximetry, CT scan of the lungs and pleural cavities.

3) Symptomatic therapy:

Ibuprofen 400 mg 3 times a day orally

Ambroxol 1 tablet 3 times a day for 3 days, then 1 tablet 2 times a day

Task 1

A 45-year-old woman consulted a doctor with complaints of weakness, cough, sore throat, fever up to 37.5°C. A CT scan of the chest cavity revealed foci of "frosted glass".

Questions to consider:

1) Formulate the clinical diagnosis

2) Assign an examination plan indicating the expected results

3) Prescribe a treatment plan, doses, route of administration, and duration of use.

Task 2

Patient K., 23 years old female, went to the family doctor with complaints of muscle pain, headache, cough, and fever up to 37.3 °C. A few days ago, she was in contact with a patient with COVID-19. Respiratory rate – 18 breaths per min. SpO_{2} - 97 %.

Questions to consider:

1) Formulate the clinical diagnosis

2) Assign an examination plan indicating the expected results

3) Prescribe a treatment plan, doses, route of administration, and duration of use.

Task 3

B, a 25-year-old man, complains of a cough with dyspnoea, shortness of breath on exertion, and a temperature of up to 38 °C. According to the CT data, the subpleural foci of sealing are like "frosted glass".

Questions to consider:

1) Formulate the clinical diagnosis

2) Assign an examination plan indicating the expected results

3) Prescribe a treatment plan, doses, route of administration, and duration of use.

5 Content of the topic

At the practical lesson, students get acquainted with the symptoms characteristic of the mild and moderate course of coronavirus disease. Receive information about possible outpatient treatment regimens for this disease.

6 Self-assessment questions

1) Define evidence-based medicine.
2) Who is eligible for outpatient treatment?
3) What is the treatment for mild disease?
4) What treatment is given for moderate severity?
5) What are the indications for antibiotic therapy?

TOPIC 8. PRINCIPLES AND APPROACHES FOR INPATIENT MANAGEMENT OF PATIENTS WITH COVID-19

Duration – 2 hours.

1 Relevance of the topic

The detected SARS-CoV-2 – Betacoronavirus B caused an outbreak of coronavirus infection, which was first reported on December 31, 2019 in the city of Wuhan, China. By March 2020, the coronavirus that causes a new type of pneumonia, which is widespread around the world, covered 114 countries and was characterized by the WHO as a COVID-19 pandemic.

As of January 2023, more than 674 million cases have been reported worldwide; More than 6.7 million people have died and more than 646.8 million have recovered. In particular, more than 5 million infections were diagnosed in Ukraine throughout the pandemic; about 111 thousand people died and more than 5 million recovered. Statistics for the Sumy region for January 2023: 211 thousand cases detected, of which more than 3 thousand were fatal, and more than 207 thousand recovered.

2 Specific objectives.

2.1 The student should know:

- Indications for inpatient treatment with COVID-19.
- Criteria for the severity of coronavirus infection.
- Basic principles of treatment for SARS-CoV-2.

1.2 The student should be able to:

- Substantiate the final diagnosis by conducting a differential diagnosis.
- Prescribe adequate therapy for coronavirus infection (etiotropic, pathogenetic, symptomatic).
- Provide inpatient medical care for COVID-19 of varying severity (moderate, severe, critical).

- Provide emergency care for adults with coronavirus infection.
- Provide recommendations on regimen, diet, examination, supervision during the convalescence period.
- Conduct a therapeutic and diagnostic search according to the principles of evidence-based medicine.

3 Basic knowledge, skills, and abilities necessary to study the topic (interdisciplinary integration)

Table 17

Previous disciplines	**Skills acquired**
Microbiology	Knowledge of the biological properties of the pathogen, methods of specific diagnosis, preventive measures. Evaluation of the results of specific diagnostic methods
Physiology	Knowledge of the physiological norms of the respiratory system; norms of laboratory parameters and their assessment
Pathophysiology	Knowledge of the pathogenesis of impaired function of the respiratory system in pathological lesions
Epidemiology	Knowledge of the links of the epidemic process (source of infection, mechanism of transmission, susceptible organism), prevalence of the disease
Clinical pharmacology	Knowledge of pharmacokinetics and pharmacodynamics, indications, contraindications and side effects of symptomatic and pathogenetic therapies
Propaedeutic of Internal Diseases	Knowledge of the main stages and methods of clinical examination of the patient. Collection of anamnesis, clinical examination of the patient, identification of pathological symptoms and syndromes, analysis of the data obtained

Inpatient treatment is subject to patients with:

– Severe chronic diseases of the lungs and cardiovascular system.

– Renal failure.

– Immunosuppressive conditions (primary and secondary immunodeficiencies).

– Severe allergic diseases or conditions.

– Autoimmune diseases.

– Symptoms characterizing moderate, severe, and critical course of the disease.

Table 18 - Severity criteria

Medium	**Severe ≥1**	**Critical ≥1**
• RR > 22/min. • SpO_2 < 95 %. • t 0 > 38 °C • Serum CRP > 10 mg/l. • Pneumonia (confirmed on CT). • Shortness of breath during physical exertion	• HR ≥30/min. • SpO_2 ≤93 %. • Ratio PaO_2/FiO_2<300. • Lung infiltrates >50 % of the lung field within 24-48 hours. • SBP <90 mmHg or DAT <60 mmHg. • Diuresis <20 ml/h. • Arterial blood lactate >2 mmol/l. • qSOFA> 2 points; • Decreased level of consciousness and restlessness	• Acute respiratory failure with the need for respiratory support (invasive ventilation). • Septic shock. • Altered consciousness. • Multiple organ failure

Inpatient management of patients with COVID-19

Rationale. Inpatient treatment is indicated for moderate to severe COVID-19:

1 Hospitalization according to clinical criteria is indicated for patients with suspected/confirmed COVID-19 in the following cases:

- Moderate to severe condition – signs of pneumonia and/or respiratory failure (increased respiratory rate above the physiological norm, hemoptysis, SpO_2 when measured with a pulse oximeter <93 %) in the presence of radiologically confirmed pneumonia.

- Availability of clinical and instrumental data of acute respiratory distress syndrome (ARDS).

- Presence of clinical and laboratory findings of sepsis and/or septic shock (systemic inflammatory response syndrome).

- Presence of clinical and laboratory data of organ / systemic insufficiency, other than respiratory.

- Patients, regardless of the severity of the condition, who are at risk of complications: severe arterial hypertension, decompensated diabetes mellitus, immunosuppressive conditions, severe chronic pathology of the respiratory and cardiovascular systems, renal failure, autoimmune diseases, severe allergic diseases, cerebrovascular diseases in the stage of decompensation), oncological diseases.

- Patients, regardless of the severity of the condition, who have an increase in temperature above 38 °C, which is difficult to correct (temporary, no more than 1-1.5 hour decrease against the background of taking antipyretic drugs, followed by its increase).

2 When a patient is admitted to a health care institution, medical triage is carried out, namely:

- Early recognition of patients with SARS associated with COVID-19.

- The severity of the disease is assessed.

- If necessary, medical care measures are initiated.

3 Infection prevention and control measures shall be carried out in accordance with the provisions set out in Annexes 6 and 8.

4 Patients with SARS and GDRS, hypoxemia, or shock due to confirmed COVID-19 should receive immediate supportive care and monitoring.

5 All areas where patients with severe COVID-19 are cared for should be equipped with:

- Pulse oximeters,
- Functioning oxygen supply systems, and
- Disposable oxygen interfaces, namely nasal cannulas, face masks with/without reservoir bag.

6 Patients with severe confirmed COVID-19 are provided with monitoring and correction of therapeutic measures depending on concomitant pathological conditions.

7 Sampling for laboratory diagnostics is carried out taking into account the clinical picture using PPE, transportation with the appropriate referral is carried out to the laboratory center of the Ministry of Health of Ukraine according to administrative-territorial affiliation.

8 In patients with confirmed COVID-19, if oxygen therapy (SpO_2 < 90 %) is ineffective, ARDS and hypoxemic respiratory failure are evaluated and, if necessary, treated accordingly.

9 Patients with COVID-19 should be continuously monitored for signs of septic shock (systemic inflammatory response syndrome) and, if necessary, treated accordingly.

10 All patients with COVID-19 are provided with prevention of general complications.

11 Pregnant women with suspected COVID-19, regardless of gestational age, shall be admitted to a maternity hospital designated by the structural health care unit of the relevant administrative region.

Pregnant women with suspected COVID-19 shall be treated according to the above standards, taking into account the standards of pregnancy management. The use of medicines outside their instructions should be based on a risk-benefit analysis (potential benefit for the mother and safety for the foetus) and should only be prescribed by decision of a medical committee (Medical Advisory Committee) consisting of at least:

– Deputy Chief Physician
– Obstetrician-Gynaecologist

– Paediatrician
– General Practitioner
– Infectious Diseases Physician (if necessary)
– Radiologist (if necessary)
– Anaesthesiologist

The decision to recommend an emergency delivery and abortion is made by the above-mentioned Medical Council, taking into account the following factors:

1) Gestational age
2) The mother's condition
3) Fetal stability

12 The decision to discharge the patient is made by the attending physician on the basis of the absence or reduction of clinical signs of the disease, a steady tendency towards normalisation of laboratory parameters (haemogram, CRP, ALT, AST, urea, creatinine) and a negative result of laboratory tests. If, despite the absence of clinical and laboratory signs of an active infectious process, fragments of the pathogen's RNA are detected by PCR (positive or equivocal result), the patient may be discharged home for self-isolation under the supervision of a family doctor.

Testing to decide whether a patient should be discharged should begin no earlier than the 5th day of clinical improvement in the course of the disease.

Treatment for moderate severity

Main:

- Low molecular weight heparin unless contraindicated.

ENOXAPARIN (prophylactic dose of 4000 anti-Xa MO (40 mg; 0.4 mL) once daily for patients with creatinine clearance >30 mL/min. If creatinine clearance is 15-30 mL/min, the dose should be halved to 2000 anti-Xa MO (20 mg; 0.2 mL) once daily.

Additional:

a) REMDESIVIR (antiviral, nucleoside analogue).

For the first 5 days after the onset of disease symptoms. On the first day, a loading dose of 200 mg once daily (IV over 30-120 minutes), from the second day a maintenance dose of 100 mg once daily (IV over 30-120 minutes). The treatment period is 5 days.

Contraindications:

- The level of alanine aminotransferase (ALT) in the blood is more than five times higher than the upper limit of normal.
- Elevated ALT is accompanied by signs or symptoms of hepatitis or elevated conjugated bilirubin, alkaline phosphatase, or international normalized ratio (INR).
- Estimated glomerular filtration rate (eGFR) <30ml/min/1.73 m^2.
- Remdesivir is not allowed to be used outside the hospital.

b) **FAVIPIRAVIR** (antiviral drug, RNA polymerase inhibitor).

According to epidemiological observations, it is recommended to prescribe favipiravir in the first 5 days after the appearance of the first symptoms of the disease. On the first day - a loading dose of 1600 mg 2 times a day, then - 600 mg 2 times a day. The course of treatment lasts 5-14 days.

Contraindications:

- Pregnancy, lactation.
- Hypersensitivity to the components that make up this medicinal product.
- Women and men without the use of contraception.

Treatment for severe disease

Main:

a) Optimal supportive care in a hospital room (or intensive care unit/ward).

b) Oxygen support, starting from 5 l/min, adjust the flow rate until the target SpO_2 level ≥ 90 % is reached.

c) Systemic corticosteroids orally or intravenously. The duration of treatment is up to 7-10 days (or until discharge from a health care facility, if it occurs earlier).

- DEXAMETHASONE (6 mg once/day is equivalent (in terms of glucocorticoid effect)).
- METHYLPREDNISOLONE (32 mg; 8 mg every 6 hours or 16 mg every 12 hours).
- HYDROCORTISONE (150 mg; 50 mg every 8 hours).

d) Low molecular weight heparin, unless contraindicated.

- ENOXAPARIN (prophylactic dose of 4000 anti-Xa MO (40 mg; 0.4 ml) once a day for patients with creatinine clearance >30 ml/min. With creatinine clearance of 15 to 30 ml/min, the dose should be halved with 2000 anti-Xa MO (20 mg; 0.2 ml) once a day.

e) In case of addition of bacterial flora – antibacterial or antifungal agents in accordance with local epidemiology.

Additional:

a) **REMDESIVIR** (antiviral, nucleoside analogue). In the first 5 days from the onset of the first manifestations of the disease. On the first day, a loading dose of 200 mg once a day (IV for 30-120 minutes), from the second day, a maintenance dose of 100 mg once a day (IV for 30-120 minutes). The duration of treatment is 5 days, for patients who do not require mechanical ventilation or extracorporeal membrane oxygenation. If there is no effect or if the patient is on mechanical ventilation or ECMO, the course of treatment is 10 days.

Contraindications:

- The level of alanine aminotransferase (ALT) in the blood is more than 5 times higher than the upper limit of normal.
- Elevated ALT is accompanied by signs or symptoms of liver inflammation or elevated conjugated bilirubin, alkaline phosphatase, or international normalized ratio (INR);
- Estimated glomerular filtration rate (eGFR) <30ml/min/1.73 m2;
- It is not allowed to use the drug outside the hospital.

b) 10 % HUMAN IMMUNOGLOBULIN IS NORMAL.

For intravenous administration at a dose of 0.8-1.0 g/kg once a day for 2 days from the onset of deterioration (course dose 1.6-2.0 g/kg ideal body weight). The frequency of infusions and the speed of administration are determined by the doctor depending on the patient's condition. The daily dose may be adjusted to ensure that the maximum daily volume of fluid therapy is not exceeded.

Indications:

- Severe course of the disease, accompanied by increasing phenomena of intoxication syndrome and respiratory failure;
- Negative laboratory dynamics, namely: a progressive increase in the level of C-reactive protein over 50 units, progressive absolute lymphopenia, an increase in the level of ferritin and IL-6.

c) **TOCILIZUMAB** (immunosuppressant, monoclonal antibody to interleukin-6).

With the progression of the disease, it is prescribed no earlier than the 7th day from the onset of clinical symptoms or taking into account radiological changes. The recommended dose is 8 mg/kg for a single IV infusion. The total dose should not exceed 800 mg. Tocilizumab should be diluted in 100 mL of 0.9% NaCl and administered over 1 hour.

Indications:

- Interstitial pneumonia with acute respiratory failure, progressive respiratory failure, the need to connect to non-invasive or invasive ventilation, the presence of extrapulmonary organ damage;
- Negative laboratory dynamics, namely: an increase in the level of C-reactive protein, D-dimer, ferritin and IL-6.

Contraindications:

- The level of ALT/AST in the blood is more than 5 times higher than normal.
- Neutrophil count <500.
- Platelet count <50,000.
- Sepsis not caused by SARS-CoV.
- Increased level of procalcitonin by more than 2 times.
- Presence of comorbid conditions.

- It is not allowed to use the drug outside the hospital.

4) TOFACITINIB (Janus kinase inhibitor).

With progression of the course of the disease and failure of ACS, 10 mg twice daily for 14 days with continuation of ACS therapy.

Treatment in the critical course of the disease

Main:

a) Optimal supportive care in the intensive care unit/ward.

b) Mechanical ventilation.

c) Low molecular weight heparin, unless contraindicated.

- ENOXAPARIN (standard prophylactic doses, and in case of low risk of bleeding - high prophylactic doses of 4000 anti-Xa MO (40 mg; 0.4 ml) twice daily for patients with creatinine clearance >30 ml/min. For patients with a creatinine clearance of 15-30 mL/min, a reduced dose of 4000 anti-Xa MO (40 mg; 0.4 mL) once daily is recommended.
- UNFRACTIONATED HEPARIN (in case of severe renal dysfunction (creatinine clearance)).
- NADROPARIN, DALTEPARIN, BEMIPARIN (dosage according to the instructions for medical use).

d) Systemic intravenous corticosteroids. The duration of treatment is up to 7-10 days. In case of progression of respiratory failure and laboratory signs of inflammation, higher doses of systemic corticosteroids may be considered according to the instructions for medical use.

- DEXAMETHASONE (6 mg once/day is equivalent (in terms of glucocorticoid effect)).
- METHYLPREDNISOLONE (32 mg; 8 mg every 6 hours or 16 mg every 12 hours).
- HYDROCORTISONE (150 mg; 50 mg every 8 hours).

e) Special prophylaxis and treatment of acute respiratory distress syndrome.

f) Prevention of further pulmonary fibrosis.

g) In case of addition of bacterial flora – antibacterial or antifungal agents in accordance with local epidemiology. Tracking of secondary bacterial and opportunistic infections (Aspergillus).

Additional:

a) **TOCILIZUMAB.**

b) 10 % **HUMAN IMMUNOGLOBULIN NORMAL.**

Indications, contraindications and administration route see above.

4 Tasks for independent work in preparation for class

4.1 A list of basic terms, parameters, characteristics that the student must learn in preparation for the lesson

Table 19

Term	Definition
1	**2**
COVID-19	An infectious disease with an airborne transmission mechanism caused by the SARS-CoV-2 coronavirus
Epidemiologically related case	Such a suspicious case when an adequate laboratory examination has not yet been performed, but the patient has had contact with another laboratory-confirmed case of COVID-19 14 days before the onset of symptoms
Probable case of illness	A patient with suspected COVID-19 whose laboratory test for SARS-CoV-2 is questionable, or has tested positive for an antigen common to all beta coronaviruses (pancoronavirus antigen), and there is no laboratory evidence of the presence of other (non-coronavirus) respiratory pathogens
Confirmed case	A person with laboratory-confirmed COVID-19, regardless of the presence or manifestation of clinical signs and symptoms

Continuation of Table 19

1	2
qSOFA	A scale designed to determine the risk of developing organ-systemic dysfunction, predict the outcome of a critical condition and determine the location of medical care
Invasive ventilation	Application of ventilation through an invasive airway

4.2 Theoretical questions for the lesson:

1) What are the indications for hospitalization with coronavirus infection?

2) Main clinical criteria for COVID-19.

3) Degrees of infection severity and its differences.

4) Principles of treatment depending on the course of the disease.

5) The place of antiviral drugs in the treatment of COVID-19.

6) Indications for oxygen therapy and mechanical ventilation.

7) Indications for antimicrobials.

4.3 Practical tasks to be performed in the classroom

Typical example:

A 19-year-old patient came to the doctor with complaints of headache, cough, shortness of breath, fever up to 38.5 °C for 3 days, muscle pain, feeling "as if the muscles are lagging behind the bones". An objective examination revealed: blue spots on the toes. RR – 31/min., SpO_2– 92 %. History: diabetes mellitus, insulin-dependent.

Questions to consider

1) Formulate the clinical diagnosis.

2) What are the methods for diagnosing this disease?

3) Prescribe treatment, doses, route of administration and duration of use.

Answer:

1) Coronavirus disease caused by the causative agent SARS-CoV-2 (PCR, Delta strain), community-acquired pneumonia

of the lower lobe of the left lung, clinical group III, severe course. DN II Art.

2) PCR is a specific diagnostic method. Complete blood count, biochemical blood test, pulse oximetry, CT, ultrasound of the lungs and pleural cavities.

3) Anticoagulant therapy - enoxaparin 0.4 ml once a day subcutaneously.

4) Corticosteroid therapy – dexamethasone 6 mg once a day intravenously.

5) Antibiotic therapy - amoxicillin 0.5 g 2 times a day orally, the time between doses is 8 hours.

6) Antiviral therapy - remdesivir, on the first day - a loading dose of 200 mg once a day (intravenously within 30 - 120 minutes), from the second day - a maintenance dose of 100 mg once a day (intravenously within 30 - 120 minutes). The treatment period is 5 days.

Task 1

Patient K., 26 years old, was taken to the infectious diseases department by an emergency medical team with signs of respiratory failure, confusion, impaired diuresis. Blood pressure – 80/50, HR – 37/min. Cito-test for COVID-19 positive.

Questions to consider:

1) Formulate the clinical diagnosis.

2) What are the diagnostic methods and expected changes?

3) Prescribe treatment, indicate the doses, method and frequency of administration, duration of use.

Task 2

Patient N., 30 years old, consulted a family doctor with complaints of cough, fever up to 38.5 °C, accompanied by chills, impaired sense of smell and taste, shortness of breath. I took ibuprofen to reduce my fever. CT scan of the lungs shows multiple bilateral partial and subsegmental ground-glass opacities.

Questions to consider:

1) Formulate the clinical diagnosis.

2) What are the diagnostic methods and expected changes?

3) Prescribe treatment, indicating doses, route and frequency of administration, duration of use.

Task 3

A 40-year-old woman came to the doctor with complaints of cough, shortness of breath during physical exertion, fever up to 38.0 °C, heart rate - 23/min., SpO_2 – 95 %. According to the PCR results, the diagnosis was established: coronavirus disease.

Questions to consider:

1) What are the additional diagnostic methods and expected changes?

2) Prescribe treatment, indicate doses, method and frequency of administration, duration of use.

3) List the measures to prevent this disease.

5 Content of the topic

At the practical lesson, students get acquainted with the symptoms characteristic of the moderate, severe and critical course of coronavirus disease. Receive information about possible schemes of inpatient treatment of this disease.

6 Self-assessment questions

1) Define the term “coronavirus infection”.

2) What are the indications for hospitalization?

3) List the criteria for the severity of moderate, severe, and critical disease.

4) Primary and complementary treatment in the moderate course of the disease.

5) Primary and complementary treatment for severe disease.

6) Primary and complementary treatment in the critical course of the disease.

7) The role of antiviral therapy in the treatment of COVID-19.

8) Contraindications to the use of antiviral drugs.

TOPIC 9. ANTIVIRAL THERAPY AND OXYGEN SUPPORT FOR CORONAVIRUS INFECTION

Duration – 2 hours.

1) Relevance of the topic

Today, the treatment of patients with COVID-19, which caused an unprecedented pandemic, remains difficult, since drugs that have a detrimental effect on the virus are at the stage of development and testing. Clinical trials of more than 350 medicines are underway in the world. The search for effective drugs is facilitated by the WHO, which in March 2020 launched the global clinical trial program "Solidarity" [1]. The number of countries that have joined the implementation of this program continues to increase, and both new drugs and those already tested for other diseases are subject to clinical approbation.

In most cases, the disease has a mild course and goes away on its own, even without medical intervention. The decision regarding medical care in an outpatient or inpatient setting is made after a clinical assessment of the patient's condition and taking into account home safety.

2) Specific goals

2.1 The student should know:

- What is coronavirus infection.
- Classification of antiviral drugs.
- Antiviral therapy for coronavirus infection.
- Oxygen support for coronavirus infection.

2.2 The student should be able to:

- Prescribe antiviral therapy for patients with coronavirus infection.
- Provide oxygen support for patients with coronavirus infection.

3 Basic knowledge, skills, and abilities necessary to study the topic (interdisciplinary integration)

Table 20

Previous disciplines	Skills acquired
Pharmacology	The concept of antiviral drugs: classifications, mechanism of action, pharmacokinetics, pharmacodynamics
Infectious Diseases	The concept of coronavirus infection: definition, etiology, pathogenesis, classification, clinical manifestations, diagnosis, treatment
Anesthesiology and Intensive Care	The concept of oxygen therapy: the purpose of the prescription, the rules of prescription, the evaluation of treatment

4 Tasks for independent work in preparation for class

4.1 A list of basic terms, parameters, characteristics that the student must learn in preparation for the lesson

Table 21

Term	Definition
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2", formerly known as Novel Coronavirus 2019
COVID-19	It is an infectious disease that was first detected in humans in December 2019 in the city of Wuhan, Central China. The disease began as an outbreak that developed into a pandemic. The cause of the disease was the SARS-CoV-2 corona virus, the circulation of which in the human population was unknown until December 2019
PEEP	Positive end-expiratory pressure

A number of research approaches are being used for the antiviral treatment of patients with COVID-19. The efficacy of individual drugs has been determined in limited observations or in

vitro. It is important to recognize that there is still debate about their effectiveness.

Etiotropic therapy

Clinical protocols and guidelines for the treatment of patients with COVID-19 at different times in many countries included a number of drugs with a probable antiviral effect, determined on the basis of limited approbation. Subsequently, some of them underwent multicenter randomized trials, the results of which, unfortunately, did not live up to expectations.

Remdesivir is one of the antiviral drugs that is still widely used for COVID-19. This nucleotide analogue is active against SARS-CoV-2 and related coronaviruses (including SARS- and MERS-CoV) both in vitro and in animal studies. Its moderate efficacy in the treatment of patients with Ebola fever has been proven. The drug is metabolized into the active form GS-441524, a nucleotide adenine analogue that interferes with viral RNA polymerase activity and blocks the work exoribonuclease, which leads to inhibition of viral RNA synthesis. A side effect of remdesivir is an increase in serum aminotransferases, and its additional component cyclodextrin can cause toxic kidney damage.

According to the order of the Ministry of Health of Ukraine (No. 2116 of 09/17/20), for patients with severe and critical COVID-19, the recommended dose of remdesivir on the first day is 200 mg (IV for 30-120 minutes), from the second day - 100 mg once a day (IV for the same time). Duration of treatment: 5 days for patients who do not require mechanical ventilation or extracorporeal membrane oxygenation (ECMO). In the absence of effect or if the patient is on mechanical ventilation or ECMO, the course of treatment is 10 days. Prior to initiation and daily during the use of remdesivir in adult patients, it is recommended to determine the estimated glomerular filtration rate (eGFR).

Favipiravir is a synthetic antiviral drug, a selective inhibitor of RNA polymerase, active against RNA viruses. In a number of studies, favipiravir has been shown to effectively inhibit SARS-CoV-2 in cell culture. The drug is available in Japan for the treatment of patients with influenza and in clinical trials for COVID-19. It is used 1800 mg 2 times on the first day, then 600 mg 2 times a day for the next 10 days. In patients with mild to moderate infection ($SpO_2 > 93$ %) a faster rate of viral clearance and positive radiological dynamics were stated. By the tenth day, elimination of the virus was reported in 80% of patients. According to computed tomography (CT), 14 days after the end of the study therapy, normalization of indicators was recorded in 91.4 % of patients, compared to 62.2% of patients in the comparison group [7].

According to the order of the Ministry of Health of Ukraine (No. 2116 of 17.09.20), favipiravir should be used to treat patients with moderate and severe disease, 1600 mg 2 times on the first day, then 600 mg 2 times a day, for 5-14 days. It is noted that favipiravir has a teratogenic effect on the fetus, therefore it is contraindicated in pregnancy. It should also not be used for lactation and hypersensitivity to the components that make up the drug. It is recommended to use reliable contraception up to 7 days after the last dose of the drug.

Lopinavir-ritonavir appears to play little or no role in the treatment of COVID-19. This combination protease inhibitor, which has so far been used to treat individuals with HIV infection, is active in vitro against SARS-CoV and against MERS-CoV in animal studies. However, in a randomized trial of 199 patients with severe COVID-19 who received lopinavir-ritonavir (400/100 mg) twice daily for 14 days, In addition to standard treatment, no difference was found in the rate of symptom relief. Therefore, this treatment regimen has been removed from international clinical protocols.

Convalescent plasma. The first studies of the use of such plasma in patients with COVID-19 were conducted in China. Five patients had positive clinical changes on days 10 and 22. They had severe pneumonia with rapid progression, low PaO_2/FiO_2 levels, and

were on ventilators, steroids, and antivirals. Approximately one week after the plasma infusion, the patients' body temperature returned to normal and their PaO_2/FiO_2 levels recovered. So, this pioneering study showed promising results. But the extremely small sample of patients and the absence of a comparison group did not give grounds to clearly note the effectiveness of such therapy.

Another study showed a decrease in viral clearance under the influence of the use of convalescent plasma in patients with COVID-19, but such patients had a higher mortality rate than those who did not receive it. Also C. Duan et al. described ten people with severe COVID-19 in China, for the treatment of whom convalescent plasma was used. Already on the 16th day of follow-up, the authors noted a significant improvement in the condition of patients, a decrease in the need for ventilation therapy and a reduction in hospital stay. All patients recovered and were discharged from the hospital. At the same time, there were three deaths in the comparison group, six patients remained in serious condition, and only one patient had positive clinical dynamics.

In Korea, two cases of severe COVID-19 complicated by acute respiratory distress syndrome have been described. The patients received convalescent plasma. On the 6th and 22nd days of the disease, SARS-CoV-2 RNA was not detected in both. Rapid improvement of clinical, biochemical and x-ray parameters made it possible to reduce the duration of inpatient treatment. The successful use of convalescent plasma in a 6-year-old child who had severe COVID-19 with the development of aplastic anemia and no effect of antiviral therapy was also reported. Plasma treatment was found to lead to the elimination of SARS-CoV-2 and subsequent recovery.

The data of US scientists indicating the safe use and effectiveness of convalescent plasma in the treatment of patients with COVID-19 at the initial stage of the disease are promising. Such individuals had a reduced need for oxygen therapy and a reduced mortality rate. Subsequently, two randomized clinical trials were conducted. It has been established that such plasma is more effective at the onset of the disease in patients with a severe, but not critical

course of the disease. A reduction in the mortality rate has been achieved.

Oxygen support

Patients with severe COVID-19 require oxygen support. The most commonly used are high-speed oxygen therapy and noninvasive positive pressure ventilation. If acute respiratory distress syndrome develops, mechanical ventilation is indicated.

Adults with devastating symptoms (difficulty or no breathing, severe respiratory failure, central cyanosis, shock, coma, and/or seizures) should be given emergency airway management and oxygen therapy until the target $SpO_2 \geq$ of 94 % is reached. Once stabilized, the target SpO_2 value in adult patients should be >90 % (in pregnant women ≥ 92–95 %). Ensure the desired oxygen flow rate with appropriate devices (e.g., use nasal cannula for flow rates up to 5 l/min, mask Venturi for a flow rate of 6-10 L/min and a mask with a breathing bag for a flow rate of 10-15 L/min). Children with devastating symptoms (difficulty or absence of breathing, severe respiratory failure, central cyanosis, shock, coma, or seizures) should be treated with emergency airway management and oxygen therapy until the target $SpO_2 \geq$ of 94 % is reached. Once stabilized, the target SpO_2 value in children should be >90 %

In adults, techniques such as changing body position, such as sitting with a high headboard, can help optimize oxygenation, reduce shortness of breath, and reduce energy loss.

For mild acute respiratory distress syndrome, noninvasive or high-flow nasal oxygen therapy (HFNO) systems are used. Patients receiving HFNO as a trial treatment should be constantly monitored by experienced personnel experienced in HFNO and the intubation techniques necessary if the patient's condition deteriorates sharply or does not improve after a short (about 1 hour) trial period. In this situation, intubation should be done without delay.

If a patient with acute respiratory distress syndrome does not respond to standard oxygen therapy, they are intubated and put on mechanical ventilation. During intubation, patients with ARDS, especially children, obese patients, and pregnant women, may develop desaturation rapidly. In this regard, oxygen therapy with pure oxygen (FiO_2 100 %) for 5 minutes should be performed first, preferably with a face mask with a breathing bag. Tidal volume (inspiratory and expiratory volume) is set at 4-8 mL/kg (recommended 6 mL/kg) of the predicted body weight (PDW), which is calculated using the formula:

$$25 \times (\text{height in meters})^2.$$

A person with COVID-19 may continue to experience respiratory distress or hypoxemia even if oxygen is delivered through a mask with a reservoir (flow rate 10-15 L/min, which is usually the minimum flow rate required to maintain bag inflation; FiO_2 0.60-0.95). Hypoxemic respiratory failure in acute respiratory distress syndrome (ARDS) is usually the result of a mismatch between intrapulmonary ventilation and perfusion or bypass surgery and usually requires mechanical ventilation.

High-flow nasal oxygen (HFNO) or noninvasive ventilation (NIV) is used only in some patients with hypoxemic respiratory failure. Patients receiving NIV therapy are at high risk of treatment failure. Patients receiving HFNO or NIV should be closely monitored for clinical deterioration.

HFNO systems can provide a gas flow of 60 L/min and a FiO_2 of up to 1.0; Pediatric circuits usually only operate at speeds up to 15 L/min and many children require an adult circuit to ensure adequate flow.

Compared to standard oxygen therapy, HFNO reduces the need for intubation. Patients with hypercapnia (exacerbation of obstructive pulmonary disease, cardiogenic pulmonary edema, pulmonary edema), hemodynamic instability, multiple organ failure, or psychiatric disorders are not routinely treated with NIV, although

emerging evidence suggests that HFNO may be safe for patients with mild to moderate hypercapnia. Patients receiving HFNO should be in a controlled environment with experienced medical personnel capable of performing endotracheal intubation if the patient's condition worsens acutely or does not improve after a short trial (about one hour). However, it should be remembered that there are no evidence-based recommendations for HFNO, nor are reports on the use of GFNO in patients with Middle East respiratory syndrome caused by coronavirus.

Patients with hemodynamic instability, multiple organ failure, or mental status disorders.

Recent publications suggest that newer HFNO and NIV with a sealed interface do not produce a wide dispersion of exhaled air and should therefore be associated with a low risk of airborne transmission.

Intubation should be performed by a trained and experienced physician with airway safety precautions. Patients with ARDS, especially young children, or those who are obese or pregnant, may have a rapid loss of acid-base balance during intubation.

Criteria for switching to mechanical ventilation:

Indications for intubation and transition to mechanical ventilation are NIV or HFNO-refractory hypoxemia SpO_2 less than 85 %, impaired consciousness, psychomotor agitation, tachypnea greater than 45 breaths/min involving accessory respiratory muscles.

Pre-oxygenation of FiO_2 100 % for five minutes is done using a bag face mask, valve mask, HFNO, or NIV.

Rapid intubation is appropriate after an airway assessment that shows no evidence of difficult intubation.

Mechanical ventilation in adult patients with respiratory failure should be performed using a lower tidal volume (4-8 mL/kg ideal body weight (BMI) and lower body weight (MMT) and lower inspiratory pressure (plateau pressure <30 cm H2O), a MAC of 8-12 cm water column. Initial tidal volume is 6 mL/kg body weight; tidal volume up to 8 ml/kg body weight is allowed, if undesirable side effects occur (e.g., dyssynchrony, pH <7.15).

Hypercapnia is allowed if the target pH level of 7.30-7.45 is reached. Deep sedation may be required to ensure synchronization with the ventilator and achieve the target volume.

Patients with severe ARDS are advised to ventilate supine for >12 hours a day, changing body position every 3 to 4 hours. Supine mechanical ventilation is recommended for adults and children with severe ARDS, but it can only be performed safely if the necessary human resources and experience are available.

4.2 Theoretical questions for the lesson:

1) What is COVID-19 and SARS-CoV-2?
2) Features of etiotropic therapy in coronavirus infection.
3) Efficacy of remdesivir.
4) Efficacy of favipiravir.
5) Research into the use of convalescent plasma in the treatment of coronavirus infection.
6) Oxygen support and its features.

4.3 Practical tasks to be performed in the classroom

Typical example:

A 34-year-old woman was admitted to the intensive care unit in a very critical condition. Objectively: shortness of breath, dry cough, t 40 ºC, blood pressure 90/60, Ps 130, SpO_2 71 %. According to the man, she became ill about a week ago, her temperature began to rise, she lost her sense of smell and taste, and she started coughing. Two days ago she had a positive PCR test.

Questions to consider:

1) Formulate a preliminary diagnosis.
2) Specify the main diagnostic methods.
3) Develop a treatment plan.

Answer:

1) Coronavirus disease caused by the causative agent SARS-CoV-2 (PCR, omicron strain) is severe. DN of the III century.

2) Complete blood count, complete urinalysis, blood biochemistry, coagulogram, blood glucose, chest x-ray.

3) Bed rest.
4) Diet No. 13.
5) Oxygen therapy with 50 % oxygen.

Dexamethasone 6 mg, IV, 1 r/d for 5 days.
Phys. 400 mL IV, 1 r/d for 5 days.
Enoxaparin 0.4, subcutaneous, morning at 6:00, 5 days.
Paracetamol 1000 mg IV, for fever.
Remdesivir 200 mg 1 r/d, 5 days.

Task 1

A 25-year-old man came to the family doctor with complaints of cough, runny nose, muscle pain, frequent headaches, an increase in t 39.2 ºC. The doctor immediately offered to do a rapid test for COVID-19, which turned out to be positive.

Questions to consider:

1) Formulate the clinical diagnosis.
2) Specify the main diagnostic procedures.
3) Prescribe treatment, specifying doses, method and frequency of administration, duration of use.

Task 2

Patient R., 29 years old, was brought by ambulance to the Emergency Department of the City Hospital No. 5 in critical condition with signs of respiratory failure. Objectively: HR 30/min, BP 80/50, SpO_2 85 %.

Questions to consider:

1) Formulate the clinical diagnosis.
2) Specify the main diagnostic procedures.
3) Prescribe treatment, specifying doses, method and frequency of administration, duration of use.

Task 3

Patient O., 35 years old, consulted a doctor with complaints of fever up to 38 °C, runny nose, headache, chest tightness, dry

cough. During an objective examination: RR - 28/min, blood pressure - 90/70 mm Hg. Art., SpO_2 - 92 %.

Questions to consider:

1) Formulate the clinical diagnosis.
2) Specify the main diagnostic procedures.
3) Prescribe treatment, specifying doses, method and frequency of administration, duration of use.

5 Content of the topic

At the practical lesson, students get acquainted with antiviral therapy drugs for coronavirus infection and learn the rules of oxygen therapy. Receive information about drug research and testing. A treatment plan for patients with coronavirus infection is being developed.

6 Self-assessment questions:

1) What are the names of drugs used to treat coronavirus infection?
2) What is the most commonly used form of oxygen support?
3) What medications should be prescribed in the first 5 days of illness?

TOPIC 10. PRINCIPLES AND APPROACHES TO THE TREATMENT OF PATIENTS WITH COVID-19 IN THE INTENSIVE CARE UNIT

Duration - 2 hours.

1 Relevance of the topic

Coronavirus disease 2019 (COVID-19) is an acute respiratory infection caused by severe acute respiratory syndrome virus 2 (SARS-CoV-2). The clinical presentation of this disease is consistent with a respiratory infection, with symptom severity varying from mild cold-like illness to severe viral pneumonia leading to potentially fatal acute respiratory distress syndrome. Management of severe and extremely severe COVID-19 cases requires intensive care unit conditions. The proportion of hospitalized patients requiring Intensive Care Unit (ICU) care remains quite high, leading to the use of conventional treatment methods.

2 Specific objectives

2.1 The student should know:

- Indications according to clinical criteria for ICU admission.
- Treatment algorithms for severe and critical COVID-19 in the ICU.
- Complications of SARS-CoV-2 in patients with severe comorbidities and principles of their management.

2.2 ***The student should be able to:***

- Determine the course of COVID-19, the presence of comorbidities, and objectively assess the patient's condition prior to ICU admission.
- Adhere to algorithms for prescribing treatment according to the severity of SARS-CoV-2 in the ICU.

3 Basic knowledge, skills, and abilities necessary to study the topic (interdisciplinary integration)

Table 22

Previous disciplines	Skills acquired
Propaedeutics of internal diseases	Possess the method of examining a patient with diseases of the respiratory system. Interpret clinical studies and the main symptoms of diseases of the respiratory system
Pathological Physiology	Based on the pathogenesis of the disease, analyze its clinical manifestations
Infectious diseases	Carry out differential diagnosis of different strains of COVID-19 depending on clinical manifestations and know the features of the pathogenesis of each of them
Pharmacology	Know the pharmacological groups, the mechanism of action of drugs, their doses, indications and contraindications for use
Microbiology	Know the etiology, epidemiology of the virus. Methods of specific diagnostics
Anesthesiology, Resuscitation and Emergency Critical Care	Master the Technique of Cardiopulmonary Resuscitation. Types and methods of respiratory support. Differential diagnosis of acute respiratory failure, ARDS, sepsis and septic shock

4 Tasks for independent work in preparation for class

4.1 A list of basic terms, parameters, characteristics that the student must learn in preparation for the lesson

Table 23

Term	Definition
1	2
ARDS	Acute respiratory distress syndrome characterized by acute respiratory failure secondary to lung damage of various etiology, non-cardiac pulmonary edema, impaired external respiration, and hypoxia

Continuation of Table 23

1	2
Systemic Inflammatory Response Syndrome (SIRS)	A systemic inflammatory response to a variety of severe clinical lesions, manifested by two or more of the following: 1) Body temperature above 38 °C or below 36 °C. 2) Heart rate over 90 bpm. 3) Respiratory rate greater than 20 minutes or $PaCO_2$ less than 32 mmHg 4) The number of leukocytes is more than 12 × 109/L, less than 4 × 109/L, or more than 10 % of juvenile forms
Sepsis	A systemic inflammatory response to a well-documented infection in the absence of other possible causes of similar changes characteristic of SIRS. Clinical manifestations include two or more of the following: 1) Body temperature above 38 °C or below 36 °C. 2) Heart rate greater than 90 bpm. 3) Respiratory rate greater than 20 per minute or $PaCO_2$ less than 32 mmHg. 4) Leukocyte count greater than 12 × 109/L, less than 4 × 109/L, or greater than 10 % of juvenile forms
Severe sepsis	Sepsis accompanied by organ dysfunction, hypoperfusion, or hypotension. Hypoperfusion and perfusion disorders may include (but are not limited to) acidosis due to lactic acid accumulation, oliguria, or acute mental status disturbance. Sepsis-induced hypotension: systolic blood pressure below 90 mm Hg or a decrease in blood pressure of 40 mm Hg from baseline. from baseline in the absence of other causes of hypotension
Septic shock	This is a complication of severe sepsis and is defined as: sepsis-induced hypotension that cannot be corrected by adequate fluid replenishment; perfusion disorders, which may include (but are not limited to) acidosis, oliguria, or acute mental status disorder

Continuation of Table 23

1	2
Mean arterial pressure (SerBP)	Indicator calculated by the formula: DAT + ((CAT – DAT) / 3). The norm is 70-110 mm Hg
NIV	Non-invasive ventilation
Ventilator	Bag-valve-mask ventilation or ventilator
ECMO	It is extracorporeal membrane oxygenation using a device containing an oxygenator and a pump to pump blood

Intensive care unit treatment is indicated when the patient is in a severe or critical condition, such as ARDS, sepsis, and septic shock.

The Glasgow Scale is used to assess the patient's level of consciousness. The score is based on three indicators: ocular response, verbal response, and motor response. For each of the indicators, points are assigned according to the scale. Once all the indicators have been assessed, the points are summed and a total score is obtained, with a minimum of 3 corresponding to a critical condition and a maximum of 15 corresponding to a satisfactory condition.

Occular Response (4)

1) Eyes do not open
2) Eyes open to pain
3) Eyes open to sound
4) Eyes open spontaneously.

Verbal Response (5)

1) No verbal response
2) Incomprehensible sounds.
3) Inappropriate words (patient responds with random words that make no sense).

4 Confusion (e.g., patient does not understand where he is)

5 Oriented (patient responds correctly to simple questions - "What is your name?", "Where are you?").

Motor Response (6)

1 No motor response.

2) Abnormal extension of limb in response to pain.

3) Abnormal flexion of the limb in response to pain.

4) Pain avoidance (normal flexion of the limb in response to pain).

5) Pain localization (the patient removes the hand from the object causing the pain).

6) Execution of commands (e.g., thumbs up or tongue out).

The qSOFA scale is used to assess the risk of developing organ dysfunction and death. To do this, three indicators are used, if each is present, 1 point is added:

- Glasgow score <15.
- Respiratory rate >22/min.
- Systolic blood pressure <100 mmHg.

Score:

0 points - risk of death <1 %.

1 point - risk of death 2-3 %.

2 points and above - risk of death >10 %.

Clinical signs of septic shock

Adults:

- Persistent hypotension despite replenishment of circulating blood volume,
- Persistent hypotension requires use vasopressors to maintain a mean arterial pressure of ≥65 mm Hg.
- Serum lactate level > 2 mmol/L.

Children:

Any level of hypotension (mean arterial pressure <5th centile or >2 points standard deviation below normal by age) or two or three of the following:

- Altered mental state.
- Tachycardia or bradycardia (heart rate <90 bpm or > 160 bpm in infants and heart rate <70 bpm or >150 bpm in children).
- Pale spot symptom (>2 sec) or weak pulse.
- Tachypnea.
- Blotchy or cool skin or petechial or purple rashes
- Increased lactate.
- Oliguria;.
- Hyperthermia or hypothermia.

If lactate is not available, use mean arterial pressure (MAP) and clinical signs of perfusion to diagnose shock.

Early maintenance therapy for ARDS

Oxygen therapy. Oxygen therapy should be initiated starting at 5 L/min using nasal cannulas and adjust the flow rate until the target level of $SpO_2 \geq 93$ % in adults and $SpO_2 \geq$ 92-95 % in pregnant women is reached. The next step is to use face masks with a tank with a minimum flow rate of 10 to 15 L/min to keep the tank full. Children with emergency signs (difficulty or no breathing, ARDS, central cyanosis, shock, coma, or seizures) should receive oxygen therapy during resuscitation until a $SpO_2 \geq$ of 94 % is achieved; otherwise, the target SpO_2 is ≥ 90 %.

A COVID-19 patient may continue to experience respiratory distress or hypoxemia even when oxygen is delivered through a face mask with a reservoir bag. Hypoxemic respiratory failure in ARDS is usually due to mismatch between intrapulmonary ventilation and perfusion or shunt and usually requires mechanical ventilation.

Nasal oxygen or noninvasive ventilation (NIV) is used only in some patients with hypoxemic respiratory failure. Patients treated

with NIV therapy are at high risk of treatment failure. Patients treated with NKVP or NIV should be closely monitored for clinical deterioration.

Endotracheal intubation should be performed by a trained and experienced physician with airborne safety precautions. Pre-oxygenation of 100 % FiO_2 for five minutes is carried out using a face mask with a reservoir bag, valve mask, NKVP, or NIV.

Mechanical ventilation should be given in adult patients with respiratory failure due to sepsis who do not meet the criteria for ARDS, using a lower inspiratory volume (4 to 8 mL/kg ideal body weight (PBW) and a lower inspiratory pressure (plateau pressure <30 cm H_2O).

Patients with severe ARDS are advised to ventilate on their stomach for >12 hours per day. Abdominal ventilation is recommended for adults and children with severe ARDS. For patients with ARDS without tissue hypoperfusion, a moderate restrictive strategy of intravenous infusions is used, the main effect of which is to reduce the duration of ventilation.

No signs of shock. Patients in severe condition without signs of shock should be cautiously given intravenous fluids (restrictive fluid management strategy), as rapid fluid administration may impair oxygenation, especially in settings with limited access to mechanical ventilation.

Sepsis. Critically ill patients with signs of sepsis should be given empirical antimicrobials, taking into account all possible causative agents, within one hour of sepsis diagnosis. Empirical antibiotic treatment should be based on clinical diagnosis (e.g., community-acquired or community-acquired pneumonia), epidemiological data, and regional/local data on antimicrobial resistance. Antibiotic therapy should be adjusted based on microbiological findings and clinical and laboratory findings (e.g., blood procalcitonin levels).

Septic shock. Standard care includes treatment within one hour of recognition: antibiotics, fluid resuscitation and vasopressors for refractory hypotension.

Isotonic crystalloids (0.9 % sodium chloride solution, Ringer's solution) are used for infusion therapy. Do not use hypotonic crystalloids, starches, or gelatins for intensive care. Also, the use of hydroxyethyl starch solutions is not recommended due to the increased risk of death and acute kidney damage.

In intensive care of septic shock, it is recommended that adults administer at least 30 mL/kg of isotonic crystalloid within the first 3 hours. Children- 20 ml/kg in the form of a rapid bolus and up to 40-60 mL/kg in the first hours. Excessive fluid administration can lead to volume overload, including respiratory failure. If there is no response to fluid and signs of volume congestion (e.g., jugular vein distention) appear, fluid administration should be reduced or stopped.

Vasopressors should be used if shock persists during or after fluid administration. The initial target for blood pressure is mean BP $\geq$ 65 mmHg in adults and age-matched in children.

Vasopressors (i.e. norepinephrine, epinephrine, vasopressin and dopamine) are safest when administered through a central venous catheter at a tightly controlled rate, but can also be safely administered through a peripheral vein and an intraosseous needle. Monitor blood pressure frequently and titrate the vasopressor to the minimum dose required to maintain perfusion and prevent side effects. Norepinephrine is considered a first-line agent in adult patients; epinephrine or vasopressin may be added to achieve the target mean arterial pressure. Because of the risk of tachyarrhythmias, reserve dopamine for selected patients at low risk of tachyarrhythmias or those with bradycardia.

Pathogenetic therapy for all variants of the critical course:

- Mechanical ventilation.
- Prescribing low molecular weight heparin (lmwh) unless contraindicated.
- Intravenous systemic corticosteroids. Dexamethasone or other corticosteroids such as hydrocortisone, methylprednisolone may be used.

A dose of dexamethasone 6 mg once/day is equivalent (in terms of glucocorticoid effect) to 32 mg methylprednisolone (8 mg

every 6 hours or 16 mg every 12 hours) or 150 mg hydrocortisone (50 mg every 8 hours).

The duration of treatment is up to 7-10 days.

In case of progression of respiratory failure and laboratory signs of inflammation, higher doses of systemic corticosteroids may be considered according to the instructions for medical use.

Options for adjunctive therapy (according to clinical indications):

a) *Tocilizumab.* Indications for tocilizumab: interstitial pneumonia with acute respiratory failure, progressive respiratory failure, need for non-invasive or invasive ventilation, presence of extrapulmonary organ damage, 5-fold increase in C-reactive protein levels, increased levels of IL-6, D-dimer and ferritin in critically ill patients.

The recommended dose of tocilizumab is 8 mg/kg as a single intravenous infusion. The total dose should not exceed 800 mg. Tocilizumab should be diluted in 100 mL of 0.9% sodium chloride and administered over 1 hour. A second dose should not be considered because of uncertainty about the evidence of additional benefit.

b) *10 % human immunoglobulin* is normal for intravenous administration as part of the complex therapy of adult patients with severe pneumonia caused by SARS-CoV-2/COVID-19 coronavirus infection.

In patients with a critical course of the disease, accompanied by increasing phenomena of intoxication syndrome and respiratory failure, negative laboratory dynamics, namely: a progressive increase in the level of C-reactive protein over 50 units, progressive absolute lymphopenia, an increase in the level of ferritin and IL-6 (if a definition is available), consider the possibility of using 10 % normal human immunoglobulin for intravenous administration at a dose of 0.8-1.0 g/kg once a day for 2 days from the onset of deterioration (course dose of 1.6-2.0 g/kg of ideal body weight).

4.2 Theoretical questions for the lesson:

1) The main indications for hospitalization of patients with COVID-19 in the intensive care unit according to clinical criteria.

2) Treatment algorithms for different courses of COVID-19 in the intensive care unit.

3) The main complications caused by SARS-CoV-2 in patients with severe comorbidities and approaches to their treatment.

4.3 Practical tasks that are performed in the classroom

A typical example:

Patient O., 45 years old, blood pressure - 160/100 mmHg, PS - 120 bpm, t° - 39.4 °C, SpO_2 – 85 %, RR – 32 bpm, has short-term episodes of loss of consciousness, signs of acute respiratory failure. He has a confirmed PCR test for COVID 19.

Questions to consider:

Determine the severity of COVID 19 and whether there are indications for hospital treatment?

Answer:

The patient has a severe course of the disease, which leads to immediate hospitalization according to clinical criteria in the intensive care unit.

Task 1

Patient K., 67 years old, was hospitalized in the intensive care unit in extremely serious condition. Blood pressure - 200/100 mmHg, PS - 140 bpm, t° - 38.4 °C, SpO_2 – 78 %, HR – 40 bpm, consciousness is disturbed, the patient reacts only to painful stimuli, has signs of ARDS. 3 days ago, the patient received the results of a positive PCR test for SARS-CoV-2.

Questions to consider:

Prescribe this patient a treatment algorithm and a method of respiratory support in the intensive care unit

Task 2

Patient K., 60 years old, has been in the intensive care unit for 5 days. Objectively: Blood pressure - 60/40 mmHg, PS - 110 bpm, t° - 39.6 °C, SpO_2 – 75 %, RR – 45 bpm, anuria, impaired consciousness, coma I.

Questions to consider:

What complication did this patient develop? How will the treatment algorithm change?

5 Content of the topic

At the practical lesson, students get acquainted with the basic approaches and principles of treatment of patients with COVID-19 in the intensive care unit. Indications according to clinical criteria for admission to the intensive care unit are examined. Treatment algorithms for severe and critical COVID-19 are being studied according to clinical guidelines and protocols. They get acquainted with the main complications caused by SARS-CoV-2 in patients with severe comorbidities and the principles of their treatment.

6 Self-assessment questions:

1) What are the main clinical criteria for admission to the intensive care unit of patients with COVID-19?

2) What are the types of oxygen therapy?

3) Who uses noninvasive ventilation (NIV)?

4) What are the indications for mechanical ventilation?

5) What are the options for adjunctive therapy (according to clinical indications) in the critical course of COVID-19?

6) What are the indications for tocilizumab?

7) What does ARDS stand for?

8) What scale is used to assess the level of impairment of consciousness?

TOPIC 11. IMPLEMENTATION OF COVID-19 PREVENTION MEASURES AIMED AT THE SOURCE OF INFECTION, THE MECHANISM OF TRANSMISSION OF THE PATHOGEN AND THE SUSCEPTIBLE ORGANISM

Duration – 2 hours.

1 Relevance of the topic

Coronavirus infection 2019 (COVID-19) is an extremely serious problem in the world due to the pandemic and does not lose its relevance despite the war. It is an acute infectious disease caused by viruses of the family Coronaviridae, subfamily Orthocoronavirinae, genus Betacoronavirus – SARS-CoV, with contact and droplet routes of infection, with infection more likely in close family and during 102ospitalization. In the case of the contact route, contaminated environmental surfaces act as transmission factors. The group of people at highest risk of infection are those who have been in contact with patients or who provide medical care.

2 Specific goals

2.1 The student should know:

- Source of coronavirus infection.
- Mechanism and ways of transmission of the COVID-19 pathogen.
- Rules for identifying contacts with a COVID-19 patient and rules for their monitoring.
- Anti-epidemic measures at the site of infection.
- Rules for the use of personal protective equipment in the focus of infection;
- Non-specific prophylaxis for COVID-19.
- Specific prophylaxis for COVID-19.
- Contraindications to vaccination against COVID-19.

2.2 The student should be able to:

- Identify and monitor contacts with a COVID-19 patient.

- Draw up anti-epidemic measures at the site of infection.
- Be able to use personal protective equipment at the site of infection;
- Draw up a non-specific prophylaxis plan for COVID-19;
- Draw up a specific prevention plan for COVID-19.

3 Basic knowledge, skills, and abilities necessary to study the topic (interdisciplinary integration)

Table 24

Previous disciplines	Skills acquired
Infectious diseases	Carry out differential diagnosis of different strains of COVID-19 depending on clinical manifestations and know the features of the pathogenesis of each of them
Microbiology	Know the etiology, epidemiology of the virus. Methods of specific diagnostics
Epidemiology	Be aware of the driving forces of the epidemic process, which include the source of infection, the mechanism of transmission of the pathogen, the susceptible organism and methods of influencing them

4 Tasks for independent work in preparation for class

4.1 A list of basic terms, parameters, characteristics that the student must learn in preparation for the lesson

Table 25

Term	Definition
1	2
Population	A set of individuals of the same biological species, which is relatively isolated in its natural life from other individuals of the species in a certain territory

Continuation of Table 25

1	2
Epidemic process	A continuous process of interaction between a parasitic pathogen and the human body at the population level, which under certain social and natural conditions is manifested by single or multiple diseases, as well as asymptomatic forms of infection
Source of infection	Infected human organism (sick, sometimes healthy) or animal (an object that is the place of natural residence and reproduction of pathogens and from which the pathogen can infect healthy people in one way or another)
Pathogen transmission mechanism	The process of moving pathogens from the source of infection to a susceptible organism that arose in the process of evolution
Susceptible organism	The specific property of the human or animal organism to respond with an infectious process to the introduction of a pathogen
Contact person	A person who has been in contact with the source of infection at the approximate time of infection
Insulation	A set of measures aimed at preventing the transmission of the pathogen from patients with potentially contagious disease to other patients/employees of a health care facility
Quarantine	A set of regime-restrictive, medical-sanitary and administrative measures aimed at complete isolation of patients, elimination and prevention of the introduction and spread of quarantine infections
Observation	A system of measures that provide for a number of isolation-restrictive and therapeutic and prophylactic measures aimed at preventing the spread of infectious diseases (isolation and medical observation of persons in contact with patients with quarantine infections, or healthy persons traveling outside the center)

Continuation of Table 25

1	2
Current disinfection	It is carried out at home either by the patient himself or by his caregivers
Final disinfection	It is carried out after hospitalization or recovery of the patient using physical methods of disinfection and the use of household detergents
Non-specific prophylaxis	A set of procedures and recommendations that will help to avoid infection with the infectious agent
Specific prophylaxis	Creating or increasing the level of immunity of the population to infectious diseases with the help of medical immunobiological preparations (MIBP): vaccines / toxins and serums / immunoglobulins (impact on the III link of the epidemic process)

A contact is defined as a person who, within two days before and fourteen days after the onset of symptoms in a patient with a probable or confirmed case of COVID-19:

- Had direct physical contact with a probable or confirmed case of COVID-19.
- Had unprotected contact (without PPE) with mucous secretions from the respiratory tract of a COVID-19 patient (e.g., being near the patient while coughing or touching used tissues with hands).
- Was in contact with COVID-19 patient(s) within one metre for 15 minutes or more, provided appropriate PPE was NOT being used, or if improper use was suspected (e.g., respiratory valve integrity compromised).
- Was in an enclosed space (e.g. auditorium, conference room, healthcare facility waiting room) with a COVID-19 patient for 15 minutes or more at a distance of less than one meter.
- Other cases that, in a situational analysis, have a risk of COVID-19 infection (e.g., living in the same household with a probable or confirmed COVID-19 case, contacts in closed institutions or institutions with a high risk of infection (sanatoriums, long-term care homes, orphanages, hostels, refugee accommodation centres, social institutions with temporary accommodation,

penitentiary institutions, public transport, other crowded places and situations (work-shops, offices, private social events, etc.).

Identification of contact persons:

- Primary information about contact persons is collected by a medical worker who has identified a person with suspected COVID-19 and is entered into additional information in the form 058/o, which is transferred to the Laboratory Center of the Ministry of Health of Ukraine(hereinafter referred to as the LC) by administrative-territorial affiliation.
- Laboratory Centers of the Ministry of Health of Ukraine determine the responsible person or group of persons for working with contact persons.
- Upon receipt of information on laboratory confirmation of COVID-19 cases, the responsible persons of the LC verify the information from the initial emergency message in the form 058/o on the list of contact persons and identify additional contact persons using telephone. Information on each of the verified contacts is entered into the relevant section of the Electronic Integrated Disease Surveillance System (EIDSS) for each confirmed case.

Monitoring and follow-up of contacts:

- Contact tracing and surveillance shall be carried out for a period of 14 days after the last contact with a confirmed or probable case, whether or not the contact has been vaccinated against COVID-19.
- Contact persons whose vaccination with the second dose of the vaccine has passed 14 days (with the 2-dose regimen) or 14 days after receiving a single dose of the vaccine (with the 1-dose regimen), as well as those who have been ill with COVID-19 in the last 6 months (with documentary evidence), are not subject to self-isolation in the absence of symptoms. If such a person develops symptoms of COVID-19, they are subject to testing for SARS-CoV-2 antigen using rapid tests and/or a test for the determination of SARS-CoV-2 antigen by ELISA (if it is impossible to determine the SARS-CoV-2 antigen using rapid tests and/or a test for the determination of SARS-CoV-2 antigen by ELISA, SARS-CoV-2

RNA is detected by PCR) and self-isolation until the test result is obtained. In case of a positive test result, all appropriate measures are taken against these persons as a person who meets the definition of a COVID-19 case.

- Contact persons, regardless of the presence of symptoms, should be examined within 5 to 7 days after exposure for SARS-CoV-2 antigen using rapid tests and/or SARS-CoV-2 antigen test by ELISA (if it is impossible to determine SARS-CoV-2 antigen using rapid tests and/or SARS-CoV-2 antigen test by ELISA, SARS-CoV-2 RNA is detected by PCR) and self-isolation until the test result is obtained. In case of a positive result, all appropriate measures are taken against these persons as a person who meets the definition of a COVID-19 case.

Contact persons with mild symptoms of COVID-19:

- The family doctor refers for a laboratory examination by PCR for COVID-19.
- In case of a positive test result for COVID-19 or in case of failure to test, the patient must self-isolate for at least 13 days from the date of onset of symptoms.
- The patient must strictly adhere to respiratory hygiene and cough etiquette (including wearing a medical (surgical) mask), hand hygiene and physical distancing, in cases where self-isolation is not possible.
- The patient should avoid communication and any contact with persons at risk of developing severe complications in cases where self-isolation is not possible.

Contact persons at risk of severe complications are subject to mandatory laboratory testing by PCR for COVID-19 if they have been in contact with a patient with mild symptoms of COVID-19, regardless of the laboratory test result, including if the test has not been performed.

In case of a positive result of a laboratory PCR test for COVID-19 and there is no need for hospital treatment, retesting is not performed (the patient must self-isolate for 13 days from the date of onset of symptoms.

A contact person who has been in close contact (within one metre) for 15 minutes or more with a person with a laboratory-confirmed case of COVID-19 infection, but who has no symptoms of coronavirus (COVID-19) infection:

- Laboratory testing by PCR for COVID-19 is indicated only for persons at risk of developing severe complications.

- A negative PCR laboratory test does not mean that the person will not later develop an infectious process and does not need to remain in self-isolation.

- If the patient has symptoms of coronavirus disease (COVID-19), the following should be taken in accordance with the above provisions.

The contact has no symptoms of COVID-19 and has not been in close contact with a laboratory-confirmed COVID-19 patient:

- Laboratory testing by PCR for COVID-19 is not performed (a negative test does not mean that the person will not subsequently develop an infectious process).

- If a person is laboratory tested for COVID-19 by PCR on their own initiative, they must isolate themselves until the test results are known and contact a general practitioner. This requirement does not apply to screening and surveillance tests as defined in these standards.

Impact on the mechanism of transmission of the infectious agent

Disinfection (current, final)

The mechanism of transmission of SARS-CoV-2 is airborne (the pathways are aerosol and dust). Infection occurs in conditions of close household, family and hospital stay. There are many cases of infection of health care workers, as well as persons who have visited patients. In these cases, transmission occurred through the ingress of

patients' secretions into the oral cavity, on the conjunctiva of healthy individuals.

Basic principles of surface cleaning

Cleaning surfaces should precede any disinfection process. It helps to remove microorganisms or significantly reduce their number on the contaminated surface. Cleaning is carried out with soap and water or neutral detergents by mechanical action (cleaning or rubbing). In this way, dirt, debris and organic matter such as body fluids are removed and/or reduced, but microorganisms are not destroyed.

Surfaces should be cleaned sequentially from least soiled (cleanest) to most soiled (dirtiest) areas and from higher levels to lowest. The floor must be cleaned last. At the beginning of each cleaning, it is necessary to use clean rags and napkins and make sure that during cleaning the cloth/napkin does not dry out and is constantly saturated with the solution. In wards where patients with COVID-19 are staying, it is necessary to use a new cloth to clean each individual bed. After use, the rags should be thoroughly disinfected, it is advisable to use new ones as often as possible.

Equipment (buckets, mops, etc.) used for rooms where patients with COVID-19 are directly staying (wards, “dirty areas”) should be clearly marked and located separately from the cleaning equipment for other rooms. Cleaning solutions get dirty quickly and prolonged use of the same solution can transfer microorganisms to each subsequent surface. Therefore, the cleaning solution should be replaced as often as possible, preferably after each area of stay of patients (after each ward, and if necessary, several times during cleaning of one ward). It is recommended to prepare fresh solutions every day or before each cleaning. After use, buckets should be washed with detergent, rinsed, dried and stored upside down to completely drain any remaining moisture.

Principles of surface disinfection

Residues of organic substances can prevent the disinfectant from coming into contact with the surface, inactivate disinfectants, or interfere with the interaction of several active substances of the product. Therefore, cleaning should always precede the disinfection process.

Disinfection solutions must be prepared and used, observing the concentration and exposure time in accordance with the manufacturer's recommendations. Too high concentrations increase toxic effects on persons in contact with the solution and can damage surfaces. A sufficient amount of disinfectant solution should be used to keep surfaces moist for the duration of exposure and the disinfectant can kill the pathogen.

Choosing a disinfectant

After cleaning, the following disinfectants can be applied to achieve a reduction in the SARS-CoV-2 virus load on surfaces, which are also effective against other pathogens that are of significant importance in health care settings:

- Ethanol 70-90 %.
- Chlorine-based products (for example, hypochlorite - 0.1 % (1000 ‰) for general disinfection of the internal environment of the institution or 0.5 % (5000 ‰) when contaminated with a large amount of biological fluid).
- Hydrogen peroxide >0.5 %.

For these disinfectants, it is recommended to observe an exposure time of at least one minute or in accordance with the manufacturer's recommendations. Other disinfectants can be used if the manufacturer indicates their effectiveness for the target group of microorganisms (in the case of the causative agent of COVID-19 - lipophilic viruses).

Use of chlorine-containing disinfectants

In the context of providing medical care to patients with COVID-19, the recommended concentration of sodium hypochlorite solution is 0.1 %, which is sufficient to inactivate most other pathogenic microorganisms that may be present in a healthcare facility. But in the case when it is necessary to disinfect a surface contaminated with a large amount of biological fluid (more than 10 mL), it is recommended to use a concentration of 0.5 %. It should be remembered that hypochlorite is quickly inactivated in the presence of organic substances, therefore, regardless of the concentration of the solution, it is necessary to first clean the surface. High concentrations of chlorine can corrode the metal and irritate the skin or mucous membranes. Also, chlorine vapors are toxic to humans and pose a particular danger to people with diseases of the respiratory system.

Solutions of chlorine-containing disinfectants should be stored in opaque containers in a well-ventilated, closed room that is not exposed to direct sunlight. A fresh solution should be prepared every day.

Non-contact disinfection methods

It is not recommended to carry out indoor disinfection measures by spraying disinfectants or fumigating in order to destroy the SARS-CoV-2 virus. These methods may not be effective outside of direct spraying zones, if surfaces are contaminated with organic matter, skip areas that are shielded by objects or covered with fabrics or have a complex design. Also, such approaches to disinfection measures can create additional risks of damage to the skin, mucous membranes of the eyes and respiratory tract of persons who carry it out. Disinfection is recommended by wiping using a cloth or napkin moistened with the solution.

Open ultraviolet emitters (hereinafter referred to as UV irradiators) can be used to disinfect the air in enclosed spaces and surfaces after the use of disinfectants in the absence of people.

Shielded UV irradiators can be used indoors in the presence of people to combat airborne infections (tuberculosis, measles and diseases caused by VZV). Data on efficacy against droplet pathogens are contradictory. Shielded UV irradiators can be used in case of inadequate ventilation, for example, in rooms where aerosol-generating procedures are carried out.

The non-contact disinfection methods described above can complement the standard methods (cleaning and disinfection by hand), but in no case do they replace.

Impact on a susceptible organism

Specific prophylaxis:

- Vaccines are available for adults and children 12 years of age and older.
- Vaccines that are already available or under development are given either as injections or as a nasal spray.
- Vaccines provide, at best, a protective effect of more than 90% and almost complete protection against severe forms of the disease.
- mRNA vaccines have been associated with myocarditis and pericarditis as rare side effects, occurring in most cases in young men. Cases were usually mild.
- According to available preliminary data, vaccination with two different types of vaccines (adenovirus vaccine and mRNA vaccine) provides very good protection.
- Risk groups are often defined by age (seniors), certain types of medical staff (especially those working with suspected or confirmed COVID-19 cases or their laboratory specimens, as well as those working on mission-critical tasks/in areas such as transplant units, oncology units, advanced emergency surgery units), need for ongoing care (residents and staff of various social and health care

facilities), and people with medical conditions that cause severe COVID-19 infection (e.g., chronic kidney, liver, and lung disease, immunocompromised, type 2 diabetes, coronary heart disease, e.g., sleep apnea).

Pfizer-BioNTech vaccine:

- mRNA vaccine, also known as tosinamerane BNT162b2, trade name Comirnaty.
- doses at 3-week intervals (some countries use a longer interval, e.g., 8-12 weeks).
- Storage temperature is -70 °C
- Mild side effects included pain at the injection site, fatigue, and headache. Serious adverse events were infrequent and their incidence was similar in the vaccination and placebo groups.

Moderna vaccine:

- mRNA vaccine, codename - mRNA-1273, trade name - Spikevax.
- Doses 4 weeks apart (some countries use a longer interval, e.g., 8-12 weeks).
- Storage temperature is -20 °C.

AstraZeneca vaccine:

- Adenovirus vaccine AZD1222, trade name - Vaxzevria.
- Doses at 3-week intervals (in some countries a longer interval is used).
- Can be stored at refrigerator temperature.
- The vaccine has been suspended or restricted in several EU countries due to rare thromboembolic complications.

Janssen (Johnson & Johnson) vaccine:

- Adenovirus vaccine JNJ-78436735.
- Administered once.
- Store at a regular freezer temperature.

List of medical contraindications and warnings for which contraindications to vaccination against COVID-19 are granted:

1 Acute illness with a fever of more than 38.0 °C (acute severe febrile illness; excluding COVID-19).

2 History of COVID-19 (history of 0 doses). Vaccination of people with a documented history of COVID-19 may be delayed for 3 months from the time of the course of COVID-19.

3 History of COVID-19 (history of 1 dose).

In this case, the second dose can be administered in accordance with the approved vaccination schedules for specific vaccines, but not earlier than 28 days (4 weeks) from the first day of the onset of symptoms or laboratory confirmation of the diagnosis of COVID-19 by PCR/determination of the SARS-CoV-2 virus antigen.

4 Treatment with monoclonal antibodies or convalescent plasma.

If SARS-CoV-2 monoclonal antibody preparations or convalescent plasma were used to treat the infection, COVID-19 vaccination should be delayed for at least 90 days.

5 Pregnancy.

As interim guidance, the WHO recommends Comirnaty for use during pregnancy when the benefits of vaccinating a pregnant woman outweigh the potential risks associated with it.

Routine pregnancy testing prior to COVID-19 vaccination is not recommended.

6 Lactation - only for vaccines indicating the lactation period as a contraindication.

7) Administration of vaccines against other infectious diseases.

A 14-day interval between the administration of the COVID-19 vaccine and the planned administration of vaccines against other infectious diseases (with the exception of inactivated influenza vaccine) should be observed.

8 Tuberculin Test or Interferon-γ Release Assa (IGRA).

If a tuberculin or IGRA test is necessary, it should be performed and interpreted prior to vaccination or postponed for at least 4 weeks after COVID-19 vaccination.

9 Thrombosis and/or thrombocytopenia.

Vector platform vaccines only (Astra Zeneca/COVISHIELD and Janssen):

Contraindications:

Individuals with a history of the following conditions should not receive vector platform vaccines:

- Heparin-induced thrombocytopenia (HIT)ю
- Thrombotic antiphospholipid antibody syndrome (APS).
- Significant venous or arterial thrombosis with thrombocytopenia after administration of the COVID-19 vaccine on the vector platform.

10 Myocarditis and/or pericarditis.

For mRNA COVID-19 vaccines only (Comirnaty, Moderna).

11 History of Allergic Reaction.

- History of anaphylactic reaction to a previous dose of vaccine.
- The presence of an anaphylactic reaction to the components of the COVID-19 vaccine is clearly established.

12 Autoimmune Conditions.

Patients treated with rituximab should delay vaccination for at least 4 weeks after the last dose of rituximab, unless the prescribing physician prescribes otherwise.

4.2 Theoretical questions for the lesson:

1) The main links in the epidemic process.

2) Conditions for the identification of COVID-19 contacts.

3) Rules for monitoring and follow-up of contacts.

4) Basic recommendations for home care of a patient with COVID-19.

5) Principles of surface disinfection.

6) Rules for the use of noncontact disinfection methods.

7) Types of protective measures to prevent COVID-19 infection.

8) Specific prophylaxis for COVID-19.

9) Contraindications to vaccination with COVID-19.

4.3 Practical tasks to be performed in the classroom

Typical example:

The boy, 17 years old, was vaccinated with the first dose of the Moderna vaccine. After 7 days, shortness of breath, dry mouth, noises and ringing in the ears, palpitations appeared. Auscultatory dullness of 1 tone. On the ECG, an increase in the T wave, a shift of the ST segment above the baseline, a deformation of the QRS complex.

Questions to consider:

1) What complication has occurred after vaccination?

2) What are your next steps for continuing the vaccination?

Answer:

1) Myocarditis after COVID-19 vaccination after receiving an mRNA vaccine. \

2) The second dose in the mRNA COVID-19 vaccine series should be delayed. If a person is at high risk for COVID-19 or severe COVID-19 due to the presence of a comorbidity, the decision to administer the second dose should be made in consultation with a specialist (preferably a cardiologist) and with the informed consent of the recipient of the vaccine. Select an adenovirus vaccine.

Task 1

A 43-year-old female has varicose veins of the right lower extremity and a history of lower extremity thrombophlebitis complicated by pulmonary embolism. She wants to be vaccinated with the Janssen vaccine. She justifies her choice by the fact that it is convenient to be vaccinated once a year, all her friends have chosen this particular vaccine.

Questions to consider:

1) What is your tactic in this case?

2) What vaccine can you recommend for this patient?

Task 2

A 49-year-old man is being treated with rituximab for non-Hodgkin's lymphoma. He and his family want to be vaccinated against COVID-19.

Question to consider:

What advice would you give to this patient?

Task 3

A 29-year-old woman, a healthcare worker, was vaccinated with the first dose of AstraZeneca. Vaccination against hepatitis B is required at the place of work.

Question to consider:

What will your tactics be in this case and what would you advise this patient to do?

5 Content of the topic

At the practical lesson, students will get acquainted with the main links of the epidemic process and ways to influence them. They study the peculiarities of identifying contact persons and monitoring them. They will learn how to disinfect surfaces. Types of prevention for COVID-19 are being studied.

6 Self-assessment questions:

1 What determines the emergence and continuity of the epidemic process?

2 What are the conditions for identifying COVID-19 contacts?

3 How can contacts be properly monitored?

4 What precedes surface disinfection in COVID-19?

5 What should be considered when choosing a disinfectant for use in a healthcare facility?

6 How is a disinfectant selected?

7 What are the types of COVID-19 prophilaxes?

8 What are the absolute and relative contraindications to COVID-19 vaccination?

TOPIC 12. LEGAL BASIS FOR THE IMPLEMENTATION OF MEASURES TO PREVENT AND COMBAT THE RISK OF THE SPREAD OF COVID-19

Duration - 2 hours.

1 Relevance of the topic

With the onset of the SARS-CoV-2 pandemic, the Cabinet of Ministers of Ukraine, in accordance with Article 29 of the Law of Ukraine "On Protection of the Population from Infectious Diseases", established restrictions and made recommendations to prevent the spread of a particularly dangerous infection. Extract from Resolution No. 1236 of 9 December 2020: "In order to prevent the spread of the acute respiratory disease COVID-19 caused by the coronavirus SARS-CoV-2" (hereinafter referred to as COVID-19) on the territory of Ukraine, a quarantine is established on the territory of Ukraine from 19 December 2020 to 30 June 2023.

2 Specific goals

2.1 The student should know:

- The concept of quarantine.
- Article 29 of the Law of Ukraine and its interpretation.
- Resolutions and legal acts adopted during the COVID-19 pandemic (the main one being Resolution No. 1236 of 9 December 2020, subsequently amended).
- The principle of quarantine and anti-epidemic norms under martial law (levels of epidemiological danger, masks regime, availability of COVID documents for using the services of cultural institutions, gyms, restaurants, etc.).
- Levels of epidemic risk.
- Prohibitions and recommendations for each level of epidemic danger.
- The procedure for implementing anti-epidemic measures during the organization and conduct of elections.

– A list of the main types of economic activity subject to restrictive anti-epidemic measures.

– The essence of the current resolutions of the Cabinet of Ministers of Ukraine and those that have expired

– Liability for violation of quarantine rules.

2.2 The student should be able to:

– Impose restrictive measures according to the incidence in an administrative unit or state.

– Determine the level of epidemic danger.

3 Basic knowledge, skills, and abilities necessary to study the topic (interdisciplinary integration)

Table 26

Previous disciplines	**Skills acquired**
Medical informatics	Search for the necessary information in the literature, databases, data and other sources
Public health	Laws of Ukraine, legislative acts and resolutions of the Cabinet of Ministers

4 Tasks for independent work in preparation for class

4.1 A list of basic terms, parameters, characteristics that the student must learn in preparation for the lesson

Table 27

Term	**Definition**
1	**2**
Quarantine	Administrative and medical-sanitary measures used to prevent the spread of especially dangerous infectious diseases
Restrictive anti-epidemic measures	Medical, sanitary and administrative measures carried out within the focus of an infectious disease in order to prevent its spread

Continuation of Table 27

1	2
Sanitary and anti-epidemic rules and regulations	Normative legal acts of the central executive body that provides for the formation of state policy in the field of health care, the requirements of which are aimed at preventing the occurrence and spread of infectious diseases
Anti-epidemic measures	A set of organizational, medical, veterinary, engineering, technical, administrative and other measures carried out to prevent the spread of infectious diseases, localize and eliminate them foci, outbreaks and epidemics
Prophylactic vaccinations	Introduction of medical immunobiological preparations into the human body to create specific immunity to infectious diseases
Self-isolation	Stay of a person in respect of whom there are reasonable grounds for the risk of infection or spread of an infectious disease in a place (premises) determined by him/her in order to comply with anti-epidemic measures on the basis of the person's obligation

Cabinet of Ministers Resolution No. 1236 of 9 December 2020 established a quarantine on the territory of Ukraine from 19 December 2020 to 30 June 2023 to prevent the spread of acute respiratory disease COVID-19 caused by coronavirus SARS-CoV-2 on the territory of Ukraine.

The quarantine is established and lifted by the Cabinet of Ministers of Ukraine. The issue of the introduction of quarantine is submitted to the Cabinet of Ministers of Ukraine by the central executive authority, which provides for the formation of state policy in the field of public health, on the basis of a proposal by the Chief State Sanitary Doctor of Ukraine.

The decision to impose a quarantine, as well as its lifting, is immediately brought to the attention of the population of the affected area through the media. On the territory of Ukraine, a number of

restrictions have been imposed on the movement of people who are in public places.

At **the green level** of epidemic danger, it is forbidden:

– To stay in public buildings, public transport without wearing personal protective equipment, in particular breathing masks or masks covering the nose and mouth, including home-made ones.

– To be on the street without identity documents, confirmation of citizenship or its special status, certificate of registration as a homeless person, certificate of application for protection in Ukraine.

– Leaving places of self-isolation and observation without permission.

– To hold mass events (cultural, sports, entertainment, social, religious, promotional, scientific, educational, professional and other) (including in entertainment establishments (night clubs) and catering establishments) without personal protective equipment worn by all participants and organizers of the event, in particular protective masks or respirators covering the nose and mouth, including home-made ones.

– The carriage of passengers by road on a regular or irregular basis, in particular the carriage of passengers on urban bus routes in the form of fixed-route taxis, electric (trams, trolleybuses), railway, urban, suburban, intercity, intra-regional and inter-regional transport, in excess of the number of seats provided for by the technical characteristics of the vehicle and specified in the registration documents for such a vehicle.

The yellow level of epidemic danger provides for the application of the previous prohibitions along with the new ones:

– Holding all mass (cultural, sports and entertainment, social, religious, advertising, scientific, educational, professional-thematic and other) events, with the exception of certification of applicants in the form of a unified state qualification exam and test exams of the licensed integrated exams “KROK”, holding events to assess the quality of education, the implementation of which is one of the tasks of the Ukrainian Center for Education Quality

Assessment and its regional branches, holding official sports events included in the Unified Calendar Plan of Physical Culture, Health and Sports Events of Ukraine, and matches of team sports of professional sports clubs without spectators, provided that the participants in such events comply with the relevant sanitary and anti-epidemic measures and implement mandatory daily monitoring of the health of the participants.

– Receiving visitors in movie theaters, other cultural institutions and receiving visitors by other entities operating in the field of culture.

– Reception of visitors by business entities that carry out activities in the field of public catering (bars, restaurants, cafes, etc.), except for the provision of catering services with the implementation of targeted delivery of orders and takeaway orders.

– Visits to educational institutions by students in the event that more than 50 percent of students and staff of the educational institution are in self-isolation due to contact with a patient with a confirmed case of COVID-19.

– Holding mass events (performances, holidays, concerts) in educational institutions with the participation of students from more than one group (class) and in the presence of spectators (visitors).

– Reception of visitors in gyms, fitness centres, swimming pools, except for athletes of national teams of Ukraine and their coaches, subject to compliance with appropriate sanitary and anti-epidemic measures.

– The carriage of passengers by air and rail in interregional and international transport, unless they (except for persons under 18 years of age) have a negative result to a polymerase chain reaction test for COVID-19 or a rapid test for the determination of SARS-CoV-2 coronavirus antigen, carried out not more than 72 hours prior to the date of travel; or a document certifying receipt of a full course of vaccination; or a document certifying receipt of one dose of a two-dose vaccine that can be used within 30 days of

the date of administration of the dose; or an international, national or foreign certificate.

At the red level of epidemic danger, additional prohibitions are imposed on:

– Reception of visitors in establishments engaged in public catering (bars, restaurants, cafes, etc.), except for the provision of catering services with the implementation of targeted delivery of orders and take-away orders.

– Reception of visitors in shopping and entertainment centers, with the exception of reception of visitors in institutions and centers or points of vaccination of the population against COVID-19.

– Reception of visitors in other entertainment facilities.

– Reception of visitors by business entities engaged in trade and consumer services for the population.

– Reception of visitors in cinemas, other cultural institutions and reception of visitors by other subjects of activity in the field of culture.

– Reception in gyms, fitness centers, swimming pools, visitors, except for athletes of national teams of Ukraine and their coaches, subject to compliance with appropriate sanitary and anti-epidemic measures.

– visits to educational institutions by students, except for pre-school children, students of special educational institutions and grades 1-4 of general secondary schools, as well as except for educational institutions where all employees admitted to work in the institution have a document confirming the receipt of a full course of vaccination; or an international, national or foreign certificate (except for certificates confirming vaccination against COVID-19 with one dose of a two-dose vaccine (yellow certificate) and a negative test result for COVID-19 by polymerase chain reaction); or a medical report on the presence of contraindications to vaccination against COVID-19.

Also, in order to counteract the spread of COVID-19, there are groups of people subject to self-isolation. These include:

– Persons who have had contact with a patient with a confirmed case of COVID-19.

– Persons with suspected infection or with a confirmed diagnosis of COVID-19 in a mild form, provided that the person does not require hospitalization.

– Persons with a confirmed diagnosis of COVID-19, discharged from a health care facility, until recovery in accordance with industry standards in the field of health care.

– Foreigners and stateless persons crossing the state border to enter the Ukraine.

– The obligation to self-isolate is terminated automatically upon the expiration of the self-isolation period or on other grounds established by this Resolution.

In Ukraine, **under quarantine conditions, certain rights of individuals and legal entities may be restricted**.

- *The right to freedom of movement*. The Law of Ukraine "On Protection of the Population from Infectious Diseases" empowers local bodies of executive power and bodies of local self-government to establish a special regime for entry into and exit from the quarantine territory of citizens and vehicles, and, if necessary, to conduct sanitary inspection of belongings, luggage, vehicles and cargo under quarantine conditions, as well as to create checkpoints at the entrances and exits from the quarantine territory. Yes, this is a restriction of human rights to freedom of movement enshrined in Article 33 of the Constitution of Ukraine. However, Article 2 § 4 of Protocol No. 4 to the Convention for the Protection of Human Rights and Fundamental Freedoms provides that the right to free movement in certain areas may be subject to restrictions established by law and justified by the public interest in a democratic society.

Until the quarantine is lifted, persons who have presented a certificate entitling them to travel outside the quarantine territory may leave its territory (Article 29 of the Law of Ukraine "On Protection of the Population from Infectious Diseases").

- *The right to education*. During the quarantine, there are certain restrictions on the right to education, which consists in

prohibiting students from attending educational institutions during quarantine, but no one restricts the right of educators to receive education remotely.

- *The right to peaceful assembly*. A person's right to freedom of peaceful assembly is also restricted.

Liability for violations committed during the quarantine period is provided for by the Code of Ukraine on Administrative Offenses and the Criminal Code of Ukraine.

The Code of Ukraine **on Administrative Offenses** provides for liability for:

Article 44-3: Violation of the rules on quarantine of people, sanitary and hygienic, sanitary and anti-epidemic rules and norms provided for by the Law of Ukraine "On Protection of the Population from Infectious Diseases", other legislative acts, as well as decisions of local self-government bodies on the issues of combating infectious diseases (entails the imposition of a fine on citizens from one to two thousand non-taxable minimum incomes of citizens and on officials - from two to ten thousand non-taxable minimum incomes of citizens).

Staying in public buildings, structures, public transport during quarantine without wearing personal protective equipment, in particular respirators or protective masks that cover the nose and mouth, including self-made ones (entails the imposition of a fine of ten to fifteen thousand rubles).

The Criminal Code of Ukraine provides for liability for:

Article 325: Violation of the rules and norms established for the purpose of preventing and combating epidemic and other infectious diseases, as well as mass non-communicable diseases (poisoning), if such actions have caused or knowingly could have caused the spread of these diseases (punishable by a fine of one thousand to three thousand non-taxable minimum incomes of citizens or arrest for a term of up to six months, or restriction of liberty for a term of up to three years, or imprisonment for the same term).

The same acts, if they caused the death of people or other grave consequences (punishable by imprisonment for a term of five to eight years).

4.2 Theoretical questions for the lesson:

1) Define the concept of quarantine.

2) The content of Article 29 of the Law of Ukraine and its interpretation.

3) Content of Resolution No. 1236 of December 9, 2020

4) The principle of quarantine and anti-epidemic norms under martial law (levels of epidemiological danger, mask regime, availability of COVID documents for using the services of cultural institutions, gyms, restaurants).

5) Levels of epidemic danger.

6) Prohibitions, restrictions and recommendations established for the green level of epidemiological danger.

7) Prohibitions, restrictions and recommendations established for the yellow level of epidemiological danger.

8) Prohibitions, restrictions and recommendations established for the orange level of epidemiological danger.

9) Prohibitions, restrictions and recommendations established for the red level of epidemiological danger.

10) The principle of quarantine and anti-epidemic norms under martial law (levels of epidemiological danger, mask regime, availability of COVID documents for using the services of cultural institutions, gyms, restaurants).

11) Procedure for the implementation of anti-epidemic measures during the organization and conduct of elections.

12) The list of the main types of economic activity in respect of which restrictive anti-epidemic measures are carried out.

13) List of persons and conditions under which self-isolation is imposed.

14) Terms and control of compliance with self-isolation.

15) Measures and actions that are temporarily allowed for the period of quarantine.

16) Liability for violation of quarantine rules.

4.3 Practical tasks to be performed in the classroom

A typical example:

The infectious disease has begun to spread rapidly throughout the country.

Question to consider:

What steps will the 0fficials take to limit the spread of the disease?

Answer:

The Cabinet of Ministers will decides to impose a quarantine.

Task 1.

Competitions are planned at the Children's Sports School, the area where the competition is planned is in the Green Zone.

Question to consider:

Are competitions allowed, and if so, with what restrictions?

Task 2

In a family of 4 persons, the father has been diagnosed with COVID-19, other family members tested negative.

Question to consider:

What measures should be done about other family members?

5 Content of the topic

At the practical lesson, students get acquainted with the restrictions imposed by quarantine depending on the epidemic situation. The list of person's subject to self-isolation is being studied. They get acquainted with the responsibility for quarantine violations.

6 Self-assessment questions:

1) What is quarantine?
2) Who has the right to impose quarantine on the territory of Ukraine?
3) What restrictions are imposed in the Green Quarantine Zone?

4) What are the restrictions in the Yellow quarantine zone?

5) What are the restrictions in the Red quarantine zone?

6) Who should self-isolate?

7) What are the responsibilities of people who violate quarantine?

8) How is the right to education exercised during quarantine restrictions?

TOPIC 13. BASIC REQUIREMENTS FOR THE ORGANIZATION OF THE WORK OF MEDICAL ORGANIZATIONS AND THEIR STRUCTURAL SUBDIVISIONS PROVIDING OUTPATIENT MEDICAL CARE AIMED AT PREVENTING THE SPREAD OF COVID-19. RULES FOR THE COLLECTION OF BIOLOGICAL MATERIAL

Duration – 2 hours.

1 Relevance of the topic

Coronavirus infection is a viral disease from the SARS group, which is characterized by damage to the upper respiratory tract, intoxication and a high risk of complications and can be fatal.

The spread of acute coronavirus disease has become a real test for the health care system not only in Ukraine, but throughout the world. In a relatively short period of time, scientists and medical professionals have made every effort to find a way to help patients. There was a prompt re-profiling of the admission departments of medical institutions and hospitals of infectious diseases departments, the arrangement of additional medical centers to provide assistance to patients of this profile, within a relatively short period of time, logistics were established not only in cities, regions, but also international in terms of medicines, personal protective equipment, rapid test systems, medical equipment.

Despite the termination of quarantine measures in the country, the relevance of coronavirus disease remains to this day.

2 Specific objectives

2.1 The student should know:

- Etiology, epidemiology of coronavirus disease.
- Rules for the use of disinfectants.
- Requirements for disinfection of surfaces in medical institutions.

- Preventive measures while working in a medical institution.
- Procedure for sampling biological material from persons suspected of having coronavirus disease.

2.2 The student should be able to:

- Choose personal protective equipment that corresponds to the current situation.
- Decide on the amount of disinfection and cleaning of the premises.
- Choose a suitable disinfectant.
- Take biological material for research from a patient suspected of having coronavirus disease.
- Organize appropriate conditions for transporting samples of biological material to the laboratory.

3 Basic knowledge, skills, and abilities necessary to study the topic (interdisciplinary integration)

Table 28

Previous disciplines	Skills acquired
Microbiology	The concept of nutrient media, the conditions for their preparation, collection and transportation of biological samples
Epidemiology and fundamentals of evidence-based medicine	The concept of the components of the epidemic process, methods of disinfection and sterilization Using evidence-based recommendations

4 Tasks for independent work in preparation for class

4.1 List of basic terms that a student must learn when preparing for a lesson

Table 29

Term	Definition
Disinfection	A system of measures for disinfection of environmental objects aimed at the complete, partial or selective destruction of potentially pathogenic microorganisms for humans in order to break the transmission of infectious agents from the source of infection to people sensitive to it
Biological material	Tissues, cells, body fluids, secretions and wastes, physiological secretions, swabs, scrapings, smears, human biopsy material, and material of embryo-fetal origin
Infection control	A set of organizational, preventive and anti-epidemic measures aimed at preventing the occurrence and spread of infectious diseases associated with the provision of medical care, based on the results of epidemiological surveillance

Basic preventive individual measures

The main individual preventive measures include:

– Hand hygiene - frequent washing with liquid soap or treatment with alcohol-based antiseptics at least every three hours and after each contact with animals, visiting public places, using the toilet, cleaning, before cooking, etc.

– Coughing - cover mouth and nose when coughing and sneezing with an arm bent at the elbow or a disposable tissue that must be neutralized immediately after use.

– Avoiding contact with people who have symptoms of respiratory illness - cough, fever, body aches, or maintaining a

mandatory distance and limiting the time of contact (at least 1 meter).

– Do not touch your face with your hands.

– If you have symptoms of the disease, such as fever, cough, body aches, etc., stay at home and avoid visiting crowded places.

– In the presence of the above respiratory symptoms, medical masks should be used and replaced in a timely manner (every three hours or immediately after contamination), followed by disinfecting and washing hands with soap or an alcohol-based antiseptic immediately after removing the mask.

Preventive measures for the organization of work:

– Educate employees on individual prevention measures and how to respond if symptoms are detected in employees.

– Print and/or update informational posters and staff reminders about the importance and technique of handwashing and/or treating hands with alcohol-based hand sanitizers (attached).

– Do not allow employees with signs of respiratory illness to work and serve the public.

– Ensure and control the availability of liquid soap, disposable paper towels, and alcohol-based antiseptics in employee rest areas, service areas, and transportation settling tanks, as well as in waiting rooms, foyers, and passenger service areas.

– Where possible, provide alcohol-based hand sanitizers or hand sanitizer dispensers on long-distance and international flights and at transfer stations.

– Where possible, provide disposable tissues to passengers on intercity and international routes.

– Ensure the availability of personal protective equipment (PPE) for each employee working on the route and/or in areas in contact with passengers at the rate of 1 medical mask per 3 hours of work per person and 1 alcohol antiseptic (100 ml) per 1 person per shift (up to 12 hours), provide appropriate training on the use and

disposal of used masks and tissues, and establish appropriate controls to ensure compliance.

- Do not distribute or minimize the amount of handouts (magazines, brochures, promotional information) on routes;

- Update contact information for health care facilities that provide medical care for patients with infectious diseases, use in your work, and distribute to employees.

Disinfection, cleaning and disposal:

– Ensure wet cleaning with detergents and disinfectants (at the end of the shift), ventilation of waiting rooms, foyers, passenger service areas at least every 3 hours and at the end of the shift.

– Treat surfaces that come into contact with passengers' hands (door handles, seats, folding tables, sinks, information kiosks, etc.) with alcohol-based disinfectants with a minimum contact time according to instructions.

– Ventilation and cleaning of vehicles, selective disinfection at the end of the shift or at least twice a day for international routes.

– For international routes from and/or through the territory of countries where cases of covid-19 have been detected, additional disinfection measures are carried out, during which all surfaces of the cabin are subjected to disinfection.

– Ensure that personal protective equipment used by staff and disposable tissues and disposable tableware used by passengers on intercity and international flights are collected in re-sealable plastic bags.

– Ensure that the collected materials are decontaminated (disinfected) prior to decontamination during or at the end of the shift and/or at the end of the route.

Use of disinfectants

When disinfecting, it is necessary to use standard disinfectants that are registered in accordance with the law and have a valid Certificate of State Registration. It is necessary to follow the instructions for each individual disinfectant, in particular regarding the observance of its effective concentration and exposure (observance of the time spent on the treated surface).

Disinfectants and antiseptics registered in accordance with the law and having a valid Certificate of State Registration can be used for disinfection:

– Antiseptics for the treatment of the skin of the hands – alcohol-containing preparations (active ingredients – isopropyl, ethyl alcohol or their combinations);

– Preparations for disinfection of surfaces with a minimum exposure period (exposure from 30 s to 2 minutes) – alcohol-containing preparations (active ingredients – isopropyl, ethyl alcohol or their combinations);

– For surfaces, equipment, etc. – disinfectants based on quaternary ammonium compounds or chlorine-containing preparations (preferably tablet forms to ensure a clear dosage).

Table 30 - Recommended frequency of cleaning of indoor surfaces in healthcare facilities according to the areas of stay of patients with suspected or confirmed COVID-19 disease

Type of premises	**Frequency**	**Additional considerations**
1	**2**	**3**
Screening or triage area	At least twice a day	It is necessary to pay attention to frequently touched surfaces, and last but not least, to the floor

Continuation of Table 30

1	2	3
Inpatient wards during patients' stay	At least twice a day, preferably three times	Pay attention to frequently touched surfaces, starting with those that are meant to be shared. In the future, you need to go to each bed, using a new cloth / napkin each time, if possible. Last but not least is the floor
Wards of inpatient stay of patients after release	After the liberation of the chamber	Cleaning and disinfection should take place in the following sequence: rarely touched surfaces; that are frequently touched; Waste and linen should be removed from the ward, and beds should be thoroughly disinfected
Premises for outpatient reception of patients; Emergency Branch	After each patient, paying attention to the surfaces to which the touch, and at least once a day final cleaning	After each patient: Treat frequently touched surfaces. who are rarely touched, who are often touched, the floor; garbage collection; Thorough cleaning and disinfection of examination couches
Halls and corridors	At least twice a day	Frequently touched surfaces, such as handrails on stairs, etc.; Last but not least, the floor
Patient toilets and bathrooms	In single rooms: at least twice a day. General use: at least three times a day	In the following order: frequently touched surfaces, including door handles, light switches, faucets; Sinks; Toilets; Avoid sharing the toilet between staff and patients

Infection prevention and control measures during the provision of medical care to a patient subject to the definition of a COVID-19 case

Preventive measures are carried out by employees and managers of health care institutions, as well as infection control commissions.

Preventing or limiting transmission in health care settings includes the following steps:

– **Early detection and control of the source of infection.** This phase involves the implementation of clinical triage of patients, which includes early detection and immediate placement of patients in an isolated area, which is an important measure for the rapid identification, isolation and provision of care to patients suspected of having COVID-19.

– **Use of standard precautions for all patients.** Standard safety precautions include hand hygiene, cough etiquette, and respiratory hygiene; use of personal protective equipment (hereinafter referred to as PPE) depending on the risk; preventing injury from needles or sharp objects; safe waste management; sanitary and epidemiological measures, disinfection and sterilization of equipment and linen used in patient care.

– **Implementation of measures aimed at preventing transmission.** Contact and droplet safety measures, as well as compliance with airborne safety measures during aerosol-generating procedures in case of suspicion of COVID-19.

– **Exercising administrative control.** Administrative control includes the following aspects of activities: the establishment of resilient IPC infrastructures and activities; training of health workers; training of patient care providers; preventing the occurrence of an excessive number of patients, especially in the emergency department; ensuring regular supplies of medical equipment, etc.

– **Implementation of sanitary, anti-epidemic and engineering control.** This stage involves control over the basic infrastructure of medical institutions. These approaches relate to

ensuring proper ventilation of the medical facility in all premises, as well as their proper cleaning. A spatial separation of at least one meter must be maintained between a patient with suspected COVID-19 and other people. Both controls can help reduce the spread of many pathogens during health care.

Rules for sampling biological material:

1 All manipulations for sampling from patients, opening thermal containers with material samples and research are carried out by medical personnel using personal protective equipment:

- Respirator No. 95 (or disposable mask).
- Bathrobe and hat.
- Rubber gloves.
- Safety goggles (face shield).

2 Preliminary preparation of samples and all manipulations with clinical samples during the polymerase chain reaction test are carried out in the laboratory of the second or third level of biosafety, depending on the epidemic situation, using personal protective equipment.

3 Virological studies (contamination of cell cultures or chicken embryos for the purpose of isolation and identification of the virus), as well as work related to the formation of an aerosol of influenza viruses with pandemic potential, are carried out in a laboratory with the third level of biosafety (BSL-3).

Disinfection measures:

1 All items that have been in contact with potentially infected materials must be disinfected.

2 Disinfection of surfaces of premises (floors, walls, doors), equipment, work tables in laboratory diagnostics of diseases caused by influenza viruses is carried out with modern disinfectants that are registered in Ukraine and have virucidal activity against respiratory viruses and do not affect the course of the study.

3 Disinfection of laboratory glassware, tips, virus-containing liquids, agarose gel, metal instruments, disposable personal

protective equipment and waste material is carried out by autoclaving (pressure 2.0 kgf/cm3,temperature 132 °C ± 2 °C for 45 minutes). Disinfection of dispensers is carried out by wiping twice with an interval of 15 minutes with 70% ethyl alcohol or according to the manufacturer's instructions.

Rules for the selection of clinical material:

1 Detection of a reliable positive test result for influenza and acute respiratory infections (hereinafter referred to as ARI) depends on compliance with the rules for sampling materials, their prompt delivery to the laboratory center and proper storage until laboratory diagnostics.

2 Samples of clinical material are taken when the patient seeks medical help or is hospitalized no later than 72 hours from the onset of symptoms of the disease to the start of antiviral therapy.

3 Specimens from persons who have died from influenza, or suspected of having ARI should be taken within 6 to 12 hours of biological death.

4 Selection of clinical material and its packaging is carried out by medical staff of the institution with sterile instruments in sterile disposable cryovials, tubes, containers with screw caps.

5 Employees of the institution must be trained on the rules of biological safety when working with infectious material.

6 During the examination of the patient, the doctor of the institution determines the methods of sampling material for laboratory research:

- Pharyngeal swab.
- Nasal swab.
- Nasopharyngeal swab or aspirate.
- Pharyngeal or bronchial aspirate.
- Blood samples at the onset of the disease and after 10 to 14 days.

7 Throat and nasal swabs can be combined into one sample and transported in sterile cryotubes or cryovials using a transport medium.

8 Samples of materials from the respiratory tract for examination shall be taken by medical professionals, and the following materials are used:

– Personal protective equipment.

– Plastic sticks with sterile dacron or viscose swabs (wooden sticks with calcium alginate or cotton swabs may contain substances that inactivate viruses and slow down PCR testing, so they are used only in the absence of Dacron or viscose swabs), tongue spatula (for taking throat swabs).

– Plastic tubes (cryotubes, cryovials) with a capacity of 2-3 ml, withstanding temperatures in the range from minus 70 °C to minus 180 °C (liquid nitrogen).

– Alcohol-resistant marker for marking samples.

Material Sampling Mechanism:

1 When taking swabs from the nose and throat, it is mandatory to follow safety rules (hand hygiene, personal protective equipment, etc.).

2 During sampling, the swab stick is clamped between the thumb, index and middle fingers so that the stick passes like a pencil (Fig. 1) and does not rest on the palm of your hand (Fig. 2). This is necessary to ensure the safety of the patient: in the first case, the stick will slip in a safe direction, in the second, the movement of the stick will be limited, so the patient may be injured.

Figure 1 – The swab stick is taken correctly

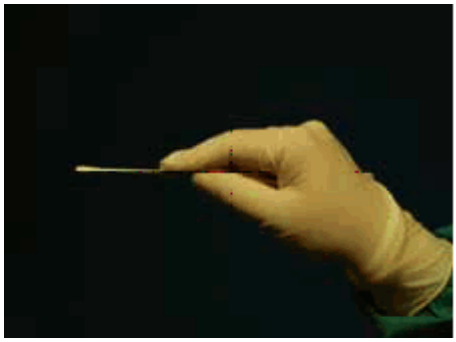

Figure 2 – The swab stick is taken incorrectly

Selection methods:

1 Method of taking swabs from the posterior pharyngeal wall (pharyngeal swabs):

– Take a swab and slowly swab the posterior pharyngeal wall and tonsils (Fig. 3).

– Ask the patient to open his mouth so that the uvula on the palate rises (pronounce a long vowel sound).

– Hold the tongue with a spatula.

– Smear sampling should be carried out without touching the soft palate with a swab.

– Place the swab in a sterile tube with 2 to 3 ml of transport medium.

– Break off the swab stick so that its end remains in the test tube and the cap closes. If the plastic stick does not break, it is cut off with scissors (cooled after sterilization on fire).

– Indicate in the label the individual number, date of sampling, type of sample in the tube (pharyngeal swab, nasal, etc.) And stick it on the container with the sample, do not mark the cap.

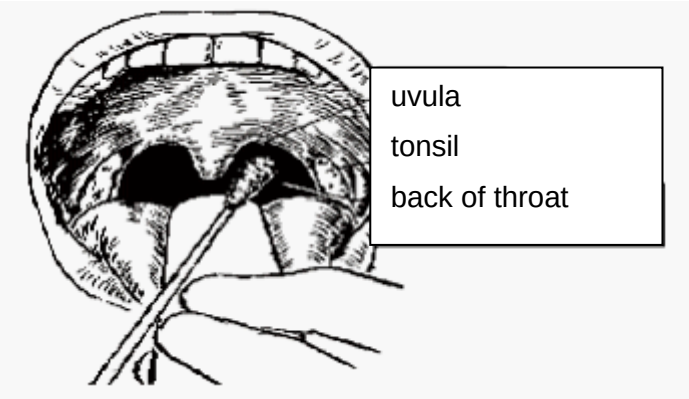

Figure 3 – Throat swab

2 Anterior nasal swab method:

– Insert the tip of the swab into the nostril 2 to 3 cm from the nasal opening, touching the anterior turbinate and septal mucosa, turning the swab to collect nasal mucosal secretions (Fig. 4).

– Insert a tampon into the nostril parallel to the palate.

– Absorb secretions, take samples from both nostrils with one swab.

– Place the swab in a sterile tube with 2 to 3 ml of transport medium along with a pharyngeal swab.

– Break off the swab stick so that its end remains in the test tube and the cap closes.

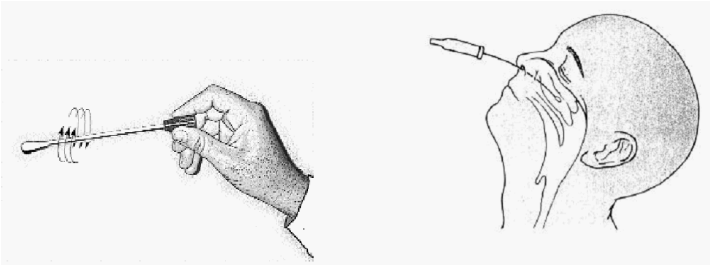

Figure 4 – Nasal swab

3 Pharyngeal aspirate sampling method:

– Aspirate nasopharyngeal secretions with a vacuum suction pump and a catheter attached to a sampling vial.

– The catheter is inserted into the nostril parallel to the palate (fig. 5).

– Perform vacuum aspiration, during which the catheter is removed slowly using a rotating motion. Mucus from the second nostril should be collected with the same catheter.

– Place the sample in a sterile tube with 2-3 ml of transport medium.

In the case of PCR testing, the sample of material is placed in a sterile disposable tube that does not contain deoxyribonuclease and ribonuclease, and the lid of the tube is tightly closed.

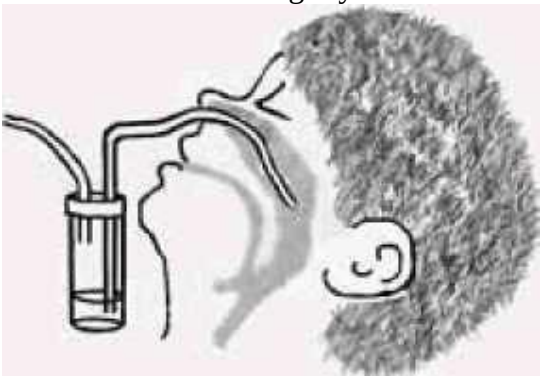

Figure 5 – Pharyngeal aspirate sampling

4 Method of selection of sectional material:

– For the study, take 3-4 samples of material from the lungs, trachea, segmental bronchi with signs of pathomorphological changes with a volume of up to 1 cm3.

– Samples should be placed in sterile disposable polypropylene cryovials with tight-fitting screw caps.

– Samples should be transported frozen in accordance with the Instruction on laboratory diagnostics of respiratory diseases and influenza, in particular with pandemic potential, approved by the

Order of the Ministry of Health of Ukraine of 6 November 2015 No. 732.

– In order to minimise infection of personnel, a biopsy needle should be used (Fig. 6).

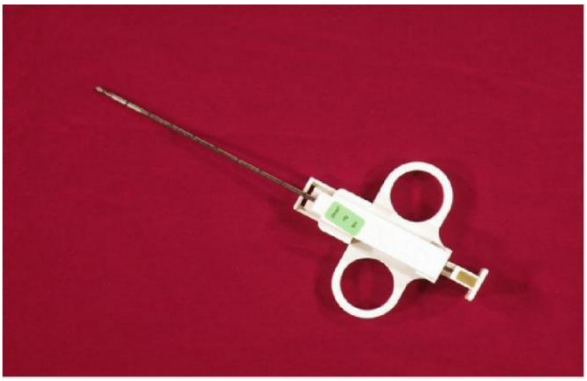

Figure 6 – Biopsy needle for sampling sectional materials

A sample should be taken from the area of the lung where signs of pneumonia are radiologically determined. For control, take 1 biopsy from the unaffected area. At least 4 samples are taken from the deep layer of tissues with signs of pneumonia, in the presence of liquid nitrogen - 5 samples.

Samples of materials for the examination of the respiratory tract

Figure 7 – Swab sample

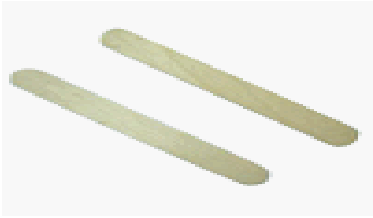

Figure 8 – Example of a spatula for collecting material from the throat

Storage, packaging and transportation of selected material samples:

1 Selected samples of materials are stored in plastic tubes with a transport medium at a temperature of 4 °C for no more than 48 hours.

To transport material samples, use 2 to 3 mL of transport medium (commercial or prepared) poured into plastic tubes.

Composition of the transport medium:

– 10 g of peptone.
– 2 g of bovine albumin (fraction V).
– 0.8 ml of gentamicin sulphate solution (50 mg/ml).
– 3.2 mL Amphotericin B (250 mcg/mL).

Fill to 400 ml with sterile distilled water. Sterilize by filtration.

The manufactured transport medium is stored in sterile conditions without access to light at a temperature of 4–8 °C for one month or minus 20 °C for one year.

2 If it is impossible to examine material samples within 24-48 hours, they are frozen at a temperature of minus 70 °C or in liquid nitrogen. After selection, sectional material is subject to mandatory freezing. Airway specimens in the transport medium are delivered within 24 to 48 hours of sampling to the laboratory site. If it is not possible to deliver to the laboratory in a timely manner, samples of materials are frozen at a temperature of minus 70 °C or in liquid nitrogen and thawed immediately before the test. Each sample for

long-term storage at minus 70 °C is divided into aliquots for additional, retesting or archiving.

3 The number of freeze/thaw cycles should be kept to a minimum, as this can destroy the virus in the sample. Material samples should not be stored in a freezer (-20 °C) with a freeze/thaw cycle; In this case, the sample can be kept on ice for a week.

4 Samples shall be packaged in accordance with the packaging requirements P650 for infectious substances UN 3373 category B. Transportation of samples of materials is carried out in accordance with the rules of postal and courier transportation.

Samples of materials are packed in three layers:

– The first is a cryotube (a cryovial with a screw cap).

– The second is a container that does not allow liquid to pass through (a bag with a zipper, a plastic container).

– The third is hard outer packaging (cooler bag).

An absorbent material sufficient to absorb the entire volume of liquid material samples is placed between the cryotube (cryovial) and the second waterproof layer.

Categories of persons, biological material for research, terms of its selection, list of tests

Table 31

Persons to be tested	**Biological material to be tested**	**Biological specimen collection terms**	**List and sequence of tests**
1	**2**	**3**	**4**
Patients with clinical signs of coronavirus disease	Upper respiratory tract: nasopharyngeal swabs, oropharyngeal swabs, pharyngeal aspirate. Lower respiratory tract: sputum, aspirate, broncho-alveolar lavage. Serum/plasma	Immediately upon detection	1 PCR. 2 IgM ELISA if PCR is negative. 3 IgM ELISA in case of impossibility of PCR for one day

Continuation of Table 31

1	2	3	4
Patients with pneumonia	Oropharyngeal swabs, sputum, aspirate, broncho-alveolar lavage. Serum/plasma	Immediately upon detection	1 PCR. 2 IgM ELISA if PCR is negative. 3 ELISA IgM if it is impossible to perform PCR within one day
Contacts of a confirmed case	Upper respiratory tract: nasopharyngeal swabs, oropharyngeal swabs, pharyngeal aspirate. Serum/plasma	On the 14th day after exposure	1 PCR. 2 IgM ELISA in case of impossibility of PCR for one day
Persons requiring planned hospitalization and/or surgery	Upper respiratory tract: nasopharyngeal swabs, oropharyngeal swabs, pharyngeal aspirate Serum/plasma	Before hospitalization and/or surgery	1 PCR is mandatory for immunosuppressed persons 2 For other ELISA groups, IgM. 3 PCR if ELISA is positive
Healthcare professionals who directly provide medical care to patients or care for patients with COVID-19 in a hospital setting	Serum/plasma Upper respiratory tract: nasopharyngeal swabs, oropharyngeal swabs, pharyngeal aspirate	1 time in 14 days (until the first positive results are obtained in a particular person)	1 IgM ELISA and IgG ELISA. 2 PCR if ELISA is positive

Continuation of Table 31

1	2	3	4
Laboratory workers who process samples from the respiratory tract obtained from patients with COVID-19Employees of pathological, forensic medical bureaus, departments involved in autopsy, including taking samples of sectional material			
Employees of the National Police, National Guard, State Border Guard Service. Other medical and pharmaceutical workers	Serum/plasma. Upper respiratory tract: Nasopharyngeal swabs, oropharyngeal swabs, pharyngeal aspirate	1 time in 30 days (up to obtaining the first positive results in a particular person)	1 IgM ELISA and IgG ELISA. 2 PCR, if ELISA is positive

4.2 Theoretical questions for the lesson:

1) Specify biological material to be tested in patients with clinical signs of coronavirus disease.

2) Identify the composition of the transport medium used to transport specimens collected from patients. taken from patients.

4.3 Practical tasks to be performed in the classroom

Task 1. List what is included in the most important individual preventive measures.

Example answer: Hand hygiene, cough hygiene, avoidance of contact with people with symptoms of respiratory diseases, avoidance of touching the face with the hands, in case of symptoms

of illness such as fever, cough, body aches, etc., stay at home and avoid visiting crowded places; In the presence of the above respiratory symptoms, medical masks should be used and changed in a timely manner (every three hours or immediately after contamination), followed by disarming and washing hands with soap or treating hands with an alcohol-based antiseptic immediately after removing the mask.

Task 2. What measures will help reduce the spread of coronavirus in the workplace?

Task 3. The patient went to the family doctor with complaints of runny nose, cough, fever up to 38 °C. According to his medical history, he had been in contact with a person with a confirmed case of coronavirus disease. Describe the procedure for collecting biological material from such a patient.

5 Content of the topic

During the practical training the students had an opportunity to get acquainted with the basic requirements for the organization of the work of medical organizations and their structural units providing medical care aimed at preventing the spread of COVID-19. We had an opportunity to get acquainted with the rules of biological material sampling: rules of selection of clinical (sectional) material, method of taking swabs from the posterior pharyngeal wall (pharyngeal swabs), method of taking anterior nasal swab, method of taking pharyngeal aspirate, method of taking sectional material. We have mastered the obligatory criteria for the quality of medical care in outpatient and hospital conditions. We learned about infection prevention measures and the principles of infection control when providing medical care to a patient who falls under the definition of a COVID-19 case. We studied standard disinfectants that are legally registered and have a valid certificate of state registration, which must be used during disinfection. We have formulated for ourselves the main points that will help protect against coronavirus infection.

6 Self-assessment questions:

1) What are the main individual preventive measures?

2) List infection prevention measures and infection control principles when providing care to a patient subject to COVID-19 case determination.

3) Describe the step-by-step method for taking an anterior nasal swab.

TOPIC 14. RESPONSIBILITIES OF A MEDICAL ORGANIZATION WHEN A LABORATORY TEST OF BIOLOGICAL MATERIAL IS POSITIVE FOR COVID-19

Duration - 2 hours.

1 Relevance of the topic

In the context of an increase in the incidence of coronavirus disease, or the occurrence of an epidemic, the algorithm of actions in case of obtaining a positive result of a laboratory test of the material for COVID-19 allows you to quickly and correctly make a decision on the patient's further route, thus providing timely medical care to the patient and preventing the spread of the disease.

2 Specific objectives

2.1 The student should know:

- Current regulatory documents related to the provision of medical care for coronavirus disease.
- Registration forms used to register a case of coronavirus disease.
- Groups of people subject to screening for covid-19.
- Rules for monitoring contact persons.

2.2 The student should be able to:

- Register new cases of coronavirus disease.
- Determine the person's belonging to the group to be screened.
- Determine the need to confirm a positive laboratory test result for COVID-19 by other research methods.
- Monitor health contact workers.

3 Basic knowledge, skills, and abilities necessary to study the topic (interdisciplinary integration)

Table 32

Previous disciplines	Skills acquired
Infectious diseases	Knowledge of the peculiarities of the course of viral pneumonia, acute respiratory distress syndrome. Specific diagnosis of viral diseases
Epidemiology and fundamentals of evidence-based medicine	Organization of the work of a family doctor in the center of an infectious disease

4 Tasks for independent work in preparation for class

Organize the work of a medical institution to detect COVID-19 and to provide medical care to persons who have a positive result in a laboratory test.

1) Clinical pathways of patients at all levels of medical care have been adapted and approved in medical institutions. Medical care is provided in accordance with the definition of a case of coronavirus disease (COVID-19).

2) A healthcare professional who has identified a person who meets the definition of a COVID-19 case:

a) Subject to the availability of appropriate technical capability:

– In the event of COVID-19, enters the relevant medical records in the Register of Medical Records, Referral Records and Prescriptions of the Electronic Health Care Register System (hereinafter referred to as the Register) within the specified period and informs the management of the health care institution to organize further clinical observation, timely medical care and anti-epidemic measures at the individual level and at the community level.

– Registration of cases in the form of primary accounting documentation No. 060/o “Journal of Infectious Diseases” and filling

out the form of primary accounting documentation No. 058/o "Expedited Notification of Infectious Disease, Food Poisoning, Acute Professional Poisoning, Uncommon Reaction to Immunization", approved by Order No. 1 of the Ministry of Health of Ukraine of January 10, 2006, registered with the Ministry of Justice of Ukraine on June 08, 2006 under No. 686/12560 (hereinafter - form No. 060/o and form No. 058/o), in this case is not carried out, and information is not promptly transmitted by telephone.

– Data on the patient's repeated case of the disease should be indicated in the form No. 058/o for the transfer of relevant information to the Center for Disease Prevention and Control of the Ministry of Health of Ukraine by administrative-territorial affiliation for conducting an epidemiological investigation and entering data into the electronic integrated disease surveillance system.

b) In the absence of appropriate technical possibilities:

– Registers the case in form No. 060/o and fills in the form No. 058/o and informs the management of the health care institution in order to organize further clinical observation, timely medical care and anti-epidemic measures at the individual level and at the community level.

– Within 12 hours from the moment of detection of a case of COVID-19 on the form No. 058/o informs the Center for Disease Prevention Control of the Ministry of Health of Ukraine by administrative-territorial affiliation.

c) In case of detection of a person who meets the COVID-19 case definition, with signs of other acute respiratory viral infections, with signs of pneumonia, sampling of material is performed in the health care facility and transportation is ensured with appropriate referral of selected samples to the Center for Disease Prevention and Control of the Ministry of Health of Ukraine by administrative-territorial affiliation.

d) If a person is tested for SARS-CoV-2 by PCR on his/her own initiative and upon receipt of a positive test result:

– If technically feasible, the laboratory shall enter the appropriate medical documentation into the Registry and the information on the entry shall be routinely transmitted to the primary health care facility where the person is served.

– In the absence of appropriate technical capability, the results of the study should be transferred by the laboratory to the primary health care institution where the person is served, for further entry of the relevant medical documentation into the Register (in the presence of appropriate technical capability) or registration of the case on the form No. 060/o and sending the form No. 058/o to the Center for Disease Prevention Control of the Ministry of Health of Ukraine by administrative-territorial affiliation (in the absence of appropriate technical capability), clinic, and the Ministry of Health of Ukraine on the administrative-territorial affiliation (in the absence of appropriate technical capability).

3) Active epidemiological search for cases is carried out by laboratory testing for SARS-CoV-2 among persons who meet the criteria for a suspicious case, or as part of differential diagnosis in patients with viral pneumonia and/or SARS and/or other acute respiratory viral infections.

4) The main importance for the etiological laboratory diagnosis of COVID-19 is the detection of SARS-CoV-2 RNA using the PCR method.

Laboratory testing for SARS-CoV-2 RNA is performed in the following persons:

– Suspected of having COVID-19.
– With signs of other acute respiratory viral infections.
– With signs of pneumonia.

Preliminary screening for SARS-CoV-2 antigen using rapid SARS-CoV-2 antigen tests and/or antigen test SARS-CoV-2 ELISA is performed on the following persons:

– Suspected of having COVID-19.
– With signs of other acute respiratory viral infections.
– With signs of pneumonia.

– Who have been in close contact with a person with a confirmed case of COVID-19.

– Subject to planned hospitalization.

– Crossing the entry-exit checkpoint.

– That should be tested in the course of an outbreak investigation.

– Healthcare professionals who directly provide medical care to patients or care for patients with COVID-19.

– Laboratory workers who work with respiratory tract samples obtained from patients with COVID-19.

– Employees of pathological, forensic medical bureaus, departments involved in autopsy, including sampling.

– Other medical and pharmaceutical professionals.

– Patients with planned hospitalization without signs of SARS and/or other acute respiratory viral infections.

– Social workers.

– Employees of the National Police of Ukraine, the Security Service of the President of Ukraine, the Department of State Security and other persons who have direct contact with the President of Ukraine.

– Employees of the National Guard of Ukraine, the State Border Guard Service of Ukraine.

– Employees of the State Service of Ukraine for Food Safety and Consumer Protection.

– Conscripts.

– Military personnel.

– Employees of closed institutions.

Persons defined in paragraphs fourteen to nineteen, if it is not possible to conduct a test for the determination of SARS-CoV-2 antigen using rapid tests and/or a test for the determination of SARS-CoV-2 antigen by ELISA, are detected for SARS-CoV-2 RNA using the PCR method.

A positive result of the SARS-CoV-2 rapid antigen test and/or the SARS-CoV-2 antigen test by ELISA must be confirmed by PCR.

An exception is a positive result of the SARS-CoV-2 rapid antigen test and/or the SARS-CoV-2 antigen test by ELISA in patients who meet the definition of suspected or probable cases of COVID-19.

In case of a negative result of the rapid test for the determination of SARS-CoV-2 antigen and/or the test for the determination of SARS-CoV-2 antigen by ELISA, the person must be examined by PCR in case of symptoms of suspected or probable cases of COVID19.

Laboratory testing for COVID-19 using the PCR method is mandatory for the following persons:

– Patients who meet the definition of a suspect, probable case of COVID-19, with signs of SARS, viral pneumonia, who have not undergone a screening rapid test for the determination of SARS-CoV-2 antigen and/or a test for the determination of SARS-CoV-2 antigen by ELISA.

– Patients with community-acquired pneumonia.

– Contact persons with symptoms that do not exclude COVID-19.

Samples of the first five positive cases and the first ten negative cases that meet the definition of a COVID-19 case must be confirmed for testing using PCR, ELISA, ICLA methods:

– Centers for Disease Prevention Control of the Ministry of Health of Ukraine - in the laboratory of the State Institution “Public Health Center of the Ministry of Health of Ukraine”.

– All other laboratories that conduct research on COVID-19 - in the centers for disease prevention control of the Ministry of Health of Ukraine by administrative-territorial affiliation.

Methods of research of biological material for laboratory diagnosis of COVID-19 using tests for the determination of SARS-CoV-2 antigen, which are used for preliminary screening examination, as well as methods of PCR research, including for the detection of strains of the SARS-CoV-2 virus, must be verified in the laboratory of the State Institution “Public Health Center of the Ministry of Health of Ukraine” or the Centers for Disease Prevention Control of the Ministry of Health Ukraine in accordance with the

Procedure for Verification of the Methodology for the Study of Biological Material for the Purpose of Laboratory Diagnosis of Coronavirus Disease (COVID-19), based on the results of which the Protocol for Verification of the Research Methodology is drawn up (Annex 16).

The detection of antibodies to SARS-CoV-2 is of auxiliary importance for the diagnosis of COVID-19 and is of fundamental importance for assessing the immune response to an existing or past infectious disease.

Testing for antibodies to the SARS-CoV-2 virus is recommended in the following cases:

– An additional method for diagnosing an acute infectious disease (taking into account the seronegative period) in the presence of clinical symptoms and in the presence of a negative PCR test result, the method can be used only in unvaccinated persons.

– Establishing the fact of a previous disease during a mass study of the population to assess the level of population immunity.

– In case of planned hospitalization of patients without signs of SARS and/or other acute respiratory viral infections (rapid tests for the determination of SARS-CoV-2 antigen and/or test for the determination of SARS-CoV-2 antigen by ELISA can also be used for this purpose).

5) Primary health care providers monitor persons who have had contact with patients with COVID-19.

6) All healthcare workers who are in the patient's area and/or come into contact with mucus from the respiratory tract – that is, sputum, BAL, material taken from nasal mucosa, should use PPE.

The patient area is the area within a radius of one meter around the patient.

7) Monitoring of contact health care workers is carried out for 14 days after the last contact and includes temperature measurements, assessment of complaints and examinations. If a healthcare contact worker develops clinical signs of respiratory disease, all appropriate measures should be taken against him/her as a person who meets the definition of a COVID-19 case.

In order to register contact employees and record monitoring data in a health care institution, a journal of any form should be kept indicating at least the following:

– Date(s) of contacts.
– Last name, first name, patronymic.
– Address of residence.
– Contact phone number.
– Monitoring data by day (temperature, presence of complaints).

8) Infection prevention and control measures should be followed in health care facilities when providing medical care and caring for patient's subject to COVID-19 case determination.

9) Treatment of patients with COVID-19 and monitoring of the results of medical care is carried out in accordance with the protocol "Provision of medical care for the treatment of coronavirus disease (COVID-19)", approved by the Order of the Ministry of Health of Ukraine dated April 2, 2020 No. 762 (as amended).

4.2 Practical tasks to be performed in the classroom

Task 1

Describe the procedure for the family doctor in case of obtaining a positive laboratory test result from a patient who has sought medical help.

Task 2

The patient went to the family doctor with complaints of cough, fever up to 38 °C, shortness of breath. X-ray - signs of focal pneumonia.

Question to consider:

What method is mandatory to confirm or exclude the diagnosis of coronavirus disease?

Task 3

Propose a method to assess the state of immunity against COVID-19 in medical school students.

5 Content of the topic

At the practical lesson, students master the organization of the work of a medical institution in case of a positive result for coronavirus disease, study groups of people who are subject to screening for COVID-19, the rules for monitoring contact persons, and the requirements for mandatory confirmation of the diagnosis of coronavirus disease.

6 Questions for self-control:

1) Where is information about a confirmed case of coronavirus disease entered?

2) Who is subject to mandatory PCR testing for COVID-19?

3) Who is subject to pre-screening for COVID-19?

4) When is it recommended to test for the presence of antibodies to COVID-19?

TOPIC 15. THE MAIN TASKS OF MEDICAL ORGANIZATIONS AND THEIR STRUCTURAL SUBDIVISIONS THAT PROVIDE AMBULANCE SERVICES, INCLUDING RAPID SPECIALIZED MEDICAL CARE, ARE AIMED AT PREVENTING THE SPREAD OF COVID-19

Duration - 2 hours.

1 Relevance of the topic

The SARS-CoV-2 virus spreads by droplets. The air (aerogenic) route is not typical for coronavirus disease (COVID-19). In addition, those most at risk of infection include those who have been in contact with the patient or are providing medical care or caring for the patient. Therefore, it is very important to apply preventive measures among health care workers to prevent infection and transmission of the pathogen in a health care facility.

Preventive measures should be taken by health care workers to protect themselves and prevent infection and transmission of the pathogen in health care facilities. Such measures, first of all, include compliance with infection control rules and the use of PPE - choosing the right type of PPE and learning how to put it on, take it off and dispose of it.

2 Specific goals

2.1 The student should know:

- Definition of the term “coronavirus disease”.
- Epidemiological features of coronavirus disease.
- Methods of prevention of viral diseases.
- Definition of the term “disinfection”.
- Types and methods of disinfection.
- Principles of surface disinfection.

2.2 ***The student should be able to:***

– Determine the best method to prevent the spread of COVID-19 to all departments of medical organizations.

– Determine the level of risk in the workplace for healthcare workers.

3 Basic knowledge, skills, and abilities necessary to study the topic (interdisciplinary integration)

Table 33

Previous disciplines	**Skills acquired**
Infectious diseases	Characteristics of COVID-19. Pathogenesis, dynamics of clinical manifestations, laboratory diagnostics, possible complications. Principles of diagnosis, therapy, prevention
Epidemiology	Prevalence of coronavirus infection; ways and mechanisms of transmission of the virus. Types and methods of disinfection

4 Tasks for independent work in preparation for class

4.1 A list of basic terms, parameters, characteristics that the student must learn in preparation for the lesson

Table 34

Term	**Definition**
Disinfection	System of measures for the disinfection of objects in the environment, aimed at the complete, partial or selective destruction of microorganisms potentially pathogenic for humans, in order to interrupt the transmission of infectious agents from the source of infection to people sensitive to it
Personal Protective Equipment (PPE)	Means used by an employee to prevent or reduce the effects of harmful and hazardous production factors and to protect against pollution

To prevent the spread of COVID-19, patients seeking emergency medical care will be interviewed by an EMS dispatcher

according to the algorithm for interviewing a person suspected of having COVID-19. If the interview does not indicate that the team should depart, appropriate recommendations are made to the patient. If there are indications that the team should depart for patients with suspected COVID-19, the team, using personal protective equipment, conducts examinations, makes a preliminary diagnosis, and determines the severity of the illness and the presence of indications for hospitalization. Patients who do not have indications for hospitalization are advised to self-isolate and contact a primary care physician (or the regional/national COVID-19 hotline if no primary care physician is available). One of the methods to prevent the spread of COVID-19 is the use of telemedicine, which is the use of video Internet tools to consult on suspected cases of coronavirus disease (COVID-19).

When leaving, it is mandatory that members of emergency medical teams use appropriate personal protective equipment during the evaluation, provision of emergency medical care, and transportation of a patient with confirmed or suspected COVID-19. Also, during the initial assessment of the patient, it is necessary to maintain a safe distance (more than 2 m) from the patient and others until the mask is put on and the patient is asked to wear a mask. During transport, it is recommended that the required distance be maintained whenever possible.

Precautions to prevent the spread of COVID-19 in the Emergency Medical Care Center:

1) In an emergency medical vehicle or transfer vehicle, medical personnel must use a medical mask, gown to protect against infectious agents, medical gloves, goggles/shield when transporting a COVID-19 suspect. During the aerosol-generating process, medical personnel must use a respirator with a level of protection no lower than FFP2, gown, medical gloves, goggles/shield, medical cap (if required), waterproof apron (if required). The driver is only involved in the transportation of a patient with suspected coronavirus disease (COVID-19) and the driver's compartment must be isolated from the patient area at a distance of at least 1 m, PPE is not required, a

medical mask, gown against infectious agents, medical gloves, goggles / shield are required when assisting with loading or unloading. If there is no direct contact with the patient, but transport without separate zones for the driver and the patient, a medical mask must be used.

2) A patient with suspected coronavirus disease (COVID-19) must use a medical mask when transported to a healthcare facility.

3) Disinfectants or persons who disinfect the car during cleaning and disinfection after and between transporting patients with suspected coronavirus disease (COVID-19) to a health care facility use a medical mask, gown protective against infectious agents, protective gloves, goggles / shield (if there is a risk of contact of organic material or chemicals with the mucous membrane of the eyes) Boots or closed shoes, Cleanable and disinfected, with shoe covers.

Epidemiological teams, including sanitary and quarantine units, do not need PPE when interviewing a person with a suspected or confirmed case of coronavirus disease (COVID-19) or contact persons anywhere if remote methods are used (for example, interviewing by phone or via video). Remote questioning is the preferred method. Epidemiological teams, including sanitary and quarantine units, need a medical mask during a survey without direct contact. Maintain a distance of at least 1 m. Surveys should be conducted outdoors, and when interviewing contacts without any respiratory manifestations who have been in contact with patients with coronavirus disease (COVID19), a distance of at least 1 m should be maintained, PPE is not required. Surveys should be conducted outdoors. If it is necessary to conduct a visit to domestic premises, use a thermal imager to confirm that the person does not have a fever, maintain a distance of at least 1 m and do not touch anything in the household area.

The following levels of risk in the workplace can be beneficial for employers and safety services and Health at work when conducting rapid risk assessments of various jobs and tasks regarding potential occupational exposure to SARS-CoV-2:

1) *Low risk* – work or tasks without frequent close contact with the public or others, which at the same time do not require contact with people with a confirmed or suspected case of SARS-CoV-2 infection.

2) ***Medium risk*** – jobs or tasks with close frequent contact with patients, visitors, providers and colleagues, but which do not require contact with people with a confirmed or suspected case of SARS-CoV-2 infection.

3) ***High risk*** – work or tasks with a high probability of close contact with people with a confirmed or suspected case of SARS-CoV-2 infection or contact with objects and surfaces possibly infected with the virus.

4) ***Very high risk*** – work or tasks with the risk of contact with aerosols containing SARS-CoV-2 in conditions of regular aerosol-generating procedures in cases of patients with COVID-19 or work with infected people in closed, crowded places without proper ventilation.

Low risk includes the following professional tasks-administrative tasks that do not involve contact with patients and visitors or close contact with other colleagues. For example, telemedicine services, remote interviewing of patients with confirmed or suspected cases of SARS-CoV-2 infection or persons who have been in contact with them, work in individual offices or office spaces with low staff density. Prevention and risk reduction measures:

Healthcare facilities:

– Organize remote work and remote services where possible and appropriate.

– Provide natural or mechanical ventilation without recirculation.

– Organize regular cleaning and disinfection.

– Implement measures to avoid crowding and social mixing and encourage employees to maintain a safe physical distance.

– Introduce measures to prevent the sharing of workplaces and equipment.

– Establish a flexible sick leave policy.

– Workers:

a) Stay at home in case of illness.
b) Observe hand and respiratory hygiene.
c) Use cloth masks in common areas and during face-to-face meetings.

Medium risk includes the following occupational tasks - jobs or tasks with close, frequent contact with patients, visitors, providers, and colleagues, but which do not require contact with people with a confirmed or suspected case of SARS-CoV-2 infection. In the case of confirmed or suspected circulation of SARS-CoV-2 to the local population, this level of risk may apply to workers who have frequent and close working contact with others in healthcare settings or in the community, where maintaining a safe physical distance may be difficult. In the absence of confirmed or suspected circulation of SARS-CoV-2 in the local population, this scenario may involve close frequent contact with people coming from areas where circulation is confirmed or suspected. Prevention and risk reduction measures:

Healthcare facilities:

– Use telemedicine services as an alternative to in-person outpatient visits, where possible and appropriate.

– Provide sneeze screens, partitions and workplace conversions and natural or mechanical ventilation without recirculation.

– Organize screening and triage for early recognition of patients with suspected COVID-19 and rapid implementation of source control measures.

– Organize regular cleaning and disinfection.

– Implement measures to avoid crowding and social mixing, such as restrictions on visitors and identifying places where patients are not allowed to access.

– Encourage employees to maintain safe physical distancing when they are not wearing PPE (e.g., in break rooms and cafeterias)

– Ensure IPC training and adequate PPE in sufficient quantity and quality.

– Establish a flexible sick leave policy.

– Workers:
  a) Stay at home in case of illness.
  b) Observe hand and respiratory hygiene.
  c) Wear medical masks and other PPE as assigned and apply standard precautions when providing patient care.

– Patients, visitors, and providers:
  a) Observe hand and respiratory hygiene.
  b) Wear medical or cloth masks in places where SARS-CoV-2 circulates among the general population or certain categories of it.

High risk includes the following occupational tasks: clinical triage with face-to-face interviewing of patients with signs and symptoms of COVID-19; cleaning areas for screening and isolation; entering rooms or isolation areas occupied by patients with a known or suspected diagnosis of COVID-19; physical examination and non-aerosol-generating direct care for patients with known or suspected COVID-19; manipulation of respiratory specimens; handling respiratory secretions, saliva, or waste from patients with COVID-19; transporting people with known or suspected COVID-19 without physical separation between driver and passenger; cleaning between flights, transportation of patients with suspected COVID-19.

Prevention and risk reduction measures

Healthcare facilities:

– Implement engineering, environmental and administrative means of IPC and ensure adequate PPE in sufficient quantity and quality.

– Provide enhanced ventilation without recirculation with a directional system of air flows “from clean to less clean”.

– Organize regular cleaning and disinfection.

– Introduce measures to avoid crowding and social mixing and restrict access for regular workers and visitors.

– Regularly conduct IPC training, including on the use of PPE.

– Establish a flexible sick leave policy.

– Employees and caregivers:

a) Use PPE appropriate for transmission prevention precautions (medical mask, gown, gloves, eye protection) and apply standard precautions when providing patient care.

d) Stay at home in case of illness.

e) Observe hand and respiratory hygiene.

- Patients, visitors, and providers:

a) Wear medical or cloth masks.

b) Observe hand and respiratory hygiene.

Very high risk includes the following occupational tasks: Working with patients infected with COVID-19 in circumstances where aerosol-generating procedures are frequently performed (e.g., tracheal intubation, noninvasive ventilation, tracheotomy, cardiopulmonary resuscitation, manual ventilation prior to intubation, sputum stimulation, bronchoscopy, autopsy procedures, dental procedures using equipment that generates sprays); working with infected people in closed, crowded places without proper ventilation. Prevention and risk reduction measures:

Healthcare facilities:

– Implement engineering, environmental and administrative means of IPC and ensure adequate PPE in sufficient quantity and quality.

– Provide mechanical ventilation with high-efficiency particle filters (HEPA) without recirculation.

– Introduce measures to avoid crowding and social mixing and restrict access for regular employees and visitors.

– Regularly conduct IPC training, including on how to put on and take off PPE
– Establish a flexible sick leave policy.
– Workers:
  a) stay at home in case of illness,
  b) observe hand and respiratory hygiene,
  c) use PPE (N95 or FFP2 or FFP3 respirator, gown, gloves, eye protection, apron) and apply standard precautions when providing patient care.

Some healthcare workers may be at greater risk of developing severe COVID-19 illness due to older age, chronic illness, or pregnancy. According to WHO recommendations, such workers should not be required to perform medium, high or very high risk tasks.

All healthcare facilities should consult with experts to evaluate the performance of their ventilation systems. When making any decision to use natural, hybrid (mixed) or mechanical ventilation, the following should be taken into account: the climate, including the prevailing wind direction, the layout of the building, and the need and cost of a ventilation system. Aerosol-generating procedures should be carried out in rooms with appropriate special conditions and taking into account air exchange considerations.

An important preventive measure for the prevention of COVID-19 is the cleaning and disinfection of surfaces in health care facilities in the context of providing medical care to patients with coronavirus disease.

Basic principles of surface cleaning

Cleaning surfaces should precede any disinfection process. It helps to remove microorganisms or significantly reduce their number on the contaminated surface. Cleaning is carried out with soap and water or neutral detergents by mechanical action (cleaning or rubbing).

Surfaces should be cleaned sequentially from least soiled to most soiled areas and from higher levels to lower. The floor must be cleaned last. After use, the rags should be thoroughly disinfected, it is advisable to use new ones as often as possible. Equipment used for rooms where patients with COVID-19 are staying should be clearly marked and stored separately from other equipment. Cleaning solutions get dirty quickly, which increases the risk of transferring microorganisms to each subsequent surface. Therefore, you should replace the cleaning solution as often as possible.

Principles of surface disinfection

Disinfection solutions must be prepared and used, observing the concentration and exposure time in accordance with the manufacturer's recommendations. Too high concentrations increase toxic effects on persons in contact with the solution and can damage surfaces. A sufficient amount of disinfectant solution should be used to keep surfaces moist for the duration of exposure and the disinfectant can kill the pathogen.

Choosing a disinfectant

When choosing a disinfectant for use in a healthcare facility, its ability to affect the SARS-CoV-2 virus, as well as other pathogenic microorganisms associated with the provision of medical care, should be taken into account.

To achieve a reduction in the SARSCoV-2 virus load on surfaces, the following disinfectants can be used, which are also effective against other pathogens that are important in health care settings: ethanol 70-90 % and chlorine-based products.

Use of chlorine-containing disinfectants

In sodium hypochlorite solutions, the active ingredient is undissociated hypochloric acid (HOCl), which exhibits a wide spectrum of antimicrobial activity. Depending on the concentration, it is effective against various common pathogens. In the context of providing medical care to patients with COVID-19, the recommended concentration of sodium hypochlorite solution is 0.1 %.

Non-contact disinfection methods

It is not recommended to carry out indoor disinfection measures by spraying disinfectants or fumigating in order to destroy the SARS-CoV-2 virus.

Open ultraviolet emitters can be used to disinfect the air in enclosed spaces and surfaces after using disinfectants in the absence of people.

Safe use of disinfectants

When preparing, diluting and using disinfectants, you should follow the manufacturer's recommendations for the safe use of the product, and take into account that disinfectants of different types should not be mixed.

Workers who clean surfaces must wear an appropriate set of PPE, as they work in rooms where there are persons with suspected or confirmed COVID-19 disease. In addition, if PPE is not used during preparation, disinfectant solutions are highly concentrated and, in case of prolonged use, can have a negative impact on the health of the worker

4.2 Theoretical questions for the lesson:

1) Steps to prevent or limit transmission in health care settings.

2) Main measures aimed at preventing the spread of COVID-19 in the Emergency Medical Care Center.

3) Basic Principles of Surface Cleaning

4) Levels of risk in the workplace of employers for employers and safety services and Health.

4.3 Practical tasks to be performed in the classroom

Task 1

Patient P., 25 years old, came to the family doctor for an outpatient appointment due to an acute respiratory viral infection, complains of a significant increase in temperature over the past three days, constant cough and shortness of breath.

Questions to consider:

1) What measures should a family doctor follow to prevent the spread of COVID-19 in an outpatient setting?

2) What should a family doctor recommend during an appointment to prevent the spread of COVID-19?

Task 2

During the call, the emergency medical assistant suspected that the patient had COVID-19 with pronounced symptoms and decided to transport her to the city clinical hospital No. 5.

Questions to consider:

1) What measures should the paramedic and emergency medical driver follow to prevent the spread of COVID-19 during the transportation of the patient?

2) Should a patient with suspected coronavirus disease be transported in an emergency medical vehicle?

5 Content of the topic

At the practical lesson students will get acquainted with the main tasks of medical organizations and their structural divisions aimed at preventing the spread of COVID-19, the basic principles of

cleaning surfaces in medical institutions. Master the skills to determine the level of risk in the employer's workplace for employers and security services and Health.

6 Self-assessment questions:

1) Define coronavirus disease.

2) What methods are available to prevent coronavirus disease?

3) What is the safe distance from the patient and others as the emergency medical team departs and until the mask is put on?

4) How should a patient with suspected coronavirus disease (COVID-19) be transported to a healthcare facility?

5) What PPE should healthcare workers use when performing administrative tasks in the administrative area?

6) What are the disinfectant solutions for cleaning surfaces in COVID-19 healthcare facilities?

7) What level of protection should a respirator be worn by healthcare workers during an aerosol-generating procedure?

TOPIC 16. LONG-TERM COVID. LONG-TERM CONSEQUENCES OF CORONAVIRUS INFECTION WITH SYMPTOMS OF NERVOUS SYSTEM DAMAGE

Duration – 4 hours.

1 Relevance of the topic

Coronavirus infection has direct and indirect mechanisms of influence on the central nervous system with its damage and the development of characteristic symptoms.

Among the common neurological symptoms that occur during the disease and after a coronavirus infection, the most common ones are: headache, loss of taste (ageusia) and smell (anosmia), ataxia, meningitis, cognitive dysfunction, memory loss, seizures and impaired consciousness, depressive states, insomnia. Long-term studies have demonstrated that the effects of SARS-CoV-2 on the brain, spinal cord and peripheral nerves can be particularly devastating and cause disruption of the body's vital functions even after the elimination of the virus. In the experimental studies carried out, a long-term persistence of the virus in the cells of the nervous system was revealed.

Therefore, it is important for the doctor to understand the mechanisms of development of neurological disorders associated with damage to the nervous system, the severity of their manifestations due to the long-term persistence of the virus in nerve cells. This will encourage doctors to further develop, search and improve methods of therapeutic intervention for the correction of neurological disorders.

2 Specific objectives

2.1 The student should know:

– Etiology and epidemiology of COVID-19.

– Features of the pathogenesis of COVID-19.

– **Clinical features of the course of different strains of COVID-19.**

– Classification of coronavirus infection.

– Diagnostic methods and rules for hospitalization of patients.

– Protocols for the treatment of coronavirus infection in adults.

– Specific prophylaxis, vaccination schemes.

– Organizational measures to counter the spread of coronavirus disease (COVID-19).

– Post-COVID syndrome, also known as Long-term COVID.

– Long-term consequences of COVID-19 and outpatient administration of patients with post-infectious syndrome.

– Providing medical care to patients with lesions of the nervous system (COVID-associated stroke, chronic cerebral ischemia, cognitive disorders, anxiety disorders, impaired sense of smell and taste, autonomic disorders).

2.2 The student should be able to:

– Determine the presence of post-infectious syndrome in the patient after a detailed medical history.

– Possess basic skills of studying the state of the nervous system and CNS functions.

– Identify dangerous and life-threatening conditions (e.g., Guillain-Barré syndrome, covid-associated stroke) and treat such conditions.

3 Basic knowledge, skills, and abilities necessary to study the topic (interdisciplinary integration)

Table 35

Previous disciplines	Skills acquired
1	**2**
Epidemiology	Prevalence of coronavirus infection; Ways and mechanisms of transmission of the virus

Continuation of Table 35

1	2
Microbiology	Features of the structure of the coronavirus; resistance in the environment and with the use of specific disinfectants Method of diagnosing the virus
Neurology	Methods of studying the state of the nervous system, the function of the CNS
	Clinical features of the course of strokes, chronic hypoxia of the brain, impairment or loss of smell and taste, methods of treatment and correction of these conditions
Psychiatry	Establishing the relationship between the development of anxiety and cognitive impairment associated with the transfer and persistence of coronavirus in nerve cells

4 Tasks for independent work in preparation for classes

4.1 A list of basic terms, parameters, characteristics that the student must learn in preparation for the lesson

Table 36

Term	Definition
1	2
SARS-CoV-2	***Severe*** ***A****cute* ***Respiratory*** ***S****yndrome* ***Coronavirus-2***) is a single-stranded RNA-containing strain of the SARS -CoV species of the beta coronavirus family that was first genetically detected by the 2019 in a SARS patient sample
COVID-19	An infectious disease caused by the SARS-CoV-2 virus
Post-infectious syndrome	Symptoms triggered by or associated with an infection, and occurring after it

Continuation of Table 36

1	2
Post-COVID syndrome (Long-term COVID)	A post-COVID-19 condition that occurs in people with suspected or confirmed SARS-CoV-2 infection, which usually manifests 3 months after the onset of COVID-19 with symptoms that cannot be explained by other causes, and lasts at least 2 months
Neurotropism	Affinity exclusively for the cells of the nervous system
Neuro-inflammation	The process of inflammation involving nerve tissues can occur under the influence of several exogenous or endogenous factors, causes the development of degenerative diseases of the nervous system, depression, mental illnesses, intellectual and mnestic disorders
Neurological complications after COVID-19	1 ***Symptoms of the central nervous system*** *are* headache and dizziness, cerebrovascular accidents, encephalopathy, encephalitis. 2 ***Symptoms of the peripheral nervous system*** *are* anosmia (loss of smell), Guillain-Barré syndrome (sensory disturbances), and other autonomic disorders. 3 ***Skeletal muscle damage***
Cognitive impairment	Decreased memory, perception, mental abilities, speech impairment due to brain damage in diseases, due to age-related changes and insufficient blood supply to the brain
Guillain-Barré syndrome	Acute autoimmune inflammatory polyradiculoneuropathy, which manifests itself as lethargic paresisandPalsies, sensitivity disorders, vegetative disorders

According to the clinical guidelines of the National Institute for Health and Care Improvement (NICE) of the United Kingdom on the "Management of the long-term effects of COVID-19" (NG188), the following clinical concepts apply to the primary clinical form and the long course of COVID-19:

– ***Acute COVID-19*** – signs and symptoms of the disease persist for up to 4 weeks.

– ***Long-term symptomatic COVID-19*** – signs and symptoms persist for 4 to 12 weeks.

– ***Post-COVID-19 syndrome*** – signs and symptoms develop during or after an infectious disease corresponding to COVID-19, persist for more than 12 weeks, and are not explained by an alternative diagnosis [4].

The American Society for Infectious Diseases (IDSA) distinguishes the following concepts: *"Long-term COVID", "post-COVID syndrome" and "post-acute COVID-19 syndrome".*

The concept of "chronic" or "long-term" course of an infectious disease indicates the persistence of the pathogen. In the absence of circulation of the pathogen and the preservation of the pathological state after the disease, they speak of such a concept as "post-covid syndrome".

Scientists from China conducted a number of studies on the impact of coronavirus on the nervous system and found that people who had COVID-19 had an increased level of cytokines (IL 2, IL 4, IL 6, and IL 17) in the blood serum 2 weeks after recovery. It is known that the release of cytokines contributes to an increase in the permeability of the blood-brain barrier (BBB) and once in the CNS, SARS-CoV-2 can infect astrocytes and microglia, activate a cascade of neuroinflammatory and neurodegeneration responses by releasing tumor necrosis factor (TNF), cytokines, and other inflammatory mediators.

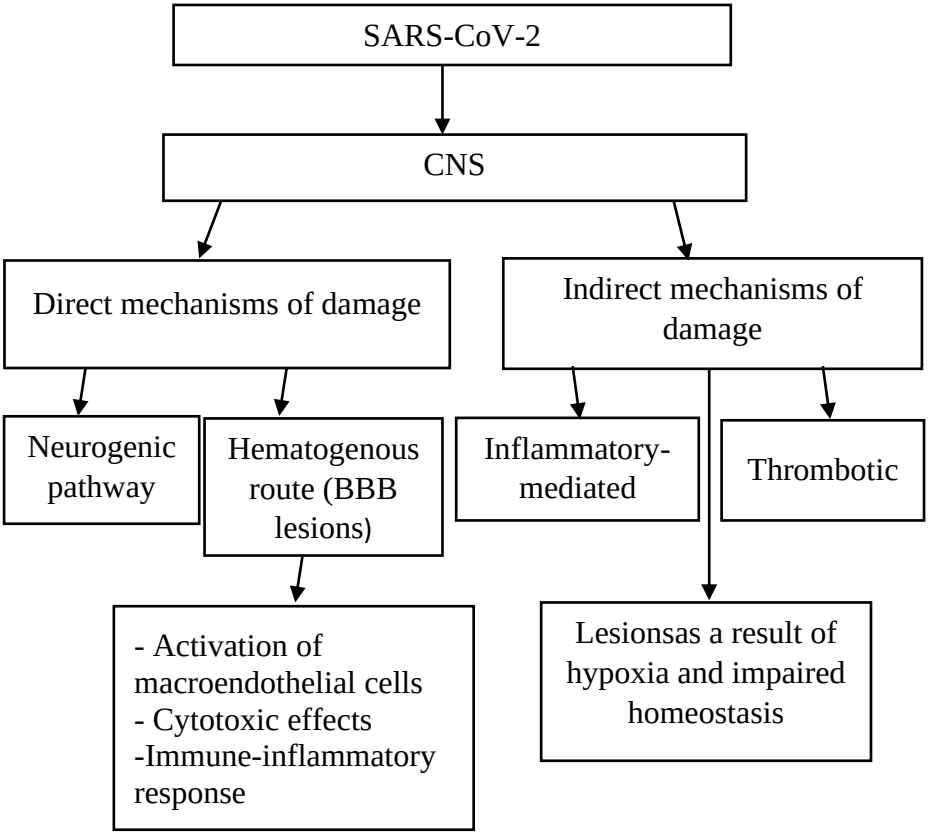

Figure 9 - Pathogenesis of CNS damage by SARS-CoV-2 virus

A Neurogenic pathway

Neurogenic transmission of the virus through peripheral nerves is carried out by retrograde movement through the olfactory nerve to the olfactory bulb, the olfactory tract, bypassing the ethmoid plate. In laboratory intranasal infection of white mice with plaque-forming units, SARS-CoV-2 resulted in 100 % mortality by the 6th day after infection. The onset of severe disease in infected mice correlated with peak levels of the virus in the brain, with these being approximately 1000 times higher than peak titers in the lungs, indicating a high replicative potential of SARS-CoV-2 in the brain.

During the autopsy of people who had COVID-19 during their lifetime, the RNA of the virus was detected in the olfactory bulb, olfactory tract, olfactory tubercle, trigeminal nerve ganglia, medulla oblongata and cerebellum, which confirms the ability of the virus to replicate in the brain, nerve endings of the eyes, nasal cavity, oropharynx.

Hypogeusia (loss of taste) is one of the common symptoms of NA damage in coronavirus infection. The sense of taste is realized through the facial nerve (from the anterior two-thirds of the tongue), the glossopharyngeal nerve, and the superior laryngeal branch of the vagus nerve (from the posterior two-thirds of the tongue), the information is transmitted to the nucleus of the solitary tract in the brainstem and then to the thalamus. Therefore, these cranial nerves also potentially provide a transneuronal route for the virus to enter the brain.

When SARS-CoV-2 enters the central nervous system through the olfactory bulb, neuroepithelial cells damaged by the virus activate inflammatory cells.

The mechanism of interaction of SARS-CoV-2 with the central nervous system, leading to dysfunction of the olfactory system, which is a sensitive indicator of various neurodegenerative diseases such as Parkinson's disease and Alzheimer's disease. The main factor in olfactory dysfunction is the cholinergic system of the basal forebrain, which regulates various neurotransmitters in the brain.

B Hematogenous route, or damage to the blood-brain barrier

The S1 spike protein SARS-CoV-2 can overcome BBB by: a) activation of brain microendothelial cells by the SARS-CoV-2 virus and high expression of vascular and intercellular adhesion molecules, induction of expression and activation of matrix metalloproteinases (MMP), which destroy tight junction proteins; b) recognition of adhesion molecules through β1 and β2 integrins, binding of circulating leukocytes to endothelial cells, resulting in transcellular

extravasation. This process contributes to the penetration of the virus into the brain parenchyma by the “Trojan horse” mechanism.

cR eplication of the SARS-CoV-2 virus due to cellular stress, leading to the degeneration of infected cells.

d) Activation of the inflammatory immune response of SARS-CoV-2, activation of leukocytes and platelets, which further contributes to BBB damage.

f) Expression of angiotensin-converting enzyme 2 (ACE2) and furin protein convertase (PCF) receptors in the membrane of endothelial cells of brain microvessels, promotes infection with SARS-CoV-2, which binds to cells through the S1 subunit of its protein.

Therefore, SARS-CoV-2 can reach the CNS in various ways and cause acute diseases, as well as persist in CNS cells and participate in the formation of delayed neurological sequelae. In addition to the described mechanisms of direct damage to the nervous system by the virus, there is often an indirect lesion associated with the activation of inflammatory and prothrombotic pathways, which may be in some way related to the pathogenesis of systemic and CNS symptoms.

C Inflammatory-mediated injury

Damage to glial cells by coronavirus induces the pro-inflammatory cytokines IL-6, IL-12, IL-15, and TNF-α. In necrotizing encephalopathy, acute necrotizing myelopathy, encephalitis, and acute disseminated encephalomyelitis with negative cerebrospinal fluid PCR, cytokine storm is the most likely mechanism of CNS injury. In patients with SARS-CoV-2, autoantibodies to the coronavirus spike protein react with human epithelial and endothelial cells and cause cytotoxicity.

Therefore, patients with COVID-19 can produce antibodies against SARS-CoV-2, which also attack human endothelial cell antigens in brain vessels or neurons, which can lead to cerebral edema and autoimmune encephalitis.

D Thrombotic injury

In patients with COVID-19, there is an increase in the level of circulating prothrombotic factors, indicating hypercoagulability. Proinflammatory cytokines cause activation of endothelial and mononuclear cells with tissue factor expression, which leads to the activation of the coagulation cascade and thrombin generation. The circulation of free thrombin activates platelets and leads to thrombosis.

E Lesions resulting from hypoxia and impaired homeostasis. Diffuse alveolar and interstitial inflammatory edema in COVID-19 has been shown to result in impaired alveolar gas exchange and CNS hypoxia. Anaerobic metabolism in the mitochondria of brain cells leads to acidosis, vasodilation, increased interstitial edema, obstruction of cerebral blood flow, intracranial hypertension and coma [14]. Most patients in the ICU develop symptoms of acute cerebral dysfunction, manifested by delirium, confusion, psychosis, which are combined under the term "critical encephalopathy" or "critical brain syndrome". At autopsy, acute hypoxic-ischemic injury was found in all cases [14]. Despite the existence of different mechanisms, in most cases the neurological manifestations of COVID-19 occur as a result of its complex effects.

Clinical manifestations of CNS involvement in COVID-19

SARS-CoV-2 infection is manifested by general symptoms and symptoms of CNS damage, such as headache, nausea, vomiting, impaired consciousness, and acute cerebrovascular diseases (stroke, venous sinus thrombosis, and intracerebral hemorrhage [3, 11, 16].

Many authors report damage to the spinal cord and peripheral nervous system in patients with COVID-19 (Guillain-Barré syndrome, acute myelitis) [14–16]. The occurrence of focal neurological symptoms as a result of demyelinating processes caused by SARS-CoV-2 infection has also been described [17]. In addition,

patients with COVID-19 also have non-specific psychological problems such as anxiety, depression, insomnia and distress.

Table 37. Neurologic manifestations in patients with COVID-19

CNS involvement	Neurological manifestations
Nonspecific neurologic manifestations	Dizziness, headache, nausea, impaired consciousness
Cerebrovascular disorders	Ischemic stroke, intracerebral hemorrhage, venous thrombosis, subarachnoid hemorrhage
Inflammatory diseases	Meningoencephalitis, meningitis, encephalitis, myelitis
Demyelinating diseases	Post-infectious acute disseminated encephalomyelitis, post-infectious stem encephalitis Acute necrotizing encephalopathy
Nonspecific psychiatric symptoms	Anxiety, depression, insomnia, distress, confusion
Lesions of the PNS	Hypogeusia and hyposmia Mononeuropathy, cranial polyneuropathy, opticoneuritis Guillain-Barré syndrome Neuralgia
Nonspecific signs of muscle damage	Myalgia, myopathy, rhabdomyolysis, elevated creatine kinase and lactate dehydrogenase

Long-term COVID

Long-term COVID includes the period of manifestation of the disease from 4 weeks or more. The residual symptomatology depends to a large extent on age, hospital stay, severity of the course, and the presence of dyspnea at the onset of the disease [19]. It should be noted that the development of symptoms of post-acute and prolonged COVID-19 does not directly depend on the severity of the course of acute COVID-19 or the place of treatment — in the hospital or outside it. Symptoms can change over time, disappear and

reappear, and can vary in intensity. Symptoms after COVID-19 are primarily related to the respiratory system, heart and nervous system, less often the kidneys, liver, pancreas, spleen, even skin and mucous membranes, blood clotting disorders with subsequent thromboembolism [18]. Residual effects are also found in mild forms of COVID-19 and can persist for a long period of time.

The most common neurological residual changes reported in patients with COVID-19 are headache, dizziness, tinnitus, muscle pain, hemosensory dysfunction (anosmia and ageusia), peripheral neuropathies, sleep disturbances, delirium (in elderly patients). Stroke is rare in the acute phase of infection, but it can also occur in the post-acute period, up to 2 - 3 months after illness. Delayed mood swings, memory and cognitive impairment, and physical discomfort have also been described [18]. People affected by COVID-19 are at increased risk for depression, post-traumatic stress, and substance abuse. Young patients have been found to be more susceptible to emotional sequelae than patients over the age of 60 [19]. Positron emission tomography in coronavirus patients who had functional complaints persisting more than 3 weeks after the onset of the first symptoms of infection demonstrated brain hypometabolism in the olfactory gyrus, associated limbic and paralimbic areas, and its extension to the brainstem and cerebellum (Fig. 10) [20]. This hypometabolism is associated with symptoms and has the value of a biomarker that allows the identification of such patients and potentially their follow-up.

Figure 10 - 18F-FDG brain PET hypometabolism in patients with long-term COVID. Compared to healthy subjects, patients show hypometabolism in the cerebral cortex, including the olfactory gyrus, right temporal lobe, amygdala, and hippocampus, and extending to the thalamus, pons, medulla oblongata, and cerebellum (p-oxel <0.001 uncorrected, p-cluster <0.05 with FWE correction; SPM8 3D rendering).

Approaches to neurological rehabilitation in COVID-19 survivors according to the Stanford Hall Consensus

– All patients who have had COVID-19 should be evaluated for any neurologic symptoms. Screening for cognitive impairment is recommended for at-risk patients (patients after resuscitation or with residual cognitive impairment).

– Patients should be assured that minor neurologic symptoms such as headache, dizziness, loss of smell or taste, and sensory disturbances are likely to improve with minimal medical intervention, and mild to moderate neurologic symptoms are likely to be completely reversed.

– Severe symptoms have the potential to cause significant impairment that can significantly affect quality of life, so multidisciplinary inpatient rehabilitation is recommended for maximum recovery in patients with moderate to severe neurological symptoms.

– The ways of regulation of neurogenesis in the process of rehabilitation of patients are *synaptic (*gymnastics, massage, classes with a speech therapist, swimming, etc.) and humoral (subsidization

of neurotrophic factors and modulation of neurotransmitter processes). To preserve the activity of mediators responsible for the regeneration and restoration of nervous tissue function, neuroprotectors are used in clinical neurology, among which citicolines (Neuroxon) occupy a key place. Neuroxone is a drug that has multimodal action, provides neuroprotection and neurorepair. It actively affects the neurotransmitter balance, enhancing the synthesis of acetylcholine in the central nervous system, which determines its prescription for cognitive disorders of various origins. In addition, Neuroxon helps to increase the content of endothelial cell precursors, increasing the activity of angio- and neovasculogenesis, and also restores the integrity of neuronal membranes, reducing the activity of phospholipase, and thus prevents the development of apoptosis.

Therefore, taking into account the multifactorial pathogenesis of COVID-19, which leads to long-term persistence of clinical symptoms as a result of impaired neuroplasticity and neurogenesis with the formation of cholinergic insufficiency, it is recommended to use Neuroxon at a dosage of 1000 mg per day, divided into 2 doses, for 30 days. It is also advisable to recommend longer medical supervision and control of people who have recovered from COVID-19 for the prevention, timely detection and correction of long-term complications.

To date, the issue of SARS-CoV-2 neutrotropism remains to be studied in detail and there is still disagreement:

– What percentage of SARS-CoV-2 infections present with neurologic symptoms and/or complications?

– Could central or peripheral nervous system involvement be one of the potentially reversible causes of life-threatening conditions (e.g., respiratory failure in Guillain-Barré syndrome or stroke) in patients in severe general condition and patients with respiratory or heart failure? Further research may provide answers to these questions. Ultimately, interventional trials based on these discoveries are needed to identify approaches to reduce or reverse the nervous system impact of COVID-19, which is experienced by a huge number of people around the world.

4.2 Theoretical questions for the lesson:

1) Disclosure of the concepts of “acute COVID-19”, “long-term symptomatic COVID-19”, “post-COVID syndrome”, “long-term COVID-19”, “chronic course”.

2) Pathogenesis of CNS damage by SARS-CoV-2 virus.

3) Brief description of the direct mechanisms of CNS damage (neurogenic and hematogenous pathways).

4) Brief description of indirect mechanisms of CNS damage (inflammatory-mediated lesion, thrombotic injury, hypoxia and homeostasis disorders).

5) Clinical manifestations of damage to the nervous system in COVID-19.

6) Long-term COVID.

7) Approaches to neurological rehabilitation in patients who have had COVID-19.

8) The use of Neuroxon in clinical neurology.

4.3 Practical tasks to be performed in the classroom

Typical example

A 45-year-old woman was admitted to the emergency department with cough and progressive shortness of breath, loss of smell and taste disorder. Her epidemiological history shows that she recently returned from a medical mission in East Asia about 10 days ago, where she was involved in the treatment of several patients with respiratory symptoms. On examination, her body temperature rises to 38.5 °C, blood pressure 140/85 mmHg. Pulse 100/min, respiration 2 2/min with an oxygen saturation of 91 %. CT scan of the chest revealed opacities of the “frosted glass” type, small reticulated opacities, and thickening of blood vessels.

Questions to consider:

1) What is the previous diagnosis of the woman?

2) What is the next step in patient management?

Answer:

1) The patient was definitively diagnosed with infection with the SARS-CoV-2 virus, which will be confirmed by a specific PCR test for SARS-CoV-2.

2) Changes on CT are nonspecific (frosted glass symptom, small reticulated opacities and thickening of blood vessels) characteristic of viral pneumonia. A PCR test will accurately confirm the diagnosis of coronavirus infection.

Dyspnea and oxygen saturation of 91 % in a young woman with no history of comorbidities (COPD) suggests moderate severity of SARS-CoV-2, which requires additional assessment of her condition and possible oxygen support. Refusal of hospitalization and self-isolation can lead to a deterioration in the patient'

s condition.

Task 1

A 30-year-old patient after hypothermia developed paralysis of the facial muscles and lacrimation from the right eye. From the epidemiological history: 2 months ago she had SARS-CoV-2, which was confirmed by PCR testing, since the disease had a mild course, was in self-isolation for the required period. Throughout the time of coronavirus infection, a loss of taste is noted, on the front two-thirds of the tongue on the right.

Questions to consider:

1) Determine the type of neuropathy and can it be associated with a coronavirus infection?

2) Prescribe treatment.

Task 2

A 33-year-old young man complains of weakness in his legs, unsteadiness when walking, urinary incontinence. Two years ago, he was ill with a coronavirus infection, after which he has a sharp decrease in vision in the left eye, followed by a sharp complete restoration of visual function. Horizontal nystagmus, absence of abdominal reflexes, clonus of the feet, pathological reflexes on the

feet were found in the neurological status. The doctor suspected the development of multiple sclerosis in the man.

Questions to consider:

1) Can the occurrence of multiple sclerosis be associated with a coronavirus infection?

2) What additional examinations should be done to confirm the diagnosis?

5 Content of the topic

At the practical lesson, students get acquainted with the basic concepts related to coronavirus infection, the mechanisms of damage to the central nervous system. They receive information about the long-term consequences of COVID-19 with symptoms of damage to the nervous system. They study the basic skills of studying the state of the nervous system and study the relationship between the infection and the development of neurological pathologies, identify dangerous and life-threatening conditions for the patient (for example, Guillain-Barré syndrome, COVID-associated stroke) and treat such conditions.

6 Self-assessment questions:

1) Define SARS-CoV-2, COVID-19, neurotropism, neuroinflammation, cognitive impairment.

2) How long do the symptoms of acute persist? COVID-19?

3) Post-COVID syndrome and chronic persistence of the virus.

4) The main mechanisms of pathogenesis of CNS damage by the SARS-CoV-2 virus.

5) Briefly describe the direct mechanisms of CNS injury in coronavirus infection.

6) Describe the indirect mechanisms of CNS injury.

7) Clinical manifestations of CNS damage in COVID-19.

8) What are the neurological manifestations in patients with COVID-19 and those who have had coronavirus infection?

9) What factors determine the presence and severity of residual effects in Long-term COVID?

10) Basic approaches to neurological rehabilitation in patients who have had COVID-19.

11) The importance of the use of neuroprotectors for the treatment of residual effects of post-COVID syndrome.

TOPIC 17. LONG-TERM COVID. LONG-TERM CONSEQUENCES OF CORONAVIRUS INFECTION WITH SYMPTOMS OF CARDIOVASCULAR DAMAGE

Duration – 2 hours.

1 Relevance of the topic

In February 2020, the World Health Organization (WHO) reported that the duration from the onset of the disease in COVID-19 to complete clinical recovery is about 2 weeks in mild cases and 3-6 weeks in severe patients. As it turned out after some time, a fairly large number of patients are bothered by the symptoms of the disease much longer.

Patients who are concerned about the consequences and symptoms of an infectious disease caused by SARS-CoV-2 suffered 3-4 months ago turn to doctors of various specialties. These are serious dysfunctions of various organs and systems - headache, fever, shortness of breath, heart disorders, increased blood pressure, pain behind the sternum, difficulty concentrating, impaired vision and hearing, kidney damage, muscle and joint pain.

Similar symptoms are found in about a quarter of people who have recovered from SARS-CoV-2, regardless of age, gender and severity. Out of 100 people who have had a coronavirus infection, every 5-6 have complications in the cardiovascular system.

Currently, about half of the patients who visit a cardiologist with disorders of the cardiovascular system are patients who have had acute COVID-19.

Thus, COVID-19 not only aggravates the course of existing CVD, but also creates prerequisites for the occurrence of cardiovascular pathology de novo through a number of direct and indirect mechanisms. Therefore, special attention should be paid to the protection of CVS during the treatment of COVID-19.

2 Specific objectives

2.1 The student should know:

- Etiological factors and pathogenesis of COVID-19.
- Principles for the prevention of the spread of coronavirus infection.
- Features of the course of coronavirus infection.
- Pathogenesis, timing and clinical manifestations of complications of SARS-cov-2.
- The concepts of acute, persistent, chronic and long-term COVID-19.
- Features of the course of SARS-cov-2 in patients with concomitant pathology of the cardiovascular system.
- Symptoms of damage to the cardiovascular system in patients with acute and long-term COVID-19.
- Pathogenetic mechanisms of damage to the cardiovascular system in acute coronavirus infection SARS-cov-2.
- Rules for discharge of patients with SARS-cov-2.
- Acute COVID-19 prognosis and risk factors for long-term COVID-19.

2.2 The student should be able to:

- Take a medical history and evaluate epidemiological data.
- Examine the patient and identify the main symptoms and syndromes of long-term COVID-19.
- Substantiate the clinical diagnosis.
- On the basis of an objective examination, timely recognize possible complications of SARS-CoV-2 with symptoms of damage to the cardiovascular system.
- Draw up a plan for laboratory and instrumental examination of a patient with symptoms of damage to the cardiovascular system.

3 Basic knowledge, skills, and abilities necessary to study the topic (interdisciplinary integration)

Table 38

Previous disciplines	Skills acquired
Microbiology	Characteristics of the pathogen, properties of viruses, features of viral replication
Immunology and Allergology	The role of the immune system in the infectious process. The concept of the regulation of the immune response, cytokine storm. Immunological aspects of complications
Epidemiology	Epidemic process. Mechanism and ways of transmission of COVID-19. The prevalence of pathology in Ukraine and in the world. Specific and non-specific prophylaxis
Infectious diseases	Etiology, epidemiology, pathogenesis and features of the course of coronavirus infection. Dynamics of clinical manifestations, possible complications
Cardiology	Symptoms of damage to the cardiovascular system. Specific markers of myocardial damage, troponin test
Resuscitation and intensive care	Emergencies: acute heart failure

4 Tasks for independent work in preparation for class

4.1 A list of basic terms, parameters, characteristics that the student must learn in preparation for the lesson

Table 39

Term	Definition
1	2
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
COVID-19	Disease caused by SARS-CoV-2
Acute COVID-19	Complaints and symptoms of COVID-19 lasting up to 4 weeks

Continuation of Table 39

1	2
Persistent symptomatic COVID-19	Complaints and symptoms of COVID-19 lasting from 4 to 12 weeks
Long-term COVID	A diagnosis that includes increased fatigue, headache, joint pain, certain cardiovascular and neurological disorders lasting weeks in patients after acute COVID ≥ 12
Cytokine storm	The reaction of the immune system, the essence of which is the uncontrolled activation of immune cells by cytokines in the focus of inflammation and the release of a new portion of cytokines by the latter
Heart failure	Disruption of the structure and function of the heart, which leads to the inability of the latter to provide oxygen and energy supply in accordance with the metabolic needs of the body's tissues
Troponin test	It is a biochemical analysis of the composition of the blood, which makes it possible to detect the presence of the troponin (Tn) in it. This protein leaks into the bleeding system from dead cardiomyocytes in MI
Myocardial infarction type 2 (MI type 2)	Myocardial ischemia due to increased oxygen demand or decreased oxygen delivery

With a wide range of effects on various body systems, it interacts with CVS at different levels and causes direct and indirect damage.

From the pathogenesis, it is known that COVID-19 penetrates the mucous membranes with the help of angiotensin converting factor 2 (ACE2). Most of it is on the surface of the cells of the respiratory tract (alveolocytes of the first and second order), which explains the damage to the virus primarily of the respiratory system.

Pathogenetic links of myocardial injury

The mechanism of acute myocardial injury caused by infection may be related to ACE2, which is widely expressed not only in the lungs but also in the cardiovascular system.

Other mechanisms of myocardial injury include cytokine storm caused by an unbalanced response of type 1 to 2 T helper cells, as well as respiratory dysfunction and hypoxemia (resulting from pneumonia), leading to cardiomyocyte ischemia and necrosis.

Cytokine storm syndrome is a serious, life-threatening condition with clinical signs of systemic inflammation, methemoglobinemia, hemodynamic instability, and multiple organ failure. A distinctive feature of cytokine storm syndrome is an uncontrolled and dysfunctional immune response, including continuous activation and proliferation of lymphocytes and macrophages. Patients with COVID-19 have high plasma levels of cytokines, including IL-2, IL-7, IL-10, granulocyte colony-stimulating factor, chemokinin 1. Activation or increased release of these inflammatory cytokines can lead to apoptosis or necrosis of myocardial cells.

A decrease in blood oxygen saturation due to severe pneumonia leads to a decrease in its supply to the heart muscle.

This is also caused by a significant decrease in blood pressure during dehydration due to high fever and shortness of breath. At the same time, inflammation and fever increase the heart rate, the heart's need for oxygen. Under conditions of restriction of its delivery due to hypoxia, conditions for myocardial ischemia are created.

Long-term ischemia causes irreversible myocardial damage, the so-called type 2 myocardial infarction.

Its marker is an increase in troponin levels, which is found in a significant proportion of patients and significantly worsens the prognosis.

According to research results, 71% of patients who have recovered from COVID-19 have an increased concentration of highly sensitive troponin in their blood.

Fever and intoxication also contribute to the occurrence of arrhythmias – atrial fibrillation and frequent extrasystoles, which can impair hemodynamics.

Based on this, the following **factors of damage to the cardiovascular system can be distinguished**:

1 primary myocardial injury (myocarditis);

2 vascular endothelial lesions (primarily coronary vascular endothelium), including atherosclerotic plaque rupture, which impairs myocardial perfusion;

3 increased pulmonary artery pressure due to pulmonary inflammation and microthromboembolism, which increases the load on the right ventricle;

4 taking medications that can cause arrhythmias (fluoroquinolones, macrolides, hydroxychloroquine, a number of antiviral drugs) or sodium and fluid retention (infusion solutions, glucocorticoids, insulin in case of reflex hyperglycemia, nonsteroidal anti-inflammatory drugs – NSAIDs).

Manifestations of CVS damage during acute SARS-CoV-2:

- Severe systemic inflammation,
- Myocardial ischemia,
- Lowering blood pressure,
- Thromboembolism and increased pulmonary artery pressure,
- Myocarditis,
- Rhythm disturbances,
- Sepsis
- Hypoxemia.

These symptoms cause the onset of HF or the progression of symptoms of pre-existing CHF.

Biomarkers of myocardial injury in COVID-19

Cardiomyocyte damage and hemodynamic load on the heart cavities (assessment using the concentrations of cardiac biomarkers: cardiac troponins T and I, natriuretic peptide type B (BNP) and N-terminal natriuretic propeptide – NT-proBNP) develop with COVID-19. The levels of biomarkers are directly proportional to the severity of the disease.

Troponin concentrations T and I, BNP and NT-proBNP should be interpreted quantitatively. In patients hospitalized for or after COVID-19, mildly elevated levels of these biomarkers are usually due to pre-existing heart disease and/or COVID-19-associated acute injury. If there is no typical angina pain and/or ischemic ECG changes, patients with mild elevated ECG levels do not need to use either the diagnostic or treatment characteristic of type 1 myocardial infarction.

In patients who have had COVID-19, as well as in patients with pneumonia of other etiologies, the concentration of troponin is measured only if the diagnosis of type 1 myocardial infarction is considered on the basis of clinical symptoms or the detection of new LV dysfunction.

Regardless of its role in diagnosis, monitoring troponin levels may be useful in assessing prognosis.

Elevated cTn T or I is found in 5% to 25% of patients with COVID-19, more often in patients in the intensive care unit.

A mildly elevated concentration of cTn T or I do not indicate the development of acute coronary syndrome unless accompanied by clinical or ECG signs of myocardial ischemia.

The immediate cause of a significantly elevated concentration of cTn T or I is a complication of COVID-19 – hypoxia and heart damage in myocarditis, stress-induced cardiomyopathy (takotsubo) and myocardial infarction caused by COVID-19.

Cardiac imaging studies

Imaging studies play a significant role in the differential diagnosis of CVD. On MRI, when infected with SARS-CoV-2 of the heart, diffuse tissue edema is visualized, indicating inflammation. Cardiac biopsy specimens revealed inflammatory infiltrates from T-lymphocytes with areas of edema and foci of necrosis.

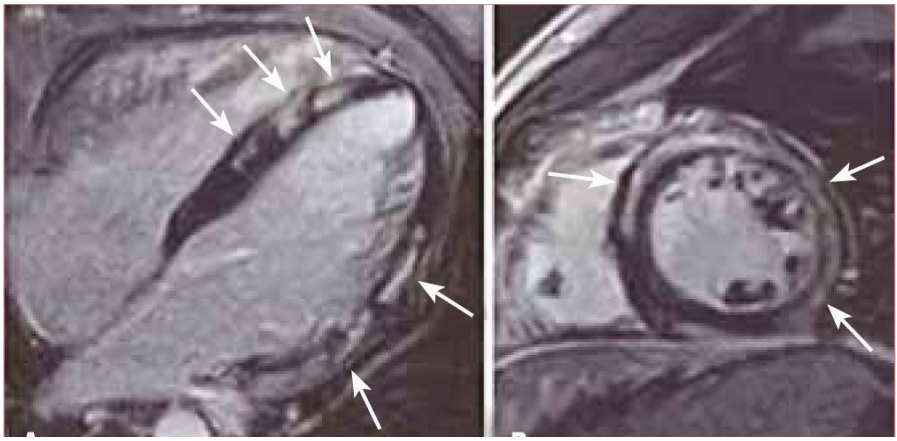

Figure 11 - CT scan of the heart. Areas of diffuse edema (inflammation of the myocardium) are indicated by arrows

When performing an MRI of the heart, the most common pathologies are:

– inflammation of the myocardium, followed by the development of a regional scar and damage to the pericardium,

– deterioration of parameters such as left and right ventricular ejection volume and fraction,

– prolonged perimyocarditis after COVID-19.

In combination with the results of histological examinations, MRI data indicate that the inflammatory process is due to COVID-19.

In 35 % of patients who died from SARS-CoV-2, viral RNA was detected during a cardiac autopsy, suggesting that the death was due to direct coronavirus damage to the myocardium.

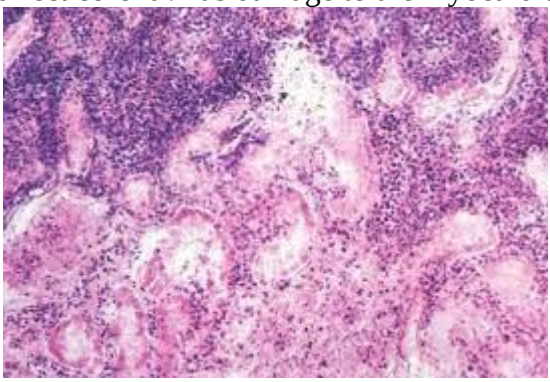

Figure 12 - Myocardium with areas of necrosis

Thus, the acute inflammatory process in acute COVID-19 leads to the worsening of ischemic disorders in the context of existing diseases of the cardiovascular system and provokes a systemic inflammatory response of the body with an increase in endothelial dysfunction and procoagulant activity of the blood.

Chronic inflammation plays a leading role in the pathogenesis of HF, inflammatory myocardial damage and, as a result, acute decompensation of HF are especially dangerous in COVID-19.

4.2 Theoretical questions for the lesson:

1) Definitions of acute COVID-19, persistent COVID-19, long-term COVID-19.

2) The main pathogenetic mechanisms of damage to the cardiovascular system in COVID-19.

3) The main clinical symptoms of damage to the cardiovascular system after acute COVID-19.

4) Laboratory changes indicating myocardial damage after acute COVID-19.

5) Additional tests needed to identify long- with symptoms of CVS involvement.

4.3 Practical tasks to be performed in the classroom

Typical example:

Patient R, 55 years old, who had an acute COVID-19 with a severe course 4 months ago, complains of pain behind the sternum, shortness of breath at rest, edema of the lower extremities has appeared in the last month. He has a history of chronic right ventricular heart failure. Complete blood count - no changes. The PCR test is negative.

Questions to consider:

1 What complication did the patient have after suffering from acute COVID-19?

2 What is the mechanism of occurrence of this condition?

Answer

Considering that the patient suffered from acute COVID-19 4 months ago, as well as clinical symptoms - pain behind the sternum, dyspnea at rest, edema and the presence of concomitant pathology - CHF, it can be assumed that the patient has decompensated heart failure. The mechanism of occurrence of this condition is explained by direct and indirect damage to the CVS in acute COVID-19 and long-term COVID.

Task 1

Patient M, 74 years old, who has been in the Infectious Diseases Department for 4 days with severe acute pneumonia caused by the SARS-CoV-2 virus, is suspected of having acute myocardial infarction type 2.

Question to consider:

What laboratory test should be carried out to clarify the diagnosis?

Task 2

A patient with moderate acute COVID-19 died on the 3rd day. At the autopsy, changes in the lungs were detected - a focus of serous inflammation, areas of compaction of the lung tissue. During

the autopsy of the heart, areas of myocardial necrosis and viral RNA were found.

Question to consider:

What was most likely to cause the death of this patient?

5 Content of the topic

During the practical part of the course, students will get acquainted with the variants of the course of COVID-19, especially the concept of long-term COVID-19. They will get information about direct and indirect pathogenetic mechanisms of cardiovascular damage in acute COVID-19. You will be able to examine the patient and identify the main symptoms and syndromes of long-term COVID-19. On the basis of an objective examination, they learn to recognize possible complications of SARS-CoV-2 with symptoms of damage to the cardiovascular system in a timely manner.

6 Self-assessment questions

1) What are the COVID-19 variants? Describe each one.
2) What organs and systems of the body do coronaviruses infect, and with what specific receptors?
3) What research has been done to understand the direct effects of coronaviruses on the cardiovascular system?
4) Does the severity of acute COVID-19 depend on its occurrence?
5) What clinical symptoms of CVS lesions occur in patients with COVID-19?
6) What pathological changes occur in the myocardium during long-term COVID-19 with symptoms of CVS damage?
7) What is the significance of a moderate/significant increase in plasma troponin in patients with acute COVID-19?
8) What other cardiac markers may indicate myocardial damage?

REFERENCES

1 COVID-19: epidemiology, clinic, diagnosis, treatment and prevention / M. A. Andreychyn [et al.] // Infectious diseases. – 2020. – No. 2. – P. 41–55.

2 Order of the Ministry of Health of Ukraine No. 762 of April 2, 2020 (as amended by the Order of the Ministry of Health of Ukraine No. 358 of February 22, 2022) PROTOCOL "PROVISION OF MEDICAL CARE FOR THE TREATMENT OF CORONAVIRUS DISEASE (COVID-19)" / RADA. Verkhovna Rada of Ukraine. Legislation of Ukraine. – Available at : https://zakon.rada.gov.ua/rada/show/v0762282-20#Text.

3 Order of the Ministry of Health of Ukraine dated March 28, 2020 No. 722 [As amended by the Order of the Ministry of Health of Ukraine]. STANDARDS of medical care "Coronavirus disease (COVID-19)" / RADA. Verkhovna Rada of Ukraine. Legislation of Ukraine. – Available at : https://zakon.rada.gov.ua/rada/show/v0762282-20#Text.

4 Sadovak I. D. et al. CLINICAL MANAGEMENT OF PATIENTS WITH COVID-19. "LIVE" CLINICAL INSTRUCTION. – Available at : https://www.researchgate.net/scientific-contributions/Sadovak-Irina-Dmitrivna-2242981238. DOI:10.31612/covid.

5 Liira Helena. Long-term symptoms of COVID-19 / EBM Guidelines 12.10.2021. / Available at : chrome-extension://efaidnbmnnnibpcajpcglclefindmkaj/https://www.dec.gov.ua/wp-content/uploads/2022/01/long-term-symptoms-of-coronavirus-infection.pdf.

6 Tkachenko, L. O. Potential Influence of Coronavirus on the Cardiovascular System in the Context of the COVID-19 Pandemic / L. O. Tkachenko, O. A. Yepanchintseva, B. M. Todurov. – 2020. – № 2. – P. 5–17. – Available at : http://nbuv.gov.ua/UJRN/karx_2020_2_3.

7 Coronavirus disease (COVID-19): features of the course and treatment of myocardial infarction and heart insufficiency /

N. M. Seredyuk [et al.] // Art of Medicine. – 2020. – No. 3. – P. 182–188.
8 Temporary local clinical protocol on the organization of work in the infectious diseases department upon admission of a patient with acute respiratory disease COVID-19 caused by coronavirus SARS-CoV-2 / Head of the National Military Medical Clinical Center "GVKG", Major General of the Medical Service A. Kazmirchuk, Head of the Ukrainian Military Medical Academy, Colonel of the Medical Service V. Savitsky. – Kyiv, 2020.
9 Epidemiology: anti-epidemic measures : textbook / M. D. Chemych [et al.]. – Vinnytsia : Nova Kniha, 2020. – 288 p.
10 PULMONARY DISEASE IN COVID-19 / Y. I. Feshchenko [et al.] // Ukr. Pulmonol. J. – 2021. – No. 1. – P. 5–14.
11 Liu Y. The effective reproductive number of the Omicron variant of SARS-CoV-2 is several times relative to Delta / Y. Liu, J. Rocklöv // Travel Med. J. – 2022 May 31. – No. 29 (3). – taac037 p. DOI: 10.1093/jtm/taac037.
12 Achaiah N. C., Subbarajasetty SB, Shetty RM. R0 and Re of COVID-19: Can We Predict When the Pandemic Outbreak will be Contained? / N. C. Achaiah, S. B. Subbarajasetty, R. M. Shetty // Indian J. Crit Care Med. – 2020 Nov. – No. 24 (11). – P. 1125–1127. DOI: 10.5005/jp-journals-10071-23649.
13 D'Amico F. COVID-19 seasonality in temperate countries / D'Amico F. [et al.] // Environ. Res. – 2021 Dec. – No. 206 (1). – 12614 p. DOI: 10.1016/j.envres.2021.112614.
14 Hirose R. Disinfectant effectiveness against SARS-CoV-2 and influenza viruses present on human skin: model-based evaluation / R. Hirose [et al.] // Clin. Microbiol. Infect. – 2021 Jul. – No. 27 (7). – P. 1042.e1-1042.e4. DOI: 10.1016/j.cmi.2021.04.009.
15 Michael A. SARS-CoV-2 inactivation by ultraviolet radiation and visible light is dependent on wavelength and sample matrix /

A. Michael // Journal of Photochemistry and Photobiology B: Biology. – 2022. – Vol. 233. Available at : https://journals.scholarsportal.info/browse/10111344/v233icomplete.

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