Chinese expert consensus on the diagnosis and treatment of severely and critically ill patients with coronavirus disease 2019

The coronavirus disease 2019 (COVID-19) threatens the health of humans worldwide, and at the time of this writing, there is no specifically effective drug for COVID-19. To reduce the mortality of severely and critically ill patients with COVID-19, the leading experts at the frontlines in China were called up to formulate the corresponding expert consensus by analyzing, discussing and summarizing data on the clinical diagnosis and treatment of this population in Wuhan and other severely affected areas. The first and revised editions were released on February 22 and March 4, 2020, respectively.

Diagnosis

To diagnose and treat suspected and confirmed cases, clinicians should refer to the Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (Trial Version 7).[3]

**Diagnosis of severe COVID-19**

COVID-19 patients meeting any of the following criteria should be considered as severe COVID-19:

1. Respiratory distress, with a respiratory rate (RR) ≥ 30 breaths/min;
2. Oxygen saturation (SpO₂) ≤ 93% at rest;
3. Arterial partial pressure of oxygen (PaO₂)/fraction of inspiration of oxygen (FiO₂) ≤ 300 mmHg (1mmHg = 0.133kPa). At high altitudes (>1000 m above sea level), PaO₂/FiO₂ should be corrected according to the following formula: PaO₂/FiO₂ × [atmospheric pressure (mmHg)/760];
4. Chest imaging evidence showing progression of lesions by more than 50% within 24–48 hours.
5. Sustained high fever (≥38.5 °C) for more than 5 days;
6. Age ≥ 65 years old, or age ≥ 50 years old with the neutrophil-to-lymphocyte ratio (NLR) of ≥ 3.13;[4]
7. Cases with serious underlying chronic conditions, including hypertension, diabetes, coronary or pulmonary heart disease, malignant tumor, structural lung disease, and immunosuppression.

**Diagnosis of critically ill COVID-19**

COVID-19 patients meeting any of the following criteria should be treated as critically ill COVID-19:

1. Respiratory failure requiring mechanical ventilation;
2. Shock;
3. Combined with organ failure requiring Intensive Care Unit (ICU) hospitalization.

Treatment

**General principles of treatment**

In addition to symptomatic treatment, clinicians should prevent and treat complications, treat underlying conditions, prevent secondary infections, and provide organ function support in time.

**Antiviral treatment**

Suggestion: There is no specific effective antiviral drug for COVID-19. Referring to The Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (Trial Version 7),[3] oral lopinavir/lopinavir can be tried (200 mg/50 mg per tablet, 2 tablets each time, twice per day, the course of treatment does not exceed 10 days). However, the adverse events caused by lopinavir/lopinavir should be paid attention to, such as diarrhea, nausea, vomiting, rash, liver function damage, and the interaction with other drugs should also be noticed; ribavirin can also be administered by intravenous dripping for 500 mg/time, 2–3 times per day and the course of treatment does not exceed 10 days (it is suggested to use in combination with interferon or lopinavir/lopinavir). It should be noted that large doses of ribavirin may cause severe side effects such as hemolytic anemia; aerosol inhalation of α-interferon (5×10⁶ IU/time or equivalent dose for adults, reconstituted with 2 ml of sterile water for injection, twice per day) for 5–7 days can also be considered, and adverse airway reactions should be paid attention to; chloroquine phosphate can also be applied orally (500 mg for adults, twice per day, the course of treatment does not exceed 10 days), but it should be noted that this drug can cause QT interval prolongation, especially in critically ill patients or patients with underlying heart diseases who should be closely monitored; arbidol can be administrated orally as well (200 mg for adults, three times a day, the course of treatment does not exceed 10 days).

Antiviral drugs can be used in combination, but should not exceed 3 different types. If any intolerable side effects occur, the respective drug should be stopped in time.

Not suggested: Use of neuraminidase inhibitors (oseltamivir, palamivir, zanamivir, etc.) and ganciclovir.
During the epidemic period of severe acute respiratory syndrome (SARS) in 2003, Chinese scholars found that the risk of ARDS and death of patients treated with lopinavir/litonavir combined with ribavirin was lower than that of patients treated with ribavirin alone. Recently, an observational meta-analysis showed that the early use of lopinavir/litonavir could reduce the mortality rate of SARS patients and the dose of glucocorticoids, which was of great significance to control the late complications of patients. The randomized controlled clinical trial (ChiCTR2000029308) targeting the efficacy and safety for the using of lopinavir/litonavir in the treatment of COVID-19 is ongoing.

Remdesivir (GS-5734) is one of the potential drugs for COVID-19 treatment by interfering with the RNA synthesis of coronavirus. But recently, a randomized controlled clinical trial indicated that remdesivir could not decrease the mortality rate of patients with severe COVID-19.

**Glucocorticoid therapy**

Not suggested: The administration of systemic glucocorticoids to severely and critically ill patients with COVID-19 is not suggested.

Suggestion: Methylprednisolone (0.5–2.0 mg·kg⁻¹·d⁻¹) should be given as early as possible for 3–5 days to patients with rapidly progressing conditions and complicated by moderate-to-severe ARDS (PaO₂/FiO₂ < 150 mmHg). COVID-19 patients on glucocorticoid therapy for other underlying conditions should continue therapy after consulting with a specialist, and the dosage should be decided based on the personal underlying condition and the severity of infection. However, those patients complicated by other underlying diseases, including hypertension, diabetes, gastrointestinal bleeding within 3 months, immunosuppression, should use with caution.

There is no consensus on the use of glucocorticoids in the treatment of patients with severe viral pneumonia. A retrospective study has reported that glucocorticoids can reduce the mortality rate of SARS patients and shorten the length of hospitalization, whereas other studies have indicated that glucocorticoids can increase the mortality rate of SARS patients and delay the clearance of SARS and MERS viruses. Histopathological and autopsy findings of a patient who died of COVID-19 have revealed bilateral diffuse alveolar injury with fibrous mucinous exudation, alveolar epithelial detachment and hyaline membrane formation in right lung, indicative of ARDS. On the other hand, the left lung showed pulmonary edema and hyaline membrane formation, suggestive of early ARDS. Therefore, glucocorticoid therapy should be considered to mitigate or prevent the progression of ARDS in severe patients.

**Antibiotic treatment**

Not suggested: The administration of antimicrobial drugs, especially combined application of broadspectrum antimicrobial drugs, to severely and critically ill patients with COVID-19 for routine microbial prevention, is not suggested.

Suggestion: Second-generation cephalosporins can be used in short term to prevent bacterial infections for patients receiving glucocorticoid therapy. Besides, third-generation cephalosporins, combined with enzyme inhibitors, can be used empirically in those patients with bacterial coinfections. For patients with a course of more than 2 weeks and low lymphocyte counts, the presence of bacterial infection cannot be determined only by procalcitonin (PCT) and C-reactive protein (CRP) levels. The body temperature, white blood count, and neutrophil percentage, as well as chest imaging and oxygenation, should also be taken into consideration. For patients with secondary bacterial infections, antimicrobials should be selected based on the results of pathogenic epidemiology of the department.

For the patients receiving the treatment of glucocorticoid combined with the support of invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO), or the patients using broad-spectrum antibiotic for more than 3 days, possible co-infections by fungi should be monitored. At the same time, PCT, CRP, D-dimer, G experiment, galactomannan experiment, etc. should be performed to evaluate comprehensively, in order to select the appropriate antimicrobials.

**Respiratory support therapy**

(1) Suggestion: Oxygen therapy is suggested for severe and critically ill patients with COVID-19 immediately.

Patients with severe COVID-19, whose SpO₂ is ≤ 93% and/or RR is ≥ 30 breaths/min, should receive oxygen therapy at 5 L/min immediately. For this population, the approach (i.e., nasal catheter, simple face mask, oxygen mask) should be selected based on the severity of hypoxia. If patients continue to have SpO₂ ≤ 90% and/or RR ≥ 30 breaths/min even when they used an oxygen mask at a flow rate of 10–15 L/min, the existence of severe acute hypoxic respiratory failure or ARDS must be considered, so that further treatment with respiratory support should be carried out as early as possible.

(2) Suggestion: Patients with severe acute hypoxic respiratory failure or mild-to-moderate ARDS (150 mmHg < PaO₂/FiO₂ ≤ 300 mmHg) should receive high-flow nasal oxygen (HFNO) as the first choice or noninvasive ventilation (NIV) as the second choice. The conditions of patients receiving HFNO or NIV should be closely monitored by
HFNO has been shown to be safe and effective in patients with acute hypoxic respiratory failure, and it can reduce the percentage of patients requiring invasive ventilation; however, the comparison between HFNO and NIV in the treatment of patients with acute respiratory failure is still controversial. Subgroup analysis showed that the 30-day mortality rate of patients with non-cardiogenic pulmonary edema and mild hypercapnia receiving HFNO was lower than that of patients treated with NIV. Moreover, in the treatment of coronavirus pneumonia, the failure rate of NIV was high in MERS patients. Due to the lack of evidence, the use of NIV in patients with respiratory failure caused by viral pneumonia is not suggested. For patients with moderate ARDS, who are not suitable for HFNO treatment, NIV can be considered; however, NIV is not suggested for patients who are unresponsive to HFNO. Nasal mask can be considered to use for the improvement of the patient compliance to NIV. During HFNO and NIV therapy, patients should be closely monitored for signs of hypercapnia, hemodynamic instability, multiple organ dysfunction, or disorder of consciousness, at which time invasive mechanical ventilation should be used.

HFNO and NIV treatment should be considered failure as patients meet any one of the following criteria: SpO₂ ≤ 90% and/or RR ≥ 30 breaths/min; hypercapnia and respiratory acidosis (pH ≤ 7.25); hemodynamic instability; multiple organ dysfunction; disorder of consciousness; extremely non-compliant.

(3) Suggestion: Patients with moderate-to-severe ARDS (PaO₂/FiO₂ < 150 mmHg) or failure in HFNO or NIV should receive invasive mechanical ventilation as the first choice. Patients should receive pre-oxygenation with 100% FiO₂ for 5 min before intubation, followed by enough sedatives and muscle relaxants to reduce the possibility of choking or coughing, in order to protect medical personnel to the maximum extent and avoid sharp dropping of SpO₂ in the patients during intubation. The endotracheal intubation should be performed by proficient medical personnel wearing the protective helmet in the environment with fresh air ventilation system.

The strategy of lung protective ventilation with low tidal volumes: As strongly recommended by ARDS treatment guidelines, the tidal volume of ARDS patients should be set at 4–8 mL/ kg (predicted body weight), based on which the respiratory dynamics need to be monitored to maintain the inspiratory plateau pressure at ≤ 30 cmH₂O (1 cmH₂O = 0.098 kPa). The initial tidal volume should be set at 6 mL/kg (predicted body weight), which could be adjusted according to the inspiratory plateau pressure and the PaCO₂ level. If the PaCO₂ > 50 mmHg during the ventilation with low tidal volume, the minute ventilation can be increased by increasing the RR. If PaCO₂ is still >50 mmHg and pH is < 7.25 after increasing RR to 35 breaths/min with enough sedatives, ECMO therapy should be considered.

Negative end expiratory pressure (PEEP) titration is suggested to set the optimal PEEP level. The ARDS Network Tools can be used as a guide for PEEP titration. If the SpO₂ > 93%, the PEEP level should be reduced. For patients with inhaled oxygen concentrations (FiO₂ > 0.60, pulmonary expandability should be evaluated. For patients with pulmonary expandability, the pressure-limited recruitment maneuver should be performed.

Proximal position ventilation should be applied more than 12 hours per day for patients with moderate-to-severe ARDS (PaO₂/FiO₂ < 150 mmHg) as early as possible. The mortality rate of patients with moderate-to-severe ARDS can be reduced by prone position ventilation within 12–24 hours of mechanical ventilation. It has to be noted that all procedures should be performed with the presence of enough professionals.

For patients receiving invasive mechanical ventilation, the treatment of sedatives and analgesics is recommended, while the routine application of muscle relaxants is not suggested. Sedatives and analgesics can reduce the inspiratory driving pressure and improve the prognosis of patients with severe ARDS. However, muscle relaxants cannot improve the survival rate of ARDS patients. The indications of using muscle relaxant are as follows: Antagonists are still active after sufficient sedation and analgesia; the target tidal volume cannot be reached; refractory hypoxemia or hypercapnia occur; during ventilation in the prone position ventilation is performed.

The closed suction pipe is suggested to avoid atelectasis caused by the interruption of PEEP. The disconnection of ventilator requires clamping its pipe.

(4) Suggestion: ECMO can be used as a remedy for patients with severe ARDS.

ECMO should be considered, if any one of the following conditions still exists after standard mechanical ventilation treatment for ARDS (including prone position ventilation and muscle relaxant treatment): PaO₂/FiO₂ < 100 mmHg, or airway platform pressure ≥ 35 cmH₂O, or PaCO₂ > 50 mmHg and pH < 7.25. Compared with standard therapy, there is little evidence on the benefits of ECMO in the prognosis of patients with severe ARDS. In a cohort study of MERS patients, ECMO has been reported to reduce the mortality rate as a remedy.

**Circulatory support therapy**

(1) Suggestion: Conservative fluid therapy is suggested for patients with ARDS who are sufficiently perfused.
Conservative fluid therapy can improve lung function in patients with acute lung injuries, shorten the time of mechanical ventilation and ICU length of stay, without increasing the incidence of organ failure. 

(2) Early identification of patients with septic shock

Suggestion: The sepsis-3 definition should be referred to identify septic shock.

(3) Suggestion: Patients with septic shock accompanied by hypotension or lactate ≥ 4 mmol/L should be supplemented with isotonic crystalloid solution rapidly within 1 h.

The treatment guidelines for sepsis and septic shock suggest rescue fluid resuscitation within one hour of diagnosis of septic shock. Isotonic crystalloid solutions, including physiological saline and balanced salt solution, should be the first choice. The amount of fluid replacement can be calculated as 30 mL/kg. After initial fluid resuscitation, fluid therapy should be guided according to the volume responsiveness.

(4) Suggestion: With sufficient rescue fluid resuscitation, vasoactive drugs should be administered to maintain the target mean arterial pressure (MAP) ≥ 65 mmHg. Norepinephrine is the first choice for vasoactive drug therapy, and it can be combined with epinephrine, vasopressin, and dobutamine.

**Renal support therapy**

For patients with excessive inflammatory reactions, the use of in vitro blood purification techniques, such as plasma exchange, adsorption, perfusion, and blood/plasma filtration should be considered as early as possible.

It has been shown that ARDS patients complicated with shock should receive restricted fluid resuscitation to limit the amount of fluids in the body, which may aggravate hypoxia and pulmonary edema. Thus, it is suggested to maintain the fluid balance as early as possible and provide continuous renal replacement therapy (CRRT), if needed. CRRT can also regulate inflammatory responses resulting in balance disorders in severe patients, reverse immune system dysfunction, improve the clinical symptoms of patients, and even reduce the mortality rate. In addition, ECMO combined with CRRT can effectively improve the capacity load and prognosis of patients.

**Liver support therapy**

Suggestion: Patients with liver failure should receive artificial liver support.

Liver failure should be diagnosed according to “The Guidelines for Diagnosis and Treatment of Liver Failure (2018 Edition)”. Patients with grade II or higher hepatic encephalopathy and the following manifestations should receive artificial liver support: Extreme fatigue, obvious anorexia, abdominal distention, nausea, vomiting, or other serious gastrointestinal symptoms; rapid progression of jaundice, and the total serum bilirubin level ≥ 10 × upper limit of the normal value or daily rise ≥ 17.1 mmol/L; obvious bleeding, with plasma prothrombin activity (PTA) ≤ 40% (or the international normalized ratio [INR] is ≥ 1.5), and other possible causes have been excluded; progressive reduction of the liver volume.

**Cardiac protective therapy**

Suggestion: COVID-19 patients accompanied with acute myocardial injury can be prescribed drugs nourishing the myocardium, such as coenzyme Q, vitamin C, sodium creatine phosphate, and glucose-insulin-potassium (GIK) solution. Please be alert to the occurrence of acute fulminant myocarditis. Patients with elevated troponin I/T levels should be monitored and reexamined daily. Drug-induced heart damage has to be noticed, for example, the combined use of arbidol and antibacterial drugs, such as azithromycin, quinolones, could possibly increase the incidence of heart failure.

**Nutritional support therapy**

(1) Suggestion: Patients should receive enteral nutrition promptly, even during the use of prone position ventilation or ECMO. The early use of parenteral nutrition alone or combined with enteral nutrition is not suggested. Nasogastric tubes should be used for severely or critically ill patients unable to eat normally. For patients unsuited for trans-gastric nutrition, post-pyloric feeding methods, such as the nasal-intestinal tube, should be used. The target feeding dose should be 104.6–125.5 kJ·kg⁻¹·d⁻¹ (25–30 kcal·kg⁻¹·d⁻¹), and a low dose should be initially used. If feeding is not tolerated by the patient, nutritive feeding [infusion rate of 41.8–83.7 kJ/h (10–20 kcal/h) or 10–30 mL/h] should be considered. The protein supply should be strengthened to reach the target protein level, which is 1.5–2.0 g·kg⁻¹·d⁻¹.

(2) Suggestion: Intestinal micro-ecological therapy should be given as early as possible to maintain the normal function of the intestinal system and also to reduce any secondary bacterial infections.

**Convalescent plasma therapy**

Human convalescent plasma containing SARS-CoV-2 antibodies can be used as a specific treatment for patients with rapidly progressing disease, or severely and critically ill patients. If convalescent plasma is used, the titer of protective antibodies should be determined.

**Other treatments**

Thymosin α1 can be administered to patients with low
lymphocyte counts and disordered cellular immune system. With insufficient evidence, the treatment of gamma globulin has to be used for critically ill patients with caution.

**Prevention of complications**

(1) Prevent ventilator-associated pneumonia:

Suggestion: Goal-oriented sedation and analgesia, with shallow sedation as long as possible; oral tracheal intubation is preferred; the head of bed should be elevated by 30–45°; closed sputum suction device should be used; ventilator circuits and humidification devices should be immediately replaced once they are contaminated.

(2) Prevent deep vein thrombosis:

Suggestion: If there is no contraindication, low molecular weight heparin (4000 U/day) should be injected subcutaneously as the first choice; for patients with contraindications to anticoagulant therapy, mechanical prophylaxis, such as intermittent pneumatic compression (IPC) and graded compression socks (GCS), should be used; for patients with severe renal insufficiency, heparin (5000 U/twice a day) should be injected subcutaneously; exercises should be advised at early stage.

(3) Prevent catheter-related bloodstream infections:

Suggestion: Maximal sterile barrier precautions should be used during arteriovenous catheterization; patients should be educated on the importance of hand washing and general hygiene; catheters should be checked daily and replaced or removed, if needed.

(4) Prevent stress ulcers:

Suggestion: Enteral nutrition should be provided at early stage; H$_2$-receptor antagonists or proton pump inhibitors should be administered to patients with a high risk of gastrointestinal bleeding.

(5) Prevent ICU-related complications.

Suggestion: Comprehensive management of ICU patients should be performed if possible. Sedation, analgesia and humanistic care should be provided, and exercises should be advised at early stage, in order to prevent short-term and long-term complications such as ICU-related myasthenia, delirium, and post-ICU syndrome.

**Traditional Chinese medicine treatment**

(1) Suggestion: The symptoms of all severely and critically ill patients should be differentiated by the doctors of traditional Chinese medicine, followed by precise treatment and taking Chinese medicine decoction. Also, the intravenous drugs should be adjusted according to the conditions of the patients. Chinese patented medicine suitable for severely and critically ill patients should be chosen.

(2) Suggestion: The selection of traditional Chinese medicine treatment should refer to “Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (Trial Version 7)”[3].

Chinese patented medicines suggested for severe patients: Xiyanping injection, Xuebijing injection, Shengmai injection, Reduning injection, Tanreqing injection and Xingnaojing injection.

Chinese patented medicines suggested for critically ill patients: Xuebijing injection, Reduning injection, Tanreqing injection, Xingnaojing injection, Shenhui injection, Shengmai injection, Shenfu injection, Suhexiang Pill and Angong Niuhuang Wan.

For drugs with similar efficacies, a single application or a combination of two drugs can be used according to the clinical conditions of patients. Traditional Chinese medicine injections can be used in combination with traditional Chinese medicine decoctions.

(3) Suggestion: Recommend usage of traditional Chinese medicine injection for severely and critically ill patients.

The use of traditional Chinese medicine injections should follow the instructions with the principle of starting from small doses and gradually dialectical adjustment. The recommended usage is as follows.

Patients with viral and/or mild bacterial infections should receive 100 mg of Xiyanping injection in 250 mL of 0.9% sodium chloride, intravenously, twice per day; 20 mL of Reduning injection in 250 mL of 0.9% sodium chloride, intravenously, once per day; or 40 mL of Tanreqing injection in 250 mL of 0.9% sodium chloride, intravenously, twice per day.

Patients with high fever accompanied with mental disorder should receive 20 mL of Xingnaojing injection in 250 mL of 0.9% sodium chloride, intravenously, twice per day.

Patients with systemic inflammatory response syndrome and/or multiple organ failure should receive 100 mL of Xuebijing injection in 250 mL of 0.9% sodium chloride, intravenously, twice per day.

Patients with immunosuppression should receive 100 mL of Shengmai injection in 250 mL of 0.9% sodium chloride, intravenously, twice per day.

Patients experiencing shock should receive 100 mL of Shenfu injection in 250 mL of 0.9% sodium chloride,
intravenously, twice per day.

**Psychotherapy**

Recommended specific measures for psychological interventions are as follows.

(1) Keep stable emotions: Clinicians should maintain consistent contact with patients, avoid short-term and discontinuous assistance, listen carefully with the aim of understanding, facilitate clinician–patient trust and encourage patients to express and release their negative emotions in a timely manner.

(2) Provide support: Clinicians should help patients to adapt to different living conditions; rebuild their support network to facilitate interactions with their primary supporters including family, friends, and communities; and provide mental health education or psychological hotline assistance.

(3) Psychiatric consultation and drug intervention, if necessary: Mirtazapine and sertraline can be prescribed for depression. Alprazolam can be prescribed for anxiety, fear, and agitation. Antipsychotics, such as olanzapine and quetiapine, can be prescribed for acute mental disturbances, hallucinations, delusions, and excessive excitement. Non-benzodiazepines, such as eszopiclone, zolpidem, or benzodiazepines, such as alprazolam, clonazepam, can be prescribed for insomnia, whereas the side effects, such as respiratory depression, have to be noticed.

**Discharge** (refer to the Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia [Trial Version 7])[9]

Discharge criteria should be as follows: A normal body temperature for at least 3 days; a significant improvement in respiratory symptoms; a significant improvement in acute exudative lesions shown by pulmonary imaging; and two consecutive negative results of pathogen nucleic acid test in respiratory tract (the interval between two sample time is at least 1 day).

Patients meeting the aforementioned criteria should be discharged from the hospital or transferred to another department for further treatment of other diseases.

Discharge instructions should be as follows: Combine exertion and rest and get adequate sleep; choose the appropriate respiratory rehabilitation exercise; have a high-protein, vitamin-rich and high-calorie diet, supplemented with fresh fruits and vegetables, lean meats, milk, etc., and take fully-cooked food. Upon discharge, patients should stay at home under quarantine for at least 2 weeks, after which they should visit the hospital for further instructions.

**Follow-up**

Patients should be followed up at 1, 3, 6, and 12 months after discharge, and examinations such as lung imaging, 6-minute walking test and pulmonary function tests, can be performed.

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