

Diagnosis and Treatment Protocol for COVID-19 Patients

(Tentative 8th Edition)

As an emerging acute respiratory infection, the Corona Virus Disease 2019 (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 (Tentative 7th Edition)* by summarizing China's recent clinical experience and referencing treatment guidelines issued by the World Health Organization (WHO) and other countries. Thus, *the Diagnosis and Treatment Protocol for COVID-19 Patients (Tentative 8th Edition)* was developed.

I. Etiological Characteristics

The 2019-novel coronavirus (SARS-CoV-2) belongs to the beta genus of coronaviruses. The enveloped viral particle is round or oval, with a diameter of 60-140 nm. It has 5 essential genes, encoding RNA-dependent RNA polymerase (RdRp) and 4 structural proteins of nucleoprotein (N), envelope protein (E), matrix protein (M) and spike protein (S), respectively. The nucleoprotein wraps the RNA genome to form a nucleocapsid, which is surrounded by the E protein with embedded M and the S proteins. The S protein enters the cell by binding to angiotensin converting enzyme 2 (ACE-2). When isolated and cultured in vitro, SARS-CoV-2 can be found in epithelial cells of human respiratory tract within 96 hours, while it takes

about 4-6 days to isolate and culture in Vero E6 and Huh-7 cell lines.

SARS-CoV-2 is sensitive to ultraviolet rays and heat. It can be inactivated under 56°C for 30 minutes, or by ether, 75% ethanol, chlorine-containing disinfectant, peracetic acid, chloroform and other lipid solvents, but not by chlorhexidine.

II. Epidemiological characteristics

1. Source of infection

The source of infection is mainly patients with SARS-CoV-2 infection as well as asymptomatic infection. Patients are infectious during the incubation period and are highly infectious within 5 days after the onset of disease.

2. Route of transmission

SARS-CoV-2 is spread mainly through droplets and close contacts. 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 SARS-CoV-2 can be isolated in feces and urine, attention should be paid to contact or aerosol transmission in an environment contaminated by the virus.

3. Susceptible population

Everyone is susceptible to COVID-19. After infection or vaccination, one can develop some immunity, with unknown duration.

III. Pathological changes

The followings are pathological changes in major organs caused by SARS-CoV-2 infection, 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 damage and exudative alveolitis. The lung lesions in different regions are complex and varied, and the old and new lesions are interlaced.

Serous and fibrinous exudates, in addition to formation of hyaline membrane can be found in the alveoli; the exudatives contain mainly mononuclear and macrophages, and occasionally multinucleated giant cells. Proliferation of type II alveolar epithelial cells can be observed, with shedding of some cells. 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, with breaks of the alveolar septum or formation of cystic cavity. Part of the epithelium of the bronchial mucosa in the lungs shed and exudates and mucus are detected in the cavity. Mucus plug can be 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 infections. 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. The antigen of the novel coronavirus can be detected by immunohistochemical staining, as well as the nucleic acid by means of PCR, in some bronchial epithelial cells, alveolar epithelial cells and macrophages.

2. Spleen, hilar lymph nodes and bone marrow

The splenic volume is reduced, with atrophy of white pulp, decreased lymphocytes, and necrosis of some cells. Hyperemia of red pulp, focal hemorrhage, and proliferation of macrophages, accompanied by phagocytosis, can be seen in the spleen. Anemic infarction can also occur in the spleen.

Lymphocyte count is reduced in lymph nodes, together with necrosis. Immunohistochemical staining shows reduced CD4+ T and CD8+ T cells in both the spleen and lymph nodes. Nucleic acid of SARS-CoV-2 may be present in lymph nodes, while the antigen can be detected by immunostaining in macrophages.

Increased and decreased hematopoietic cells may be seen in bone marrow, with increased granulocyte-to-erythrocyte ratio. Hemophagocytosis is occasionally seen.

3. Heart and blood vessels

Degeneration, necrosis, interstitial congestion, and edema can be found in some cardiomyocytes, with infiltration of few monocytes, lymphocytes and/or neutrophils. Occasionally, the nucleic acid test is positive for SARS-CoV-2.

Shedding of endothelial cells, and inflammation of intima or full-thickness can be observed in small blood vessels throughout the body. Mixed thrombosis, thromboembolism and infarction in corresponding sections can be found in blood vessels. Visible thrombosis can be seen in the microvasculatures of the major organs.

4. Liver and gallbladder

Degeneration and focal necrosis of hepatocytes, with neutrophil infiltration, can be seen, as well as liver sinusoid congestion, lymphocyte and monocyte infiltration in the portal area, and microthrombosis. The gallbladder is fully expanded. Nucleic acid for SARS-CoV-2 can be detected in the liver and gallbladder.

5. Kidneys

There are congestions of glomerular capillaries, and segmental fibrinoid necrosis, with proteinaceous exudates in Bowman's space. Degeneration of the epithelium of the proximal renal tubules can be observed, with some necrosis and shedding. Casts are seen in the distal renal tubules. There are congestion of renal interstitium, with microthrombosis. Nucleic acid test is occasionally positive for SARS-CoV-2 in kidney tissues.

6. Other organs

Congestion and edema can be seen, with degeneration, ischemic changes and loss of some neurons, and occasional phagocytic phenomenon. There is infiltration of monocytes and lymphocytes in the perivascular space. Focal necrosis of adrenal gland can also be found. The epithelium of the esophagus, stomach and intestinal mucosa show degeneration, necrosis, and shedding to varying degrees, with infiltration of monocytes and lymphocytes in the lamina propria and submucosa. Adrenal cortex cells exhibit degeneration, focal hemorrhage and necrosis. In the testes, the number of spermatogenic cells decreases in varying degrees, with degeneration of Sertoli cells and Leydig cells.

SARS-CoV-2 can be detected in the nasopharynx, 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. Anosmia and/or ageusia may be presenting symptoms in some patients. A few patients have symptoms such as nasal congestion, running 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, refractory metabolic acidosis, coagulopathy, and multiple organ failure. A very small number of patients may also have central nervous system involvement and peripheral ischemic necrosis. Severe and critically ill patients may have moderate to low-grade fever, or even no fever, during the course of the illness.

Mild patients can be characterized by low fever, mild fatigue, anosmia and ageusia. No pneumonia is present. Few patients may remain asymptomatic after novel coronavirus infection.

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

Symptoms in children are relatively mild. Some children and newborns have atypical symptoms, such as vomiting, diarrhea and other gastrointestinal symptoms. Some children just exhibit poor response and shortness of breath. Very few children may develop multiple system inflammatory syndrome (MIS-C), which often occurs in the recovery phase, with symptoms similar to Kawasaki disease or atypical Kawasaki disease, toxic shock syndrome, or macrophage activation syndrome. Clinical manifestations may include fever with rash, non-purulent conjunctivitis, mucosal inflammation, hypotension or shock, coagulopathy, and acute gastrointestinal symptoms. Once MIS-C occurs, the condition can deteriorate rapidly.

2. Laboratory tests

2.1 General tests

In the early stage of COVID-19, white cell count is often normal or decreased, while

lymphocyte count is decreased. Some patients may have increased levels of 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. Increased D-dimer level can be seen in severe and critically ill patients, together with progressive decrease in lymphocyte count, and increased inflammatory cytokines.

2.2 Etiology and serology tests

2.2.1 Etiology tests: The nucleic acid of SARS-CoV-2 can be detected in nasopharyngeal swabs, sputum and other specimens of lower respiratory tract, blood, feces, and urine, by means of real time reverse transcription-polymerase chain reaction (RT-PCR) and/or next generation sequencing (NGS). More accurate results can be obtained with specimens from the lower respiratory tract (sputum or tracheal aspirates).

The accuracy of nucleic acid tests may be affected by multiple factors, such as the course of the illness, sampling, testing, and test kits. In order to improve sensitivity, the sampling procedure should be standardized, and specimens should be sent for testing as soon as possible after collection.

2.2.2 Serology tests: The seroconversion rate within 1 week after disease onset remains very low, with regards to SARS-CoV-2-specific IgM antibody and IgG antibody.

False-positive results of serology tests may be related to the test (cutoff value), the patient (presence of interfering substances, e.g. rheumatoid factor, heterophilic antibody, complement, lysozyme, etc.), or specimen preparation (hemolysis, bacterial contamination, excessive storage time, incomplete coagulation). Serology tests cannot be used alone, they should be considered in the context of epidemiological history, clinical manifestations, and underlying diseases, in order to confirm the diagnosis.

The following patients can be diagnosed through serology tests: 1) patients who are clinically suspected of COVID-19 but have a negative nucleic acid test; 2) patients who are in the recovery phase and have a negative nucleic acid test.

2.2.3 Chest radiology: In the early stage of COVID-19, multiple small patchy shadows and interstitial changes are seen, mainly in periphery lungs. This may progress into bilateral multiple ground glass opacities and infiltrations. In severe cases, consolidation may occur, but pleural effusion is rare. In MIS-C, patients with cardiac insufficiency can show enlarged heart silhouette and pulmonary edema.

V. Diagnostic criteria

1. Suspected cases

Suspected cases can be diagnosed as follows:

- a) meeting any of the epidemiological criteria and any two of the clinical criteria
- b) meeting any two of the clinical criteria and positive SARS-CoV-2-specific IgM antibody in those not meeting any epidemiologic evidence
- c) meeting all three clinical criteria in those not meeting any epidemiology criteria

1.1 Epidemiological history

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

1.1.2 History of contact with patients with COVID-19 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 Cluster cases (2 or more cases of fever and/or respiratory symptoms occurring in small areas such as homes, offices, school classes, etc.).

1.2 Clinical criteria

1.2.1 Fever and/or respiratory symptoms consistent with COVID-19;

1.2.2 Radiologic features compatible with COVID-19;

1.2.3 Normal or decreased white cell count and lymphocyte count in the early stage.

2. Confirmed cases

Suspected cases who meeting any of the following criteria:

(1) RT-PCR test positive for SARS-CoV-2;

(2) Gene sequencing of the virus highly homologous to the known sequence of SARS-CoV-2;

(3) positive tests for SARS-CoV-2-specific IgM and IgG antibodies;

(4) seroconversion of SARS-CoV-2-specific IgG antibody, or 4-fold increase in IgG antibody titer in convalescent plasma than that in the acute phase.

VI. Clinical classification

1. Mild cases

The clinical symptoms are mild, and there is no evidence of pneumonia in chest radiology.

2. Moderate cases

Patients have fever and respiratory symptoms. Chest radiology suggests pneumonia.

3. Severe cases

Adult patients meeting any of the following:

- (1) Shortness of breath, RR \geq 30 breaths/min;
- (2) SpO₂ \leq 93% on room air in resting status;
- (3) PaO₂/FiO₂ ratio \leq 300 mmHg (1 mmHg = 0.133 kPa);

In areas with high altitude (more than 1000 meters above sea level), PaO₂/FiO₂ ratio should be adjusted according to the following formula:

PaO₂/FiO₂ x [760/atmospheric pressure (mmHg)].

- (4) rapid progression of clinical symptoms, with > 50% progression in the lung lesions in chest radiology.

Children meeting any of the following:

- (1) High fever lasting > 3 days;
- (2) Shortness of breath (< 2 months, RR \geq 60 breaths/min; 2-12 months, RR \geq 50 breaths/min; 1-5 years, RR \geq 40 breaths/min; > 5 years, RR \geq 30 breaths/min);
- (3) SpO₂ \leq 93% on room air in resting status;
- (4) Respiratory distress (nostril flapping, signs);
- (5) Drowsiness, convulsions;
- (6) Feeding difficulties with signs of dehydration.

4. Critical cases

Meeting one of the following conditions:

- (1) severe respiratory failure requiring mechanical ventilation;
- (2) Shock;
- (3) Any other organ failure requiring intensive care.

VII. High risk patient population

1. People over 65 years old;
2. Those with comorbidities, such as cardiovascular (including hypertension) and cerebrovascular diseases, chronic lung diseases (chronic obstructive pulmonary disease, moderate to severe asthma), diabetes, chronic liver disease, chronic kidney disease, and malignancies;
3. Immunosuppression (AIDS, 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 signs for severe/critical cases

1. Adults

- (1) Progressive exacerbation of hypoxemia or respiratory distress;
- (2) Deterioration of tissue oxygenation or progressive hyperlactatemia;
- (3) Rapid decrease in lymphocyte count or steady increase in 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 rapid progression of lung lesions.

2. Children

- (1) tachypnea;
- (2) Poor mental response and lethargy;
- (3) Progressive hyperlactatemia;
- (4) Significant increase of inflammatory markers such as CRP, PCT, and ferritin;
- (5) chest imaging showing bilateral or multi-lobar infiltration, pleural effusion or rapid progression of lung lesion;
- (6) Underlying diseases (congenital heart disease, bronchopulmonary dysplasia, respiratory tract malformations, abnormal hemoglobin, severe malnutrition, etc.), immunosuppression (long-term use of immunosuppressive agents) and newborns.

IX. Differential diagnosis

1. The mild cases of COVID-19 must be differentiated from upper respiratory tract infections caused by other viruses.

2. Differential diagnosis of COVID-19 includes pneumonia caused by other viruses

(influenza virus, adenovirus, respiratory syncytial virus), and *Mycoplasma pneumoniae*, through rapid antigen tests and multiplex PCR nucleic acid detection.

3. Other differential diagnosis may include non-infectious diseases such as vasculitis, dermatomyositis, and organizing pneumonia.

4. Differential diagnosis in children with rash and mucosal damage should include Kawasaki disease.

X. Case finding and reporting

Any probable case identified by healthcare workers should receive prompt quarantine in single room, followed by consultation by experts or attending physicians. If COVID-19 cannot be ruled out, the case should be reported in a web-based surveillance system within 2 hours, and specimens should be collected for nucleic acid test for SARS-CoV-2. Then the probable case should be transferred to designated hospitals under the premise of transfer safety. For close contact with positive test of other common respiratory pathogens, it is still recommended to perform a test for SARS-CoV-2. COVID-19 can be ruled out in suspected cases if two consecutive tests (at least 24 hours apart) are negative for nucleic acid of SARS-CoV-2, and both SARS-CoV-2-specific IgM and IgG antibodies are negative 7 days after disease onset.

Any confirmed cases should be reported in a web-based surveillance system within 2 hours.

XI. Treatment

1. Determining the treatment site according to the illness

1.1 Probable and confirmed cases should be quarantined and treated in designated

hospitals. suspected cases should be isolated in single rooms, while confirmed cases can be grouped together.

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

2. General treatment

2.1 Patients are advised to have bed rest, to enforce supportive treatment to ensure adequate calorie intake. Any water and electrolyte disorder should be corrected to maintain homeostasis. Vital signs, including pulse oximetry, should be closely monitored.

2.2 Routine laboratory tests include complete blood cells, urinalysis, CRP, blood chemistry (liver enzymes, cardiac enzymes, and kidney function), coagulation test, arterial blood gas analysis, and chest imaging. Serum levels of cytokines can be measured if available.

2.3 Oxygen therapy should be provided in severe and critical cases, including nasal cannula, face mask, and high flow nasal oxygen therapy. Inhalation of mixed H₂/O₂ (66.6%/33.3%) may be considered if available.

2.4 Avoid abuse or misuse of antibiotics, be cautious about combination therapy with broad-spectrum antibiotics.

3. Antiviral therapy

Although many clinical trials have been conducted under emergency situation, no antiviral drugs have been proved to be effective in randomized, double-blind, placebo-controlled trials. However, observational studies suggest potential benefit of some antiviral agents. The current consensus is that antiviral agents with potential efficacy should be used early in the course of the disease, especially in those who are at risk of becoming critically ill.

Monotherapy with lopinavir/ritonavir or ribavirin is not recommended. It is recommended against the use of hydroxychloroquine with or without azithromycin. The following antiviral agents can be used, the efficacy of which remains to be proved.

(1) Alpha-interferon: adults: 5 million units (or equivalent dose) in 2 ml sterile water for inhalation, bid. The course of treatment is up to 10 days;

(2) Ribavirin: Adults: 500 mg iv bid or tid, with treatment duration up to 10 days. Combination therapy with interferon (dose as above) or lopinavir/ritonavir (adults: 400 mg/100 mg, bid) is recommended;

(3) Chloroquine phosphate: indicated for adults aged 18 to 65 years. Body weight > 50 kg: 500 mg bid for 7 days; body weight < 50 kg: 500 mg bid on day 1 and 2, followed by 500 mg qd on day 3 to 7;

(4) Abidol: adults: 200 mg tid for up to 10 days.

Be cautious about any adverse effects, contraindications, and drug-drug interactions. It is recommended against combination therapy with 3 or more antiviral agents. Any antiviral agents should be discontinued if intolerable. For pregnant or postpartum women, antiviral agents with minimal effects on fetus should be used, with the consideration of whether to terminate the pregnancy before treatment. Informed consent must be obtained.

4. Immunotherapy

4.1 Convalescent plasma: indicated in patients with rapid progression, and severe and critically ill patients. For the usage and dosage, refer to *the Clinical Treatment Protocol of Convalescent Plasma for Patients with COVID-19 (Tentative second Edition)*.

4.2 COVID-19-specific human intravenous immunoglobulin: indicated in moderate and severe cases with rapid progression. The recommended dose is 20 ml for

moderate cases, and 40 ml for severe cases. Based on clinical response, COVID-19-specific human intravenous immunoglobulin can be administered every other day, up to 5 treatments.

4.3 Tocilizumab: indicated in patients with extensive lung disease and severe cases with elevated IL-6 levels. Recommended dose 4-8 mg/kg, or 400 mg in 100 ml normal saline iv over 1 hour. For nonresponders, the same dose can be repeated 12 hours after the first dose. Patients should not be treated with more than 2 doses, with maximum dose no more than 800 mg. Allergic reactions must be monitored. Contraindicated in patients with active infections, such as tuberculosis.

5. Glucocorticoid therapy

For patients with progressive hypoxemia, rapid progression of chest imaging, and hyperinflammatory response, short-term (3 to 5 days, no more than 10 days) glucocorticoids should be considered, with recommended daily dose as 0.5 to 1 mg/kg methylprednisolone equivalent. Of note is that higher dose of glucocorticoids may delay viral clearance due to immunosuppression.

6. Treatment of severe and critical cases

6.1 Principle: Apart from the above-mentioned treatment, principle of treatment should include treatment of underlying disease, prevention of complications including secondary infections, and life-sustaining treatments.

6.2 Respiratory support:

6.2.1 Oxygen therapy with nasal cannula or face mask:

Severe patients with $\text{PaO}_2/\text{FiO}_2$ ratio < 300 mmHg should receive oxygen therapy with nasal cannula or face mask immediately, under close monitoring for 1 to 2 hours. For those without improvement in respiratory distress and/or hypoxemia, high flow nasal cannula (HFNC) or non-invasive ventilation (NIV) should be used.

6.2.2 High flow nasal cannula or non-invasive ventilation:

Patients with $\text{PaO}_2/\text{FiO}_2$ ratio < 200 mmHg should be treated with HFNC or NIV. Prone positioning for > 12 hours per day should be performed in patients treated with HFNC or NIV, if not contraindicated.

Some patients have a high risk of treatment failure with HFNC or NIV, and they should be closely monitored for any deterioration of symptoms and signs. If the patient does not improve after a short trial (1 to 2 hours), as suggested by refractory hypoxemia, tachypnea, or excessive tidal volume or inspiratory effort, especially after prone positioning, this usually indicates treatment failure with HFNC or NIV, and invasive mechanical ventilation should not be delayed.

6.2.3 Invasive mechanical ventilation:

Intubation and invasive mechanical ventilation should not be delayed in patients with $\text{PaO}_2/\text{FiO}_2$ ratio < 150 mmHg. However, due to the atypical presentation of hypoxemia in patients with severe COVID-19, indication for endotracheal intubation and invasive mechanical ventilation should be based on integral assessment of clinical manifestation and organ function, rather than $\text{PaO}_2/\text{FiO}_2$ ratio alone. Of note is that delayed intubation may cause more harm in selected patients.

Early and appropriate treatment with invasive mechanical ventilation treatment is crucial in the management of critically ill patients with COVID-19. Lung protective mechanical ventilation strategy is the cornerstone. Recruitment maneuver should be considered in patients with moderate to severe acute respiratory distress syndrome, or when $\text{FiO}_2 > 0.5$. In selected COVID-19 patients with low recruitability, high PEEP may lead to barotrauma and should be avoided.

6.2.4 Airway management:

Active heating humidifier is recommended, with heating wires in ventilator circuit if

available, to ensure airway humidification. Closed suction is recommended to minimize the risk of aerosol transmission, while suctioning under bronchoscopy may be necessary. Vibration expectoration, high-frequency thoracic oscillation, and postural drainage is recommended to maintain airway patency. Passive and active mobilization are encouraged if tolerated, to promote sputum drainage and pulmonary rehabilitation.

6.2.5 Extracorporeal membrane oxygenation (ECMO):

ECMO is indicated if patients meet any of the following criteria, despite optimal settings of mechanical ventilation ($\text{FiO}_2 \geq 0.8$, tidal volume of 6 ml/kg ideal body weight, $\text{PEEP} \geq 5 \text{ cmH}_2\text{O}$, with no contraindications), and prone ventilation:

- ① $\text{PaO}_2/\text{FiO}_2$ ratio $< 50 \text{ mmHg}$ over 3 hours;
- ② $\text{PaO}_2/\text{FiO}_2$ ratio $< 80 \text{ mmHg}$ over 6 hours;
- ③ $\text{pH} < 7.25$ and $\text{PaCO}_2 > 60 \text{ mmHg}$ over 6 hours, and respiratory rate (RR) > 35 breaths/min;
- ④ $\text{RR} > 35$ breaths/min, $\text{pH} < 7.2$ and plateau pressure $> 30 \text{ cmH}_2\text{O}$;
- ⑤ presence of cardiogenic shock or cardiac arrest.

Critically ill patients who meet the above indications for ECMO and have no contraindications should receive ECMO as soon as possible. Delayed ECMO is associated with poor prognosis.

Mode of ECMO: Venous-venous ECMO (VV-ECMO) is most commonly used in patients requiring respiratory support only; venous-arterial ECMO (VA-ECMO) is indicated in patients requiring both respiratory and circulatory support. In patients with ischemia in the head and upper extremities during VA-ECMO treatment, veno-arterial-venous EMCO (VAV-ECMO) should be used. Lung₄₇protective

ventilation strategy is crucial even in patients treated with ECMO. Recommended initial settings include tidal volume < 4-6 ml/kg ideal body weight, plateau pressure \leq 25 cmH₂O, driving pressure < 15 cmH₂O, PEEP 5-15 cmH₂O, respiratory rate 4-10 breaths/min, and FiO₂ < 0.5. Prone positioning should be performed in patients with refractory hypoxemia, excessive inspiratory effort, bilateral consolidation in dependent regions, and needs for drainage of airway secretions.

Children with severe COVID-19 should be treated more aggressively with oxygen therapy and lung protection ventilation strategy, due to vulnerability to hypoxia and compromised cardiopulmonary reserve. Recruitment maneuver is not recommended.

6.3 Circulatory support: Critically ill patients with COVID-19 can be complicated with shock. In these patients, vasoactive agents should be administered after adequate fluid resuscitation. Vital signs, including heart rate, blood pressure, and urine output, should be closely monitored, in addition to lactate and base excess. Hemodynamic monitoring may be necessary to guide fluid therapy and titration of vasoactive agents, in order to improve tissue perfusion.

6.4 Anticoagulation therapy: Severe or critically ill patients are at high risk of thromboembolism. For those who have elevated D-dimer level and no contraindications to anticoagulation, prophylactic anticoagulation should be used. In cases of thromboembolism, patients should be receive anticoagulation therapy according to practice guidelines.

6.5 Acute kidney injury and renal replacement therapy: In critically ill patients who develop acute kidney injury, any specific etiology (such as hypoperfusion and pharmacologic nephrotoxicity) should be sought and corrected accordingly. Water, electrolyte, and acid-base disorders should be corrected. Indications for continuous renal replacement therapy (CRRT) include: 1) hyperkalemia; 2) severe acidosis; 3) pulmonary edema or fluid overload refractory to diuretics.

6.6 Blood purification: Blood purification, including plasmapheresis, plasma

absorption, hemoperfusion, blood/plasma ultrafiltration, may alleviate organ injury caused by cytokine storm by removal of inflammatory cytokines. It may be used in severe and critically ill patients with cytokine storms.

6.7 MIS-C in children: The patients should be treated under multidisciplinary approach, with early anti-inflammatory therapy, reversal of shock and coagulopathy, life-sustaining treatment, and anti-infective agents if necessary. For those with typical or atypical manifestations of Kawasaki disease, standard treatment for Kawasaki disease should be used with intravenous immunoglobulin (IVIG), glucocorticoids and oral aspirin.

6.8 Other treatment includes the use of Xuebijing injection, and probiotics to restore to gut microecology and to prevent secondary bacterial infections. For children with severe or critical COVID-19, IVIG can also be used.

Pregnancy should be terminated in patients with severe or critical COVID-19, preferably by caesarean section.

Psychological consultation is important as these patients often have anxiety and fear, and pharmacological therapy may be 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 Lan₅₁ (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 medicata 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 Qing 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 Niu Huang 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, Reduning⁵⁵ 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: 250ml of 0.9% sodium chloride injection plus Xiyanping injection 100mg bid, or 250ml of 0.9% sodium chloride injection plus 20ml of Reduning injection bid, or 250ml of 0.9% sodium chloride injection plus 40ml of Tanreqing injection bid.

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

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

Immunosuppression: 250ml of glucose injection plus 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

Early rehabilitation targeting respiratory function, physical function, and psychological disorders should be started as soon as possible, to restore physical fitness and immunity.

XII. Nursing care

Basic nursing care should be tailored based on assessment of the patient's condition. In patients with severe COVID-19, vital signs (especially mental status and pulse oxymetry) should be closely monitored. In critically ill patients, continuous monitoring of cardiopulmonary function is necessary, including hourly heart rate, respiratory rate, blood pressure, and SpO₂, in addition to body temperature every 4 hours. Venous access should be secured and patent. Postural changes should be scheduled in bedridden patients to prevent pressure sores. Protocols of nursing care should be available in patients receiving NIV, invasive mechanical ventilation, prone positioning, sedatives/analgesics, and ECMO, as well as in patients with artificial airway. Special attention is needed for oral care and fluid balance. Prevention of aspiration is important in patients with invasive mechanical ventilation. Psychological care may be of help based on careful assessment.

XIII. Discharge criteria and precautions after discharge

1. Discharge criteria

Those who meet all the following criteria can be discharged.

- (1) normalization of body temperature for > 3 days;
- (2) significant improvement in respiratory symptoms;
- (3) significant improvement in lung infiltrates in chest imaging;
- (4) two consecutive respiratory tract samples (at least 24 hours apart) negative for nucleic acid of SARS-CoV-2.

For patients who meet discharge criteria 1 to 3, but with persistent positive test of nucleic acid of SARS-CoV-2 for more than 4 weeks, it is recommended to conduct a comprehensive assessment of the infectivity through methods antibody test₈ and viral

culture, before hospital discharge.

2. Precautions after discharge

(1) Designated hospitals and local healthcare facilities should develop an infrastructure of mutual communication, to share medical records and relevant information of discharged patients.

(2) Discharged patients are recommended to continue home quarantine for 14 days, in addition to monitoring of health status. Discharged patients are advised to wear face mask, living in single room with adequate ventilation if available. Hand hygiene is important, and unnecessary public activities and close contact with family and others should be avoided.

(3) It is recommended to complete follow-up visits after 2 and 4 weeks since hospital 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. Infection control in healthcare 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. Nutrition should be balanced, and exercise customized to personal needs to ensure adequate rest and to avoid fatigue. The importance of social distancing, hand hygiene, and wearing face mask should be emphasized. People should cover their mouth and nose when sneezing or coughing. Adequate ventilation of the room needs to be maintained. People must go to fever clinics in case of respiratory symptoms. Those with recent travel history to high-risk areas or history of exposure to confirmed or suspected cases should be tested for nucleic acid of SARS-CoV-2.

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