ONOMY Science

American journal of Virology & Disease
ISSN 2643-5357

Review Article Open Access

Diagnosis and treatment of new coronavirus infection in a multidisciplinary hospital: experience of City Clinical Hospital No. 15

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Citation: Diagnosis and treatment of new coronavirus infection in a multidisciplinary hospital: experience of City Clinical Hospital No. 15. Am J of Viro and Dis. 2020; 2(4): 01-23.

Submitted: 28 October 2020; **Approved:** 02 November 2020; **Published:** 04 Navember 2020

Abstract

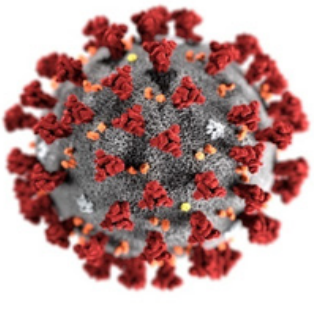
The article discusses etiology, pathogenesis, diagnostics, clinical presentation and treatment of COVID-19 caused by the coronavirus SARS-CoV-2 based on literature review and own experience of managing patients with COVID-19 of clinicians of infectious hospital on the basis of the converted City Clinical Hospital No. 15 named after O.M. Filatov. The article focuses on changes in the opinion of medical community on the pathogenesis and treatment approaches during the pandemic.

Keywords: Pandemic; coronavirus SARS-CoV-2; infectious disease COVID-19; cytokine storm; respiratory failure; ARDS; COVID-19 diagnosis; pathogenic treatment.

Introduction

COVID-19 (COronaVIrus Disease 2019) is an acute respiratory infection caused by coronavirus SARS-CoV-2 (2019-nCoV), which is characterized by variability in its course. It can occur both as a mild [39,4] or severe [17] respiratory infection.

Fig.1 Model of the COVID-19 coronavirus



The most common complication is viral pneumonia, which can lead to ARDS and, subsequently, to acute respiratory failure that often requires oxygen therapy and respiratory support [23]. The most common clinical symptoms are fever, fatigue and dry cough [6]. However, the clinical picture varies greatly. A fairly high infectiousness has led to the rapid spread of the disease around the world. The virus is transmitted by airborne droplets or by fomites with subsequent entry into the eyes, nose or mouth [36]. The disease is caused by a new virus, against which people initially have no acquired immunity [36]. People of all ages are susceptible to the infection. Despite the long period of the pandemic, there is still no specific antiviral treatment or prevention [39].

In most cases (about 80%), no specific treatment is required, and recovery occurs naturally [39,6]. In severe cases, treatment is needed to maintain the function of vital organs. Approximately 15% are severe cases, and another 5% are critical ones [13].

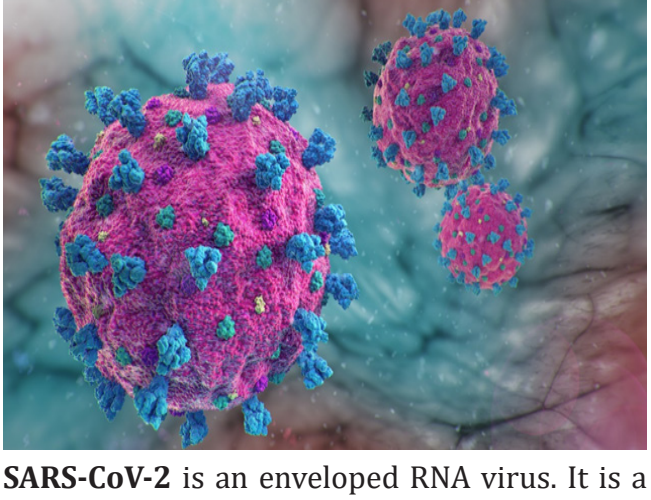
On March 11, 2020, the spread of the virus was declared as a pandemic [29]. It developed rapidly with increasing number of infected people and lethal cases. Various scientific and clinical studies are being conducted, and free access and exchange of information related to the new disease is more relevant than ever.

However, it is the first pandemic in the history of mankind that can be brought under control [37]. The main danger of the pandemic is that the simultaneous infection spread in the community may lead to an overload within the healthcare system, which may not be ready for an unusually large number of seriously ill patients [16]. Therefore, the most important response to the infection may be not only treatment, but containment [13]. The epidemic will end as soon as the population achieves herd immunity [34].

Etiology

Etiological agent of COVID-19 is a previously unknown beta-coronavirus SARS-CoV-2, which was detected in lung fluid samples of a group of patients with pneumonia in the Chinese city of Wuhan in December, 2019. The virus belongs to the subgenus Sarbecovirus and is the seventh known coronavirus that can infect people [25].

Fig.2 Model of the coronavirus



SARS-CoV-2 is an enveloped RNA virus. It is a recombination of a bat coronavirus with another yet unknown coronavirus. It is assumed that the virus was transmitted to humans from pangolins [25,18]. The full genome of the virus has already been decoded [25].

The virus invades the cell by attaching its peplomer protein to the angiotensin-converting enzyme type II receptor [39]. Virus entry is also facilitated by preactivation of the peplomer by furin, which is absent in the SARS virus [22]. Once attached to the receptor, the SARS-CoV-2 virus uses cell receptors and endosomes [28] to invade the cell with help of TMPRSS2 protease [14]. The virus interacts with mucus in the respiratory tract causing a large release of cytokines and an immune response. At the same time, a decrease of lymphocytes occurs, in particular T-lymphocytes. A large number of lymphocytes is needed to fight against the virus, leading to weakening of the immune system. Such changes may cause exacerbation of chronic diseases [22].

High viral load in the pharynx is detected in the first week with the emergence of symptoms, reaching the highest level on the 4th day after onset, which indicates an active replication of the virus in the upper respiratory tract. The duration of viral shedding after the disappearance of symptoms is estimated at 8-20 days [28]. However, detection of the viral RNA after recovery does not mean the presence of a viable virus [15].

Pathogenesis of COVID-19

Thus, most cases of COVID-19 are mild or moderate, but in some cases (about 20%) SARS-CoV-2 causes intense inflammatory process called a cytokine storm, which can lead to fatal pneumonia and ARDS. At the same time, the profiles of the cytokine storm may differ [38]. Cytokine release syndrome is a potentially life-threatening systemic inflammatory response of the body to a drug or infectious agent, such as SARS-CoV-2. It is characterized by increased level of interleukin 6 (IL-6), which is correlated with respiratory failure, ARDS, and other complications [35]. Increased levels of proinflammatory cytokines may also indicate the development of secondary hemophagocyticlymphohistiocytosis [26], a life-threatening severe hyperinflammation caused by uncontrolled proliferation of activated lymphocytes and macrophages that release a large number of inflammatory cytokines. Inflammatory cytokines are signaling molecules that

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are released from immune cells such as T-helper cells (Th) and macrophages. These include not only IL-6, but also IL-1, IL-8, IL-12, IL-18, tumor necrosis factor alpha (TNF-alpha) and gamma interferon (IFN-γ) [13].

Fig.3 Normal lung tissue (gross specimen)

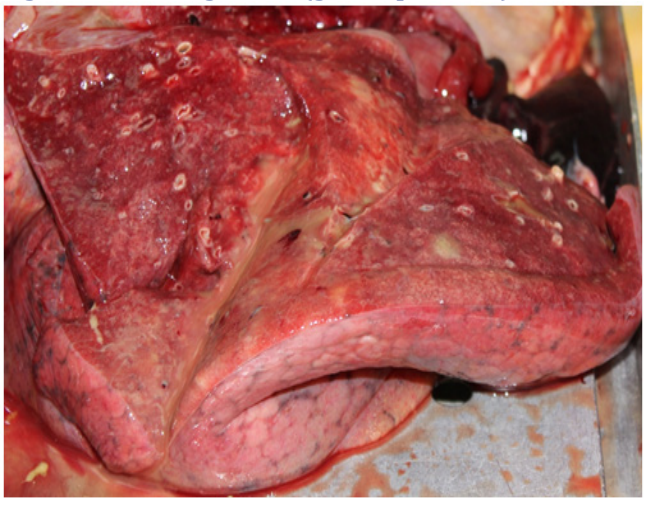
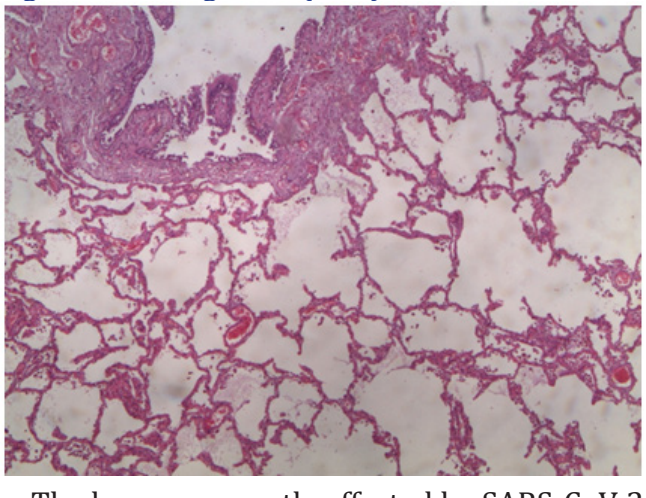


Fig.3 Normal lung tissue (slide)



The lungs are mostly affected by SARS-CoV-2 (Fig. 3,4). The virus penetrates the epithelial cells of the upper respiratory tract and descends down the mucosa, accessing the host cells via the ACE-2 (angiotensin-converting enzyme type II), which is most common in alveolar type II cells [34]. The diffuse inflammation of lungs starts with single foci that gradually merge and infect almost all of the lung tissue. The process is usually bilateral and symmetrical.

It starts with an inflammation of the pulmonary interstitium with thickening of the intra-alveolar septa and partial filling of the alveoli with pathological substrate. Alveolar volume decreases due to incomplete inspiration. If the pathological process continues to develop, all the structural components of the lungs are gradually becoming affected. There are 3 phases: exudative, proliferative and fibrotic.

Cytokine-activated alveolar macrophages and neutrophilic leukocytes attach to the endothelium of the pulmonary capillaries and release proteases and toxic oxygen metabolites containing in their cytoplasmic granules [34]. This causes damage to the capillary endothelium and the epithelium of the alveoli, breaking the blood-air barrier. The exudate penetrates the pulmonary parenchyma and alveolar air space, which leads to gas exchange disorder resulting in hypoxia [26]. Type II pneumocytes, which are forming pulmonary surfactant, are damaged. In this case an alveolar collapse, a decrease in the lung compliance, and pulmonary shunt occur. In addition, pulmonary hypertension develops as a result of pulmonary embolism, hypoxic pulmonary vasoconstriction, and effect of inflammatory mediators (thromboxane, leukotrienes, endothelin).

Fig. 5 Viral damage to lungs and trachea

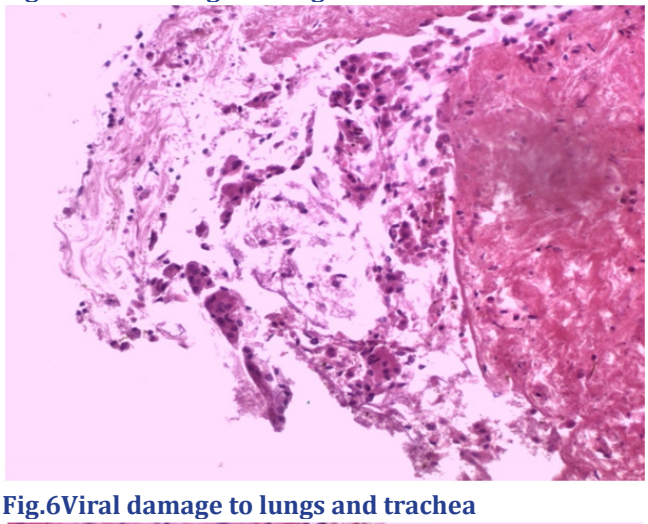
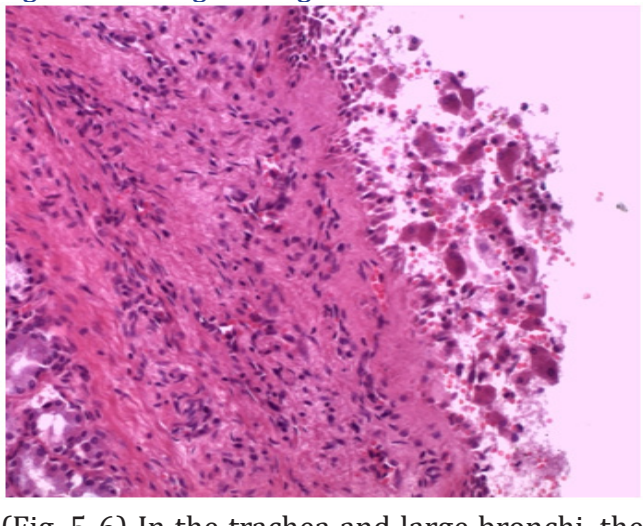


Fig.6Viral damage to lungs and trachea



(Fig. 5-6) In the trachea and large bronchi, the epithelium is partially desquamated, with signs of viral damage (the presence of multinucleated and deformed cells). No inflammatory infiltration.

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As a result of direct viral damage, the microcirculatory bed is presented with capillary congestion of the interalveolar septa and branches of the pulmonary arteries and veins with red blood cell sludge, fresh fibrin and organizing thrombi. Intrabronchial, intrabronchoalveolar and intra-alveolar hemorrhages are seen. Formation of hemorrhagic infarcts is possible. These hemorrhages are a source for hemoptysis.

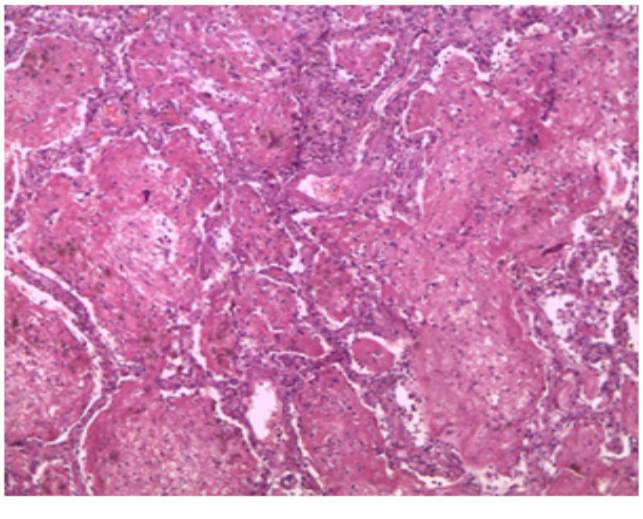
It is important to distinguish thrombi from thromboemboli, since PATE is also characteristic of COVID-19. Pulmonary embolism can extend to the right chambers of the heart. Cases of arterial thrombosis of various organs with the development of their infarcts are also known.

Such lung lesions (Fig. 5,6) are the cause of death without bacterial or fungal superinfection [20]. The processes that occur in the lungs and other organs are illustrated by photographs of macro and micro samples that were obtained during autopsies in the Filatov hospital (Fig. 5,6).

If the disease is in proliferative phase, the lung function restores in most cases. Exudate and cell infiltration are being removed. Type II pneumocytes proliferate, form a new surfactant and differentiate into type I pneumocytes.

But even in this period many patients still have shortness of breath and hypoxemia. In some patients, the process reaches the fibrotic phase

Fig. 7-8 Fibrin, fibroblast tissue growth, areas of obliterating bronchiolitis and loose fibrosis with slit-like structures lined with metaplastic squamous epithelium, interstitial inflammation with thickening and edema of the intra-alveolar septa, edema and myxomatosis of the perivascular stroma in alveolar lumina



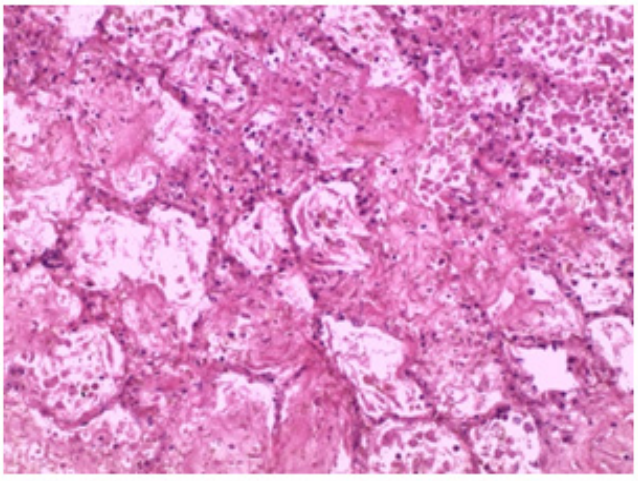
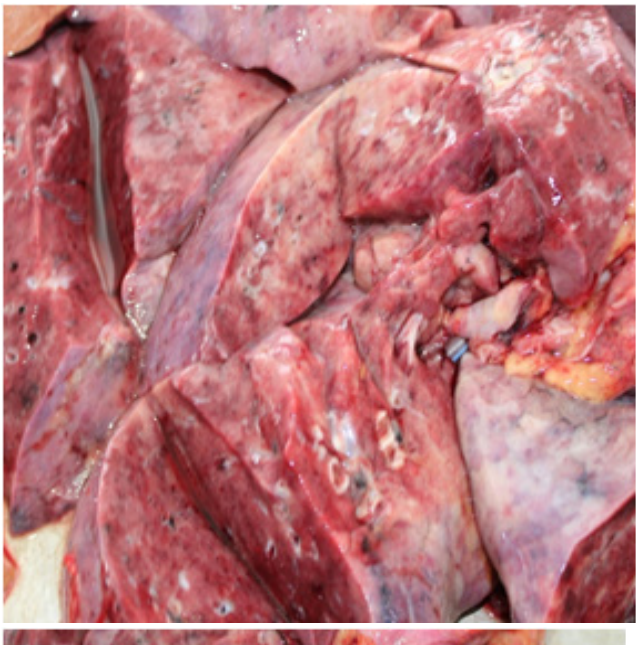


Fig. 9-10 Phase of organization and growth of fibroblastic tissue. Areas of obliterating bronchiolitis, loose and dense fibrosis



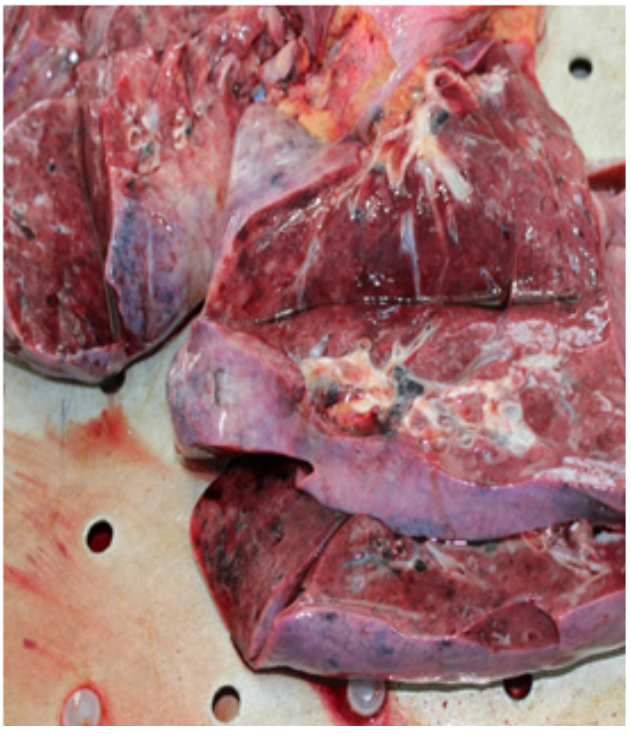


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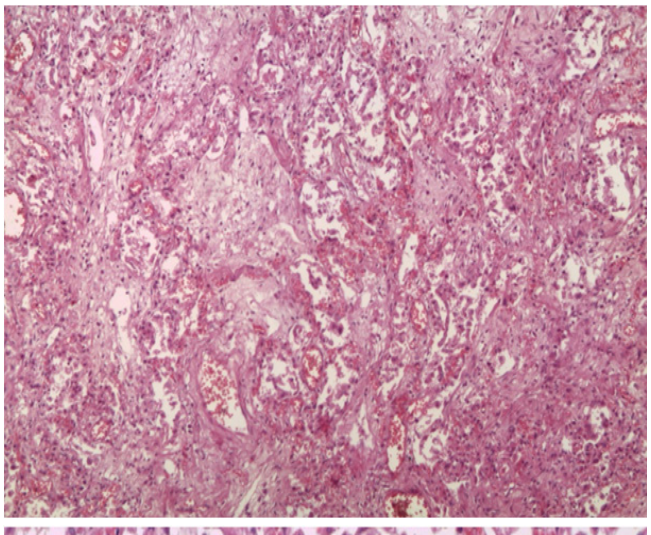
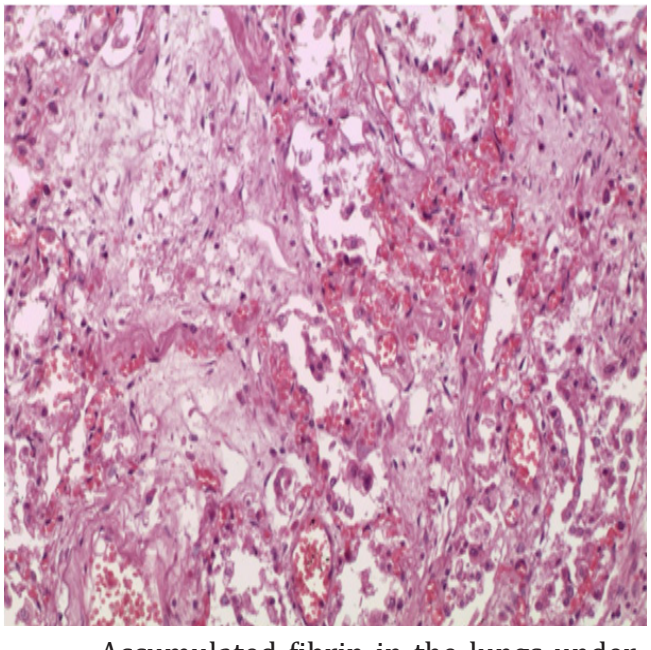
Fig. 11-12 Areas of fibrosis with slit-like structures lined with metaplastic squamous epithelium, growth of granulation tissueedema of the intra-alveolar septa, edema and myxomatosis of the perivascular stroma





Accumulated fibrin in the lungs undergoes remodeling leading to fibrosis.

But the lungs, unfortunately, are not the only organ that suffers from COVID-19. While monitoring the patients, it quickly became clear that almost all organs and systems are involved in the pathological process.

The reason for the fairly frequent involvement of the gastrointestinal tract (GI) is the massive expression of ACE-2 in the gastric gland cells, in the endothelial cells of blood vessels, enterocytes in the small intestine and in the epithelium of the rectum. Severe intestinal lesion with damage of the components of the intestinal wall, separation of intercellular interactions occurs. Along with these functional and dyspeptic disorders, there may be intestinal necrosis as a consequence of mesenteric thrombosis, as well as segmental necrosis due to microvascular thrombosis (Fig. 13).

Fig.13 Focal segmental necrosis of the small intestine

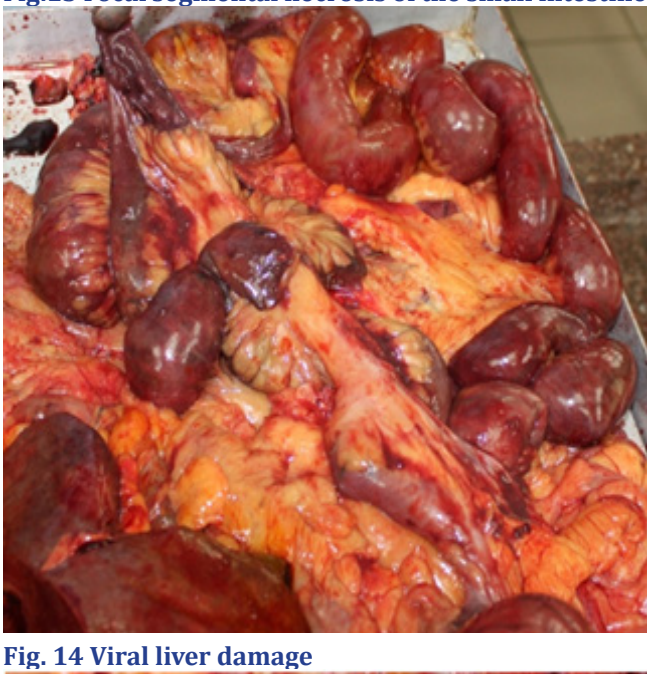
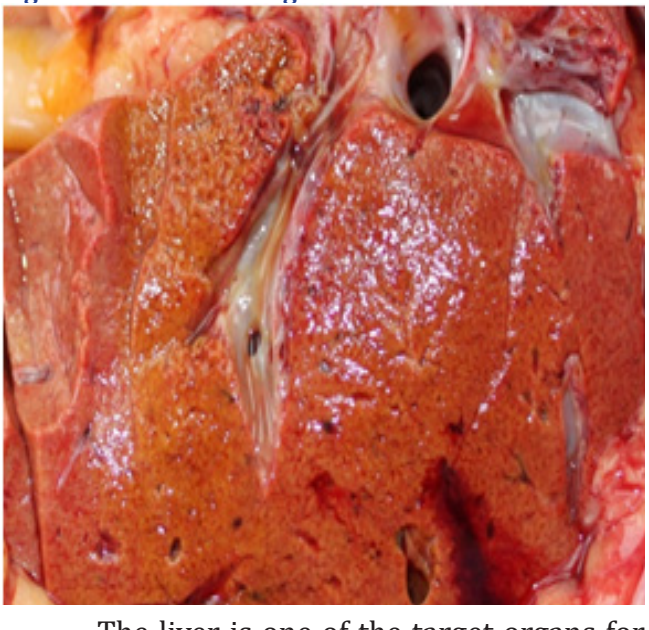


Fig. 14 Viral liver damage



The liver is one of the target organs for COVID-19. During autopsy, severe acute fatty liver dystrophy is detected (Fig. 14).

The consequences of thrombosis and thrombembolism are extensive infarctions, up to liver necrosis. These processes lead to hepatocyte deficiency up to complete liver rejection.

As for the spleen and lymph nodes, a histological investigation revealed a significant lymphoid depletion. Almost the entire lymphocyte pool is involved in the pathological immune response (Fig. 15-16).

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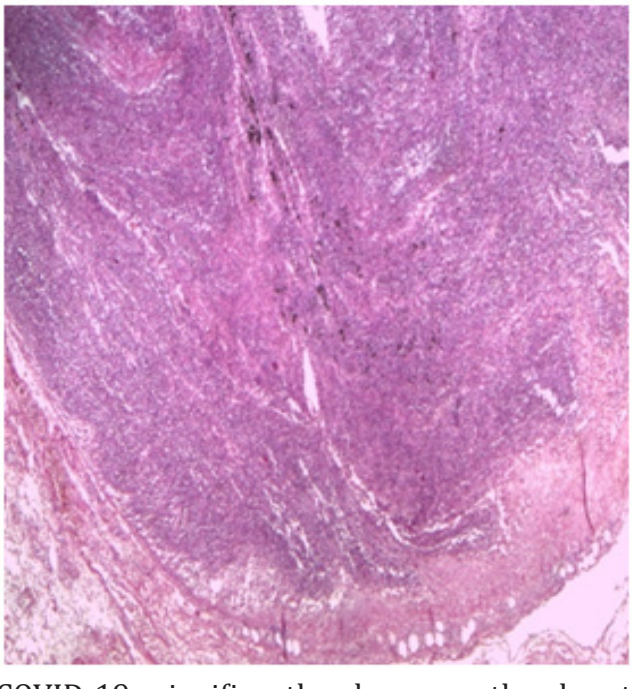
Fig. 15-16 Spleen: significant depletion of lymphoid tissue, necrosis and hemorrhage in the red pulp. Lymph node: depletion of lymphoid tissue (hypoplasia of lymphoid follicles)



COVID-19 significantly damages the heart, which can affect the clinical picture and prognosis of the disease. In the myocardium, damage to cardiomyocytes occurs by contracture and separation of myofibrils with lymphoid infiltration (Fig. 17,18).

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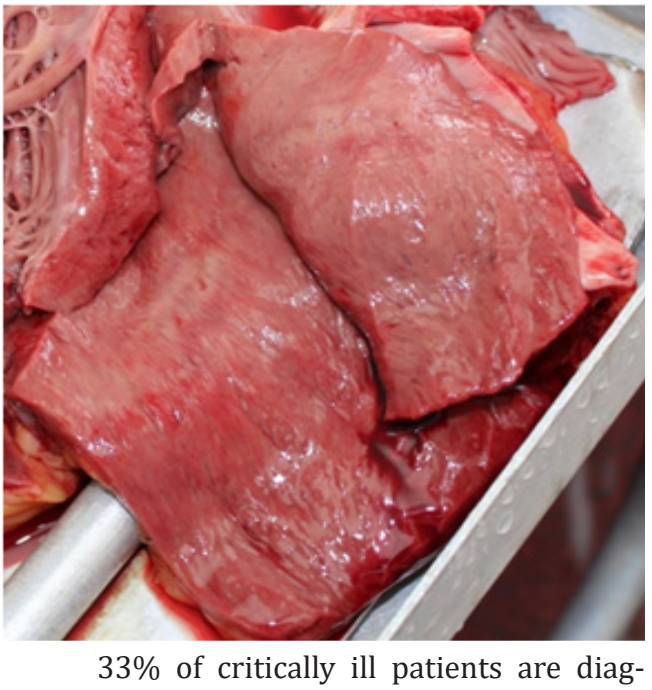
Fig. 17-18 Diffuse hypoxic, metabolic and ischemic injuries, microangiopathy and small focal hemorrhages in the myocardium are detected. Coronary artery thrombosis features focal myocardial infarctions



33% of critically ill patients are diagnosed with secondary cardiomyopathy. In addition, coronarogenic myocardial infarctions are diagnosed intra vitam (instability of the atherosclerotic plaque due to inflammation or thrombosis), as well as focal myocardial lesions of type 2 due to direct influence of hyperimmune inflammation on the myocardium (cytokine alteration with microvascular thrombosis).

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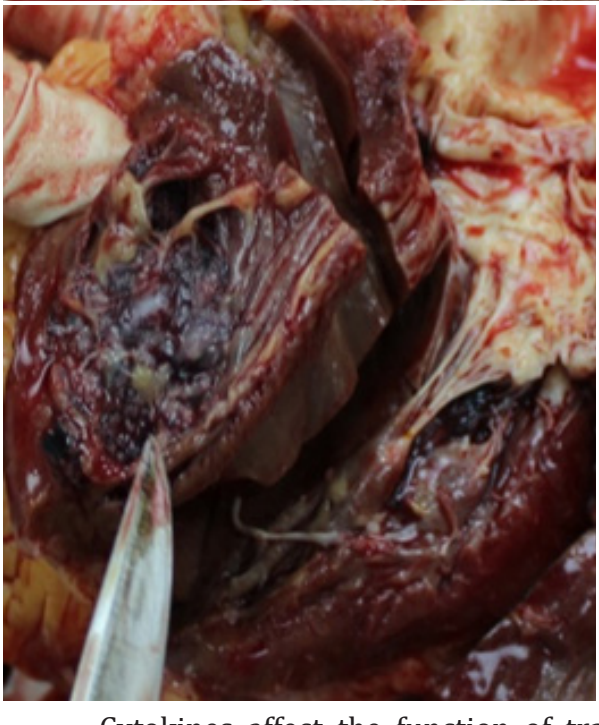
Fig. 19-20 Focal infarctions with secondary extensive hemorrhages, fibrosis, and intraventricular thrombosis in the myocardium are detected



Cytokines affect the function of transporters and nephron ion channels. As a result, there is a change in the ion-potassium channel activity, causing changes in the transepithelial transport of solutes and water in the kidneys [13]. This can explain the hypokalemia that often develops in this disease.

When entering the human body, SARS-CoV-2 can affect the brain and central nervous system that explain changes in the sense of smell in the early stages of the disease, as well as behavioral disorders, periods of agitation and, in contrast, psychomotor retardation. Soporose state and coma may occur.

It was found that the dissemination of SARS-CoV-2 from the systemic blood flow through lattice bone plate can lead to brain damage. Hyposmia can indicate both damage to the central nervous system, as mentioned above, and by penetration across the blood-brain barrier.

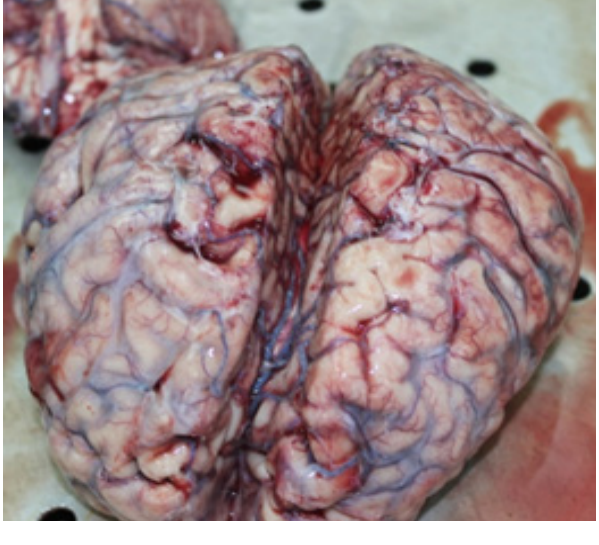
In addition, cases of anosmia were recorded both in the case of edema of the nasal mucosa and in the absence of it (MRI data) [14]. Thus, in the second case, there is a primary lesion by the SARS-CoV-2 virus directly to the neural pathways by penetrating the peripheral olfactory neurons. The virus rises directly to the area of the piriform and infralimbic cortex and basal ganglia.

To complete the description of the nature of damage to the central nervous system, we can add that in presence of developing anoxia, COVID-19 causes edema of the soft meninges and brain matter.

In addition, cases of anosmia were recorded both in presence of nasal mucosa edema and in the absence of it (MRI data) [14]. Thus, in the second case, SARS-CoV-2 virus causes a primary lesion of the neural pathways by penetrating the peripheral olfactory neurons. The virus rises directly to the area of the piriform and infralimbic cortex and basal ganglia.

To complete the description of the nature of damage to the central nervous system, we can add that in presence of developing anoxia, COVID-19 causes edema of the soft meninges and brain matter.

Fig. 21-22 Gross specimen. Edema of the soft meninges and brain matter, subcortical nuclei and cortex with areas of pinkish-yellow color on sections (anoxic encephalopathy)



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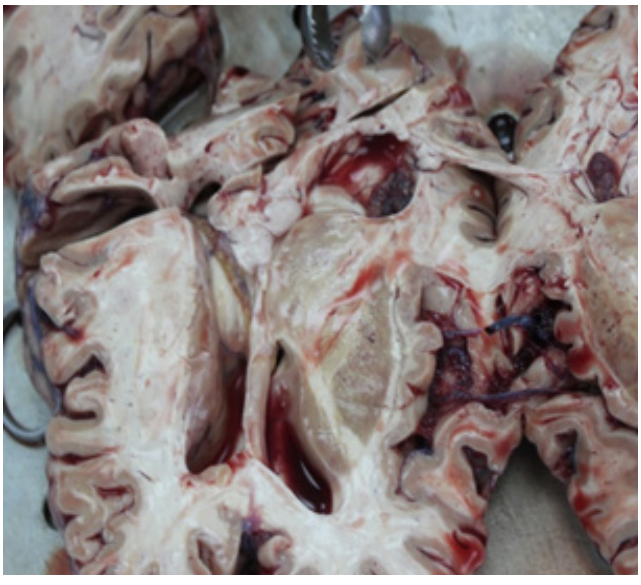


Clinical picture of COVID-19

The incubation period of SARS-CoV-2 is 1-14 days. The infection can be asymptomatic in mild form, as well as cause risk of death in its severe form [30]. On average, symptoms develop in 5-6 days after exposure. Patients with mild symptoms recover within a week [31].

The symptomatic disease usually presents in three ways:

1) Acute respiratory viral infection, in most cases, with symptoms of upper respiratory tract infection as manifestation of a mild disease [17];

2) Non-life-threatening pneumonia;

3) Severe pneumonia with acute respiratory distress syndrome.

In a study of 1099 hospitalized patients in China, fever was the most common symptom. At the same time, elevated body temperature was not typical for all patients. In this study fever above 39oC occurred only in 12.3% [21].

In general, the clinical picture is presented by the following symptoms [40.4]:

- Fever (83%-99%)
- Cough (59%-82%)
- Fatigue (44%-70%)

Other symptoms include [4]:

- Loss of appetite (40%-84%)
- Shortness of breath (31%-40%)
- Sputum production (28%-33%)
- Muscle pain (f11%-35%)

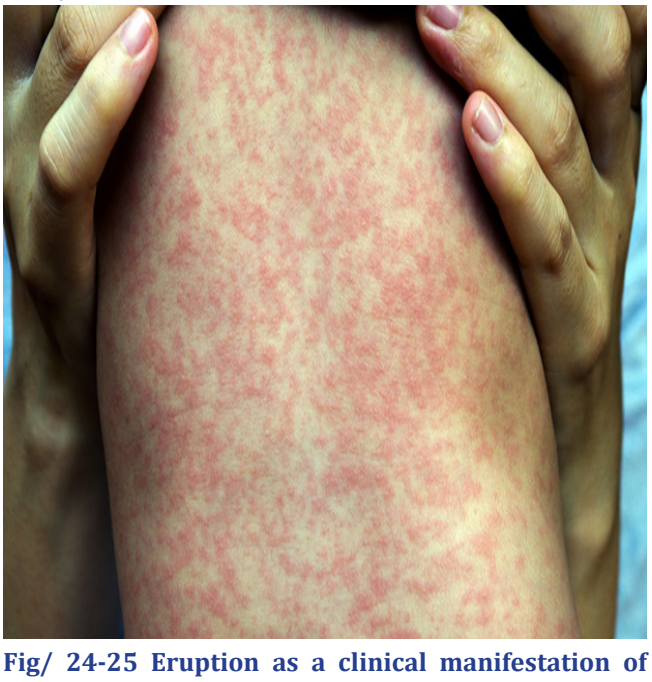
Headache, delirium, rhinorrhea, sore throat, and hemoptysis are less common (less than 10%) [4].

The gastrointestinal tract is also involved in the process: gastroenteritis is observed in about 15% of cases, while 10% of patients had no respiratory symptoms at all, which led to a late diagnosis of the disease. Loss of taste and smell may even precede the appearance of respiratory symptoms [27].

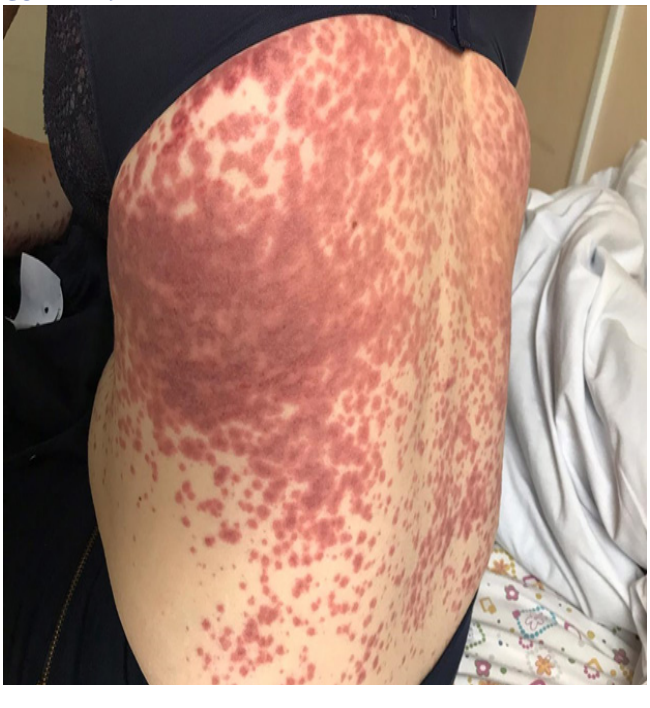
Polymorphous eruptions and color changes (hyperemia, cyanosis) of the skin of the face, fingers and toes are also possible [2].

While monitoring the patients in out hospital, we have also noticed polymorphous eruptions (Fig. 23-25).

Fig.23Eruption as a clinical manifestation of COVID-19



Fig/ 24-25 Eruption as a clinical manifestation of COVID-19



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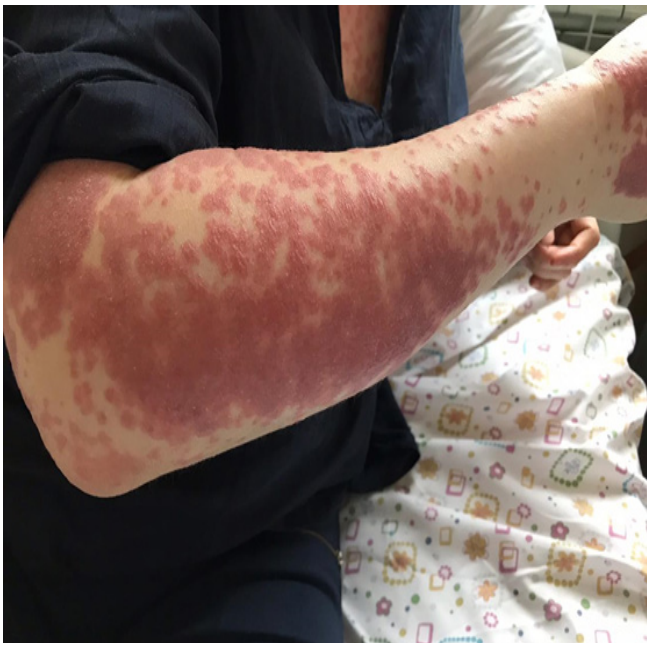

The variety of skin manifestations can be systematized in the following way [10,20]:

1. Infectious or hypersensitivity cutaneous vasculitis, which is presented by lesions of cutaneous small vessels by circulating immune complexes in the form of viral antigen deposits;
2. Papulosquamous eruptions and pityriasisrosea without herald patch;
3. Morbilliform eruptions and erythema infectiosum;
4. Papulo-vesicular extended eruption on the background of sweating;
5. Toxicodermatosis related to drug interaction;
6. Urticaria often appears along with the first symptoms of COVID-19 or is associated with drug reaction;
7. Trophic changes in facial tissues associated with long-term prone positioning.

Complications of COVID-19

1. ARDS accounts for 15% to 33% of all complications [4,40].

The patient complains of shortness of breath or chest pain. During the examination tachypnea, tachycardia, respiratory muscle involvement in breathing, cyanosis of the skin are detected.

In general, typical factors are:

- Acute onset
- Predisposing factors
- Bilateral infiltrates on chest X-ray
- PaO2/EiO2less than 200 mmHg
- No signs of left ventricular failure, pulmonary capillary wedge pressure is not higher than 18 mm Hg

2. 8% of patients develop acute respiratory failure [36] resulting in severe life-threatening hypoxemia. In patients with COVID-19, acute respiratory failure is primary due to massive lung injury. Oxygen saturation is below 95%.

3. Another complication is disseminated intravascular coagulation [4,27]. The detection rate is up to 71% during autopsy. This is a pathological non-specific process characterized by formation of disseminated microvascular thrombi (fibrin, erythrocyte, and hyaline) with incoagulability leading to multiple massive hemorrhages. It seems that the SARS-CoV-2 virus is able to start this complex process. However, it often occurs at the septic stage.

4. In 7%-20% of cases, especially in case of comorbid cardiovascular disease, acute heart failure occurs [4,31]. Myocardial infarctions, myocarditis, cardiomyopathy may develop. It results in exacerbating hypoxia of organs and tissues, acidosis and other metabolic disorders.

5. Secondary bacterial infection develops in 6-10% of COVID-19 cases [27,29]. It is necessary to pay attention to this relatively small percentage and take it into account when prescribing antibacterial therapy (it should not be prescribed for everyone). In addition, there are other factors leading to secondary infection. Most often, this occurs in patients suffering from chronic respiratory diseases (chronic bronchitis, COPD, bronchial asthma), CHF, diabetes mellitus; in those who are long-term inpatient, in the intensive care unit and on the ventilator. Bacterial pneumonia can develop against the background of a massive pulmonary infarction. It usually starts with new-onset fever, productive cough with mucopurulent sputum; the level of white blood cells increases due to neutrophilia, CRP and procalcitonin. MSCT shows areas of pulmonary consolidation. In such cases, a microbiological examination of sputum or bronchial lavage is required.

6. A fairly large number of patients (14%-53%) develop acute renal failure (Fig. 26,27) [13].

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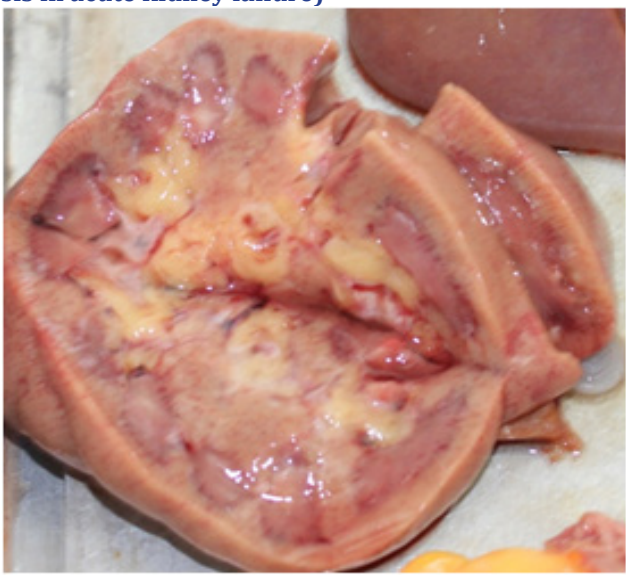
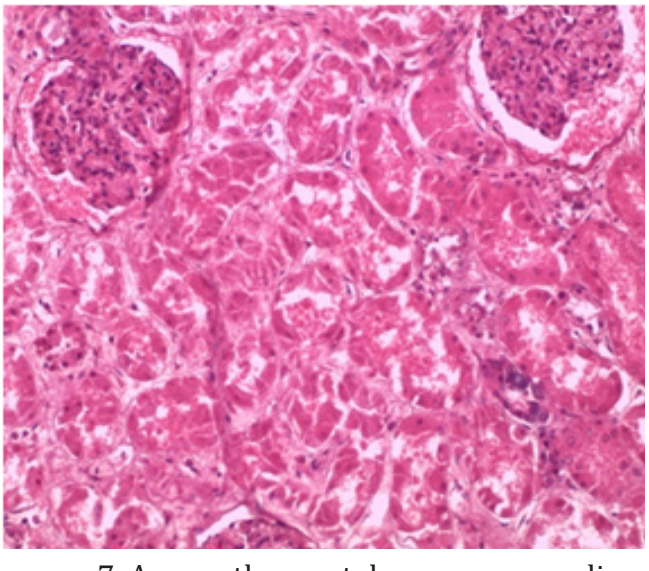
Fig. 26-27 Diffuse necrosis of the renal tubule epithelium, interstitial edema, anemia of the renal cortex. In the lumen of most of the glomerular capsule filtrate containing protein is detected (osmotic nephrosis in acute kidney failure)



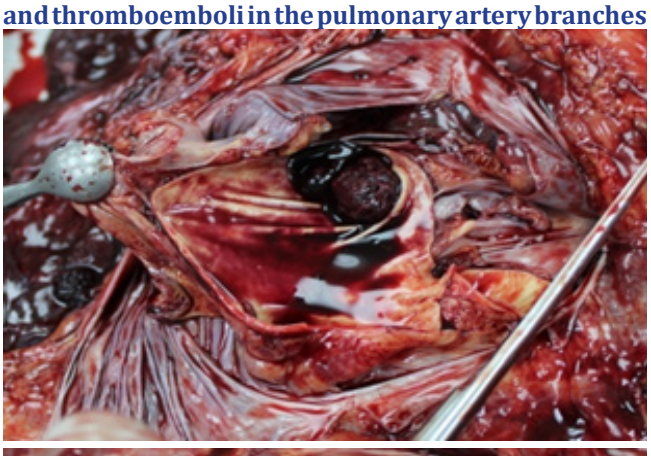


7. Among the most dangerous complications are sepsis and septic (toxic) shock [13].

8. Thromboembolic disorder is the cause of increased respiratory failure that often results in fatal outcome (Fig. 28-30) [15]

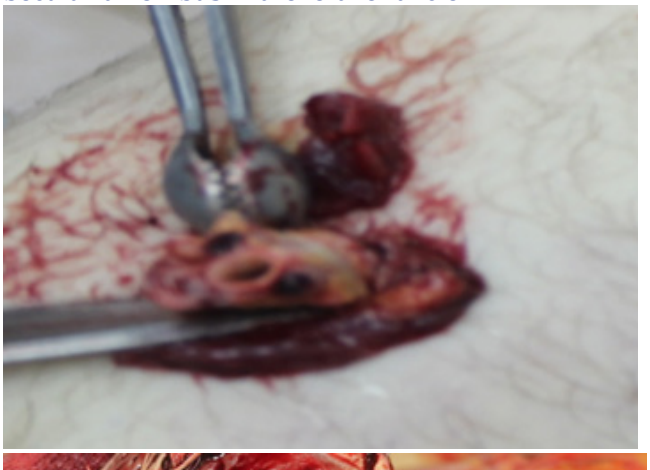
Fig. 28 Macrophotography of fresh fibrin and organizing thrombi in the pulmonary artery and vein branches

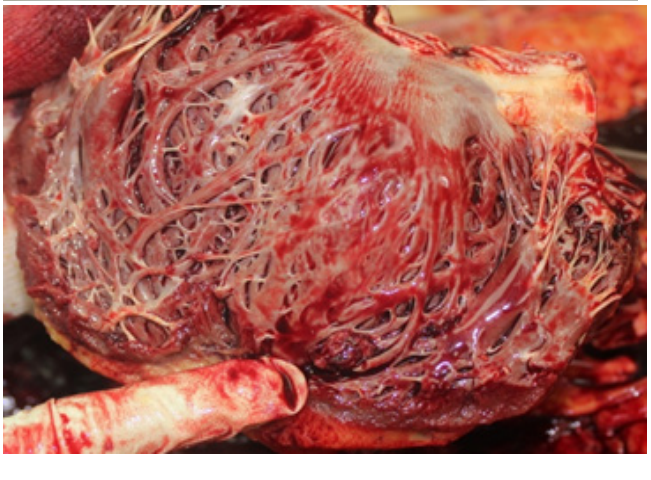
Fig. 29-30 Macrophotography of fresh fibrin thrombi and thromboemboli in the pulmonary artery branches



The formation of both parietal thrombi in citu and massive thromboemboli in the pulmonary arteries is of interest (Fig. 31, 32).

Fig. 31-32 Thrombi in the femoral vein, an intertrabecular thrombus in the left ventricle





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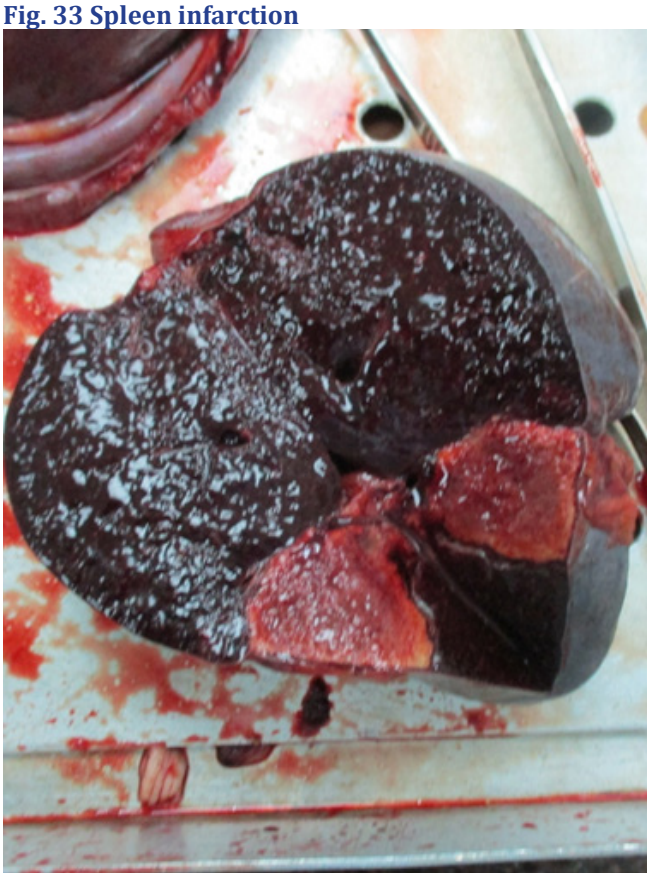
Thrombembolic disorder can also affect the major systemic vessels. Spleen infarctions are common (Fig. 33).

Fig. 33 Spleen infarction



Covid-19 classification

According to the recommendations of the Ministry of Health of the Russian Federation, the classification of COVID-19 is the following: mild, moderate-to-severe, severe and extremely severe illness [10].

As doctors of an infectious diseases hospital, we have been monitoring mostly severe and extremely severe cases.

Severe cases:

- Respiratory rate >30 per min
- SpO2 ≤ 93%
- PaO2/FiO2 ≤ 300 mmHg
- Decreased level of consciousness
- Hemodynamic instability

BP < 90/60 mmHg

- CT score 3-4 with changes characteristic of the viral damage
- Arterial lactate > 2 mmol/L
- qSOFA> 2 points

Extremely severe cases:

- Acute respiratory failure with required respiratory support (ventilator)
- Septic shock
- Multiple organ failure
- Changes on CT: CT critical score 4 or clinical picture of ARDS
- qSOFA> 2 points

Diagnosis of coronavirus infection

A case with a characteristic clinical picture without laboratory confirmation can be considered as suspicious for COVID-19.

A probable COVID-19 case is presented with clinical picture and specific epidemiological history, as well as lung CT-image, regardless of the results of a single laboratory test for SARS-CoV-2 and epidemiological history.

A confirmed case can be considered with a positive result of SARS-CoV-2 nucleic acid amplification tests, regardless of clinical manifestations.

A patient with a coronavirus infection caused by SARS-CoV-2 is given a complex clinical examination, including the collection of anamnesis, physical data, clinical analysis of diagnostic material and pulse oximetry.

In addition to complaints, anamnesis and epidemiological history are collected in detail.

Physical examination includes an assessment of all organs and systems. Special attention is paid to the mucous membranes of the upper respiratory tract, thermometry, assessment of the level of consciousness, heart rate, blood pressure, respiratory rate.

It is mandatory to perform pulse oximetry with SpO2 measurement to detect respiratory failure and assess the severity of hypoxemia.

Etiological laboratory diagnosis

1. Detection of SARS-CoV-2 RNA using nucleic acid amplification tests
2. Detection of IgM and IgG to SARS-CoV-2

Predictive laboratory markers [4,27]

In most cases, white blood cell count is normal; one-third of patients have leukopenia. The most common and characteristic feature is lymphopenia. Thrombocytopenia is moderate, however, it is more significant among severe and subsequently lethal cases of COVID-19.

High levels of D-dimer, prothrombin time and fibrinogen are of clinical significance. 3-4 times elevated D-dimer levels are of unfavorable prognostic value.

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Levels of C-reactive protein (CRP) correlate with severity of the disease, severity of inflammatory infiltration andrisk of developing pneumonia. High erythrocyte sedimentation rate, interleukin-6, interleukin-10 and TNF-α are also typical.

The number of CD4 and CD8 T-cells associated with lymphopenia decreases. It was noticed that the acute phase protein (ferritin) elevates in the unfavorable course of disease.

A sudden increase in clinical manifestations after 1-2 weeks from the onset of the disease, persistent or new-onset febrile fever, severe lymphopenia (T- and B-lymphocytes), significant increase in CRP (more than 75 mg/L) and interstitial lung disease may be laboratory signs of a cytokine storm and ARDS.

When developing ARDS, it is necessary to control the levels of interleukin-6, D-dimer, ferritin, fibrinogen, CRP, triglycerides, and LDH every 48-72 hours.

A marker of secondary infection is the level of procalcitonin. If its value exceeds 0.5 mcg/L, bacterial infection is likely to emerge. In case of subsequent increase, sepsis is likely to develop.

When ARDS or septic condition occurs, the probability of multiple organ dysfunction syndrome is high. The syndrome is presented by deviations in biochemical parameters that reflect dysfunction of certain organs.

The development of cardiovascular complications increases the level of creatine kinase MB, highly sensitive troponin and brain natriuretic peptide (NT-proBNP). In this case, it is necessary to differentiate between severe myocarditis, acute myocardial infarction of type I (coronarogenic due to atherosclerotic plaque instability and thrombosis) and type II, as a consequence of the damaging effect of the systemic hyperimmune response (cytokine storm).

Instrumental diagnostics

The most important method for assessing hypoxemia is pulse oximetry with measurement of oxygen saturation (SpO2) [37].

Fig. 34 Pulse oximetry

Pulse oximetry (hemoxymetry) is a non-invasive method to assess oxygen saturation in the blood. The method is based on spectrophotometry for determining blood oxygen saturation. It is performed using a pulse oximeter (Fig. 34).

Decrease in blood oxygen saturation determines the level of necessary respiratory support. Patients with signs of acute respiratory failure are recommended to check arterial blood gases with the determination of PaO2, PaCO2, pH, bicarbonates and lactate.

Methods of radiological diagnostics of chest in patients with suspected/confirmed COVID-19 pneumonia include:

- Plain Chest X-ray
- Computed Tomography (CT) of the Lungs
- Ultrasound Examination of the Pleurae and Lungs

Standard X-ray (Fig. 35) has low sensitivity in detecting initial changes and cannot be used for early diagnosis. The method allows detecting severe forms of pneumonia and pulmonary edema (ARDS).

Fig. 35 Plain Chest X-ray

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Fig. 36 Computed Tomography (CT)

CT (Fig. 36) is highly sensitive in detecting changes in the lungs typical for COVID-19. CT can show typical changes in the lungs in patients with COVID-19 even before positive PCR tests.

At the same time, the CT-detection of changes in asymptomatic and mild cases does not affect the management of patients who do not need hospitalization.

Therefore, mass use of computed tomography for screening of asymptomatic and mild cases is not recommended.

Main CT patterns for COVID-19 [3,10]

Location: bilateral, mostly basal and subpleural distribution.

1) Ground-glass opacity of the lung tissue;
2) Areas of ground-glass opacity with reticular changes (interlobular septal thickening);
3) Areas of pulmonary consolidation;
4) Reversed halo sign (organizing pneumonia);
5) Increased blood vessel diameter in the consolidated lung tissue;
6) Traction bronchiectasis.

Stages of coronavirus infection seen on CT-scan:

1) Early stage (0-4 days). CT-images show no signs of pathological changes in the lungs or initial ground-glass opacity changes of lung tissue in the subpleural sections (more than 50% of patients have no pathological changes in the lungs in the first two days of the disease).

2) Disease progression (4-8 days) is characterized by extension of pulmonary consolidation areas with appearance of reticular changes, such as crazy paving.

3) Maximum clinical manifestation. Areas of pulmonary consolidation in form of ground-glass opacity are detected. CT-image shows ground-glass opacity with reticular changes, such as crazy paving, and areas of pulmonary consolidation that often reflect secondary bacterial infection.

4) Regression, clinical consequences of the disease.

Fig. 37 Lung CT on admission to hospital (K., 53)

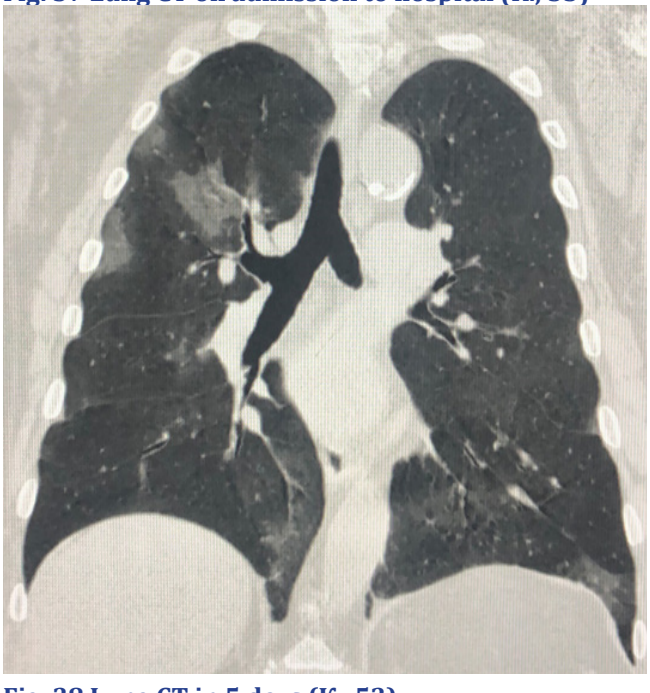

Fig. 38 Lung CT in 5 days (K., 53)

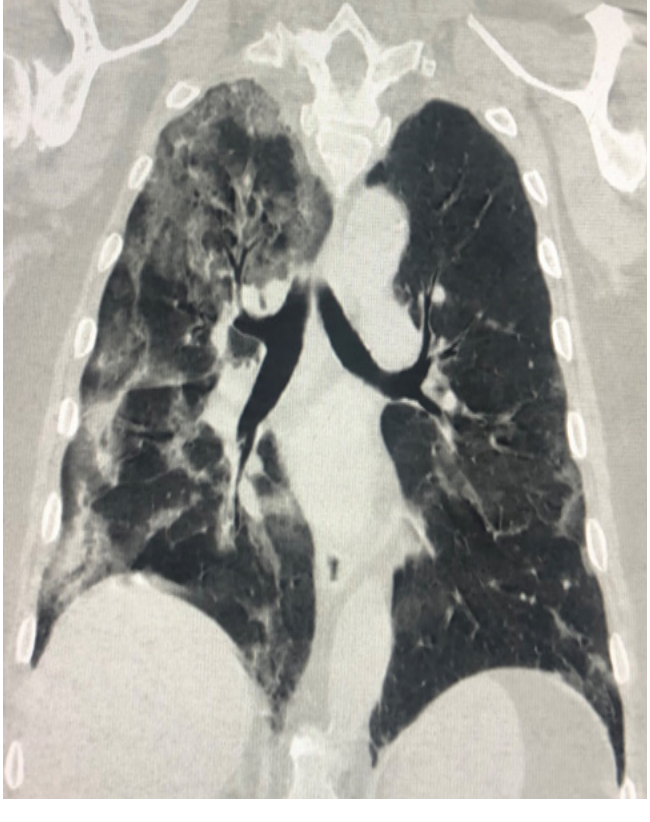

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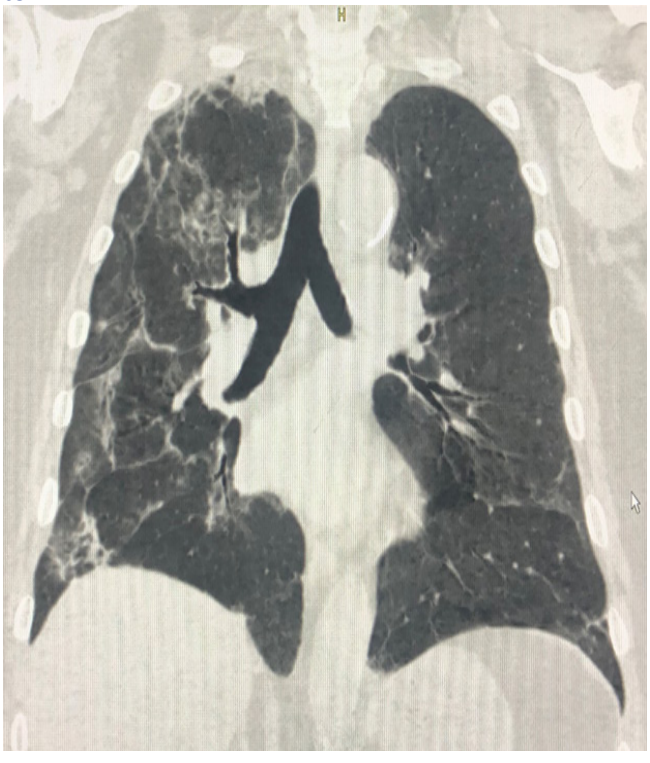
Fig. 39 Lung CT in 10 days (K., 53). Crazy paving pattern

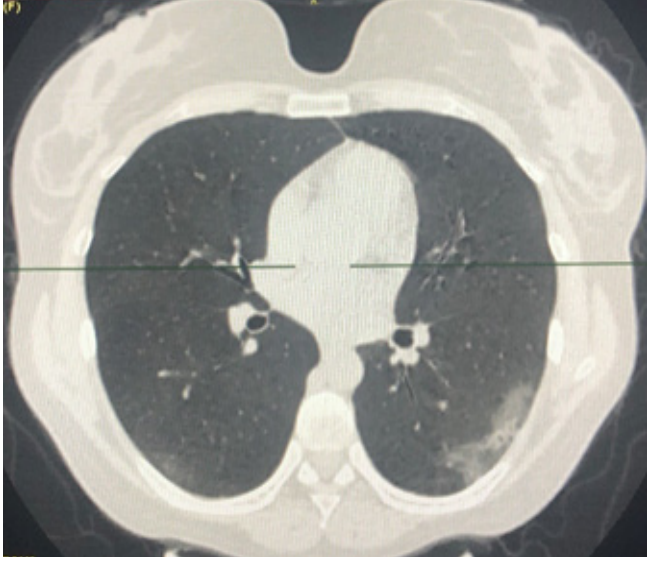


Imaging algorithmand clinical probability in COVID-19 cases (Table 1)

Table 1 CT signs of COVID-19 (Fig. 40-43)

CT pattern	Prevalence	Stage (severity)
Only ground-glas-sopacity	Up to three local pathological areas (up to 3 cm in diameter)	Mild CT-1
Only ground-glas-sopacity	Up to three local pathological areas (up to 5 cm in diameter)	ModerateCT-2
Ground-glass opacity with single areas of consolidation		Moderately severeCT-3
Ground-glass opacity and consolidation in combination with reticular patters	Almostdiffusely	Severe CT-4

Fig. 40 Variety of CT signs (CT-1)



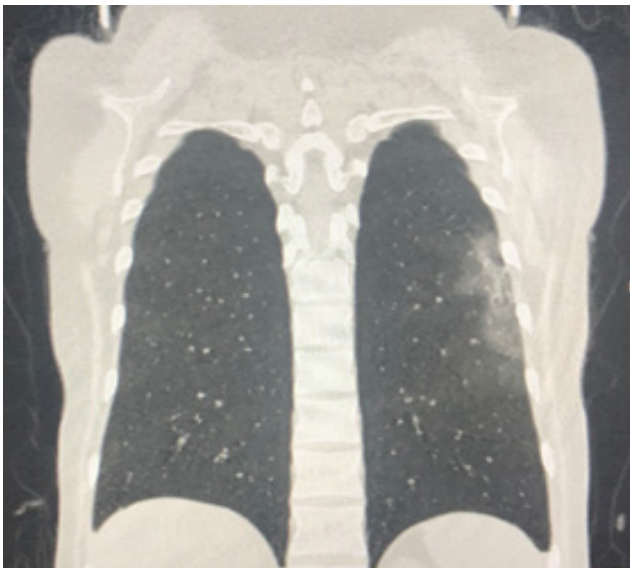
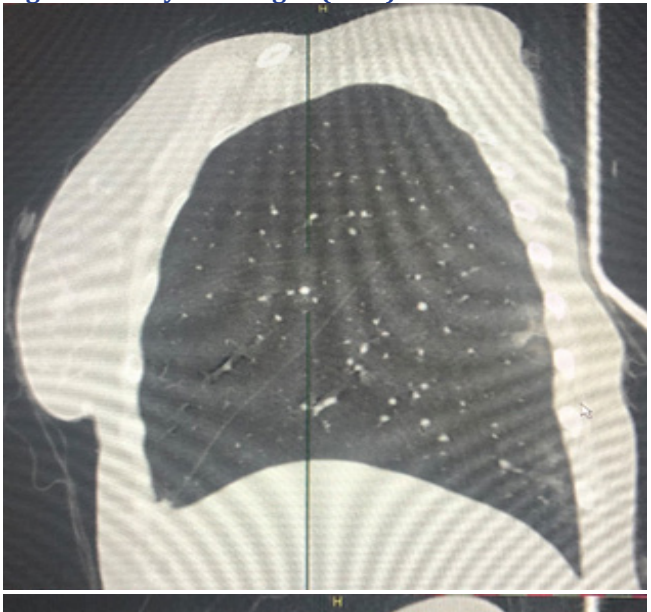


Fig. 41 Variety of CT signs (CT-2)



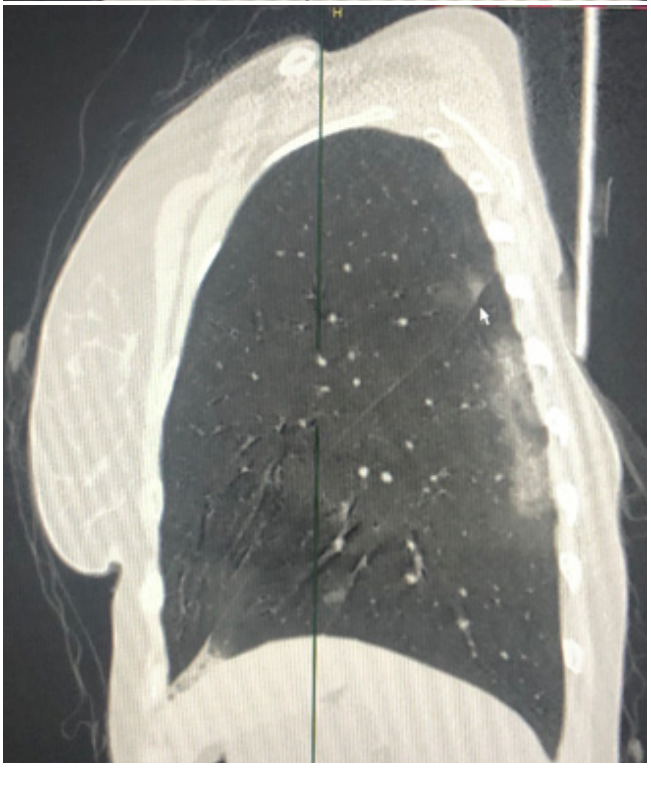


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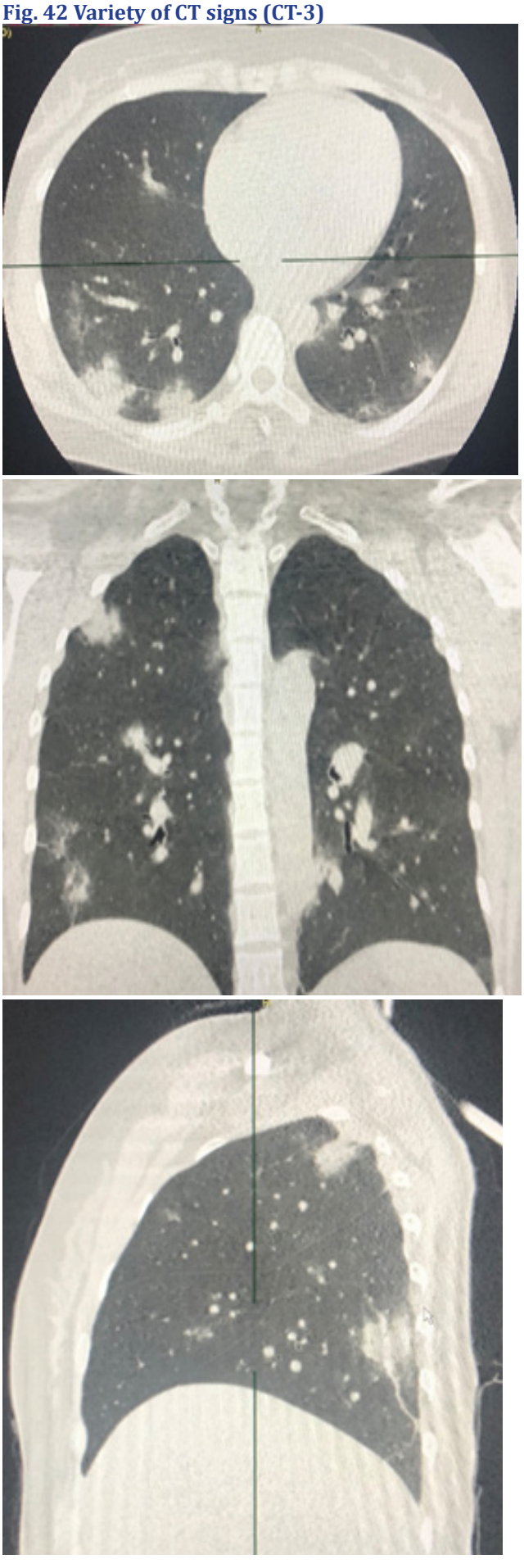
Fig. 42 Variety of CT signs (CT-3)



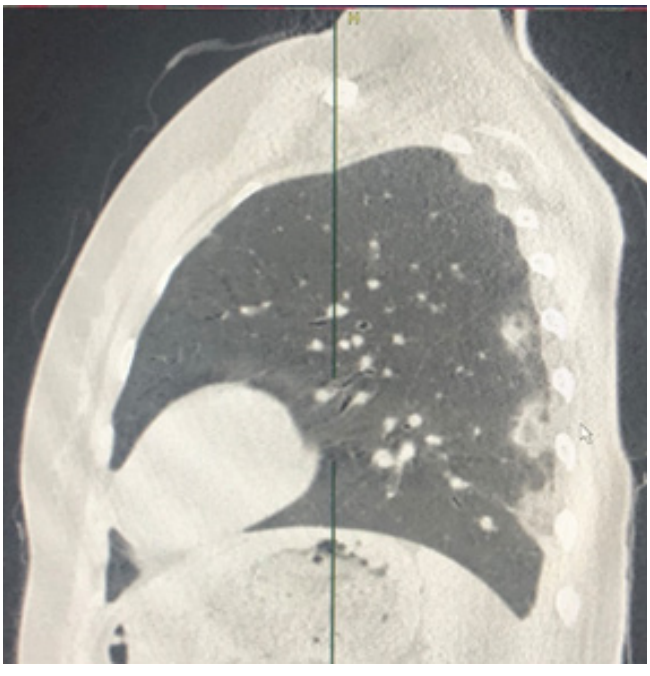
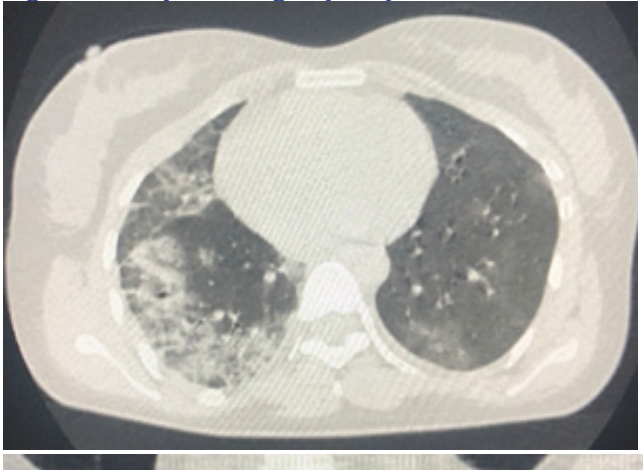
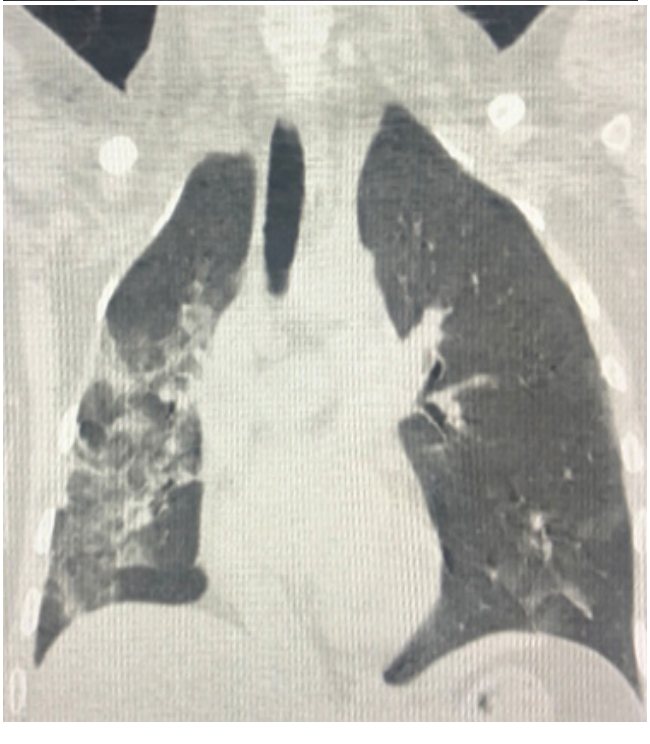


Fig. 43 Variety of CT signs (CT-4)





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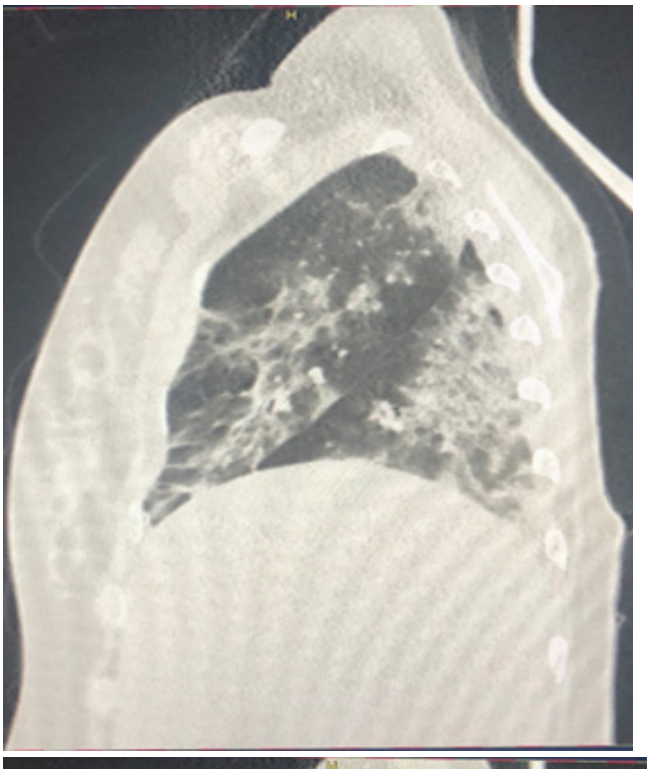
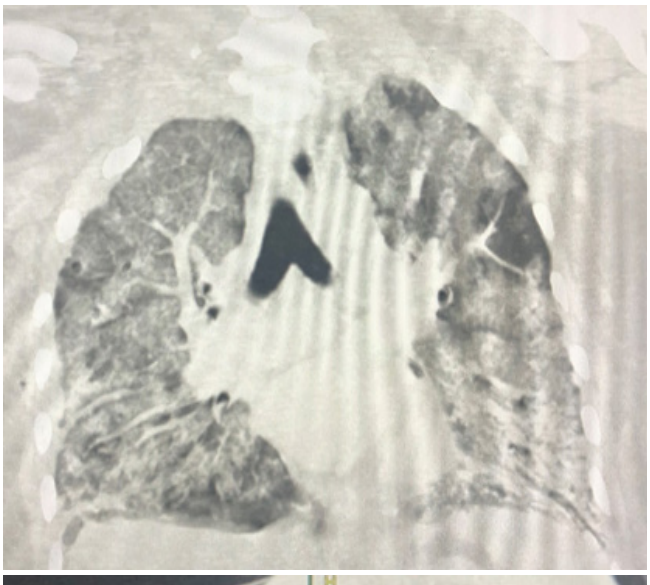
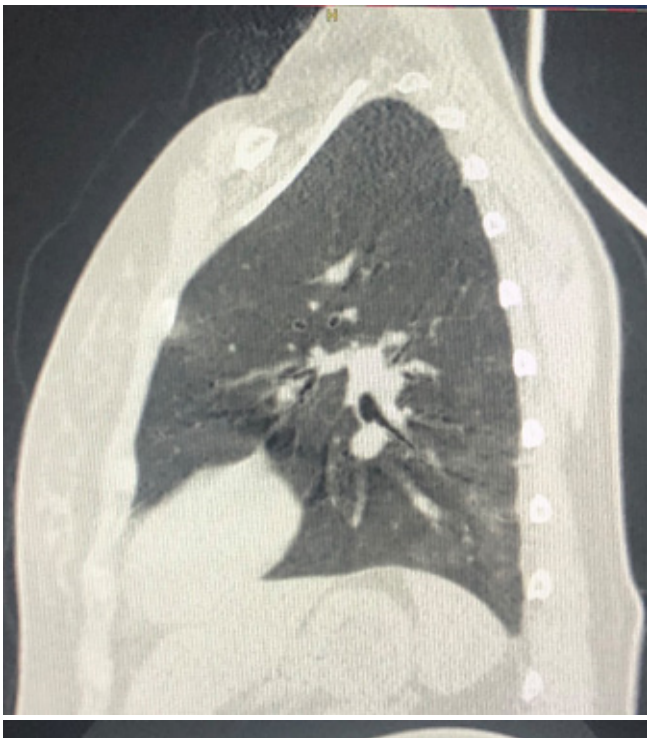
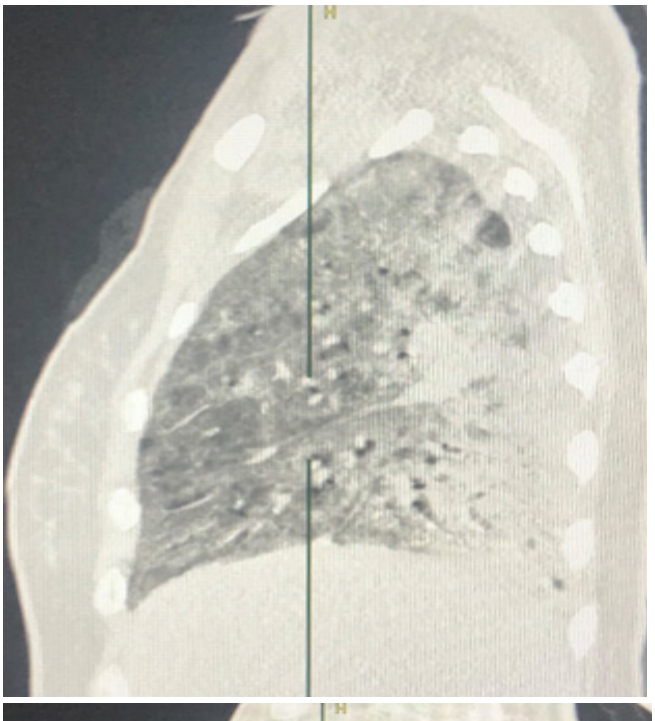
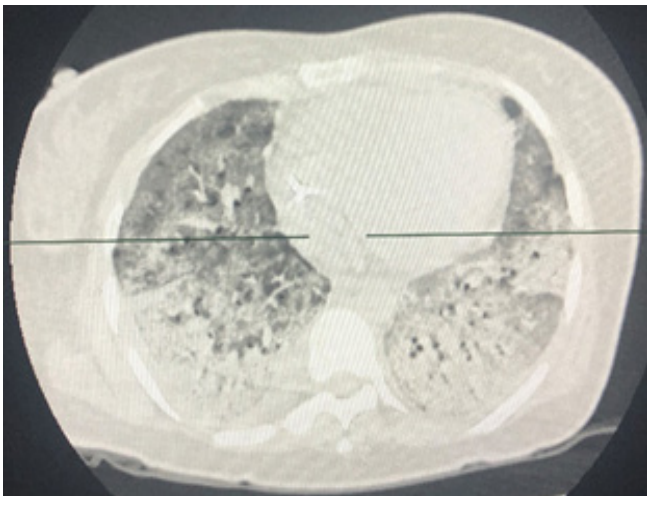
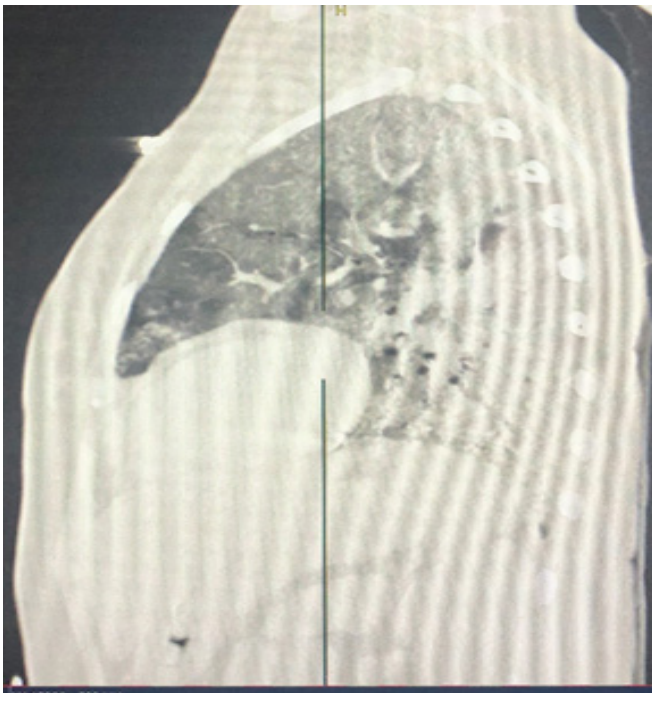

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Lung ultrasound in COVID-19 [14]

This type of investigation provides assistance in three key areas.

1) Changes in the lungs are so specific for COVID-19 that they can be differentiated from other possible causes of ARF.

2) Detection of lung changes in a prone positioned patient on a ventilator.

3) Lung ultrasound is easy to perform at the patient's bedside, if for some reason it is impossible to perform computed tomography.

Table 2 Disease severity based on ultrasound findings

Severity	Ultrasound signs	Additional information
Mild	Single B-lines in the intercostal space - mild interstitial changeS	Monitoring possible in an outpatient setting
Moderate	Single B-lines, pleural thickening - moderate interstitial changes	Urgent computed tomography is recommended
Severe	Consolidation in the basal parts of the lung	ICU admission and urgent computed tomography is recommended

Triage of patients with confirmed and unconfirmed (on admission) COVID-19

On admission to the COVID hospital patients are triaged into those with confirmed diagnosis of COVID-19 and suspected COVID-19. Thustwo patient flows do not mix, which allows avoiding cross infection.

If the patient presents with clinical features and epidemiological history and passes one of the diagnostic criteria (positive PCR, IgM exceeding the norm or CT signs of a high probability of viral infection), then such a patient is transferred to the red zone.

In cases of suspected COVID infection, the patient stays in the observation ward and an additional examination is performed within 24 hours. If at least one of the above criteria is present, then the patient is also transferred to the red zone.

If the diagnosis is not confirmed at the moment, but the patients suffers from another disease or complications of the past COVID-19, then this patient is hospitalized in the blue zone.

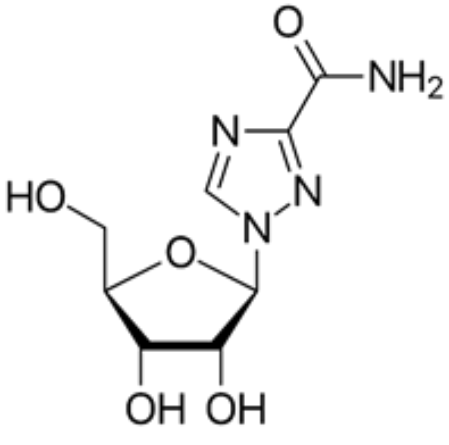
The red and blue zones are separate buildings of the hospital, and each of them has its own admission department.

Treatment of COVID-19

Since the beginning of the epidemic in China, which escalated to a pandemic, the virus itself, its effect on the body, the pathogenesis of the disease were continuously studied with one single goal: to find a "weapon" to combat it. Treatment regimens have changed as the medical community has become more aware of the SARS-CoV-2 coronavirus and the disease it causes, COVID-19 [14,26,32,4-10]. Unfortunately, etiotropic treatment has yet to be found. Most drugs are prescribed off-label (lack of evidence based on international recommendations and balance of benefits and risks).

In Russia, the clinical guidelines were developed by the Ministry of Health of the Russian Federation (MH RF). Given the number of revisions (seven at the time of publication) in a relatively short period of time, it becomes clear how rapidly the approaches to treating patients with COVID-19 have changed.

Fig.44Ribavirin molecular structure



The first version of the clinical guidelines of the Ministry of Health of the Russian Federation was published on January 29, 2020 [4], where ribavirin has been suggested as an antiviral therapy. The treatment experience of SARS- and MERS-CoV was used. Ribavirin (Fig. 44) was recommended in combination with lopinavir and ritonavir. Interferon-gamma drugs were supposed to have a pathogenetic effect on the disease caused by 2019-nCoV (as the new virus was previously named).

Treatment with antimicrobial drugs of almost all groups, in various combinations was recommended for patients with lower respiratory tract infection (pneumonia).

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Pathogenetic therapy consideredthe useof proteolysis inhibitors (proteases and systemic glucocorticosteroids) in cases of severe pneumonia complicated by septic shock. The recommendations highlight the issue of the advisability of prescribing vitamins and detoxification therapy. It was assumed that symptomatic therapy should focus on fever, rhinitis, bronchitis (bronchodilators, mucoactive drugs).

The second version of the clinical guidelines was published on February 03, 2020 [5]. It offered no additions to the main antiviral drugs, but recommended the use of antiviral drugs in cases of moderate-severe and severe infection, when the intended benefit outweighs the potential risk of developing adverse events, meaning the authors of these recommendations drew attention to the side effects of these drugs. Also, glucocorticosteroids were removed from the treatment recommendations.

The third version was published on March 03, 2020 [6]. This edition recommended the use of antiviral drugs in combinations (previously used as monotherapy).

The fourth version was published on March 27, 2020 [7]. The following recommendations were considered as etiotropic treatment: a combination of lopinavir/ritonavir (Kaletra®), interferon drugs. Chloroquine and hydroxychloroquine appeared in the recommendation. The authors proposed to make use of the properties of these antimalarial drugs as anti-inflammatory and immunosuppressive treatment. Preference was given to hydroxychloroquine with less cytotoxicity and more pronounced antiviral effect. Small clinical studies proved that the combination of azithromycin with hydroxychloroquine enhances the antiviral effect of the latter. However, it was recommended thata cardiologist should monitor patients undergoing this treatment by due to drugs' cardiotoxicity. The risk groups for cardiovascular complications and the need to control the QT interval have been noted.

Pathogenesis of COVID-19-induced ARDS features an excessive immune system response with a rapidly developing fatal cytokine storm. This reaction is associated with an increase in IL-6. The most studied (in China) inhibitor of interleukin-6 is tocilizumab (400 mg intravenously).

According to the recommendations of WHO experts, glucocorticosteroids are added to treatment regimens only in case of septic shock, but low doses and short courses are more preferable.

Antibiotic therapy is still recommended for all patients with pneumonia, along with treatment for symptoms.

A large section of clinical guidelines is devoted to ICU patients, with special mention going to children and pregnant women.

The fifth version of the clinical guidelines was published on April 08, 2020 [8]. The list of antiviral drugs remained the same. The pathogenesis of the disease was presented more extensively.

Indications for the use of tocilizumab have been developed: persistent or re-emerging fever from 8 to 14 days, D-dimer level above 1500 ng/ml, IL-6 level above 40 pg/ml and/or increased C-reactive protein level above 75 mg/L with interstitial lung damage. Contraindications included sepsis, neutropenia less than 0.5 x 109/L, an increase in ALT or AST more than 5 times, thrombocytopenia less than 50 x 1012/L.

Recommended dose is 4-8 mg / kg (average dose of 400 mg per day); if the response is inadequate, this dose is repeated after 12 hours. A maximum of 4 doses is allowed with an interval of 12 hours.

For the first time, in severe COVID-19 cases it was advised to include low molecular weight anticoagulants, since the risk of developing disseminated intravascular coagulation and venous thromboembolism is high.

The sixth version of the clinical guidelines was published on April 28, 2020 [9]. Along with the already generally recognized etiotropic drugs (hydroxychloroquine, lopinavir/rotanavir, azithromycin with hydroxychloroquine, interferon drugs), umifenovir, remdesivir, favipiravir were still at the stage of clinical trials. There were indications that a randomized controlled trial found that lopinavir/ritonavir mono-regimen did not show any benefit over symptomatic therapy. Thus, the effectiveness of kaletrawas questioned.

In addition, hydroxychloroquine also did not demonstrate its antiviral activity, especially when administered in mono regimen.

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At the same time, its combination with kaletra or azithromycin poses a threat of side effectcumulation.

It was mentioned that protocols for the clinical use of anticoid plasma are being developed.

As before, IL-6 inhibitors (tocilizumab, sarilumab) wereconsidered a proactive cytokine storm therapy. If these drugs are unavailable, glucocorticosteroid therapy (GCS) should be started. In addition, baricitinib (a Janus kinase inhibitor) can be prescribed for moderate to severe pneumonia.

This edition of the clinical guidelines expands the indications for dexamethasone to patients with ARDS; dexamethasone should be used in low doses and as a short course (evidence shows that in the case of ARDS without COVID-19 dexamethasone significantly reduced mortality).

The tactics of prescribing anticoagulant, antibacterial and symptomatic treatment remained the same.

The seventh version (and so far the last) of the clinical guidelines was published on June 03, 2020 [10]. These recommendations provide a more expanded section on pathogenesis of COVID-19. For the first time, skin rashes have been described in this disease.

Etiotropic drugs remained the same. The emphasis was placed on the use offavipiravir. It should be noted that at this point in time, it is impossible to make an unambiguous conclusion about its effectiveness or inefficiency. Therefore, the medical board should in each case decide if the potential benefit exceeds the risks. Favipiravir was developed as an inhibitor of the RNA-dependent RNA polymerase of the influenza virus. The study was conducted in China, Japan, and started in Russia.

Hydroxychloroquine is still recommended for use, but in smaller doses and with mandatory ECG monitoring.

This edition of the clinical guidelines indicates that kaletra can be used if patients have contraindications to antimalarial drugs.

The guidelines note the benefit of **interferon beta-1b.**

Manufacturing, indications and contraindications of anticoid plasma are described in detail.

Pathogenetic therapy focuses on targeted drugs and glucocorticosteroids.

Tocilizumab and sarilumab are IL-6 inhibitors. To quickly relieve the cytokine storm, tocilizumab is administered at a dose of 4-8 mg/kg intravenously in combination with glucocorticosteroids (0.5-1 mg/kg of methylprednisolone intravenously every 12 hours or 20 mg/day of dexamethasone for 2-3 days with a gradual dose reduction by 20-25% per administration, every 1-2 days). In the future, the need for a maintenance dose of methylprednisolone 8-12 mg/day depends on the clinical situation. One should combine it with low molecular weight heparins up to discharge.

The seventh version of clinical guidelines describes the possible use of canakinumab, anti-IL-1β monoclonal antibody, at a dose of 4-8 mg/kg intravenously.

In moderate and moderately severe forms of pneumonia, the use Janus kinase inhibitors: baricitinib and tofacitinib, as well as okolizumab, the IL-6 inhibitor, can be considered as additional therapy. Their effectiveness at the time of writing the recommendations was not sufficiently studied.

The seventh version of the clinical guidelines presents, for the first time, strict indications for antibiotic therapy - convincing signs of additional bacterial infection (procalcitonin increase for more than 0.5 ng/ml, leukocytosis more than 10x109/L, presence of purulent sputum). Also the recommendations provide the principles of emergency treatment, details of patient stay in ICU, indications and contraindications for extracorporeal membrane oxygenation (ECMO).

Guidelines propose treatment with helium-oxygen mixtures and methods of extracorporeal detoxification, hemocorrection and nutritional support.

The tactics of managing special groups of patients (with arterial hypertension, acute coronary syndrome, diabetes mellitus, etc.) have been developed.

The principles of medical rehabilitation at stages 1, 2 and 3 and the discharge procedure are listed, and many more questions and issues are raised and highlighted in the seventh version of the clinical guidelines of the Ministry of Health of the Russian Federation.

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However, the medical community is currently awaiting a revision of the guidelines. New data from clinical studies and observations requires to exclude some etiotropictreatment as innefective, and highlight the importance ofpathogenetic drugs, in particular, glucocorticosteroids and anticoagulants in a therapeutic dose.

Experience of COVID-19 treatment in other clinics

Various clinics, especially those with a research capacities, have tried to offer their insights to pathogenetic treatment.

Our clinic was interested in the recommendations and experience of the Medical Research and Education Center of Moscow State University named after M.V. Lomonosov.

Treatment protocol shows that the basic treatment regimen of hospitalized patients of moderate and severe disease is as follows:

1. Bromhexine, 8 mg x 4 times a day;
2. Spironolactone, 50 mg x 1 time per day;
3. Colchicine, 1 mg on the first day, then 500 mcg x 1 time per day;
4. Dipyridamole, 75 mg x 2 times on the first day, then 150 mg x 2 times a day;
5. Anticoagulants according to the D-dimer level and the patient's weight.

In case of clinical presentation or investigation findings of thrombosis, as well as when initiating pulse therapy, it is recommended to use therapeutic doses of low molecular weight heparins (with mandatory monitoring of renal function):

- Enoxaparin sodium (anfibra, clexane, enixum) 1 mg/kg x 2 times a day; or
- Nadroparin calcium 0.4 ml (weight less than 50 kg), 0.6 ml (weight of 50-70 kg), and 0.8 ml (weight of more than 80 kg) x 2 times a day.

Proactive anti-inflammatory therapy is prescribed if there are two or more symptoms:

1. SpO2 less than 93% when breathing air;
2. C-reactive protein more than 60 mg/L or an increase in CRP by 3 times or more on days 8-14 of the disease;
3. Fever over 38.5° C for 5 days;
4. Leukocyte count is less than 3.0-3.5 x 109/L;
5. Lymphocyte count is less than 1.0 x 109/L.

The following drugs can be used for anti-inflammatory treatment:

1. Glucocorticosteroids 0.5 mg/kg (expressed as prednisolone) 2 times a day, or pulse therapy with methylprednisolone 1000 mg intravenously 1 time a day for 3 days;
2. Colchicine 1 mg x 1 time per day for 3 days, then 500 mcg x 1 time per day;
3. Tocilizumab (anti-IL-6) 800 mg intravenously (as a single infusion or 2 injections of 400 mg at intervals of 12 hours).
4. Secukinumab (anti-IL-17A) 300 mg s/c (two separate 150 mg injections);
5. Canakinumab 450-600 mg s/c (taking into account age and body weight);
6. Ruxolitinib 5 mg x 2 times a day per os.

Many of these recommendations can be reasonably agreed with. For example, colchicine is an alkaloid of the tropolone series (homomorphinans). Given its ability to reduce the release of lysosomal enzymes of neutrophils, their readiness for inflammatory infiltration with a decrease in the migration rate, the possibility of their use in COVID-19 was considered.

Dipyridamole can also have a positive effect on the microcirculation system, which is severely affected by COVID-19, as an angioprotector and microcirculation corrector.

Bromhexine has an indirect mucolytic, expectorant and antitussive effect and improves airway patency.Ambroxol (an active metabolite of bromhexine) stimulates the synthesis of surfactant by alveolar type II pneumocytes. This promotes the separation of bronchial mucus into sol and gel, reducing its adhesiveness and restoring mucociliary clearance.

Verospironhas an inhibitory effect on aldosterone, and therefore the entire subsequent chain of reactions, including hyper-responsiveness to angiotensin (hyperangiotensinogenemia), which occures in the pathogenesis of COVID-19 (the virus uses ACE-2 receptors to enter the cell, activating them in some way).

Conclusion

At the turn of 2019-2020 humanity faced an epidemic of a new coronavirus infection, which quickly turned into a pandemic. The SARS-CoV-2 virus is different from its aggressive and virulent cousins SARS-CoV and MERS-CoV. The virus managed to move from the animals to humans, anddue to its contagious nature

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and the possibility to fast and freely move around the world using modern infrastructure, it quickly conquered almost the entire world. Not immediately, but only with the accumulation of information about its behavior, infection process, a complete picture of the disease gradually developed. The destructive power of the virus lied in the type and degree of response of the human immune system, with the virus serving as a trigger.

Our views on treatment of this disease have also changed, which explains all revisions made by the Ministry of Health of the Russian Federation to thePrevention, diagnosis and treatment of new coronavirus infection (COVID-19) recommendations and why they are classified as Interim Guidelines. This was and is a fundamental document for the Russian medical community. On the basis of these guidelines, medical institutions developed their algorithms, adapted to the conditions and capabilities of each multidisciplinary hospital that were converted to act as infectious diseases hospital during the pandemic.

Findings

What conclusions can be drawn on inpatient management of patients with COVID-19 over the past months?

1) Treatment regimens have changed, according to the changes made in all revisions to the clinical guidelines of the Ministry of Health.

2) Most drugs are prescribed off-label (no evidence base, but according to international recommendations and the benefits-risks approach).

3) Etiotropic treatment is yet been found. Attempts have been made to use various antiviral drugs that have proven themselves well in treatment of other infections (HIV, Ebola, SARS-CoV and MERS-CoV viruses). These include favipiravir, lopinavir+ritonavir, interferon drugs, umifenovir, remdesivir. An attempt was made to use the immunosuppressive effect of antimalarial drugs (hydroxychloroquine, chloroquine, infloquine), which are also used in rheumatological practice.

4) One of the macrolide antibiotics (azithromycin) was used in combination with hydroxychloroquine to potentiate the immunosuppressive response.

5) However, in practice, it was necessary to stop (although they are still mentioned in the guidelines) the widespread use of hydroxychloroquine and lopinavir/ritonavir due to poor tolerance, dyspeptic disorders, which not only made the objective status of patients more difficult, but also did not give the desired effect. Patient observation showed no signs that these drugs are able to prevent the cytokine storm and, moreover, to stop it. In addition, the use of plaquenil in conjunction with azithromycin led to a lengthening of the QT interval and a proarrhythmogenic effect in a certain percentage of patients.

6) At the moment, favipiravir is used more actively than other antiviral drugs (it was developed as an inhibitor of the RNA-dependent polymerase of the influenza virus). A number of studies already conducted on this drug in China, Japan, and Russia has shown good results. Indication for its use is the clinical presentation of COVID-19, a positive PCR for SARS-CoV-2 for nose and oropharynx samples. Favipiravir works more effectively at the onset of the disease, when the virus is still located in the upper respiratory tract. The drug has strict indications and contraindications, and can only be used in a hospital.

7) Given the hyperimmune response of the body to the virus (cytokine storm), it is reasonable to prescribe biological drugs, i.e. inhibitors of IL-6 (tocilizumab) and IL-1 (anakinra). Our clinic uses tocilizumab (actemra).

8) Indications for the use of Janus kinases (baricitinib) are the clinical presentation of cytokine storm and CT signs of stage II-III of the disease.

9) Considering the compromised immune response with elements of autoimmune damage, we began to more boldly use glucocorticosteroids with promising results. In critical situations we use it according to the pulse therapy protocol and in medium and low doses at the initial stages of the disease, but in presence of first signs of a cytokine storm.

10) In case of an acute viral infection, the use of genetically engineered biological drugs and steroids increases the risk of secondary bacterial infection. Thus antibacterial drugs are prescribed only with clear presence of clinical, laboratory and instrumental signs

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(purulent sputum, areas of consolidation in the lungs, an increase in the level of leukocytes more than 10x109/L and procalcitonin more than 0.5 ng/ml). However the drugs are not used from the first day of development of pneumonia, as it was recommended in the first few versions of clinical guidelines. The fact is that the term pneumonia in the pre-bacterial period is not entirely justified; rather pneumonitisshould be used, which implies a different treatment protocol.

11) In the pathogenesis of the disease, hyperimmune response leads to disorders in the blood coagulation system. Almost all patients, in the absence of contraindications, are prescribed low molecular weight heparins in a therapeutic dose from the first day of hospitalization to discharge.

12) To promote better sputum discharge mucoactive drugs are prescribed, as well as bronchodilators for broncho-obstructive syndrome.

13) Respiratory support has been and remains one of the main methods of treatment. Starting from inhalation with humidified oxygen, with the transition to the prone position to various modes of ventilation. In extremely severe cases, the ECMO is used (ICU treatment and extracorporeal methods were not the objectives of this article).

14) Paracetamol was used for antipyretic purposes. Non-steroidal anti-inflammatory drugs, given their anti-inflammatory effect, have also been used.

15) Some drugs, because of the COVID-19 pathogenesis, also found their niche in the off-label treatment regimen, especially in the initial mild course of the disease. These are colchicine, spironolactone, dipyridamole, high doses of ascorbic acid, and vitamin D.

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