8.1 Guidance on Clinical Practice

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8.1.1 Treatment Protocol for Severe and Critical COVID-19 Patients: Experiences from Wuhan Union Hospital

Note: This section is reprinted with permission from: Yong Gao, et al. Treatment protocol for severe and critical COVID-19 patients: Experiences from Wuhan Union Hospital. Current Medical Science (ISSN: 2096-5230), 2020, Springer. Accepted article.

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F. Cheng, Y. Zhang (eds.), The Clinical Diagnosis and Treatment for New Coronavirus Pneumonia, https://doi.org/10.1007/978-981-15-5975-4_8
Abstract
In late December 2019, a newly emerging infectious disease, COVID-19, was identified in Wuhan, China. COVID-19 spread rapidly to the entire country of China with a mortality rate of 2–4%. The West Campus of Wuhan Union Hospital, the designated hospital for admitting and treating the severe and critical COVID-19 cases, has been treating a large number of patients with great success. To standardize and share the treatment protocol for severe and critical cases, Wuhan Union Hospital has established a working group and formulated an operational guideline, including monitoring, early warning indicators, and several treatment principles for severe and critical cases.

Keywords
2019-nCoV, COVID-19, Pneumonia, Treatment guidelines

Background
An ongoing outbreak of pneumonia caused by the 2019 novel coronavirus (2019-nCoV, now formally named SARS-CoV-2 by the International Committee on Taxonomy of Viruses, ICTV) has been recently identified as a newly emerging infectious disease. 2019-nCoV is highly contagious, and it has a significant morbidity and 2–4% mortality rate. 2019-nCoV disease (named COVID-19 by the WHO) was first identified in Wuhan in late December 2019. It subsequently spread rapidly to the whole country and then to multiple countries and almost all over the world. The 2019-nCoV virus belongs to a novel type of β genus coronavirus that shares 79.5% sequence with severe acute respiratory syndrome-related coronaviruses (SARS-CoV). It mainly, but not exclusively, attacks the human respiratory system in severe and critical cases. Among the infected patients, about 14% were severe and 5% were critically ill with cellular immune deficiency, coagulation activation, cytokine storm, myocardia injury, and hepatic and kidney injury. According to minimally invasive autopsies, we learned that the lungs from COVID-19 patients manifest significant pathological changes and the injury also involves damage to the heart, vessels, liver, kidney, and other organs.

Chinese health institutions enacted immediate measures to control the disease, including isolation of suspected people, close monitoring of contacts, collection of epidemiological and clinical data, and development of diagnostic and treatment guidelines. The West Campus of Wuhan Union Hospital, as one of the three designated hospitals appointed by the National Health Commission of China for admitting and treating the severe and critical COVID-19 cases, has recruited the largest number of these patients.

Until March 20, 2020, 1617 patients were diagnosed with severe and critical types of COVID-19 disease. After treatment, 1069 patients were cured and discharged, and 147 died. Currently, there are still 401 patients under treatment. The high cure rate and control from spreading confirms the effectiveness of our management and treatment protocol. Currently, the pandemic in other countries is still serious, which has prompted international concern about the global public health
impact. To standardize and share the treatment protocol of severe and critical cases, Wuhan Union Hospital has established a working group and formulated the following operational recommendations for treating severe and critical patients. The protocol is based on the Chinese guideline (V7.0) and previous experiences accumulated from the isolation ward over the past 2 months.

### 8.1.1.1 Establishment of Baseline Disease Data on Admission

#### 8.1.1.1.1 History Collection

Upon admission, full clinical data from the patients should be accurately collected. This serves as a starting point for observation and disease control. The data to be obtained include epidemiological history, clinical manifestations, as well as the diagnosis and treatment history from other medical institutions. The severe and critical patients should be diagnosed according to the guidelines of the National Health Commission of China (V7.0). All of the data should be collected during treatment, and a flowchart should be established to depict and predict disease evolution.

#### 8.1.1.1.2 Auxiliary Examinations

On admission, patients are required to complete the following tests:

1. Complete blood count, lymphocyte subsets
2. C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), procalcitonin (PCT), and inflammatory cytokines (including IL-6, IL-10, and TNF-α)
3. Hepatic and renal functions and electrolytes
4. Disseminated intravascular coagulation (DIC) screening (including coagulation function and D-dimer)
5. Blood gas analysis
6. Chest X-ray or CT scan
7. Others: Troponin, cardiac enzymes, B-type natriuretic peptide, lactate dehydrogenase (LDH), creatine kinase, and myoglobin

It is recommended that the severe patients should be monitored with these accessory laboratory tests every 3 days, and critically ill patients daily except for radiographic images. The evolution curve can be generated through a data management program.

#### 8.1.1.1.3 Detection of Pathogens

1. 2019-nCoV detection: 2019-nCoV nucleic acid can be detected with nasopharyngeal swabs, sputum, lower respiratory tract secretions, blood, feces, and other specimens utilizing RT-PCR or NGS methods. The accuracy of RNA 2019-nCoV detection is as follows: Alveolar lavage fluid > sputum > nasal swab > throat swab. 2019-nCoV-specific IgM becomes detectable via serological tests at 3–5 days post-onset, and an IgG-positive test indicates previous infection and
convalescence. The combined detection of viral RNA and serology in COVID-19 patients can improve the sensitivity and specificity of diagnosis.

2. Secondary bacterial and fungal pathogenic tests: Severe and critical patients with COVID-19 are susceptible to bacterial and fungal infections, and clinical microbiological test should be monitored.

3. Metagenomic sequencing (mNGS): mNGS has obvious advantages of comprehensive detection, high accuracy, high sensitivity, and fast identification over RT-PCR, which significantly improves not only the detection efficiency of COVID-19, but also co-infection and secondary infection of severe and critical COVID-19 patients.

4. Sampling, transportation, and testing involving pathogenic inspections must meet biosafety requirements.

8.1.1.1.4 Comorbidities and Complications Monitoring

1. Most of the patients with the severe and critical type of COVID-19 are relatively elders and generally have a variety of comorbidities. These pathophysiological factors have a great impact on the diagnosis, treatment, and prognosis of COVID-19, which should be noted and monitored.

2. 2019-nCoV affects multiple organs other than the respiratory system, including cardiovascular, gastrointestinal, blood, and immunity, and the appropriate tests should be carried out as needed.

3. No specific drugs have yet been produced. Although several types of clinically therapeutic drugs have been tested, the interactions between drugs and drug side effects are not clear and should be taken into consideration. The clinical pharmacy-related tests are required when necessary.

8.1.1.2 Early Clinical Warning Signs of Severe and Critical Cases

Previous experiences have revealed that some COVID-19 cases can progress and deteriorate to moderate, severe, or critical ones in a short period of time. The cases with the following indicators are likely to deteriorate to severe or critical status. Early warning and treatment will be of great importance to reduce mortality.

1. The age of the patient has an independent prognosis factor, and the 2019-nCoV-infected patients with the age of \( \geq 65 \) years old or \( \geq 75 \) years old are separately prone to the severe or critical type.

2. The progressive decline of peripheral blood lymphocytes indicates the deterioration of the disease.

3. Abnormality in DIC screening tests suggests the deterioration of the disease.

4. Lung lesions >50% in size or involving the inner band suggest the progression of the disease.

5. Patients with serious underlying diseases (including structural lung disease, coronary heart disease, critical hypertension, rheumatic immune disease, neoplastic disease, or other infectious diseases), immunosuppressive treatment, organ transplantation, blood purification, and chemotherapy have a poor prognostic outcome.
8.1.1.3 Principles for Treating the Severe and Critical Patients

1. Basic treatment
   (a) Bed rest with strong nutritional support.
   (b) Maintain water, electrolyte, and acid–base balance.
   (c) Energy mixture, ATP, or CoA can be used for anti-hypoxia treatment.
   (d) Underlying diseases should be treated.
   (e) Measures should be taken to prevent secondary infection.
   (f) Prevent and treat complications, including cardiac injury, cardiogenic shock, myocarditis, venous thrombosis (VTE), DIC, ventilator-induced dysfunctions, and multifunctional organ failure.
   (g) Cytokine storm treatment

2. Antiviral therapy
   The following antiviral drugs are recommended within 10 days of COVID-19 onset, but at best, no more than two drugs in combination: ribavirin (500 mg for adults, twice or three times via intravenous injection daily, administered no longer than 10 days), lopinavir/ritonavir (used to be recommended by Chinese guidelines, but it was recently reported that no benefit was observed with lopinavir/ritonavir treatment beyond standard care in a randomized, controlled, open-label trial), chloroquine phosphate (500 mg for 7 days for adults aged 18–65 with body weight over 50 kg; 500 mg for days 1 and 2, and 500 mg for days 3–7 for adults with body weight below 50 kg), hydroxychloroquine (found to be more potent than chloroquine at inhibiting 2019-nCoV in vitro), and Arbidol (200 mg tid for adults, no longer than 10 days). Some medicine under clinical trial can also be tried if the above antiviral treatments fail to work. Be aware of adverse reactions, contraindications (e.g., chloroquine cannot be used for patients with heart diseases), and interactions of the abovementioned drugs. If an intolerable toxic side effect occurs, the respective drug should be discontinued.

3. Oxygen Therapy and Respiratory Support
   (A) High-flow nasal-catheter oxygenation (HFNC) is suitable for patients with hypoxemia and oxygenation index (PaO₂/FiO₂) of 200–300 mmHg. During the implementation of HFNC treatment, the symptoms and signs of the patients should be closely monitored and evaluated every 20–30 min. The following conditions indicate failure of HFNC treatment, and alternative respiratory support therapy should be added:
      (a) Hypoxemia not able to correct (SpO₂ < 93%)
      (b) Tachypnea (RR ≥ 35 beats/min)
      (c) Significantly difficult to inspirates
   (B) Noninvasive ventilator (NIV) is suitable for patients with hypoxemia and PaO₂/FiO₂ of 150–200 mmHg. During the implementation of NIV treatment, the symptoms and signs of the patients should be closely monitored and evaluated every 20–30 min. The following situations indicate failure of NIV treatment, and alternative respiratory support therapy should be considered in time:
      (a) Hypoxemia not able to correct (SpO₂ < 93%)
      (b) Tachypnea (RR ≥ 35 beats/min)
(c) Excessive tidal volume
(d) Excessive negative inspiratory pressure
(e) Unstable circulation and abnormal tissue perfusion

(C) **Invasive mechanical ventilation (IMV)** is suitable for patients with hypoxemia and \( \text{PaO}_2/\text{FiO}_2 < 150 \text{ mmHg} \). Based on lung protective ventilation strategy, patients with hypoxemia and \( \text{PaO}_2/\text{FiO}_2 < 150 \text{ mmHg} \) require repeated monitoring of the lung recruitment maneuver potential. Use the PEEP strategy to restore the lung potential and closely observe the oxygenation index, pressure of carbon dioxide, right heart enlargement, and pulmonary barotrauma. Prone position ventilation is recommended. Patients who have reached the following conditions can withdraw mechanical ventilation: \( \text{PaO}_2/\text{FiO}_2 \) maintains \( >200 \text{ mmHg} \), the primary disease is improved, the patient gains consciousness, and the patient is dynamically stable.

(D) **Extracorporeal membrane oxygenation (ECMO)**

*Indications of ECMO therapy:*

(a) \( \text{PaO}_2/\text{FiO}_2 < 50 \text{ mmHg} \) for more than 3 h

(b) \( \text{PaO}_2/\text{FiO}_2 < 80 \text{ mmHg} \) for more than 6 h

(c) \( \text{FiO}_2 1.0, \text{PaO}_2/\text{FiO}_2 < 100 \text{ mmHg} \)

(d) Arterial blood pH < 7.25 and \( \text{PaCO}_2 > 60 \text{ mmHg} \) more than 6 h, or related complications caused by carbon dioxide retention: severe internal environment disorder and right heart failure

(e) When the respiratory rate >35 per min, the arterial blood pH < 7.2, and the airway plateau pressure >30 cm H\(_2\)O

(f) Combined with cardiogenic shock or cardiac arrest

*Contraindications of ECMO therapy:* Combined with irreversible primary diseases, contraindication for anticoagulation, ventilation for more than 7 days under a higher mechanical ventilation setting (\( \text{FiO}_2 > 0.9 \), airway plateau pressure >30 cm H\(_2\)O), age >70 years old, the use of immunosuppression, and the presence of peripheral vascular anatomical malformations or vascular lesions.

4. Rational use of antibiotics

(a) Avoid blind or inappropriate use of antibiotics if there is no clear evidence of bacterial infection.

(b) For severe and critical cases with a course of disease \( \geq 7 \) days, surveillance of pathogens related to secondary bacterial or fungal infection should be effectively carried out.

(c) Bacterial infection should be suspected and confirmed according to body temperature, white blood cell count (WBC), neutrophil percentage, pulmonary imaging, oxygenation function, and pathogen examination. The third-generation cephalosporin/enzyme inhibitor complex can be empirically used.

(d) When septic shock occurs in severe and critically ill patients, carbapenem drugs can be used instead. If enterococcal and staphylococcal infections are suspected, glycopeptide antibiotics (vancomycin) can be added for empirical treatment.
(e) Be especially cautious to catheter-related infections. Empirical antibiotic treatment should cover methicillin-resistant staphylococci with the use of glycopeptide drugs (vancomycin).

(f) Some patients often have secondary aspergillosis infection in the later stages of critical illness. Voriconazole can be used, but the combination of two antifungal drugs is not recommended.

5. Prophylactic anticoagulant therapy
   
(a) Severe and critically ill COVID-19 patients have a higher risk for DIC and VTE. Coagulation and bleeding should be closely monitored during treatment. Unless there is significant bleeding or a coagulation disease, low-molecular-weight heparin is recommended for the vast majority of critically ill patients.

(b) When DIC occurs and there is no significant hyperfibrinolysis, a therapeutic dose of low-molecular-weight heparin can be added, but with simultaneous replacement therapy such as platelet transfusion, and/or supplemented with fresh plasma to replenish coagulation factors; hematologists should be invited for consultation as soon as possible.

(c) The risk of VTE in severe and critically ill patients should be regularly assessed according to the Caprini Risk Assessment Model: when the score >3, medication and physical prophylaxis are recommended. Encourage patients to exercise at an early stage and invite a vascular surgeon to consult when VTE is suspected.

6. Convalescent plasma treatment
   
The 2019-nCoV-specific antibodies in the plasma of COVID-19 convalescent patients have a certain therapeutic effect on COVID-19 patients via reducing 2019-nCoV viral copy numbers. Convalescent plasma treatment can be used for severe patients above 18 years of age and only for the certain critical patients with mechanical ventilation ≤48 h and heart, liver, and kidney function still being in a compensatory state.

7. IL-6 monoclonal antibody treatment
   
Cytokine release syndrome (CRS), which is closely associated with the increased level of IL-6, is an important cause of death in critically ill patients with COVID-19. It is speculated that the IL-6 monoclonal antibody (Tocilizumab) can inhibit the intensity of the cytokine storm and play a certain therapeutic role. IL-6 monoclonal antibody therapy is suitable for severe patients >18 years of age without severe comorbidities and contraindicated for patients with active infections, such as tuberculosis.

8. Glucocorticoid treatment
   
Currently, there is no evidence to support that the medical use of glucocorticoids improves the prognosis of severe COVID-19 patients. However, patients with progressive deterioration of oxygenation indicators, rapid progress in imaging, excessive activation of the body’s inflammatory response, and without contraindications can use conventional doses of glucocorticoids in a short period of time (3–5 days).
9. Other recommended treatments

There is no clinical evidence to support the application of drugs such as human immunoglobulin, thymosin, and intestinal microecological regulators to improve the prognosis of severe COVID-19 patients. They are recommended as supplemental therapeutic measures.

10. Traditional Chinese Medicine

COVID-19 belongs to the category of traditional Chinese medicine plagues. Dialectical treatment based on factors, such as seasonal and geographical aspects, has played an important role in the prevention and control of the COVID-19 epidemic in China from 2019 to 2020. According to the different local climate characteristic and individual state of illness and physical conditions, Chinese medicine prescriptions and Western medicines can be used alone or in combination.

Summary

2019-nCoV is a recently identified novel pathogen with great contagiousness and susceptibility among the human population. Based on the guidelines of the diagnosis and treatment of COVID-19, comprehensive supportive treatment is still the major treatment procedure before the development of specific antiviral drugs and effective vaccines.

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- And my colleagues Yong Gao, Yadan Wang, Hongbo Wang, Jianchu Zhang, Shu Zhou, Weici Wang, Yu Zhang, Yang Jin, Yong Zhang, Yong Liu, Zihua Zhou, Ying Su, Huiqing Li, Weimin Xiao, Kai Huang, Ping He, Gang Li, Zhaohui Fu, Shi Liu, Nengxing Lin, et al. from Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan. We appreciate all of the physicians and nurses who share their valuable experiences and for their hard work in treating COVID-19 patients, and for those who have contributed to translating and proofreading the manuscript.
8.2 Modular Medical Orders

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8.2.1 Example Medical Order for Mild Patient with COVID-19

Medical Order for Diagnosis and Treatment

• Air isolation, body temperature measurement (q4h), monitoring the oxygen saturation (q6d), heart rate/blood pressure checking (q6h)

Medical Order for Accessory Tests

• Nucleic acid testing for SARS-CoV-2
• Routine blood test, biochemical test, routine urine test, routine stool test+OB, CPR, respiratory viral test
• ECG, CT of the lung

Medical Prescriptions

• Arbidol tablets 200 mg tid
• or Favipiravir tablets D1 1600 mg bid; then change to 600 mg bid

8.2.2 Example Medical Order for Moderate Patient with COVID-19

Medical Order for Diagnosis and Treatment

• Air isolation, body temperature measurement (q4h), monitoring of oxygen saturation (q6h), heart rate/blood pressure test (q6h)

Medical Order for accessory tests

• Nucleic acid testing for SARS-CoV-2
• Routine blood test, biochemical test, routine urine test, routine stool test+OB, coagulation function+D-dimer, CPR, ESR, PCT, myocardial enzyme+quantitative test of serum cardiac troponin T, respiratory tract virus test, blood/sputum culture (recheck every 3–5 days)
• B-ultrasonic examination of deep veins of both lower limbs, ultrasonic examination of the heart, CT of the lung, EKG
Medical Prescriptions

- Arbidol tablets 200 mg tid
- or Lopinavir and ritonavir tablets 400/100 mg q12h
- or Favipiravir tablets: D1 1600 mg bid; then change to 600 mg bid
- Acetylcysteine tablets 600 mg, dissolve and take after meal bid

8.2.3 Example Medical Order for Severe Patient with COVID-19

Medical Order for Diagnosis and Treatment

- Air isolation, ECG monitoring, monitoring of oxygen saturation/body temperature, heart rate q4h, oxygen therapy support (oxygen supply by nasal cannula, oxygen supply by mask, HFNC, NIV)

Medical Order for Accessory Tests

- Nucleic acid testing for SARS-CoV-2
- Routine blood test, biochemical test, routine urine test, routine stool test+PB, coagulation function+D-dimer, BNP, blood gas analysis+lactic acid, ASO+RF+CPR, ESR, PCT, thyroid function, ferritin, myocardial enzyme+quantitative test of serum cardiac troponin T, respiratory tract virus test, blood/sputum culture, immunoglobulin+complement, T-lymphocyte subsets, cytokine, G/GM test (recheck every 2–3 days)
- B-ultrasonic examination of deep veins of both lower limbs, ultrasonic examination of the heart, CT of the lung, EKG

Medical Prescriptions

- Arbidol tablets 200 mg tid
- Lopinavir and ritonavir tablets 400/100 mg q12h
- α-Interferon (add 5,000,000 IU into 2 mL of saline for aerosol inhalation, bid)
- NS100ML+Methylprednisolone 40 mg iv gtt qd (when necessary)
- NS100ML+Pantoprazole for injection 40 mg qd (when hormone is used)
- Caltrate D, one tablet qd
- Low-molecular-weight heparin sodium (Clexane) 4000 U ih qd or bid (when there is no obvious anticoagulant contraindications)
- NS100ML+Ambroxol 30 mg iv gtt bid or acetylcysteine tablets 600 mg dissolve and take after meal bid
8.2.4 Example Medical Orders for Critical Patient with COVID-19

Medical Order for Diagnosis and Treatment

- Air isolation, ECG monitoring, monitoring of oxygen saturation/heart rate/blood pressure q1h, body temperature monitoring q4h, prevention and care of high risk pressure sore, oral care, nasal feeding, blood glucose monitoring q6h, 24-h intake and output volume, breathing support (HFNC, NIV, invasive positive pressure ventilation, ECMO)

Medical Order for Accessory Tests

- Nucleic acid testing for SARS-CoV-2
- Routine blood test qd, biochemical test qd, routine urine test, routine stool test+OB, coagulation function+D-dimer qd, blood gas analysis+lactic acid bid, BNP qd, ASO+RF+CPR qd, ESR, PCT qd, thyroid function, ferritin, myocardial enzyme+quantitative test of serum cardiac troponin T qd, respiratory tract virus test, blood culture, immunoglobulin+complement, T-lymphocyte subsets, cytokine, G/GM test
- EKG, B-ultrasonic examination of deep veins of both lower limbs, ultrasonic examination of the heart, CT of the lung, X-ray monitoring of chest at bedside (qd)

Medical Prescriptions

- Arbidol tablets 200 mg tid
- Lopinavir and ritonavir tablets two tablets q12h
- α-Interferon (add 5,000,000 IU into 2 mL of saline for aerosol inhalation, bid)
- NS100ML+Methylprednisolone 40 mg gtt q12h, reduce 3 days later in accordance with the actual condition (when necessary)
- NS100ML+Pantoprazole for injection 40 mg qd (when hormone is used)
- Caltrate D, one tablet qd
- Immunoglobulin for injection 0.4 g/kg (15–20 g/day) iv gtt qd
- Empiric antibiotic therapy
- Immunoglobulin for injection 20 g iv gtt qd
- Thymosin for injection 1.6 mg iv biw
- Low-molecular-weight heparin sodium (Clexane) 4000 U ih qd or bid (when there is no obvious anticoagulant contraindications)
- Human serum albumin 10 g iv gtt qd (albumin <30 g/L)
- NS100ML+Ambroxol 30 mg iv gtt bid or acetylcysteine tablets 600 mg bid
- Enteral nutritional suspension: Supportan or Fresubin, or Nutrison Fiber or Peptison, 20–30 kcal/kg
8.3 Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (Trial Version 7)

Released by National Health Commission & State Administration of Traditional Chinese Medicine on March 3, 2020.

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