Diagnosis and Treatment Protocol for COVID-19 Patients

(Trial Version 8)

As an emerging acute respiratory infection, the novel coronavirus disease (COVID-19) has become a major public health emergency that threatens global health. Through active prevention, control and treatment measures, China has essentially brought the situation within its borders under control. Only sporadic outbreaks and imported cases remain in some parts of the country. However, as the virus is still spreading across the globe, the pandemic may persist for a longer period of time, and the risk of COVID-19 reemerging in China still lingers. In order to further observe the principles of early detection, reporting, quarantine and treatment of COVID-19 patients, to increase recovery rates and to lower fatality rates, we have updated *the Diagnosis and Treatment Protocol for COVID-19 Patients (Trial Version 7)* by summarizing China's recent clinical experience and drawing information from treatment guidelines issued by the World Health Organization (WHO) and others. Thus, *the Diagnosis and Treatment Protocol for COVID-19 Patients (Trial Version 8)* was developed.

I. Etiological Characteristics

The novel coronavirus (2019-nCoV) belongs to the beta genus of coronaviruses. It has an envelope, round or oval particles, and a diameter of 60-140nm. It has 5 essential genes, respectively targeting RNA-dependent RNA polymerase (RdRp) and 4 structural proteins of nucleoprotein (N), envelope protein (E), matrix protein (M) and spike protein (S). The N proteinwraps the RNA genome to form a nucleocapsid, which is surrounded by an E that contains the M and the Sproteins. The S protein enters the cell by binding to angiotensin converting enzyme 2 (ACE-2). When isolated and cultured in vitro, the novel coronavirus can be found in human respiratory epithelial cells in about 96 hours, while it takes about 4-6 days to isolate

and culture in Vero E6 and Huh-7 cell lines.

Coronavirus is sensitive to ultraviolet rays and heat. 56°C for 30 minutes alone, ether, 75% ethanol, chlorine-containing disinfectant, peracetic acid, chloroform and other lipid solvents can effectively inactivate the virus, while chlorhexidine cannot.

II. Epidemiological characteristics

1. Source of infection

The source of infection is mainly patients infected with the novel coronavirus as well as asymptomatic carriers. Patients are infectious during the incubation period and are highly infectious within 5 days after the onset of disease.

2. Route of transmission

The novel coronavirus is spread through respiratory droplets. Close contact among people is the main route of transmission. Contact with items contaminated by the virus can also cause infection. Prolonged exposure to high-concentration aerosols in a relatively closed environment may spread the virus through aerosols. Since the novel coronavirus can be isolated in feces and urine, attention should be paid to contact transmission or aerosol transmission in an environment contaminated by the virus.

3. Susceptible population

Everyone is susceptible to COVID-19, with certain demographics at a higher risk. After getting infected with the virus or being vaccinated, one can develop some immunity, but the duration is not clear.

III. Pathological changes

The following are pathological changes in major organs caused by the novel coronavirus, along with the testing results (excluding underlying diseases):

1. Lungs

The lungs can show consolidation in varying degrees, which is mainly manifested by diffuse alveolar injury and exudative alveolitis. The lung lesions in different regions are complex and varied, and the old and new lesions are interlaced.

Serum, fibrinous exudate and transparent membrane formation has been identified in the alveolar cavity; the exudative cells are mainly mononuclear and macrophages, and multinucleated giant cells can be observed. Type II alveolar epithelial cells proliferate, and some shedding of cells occurs as well. Inclusion bodies are occasionally found in type II alveolar epithelial cells and macrophages. Congestion, edema, and mononuclear and lymphocyte infiltration can be seen in the alveolar septum. A few alveoli are over-inflated, while the alveolar septum breaks, or a cystic cavity is formed. Part of the epithelium of the bronchial mucosa in the lungs shed and exudates and mucus are detected in the cavity. A mucus plus is seen in the small bronchi and bronchioles. Pulmonary vasculitis, thrombosis (mixed thrombus, hyaline thrombus), thromboembolism, focal hemorrhage and hemorrhagic infarction, can be observed in the lungs, as well as bacterial and/or fungal infection. In the case of a longer course of disease, the organization of alveolar exudate (sarcoidosis) and pulmonary fibrosis can be seen.

Under electron microscope, coronavirus particles are found in the cytoplasm of bronchial mucosa epithelium and type II alveolar epithelial cells. Immunohistochemical staining shows that novel coronavirus antigen immunostaining and nucleic acid detection were positive in some bronchial epithelial cells, alveolar epithelial cells and macrophages.

2. Spleen, hilar lymph nodes and bone marrow

The spleen atrophies. White pulp and the lymphocytes are reduced, and some of these cells are necrotic. Hyperemia is found in the red pulp and focal hemorrhage can occur. Macrophages in the spleen proliferate and phagocytosis is visible. Splenic anemic infarction can appear.

Lymph nodes can have fewer lymphocytes and necrosis can be seen here. Immunohistochemical staining shows that CD4+ T and CD8+ T cells in the spleen and lymph nodes are reduced. Lymph node tissue can be positive for the novel coronavirus nucleic acid test, and immunostaining for the novel coronavirus antigen of macrophages is positive.

Bone marrow hematopoietic cells may proliferate or decrease in number, and the proportion of red granules increases; hemophagocytosis is occasionally seen.

3. Heart and blood vessels

Some cardiomyocytes can show degeneration, necrosis, interstitial congestion, or edema, and monocyte, lymphocyte and/or neutrophil infiltration. Occasionally, the novel coronavirus nucleic acid test is positive.

Endothelial cell shedding, intimal or full-thickness inflammation can be observed in small blood vessels throughout the body. Mixed thrombosis, thromboembolism and infarction in corresponding parts can be detected in blood vessels. Visible thrombosis can be seen in the micro vessels of the main organs.

4. Liver and gallbladder

Hepatocyte degeneration and focal necrosis with neutrophil infiltration can be seen, as well as liver sinusoid congestion, lymphocyte and monocyte cell infiltration in the portal area, and microthrombus formation. The gallbladder is fully expanded. The liver and gallbladder show positive nucleic acid tests for the novel coronavirus.

5. Kidneys

Glomerular capillary congestion, and segmental fibrinoid necrosis are occasionally observed. Protein exudates are seen in Bowman's space. The proximal tubules have degeneration of the epithelium, with some necrosis and shedding, and the casts in the distal tubules are easily observed. The renal interstitium can be congested, and microthrombos is identifiable. Kidney tissue occasionally tests positive for the novel coronavirus nucleic acid.

6. Other organs

Brain tissue congestion and edema, some neuronal degeneration, ischemic changes and loss, and occasional phagocytic phenomenon have been detected, along with visible infiltration of monocytes and lymphocytes in the perivascular space. The epithelium of the esophagus, stomach and intestinal mucosa show degeneration, necrosis, and shedding to varying degrees, and the lamina propria and submucosal monocyte and lymphocyte infiltration is observed. Cortical cell degeneration, focal hemorrhage and necrosis is evident in the adrenal glands. In the testes, the number of spermatogenic cells decrease in varying degrees, and Sertoli cells and Leydig cells show degeneration.

The novel coronavirus can be detected in the nasopharynx and gastrointestinal mucosa, testes, salivary glands and other organs.

IV. Clinical features

1. Clinical manifestations

The incubation period is 1 to 14 days, mostly 3 to 7 days. Main manifestations are fever, dry cough, and fatigue. Some patients have diminished or absent sense of smell and/or taste as initial symptoms. A few patients have symptoms such as nasal congestion, runny nose, sore throat, conjunctivitis, myalgia, and diarrhea. Severe

patients often develop dyspnea and/or hypoxemia one week after the onset of the disease. In critical cases, symptoms can quickly progress to acute respiratory distress syndrome, septic shock, irreversible metabolic acidosis, coagulation dysfunction, multiple organ failure, etc. A very small number of patients may also have central nervous system involvement and macrovascular necrosis. Severe and critically ill patients may have moderate to low fever during the course of their illness, or even no obvious fever.

Mild patients can be characterized by low fever, mild fatigue, olfactory and gustatory disorders, and without pneumonia. Novel coronavirus infection in a few patients may not have obvious clinical symptoms.

Most patients have a good prognosis, with a few patients becoming critically ill. Most of the critically ill patients are elderly, have chronic underlying diseases, are in late pregnancy, perinatal women, or are obese.

Symptoms in children are relatively mild. Some children and newborns have atypical symptoms, such as vomiting, diarrhea and other gastrointestinal symptoms, or poor response and shortness of breath. A very small number of children may have multiple system inflammatory syndrome (MIS-C) which has similar symptoms to Kawasaki disease or atypical Kawasaki disease, toxic shock syndrome or macrophage activation syndrome. Most of these manifestations occur during the recovery period, such as, fever with rash, non-purulent conjunctivitis, mucosal inflammation, hypotension or shock, coagulopathy, acute gastrointestinal symptoms, etc. Once this occurs, their condition can deteriorate rapidly.

2. Laboratory testing

2.1 General testing

In the early stage of the disease, the total number of white blood cells in the peripheral blood is normal or decreased, and the lymphocyte count is decreased. Some patients may have increased liver enzymes, lactate dehydrogenase, muscle enzymes, myoglobin, troponin and ferritin. C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) is elevated in most patients, while procalcitonin is normal. Severe and critically ill patients can show increased D-dimer, a progressive decrease in peripheral blood lymphocytes, and increased inflammatory factors.

2.2 Etiology and serological examination

2.2.1 Pathogenic examination: The novel coronavirus nucleic acid can be detected in samples such as nasopharyngeal swabs, sputum and other lower respiratory secretions, blood, feces, and urine using real time reverse transcription-polymerase chain reaction (RT-PCR) and/or next generation sequencing (NGS) methods. It is more accurate to detect the virus through lower respiratory tract specimens (sputum or airway extracts).

Nucleic acid testing will be affected by the course of disease, specimen collection, testing processes, testing reagents and other factors. In order to increase the positive rate of testing, the collection of specimens should be standardized and sent for testing as soon as possible after collection.

2.2.2 Serological examination: the novel coronavirus-specific IgM antibody and IgG antibody tests are positive, and the positive testing rate within 1 week of onset is relatively low.

Due to the positive judgment value of the reagent itself, or the presence of interfering substances in the body (rheumatoid factor, heterophilic antibody, complement, lysozyme, etc.), or the cause of the specimen (hemolysis of the specimen, bacterial contamination of the specimen, excessive storage time of the specimen, incomplete coagulation of the specimen), the antibody test may show false positives. Generally, serological testing is not used as a diagnostic basis alone, and comprehensive judgments must be made in conjunction with epidemiological history, clinical

manifestations, and underlying diseases.

The following patients can be diagnosed through antibody testing: Patients who are clinically suspected of COVID-19but have a negative nucleic acid test; or patients who are in recovery and have a negative nucleic acid test.

2.2.3 Chest imaging: In the early stage of disease, multiple small patchy shadows and interstitial changes are seen, which are obvious in the periphery of the lung. This develops into multiple ground glass shadows and infiltration shadows in both lungs. In severe cases, lung consolidation may occur, but pleural effusion is rare. In MIS-C, patients with cardiac insufficiency can show enlarged heart shadows and pulmonary edema.

V. Diagnostic criteria

1. Suspected cases

According to the comprehensive analysis of the following epidemiological history and clinical manifestations, the criteria needed to confirm a diagnosis is:having met one of the epidemiological history criteria, and showingtwo clinical manifestations; if there is no clear epidemiological history, meeting any two of the clinical manifestations, and the novel coronavirus-specific IgM antibody is positive; or patients with three of the clinical manifestations.

1.1 Epidemiological history

1.1.1 Travel history or residence history in a community with case reports within 14 days before the onset;

1.1.2 A history of contact with patients with novel coronavirus infection or asymptomatic infection within 14 days of the onset;

1.1.3 Contact with patients with fever or respiratory symptoms from communities with case reports within 14 days of the onset;

1.1.4 Clustering disease (2 or more cases of fever and/or respiratory symptoms occurring in small areas such as homes, offices, school classes, etc.) within 14 days.

1.2 Clinical manifestations

1.2.1 Fever and/or respiratory symptoms and other above-mentioned clinical manifestations related to COVID-19;

1.2.2 Developing the above-mentioned imaging characteristics of COVID-19;

1.2.3 The white blood cell and lymphocyte count is low or normal.

2. Confirmed cases

Suspected cases having one of the following etiological or serological evidence:

(1) A positive real time RT-PCR detection of thenovel coronavirus nucleic acid;

(2) Viral gene sequencing, highly homologous to the known novel coronavirus;

(3) The novel coronavirus-specific IgM antibody and IgG antibody test is positive;

(4) The novel coronavirus-specific IgG antibody changes from negative to positive or the IgG antibody titer in the recovery phase is 4 times or higher than that in the acute phase.

VI. Clinical classification

1. Mild

The clinical symptoms are mild, and there is no pneumonia manifestation in imaging tests.

2. Moderate

Fever, respiratory symptoms, other clinical manifestations, and pneumonia can be seen on imaging.

3. Severe

Adults meeting any of the following:

(1) Shortness of breath, RR≥30 times/min;

(2) In the resting state, during inhalation, the oxygen saturation is ≤93%;

(3) Arterial partial pressure of oxygen (PaO2)/inhaled oxygen concentration (FiO2) ≤300mmHg (1mmHg=0.133kPa);

In areas with high altitude (more than 1000 meters above sea level), PaO2/FiO2 should be adjusted according to the following formula: PaO2/FiO2 × [760/atmospheric pressure (mmHg)].

(4) The clinical symptoms are progressively worsening, and lung imaging shows that within 24 to 48 hours the lesion has progressed significantly >50%.

Children meeting any of the following:

(1) High fever lasting more than 3 days;

(2) Shortness of breath (<2 months old, RR≥60 beats/min; 2-12 months old, RR≥50 beats/min; 1 to 5 years old, RR≥40 beats/min; >5 years old, RR≥30 Times/min);

(3) In the resting state, during inhalation, the oxygen saturation is ≤93%;

(4) Respiratory distress (nostril flapping, three concave signs);

(5) Drowsiness, convulsions;

(6) Feeding difficulties with signs of dehydration.

4. Critical

Meeting one of the following conditions:

(1) Respiratory failure and mechanical ventilation are required;

(2) Shock;

(3) Other organ failures, ICU monitoring and treatment is required.

VII. Groups at high risk of severe/critical illnesses

1. People over 65 years old;

2. Those with cardio-cerebrovascular diseases (including hypertension), chronic lung diseases (chronic obstructive pulmonary disease, moderate to severe asthma), diabetes, chronic liver or kidney disease, tumors and other underlying diseases;

3. Immune function deficiency (AIDS patients, long-term use of corticosteroids or other immunosuppressive drugs that lead to a weakened immune function);

4. Obesity (body mass index ≥ 30);

5. Late pregnancy and perinatal women;

6. Heavy smokers.

VIII. Early warning indicators for severe/critical illnesses

1. Adults

(1) Progressive exacerbation of hypoxemia or respiratory distress;

(2) Deterioration of tissue oxygenation index or progressive increase of lactic acid;

(3) Progressive decrease in peripheral blood lymphocyte count or an increase in peripheral blood inflammatory markers such as IL-6, CRP, and ferritin;

(4) Significant increase of D-dimer and other related indexes of coagulation function;

(5) Chest imaging showing obvious progression of lung disease.

2. Children

(1) Increased breathing rate;

(2) Poor mental response and lethargy;

(3) Progressive increase in lactic acid;

(4) Significant increase of CRP, PCT, ferritin and other inflammatory markers;

(5) Imaging showing bilateral or multiple lung lobes infiltration, pleural effusion or rapid progression of the disease in a short period of time;

(6) Underlying diseases (congenital heart disease, bronchopulmonary dysplasia, respiratory malformations, abnormal hemoglobin, severe malnutrition, etc.), immunodeficiency (long-term use of immunosuppressive agents) and newborns.

IX. Differential diagnosis

1. The mild manifestations of novel coronavirus pneumonia must be differentiated from upper respiratory tract infections caused by other viruses.

2. For suspected cases, the novel coronavirus pneumonia is mainly distinguished from other known viral pneumonias such as influenza virus, adenovirus, respiratory syncytial virus, and mycoplasma pneumoniae infection through rapid antigen detection and multiple PCR nucleic acid detection.

3. Differentiation from non-infectious diseases such as vasculitis, dermatomyositis and organizing pneumonia.

4. Children with rashes and mucosal damage should be differentiated from Kawasaki disease.

X. Case finding and reporting

After medical staff find a suspected case that meets the case definition, they should immediately carry out single-person and single-room isolation treatment, consult with experts or attending physicians in hospital, report directly online within 2 hours, collect specimens for novel coronavirus nucleic acid testing, and immediately transfer suspected cases to designated hospitals under the premise of ensuring the safety of transfer. For those who have been in close contact with people infected with COVID-19, even if they test positive for common respiratory pathogens, it is recommended to conduct a novel coronavirus pathogen test immediately. Suspected cases with negative results for two consecutive nucleic acid tests (at least 24 hours apart) and negative results for the novel coronavirus-specific IgM antibody and IgG antibody tests 7 days after the onset of the disease can be ruled out for infection.

For confirmed cases, direct online reporting should be made within 2 hours.

XI. Treatment

1. Determining the treatment site according to the condition

1.1 Suspected and confirmed cases should be treated in isolation in designated hospitals with effective isolation and protection protocols. Suspected cases should be treated in isolation in a single room, while multiple confirmed cases can be admitted to the same ward.

1.2 Critical cases should be admitted to the ICU for treatment as soon as possible.

2. General treatment

2.1 Bed rest, supportive treatment to ensure adequate energy intake, maintain water and electrolyte balance, maintain a stable internal environment, closely monitor vital signs, oxygen saturation, etc.

2.2 Monitor blood routine, urine routine, CRP, biochemical indicators (liver enzymes, myocardial enzymes, kidney function, etc.), blood coagulation function, arterial blood gas analysis, chest imaging, etc., according to the condition. If possible, cytokine testing is feasible.

2.3 Give effective oxygen therapy measures in time, including nasal cannula, mask oxygen and nasal high flow oxygen therapy. If possible, use hydrogen and oxygen mixed inhalation gas (H2/O2: 66.6%/33.3%) for treatment.

2.4 Antibacterial treatment: Avoid blind or inappropriate use of antibacterial drugs, especially the combined use of broad-spectrum antibacterial drugs.

3. Antiviral treatment

A number of emergency clinical trials of antiviral drugs have been carried out. Although no antiviral drugs have been found to be effective by strict "randomized, double-blind, placebo-controlled studies", some drugs have been clinically observed

to have shown a certain therapeutic effect. The current consensus is that drugs with potential antiviral effects should be used early in the course of the disease, and it is recommended to focus on severely ill patients with high-risk factors.

It is not recommended to use lopinavir/ritonavir and ribavirin alone. Hydroxychloroquine or the combined use with azithromycin is not recommended either. The following drugs can continue to be tried and further evaluated in clinical application:

(1) Alpha-interferon: 5 million U per adult (or equivalent dose) inhaled through aerosolor combined with 2ml of sterile water for injection, twice a day. The course of treatment shall not exceed 10 days;

(2) Ribavirin: It is recommended to use it in combination with interferon (the same dose as alpha-interferon) or with lopinavir/ritonavir (200mg/50mg/capsule for adults). 2 capsules of lopinavir/ritonavir should be administered 2 times a day and 500mg of Ribavirin should be intravenously infused 2 to 3 times a day for adults. The course of treatment does not exceed 10 days;

(3) Chloroquine phosphate: used for adults between 18 and 65 years old, weighing >50kg: 500mg twice a day, for 7 days; weighing <50kg: 500mg twice a day on the first and second days, and 500mg once a day on the third to seventh days;

(4) Abidol: 200mg for adults, 3 times a day. The course of treatment should not exceed 10 days.

Monitoring of adverse reactions, contraindications and drug interactions must be done. It is not recommended to use more than 3 antiviral drugs at the same time, and relevant drugs should be discontinued when intolerable side effects occur. For the treatment of pregnant or postpartum women, healthcare providers should consider the number of weeks of pregnancy, choosing drugs with the least amount of impact on the fetus, and consider whether to terminate the pregnancy before treatment. Informed

consent is required.

4. Immunotherapy

4.1 Convalescent plasma: suitable for patients with rapid disease progression, severe and critically ill patients. For the usage and dosage, refer to *the Clinical Treatment Protocol of Convalescent Plasma for Patients with COVID-19 (Trial Version 2)*.

4.2 Intravenous injection of COVID-19 human immunoglobulin: can be used in emergency situations for moderate patients with rapid disease progression and those in severe condition. The recommended dosage is 20ml for moderate patients and 40ml for severe patients. According to the improvement of the patient's condition, it can be infused every other day, with the total number not exceeding 5.

4.3 Tocilizumab: eligible for patients with extensive lung disease and severe patients with elevated IL-6 levels. Specific usage: The first dose is 4-8mg/kg, with the recommended dose of 400mg, 0.9% saline to dilute to 100ml, and the infusion time of more than 1 hour. If the first dose is not effective, the same dose can be applied 12 hours after the first dose. The maximum number of administrations is 2 and the maximum single dose does not exceed 800mg. Allergic reactions must be monitored. Contraindicated in active infections, such as tuberculosis.

5. Glucocorticoid therapy

For patients with progressive deterioration of oxygenation indicators, rapid imaging progression, and excessive activation of the body's inflammatory responses, glucocorticoids should be used for a short duration (3 to 5 days, and no more than 10 days), and the recommended dose is equivalent to methylprednisolone0.5-1mg/kg/day. Larger doses of glucocorticoids may delay the clearance of the virus due to immunosuppressive effects.

6. Treatment of severe and critical cases

6.1 Treatment principle: actively prevent and treat complications, treat underlying diseases, prevent secondary infections, and provide timely organ function support.

6.2 Respiratory support:

6.2.1 Oxygen inhalation through a nasal cannula or mask:

Severe patients with PaO2/FiO2 lower than 300 mmHg should be given oxygen therapy immediately. After receiving oxygen through a nasal cannula or mask, patients must be closely observed for 1-2 hours. If respiratory distress and/or hypoxemia does not improve, nasal high-flow oxygen therapy (HFNC) or non-invasive ventilation (NIV) should be used.

6.2.2 Nasal high-flow oxygen therapy or non-invasive ventilation:

Patients with PaO2/FiO2 less than 200 mmHg should be given HFNC or N4. For patients with no contraindications receiving HFNC or NIV, it is recommended to perform awake prone position ventilation at the same time, and the treatment time in prone position should be more than 12 hours.

Some patients have a high risk of failure with HFNC or NIV treatment, and patients' symptoms and signs need to be closely observed. If there is no improvement in hypoxemia or the frequency of breathing within 1-2hours, or there is excessive tidal volume or excessive inhalation effort, etc., especially after the prone position treatment, this indicates that the HFNC or NIV treatment is not effective, and invasive mechanical ventilation should be performed immediately.

6.2.3 Invasive mechanical ventilation:

If the PaO2/FiO2 is less than 150 mmHg, tracheal intubation should be considered, and invasive mechanical ventilation should be implemented. However, in view of the atypical clinical manifestations of hypoxemia in patients with severe novel coronavirus pneumonia, the patient's clinical manifestations and organ functions

should also be taken into consideration for mechanical ventilation. The situation should be evaluated in real time, as the delay of tracheal intubation may cause greater harm.

Early and appropriate invasive mechanical ventilation treatment is an important treatment for critically ill patients. Lung protective mechanical ventilation strategies must be implemented. For patients with moderate to severe acute respiratory distress syndrome, or when FiO2 of invasive mechanical ventilation is higher than 50%, lung recruitment therapy can be used and repeated as necessary. Some patients with COVID-19 have poor lung re-expansion, and excessive PEEP should be avoided to prevent barotrauma.

6.2.4 Airway management:

To strengthen airway humidification, it is recommended to use an active heating humidifier, and conditionally use loop heating guide wire to ensure the humidification effect. Closed suction, and if necessary, tracheostomy suction; active airway clearance treatment, such as vibration expectoration, high-frequency thoracic oscillation and postural drainage is recommended to maintain airways. When the oxygenation and hemodynamics are stable, passive and active exercises should be done as soon as possible to promote sputum drainage and pulmonary rehabilitation.

6.2.5 Extracorporeal membrane oxygenation (ECMO):

Under optimal mechanical ventilation conditions (FiO2≥80%, tidal volume of 6 ml/kg ideal body weight, PEEP≥5 cmH2O, and no contraindications), when protective ventilation and prone ventilation are proving ineffective, one should consider evaluating and implementing ECMO as soon as possible while meeting one of the following:

① PaO2/FiO2<50 mmHg over 3 hours;

② PaO2/FiO2<80 mmHg over 6 hours;

③ Arterial blood pH<7.25 and PaCO2>60 mmHg for more than 6 hours, and respiratory rate (RR)>35 times/min;

④RR >35 times/min, arterial blood pH <7.2 and the plateau pressure >30cmH2O;

⑤ Combined with cardiogenic shock or cardiac arrest.

Critically ill patients who meet the ECMO indications and have no contraindications should start ECMO treatment as soon as possible to delay a poor prognosis.

ECMO mode selection: Venous-venous ECMO (VV-ECMO) is the most commonly used method when only breathing support is required; Venous-arterial ECMO (VA-ECMO) is used when both breathing and circulation support are required; When a patient on VA-ECMO develops hypoxia showing in the brain and upper limbs, veno-arterial-venous EMCO (VAV-ECMO) should be used. After ECMO therapy, intensivists should strictly implement lung protective ventilation strategies.

Recommended initial settings: tidal volume <4-6ml/kg ideal body weight, plateau pressure ≤ 25cmH2O, driving pressure <15cmH2O, PEEP 5-15cmH2O, breathing rate 4-10 times/min, FiO2<50%. For patients whose oxygenation function is difficult to maintain, or with a strong inspiratory effort, obvious consolidation of the gravity-dependent areas of the lungs, or active drainage of airway secretions, prone ventilation can be combined.

Children's cardiopulmonary compensatory ability is weaker than that of adults, and they are more sensitive to hypoxia. They need to use more active oxygen therapy and ventilation support strategies than adults. The indications should be appropriately relaxed. Routine recruitment of the lungs is not recommended.

6.3 Circulation support: Critically ill patients can go into shock. On the basis of adequate fluid resuscitation, vasoactive drugs should be used rationally, while blood pressure, heart rate and urine output changes, as well as lactic acid and base excess should be closely monitored. If necessary, perform hemodynamic monitoring, advise the use of infusion and vasoactive drugs, and improve tissue perfusion.

6.4 Anticoagulant therapy: severe or critically ill patients have a higher risk of thromboembolism. For those who have no contraindications to anticoagulation, and for those who have significantly increased D-dimer, it is recommended to use anticoagulant drugs preventively. When a thromboembolic event occurs, anticoagulant therapy should be performed in accordance with the corresponding guidelines.

6.5 Acute kidney injury and renal replacement therapy: critically ill patients are susceptible to acute kidney injury, and the cause should be actively sought after. While actively correcting the cause, pay attention to maintaining water, electrolyte, and acid-base balance. Indications for continuous renal replacement therapy (CRRT)

include: ① hyperkalemia; ② severe acidosis; ③ pulmonary edema or excessive water load with ineffective diuretics.

6.6 Blood purification treatment: The blood purification system includes plasma exchange, absorption, perfusion, blood/plasma filtration, etc., which can remove inflammatory factors and block the "cytokine storm", thereby reducing the damage to the body caused by inflammation. It can be used for severe and critically ill patients during the early and mid-term treatment of cytokine storms.

6.7 Children's multi-system inflammatory syndrome: The treatment principle is multidisciplinary cooperation, anti-inflammatory treatment, correcting shock and coagulation dysfunction, organ function support, and anti-infection treatment when necessary. For those with typical or atypical manifestations of Kawasaki disease, the standard treatment for Kawasaki disease, which is intravenous immunoglobulin (IVIG), glucocorticoids and oral administration of aspirin, should be used.

6.8 Other possible treatment measures include the use of Xuebijing injection. Intestinal microecological regulators can be used to maintain intestinal microecological balance and prevent secondary bacterial infections. For children in severe or critical condition, the use of IVIG can also be considered when necessary.

Pregnant patients in severe or critical condition should terminate the pregnancy by the preferred method of caesarean section.

As patients often have anxiety and fear, psychological counseling should be strengthened and supplemented with medication when necessary.

7. Traditional Chinese medicine (TCM) therapy

This disease belongs to plague in traditional Chinese medicine (TCM), caused by the epidemic pathogenic factors. According to the different local climate characteristic and individual state of illness and physical conditions, the following treatment Protocol may vary. The use of over-pharmacopoeia doses should be directed by a physician.

7.1 During medical observation

Clinical manifestation 1: fatigue and gastrointestinal discomfort

Recommended Chinese patent medicine: Huoxiang Zhengqi capsules (pills, liquid, or oral solution)

Clinical manifestation 2: fatigue and fever

Recommended Chinese patent medicines: Jinhua Qinggan granules, Lianhua Qingwen capsules (granules), Shufeng Jiedu capsules (granules)

7.2 During clinical treatment (confirmed cases)

7.2.1 Qingfei Paidu decoction

Scope of application: It is suitable for light, moderate and severe patients, and can be used reasonably in combination with the actual situation of patients in the treatment of critically ill patients.

Prescription composition: Ma Huang (Ephedrae Herba) 9g, Zhi Gan Cao (Glycyrrhizae Radix) 6g, Xing Ren (Armeniacae Semen) 9g, Sheng Shi Gao (Gypsum fibrosum) (decocted first) 15-30g, Gui Zhi (Cinnamomi Ramulus) 9g, Ze Xie (Alismatis Rhizoma) 9g, Zhu Ling (Polyporus) 9g, Bai Zhu (Atractylodis macrocephalae Rhizoma) 9g, Fu Ling (Poria) 15g, Chai Hu (Bupleuri Radix) 16g, Huang Qin (Scutellariae Radix) 6g, Jiang Ban Xia (Pinellinae Rhizoma Praeparatum)

9g, Sheng Jiang (Zingiberis Rhizoma recens) 9g, Zi Wan (Asteris Radix) 9g, Kuan Dong Hua (Farfarae Flos) 9g, She Gan (Belamcandae Rhizoma) 9g, Xi Xin (Asari Radix et Rhizoma) 6g, Shan Yao (Dioscoreae Rhizoma) 12g, Zhi Shi (Aurantii Fructus immaturus) 6g, Chen Pi (Citri reticulatae Pericarpium) 6g, Huo Xiang (Pogostemonis Herba) 9g.

Suggested use: Traditional Chinese medicine decoction pieces for decocting in water. One dose daily with half of the dose taken in the morning and half in the evening (forty minutes after meal) with warm water. Three days make a course of treatment.

If conditions permit, the patient can take half a bowl of rice soup each time after taking the medicine, and can take up to one bowl if the patient has a dry tongue and is deficient in bodily fluids. (Note: If the patient does not have a fever, the amount of gypsum should be little. If having a fever or high fever, the amount of gypsum can be increased). If the symptoms improve but do not fully recover, then take the second course of treatment. If the patient has special conditions or other underlying diseases, the prescription of the second course of treatment can be modified based on the actual situation and the medicine should be discontinued when the symptoms disappear.

Source of prescription: *Notice on Recommending the Use of 'Qingfei Paidu decoction' in Treatment of COVID-19 by Integrated Traditional Chinese and Western Medicine* by the Office of the National Administration of Traditional Chinese Medicine & the General Office of the National Health Commission. (2022 No.22)

7.2.2 Mild cases

7.2.2.1 Cold-dampness and stagnation lung syndrome

Clinical manifestations: fever, fatigue, sore body, cough, expectoration, chest tightness, suffocation, loss of appetite, nausea, vomiting, sticky stools. Tongue has thin fat tooth mark or is light red, and the coating is white thick rot or white greasy and the pulse is soggy or slippery.

Recommended prescription: epidemic due to cold-dampness formula

Prescription composition: Sheng Ma Huang (Ephedrae Herba) 6g, Sheng Shi Gao (Gypsum fibrosum) 15g, Xing Ren (Armeniacae Semen) 9g, Qiang Huo (Notopterygii Rhizoma seu Radix) 15g, Ting Li Zi (Lepidii/Descurainiae Semen) 15g, Guan Zhong (Cyrtomii Rhizoma) 9g, Di Long (Pheretima) 15g, Xu Chang Qing (Cynanchi paniculati Radix) 15g, Huo Xiang (Pogostemonis Herba) 15g, Pei Lan (Eupatorii Herba) 9g, Cang Zhu (Atractylodis Rhizoma) 15g, Yun Ling (Poria) 45g, Sheng Bai Zhu (Atractylodis macrocephalae Rhizoma) 30g, Jiao San Xian (Jiao Shan Zha (Crataegi Fructus), Jiao Shen Qu (Massa medicate fermentata), and Jiao Mai Ya (Hordei Fructus germinatus)) 9g each, Hou Po (Magnoliae officinalis Cortex) 15g, Jiao Bing Lang (Arecae Semen) 9g, Wei Cao Guo (Tsaoko Fructus) 9g, Sheng Jiang (Zingiberis Rhizoma recens) 15g.

Suggested use: One dose daily, boiled with 600ml water, taking 1/3 of the dose in the morning, at noon and in the evening respectively before meal.

7.2.2.2 Dampness and heat-accumulation lung syndrome

Clinical manifestations: low or no fever, slight chills, fatigue, heavy head and body, muscle soreness, dry cough, sore throat, dry mouth without desire of drinking much water, or accompanied by chest tightness, no sweat or sweating, or vomiting and loss of appetite, diarrhea or sticky stool. The tongue is reddish, and the coating is white, thick and greasy or thin yellow, and the pulse is slippery or soggy.

Recommended prescription: Bing Lang (Arecae Semen) 10g, Cao Guo (Tsaoko Fructus) 10g, Hou Po (Magnoliae officinalis Cortex) 10g, Zhi Mu (Anemarrhenae Rhizoma) 10g, Huang Qin (Scutellariae Radix) 10g, Chai Hu (Bupleuri Radix) 10g, Chi Shao (Paeoniae Radix rubra) 10g, Lian Qiao (Forsythiae Fructus) 15g, Qing Hao

(Artemisiae annuae Herba) (added later) 10g, Cang Zhu (Atractylodis Rhizoma) 10g, Da Qjng Ye (Isatidis Folium) 10g, Sheng Gan Cao (Glycyrrhizae Radix) 5g.

Suggested use: One dose daily, boiled with 400ml water, taking half of the dose in the morning and the other half in the evening.

7.2.3 Moderate cases

7.2.3.1 Dampness and stagnation lung syndrome

Clinical manifestations: fever, cough and scanty sputum, or yellow sputum, suffocation, shortness of breath, bloating, and constipation. The tongue is dark red and fat; the coating is greasy or yellow and the pulse is slippery or stringy.

Recommended prescription: lung-diffusing and toxin-resolving formula

Prescription composition: Sheng Ma Huang (Ephedrae Herba) 6g, Ku Xing Ren (Armeniacae Semen) 15g, Sheng Shi Gao (Gypsum fibrosum) 30g, Sheng Yi Yi Ren (Coicis Semen) 30g, Mao Cang Zhu (Atractylodis Rhizoma) 10g, Guang Huo Xiang (Pogostemonis Herba) 15g, Qing Hao Cao (Artemisiae annuae Herba) 12g, Hu Zhang (Polygoni cuspidati Rhizoma) 20g, Ma Bian Cao (Verbenae Herba) 30g, Gan Lu Gen (Phragmitis Rhizoma) 30g, Ting Li Zi (Lepidii/Descurainiae Semen) 15g, Hua Ju Hong (Citri grandis Exocarpium rubrum) 15g, Sheng Gan Cao (Glycyrrhizae Radix) 10g.

Suggested use: One dose daily, boiled with 400ml water, taking half of the dose in the morning and the other half in the evening.

7.2.3.2 Cold-dampness lung syndrome

Clinical manifestations: low fever, submerged fever or absence of fever, dry cough, scanty sputum, fatigue, chest tightness, stuffy and full sensation in the stomach, or nausea. The tongue is pale or red, and the coating is white or greasy, and the pulse is

soggy.

Recommended prescription: Cang Zhu (Atractylodis Rhizoma) 15g, Chen Pi (Citri reticulatae Pericarpium) 10g, Hou Po (Magnoliae officinalis Cortex) 10g, Huo Xiang (Pogostemonis Herba) 10g, Cao Guo (Tsaoko Fructus) 6g, Sheng Ma Huang (Ephedrae Herba) 6g, Qiang Huo (Notopterygii Rhizoma seu Radix) 10g, Sheng Jiang (Zingiberis Rhizoma recens) 10g, Bing Lang (Arecae Semen) 10g.

Suggested use: one dose daily, boiled with 400ml water, taking half of the dose in the morning and the other half in the evening.

7.2.4 Severe cases

7.2.4.1 Plague poison and lung-closing syndrome

Clinical manifestations: fever, flushing, cough, yellowish phlegm, or blood in sputum, wheezing, shortness of breath, tiredness, fatigue, dryness, bitterness and stickiness in the mouth, nausea, loss of appetite, poor stool, and short urination. The tongue is red; the coating is yellow greasy and the pulse is slippery.
Recommended prescription: dampness-removing and toxin-resolving formula

Prescription composition: Sheng Ma Huang (Ephedrae Herba) 6g, Xing Ren (Armeniacae Semen) 9g, Sheng Shi Gao (Gypsum fibrosum) 15g, Gan Cao (Glycyrrhizae Radix) 3g, Huo Xiang (Pogostemonis Herba) (added later) 10g, Hou Po (Magnoliae officinalis Cortex) 10g, Cang Zhu (Atractylodis Rhizoma) 15g, Cao Guo (Tsaoko Fructus) 10g, Fa Ban Xia (Pinellinae Rhizoma Praeparatum) 9g, Fu Ling (Poria) 15g, Sheng Da Huang (Rhei Radix et Rhizoma) (added later) 5g, Sheng Huang Qi (Astragali Radix) 10g, Ting Li Zi (Lepidii/Descurainiae Semen) 10g, Chi Shao (Paeoniae Radix rubra) 10g.

Suggested use: one or two doses daily, boiled with 100-200ml water, finish the dose(s) in 2-4 times across the day, oral or nasal feeding.

7.2.4.2 Blazing of both qi and *ying* syndrome

Clinical manifestations: Hot fever, thirst, shortness of breath, delirium and unconsciousness, blurred vision, or spotted rash, or hematemesis, epistaxis, or convulsions in the limbs. The tongue is crimson with little or no coating. The pulse is deep, fine and rapid, or floating, large and rapid.

Recommended prescription: Sheng Shi Gao (Gypsum fibrosum) (decocted first) 30-60g, Zhi Mu (Anemarrhenae Rhizoma) 30g, Sheng Di (Rehmanniae Radix) 30-60g, Shui Niu Jiao (Bubali Cornu) (decocted first) 30g, Chi Shao (Paeoniae Radix rubra) 30g, Xuan Shen (Scrophulariae Radix) 30g, Lian Qiao (Forsythiae Fructus) 15g, Dan Pi (Moutan Cortex) 15g, Huang Lian (Coptidis Rhizoma) 6g, Zhu Ye (Phyllostachys nigrae Folium) 12g, Ting Li Zi (Lepidii/Descurainiae Semen) 15g, Sheng Gan Cao (Glycyrrhizae Radix) 6g.

Suggested use: 1 dose per day, decoction, first decoct Sheng Gan Cao (Glycyrrhizae Radix) and Shui Niu Jiao (Bubali Cornu), then apply other pieces, boiled with 100-200ml water, finish the dose(s) in 2-4 times across the day, orally or nasally.
Recommended Chinese patent medicines: Xiyanping injection, Xuebijing injection, Reduning injection, Tanreqing injection, Xingnaojing injection. Drugs with similar efficacy can be selected according to individual conditions, or can be used in combination according to clinical symptoms. Traditional Chinese medicine injection can be used in combination with TCM decoction.

7.2.5 Critical cases (Internal blockage and external desertion syndrome)

Clinical manifestations: dyspnea, asthma or mechanical ventilation needed, fainting, irritability, sweating, cold limbs, dark purple tongue, thick greasy or dry coating, and large floating pulse without root.

Recommended prescription: Ren Shen (Ginseng Radix) 15g, Hei Shun Pian (Aconiti Radix lateralis praeparata) (decocted first) 10g, Shan Zhu Yu (Corni Fructus) 15g,

delivered with Suhexiang Pill or Angong Niuhuang Pill.

For patients on mechanical ventilation with abdominal distention or constipation: 5-10g of Sheng Da Huang (Rhei Radix et Rhizoma). For patients with human-machine asynchronization: 5-10g of Sheng Da Huang (Rhei Radix et Rhizoma) and 5-10g of Mang Xiao (Natrii Sulfas) while administering sedatives and muscle relaxants.

Recommended Chinese patent medicines: Xuebijing injection, Reduning injection, Tanreqing injection, Xingnaojing injection, Shenfu injection, Shengmai injection, Shenmai injection. Drugs with similar efficacy can be selected according to individual conditions, or can be used in combination according to clinical symptoms. Traditional Chinese medicine injection can be used in combination with TCM decoction.

Note: Recommended usage of TCM injections for severe and critical cases

The use of TCM injections follows the principle of starting from a small dose and gradually adjusting the dosage according to the instructions of the drug. The recommended usage is as follows:

Viral infection or combined mild bacterial infection: 0.9% sodium chloride injection 250ml plus Xiyanping injection 100mg bid, or 0.9% sodium chloride injection 250ml Reduning injection 20ml, or 0.9% sodium chloride injection 250ml plus Tanreqing injection 40ml bid.

High fever with disturbance of consciousness: 250ml of 0.9% sodium chloride injection and 20ml bid of Xingnaojing injection.

Systemic inflammatory response syndrome or/and multiple organ failure: 250ml of 0.9% sodium chloride injection and 100ml of Xuebijing injection.

Immunosuppression: 250ml of glucose injection with 100ml of Shenmai injection or 20-60ml of Shengmai injection, bid.

7.2.6 Convalescent period

7.2.6.1 Lung and spleen qi deficiency syndrome

Clinical manifestations: shortness of breath, fatigue, anorexia, nausea, fullness, loose stool, and uneasiness. The tongue is pale and greasy.

Recommended prescription: Fa Ban Xia (Pinellinae Rhizoma Praeparatum) 9g, Chen Pi (Citri reticulatae Pericarpium) 10g, Dang Shen (Codonopsis Radix) 15g, Zhi Huang Qi (Astragali Radix) 30g, Chao Bai Zhu (Atractylodis macrocephalae Rhizoma) 10g, Fu Ling (Poria) 15g, Huo Xiang (Pogostemonis Herba) 10g, Sha Ren (AmomiFructus) (added later) 6g, Gan Cao (Glycyrrhizae Radix) 6g.

Suggested use: One dose per day, boiled with 400ml of water, taking half of the dose in the morning and the other half in the evening.

7.2.6.2 Deficiency of both qi and yin syndrome

Clinical manifestations: fatigue, shortness of breath, dry mouth, thirst, palpitations, sweating, poor appetite, low or no fever, dry cough, dry tongue, fine or weak pulse.

Recommended prescription: Nan Sha Shen (Adenophorae Radix) 10g, Bei Sha Shen (Glehniae Radix) 10g, Mai Dong (Ophiopogonis Radix) 15g, Xi Yang Shen (Panacis quinquefolii Radix) 6g, Wu Wei Zi (Schisandrae Fructus) 6g, Sheng Shi Gao (Gypsum fibrosum) 15g, Dan Zhu Ye (Lophatheri Herba) 10g, Sang Ye (Mori Folium) 10g, Lu Gen (Phragmitis Rhizoma) 15g, Dan Shen (Salviae miltiorrhizae Radix) 15g, Sheng Gan Cao (Glycyrrhizae Radix) 6g.

Suggested use: One dose per day, boiled with 400ml of water, taking half of the dose in the morning and the other half in the evening.

8. Early rehabilitation therapy

Actively implement early rehabilitation training and intervention for patients with COVID-19for respiratory and physical function, and psychological disorders to restore physical fitness and immunity as much as possible.

XII. Nursing

According to the patient's condition, nurses must clarify the key points of care and maintain proper basic care. In critically ill patients, close observation of the patient's vital signs, state of consciousness and monitoring of blood oxygen saturation must be achieved. Critically ill patients must have 24-hour continuous ECG monitoring, measurements of the patient's heart rate, respiratory rate, blood pressure, and SpO2 every hour, as well as measuring and recording body temperature every 4 hours. Venous access must be done correctly, and all conduits must be unobstructed and properly fixed. Bedridden patients must change their positions regularly to prevent pressure sores. Implementation of noninvasive mechanical ventilation, invasive mechanical ventilation, artificial airway, prone position ventilation, sedation and analgesia, and ECMO is done in accordance with nursing regulations. Special attention is needed for patients' oral care and fluid inflow and outflow management, as well as aspiration prevention in patients with invasive mechanical ventilation. Proper psychological status and care should be considered for conscious patients.

XIII. Discharge criteria and precautions after discharge

1. Discharge criteria

(1) Body temperature must return to normal for more than 3 days;

(2) Significantly improved respiratory symptoms;

(3) Lung imaging shows significant improvement in acute exudative lesions;

(4) Two consecutive respiratory tract samples are negative for nucleic acid detection (at least 24 hours apart).

Those who meet the above conditions can be discharged.

For patients who meet the above criteria 1, 2 and 3, but the nucleic acid continues to be positive for more than 4 weeks, it is recommended to conduct a comprehensive assessment of the infectivity of the patient through methods such as antibody testing, and virus culture and isolation, to determine whether to discharge.

2. Precautions after discharge

(1) Designated hospitals should communicate with the primary medical institutions in the patient's place of residence, share medical records, and promptly share the information of discharged patients to the patient's jurisdiction or primary medical institution.

(2) It is recommended to continue 14 days of isolation management and health monitoring after discharge from the hospital. As well as wearing a mask, paying attention to hand hygiene, avoiding public activities, and if possible, to live in a well-ventilated single room and to reduce close contact with family members.

(3) It is recommended to go to the hospital for follow-ups in the 2nd and 4th week after discharge.

XIV. Patient transfer

Healthcare providers are required to follow *the Work Plan for the Transfer of*

Pneumonia Cases Infected by the Novel Coronavirus (Trial) issued by the National Health Commission.

XV. Control of nosocomial infection in medical institutions

Medical institutions shall strictly follow the requirements of *the Technical Guideline for the Prevention and Control of Novel Coronavirus Infection in Health Care Settings (First Edition)* issued by the National Health Commission and *The Guidelines for the Use of Common Medical Protective Products in the Prevention of Novel Coronavirus Infection (Trial)*.

XVI. Prevention

People are encouraged to maintain good personal and environmental hygiene, a balanced nutrition, moderate exercise, adequate rest, and to avoid excessive fatigue. Health literacy should be improved, hygienic habits should be developed, and social distancing should be maintained. People should wash hands frequently, wear masks, cover their mouth and nose when sneezing or coughing, and use serving utensils when two or more are dining together. Indoor spaces should be well ventilated. Everyone should protect themselves through appropriate measures and must visit a fever clinic when developing respiratory symptoms. Those who have recently travelled to high-risk areas or have an exposure history with confirmed or suspected cases should have nucleic acid testing done.