Treatment Protocol for COVID-19 Severe and Critical Cases (Trial version 2)

(Issued by: National Health Commission &
National Administration of Traditional Chinese Medicine)
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I. Target patients

Severe and critical cases as defined in the *Protocols for the Diagnosis and Treatment of COVID-19 (Trial revised version 5)*[*] issued by the National Health Commission.

1. Severe cases

Patients who meet any of the following criteria:

(1) Respiratory distress with respiratory rate (RR) ⩾30 breaths/min;

(2) Percutaneous oxygen saturation (SpO_2) at rest on room air⩽93%;

(3) Partial arterial oxygen pressure (PaO_2) / Fraction of inspiration O_2 (FiO_2) ⩽300 mmHg;

(4) The patient should be treated as a severe case if any of the above criteria is met. Or if none of the above criteria is met, the patient should also be treated as a severe case when one of the following exists: lesions on lung radiological imaging progressed by >50% within 24-48 hours; age >60 years old with severe chronic underlying disease such as hypertension, diabetes, coronary heart diseases, cancer, structural lung diseases, pulmonary heart disease and immunosuppression.

2. Critical cases

Patients who meet any of the following criteria:

(1) Respiratory failure that requires mechanical ventilation;

(2) Shock;

(3) Complicated with other organ failure that requires treatment and monitoring in ICU.

[*] Notes of translator: This Protocol has been updated to Version 6 as of April 9, 2020.

II. Diagnosis and treatment of severe cases

1. Clinical warning indicators

Severe cases should be assessed of their vital signs, SpO_2, state of consciousness and organ functions. The following items should be monitored based on the conditions of the patient: hematologic test, urine routine test, biochemical examination (liver and kidney functions, lactic acid, blood sugar, electrolytes, lactate dehydrogenase, etc), myocardial injury marker, C-reactive protein, procalcitonin, coagulation functions, arterial blood gas analysis, electrocardiogram and chest imaging.

In addition, changes in the following indicators suggest the possibility of disease progression:

(1) Progressive decrease in lymphocyte count; B lymphocyte count is significantly lower; continuously decrease in CD4+ and CD8+ T cell count;

(2) The plasma/serum level of inflammatory factors such as IL-6 and C-reactive protein increases progressively;

(3) Blood lactic acid, (a tissue oxygenation and/or perfusion indicator), progressively increases;

(4) High-resolution CT shows rapid progression of pulmonary infiltration.

2. Treatment

(1) Principles of treatment

Bed rest with supportive treatment to ensure adequate energy intake; maintain the water-electrolyte, and acid-base balance; timely provide oxygen therapy, mechanical ventilation and other life support measures to prevent and treat complications; treat comorbidities; prevent secondary infection. In short, provide the most effective and suitable life support measures to help the patient get through the critical stage of the disease.

(2) Oxygen therapy and respiratory support

1) Patients with PaO_2/FiO_2 between 200 and 300 mmHg

a. The patient should be administered oxygen therapy by nasal catheter or mask, and timely assessed whether respiratory distress and/or hypoxemia has improved. It is recommended that the oxygen flow rate be no more than 5 L/min for nasal catheter and 5-10 L/min for mask oxygenation.

b. High-flow nasal cannula (HFNC) oxygen therapy: If there is no improvement of the respiratory distress and/or hypoxemia after 2-hour oxygen therapy by nasal catheter or mask, HFNC should be considered.

If the oxygenation level still does not improve or even deteriorates after 2-hours after HFNC oxygen therapy, non-invasive ventilation (NIV) or invasive ventilation should be started.

2) Patients with PaO_2/FiO_2 between 150 and 200mmHg

NIV treatment is optimal. The failure rate of noninvasive mechanical ventilation in these patients is high, so closely monitoring for clinical deterioration is needed. If no improvement or even deterioration of oxygenation within 1-2 hours, endotracheal intubation and invasive mechanical ventilation should be performed promptly.

3) Patients with PaO_2/FiO_2 below 150 mmHg.

a. Invasive mechanical ventilation

Implement pulmonary protective mechanical ventilation strategy, that is, mechanical ventilation at low tidal volume (4-6 ml/kg of ideal body weight) and low inspiratory pressure (plateau pressure < 30 cmH2O) to minimize ventilator-induced lung injury. The feasibility of implementation of lung recruitment maneuvers should be assessed, and the PEEP should be set according to the best oxygenation method or the FiO_2-PEEP Table (low PEEP setting method in ARDS net protocol).

b. Lung recruitment maneuver

Lung recruitment maneuver can be used if FiO_2 greater 0.5 with invasive mechanical ventilation is needed to maintain oxygenation target (or meeting the criteria of moderate or severe ARDS). Before implementation of lung recruitment maneuver, the lung recruitability should be evaluated by ultrasound, pressure-volume curve (P-V curve), and electrical impedance tomography (EIT).

c. Prone position ventilation.

If PaO_2/FiO_2 remains below 150 mmHg, prone position at least 12 hours per day should be considered.

d. Ventilator weaning.

If the oxygenation status of the patient improves (PaO_2/FiO_2 remains greater than 200 mmHg) after treatment and the patient is conscious with stable circulation, ventilator weaning can be considered after assessment.

4) Extracorporeal membrane oxygenation (ECMO)

a. Timing for initiation of ECMO. When the patient does not respond well to lung protective ventilation and prone position, and meets the following criteria, ECMO should be considered as early as possible.

The patient has no contraindications for ECMO and meets any criteria below despite optimal setting of mechanical ventilation had been implemented (FiO_2>= 0.8, tidal volume = 6 ml /kg of ideal body weight, PEEP>=10 cmH_2O):

a) PaO_2/FiO_2 < 50 mmHg for > 3 hours;
b) PaO_2/FiO_2< 80 mmHg for > 6 hours;
c) FiO_2 is 1.0 and PaO_2/FiO_2<100 mmHg;
d) pH of arterial blood < 7.25 and $PaCO_2$ > 60 mmHg for > 6 hours and respiratory rate > 35 breaths/min;
e) Respiratory rate > 35 breaths/min, pH of arterial blood < 7.2 and plateau pressure >30 cmH_2O;
f) Complicated with cardiac shock or cardiac arrest.

a. Contraindications for ECMO

Complicated with irreversible underlying conditions; complicated with contraindications to anti-coagulation; use of mechanical ventilation for > 7 days with FiO_2> 0.9 and plateau pressure > 30 cmH_2O; over 70 years old; with immunosuppression; with peripheral vascular disease or malformation.

b. Selection of V-V or V-A mode

VV- ECMO mode is recommended. For patient complicated with circulatory failure, physician should find out the reasons. If there is cardiac shock, VA- ECMO can be considered.

(3) Monitoring and support of the circulation

1) Closely monitor the patient's circulation following the tissue-perfusion-oriented hemodynamic treatment principles. For patient with hemodynamics unstable (shock, or systolic blood pressure < 90 mmHg or 40 mmHg lower than the baseline level, or require vasoactive drug, or with serious arrhythmia), careful assessment should be conducted to find out the cause of unstable hemodynamics. Appropriate treatment should be provided based on the type of shock to improve tissue perfusion and manage the serious arrhythmia.

2) Hemodynamic monitoring technology that is simple, easy to maintain and manage should be selected. Bedside invasive hemodynamic monitoring with complex techniques is not recommended. If possible, it is recommended to use ultrasonic doppler monitoring which is a non-invasive and convenient monitoring method.

3) In cases with unstable hemodynamics, volume should be maintained at the minimum level that can meet tissue perfusion demand, in order to avoid volume overload or aggravation of lung exudation. Appropriate volume resuscitation should be given. If necessary, common vasoactive agents such as norepinephrine could be considered.

As the pulmonary lesions are severe and patients are under high level of respiratory support therapy, acute cor pulmonale (ACP) is likely to develop in these patients. Right cardiac function should be closely monitored. Lung protective ventilation strategies should be used to improve oxygenation status to reduce the resistance in pulmonary circulation.

If the patient has significantly elevated myocardial enzymes (especially troponin) and/or elevated BNP, cardiac functions should be closely monitored in cases of cardiac shock.

(4) Nutritional support treatment

1) For nutrition risk assessment of severe cases with COVID-19, NRS2002 scoring tool should be used.
2) Enteral nutrition (EN) should be initiated as early as possible. Parenteral nutrition (PN) alone or combination of supplementary PN with EN is not recommended in early stage.

3) For patients with unstable hemodynamics, nutritional support should be started as soon as fluid resuscitation is completed, and hemodynamics are stable. For patients with non-life-threatening, controllable hypoxemia or compensatory/permissive hypercapnia, it is not recommended to delay the initiation of nutritional support therapy, even for patients with prone ventilation or ECMO therapy.
4) Intra-gastric nutrient through indwelling nasogastric tube is recommended for severe patients. For patients who are not suitable for intra-gastric feeding, postpyloric feeding by nasointestinal tube is recommended.
5) For severe cases, the target energy goal is 25-30 kcal/kg/day, and starts with small amount. For patients with gastrointestinal intolerance, trophic EN should be considered (defined as 10-20 kcal/h or 10-30 ml/h).
6) Sufficient (high-dose) protein should be provided for severe cases. Protein requirements are expected to be in the range of 1.5–2.0 g/kg actual body weight per day. In cases with insufficient protein intake, protein powder in addition to standard dosage of intact-protein enteral nutritional suspension is recommended.
7) Enteral nutrition rich in Ω-3 fatty acids could be used for COVID-19 severe cases. Fat emulsion rich in EPA and DHA can be added into the parenteral nutrition.
8) Appropriate measures should be taken for patients with enteral nutrition to prevent vomiting and reflux.
9) For patients with feeding-related diarrhea, it is recommended to change the nutrition infusion method or the composition of nutrient formula.

(5) Antiviral treatment

Lopinavir/ritonavir can be given to the patient for up to 2 weeks if within 10 days after the onset. Close monitoring for adverse drug reactions in needed, and various drug interactions should be monitored during treatment.

(6) Human immunoglobulin (IVIG)

Currently, the evidence to support the use of IVIG in COVID-19 patients is inadequate. It could be used as appropriate in critical cases.

(7) Convalescent plasma

Convalescent plasma containing neutralizing antibodies against COVID-19 can be an option of specific treatment for early critically ill patients. Protective antibody titer against COVID-19 in the plasma should be evaluated before the convalescent plasma is used.

(8) Glucocorticoid

Currently, there are no sufficient evidences to support the clinical use of glucocorticoid to improve patient's prognosis, therefore it is not recommended for routine use. For patients with progressive deterioration in oxygenation indicators, rapid disease progression on imaging finding and excessively activated inflammatory response, a short-term treatment of methylprednisolone could be used (40 mg, q12 h for 5 days). Patients should be assessed for contraindications before glucocorticoid is used.

(9) Antibacterial treatment

Routine use of antimicrobial agents is not recommended if there is no clear evidence of bacterial infection. It is important to note that the course of disease in severe cases is usually longer than 5-7 days, and the manifestations of cellular immunosuppression is common in these patients, especially in the cases admitted to ICU and requiring invasive mechanical ventilation. More attention should be paid to monitoring the occurrence of secondary bacterial or fungal infections in these patients.

If possible, respiratory pathogen detection should be actively conducted to allow targeted antibiotic treatment. If the patient has a history of antimicrobial use over the past 90 days, or has been hospitalized for more than 72 hours, or has a pre-existing structural lung disease, the selected antimicrobial should also be effective against drug-resistant bacteria.

(10) Other medications

Consider giving thymosin α1 to patients with low lymphocyte count and low cellular immune function. Intestinal microecological regulator can be used to maintain the intestinal microecological balance. The use of traditional Chinese patent medicine is still in clinical trials but Xuebijing can be considered for use.

(11) Venous thromboembolism (VTB)

Because of long bedridden time and frequently occurrence of abnormal coagulation, severe cases

should be closely watched for the risk of VTE and anticoagulation treatment could be given as appropriate.

(12) Analgesics-sedatives treatment

Appropriate analgesics-sedatives treatment should be given to patients with invasive mechanical ventilation. The goals of analgesics-sedatives treatment should be set based on the patient's condition and treatment measures. Attention should be given to humanistic care for severe cases with COVID-19.

(13) AKI and multiple organ functions

Severe patients may have dysfunctions of multiple organs such as brain, kidney, liver, digestive tract and coagulation system. During treatment, organ functions of the patient should be monitored, and appropriate organ support therapy should be provided for patients with organs dysfunction.

The incidence of AKI in these patients is not high and the timing of renal replacement therapy should be carefully evaluated. In general, renal replacement therapy should be used in patients with stage 2 AKI (serum creatinine increase 2.0–2.9 times baseline, and the urine volume less than 0.5 ml/kg/h for more than 12 hours) according to KDIGO standards.

(14) Traditional Chinese medicine treatment

1) Refer to the recommended prescriptions for severe and critical cases in the Protocol for Diagnosis and Treatment of COVID-19 Cases (Trial revised version 5).

2) Refer to the recommended prescription in the *Notice on Using "Lung Cleansing and Detoxification Decoction (Qing Fei Pai Du Tang" in the Integrated TCM and Western Medicine Treatment of COVID-19 Cases*.

3) Intravenous injection

Severe cases:

In addition to 100 ml of Xuebijing Injection and 250 ml of saline, qd, administer 100 ml of Shengmai Injection and 250 ml of saline, qd.

For patients with body temperature higher than 38.5C: 100mg of Xiyanping Injection and 250 ml of

saline, qd. (Note: Increased bowel movement after drug administrative is normal reaction, which has the function of clearing and dispersing heat.)

Critical cases:

In addition to 100 ml of Xuebijing Injection and 250 ml of saline, qd, administer 100 ml of Shengmai Injection and 250 ml of saline, qd. while deduct the same amount of liquid to ensure liquid supportive treatment for the patient without excessive volume of liquid that may cause pneumonedema or add burden to the heart.

Patients with persistent high fever: An Gong Niu Huang Pill, qd.

Patients with shock: Add 100 ml of Shenfu Injection and 250 ml of saline, qd.

III. Criteria for discharge from ICU

When severe cases of COVID-19 become stable in their condition with improved oxygenation status and do not need life support treatment, they should be discharged from the ICU as soon as possible. All the following criteria should be met before they can be discharged from the ICU:

1. Be conscious; compliant with doctor's orders; without analgesics-sedatives and muscle relaxants treatment;

2. Taken off mechanical ventilation; respiratory rate is < 30 breaths/min and SpO_2>93% on room air or low flow-oxygen therapy (nasal catheter or ordinary mask);

3. Blood circulation is stable without vasopressor or liquid resuscitation;

4. Without any acute progressive organ dysfunctions; no need for organ support therapy such as blood purification.