Coronavirus disease 2019 (COVID-19) is an emerging acute respiratory tract infectious disease, and it has become a major global public health issue. By taking a series of active control and treatment measures, the epidemic situation in China has been contained effectively. However, as the pandemic persists globally, the risk for the pandemic transmission and spread in China remains. Currently, the administration of COVID-19 vaccines is carried out systematically worldwide, with novel coronavirus (2019-nCov)-specific antibodies detected in most vaccinated individuals. In order to further strengthen the diagnosis and treatment of COVID-19, we revised the Diagnosis and Treatment Protocol for COVID-19 (Trial Version 8) to Diagnosis and Treatment Protocol for COVID-19 (Revised Trial Version 8).

1. Etiological characteristics

2019-nCov belongs to the β-genus coronaviruses. It has an envelope, and the virus particle is round or oval, with a diameter ranging from 60 to 140 nm. The genome of 2019-nCov contains five essential genes, which encode four structural proteins, namely, the nucleoprotein (N) protein, the envelope (E) protein, the matrix protein (M) and the spike (S) protein, and an RNA-dependent RNA polymerase (RdRp). The RNA genome is wrapped in the N protein, forming a nucleocapsid surrounded by lipid bilayer membrane, in which the E protein, the M protein and the S protein are embedded. The S protein interacts with angiotensin-converting enzyme 2 (ACE2) to enter cells. When isolated and cultured in vitro, 2019-nCov can be found in human respiratory epithelial cells in approximately 96 hours; nevertheless, it takes approximately 4–6 days for the virus to be found if isolated and cultured in Vero E6 and Huh-7 cell lines.

The coronavirus is sensitive to ultraviolet light and heat. Exposure to 56 °C for 30 minutes and to lipid solvents, such as ether, 75% ethanol, chlorine-containing disinfectant, peracetic acid and pressure to 56 °C for 30 minutes and to lipid solvents, such as ether, can effectively inactivate the virus, but chlorhexidine fails to inactivate the virus.

2. Epidemiological characteristics

2.1. Source of infection

2019-nCov–infected patients are the main source of infection. The infection can be contagious at the incubation stage and is strongly infectious within 5 days after symptom onset.

2.2. Route of transmission

Transmission of the virus happens mainly via respiratory droplets and close contact. Contact with objects contaminated with the virus can also cause infections. There is the possibility of aerosol transmission in a relatively closed environment after a long-time exposure to high concentrations of aerosols. As 2019-nCov can be isolated from feces and urine, attention should be paid to a feces- or urine-contaminated environment that may lead to aerosol or contact transmission.

2.3. Susceptible groups

People are generally susceptible. Immunity can be acquired after infection or vaccination, but the duration remains currently unclear.

3. Pathological changes

3.1. Lungs

The alveoli are filled with serous fluid and fibrin with a hyaline membrane. Monocytes and macrophages as well as many multinucleated syncytial cells are identified within the alveolar exudates. Type II pneumocytes show marked hyperplasia and focal desquamation. Viral inclusion bodies are occasionally seen in type II pneumocytes and macrophages. In addition, there is prominent edema and congestion in the alveolar septa, which are infiltrated by monocytes and lymphocytes. Hyperventilation, alveolar septum rupture, or cysts are seen in a few alveoli. Drop of partial epithelial cells exists in the mucosa of bronchi, with exudates and mucus. Mucus plugs are often seen in the bronchia and the bronchiolo. Pulmonary vasculitis, thromboembolism (mixed thrombus or hyaline thrombus) and thromboembolism are observed. Focal hemorrhage is often seen in the lung tissues, and hemorrhagic infection and bacterial and/or fungal infections are found. For cases with a long disease course, organization (calcification) of alveolar exudates and interstitial fibrosis are also present.

By electron microscopy, 2019-nCov virions are observed in the cytoplasm of bronchial epithelium and type II pneumocytes. Immunohistochemical staining reveals 2019-nCov viral antigen immunoreactivity and positive 2019-nCov nucleic acids in some bronchial epithelial cells alveolar epithelial cells and macrophages.
3.2. Spleen, hilar lymph nodes and bone marrow

The spleen shrinks. The white pulp is atrophic with a decreased number of lymphocytes and focal necrosis; the red pulp is congested with focal hemorrhage. Macrophage proliferation and phagocytosis are present in the spleen. Anemic infarct of the spleen can develop. Reduction of lymphocytes and focal necrosis are noted in lymph nodes. Immunohistochemistry highlights a decreased number of CD4⁺ and CD8⁺ T cells in the spleen and lymph nodes. The lymph node tissues can be positive for 2019-nCov nucleic acids, and macrophages can be positive for 2019-nCov viral antigen immunoreactivity. Hematopoietic cells are proliferated or decreased in bone marrow with an increased granulocyte-to-erythrocyte ratio. Hemophagocytosis develops occasionally.

3.3. Heart and blood vessels

Myocardial cells are partially degenerated or necrosed. Congestion and edema can be seen in the cardiac interstitium, along with infiltration of some monocytes, lymphocytes, and/or neutrophils. The cardiac tissue is occasionally positive for 2019-nCov nucleic acids.

Shedding of endothelial cells, endovasculitis and vasculitis are seen in small blood vessels across all major body parts. Formation of mixed thrombus, thromboembolism and infarction are present in vessels, and formation of hyaline thrombus is seen in the capillaries of major organs.

3.4. Liver and gallbladder

Degeneration and focal necrosis of hepatocytes are found, accompanied by infiltration of neutrophils. The hepatic sinusoids are congested. The portal areas are infiltrated by lymphocytes and monocytes. Microthrombosis may develop. The gallbladder is prominently distended. The liver and gallbladder can be positive for 2019-nCov nucleic acids.

3.5. Kidneys

Glomerular capillaries are congested, occasionally with segmental fibrinoid necrosis; proteinaceous exudates are found in the Bowman capsule. Degeneration of epithelial cells is seen in the proximal tubule, with partial necrosis and shedding; casts are seen in the distal tubule. The renal interstitium is congested along with microthrombi. The renal tissue is occasionally positive for 2019-nCov nucleic acids.

3.6. Other organs

Cerebral hyperemia and edema are present, along with degeneration, ischemic changes and loss of some neurons, and occasional neuronophagia; infiltration of monocytes and lymphocytes is found in perivascular spaces. Necrotic foci are noted in the adrenal glands. Variable degrees of degeneration, necrosis and desquamation of epithelial mucosa are observed in the esophagus, stomach, and bowel; infiltration of monocytes and lymphocytes is found in the lamina propria and submucosa. Degeneration, focal hemorrhage, and necrosis of cortex cells are seen in adrenal glands. A decreased number of spermatogenic cells and degeneration of Sertoli cells and Leydig cells are found in the testis.

2019-nCov is detected in nasopharyngeal and gastrointestinal mucosa and organs including testis and salivary glands.

4. Clinical characteristics

4.1. Clinical manifestations

The incubation period is 1–14 days, mostly 3–7 days. The main manifestations include fever, fatigue and dry cough. Some patients show symptoms such as decrease in or loss of smell and taste. Nasal congestion, runny nose, sore throat, conjunctivitis, myalgia and diarrhea are found in a few cases. Severe patients develop dyspnea and/or hypoxemia after 1 week and may progress rapidly to acute respiratory distress syndrome, septic shock, refractory metabolic acidosis, coagulopathy and multiple organ failure. Rare cases may manifest central nervous system involvement and avascular necrosis of the extremities. It is noteworthy that severe and critical cases may show only moderate to low fever, or even no fever at all.

Patients with mild symptoms usually do not develop pneumonia, but have low fever, mild fatigue and smell and taste disorders. A small number of patients may show no obvious clinical symptoms after infection with 2019-nCov.

Most patients have a good prognosis, and only a small percentage of patients become critically ill. The prognosis is poorer for the elderly, patients with chronic underlying diseases, women in the third trimester of pregnancy and in the perinatal period, and obese people.

Symptoms in children are relatively mild. Some children and neonatal patients may have atypical symptoms, presenting with gastrointestinal symptoms such as vomiting and diarrhea or manifesting only as low response and shortness of breath. Extremely rare cases of infected children develop multisystem inflammatory syndrome (MIS-C), present with Kawasaki syndrome or atypical Kawasaki syndrome, have toxic shock syndrome, or display macrophage activation syndrome, mostly occurring at the convalescence stage. The main manifestations are fever with rash, nonsuppurative conjunctivitis, mucosal inflammation, hypotension or shock, coagulation disorder and acute gastrointestinal symptoms. Once it happens, the disease can deteriorate rapidly within a short time.

4.2 Laboratory tests

4.2.1. General findings

In the early stages of the disease, the peripheral white blood cell count is normal or decreased, and the lymphocyte count is decreased. Some patients have elevated levels of liver enzymes, lactate dehydrogenase, muscle enzymes, myoglobin, troponin and ferritin. Most patients have elevated levels of C-reactive protein (CRP) and erythrocyte sedimentation rate and normal levels of procalcitonin (PCT). Among severe and critical cases, D-dimer increases, peripheral blood lymphocytes progressively decrease, and inflammatory factors increase.

4.2.2. Pathogenic and serological findings

(i) Pathogenic findings

2019-nCov nucleic acids can be detected in nasopharyngeal swabs, sputum and other lower respiratory tract secretions, blood, feces, urine and other specimens using reverse transcriptase–polymerase chain reaction (PCR) and/or next-generation sequencing methods. It is more accurate and precise if specimens are obtained from the lower respiratory tract (sputum or airway extractions).

2019-nCov nucleic acid detection can be affected by factors including the course of disease, specimen collection, detection process and detection reagents. To increase the accuracy of detection, specimen collection should be standardized, and the specimens should be submitted for testing as soon as possible after collection.

(ii) Serological findings

2019-nCov–specific immunoglobulins M (IgM) and G (IgG) antibodies are positive. The positive rate is low within 1 week after onset.
Because of the positive cutoff value of the reagent, the presence of interfering substances in patients (rheumatoid factors, heterophile antibodies, complement, lysozyme, etc.), or the state of specimens (specimen hemolysis, contamination by bacteria, excessive storage time, incomplete solidification, etc.), serological antibody tests can yield false-positive results. Diagnosis is normally not made according to serological findings alone, but in combination with epidemiological history, clinical manifestations and underlying diseases.

4.3. Chest imaging

In the early stage, chest imaging shows multiple small patchy shadows and interstitial changes, more apparent in the lung periphery. As the disease progresses, imaging shows multiple ground-glass opacities and infiltrates in both lungs. In severe cases, pulmonary consolidation may occur. However, pleural effusion is rare.

In cases of MIS-C, heart enlargement and pulmonary edema are seen in patients with cardiac dysfunction.

5. Diagnosis

5.1. Principle

Diagnosis should be made based on comprehensive analysis of epidemiological history, clinical manifestations and laboratory findings. A positive nucleic acid test for 2019-nCov is the primary diagnostic criterion. For individuals not vaccinated with a COVID-19 vaccine, presence of 2019-nCov–specific antibodies can be used as an indication for diagnosis; for vaccinated individuals or individuals previously infected with 2019-nCov, diagnosis should not be based on serological antibodies.

5.2. Case definitions

5.2.1. Suspected cases

A suspected case has any of the epidemiological history criteria plus any two of the clinical manifestations.

If there is no clear epidemiological history, a suspected case has all three of the clinical manifestations, or two of the clinical manifestations plus positive 2019-nCov–specific IgM (except for individuals recently vaccinated with COVID-19 vaccine).

(i) Epidemiological history
a. History of travel to or residence in communities where cases have been reported within 14 days before the onset of the disease;
b. History of contact with 2019-nCov–infected patients or asymptomatic carriers within 14 days before the onset of the disease;
c. In contact with patients who have fever or respiratory symptoms from communities where confirmed cases have been reported within 14 days before the onset of the disease; or
d. Clustered cases (two or more cases with fever and/or respiratory symptoms in a small area such as families, offices, schools and so on within 14 days).

(ii) Clinical manifestations
a. Clinical manifestations related to COVID-19, such as fever and/or respiratory symptoms;
b. Presence of aforementioned imaging characteristics of COVID-19; or
c. Normal or decreased white blood cell counts or lymphocyte counts in the early stage of onset.

5.2.2. Confirmed cases

When suspected cases display one of the following etiological or serological evidence:

(i) Positive for 2019-nCov nucleic acids; or
(ii) 2019-nCov–specific IgM and IgG are positive for individuals not vaccinated with a COVID-19 vaccine.

6. Clinical classification

6.1. Mild cases

The clinical symptoms are mild, and there is no sign of pneumonia on imaging.

6.2. Moderate cases

Showing fever and respiratory symptoms with radiological findings of pneumonia.

6.3. Severe cases

Adult cases meeting any of the following criteria:

(i) High fever lasting >3 days;
(ii) Tachypnea (RR ≥ 30 breaths/min);
(iii) Oxygen saturation ≤ 93% on fingertip pulse oximeter taken at resting state; or
(iv) Arterial partial pressure of oxygen (PaO₂)/fraction of inspired oxygen (FiO₂) ≤ 300 mm Hg (1 mm Hg = 0.133 kPa). In high-altitude areas (at an altitude of >1000 m above the sea level), PaO₂/FiO₂ shall be corrected according to the following formula: PaO₂/FiO₂ = [760/altitude pressure (mm Hg)]
(v) Cases with chest imaging that shows obvious lesion progression >50% within 24–48 hours shall be managed as severe cases.

Child cases meeting any of the following criteria:

(i) High fever lasting >3 days;
(ii) Tachypnea (RR ≥ 60 breaths/min for infants aged <2 months; RR ≥ 50 breaths/min for infants aged 2–12 months; RR ≥ 40 breaths/min for children aged 1–5 years, and RR ≥ 30 breaths/min for children aged >5 years) independent of fever and crying;
(iii) Oxygen saturation ≤ 93% on fingertip pulse oximeter taken at resting state;
(iv) Labored breathing (nasal fluttering and three concave signs);
(v) Lethargy and convulsion; or
(vi) Difficulty in feeding and signs of dehydration.

6.4. Critical cases

Cases meeting any of the following criteria:

(i) Respiratory failure and requiring mechanical ventilation;
(ii) Shock; or
(iii) With other organ failure that requires intensive care unit management.

7. Populations at high risk of severe and critical conditions

(i) The elderly >60 years old;
(ii) Patients with underlying conditions such as cardiovascular and cerebrovascular diseases (including hypertension), chronic lung diseases, diabetes, chronic liver and kidney diseases and tumors;
(iii) Individuals with immune deficiency (such as AIDS patients, or in a state of immune dysfunction due to long-term use of corticosteroids or other immunosuppressive drugs);
(iv) Obese people (body mass index ≥ 30 kg/m²);
(v) Women in the third trimester of pregnancy and in the perinatal period; and
(vi) Heavy smokers.
8. Clinical early warning indicators of severe and critical cases

8.1. Adults

Adults with following indications are at risk of deterioration.
(i) Progressive exacerbation of hypoxemia or respiratory distress;
(ii) Deterioration of tissue oxygenation index or progressive elevation of lactic acid;
(iii) The peripheral blood lymphocytes decrease progressively, or peripheral blood inflammation markers, such as interleukin 6 (IL-6), CRP and ferritin, increase progressively;
(iv) Coagulation function–related indicators such as D-dimer significantly increase; and
(v) Chest imaging shows rapid development of lung lesions in a short period.

9. Differential diagnosis

(i) Mild manifestations of COVID-19 need to be distinguished from those of upper respiratory tract infections caused by other viruses.
(ii) COVID-19 is mainly distinguished from Mycoplasma pneumonia and other known viral pneumonias, such as influenza virus infection, adenovirus infection and respiratory syncytial virus infection. For suspected cases, efforts should be made to use methods such as rapid antigen detection and multiplex PCR nucleic acid testing for detection of common respiratory pathogens.
(iii) COVID-19 should also be distinguished from noninfectious diseases such as vasculitis, dermatomyositis and organizing pneumonia.
(iv) In children with rash and mucous membrane damage, COVID-19 should be distinguished from Kawasaki disease.

10. Case finding and reporting

Health professionals in medical institutions of all types and at all levels, upon discovering suspected cases that meet the suspected diagnosis definition should immediately keep each case in single rooms for isolation and treatment. If the cases are still considered as suspected after consultation made by hospital experts or attending physicians, they should be reported directly online within 2 hours and samples should be collected for 2019-nCov nucleic acid testing. Then suspected cases should be reported directly online within 2 hours and samples should be collected for 2019-nCov nucleic acid testing.

11. Treatment

11.1. Treatment venue determined by the severity of the disease

(i) Suspected and confirmed cases should be isolated and treated at designated hospitals with effective isolation, protection and prevention conditions in place. A suspected case should be treated in isolation in a single room. Confirmed cases can be treated in the same room.
(ii) Critical cases should be admitted to intensive care unit as soon as possible.

11.2. General treatment

(i) Let patients rest in bed and provide strengthening support therapy, ensure sufficient caloric intake for patients, monitor their water and electrolyte balance to maintain internal environment stability, and closely monitor vital signs and oxygen saturation.
(ii) According to patients’ conditions, monitor blood routine results, urine routine results, CRP, biochemical indicators (liver enzyme, myocardial enzyme, renal function, etc), coagulation function, arterial blood gas analysis and chest imaging. Cytokines can be detected if possible.
(iii) Timely provide effective oxygen therapy, including nasal catheter and mask oxygenation and high-flow nasal oxygen therapy. If possible, inhalation of mixed hydrogen and oxygen ($H_2/O_2$: 66.6%/33.3%) can be applied.
(iv) Antibiotic drug treatment: blind or inappropriate use of antibiotic drugs should be avoided, especially combined use of broad-spectrum antibiotics.

11.3. Antiviral therapy

In the process of emergency test use of antiviral drugs for clinical treatment, a number of clinical trials have been carried out. Although no antiviral drugs have proven effective by strict “randomized, double-blind, placebo-controlled study,” some drugs have been shown to have certain therapeutic effects through clinical observation studies. At present, there is a consensus that drugs with potential antiviral effects should be used in the early stage of the disease, and it is recommended to be used mainly on patients with high risk factors and propensity for developing severe conditions. Lopinavir/ritonavir or ribavirin alone is not recommended. Hydroxychloroquine or hydroxychloroquine combined with azithromycin is not recommended. The following drugs can be put into test use for further evaluation of efficacy in clinical applications.

11.3.1. $\alpha$-Interferon

For adults, 5 million units or equivalent dose is administered, each time adding 2 mL of sterilized water, atomization inhalation twice daily (BID), no longer than 10 days.

11.3.2. Ribavirin

Suggested to be used jointly with interferon (same dose as described in 11.3.1) or lopinavir/ritonavir (200 mg/50 mg per pill for adults, two pills each time, BID), 500 mg each time for adults, twice or three times of intravenous injection daily, no longer than 10 days.

11.3.3. Chloroquine phosphate

It can be used for adults aged 18–65 years. For adults with body weight greater than 50 kg, 500 mg BID for 7 days; for adults with body weight less than 50 kg, 500 mg BID at Days 1 and 2 and 500 mg every day (QD) at Days 3–7.

11.3.4. Arbidol

For adults, 200 mg three times a day (TID), no longer than 10 days.
Be aware of the adverse reactions, contraindications and interactions of the aforementioned drugs. Using three or more antiviral drugs at the same time is not recommended; if an intolerable toxic adverse effect occurs, the respective drug should be discontinued. For the treatment of pregnant women, issues such as the number of gestational weeks, choice of drugs having the least impact on the fetus, and whether pregnancy is terminated before treatment should be considered, with patients being informed of these considerations.

### 11.4. Immuno therapy

#### 11.4.1 Convalescent plasma treatment

It is suitable for patients with rapid disease progression and severe and critical cases. Usage and dosage should refer to Protocol of Clinical Treatment With Convalescent Plasma for COVID-19 Patients (Trial Version 2).

#### 11.4.2. Intravenous injection of COVID-19 human immunoglobulin

It can be used in emergency for moderate and severe cases with rapid disease progression. The recommended dose is 20 mL for moderate cases and 40 mL for severe cases and can be given every other day according to the improvement of the patient’s condition, no more than five times in total.

#### 11.4.3. Tocilizumab

For patients with extensive lung lesions and severe cases who also show an increased level of IL-6 in laboratory testing, tocilizumab can be used for treatment. The initial dose is 4–8 mg/kg with the recommended dose of 400 mg, diluted with 0.9% sodium chloride to 100 mL. The infusion time should be more than 1 hour. If the initial medication is not effective, one extra administration can be given after 12 hours (same dose as before). No more than two administrations should be given, with the maximum single dose no more than 800 mg. Watch out for allergic reactions. Administration of tocilizumab is prohibited for people with active infections such as tuberculosis.

#### 11.5. Glucocorticoid therapy

For patients with progressive deterioration of oxygenation indicators, rapid progress in imaging, and excessive activation of the body’s inflammatory responses, glucocorticoids can be used for a short period (generally 3–5 days, no longer than 10 days). It is recommended that doses should be the equivalent of methylprednisolone 1–2 mg/kg per day. Note that a larger dose of glucocorticoid will delay the clearance of coronavirus because of immunosuppressive effects.

### 11.6. Treatment of severe and critical cases

#### 11.6.1. Treatment principle

On the basis of the aforementioned treatment, complications should be proactively prevented, underlying diseases should be treated, secondary infections should also be prevented, and organ function support should be provided timely.

#### 11.6.2. Respiratory support

(a) Nasal cannulas or masks for oxygen inhalation

Severe cases with PaO2/FIO2 lower than 300 mm Hg should receive oxygen therapy immediately. The patients should be closely observed for a short time (1–2 hours) after receiving nasal cannulas or masks for oxygen inhalation. If respiratory distress and/or hypoxemia of the patient cannot be alleviated, high-flow nasal-catheter oxygenation (HFNC) or noninvasive ventilation (NIV) should be used.

(b) HFNC or NIV

Patients with PaO2/FIO2 lower than 200 mm Hg should receive HFNC or NIV. Patients who are receiving HFNC or NIV without contraindications, prone position ventilation, namely, awake prone position ventilation, is recommended at the same time, and the treatment time in prone position should be >12 hours.

Some patients are at high risk of failure when treated with HFNC or NIV, and their symptoms and signs need to be closely monitored. If the condition does not improve after a short period of treatment (1–2 hours), especially if hypoxemia still does not improve or respiratory frequency or tidal volume is too large or respiratory effort is too strong after prone position treatment, it is likely that HFNC or NIV treatment is not effective. Invasive mechanical ventilation should be applied in time.

(c) Invasive mechanical ventilation

In general, when PaO2/FIO2 is lower than 150 mm Hg, endotracheal intubation should be considered for invasive mechanical ventilation. However, in view of the atypical clinical manifestations of hypoxemia in patients with severe COVID-19, PaO2/FIO2 should not be used as the only indication of endotracheal intubation and invasive mechanical ventilation. Real-time evaluation should be conducted based on the clinical manifestations and organ functions of patients. It is worth noting that delayed endotracheal intubation may be more harmful.

Early and appropriate invasive mechanical ventilation is an important treatment for critical cases. Pulmonary protective ventilation strategy should be used. Pulmonary repositioning is recommended for patients with moderate to severe acute respiratory distress syndrome, or when FIO2 of invasive mechanical ventilation is higher than 50%. Whether to repeatedly perform pulmonary repositioning techniques can be determined according to its reactiveness. It should be noted that some COVID-19 patients have poor reactivity to pulmonary repositioning, and barotrauma caused by excessive positive end-expiratory pressure (PEEP) should be avoided.

(d) Airway management

It is recommended to use an active heating humidifier for airway humidification and use a loop heating guide wire if possible to ensure the humidification effect. It is recommended to use closed sputum suction and bronchoscope suction if necessary and actively carry out airway clearance treatment, such as vibration expectoration, high-frequency thoracic oscillation, postural drainage and so on; in the case of stable oxygenation and hemodynamics, passive and active activities should be carried out as soon as possible to promote sputum drainage and pulmonary rehabilitation.

(e) Extracorporeal membrane oxygenation

Timing of extracorporeal membrane oxygenation (ECMO): if the outcome of protective ventilation and prone position ventilation is poor under optimal mechanical ventilation conditions (FIO2 ≥80%, tidal volume of 6 mL/kg of ideal body weight, PEEP ≥5 cm H2O, and no contraindications) and one of the following indications is met, ECMO should be considered as soon as possible:

- a. PaO2/FIO2 <50 mm Hg for >3 hours
- b. PaO2/FIO2 <80 mm Hg for >6 hours
- c. Arterial blood pH <7.25, PaCO2 >60 mm Hg for >6 hours, and RR >35 breaths/min
d. RR >35 breaths/min, arterial blood pH <7.2, and platform pressure >30 cm H$_2$O or
e. With cardiogenic shock or cardiac arrest.

Critical cases that meet the ECMO indications and have no contraindications should start ECMO treatment as soon as possible to avoid delay in treatment and a poor prognosis.

Mode selection of ECMO: venovenous ECMO mode, which is the most frequently used mode, can be selected when only respiratory support is required; venoarterial ECMO (VA-ECMO) mode can be selected when both respiratory and circulatory support are required simultaneously; in case of brachiocephalic hypoxia during VA-ECMO, venous-arterial-venous ECMO can be applied. After the implementation of ECMO, lung protective ventilation strategy can be strictly administered. Recommended initial setup parameters are as follows: tidal volume <4-6 mL/kg ideal body weight, platform pressure ≤25 cm H$_2$O, generated pressure <1.5 cm H$_2$O, PEEP 5–1.5 cm H$_2$O, RR 4–10 breaths/min, and FiO$_2$ < 50%. Extracorporeal membrane oxygenation can be used in combination with prone ventilation for patients with difficulty in maintaining oxygenation or with strong respiratory effort, with significant consolidation of gravity-dependent region in both lungs, or requiring active secretion drainage from airways.

The cardiopulmonary compensation ability of children is weaker than for adults, and they are more sensitive to hypoxia. Therefore, more active oxygen therapy and ventilator support strategies and more relaxed indications should be applied for children than for adults. Routine application of pulmonary retensioning is not recommended.

11.6.3. Circulatory support.
For critical cases complicated with shock, on the basis of adequate fluid resuscitation, vasoactive drugs should be used, and changes in blood pressure, heart rate and urine volume as well as lactate and base excess should be closely monitored. As necessary, use hemodynamic monitoring to guide infusion and usage of vasoactive drugs and improve tissue perfusion.

11.6.4. Anticoagulation treatment
Severe or critical cases have a higher risk of thromboembolism. Prophylactic use of anticoagulants is recommended for those without anticoagulant contraindications and with a significant increase of D-dimer. When a thromboembolic event occurs, anticoagulation treatment should be performed according to corresponding guidelines.

11.6.5. Acute kidney injury and renal replacement therapy
Active efforts should be made to look for causes of acute kidney injury in critical cases, such as low perfusion and drugs. While actively eliminating the causes, the balance of fluid, acid-base and electrolyte should be maintained. The indications of continuous renal replacement therapy include the following: (a) hyperkalemia, (b) severe acidosis, and (c) pulmonary edema or water overload that does not respond to diuretics.

11.6.6. Blood purification treatment
Blood purification system, including plasma exchange, absorption, perfusion and blood/plasma filtration, can remove inflammatory factors and block a “cytokine storm”, so as to reduce the damage of inflammatory reactions to the body. It can be used for the treatment of severe and critical cases in the early and middle stages of a cytokine storm.

11.6.7. MIS-C
The treatment principle is multidisciplinary cooperation, including early anti-inflammatory management, correction of shock, correction of bleeding and coagulation dysfunction, organ function support, and anti-infection treatment when necessary. Patients with typical or atypical manifestations of Kawasaki disease can be treated similarly to the classic treatment regimen for Kawasaki disease, mainly medicated with intravenous infusion of γ-globulin (IVIG), glucocorticoid and oral aspirin.

11.6.8. Other treatment measures
Treatment with Xuebijing injection can be considered. Intestinal microecological modulators can be used to maintain intestinal microecological balance and prevent secondary bacterial infections. Severe and critical child cases can be given IVIG.

For gestational severe and critical cases, pregnancy should be terminated preferably with cesarean section.

Patients often suffer from anxiety and fear, and they should be strongly supported by psychological counseling, supplemented by medications when necessary.

11.7. Traditional Chinese medicine treatment
COVID-19 belongs to plague in traditional Chinese medicine (TCM), caused by epidemic pathogenic factors. According to the different local climate characteristics, individual state of illnesses and physical constitutions, treatment regimens should be selected referring to the following protocol. The use of over-pharmacopeial doses should be directed by a physician.

11.7.1. During medical observation
Clinical manifestation 1: fatigue with gastrointestinal discomfort
Recommended Chinese patent medicine: Huoxiang Zhengqi capsules (pills, liquid, or oral solution)
Clinical manifestation 2: fatigue with fever
Recommended Chinese patent medicines: Jinhua Qinggan granules, Lianhua Qingwen capsules (granules), Shufeng Jiedu capsules (granules)

11.7.2. During clinical treatment (confirmed cases)
(i) Qingfei Paidu decoction
Scope of application: According to the clinical observation of physicians from varied locations, it is suitable for mild, moderate and severe cases and can be used reasonably for the treatment of critically ill patients considering their actual situations.

Basic formula: Ephedrae Herba (Ma Huang) 9 g, Prepared Glycyrrhizae Radix (Zhi Gan Cao) 6 g, Armeniacae Semen (Xing Ren) 9 g, Natural Gypsum Fibrosum (Sheng Shi Gao) (decocted earlier) 15–30 g, Cinnamomi Ramulus (Gui Zhi) 9 g, Alismatis Rhizoma (Ze Xie) 9 g, Polyergus (Zhu Ling) 9 g, Atractylodis Macrocephalae Rhizoma (Bai Zhu) 9 g, Porta (Fu Ling) 15 g, Bupleuri Radix (Chai Hu) 16 g, Scutellariae Radix (Huang Qin) 6 g, Pinelliae Rhizoma Praeparatum (Jiang Ban Xia) 9 g, Zingiberis Rhizoma Recens (Sheng Jiang) 9 g, Asteris Radix (Zi Wan) 9 g, Farfarae Flos (Kuan Dong Hua) 9 g, Belamcandae Rhizoma (She Gan) 9 g, Asari Radix et Rhizoma (Xi Xin) 6 g, Dioscoreae Rhizoma (Shan Yao) 12 g, Aurantii Fructus Immaturus (Zhi Shi) 6 g, Citri Reticulatae Pericarpium (Chen Pi) 6 g, Pogostemonis Herba (Huoxiang) 9 g.

Suggested use: traditional Chinese herbal pieces for decocting in water. One dose daily with half of the dose taken in the morning and half in the evening (40 minutes after meal) while the decoction is warm. Three doses constitute a course of treatment.

If possible, a half bowl of rice soup after taking the decoction is advised. For the patients with dry tongue due to fluid depletion, one bowl of rice soup is suggested. (Note: If no fever, the amount
of Natural Gypsum Fibrosum should be little; in cases with fever or high fever, the amount can be increased.) If the symptoms improve but not totally recover, then take a 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 and the General Office of the National Health Commission (2020, no. 22).

(ii) Mild cases

a. Cold-dampness stagnation in lung syndrome

Clinical manifestations: fever, fatigue, sore body, cough, expectoration, chest tightness, suffocation, loss of appetite, nausea, vomiting, sticky stools and mild constipation. Tongue is pale and enlarged with teeth marks or is light red; the coating is white, thick, greasy and curdy or white and greasy; the pulse is soggy or slippery.

Recommended prescription: Hanshiyì formula

Basic formula: Raw Ephedrae Herba (Sheng Ma Huang) 6 g, Natural Gypsum Fibrosum (Sheng Shi Gao) 15 g, Armeniacae Semen (Xing Ren) 9 g, Notopterygii Rhizoma Seu Radix (Qiang Huo) 15 g, Lepidii/Descurainiae Semen (Ting Li Zi) 15 g, Cyrtomii Rhizoma (Guan Zhong) 9 g, Peretetima (Di Long) 15 g, Cynanchi Paniculati Radix (Xu Chang Qing) 15 g, Pogostemonis Herba (Huo Xiang) 15 g, Eupatoriis Herba (Pei Lan) 9 g, Atractylodis Rhizoma (Cang Zhu) 15 g, Poria (Yun Ling) 45 g, Raw Atractylodis Macrocephalae Rhizoma (Sheng Bai Zhu) 30 g, Prepared Crataegi Fructus, Massa Medicata Fermentata, and Hordei Fructus Germinatus (Jiao Shan Zha, Jiao Shen Qu, and Jiao Mai Ya) 9 g each, Magnoliae Officinalis Cortex (Hou Po) 15 g, Prepered Arecae Semen (Jiao Bing Lang) 9 g, Prepered Tsaoko Fructus (Wei Cao Guo) 9 g, Zingeribis Rhizoma Recens (Sheng Jiang) 15 g.

Suggested use: one dose daily, 600 mL after decocting, taking one-third (200 mL) in the morning, afternoon and evening, respectively, before meals.

b. Dampness-heat accumulation in 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 and gastric stuffiness, no sweat or difficulty in sweating, or vomiting and loss of appetite, diarrhea, or sticky stool. The tongue is reddish; the coating is white, thick, and greasy or thin and yellow; the pulse is slippery or soggy.

Recommended prescription: Arecae Semen (Bing Lang) 10 g, Tsaoko Fructus (Cao Guo) 10 g, Magnoliae Officinalis Cortex (Hou Po) 10 g, Anemarrhena Rhizoma (Zhi Mu) 10 g, Scutellariae Radix (Huang Qin) 10 g, Bupleuri Radix (Chai Hu) 10 g, Paeoniae Radix Rubra (Chi Shao) 10 g, Forsythiae Fructus (Lian Qiao) 15 g, Artemisiae Annuae Herba (Qing Hao) (decocoted later) 10 g, Atractylodis Rhizoma (Cang Zhu) 10 g, Isatidis Folium (Da Qing Ye) 10 g, Raw Glycyrrhizae Radix (Sheng Gan Cao) 5 g.

Suggested use: one dose daily, 400 mL after decocting, taking half of the dose in the morning and the other half in the evening.

(iii) Moderate cases

a. Dampness toxin stagnation in 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 enlarged; the coating is yellow and greasy or yellow and dry; the pulse is slippery and rapid or wiry and slippery.

Recommended prescription: Xuanfei Baidu formula

Basic formula: Raw Ephedrae Herba (Sheng Ma Huang) 6 g, Armeniaca Semen (Ku Xing Ren) 15 g, Natural Gypsum Fibrosum (Sheng Shi Gao) 30 g, Raw Coecis Semen (Sheng Shi Gao) 30 g, Atractylodis Rhizoma (Mao Cang Zhu) 10 g, Pogostemonis Herba (Guang Huo Xiang) 15 g, Artemiae Annuae Herba (Qing Hao Cao) 12 g, Polygoni Cuspidati Rhizoma (Hu Zhong Xiang) 20 g, Verbenae Herba (Ma Bian Cao) 30 g, Dried Pharagmites Rhizoma (Gan Lu Gen) 30 g, Lepidii/Descurainiae Semen (Ting Li Zi) 15 g, Citri Grandis Exocarpium (Hua Ju Hong) 15 g, Raw Glycyrrhizae Radix (Sheng Gan Cao) 10 g.

Suggested use: one dose daily, 400 mL after decocting, take half of the dose in the morning and the other half in the evening.

b. Cold-dampness obstruction in lung syndrome

Clinical manifestations: low fever, unsusurfaced fever or absence of fever, dry cough, scanty sputum, lassitude, chest tightness, gastric stuffiness, or nausea and loose stool. The tongue is pale or light red; the coating is white or white and greasy; the pulse is soggy.

Recommended prescription: Atractylodis Rhizoma (Cang Zhu) 15 g, Citri Reticulatae Pericarpium (Chen Pi) 10 g, Magnoliae Officinalis Cortex (Hou Po) 10 g, Pogostemonis Herba (Huo Xiang) 10 g, Tsaoko Fructus (Cao Guo) 6 g, Raw Ephedrae Herba (Sheng Ma Huang) 6 g, Notopterygii Rhizoma Seu Radix (Qiang Huo) 10 g, Zingeribis Rhizoma Recens (Sheng Jiang) 10 g, Arecae Semen (Bing Lang) 10 g.

Suggested use: one dose daily, 400 mL after decocting, take half of the dose in the morning and the other half in the evening.

(iv) Severe cases

a. Epidemic toxin blocking in lung syndrome

Clinical manifestations: fever, flushing, cough, scanty yellowish sputum or blood in sputum, wheezing, shortness of breath, tiredness, fatigue, dryness and bitterness, as well as stickiness in the mouth, nausea, loss of appetite, constipation and scanty dark urine. The tongue is red; the coating is yellow and greasy; the pulse is slippery and rapid.

Recommended prescription: Huashi Baidu formula

Basic formula: Raw Ephedrae Herba (Sheng Ma Huang) 6 g, Armeniaca Semen (Xing Ren) 9 g, Natural Gypsum Fibrosum (Sheng Shi Gao) 15 g, Glycyrrhizae Radix (Gan Cao) 3 g, Pogostemonis Herba (Huo Xiang) (decocoted later) 10 g, Magnoliae Officinalis Cortex (Hou Po) 10 g, Atractylodis Rhizoma (Cang Zhu) 15 g, Tsaoko Fructus (Cao Guo) 10 g, Pinelliae Rhizoma Praeparatum (Fa Ban Xia) 9 g, Poria (Fu Ling) 15 g, Raw Rhei Radix et Rhizoma (Sheng Da Huang) (decocoted later) 5 g, Raw Astragali Radix (Sheng Huang Qi) 10 g, Lepidii/Descurainiae Semen (Ting Li Zi) 10 g, Paeoniae Radix Rubra (Chi Shao) 10 g.

Suggested use: one or two doses daily, decocting in water, take the dose(s) two to four times across the day, 100-200 mL each time, oral administration or nasal feeding.

b. Blazing of both qi and ying syndrome

Clinical manifestations: high 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, thready, rapid, or hollow and rapid.

Recommended prescription: Natural Gypsum Fibrosum (Sheng Shi Gao) (decocoted earlier) 30–60 g, Anemarrhena Rhizoma (Zhi Mu) 30 g, Raw Rehmanniae Radix (Sheng Dì) 30–60 g, Bubali Cornu (Shui Niu Jiao) (decocoted earlier) 30 g, Paeoniae Radix Rubra (Chi Shao) 30 g, Scrophulariae Radix (Xuan Shen) 30 g, Forsythiae Fructus (Lian Qiao) 15 g, Moutan Cortex (Dan Pi) 15 g, Coptidis Rhizoma (Huang Lian) 6 g, Phylllostachys Nigrae Folium (Zhu Ye) 12 g, Lepidii/Descurainiae Semen (Ting Li Zi) 15 g, Raw Glycyrrhizae Radix (Sheng Gan Cao) 6 g.
Suggested use: one dose per day, Raw Glycyrrhizae Radix and Bubali Cornu decocted earlier and other pieces decocted later, decoct in water, take the dose(s) two to four times across the day, 100–200 mL each time, oral administration, or nasal feeding.

Recommended Chinese patent medicines: Xiyanying 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.

(v) Critical cases
Internal blockage and external desertion syndrome
Clinical manifestations: dyspnea, asthma, or mechanical ventilation needed; unconsciousness; irritability; sweating; cold limbs; dark purple tongue; thick greasy or dry coating; and floating and large pulse without root.

Recommended prescription: Ginseng Radix (Ren Shen) 15 g, Aconiti Radix lateralis praeparata (Hei Shun Pian) (decocted earlier) 10 g, Shan Corni Fructus (Zhu Yu) 15 g, delivered with Suhexiang pill or Angong Niuhuang pill.

For patients on mechanical ventilation with abdominal distention or constipation: 5–10 g of Raw Rhei Radix et Rhizoma. For patients with human-machine asynchronization: 5–10 g of Raw Rhei Radix et Rhizoma and 5–10 g of 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 principle of TCM injection use is starting with a small dose and gradually adjusting the dosage according to the instructions of the drug. The recommended usage is as follows:

- Viral infection or complicated with mild bacterial infection: 250 mL of 0.9% sodium chloride injection plus 100 mg of Xiyanying injection BID, or 250 mL of 0.9% sodium chloride injection plus 20 mL of Reduning injection, or 250 mL of 0.9% sodium chloride injection plus 40 mL of Tanreqing injection BID.
- High fever with disturbance of consciousness: 250 mL of 0.9% sodium chloride injection and 20 mL of Xingnaojing injection BID.
- Systemic inflammatory response syndrome and/or multiple organ failure: 250 mL of 0.9% sodium chloride injection and 100 mL of Xuebijing injection BID.
- Immunosuppression: 250 mL of glucose injection with 100 mL of Shenmai injection or 20–60 mL of Shengmai injection, BID.

(vi) Convalescent period
- a. Lung-spleen qi deficiency syndrome
- Clinical manifestations: shortness of breath, fatigue, anorexia, nausea, vomiting, abdominal stuffiness and fullness, uneasiness of defecation and loose stool with sensation of incomplete defecation. The tongue is pale and enlarged, and the coating is white and greasy.
- Recommended prescription: Pinelliae Rhizoma Praeparatum (Fa Ban Xia) 9 g, Citri Reticulatae Pergariun (Chen Pi) 10 g, Codonopsis Radix (Dang Shen) 15 g, Prepared Astragalus Radix (Zhi Huang Qi) 30 g, Prepared Atractylodis Macrocephalae Rhizoma (Chao Bai Zhu) 10 g, Poria (Fu Ling) 15 g, Pogostemonis Herba (Huo Xiang) 10 g, Amomum Fructus (Sha Ren) (decocted later) 6 g, Glycyrrhizae Radix (Gan Cao) 6 g.

Suggested use: one dose per day, 400 mL after decocting, take half of the dose in the morning and the other half in the evening.

13.1. Discharge criteria and postdischarge considerations

13.1.1. Discharge criteria

(i) Body temperature is back to normal for >3 days;
(ii) Respiratory symptoms improve obviously;
(iii) Pulmonary imaging shows obvious absorption of acute exudative inflammation; and
(iv) Nucleic acid tests are negative twice consecutively on respiratory tract samples (sampling interval being at least 24 hours).

Those who meet the aforementioned criteria can be discharged. For patients who meet criteria 1, 2 and 3 and whose nucleic acids remain positive for more than 4 weeks, methods including...
antibody detection, virus culture and isolation are recommended for a comprehensive assessment of the infectivity of the patient, before deciding whether to discharge.

13.2. Postdischarge considerations

(i) The designated hospitals should contact the local primary health care facilities and share the patients’ medical record, to timely send the information of the discharged patients to the community committee and primary health care facility where the patients reside.
(ii) After discharge, it is recommended for patients to monitor their own health status in isolation for 14 days, wear a mask, live in a well-ventilated single room if possible, minimize close contacts with family members, separate dining, practice hand hygiene, and avoid going out.
(iii) It is recommended for the patients to return to the hospitals for follow-up and revisit 2 and 4 weeks after discharge.

14. Patient transportation principles

Patients should be transported in accordance with the Work Protocol for Transfer of the COVID-19 Patients (Trial Version) issued by the National Health Commission.

15. Nosocomial infection prevention and control

Measures to prevent and control nosocomial infection should be implemented in accordance with the requirements of the Technical Guidelines for the Prevention and Control of Infection by the 2019-nCov in Medical Institutions (Second Edition) formulated by the National Health Commission.

16. Prevention

16.1. 2019-nCov vaccination

2019-nCov vaccination is an effective means of preventing 2019-nCov infection and reducing the incidence and severe illness rate. Anyone who meets the requirements can be vaccinated.

16.2. General precautions

Maintain a good personal and environmental hygiene, keep a balanced diet, get proper exercise and adequate rest, and avoid over fatigue. Improve health literacy and develop good hygienic habits and lifestyles, such as keeping “1-meter distance,” washing hands frequently, wearing masks, using communal chopsticks and covering mouth and nose when coughing or sneezing. Keep indoor ventilation and apply scientific personal protection. Visit the fever clinic for medical treatment in time when having respiratory symptoms. For those who have recently traveled to high-risk areas or have a contact history with confirmed or suspected cases, nucleic acid tests should be carried out on their own initiative.

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