Chinese Clinical Guidance for COVID-19 Pneumonia Diagnosis and Treatment (7th edition) （published by China National Health Commission on March 4, 2020）

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Since December 2019, a novel coronavirus pneumonia epidemic has appeared in Wuhan City, Hubei Province. With the spread of the epidemic, other cities in China and many countries abroad have also found such cases. As an acute respiratory infectious disease, the disease has been included in the Class B infectious diseases stipulated in the Law of the People's Republic of China on the Prevention and Control of Infectious Diseases, and is managed as a Class A infectious disease. Through the adoption of a series of preventive control and medical treatment measures, the upward trend of the epidemic situation in China has been contained to a certain extent. The epidemic situation in most provinces has eased, but the number of outbreaks abroad is on the rise. With the deepen understanding of the clinical manifestations, pathological features of this disease and the accumulation of experience in diagnosis and treatment, in order to further strengthen the early diagnosis and early treatment of the disease, improve the cure rate, reduce the mortality rate, and avoid in-hospital infection, and alert for the disease transmission caused by overseas input cases, we revised the previous clinical guidance to form this 7th version.

1. Etiology

The novel coronavirus (termed as COVID-19 by World Health Organization) belongs to the coronavirus β genus, which is encapsulated in round or oval shape, and 60-140mm in diameter. The genetic characteristics of COVID-19 are significantly different from SARS-CoV and MERS-CoV. It shares more than 85% homology with SARS-like coronavirus isolated from bat (bat-SL-CoVZC45). The COVID-19 can be detected in human respiratory epithelial cells for about 96 hours *in vitro*, but it takes about 6 days to isolate and culture in Vero E6 and Huh-7 cell lines.

Our current understandings on the biochemical features of COVID-19are mostly derived from previous studies on SARS-CoV and MERS-CoV. COVID-19 is fragile to ultraviolet and heat (56 °C for 30 minutes). It can also be inactivated by liposoluble solvents, such as ether, 75% ethanol (w/v), chlorine-containing disinfectant and chloroform. However, chlorhexidine has been proved generally ineffective.

2. Epidemiology

a) Source of infection

Infected patients (symptomatic or asymptomatic) are the main source of infection.

b) Route of transmission

COVID-19 is transmitted through respiratory droplets and close contact. Aerosol transmission is plausible when patients are exposed to high concentration virus-containing aerosols for a long period of time and in a relatively closed environment. In addition, because COVID-19 has been isolated from stool and urine specimens, special attention should be paid to human waste disposal to avoid direct contact and/or environment contamination.

c) Susceptible population

Human beings are generally susceptible to COVID-19.

3. Pathology

The following summary is based on limited numbers of autopsy and biopsy findings.

a) Lungs

Lung consolidation was observed in various degrees.

Fibrinous exudation and hyaline membrane formation were filled in alveolar cavity. Exudative cells mainly consist of mononuclear cells and macrophages. Polynuclear giant cells were prominent. Type II alveolar epithelial cells were markedly proliferated, and some were detached into alveolar cavity. Inclusion bodies were found in type II alveolar epithelial cells and macrophages. Hyperemia and edema were apparent in alveolar septal areas. Mononuclear cell and lymphocyte infiltration, intravascular hyaline thrombosis, focal hemorrhage and necrosis of lung tissue could be seen, and hemorrhagic infarction occurred. Pathological features of organizing pneumonia and pulmonary interstitial fibrosis could be observed in pulmonary parenchyma.

Intrapulmonary bronchial epithelial cells were detached, and bronchial cavity was filled with mucus plugs. In some area, pulmonary alveoli were hyperinflated, alveolar septa fractured, and cystic cavities formed.

Coronavirus particles were found in the cytoplasm of bronchial epithelium and type II alveolar epithelial cells under electron microscope. Immunohistochemical staining showed that some alveolar epithelial cells and macrophages were positive for COVID-19 antigens. COVID-19 nuclear acids were detected through RT-PCR.

b) Spleen, hilar lymph nodes, and bone marrow

Spleen was markedly shrunk, in which lymphocytes were significantly reduced in numbers, with apparent focal hemorrhage and necrosis. Macrophage proliferation and phagocytosis were also observed. In lymph nodes, lymphocytes were also depleted and necrotized. In addition, immunohistochemical staining showed that the number of CD4+ T and $CD8^+$ T cells in both spleen and lymph nodes were significantly decreased. All hematopoietic cell linages were reduced in bone marrow.

c) Cardiovascular system

It was found that some cardiomyocytes were degenerated and necrotized, and a small number of monocytes, lymphocytes and/or neutrophils are infiltrated in the myocardium. In some areas, vascular endothelial cells were detached where inflammation and thrombosis occurred.

d) Liver and gallbladder

Liver was characterized by increased volume, dark red color, hepatocyte degeneration, focal necrosis with neutrophil infiltration, hepatic sinus congestion, infiltration of lymphocytes and monocytes in the portal area, and microthrombus formation. Gallbladder was also significantly increased in size.

e) Kidney

Protein exudate was found in Bowman's capsules. Renal tubular epithelium was denatured and exfoliated, and hyaline cast was formed. Interstitial hyperemia, micro thrombus and focal fibrosis could be seen.

f) Other organs

The brain tissue was congested and edematous, and some neurons were degenerated. Focal necrosis was observed in the adrenal gland. The epithelium of esophagus, stomach and intestines were denatured, necrotic and exfoliated with different degrees.

4. Clinical features

a) Clinical manifestation

Based on the current epidemiological survey, the incubation period of COVID-19 is 1-14 days. Most patients show clinical symptoms in 3-7 days.

Fever, dry cough, and fatigue are the main manifestations. Other symptoms include nasal obstruction, runny nose, sore throat, myalgia and diarrhea. In severe cases, patients presented dyspnea and/or hypoxemia within one week after onset. Some of them rapidly deteriorated to acute respiratory distress syndrome (ARDS), septic shock, refractory metabolic acidosis, coagulation dysfunction, and multiple organ failure. Notably, some severe patients only presented mild- to moderate-grade fever in their entire course of disease, and some even did not show fever at all.

Some children and newborns presented atypical symptoms, such as vomiting, diarrhea and other gastrointestinal discomfort, or only exhibited drowsiness and shortness of breath.

In mild cases, patients only presented low-grade fever and slight fatigue, without evident pneumonia.

From our current observation, most patients have a good prognosis, and only a few patients are critically ill. The prognosis for the elderly and those with chronic comorbidities is relatively worse. The clinical course of COVID-19 pneumonia in pregnant women is similar to that of the same age group. The severity of symptoms in children is relatively mild.

b) Laboratory examination

i. Routine examination

In the early stage of the disease, the total count of peripheral leukocytes could be normal or decreased, and the lymphocyte decreased. In some patients, liver transaminases, lactate dehydrogenase (LDH), creatine kinase and myoglobin were elevated. In some critically severe patients, troponins were also increased. In most patients, C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were increased, while procalcitonin generally remains in normal range. Notably, D-dimer was significantly increased in severe patients, and peripheral lymphocytes were progressively decreased. Inflammatory biomarkers are often elevated in severe and critically severe patients.

ii. Etiological and serological examination

(1) Etiological examination: COVID-19 nucleic acids can be detected in nasopharyngeal swabs, sputum and other lower respiratory tract secretions, blood and feces by using RT-PCR and next generation sequencing technology (NGS). It is more accurate to detect the lower respiratory tract specimen (sputum or airway extract). Once collected, specimen examination should be performed as soon as possible.

(2) Serological examination: the COVID-19-specific IgM antibody starts to show positive after 3-5 days from onset. In comparison, the titer of COVID-19-specific IgG antibody is 4 times higher in recovery period than that in acute phase.

iii. Chest imaging

At the early stage of the disease, multiple small patchy shadows and interstitial changes appear, which are more obvious in the periphery of the lung. Then it developed into multiple ground-glass shadows and infiltrates shadows. In severe cases, pulmonary consolidation may occur. Pleural effusion is rare.

5. Diagnostic criteria

a) Suspected cases

Comprehensive analysis of the following epidemiological history and clinical manifestations:

i. Epidemiological history

(1) Travel or residence history of Wuhan and surrounding areas, or other communities with documented COVID-19 positive cases within 14 days before the onset of illness.

(2) History of contact with COVID-19-infected persons (positive for nucleic acid detection) within 14 days before the onset of illness.

(3) History of contact with the patients presenting fever or respiratory symptoms, who travel to or reside in Wuhan and surrounding areas, or in other communities with documented COVID-19 positive cases within 14 days

before the onset of illness.

(4) Clustering onset (2 or more cases of fever and/or respiratory symptoms within 2 weeks in small areas such as home, office, school class, *etc.*)

ii. Clinical manifestation

(1) Presenting with fever and/or respiratory symptoms.

(2) With imaging features of above mentioned COVID-19 pneumonia.

(3) In the early stage of the disease, the total number of leukocytes was normal or decreased, and the lymphocyte count was normal or decreased.

A case that meets any one of the epidemiological history criteria and any two of the clinical manifestations can be identified as a suspected case. If there is no clear epidemiological history, 3 of the clinical manifestations is required.

b) Confirmed cases

Suspected cases with one of the following etiology or serological evidence can be identified as confirmed cases:

(1) Real-time RT-PCR detection is positive for COVID-19 nucleic acid.

(2) The viral gene identified by gene sequencing is highly homologous with known COVID-19;

(3) The COVID-19-specific IgM and IgG antibodies are tested positive. The titer of COVID-19-specific IgG antibody is 4 times higher in recovery period than that in acute phase.

6. Clinical classification

a) Mild type

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

b) Moderate type

These patients had fever and respiratory symptoms. Radiologic assessments found signs of pneumonia.

c) Severe type

Adults meet any of the following criteria:

(1) Shortness of breath, RR≥30 times/min;

(2) Oxygen saturation≤93% at rest;

(3) Alveolar oxygen partial pressure/fraction of inspiration O_2 (PaO_2/FiO_2) ≤300 mmHg (1mmHg=0.133 kPa).

At high altitudes (above 1000 meters), PaO_2/FiO_2should be corrected according to the following formula: PaO_2/FiO_2×[Atmospheric Pressure (mmHg)/760].

Patients whose pulmonary imaging showed significant progression of lesion> 50% within 24-48 hours should be treated as severe type.

Children meet any of the following criteria:

(1) Shortness of breath (<2 months of age, RR≥60 beats/min; 2 to 12 months of age, RR≥50 beats/min; 1 to 5 years old, RR≥40 beats/min;> 5 years old, RR≥30 beats/min), excluding the effects of fever and crying;

(2) In the resting state, the oxygen saturation is ≤92%;

(3) Assisted breathing (groaning, wing flaps, tri-retraction sign), cyanosis, intermittent apnea;

(4) Lethargy and convulsions;

(5) Refuse to feed, and have signs of dehydration.

d) Critically severe type

Patients meet any of the following conditions:

(1) Respiratory failure requiring mechanical ventilation;

(2) Shock;

(3) Patients combined with other organ failure needed ICU monitoring and treatment.

7. Warning signals for severe and critically severe types

a) Adults

(1) Progressive decline in the number of peripheral lymphocytes;

(2) Progressive increase in the levels of peripheral inflammatory biomarkers, such as IL-6 and CRP;

(1) Progressive increase in lactic acid concentration;

(2) Pulmonary lesions progress rapidly in a short time.

b) Children

(1) Increased respiration rate;

(2) Poor mental responsiveness and drowsiness;

(3) Progressive increase in lactic acid concentration;

(4) Imaging showed bilateral or multilobes infiltration and pleural effusion; or pulmonary lesions progress rapidly in a short time;

(5) Infants under 3 months of age, or children having coexisting conditions (congenital heart disease, bronchopulmonary dysplasia, respiratory deformity, abnormal hemoglobin, severe malnutrition, *etc.*), or children with immunodeficiency or under immunosuppressive state (long-term use of immunosuppressants).

8. Differential diagnosis

a) The mild manifestations of COVID-19 infections need to be distinguished from upper respiratory tract infections caused by other viruses.

b) The COVID-19 pneumonia needs to be distinguished from other known viral pneumonia or mycoplasma pneumoniae infections, such as influenza virus, adenovirus and respiratory syncytial virus. For suspected cases, technique such as rapid antigen

detection and multiplex PCR nucleic acid detection should be taken to detect common respiratory pathogens.

c) It should also be distinguished from non-infectious diseases such as vasculitis, dermatomyositis, and organizing pneumonia.

9. Identifying cases and filing reports

When a COVID-19 suspected case is found by any medical practitioners, it is critical to immediately isolate the suspected person in a solitary cell for further monitoring and treatment. If COVID-19 infection is still suspected after comprehensive evaluation by medical experts and/or physicians, a case report should be submitted through internet to Centers for Disease Control (CDC) within 2 hours after the initial suspicion. In addition, specimens should be collected for COVID-19 nucleic acid test. Meanwhile, the suspected person should be immediately transferred to a predesignated hospital with secured transportation modalities. If the suspected person has a close contact history with patient(s) already diagnosed with COVID-19 pneumonia, COVID-19 nucleic acid test should be performed, even if his or her common respiratory pathogen detection test has shown positive result(s).

If COVID-19 nucleic acid tests are negative for two consecutive times (with at least 24 hours interval between each test), and if COVID-19-specific IgM and IgG antibodies remain negative after 7 days from onset, the suspected diagnosis of COVID-19 can be ruled out.

10. Treatment

a) Determine the treatment place according to patients' condition.

(1) Suspected and confirmed cases should be isolated and treated in designated hospitals with effective isolation and protection conditions. Suspected cases should be isolated in a single ward, while confirmed cases can be admitted to multiple bedded ward.

(2) Critically severe cases should be admitted to ICU as soon as possible.

b) General treatment.

(1) Rest in bed with supportive treatment to ensure sufficient energy supply. The water and electrolyte balance should be noticed to maintain internal environment stability. Vital signs and oxygen saturation should be closely monitored.

(2) Monitor the blood routine, urine routine, CRP, biochemical indicators (liver enzyme, myocardial enzyme, renal function, *etc.*), coagulation function, arterial blood gas analysis, chest imaging according to the condition. If possible, cytokine test should be performed.

(3) Effective oxygen therapy measures should be given in time, including nasal cannula, mask oxygen and high-flow nasal cannula oxygen therapy. Hydrogen-oxygen inhalation (H_2/O_2: 66.6%/33.3%) treatment can be considered for use.

(4) Antiviral therapy: α-interferon (5 million U or equivalent for adult, add 2ml of sterile water, 2 times daily inhalation), lopinavir/ritonavir (200 mg/50 mg/capsule, 2 capsules each time for adults, twice a day, the course of treatment should not exceed 10 days). Ribavirin (combination with interferon or lopinavir/ritonavir is recommended, 500 mg each time for adults, 2 to 3 times intravenous infusions per day, the course of treatment should not exceed 10 days), chloroquine phosphate (for adults whose weigh over 50 kg, 500 mg each time, twice daily for 7 days; for those whose weigh less than 50 kg, 500 mg each time, twice daily for day 1 and day 2, once daily for day 3- day 7), Abidol (200 mg each time, three times a day for adults, the course of treatment should not exceed 10 days) can be tried. Attention should be paid to the adverse reactions of the above drugs, contraindications (such as chloroquine should not be used in patients with heart disease), and interaction with other drugs. It is not recommended to use 3 or more antiviral drugs at the same time. The use of related drugs should be stopped when intolerable side effects occur. The treatment of pregnant women should consider the number of weeks of gestation and choose drugs that have less impact on the fetus.

(5) Antibacterial drug treatment: inappropriate use of antibacterial drugs should be avoided, especially the broad-spectrum antibacterial drugs.

c) Treatment of severe and critically severe cases.

(1) Principles of treatment:

In addition to symptom treatments, it is important to actively prevent complications, treat underlying diseases, prevent secondary infections, and provide organ function support.

(2) Respiratory support:

a) Oxygen therapy: Severe patients should receive nasal cannula or mask to inhale oxygen, and evaluate in time whether respiratory distress and/or hypoxemia is relieved.

b) High-flow nasal cannula oxygen therapy or non-invasive mechanical ventilation: When patients with respiratory distress and / or hypoxemia cannot be relieved after receiving standard oxygen therapy, high-flow nasal cannula oxygen therapy or non-invasive ventilation can be considered. If the condition does not improve or worsens within a short time (1-2 hours), tracheal intubation and invasive mechanical ventilation should be performed in time.

c) Invasive mechanical ventilation: Using lung protective ventilation strategy, that is, small tidal volume (6-8 mL/kg ideal body weight) and low level of airway plateau pressure (≤30 cm H_2O) for mechanical ventilation to reduce ventilator-related lung injury. When the airway plateau pressure is ≤35 cm H_2O, high PEEP can be appropriately used. Keep the airway warm and humid, avoid prolonged sedation, and awaken patients early and perform pulmonary

rehabilitation treatment. For those patients with problem of man-machine synchronization, sedation and muscle relaxants should be used in time. According to the airway secretions, closed sputum suction should be considered, and bronchoscopy should be performed if necessary.

d) Salvage treatment: For patients with severe ARDS, it is recommended to perform lung expansion. Prone ventilation should be performed for more than 12 hours per day. When prone position mechanical ventilation is not effective, if conditions permit, extracorporeal membrane pulmonary oxygenation (ECMO) should be considered as soon as possible. Related indications: ① When FiO_2> 90%, the oxygenation index is less than 80mmHg, which lasts more than 3-4 hours; ② Patients with simple respiratory failure with airway plateau pressure ≥35 cm H_2O, the VV-ECMO mode is preferred; if circulatory support is needed, then VA-ECMO mode will be selected. When the underlying disease is under control and cardiopulmonary function shows signs of recovery, weaning trials should be considered to begin.

(3) Circulation support:

Based on adequate fluid resuscitation, improvement of microcirculation and use of vasoactive drugs may be considered. Changes in patients' blood pressure, heart rate, and urine output, as well as lactic acid and alkali residuals in arterial blood gas analysis should be closely monitored. Noninvasive or invasive hemodynamic monitoring, such as Doppler echocardiography, echocardiography, invasive blood pressure or continuous cardiac output (PiCCO) monitoring, is necessary. In the process of treatment, attention should be paid to the liquid balance to avoid excess and deficiency.

When the patient's heart rate suddenly increases over 20% of the baseline value or the blood pressure has dropped by more than 20% of the baseline value, accompanying symptoms such as poor skin perfusion and decreased urine output, it should be alert whether patients have septic shock, gastrointestinal bleeding, or severe heart failure.

(4) Renal failure and renal replacement therapy:

When renal insufficiency occurs in critically severe patients, the causes of renal function insufficiency, such as hypoperfusion and drugs, should be analyzed. The treatment of patients with renal failure should pay attention to fluid balance, acid-base balance and electrolyte balance. For nutrition support treatment, attention should be paid to nitrogen balance, and supplement of calorie and minerals. Renal replacement therapy (CRRT) can be considered in severe patients. The indications include: ① hyperkalemia; ② acidosis; ③ pulmonary edema or excessive water load; ④ fluid management when multiple organ dysfunction occurs.

(5) Recovered patients' plasma therapy:

It is suitable for severe and critically severe patients with rapid disease progression.

(6) Blood purification treatment:

The blood purification system includes plasma exchange, adsorption, perfusion, blood/plasma filtration, etc., which can remove inflammatory factors and stop the "cytokine storm", thereby reducing the damage to the body caused by the inflammatory response. It can be used for treatment of early and mid-term cytokine storms in severe and critically severe patients

(7) Immunotherapy:

For patients with extensive lung lesion and severe patients with elevated IL-6 levels, tocilizumab treatment can be tried. The first dose is 4-8mg/kg, the recommended dose is 400mg with dilution of 0.9% physiological saline to 100ml, and the infusion time should be more than 1 hour. If the first medication is not effective, it can be applied once more after 12 hours (the dose is the same as before), cumulative number of administrations should not be more than 2 times, and the maximum single dose should not exceed 800 mg. Pay attention to allergic reactions. It is not recommended for people with active infections such as tuberculosis.

(8) Other treatment measures

For patients with progressive deterioration of oxygenation indicators, rapid imaging progress, and excessive activation of inflammatory response, the use of glucocorticoids in the short term (3 to 5 days) should be considered. The dosage of methylprednisolone should not be over 1-2mg/kg/day. It should be noted that large doses of glucocorticoids will delay the removal of coronavirus due to immunosuppressive effects. Intestinal microecological regulators can be used to maintain intestinal microecological balance and prevent secondary bacterial infections.

For severe and critically severe children patients, intravenous gamma globulin should be considered.

Pregnant women with severe or critically severe COVID-19 pneumonia should consider pregnancy termination, and cesarean delivery is preferred.

Psychological counseling should be strengthened in patients with anxiety and fear.

d) Traditional Chinese medicine treatment

According to the local climate characteristics, patients' illness states and physical conditions, traditional Chinese medicine treatments can be used under the guidance of doctors. Huoxiang Zhengqi Capsules, *ect.* are recommended for patients with asthenia and gastrointestinal discomfort. Jinhua Qinggan granules, Lianhua Qingwen capsules

and Shufeng Jiedu Capsules, *ect.* are recommended for patients with asthenia and fever.

11. Discharge criteria and precautions after discharge

a) Discharge criteria.

(1) The body temperature returns to normal for more than 3 days;

(2) Significant improvement in respiratory symptoms;

(3) Pulmonary imaging shows a marked improvement in acute exudative lesions;

(4) Negative nucleic acid test for sputum, nasopharyngeal swabs and other respiratory specimens for two consecutive times (at least 24 hours interval between each test).

Those who meet all the above conditions can be discharged.

b) Precautions after discharge.

(1) The hospital should make good contact with the basic medical and health institutions where the patients live, share the medical records, and timely send the discharged patients' information to the residential committee and the basic medical and health institutions.

(2) After the patient is discharged from the hospital, it is recommended to continue the isolation management and health monitoring for 14 days, wear a mask, and live in a well-ventilated single room, reduce close contact with family members, wash hands frequently, and avoid going out.

(3) It is recommended to follow up and return to the hospital in the 2nd and 4th week after discharge.

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