Guideline

Guidance for the management of adult patients with coronavirus disease 2019

Jie-Ming Qu, Chen Wang, Bin Cao, on behalf of Chinese Thoracic Society and Chinese Association of Chest Physician

Correspondence to: Prof. Jie-Ming Qu, Department of Pulmonary and Critical Care Medicine, Ruijin Hospital, Institute of Respiratory Diseases, Shanghai Jiaotong University School of Medicine, Shanghai 200025, China

E-Mail: jmqu0906@163.com;

Prof. Chen Wang, Department of Pulmonary and Critical Care Medicine, Center of Respiratory Medicine, China-Japan Friendship Hospital, Beijing 100029, China; National Clinical Research Center for Respiratory Diseases, Beijing, China; Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China; Institute of Respiratory Medicine, Chinese Academy of Medical Sciences, Beijing, China; Department of Respiratory Medicine, Capital Medical University, Beijing, China

E-Mail: cyh-birm@263.net;

Prof. Bin Cao, Department of Pulmonary and Critical Care Medicine, China-Japan Friendship Hospital, Beijing 100029, China

E-Mail: caobin_ben@163.com

In December 2019, a novel coronavirus was identified in Wuhan City, Hubei Province, China and subsequently developed into an epidemic.[1-3] On January 7, 2020, the WHO temporarily named the new coronavirus as "2019 novel coronavirus (2019-nCoV)." On February 8, the National Health Commission of the People's Republic of China announced that the name of the pneumonia caused by 2019-nCoV was "novel coronavirus pneumonia

(NCP)." On February 12, Coronaviridae Study Group of the International Committee on Taxonomy of Viruses proposed to officially name the new coronavirus "SARS-CoV-2." On the same day, the WHO announced the official name of the disease caused by the virus as "coronavirus disease 2019 (COVID-19)." On February 22, the National Health Commission issued a notice to amend the English name of "NCP" to "COVID-19".[4] Currently, although the epidemic situation in China is under control, the number of cases globally has been increasing. On March 11, 2020, the World Health Organization (WHO) officially announced that COVID-19 had reached global pandemic status. As experience and understanding of disease prevention, control, diagnosis, and treatment continue to accumulate, a summary of the results of available studies and experience is needed to guide the prevention, control, clinical diagnosis, and treatment of the disease. This guidance explains the up-to-date etiology, pathogenesis, epidemiology, clinical characteristics, treatment principles, rehabilitation, and prevention and control measures of COVID-19.

I Definition, etiology, and pathogenesis of COVID-19

1 Definition

Novel coronavirus pneumonia is an acute respiratory infectious disease caused by the newly emerged severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The incubation period of this disease is generally 1–14 days, and the main manifestations are fever, dry cough, and fatigue. Most patients have mild clinical symptoms and good prognosis; however, more severe cases can quickly deteriorate to acute respiratory distress syndrome and septic shock.[1] Furthermore, myocardial injury, acute kidney injury, and other organ dysfunction often occur in patients with severe disease.[2,3]

2 Etiology

In December 2019, after an unexplained viral pneumonia epidemic emerged in Wuhan, the National Health Commission designated the Chinese Center for Disease Control and Prevention, the Chinese Academy of Medical Sciences, the Academy of Military Medical Sciences of the Academy of Military Sciences, the Hubei Provincial Center for Disease Control and Prevention, the Wuhan Institute of Virology, and the Chinese Academy of Sciences, among others, as parallel testing units. This combined effort resulted in the joint

identification of a new type of coronavirus as the pathogen that caused the outbreak. On January 8, the results of the preliminary pathogen identification were announced, and the complete genome sequence of the virus was actively announced to the world.[2,5-7] The Coronaviridae Study Group of the International Committee on Taxonomy of Viruses named the virus SARS-CoV-2.[8]

SARS-CoV-2 belongs to the β-coronavirus genus of coronaviruses, which is the same branch as SARS-CoV. Sequence alignment of the virus genome shows that SARS-CoV-2 is homologous to the SARS coronavirus by approximately 79% and to the Middle East respiratory syndrome (MERS) coronavirus by only approximately 52%.[5] Similar to SARS-CoV, SARS-CoV-2 uses angiotensin-converting enzyme II (ACE2) as a receptor, which is widely distributed in many organs such as the lung, heart, kidney, and gastrointestinal tract.[7,9]

3 Pathogenesis

Although most patients infected with SARS-CoV-2 have only mild respiratory symptoms, the disease in approximately 5% of patients will progress to severe lung injury or even multiple organ dysfunction, with a mortality rate of 2%.[10] Since SARS-CoV-2 first emerged in Wuhan, a substantial amount of research has been conducted in China. This has resulted in a basic understanding of the disease characteristics of COVID-19. However, the pathogenesis remains unknown, and further research is needed.

Based on the recent findings of studies on SARS-CoV-2 and those of previous studies on SARS-CoV, we speculate that the pathogenesis of severe COVID-19 follows three potential mechanisms. (1) Direct infection by SARS-CoV-2 contributes to multiple organ damage. Electron microscopy of autopsy specimens has revealed a large number of virus particles in alveolar epithelial cells,[1] and live virus particles have also been isolated from respiratory specimens and urine and stool samples.[11, 12] (2) An imbalance of the host immune response, characterized by cytokine storms and lymphopenia, is an important precursor of the onset of severe COVID-19.[2] (3) Multiple organ injury and coagulopathy caused by the virus also participate in the pathogenesis of severe COVID-19.[3]

4 Pathological changes

(1) Autopsy and gross observation

Following severe COVID-19, the lung lobes on both sides atrophy to varying degrees. On the cut surface, the lung air content decreases and solid changes are observed at varying degrees; no significant secretion is retained in the trachea, main bronchi, or lobar bronchi. Most patients have adhesions to the chest wall, especially in the middle and lower lobe of the lung.

(2) Light microscopic observation

The main pathological changes noted in the lungs are a large number of macrophages and serous fibrous exudation in the alveolar cavity, accompanied with intra-alveolar hemorrhage [Figure 1]; diffuse alveolar damage, carnification in alveolar cavity, and pulmonary consolidation [Figure 2]; transparent membrane formation at alveolar cavity surface in some patients; Type II alveolar epithelium proliferation to varying degrees; alveolar septa widening to varying degrees and interstitial fibrous tissue proliferation, with a small amount of lymphocyte infiltration [Figure 3]; and retention of mucinous secretion and even mucus plugs in some small airways (mainly bronchioles and terminal bronchioles). Some patients have secondary bacterial infections, which are manifested as inflammatory cells, mainly neutrophils, infiltrating the lesion, and a few patients have secondary fungal infections, which are manifested as fungal mycelia and sporophytes in the lesion. These findings are consistent with viral pneumonia with or without secondary bacterial or fungal infection.

II Epidemiology of COVID-19

1 Source of infection

Currently, it is believed that patients infected with SARS-CoV-2 are the main source of infection. Latent patients with asymptomatic or mild transient symptoms may also become sources of infection. These patients are difficult to diagnose and isolate in a timely manner because they have no obvious symptoms. The accumulation of infectious sources at the community level has also hindered disease control. Current evidence suggests that patients in the incubation period may be infectious to some extent and that the presence of the virus can be detected in patients in the early recovery period, who may also be somewhat infectious.[1]

2 Modes of transmission

At present, respiratory droplets and close contact are considered to be the main route of transmission.[13] The virus is thus primarily transmitted through droplets produced by infected individuals when they cough and talk, and individuals who are susceptible become infected after inhaling these droplets. The droplets containing the virus can also be deposited on the surface of items and then manually transmitted to the mucous membranes of the mouth, nose, and eyes and subsequently to the respiratory tract, where the infection develops. Aerosol transmission is also possible via prolonged exposure to high concentrations of virus aerosols in a relatively closed environment. As SARS-CoV-2 has also been isolated from feces and urine, there is a risk of fecal-oral transmission. A possible connection between environmental pollution caused by feces and urine and aerosol or contact transmission routes should be considered. Further studies are needed to determine whether mother-to-child transmission can occur.

3 Susceptible populations

As COVID-19 is a novel infectious disease, the global population lacks immunity to SARS-CoV-2, and thus, people of all ages are susceptible to infection. Elderly adults and people with comorbidities, such as chronic obstructive pulmonary disease, diabetes, hypertension, and heart disease, have an increased risk of infection. Close contacts with symptomatic and asymptomatic infected patients are at high risks of developing COVID-19. Medical staff are also at a higher risk of infection.

III Clinical features of COVID-19

1 Clinical manifestation

The incubation period is generally 3–7 days, with the shortest and longest known incubation periods of 1 day and 14 days, respectively. Acute onset of fever and fatigue occur in the early stage, and the primary respiratory symptom is dry cough. A minority of patients also have symptoms of nasal congestion, runny nose, sore throat, muscle pain, and/or diarrhea. In severe cases, chest tightness and dyspnea may gradually develop after 7–10 days. Acute respiratory distress syndrome, septic shock, metabolic acidosis that is particularly difficult to correct, and coagulation dysfunction can occur in critically ill patients. Notably, patients with

severe illness can have moderate to low fever, even without obvious fever symptoms. Mild cases of infection generally manifest as low fever, fatigue, and no symptoms of pneumonia. Although most patients have a good prognosis, a few patients (approximately 5%) become critically ill and may die.

2 Laboratory and radiological investigation

(1) General inspection

In the early stage of the disease, the total number of white blood cells is normal or decreased, and the lymphocyte count is decreased. Some patients have increased levels of liver enzymes, muscle enzymes, and myoglobin. In most patients, C-reactive protein levels and erythrocyte sedimentation rates are elevated, and procalcitonin levels are normal. In severe cases, D-dimer levels are elevated, and inflammatory factors may also be elevated.

(2) Etiology and serology

On etiological examination, SARS-CoV-2 nucleic acid can be detected in nasopharyngeal swabs, sputum, and other lower respiratory tract secretions, blood, stool, and other specimens using real-time fluorescence quantitative reverse transcription polymerase chain reaction (RT-PCR) or second-generation gene sequencing (NGS). Detection with lower respiratory tract specimens (sputum and airway extracts) is more accurate. On serological examination, new specific immunoglobin M (lgM) antibodies are typically observed 3−5 days after onset, and the immunoglobin G (lgG) antibody titers in the recovery period are four-fold or higher than those in the acute phase.

(3) Chest imaging

Multiple small patchy shadows and interstitial changes appear in the early stage and are obvious in the extrapulmonary zone. These then develop into multiple ground-glass infiltrates in the lungs. In severe cases, pulmonary consolidation may appear, and pleural effusion is rare. Chest imaging findings are not specific and must be combined with clinical manifestations and dynamic observations. If short-term disease progression is obvious, the presence of multiple lung lesions is supportive of a definitive diagnosis; however, if the patient has an underlying lung disease, it is often difficult to distinguish viral lesions from other lung lesions, and thus, diagnosis must be confirmed with other tests.[1]

IV Diagnosis of COVID-19

1 Etiological diagnosis

(1) Detection of SARS-CoV-2 nucleic acid using RT-PCR and/or NGS

Various specimens, including nasopharyngeal swabs, sputum and other lower respiratory tract secretions, blood, and stool, are used to test positivity for SARS-CoV-2 nucleic acid, and positive findings can confirm viral infection. The most commonly used method for detecting nucleic acid is RT-PCR, which is the standard for COVID-19 etiological diagnosis. However, RT-PCR results can present with a false negative. SAR-CoV-2 infection mainly invades bronchial epithelial cells and alveolar epithelial cells; thus, lower respiratory tract specimens (i.e., sputum or airway extracts) should be used to more accurately determine infection. Qualified sample collection, rapid delivery of specimens for inspection, standardized testing operation procedures, and use of standard-compliant test kits can effectively improve the accuracy of sample detection. In addition, nicking enzyme amplification reaction, which does not rely on the extraction of nucleic acids, can be used for rapid SARS-CoV-2 detection and screening.

(2) Serological detection of SARS-CoV-2 specific antibodies

Most SARS-CoV-2-specific IgM antibodies are positive 3−5 days after onset. IgG antibody can serve as a confirmatory test when the titers in the recovery period are at least four times the amount in the acute phase. Enzyme-linked immunosorbent assay, the antibody gelatin method, and immunochromatography methods can detect serum-specific IgM and IgG antibodies, with a sensitivity of 50% or more, and a specificity of 90−99%. The combined detection of IgM and IgG can improve diagnostic sensitivity. Serum antibody detection is a newly added basis for etiological diagnosis in the "Novel Coronavirus Pneumonia Diagnosis and Treatment Plan (Trial Version 7)",[1] and has the advantages of simplicity, rapidness, low price, and easy dissemination. Serum antibody detection can determine not only the presence of infection, but also the patient's immune status and can compensate when false-negative results of nucleic acid detection are observed, particularly in cases with low virus loads in the upper respiratory tract. Although serum antibody detection is an effective supplementary method for SARS-CoV-2 nucleic acid detection, there is an early window period in which serum antibodies cannot be detected. Additionally, this method has relatively low sensitivity, can only provide evidence of recent infection, and cannot confirm

the presence of a live virus.

2 Diagnostic criteria and systems

The diagnosis of COVID-19 is based on a comprehensive diagnostic system of epidemiological history, clinical manifestations, and pathogenic confirmation. As a serious acute infectious disease, complete epidemiological history is particularly critical in the diagnosis of the disease. The average incubation period is 1−14 days, and a history of residence in or travel to Wuhan or severely infected areas within the past 14 days is an important epidemiological factor. The most common clinical manifestations are fever and respiratory symptoms such as dry cough and shortness of breath. More than 86% of patients also develop abnormalities visible on lung imaging. In addition to the typical manifestations of viral pneumonia (normal or decreased white blood cells), most COVID-19 cases are associated with decreased lymphocytes. Etiological confirmation of SARS-CoV-2 infection remains the gold standard for diagnosis. As asymptomatic viral carriers are also infectious and clustered onset has been observed, clinicians should pay close attention to it, which requires dynamic observation and repeated pathogenic examinations.

The COVID-19 diagnostic criteria for suspected and confirmed cases are as follows[1].

(1) Suspected cases

For suspected cases, a comprehensive analysis of the following epidemiological history and clinical manifestations should be performed.

Epidemiological history: (i) Travel history or residence history in Wuhan and surrounding areas or other communities with case reports within 14 days before onset; (ii) history of contact with SARS-CoV-2-infected persons (with positive nucleic acid test) within 14 days before onset; (iii) history of contact with patients from Wuhan and surrounding areas, or patients with fever or respiratory symptoms from a case-reporting community within 14 days before the onset of illness; and (iv) clustered cases.

Clinical manifestations: (i) Fever and/or respiratory symptoms; (ii) consistent with the imaging of COVID-19; and (iii) normal or decreased total number of white blood cells in the early stage of the disease and normal or decreased lymphocyte count.

Patients who meet any one of the epidemiological items and any two of the clinical manifestations are suspected to have the disease. If there is no clear epidemiological history,

three of the clinical manifestations should be met.

(2) Confirmed cases

Suspected cases can be confirmed by one of the following pathogenic or serological positive results: (i) positive RT-PCR results for SARS-CoV-2 nucleic acid; (ii) viral gene sequencing highly homologous to the known SARS-CoV-2; or (iii) serum samples positive for SARS-CoV-2-specific IgM and IgG antibodies. The SARS-CoV-2-specific IgG antibody will need to change from negative to positive or the titers in the recovery period will need to be four times or higher than those in the acute phase.

(3) Severity classification

The clinical classification of COVID-19 can be mild, moderate, heavy, or critical.[1]

(i) Mild: Clinical symptoms are slight, with no pneumonia manifestation on lung imaging.

(ii) Moderate: Fever and respiratory symptoms with pneumonia manifestation visible on imaging; no dyspnea or other complications.

(iii) Severe: Patients meet any of the following: shortness of breath, respiratory rate (RR) ≥30 beats/min; resting state, mean oxygen saturation ≤93%; partial pressure of arterial oxygen (PaO_2)/ fraction of inspired oxygen (FiO_2) ≤300 mmHg (1 mmHg = 0.133 kPa). At high altitudes (>1000 m), PaO_2/FiO_2 should be corrected according to the following formula: PaO_2/FiO_2 × [atmospheric pressure (mmHg)/760]; pulmonary imaging shows that the lesions have progressed by >50% within 24–48 h.

(iv) Critical: Patients with one of the following conditions are considered critical: respiratory failure requiring mechanical ventilation; shock; and multiorgan failure requiring ICU monitoring and treatment.

(4) Risk factors for severe disease

According to the Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (Trial Version 7),[1] and the "Expert Consensus on Comprehensive Treatment of Coronavirus in Shanghai 2019",[14] in combination with the latest clinical research[3,15,16], we propose the following clinical warning signs of severe COVID-19: (i) elderly patient (age >65 years); (ii) comorbidities, such as hypertension, diabetes, and coronary heart disease; (iii) progressive decline in peripheral blood lymphocytes, CD4^{+} T lymphocyte count <250/μL; (iv) progressive increase in peripheral blood inflammatory factors, such as interleukin (IL)-6 and C-reactive

protein; (v) progressive increase in lactic acid and lactic dehydrogenase (LDH) >2 times the upper limit of the normal value; (vi) intra-pulmonary lesions significantly progressed by >50% within 2 to 3 days; (vii) metabolic alkalosis; (viii) high sequential organ failure assessment scores; and (ix) D-dimer levels >1 mg/L at admission.

(5) Differential diagnosis

Cases of mild SARS-CoV-2 should be distinguished from upper respiratory tract infections caused by other viruses, mainly common cold and influenza. Common cold primarily manifests with low fever and catarrhal symptoms, without seasonality, and although the population is generally vulnerable, it is typically self-limiting. Influenza[17] can cause more systemic symptoms, such as headache and myalgia, and influenza cases are the most prevalent from the end of November to the end of February of the following year.

For moderate, severe and critical cases with different levels of pulmonary infiltration, epidemiological and medical history, laboratory examination and imaging findings should be incorporated to distinguish from other types of pneumonia caused by viral infections or atypical pathogens.[18] In particular, potential lung changes caused by non-infectious diseases should not be overlooked.

Differential diagnoses of COVID-19 include:

(i) Other viral pneumonia: The main viruses to be identified include influenza virus, human avian influenza virus, adenovirus, respiratory syncytial virus, MERS virus, and SARS virus. The diagnosis of COVID-19 should be based on a combination of epidemiological history (such as epidemic period and epidemic area travel history), clinical characteristics, and pathogenic examination results.

(ii) Atypical pathogen pneumonia: This primarily includes lower respiratory tract infections caused by *Mycoplasma*, *Chlamydia*, and *Legionella*, which are mostly clustered. Irritating dry cough is a more characteristic clinical symptom of *Mycoplasma* infection, which is progressively aggravated. The clinical manifestations of *Chlamydia* pneumonia and *Mycoplasma* pneumonia are similar, and most cases have good prognosis. A small number of patients with *Chlamydia psittaci* infection can develop severe pneumonia. Epidemiological history of *Legionella* includes exposure to contaminated air conditioning systems or water sources, and the clinical manifestations include relatively slow pulse, fever, acute onset headache, non-drug-induced consciousness or drowsiness, non-drug-induced diarrhea,

shock, acute liver and kidney damage, hyponatremia, and hypophosphatemia.

(iii) Pulmonary changes caused by non-infectious factors: These include acute interstitial pneumonia, organizing pneumonia, pulmonary edema, alveolar hemorrhage, and secondary interstitial pneumonia caused by connective tissue disease. Detailed medical history, clinical manifestations, and specific laboratory indicators are required for definitive diagnosis.

VI Treatment of COVID-19

1 General treatment

Stratified treatment is based on the clinical severity of SARS-CoV-2 infection. The general treatment includes (i) proper bed rest, (ii) supportive treatments, such as maintaining a certain energy intake, water-electrolyte and acid-base balance, and the homeostasis of the internal environment; (iii) monitoring of vital signs, including body temperature, breathing, pulse, and blood oxygen saturation.

2 Antiviral treatment

There are currently no specific antiviral drugs for COVID-19. Based on the available evidence, the WHO lists candidate antiviral drugs, including remdesivir, lopinavir/ritonavir, or lopinavir/ritonavir plus an interferon, that should be urgently evaluated.[19] Remdesivir has strong antiviral activity against SARS-CoV-2 *in vitro* and shows good antiviral effects in both SARS and MERS animal models.[20,21] Additionally, data from previous clinical trials show that remdesivir is well tolerated.[22] At present, two randomized controlled double-blind trials in China that include hospitalized patients with mild-to-moderate and severe COVID-19 are ongoing, with the aim of obtaining efficacy and safety results for remdesivir (NCT04252664, NCT04257656). The U.S. National Institutes of Health recently began a trial of remdesivir for hospitalized patients with COVID-19, and in March 2020, remdesivir received an orphan drug designation from the U.S. Food and Drug Administration.

For lopinavir, there are no data regarding its efficacy against SARS-CoV-2 *in vitro*; however, there are available *in vitro* and *in vivo* data for both SARS and MERS.[23,24] In one study of 41 patients with SARS and 111 historical controls, the combination of lopinavir/ritonavir (in the study participants) was associated with significantly fewer adverse clinical outcomes than

ribavirin alone (in the historical controls).[25] However, the historical nature of the control comparison in that study does not allow for a valid estimate of efficacy. In 2016, Arabi et al[26] launched a randomized controlled trial (RCT) of lopinavir/ritonavir combined with interferon-β in patients with MERS-CoV in the Kingdom of Saudi Arabia (NCT02845843). In a randomized, controlled, open-label trial conducted by the Community-acquired pneumonia (CAP)-China Network and involving hospitalized adult patients with confirmed SARS-CoV-2 infection, no benefit was observed in the primary endpoint of time to clinical improvement, but the results for certain secondary endpoints were intriguing (ChiCTR2000029308).[27] Future trials in patients with COVID-19 may help confirm or exclude the possibility of treatment benefits with lopinavir/ritonavir. Common adverse events of lopinavir/ritonavir include gastrointestinal tract reactions, and attention should be paid to the interaction between lopinavir/ritonavir and other drugs metabolized by cytochrome P450.

Favipiravir and ribavirin are nucleoside analogs, and *in vitro* data have confirmed that ribavirin has weak antiviral activity against SARS-CoV and MERS-CoV. The Median effective concentration (EC50) of favipiravir against the SARS-CoV-2 *in vitro* was 61.88 μM.[28] In theory, high blood concentrations of favipiravir would be required to achieve antiviral effects in patients with COVID-19. At present, a historical cohort study and a preprint paper of an RCT reported mild clinical benefits of favipiravir treatment for COVID-19. In addition, some experts have proposed using Arbidol to treat COVID-19; however, its antiviral mechanism against the coronavirus is unclear. In brief, further RCTs are needed to clarify the efficacy and safety of potential antiviral agents against SARS-CoV-2.

3 Antibacterial treatment

The Irrational use of antimicrobials should be avoided, and a combined approach to antimicrobial stewardship (ASP) and COVID-19 prevention and control has been recommended.[29] Senior infectious disease experts and qualified clinical pharmacists are both core members of a hospital ASP team and will also have actively participated in the epidemic response and institutional preparation. An expert team can identify early potential cases, the microbiology laboratory team can identify pathogens, and the anti-infective

clinical pharmacist can help develop antimicrobial treatment programs, monitor and manage drug shortages owing to insufficient supply during an epidemic, and coordinate front-line access to new drugs in epidemic areas.

It is not recommended to use antibacterial drugs to treat mild cases of COVID-19. Antibiotics can be used to treat severely and critically ill patients with COVID-19 and pre-existing or secondary bacterial and/or fungal infections. Appropriate respiratory pathogen detection should be improved, including the detection of other respiratory viruses, bacterial smears and cultures, and fungal tests. Empirical treatment should refer to local pneumonia epidemiology and surveillance data of bacterial or fungal resistance. When sepsis is present, antibiotics should be administered within 1 h of the initial patient evaluation,[30] and step-down treatment should be administered in a timely manner according to microbiological results and clinical consultations[1, 30].

The irrational use of antibacterial drugs in the management of patients with COVID-19 will increase the risk of nosocomial infections from drug-resistant bacteria, as well as the risk of early lymphocyte decline in severely or critically ill patients. High risk factors for secondary invasive fungal infections include the use of high-dose glucocorticoids, long-term stays in the ICU, and receiving noninvasive or invasive mechanical ventilation.[31] The guidelines for hospital-acquired pneumonia and invasive fungal infection should be followed, and drugs should be selected rationally.

4 Immunomodulatory therapy

(1) Glucocorticoids

The use of glucocorticoids in the treatment of COVID-19 is controversial because no relevant RCTs have been conducted. Studies have shown that low and medium doses of glucocorticoids can reduce mortality and shorten hospital stays in patients with severe viral pneumonia without inducing secondary infection or other complications.[32] The "Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (Trial Version 7)"[1] of the National Health Commission recommends that glucocorticoids should be used as appropriate in the short term for patients with progressive deterioration of oxygenation indicators, rapid

disease progression on imaging findings, and excessive activation of the body's inflammatory response. Domestic retrospective studies in China have shown that low and medium doses of glucocorticoids have no significant effect on viral clearance time. A potential benefit of glucocorticoids in critically ill patients may exist.[33]

Given the current limited evidence, glucocorticoids should be used with caution in the management of COVID-19, and the indications and contraindications must be strictly adhered to. The specific recommendations for glucocorticoid use are as follows.[34]

Principles: (i) Use glucocorticoids with caution, and prohibit the use of glucocorticoids to reduce fever and (2) for patients who have regularly used glucocorticoids prior to SARS-CoV-2 infection for autoimmune diseases, nephrotic syndrome, bronchial asthma, and other basic diseases, the dosage of glucocorticosteroids should be individualized according to the patient's underlying disease and the severity of the infection.

Indications: (i) Imaging-confirmed pneumonia and rapid progression (lesion progression >50% within 24–48 h); (2) blood oxygen saturation (SpO_2) ≤93% or respiratory distress (respiratory rate ≥30 breaths/min) or oxygenation index ≤300 mmHg breathing room air in a resting state. Both of these conditions must be met simultaneously to justify glucocorticoid use.

Contraindications: Caution is required for patients with (i) diabetes who are receiving oral medication or insulin treatment; (ii) allergy to methylprednisolone, hydrocortisone, dexamethasone, or other excipients; (iii) refractory hypertension; (iv) epilepsy or delirium; (v) glaucoma; (vi) known active gastrointestinal bleeding in the previous 3 months; (vii) known hypokalemia that is difficult to correct; (viii) known secondary bacterial or fungal infections; (ix) known immunosuppressive status (i.e., chemotherapy, radiation therapy, within 1 month after surgery, HIV infection); and (10) severe lymphopenia (absolute peripheral lymphocytes <300/μl).

Usage, dosage, and course of treatment: It is suggested that the dosage should not exceed the equivalent of methylprednisolone 1–2 mg.kg^{-1}.d^{-1} for 5–7 days. Higher doses of glucocorticoids may delay the clearance of the coronavirus owing to immunosuppression.

Mode of administration: Based on the physician's discretion, the recommended method is intravenous drip. If the patient's condition allows, this can be gradually transferred to oral

administration.

(2) Cytokine-targeted therapy

One of the primary causes of death from COVID-19 is an excessive immune response, known as a "cytokine storm," which leads to lung tissue damage, repair imbalances, and respiratory failure.[35] In one study, more than half of 99 COVID-19 patients diagnosed at Wuhan Jinyintan Hospital had elevated IL(interleukin)-6 levels.[36] Furthermore, the levels of inflammatory factors, such as IL-2, IL-7, IL-10, Granulocyte colony-stimulating factor (G-CSF), interferon- ɣ - inducible protein (IP)-10, monocyte chemotactic protein (MCP)-1, macrophage inflammatory protein (MIP)-1α, and tumor necrosis factor (TNF)α, in patients with severe disease were significantly higher than those in patients with mild-to-moderate disease.[2] Thus, for such severely and critically ill patients, relevant markers should be actively monitored, and interventions to avoid further lung injury and respiratory failure are imperative.

The current treatment for cytokine storms lacks an evidence base, and pros and cons should be carefully weighed. Targeted therapies for cytokine storms include cytokine antagonist therapy and blockade of cytokine signaling pathways. Therapeutic modalities that are commonly used include IL-6 receptor antagonists and Janus kinase (JAK) inhibitors. The IL-6 receptor antagonist tocilizumab is a recombinant humanized monoclonal antibody directed against the IL-6 receptor and is a first-line drug for treating cytokine release syndrome.[37,38] It has been included in the Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia

(Trial Version 7).[1] Etanercept is a TNF antagonist used to treat rheumatoid arthritis, ankylosing spondylitis, and macrophage activation syndrome and can competitively bind to blood TNFα and block TNFα binding to TNF receptors on the cell surface, thereby reducing TNFα activity and controlling inflammatory responses.[39] The JAK pathway is a signaling pathway used by many inflammatory factors, and JAK inhibitors include tofacitinib and ruxolitinib. These drugs act via a temporary inhibitory or regulatory mechanism against cytokine storms, allowing for timely intervention in the critical period of excessive immune response.

However, it should be noted that in critically ill patients with viral pneumonia, bacterial infections and fungal infections are often concomitant. In these patients, the immune situation is complex, and the use of cytokine antagonists should be accompanied by extreme vigilance.

Table 1: The potential therapy of COVID-19 targeting proinflammatory mediators.

Targeted drugs	Mechanism	Dose	Ref.
Tocilizumab	IL-6 receptor antagonist	4–8 mg/kg, IV drip, qd	[1]
Etanercept	TNF antagonist	50 mg ih, qw	[39]
Tofatib	Janus kinase inhibitors	5 mg po, bid, 5-10 d	[40]
Lucotinib	Janus kinase inhibitors	0.3 mg/kg po, bid, 5-10 d	[41]

COVID-19: Coronavirus disease 2019; IL-6: interleukin-6; mg: milligram; kg: kilogram; IV: intravenous; qd: once a day; TNF: tumor necrosis factor; ih: subcutaneous injection; qw: once a week; po: take orally; d: day; bid: twice a day.

(3) Convalescent plasma treatment

Plasma treatment is a method by which the convalescent plasma of recovered patients is collected, and following strict preparation procedures the high-titer neutralizing antibody biological products are transfused into patients. This method achieves therapeutic effect by reducing the viral load. Convalescent plasma treatment may be suitable for patients with rapid disease progression or severe or early critical illness; however, its efficacy and safety need to be confirmed in further clinical studies.

Plasma treatment should follow three main principles: (i) transfusion may be more effective when performed within 14 days of onset and the course of the disease should not exceed 3 weeks. (ii) SARS-CoV-2 nucleic acid test is positive, or viremia is present. (iii) Severe patients with rapid disease progression, early critically ill patients, or patients who are assessed to need plasma therapy are appropriate recipients.

Contraindications for plasma treatment include a history of allergy to plasma infusion or allergy to human plasma protein products; history of allergy to sodium citrate; history of methylene blue allergy (in these cases, use of plasma inactivated by methylene blue is strictly prohibited); and other history of severe allergies or contraindications to plasma use. Additionally, convalescent plasma therapy should not be used in patients with poor general

condition and an estimated survival time of less than 7 days; those with severe dysfunction of major organs such as the heart, liver, or kidney; and pregnant or breast-feeding women. For specific dosage instructions and management of adverse reactions, refer to the National Health Commission's "Novel Coronary Pneumonia Convalescent Plasma Clinical Treatment Protocol (Trial Second Edition)"[42].

(4) Stem cell therapy

Some cells with immunoregulatory and anti-inflammatory capabilities could reduce lung injury, promote lung tissue repair, inhibit lung fibrosis, and have a positive effect in improving respiratory function and prognosis of patients with COVID-19.[43-45] Stem cell therapy for SARS-CoV-2 infection is currently at an exploratory stage.[46,47]

(5) Other treatments

(i) Chloroquine: Chloroquine was initially used as an antimalarial drug but was found to effectively prevent the replication of the SARS virus in cells by changing the pH value of endosomes, reducing terminal glycosylation of ACE2 receptors, and interfering with the binding of the SARS virus to ACE2 receptors; it also has good safety.[48,49] A Chinese research team has reported preliminary confirmation for in vitro anti-SARS-CoV-2 activity of chloroquine.[28] Multicenter clinical trials conducted in more than 10 hospitals have also reported clear efficacy and acceptable safety of chloroquine for SARS-CoV-2-associated pneumonia.[50]

The latest edition of the National Health Commission's "Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (Trial Version 7)" provides the following recommendations: adults aged 18–65 years and weighing >50 kg may take 500 mg chloroquine twice daily for 7 days, while patients weighing ≤50 kg may take 500 mg twice daily on the first and second days and 500 mg once daily on days 3–7. The course of treatment for all patients should be 7 days. Importantly, electrocardiogram (ECG) results must be normal prior to administering the medication, and chloroquine is prohibited for patients with heart disease.[1]

Hydroxychloroquine is a derivative of chloroquine with the same pharmacological effects of chloroquine and half the toxicity. A national multicenter RCT to evaluate the efficacy and safety of high-dose hydroxychloroquine for COVID-19 is on-going.

(ii) Arbidol: Umifenovir (Arbidol) is a non-nucleoside broad-spectrum antiviral drug that can

prevent the influenza virus from entering target cells by inhibiting hemagglutinin-mediated membrane fusion of the virus and playing a role in multiple stages of the viral replication cycle.[51] *In vitro* studies have also shown Arbidol to be effective against the coronavirus.[52] A retrospective analysis of 69 patients with SARS-CoV-2-associated pneumonia revealed that treatment with Arbidol tended to improve the discharge rate and decrease the mortality rate.[53] The National Health Commission's "Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (Trial Version 7)" recommends 200 mg for adults, 3 times daily, with a course of treatment not exceeding 10 days.[1]

(iii) Artemisinin: Artemisinin has unique efficacy in antimalarial treatment, and research has also found that artemisinin compounds have inhibitory effects on several viruses.[54] However, further studies of the clinical treatment of COVID-19 with artemisinin are needed.

5 Respiratory support

(1) Standard oxygen therapy

Patients with hypoxemia (PaO_2 <60 mmHg or SpO_2 ≤93% when breathing air at sea level) should be administered standard oxygen therapy immediately. Standard oxygen therapy devices include nasal cannula, mask, venturi mask, and non-rebreathing mask with a reservoir bag. The initial oxygen flow rate should be set to 5 L/min and then titrated to maintain SpO_2 at 94–98% (at least 95% for pregnant women). However, the SpO_2 of patients with a history of chronic hypercapnia should be maintained at 90–92%. If there is no improvement or deterioration of hypoxemia after 1–2 h with the oxygen flow rate >10 L/min, the therapy device should be immediately replaced with other respiratory support modalities.[55,56]

(2) High-flow nasal oxygen and noninvasive positive pressure ventilation

High-flow nasal oxygen (HFNO) treatment can be considered when standard oxygen therapy fails to relieve acute hypoxemic respiratory failure (PaO_2/FiO_2 ≥150 mmHg to <300 mmHg) and/or dyspnea. However, HFNO is not recommended for patients with hemodynamic instability, multiple organ failure, unconsciousness, or severe carbon dioxide retention (pH <7.3).[57] After administering HFNO treatment, patients should be closely monitored for 1–2 h. If the clinical condition does not improve or continues to deteriorate (i.e., SpO2 >90%

cannot be maintained with fraction of inspired oxygen [FiO$_2$] exceeds 0.5), a short-term noninvasive ventilation (NIV) trial or endotracheal intubation can be considered.[58,59]

Patients with no indication for tracheal intubation and PaO$_2$/FiO$_2$ >150 mmHg can be supported with NIV treatment for 1–2 h. If respiratory distress and hypoxemia do not improve or continue to worsen (i.e., SpO2 >90% cannot be maintained with FiO2 >60% and positive end-expiratory pressure [or continuous positive airway pressure] >8 cmH2O), NIV treatment should be replaced with invasive positive pressure ventilation immediately.

(3) Invasive positive pressure ventilation

If patients have refractory respiratory failure or if noninvasive respiratory support results in poor airway protection ability or hemodynamic instability, endotracheal intubation should be performed immediately with invasive positive pressure ventilation[60].

(i) Low tidal volume ventilation: Low tidal volume (4-8 ml/kg predicted body weight [PBW]) and low plateau pressure (<30 cmH2O) ventilation are strongly recommended. The initial tidal volume can be set to 6 ml/kg, which can be increased to 8 ml/kg; however, plateau pressure should be maintained at <30 cmH2O.[59,61]

(ii) Positive end-expiratory pressure (PEEP): It is recommended to titrate PEEP levels based on lung recruitability and PaO$_2$/FiO$_2$.[62] For patients with lower lung recruitability, especially when pulmonary fibrosis or organizing pneumonia occurs in the late course of COVID-19, a low PEEP setting is recommended.

(iii) Prone position ventilation: For patients with severe acute respiratory distress syndrome (ARDS; PaO$_2$/FiO$_2$ <100 mmHg), prone ventilation is strongly recommended for a duration of at least 12 h.[63]

(iv) Muscle relaxants: For patients with moderate-to-severe ARDS (PaO$_2$/FiO$_2$ <150 mmHg), muscle relaxants should not be routinely administered. When patients have severe respiratory distress, patient-ventilator asynchrony, or excessive respiratory drive, a short-term use of muscle relaxants (e.g., rocuronium bromide, cisatracurium) may be considered with sufficient sedation and analgesia. When the patient's condition improves, muscle relaxants and sedatives should be reduced or discontinued in a timely manner.

(v) Recruitment maneuver (RM): RM is primarily used as a rescue therapy for patients with refractory hypoxemia. RM cannot be routinely used in mechanically ventilated patients with ARDS. High-level continuous positive airway pressure (35–40 cmH$_2$O, maintained for 40 s)

and pressure-controlled ventilation methods (inspiratory pressure 10–15 cmH2O, PEEP 25–30 cmH2O, maintained for 1–2 min) are commonly used to implement RM. Excessive levels of RM (maximum airway pressure of 60 cmH_2O, 2 min) can worsen the prognosis of patients with ARDS, especially in patients with hemodynamic instability.[64]

(4) Extracorporeal membrane oxygenation

In view of the potential reversibility of COVID-19, extracorporeal membrane oxygenation (ECMO) should be considered when the traditional standard treatment (protective ventilation of tidal volume (Vt) 6 ml/kg, plateau pressure <30 cmH2O, PEEP ≥10 cmH2O, lung recruitment, prone ventilation, muscle relaxants, etc.) does not result in significant improvement. ECMO should be applied according to the following guidelines:(i) PaO_2/FiO_2 <100 mmHg or alveolar-arterial oxygen partial pressure difference [P (A-a) O2] >600 mmHg; (ii) frequency of ventilation >35 times/min while pH <7.2, and plateau pressure >30 cmH_2O; (iii) patient age <70 years; and (iv) mechanical ventilation duration <7 days.

ECMO can also be considered if one of the following conditions is met: (i) PaO_2/FiO_2 <50 mmHg for >3 h; (ii) PaO_2/FiO_2 <80 mmHg for >6 h; or (iii) arterial blood pH <7.25 accompanied by partial pressure of carbon dioxide ($PaCO_2$) >60 mmHg for >6 h.[65]

Early application (PaO_2/FiO_2 100–150 mmHg) of ECMO in the treatment of ARDS is beneficial for reducing respiratory drive, reducing inflammation of the lungs and the whole body, and avoiding severe impairment of the lung and other organ functions.[66,67] For some young patients who tend to respond well to treatment, if there are neither other organ failures or other serious lung infections, early treatment with "awake ECMO" can be cautiously considered.[68,69] Veno-venous ECMO (VV-ECMO) is the primary choice. If there is obvious myocardial impairment, venous-arterial ECMO can be considered. Early tracheotomy can improve airway management and can be safely performed under deep sedation and muscle relaxation and with strict personal protective equipment. To reduce the risk of tracheotomy bleeding, early tracheotomy can be performed prior to establishing ECMO. In view of the need for expertise and the high risk of complications, an ECMO center should be established and managed by an experienced team.

6 Blood purification

Acute kidney injury (AKI) may occur in patients with severe COVID-19, and the various

causes of renal injury should be actively monitored and corrected. Approximately 25–30% of critically ill COVID-19 patients will develop septic shock and multiple organ failure. Severe hypoxemia and/or systemic inflammatory response contribute to these complications.

AKI develops in 3–9% of patients with severe COVID-19.[70] There are many underlying causes of AKI, including hypovolemia, insufficient renal perfusion caused by low mean arterial pressure, or direct kidney damage caused by infections or drugs. The cause should always be determined and corrected to reduce renal injury.[1,2,36,71,72] For the treatment of AKI, refer to the "2012 Clinical Guidelines of Kidney Disease: Improving Global Outcomes (KDIGO)"[73] and the "2016 International Guidelines for Management of Sepsis and Septic Shock".[74]

In severe cases of COVID-19, the severity of AKI should be assessed following the KDIGO guidelines, and a blood purification treatment should be performed if necessary. There are multiple methods of blood purification, such as renal replacement therapy, blood/plasma perfusion, adsorption, and plasma exchange. There are multiple objectives of blood purification in the treatment of severe COVID-19, including (1) removing metabolites (creatinine, urea, etc.) and removing various inflammatory mediators by convection, adsorption, or plasma exchange to reshape immune homeostasis; (2) regulating volume status, correcting fluid overload, and helping maintain hemodynamic stability in severe cases; (3) correcting electrolyte and acid-base balance disorders and maintaining hemostasis; (4) controlling hyperthermia; and (5) regulating fluid overload status in combination with ECMO. Of note, hemoadsorption can be used to remove inflammatory cytokines.

Four major steps should be followed when performing blood purification to treat severe COVID-19: (1) assess whether the patient needs blood purification; (2) select the blood purification mode; (3) monitor and adjust parameters during the treatment process; and (4) determine when to stop performing blood purification.

7 Nutrition support

Evidence-based and rational nutritional treatment plays a critical role in the recovery and prognosis of patients with severe COVID-19. COVID-19 can progress to ARDS owing to

infection, fever, and other causes, which places patients in a high catabolic state and leads to nutritional metabolic disorders. For nutritional risk assessment of patients with COVID-19, the Nutrition Risk Screening (NRS-2002) or modified Nutrition Risk in the Critically Ill (NUTRIC) scoring tool[75] should be used. An NRS-2002 score of ≥3 suggests that patients are at a risk of malnutrition, and nutrition intervention is required. In cases with an NRS-2002 score ≥5 or modified NUTRIC score ≥5, nutritional therapy should be administered as soon as possible.

The "Expert Advice on the Medical Nutrition Treatment for COVID-19 Patients"[76] recommends the implementation of a five-stage method for nutrition therapy that includes diet with nutrition education, oral nutrition supplements, enteral nutrition (EN; i.e., tube feeding), supplemental parenteral nutrition, and total parenteral nutrition. EN should be initiated within 48 h for patients who cannot eat independently. For patients with contraindications for oral eating or EN, parenteral nutrition (PN) should be started within 3-7 days.[75]

To avoid overfeeding patients with severe disease, EN and PN should gradually reach the target feeding amount within 3−7 days. The mainstream guidelines at home and abroad and the "Novel Coronavirus Pneumonia Quick Guide" recommend 20–30 kcal.kg^{-1}.d^{-1} of caloric intake and state that the target energy should be reached as soon as possible according to the severity of the disease.[77] For patients with severe COVID-19, the recommended target feeding amount is 25–30 kcal.kg^{-1}.d^{-1}. A relatively high protein proportion is recommended according to the latest version of the National Health Commission's "Diagnosis and Treatment Protocol for Severe and Critically Ill COVID-19 Cases (Trial Second Version),[78]" the recommended protein intake is 1.5–2.0 g.kg^{-1}.d^{-1} (nitrogen 0.25–0.33 g.kg^{-1}.d^{-1}) to increase the supply of branched chain amino acids and promote protein synthesis.[1] In cases with insufficient protein intake, supplemental protein powder is recommended.

For patients with noninvasive ventilation (NIV), it is recommended to temporarily switch to a nasal mask or nasal high-flow oxygen therapy during meals to reduce the risk of hypoxemia during eating. The "button" mask is recommended for patients on NIV because this type of mask has a gastric tube outlet, which does not affect the efficiency of NIV and is more conducive to uninterrupted implementation of EN. If patients on NIV have severe flatulence, post-pyloric feeding is recommended. For patients with invasive mechanical

ventilation or ECMO, if there are no contraindications, EN should be initiated as early as possible. The stomach is the preferred EN channel. Critically ill patients with jejunal feeding and proton pump inhibitors often experience malabsorption of vitamin B$_{12}$; thus, vitamin B$_{12}$ should be supplemented.[78]

8 Venous thromboembolism prophylaxis and treatment

Patients with COVID-19 often have abnormal coagulation,[2,36] especially in severe and critically ill cases.[2,3] All patients with severe COVID-19 are at a risk for venous thromboembolism (VTE), and VTE prophylaxis should thus be considered if there are no contraindications.

Bleeding risk should be comprehensively evaluated before taking preventive measures, including assessment of basic diseases, laboratory tests (blood coagulation function, platelet, liver and kidney function, etc.), other medication, and invasive procedures.

For patients with severely and critically ill COVID-19 who have a low risk of bleeding, subcutaneous injection of low-molecular-weight heparin (LMWH) is the first-line recommendation for VTE prevention.[4,16] Most patients can receive LMWH 3,000 U or 4,000 U once per day. The dose should be adjusted based on the specific condition of the patient. As LMWH is eliminated via the kidney, the patient's renal function should be carefully monitored. LMWH should be administered with caution to patients with renal impairment. In such cases, dose adjustment should be based on anti-factor Xa activities, which should be closely monitored. Patients with severe renal dysfunction can receive a subcutaneous injection of unfractionated heparin at a dose of 5,000 U twice daily. The dose can be adjusted based on the specific condition of the patient.

Drug prevention and/or mechanical prevention are recommended for critically ill COVID-19 patients in the ICU. For patients receiving ECMO support with heparinized saline solution, additional pharmacological prophylaxis is not required and thus should be avoided to minimize the risk of bleeding.

The administration of heparin may lead to heparin-induced thrombocytopenia (HIT). For patients with thrombocytopenia or those who develop HIT during the administration of heparin, other anticoagulant drugs, such as argatroban, bivalirudin, fondaparinux sodium, and rivaroxaban, should be used.

In the event of bleeding or coagulation abnormalities, which may occur following the administration of anticoagulant drugs for VTE prevention, drug administration should be immediately stopped, and appropriate actions should be taken. Moreover, preventive treatments should be adjusted dynamically based on changes in bleeding risks. Drug prevention should be conducted throughout the entire ICU stay or until the risk factors have been eliminated. For patients with a high risk of bleeding, intermittent pneumatic compression may be considered.

Dynamic monitoring of changes in patient condition is required for moderately, severely or critically ill, and discharged patients. In particular, deep venous thrombosis (DVT) may occur in patients who are bedridden for more than 3 days, and such patients should be monitored for asymmetrical pain, unilateral or bilateral swelling or discomfort of the lower limbs, localized swelling of the extremities, or superficial venous filling in patients with central venous catheterization. Pulmonary thromboembolism (PTE) may manifest as chest pain, hemoptysis, dyspnea, hypoxemia, decreased blood pressure, or other unexplained clinical manifestations.[79] When clinical suspicion of DVT or PTE is high, the diagnosis should be based on bedside examinations (lower limb venous ultrasound and echocardiography). If the protective conditions allow, it is recommended to perform CT pulmonary angiogram (CTPA) to exclude PTE.

When patients with COVID-19 are diagnosed with DVT or PTE or there is a high suspicion of VTE based on clinical judgment, anticoagulant therapy should be initiated in cases without contraindications. Parenteral anticoagulation drugs are recommended in consideration of adverse reactions from various drug interactions. Platelet count and renal function level should be carefully monitored during anticoagulation treatment. If the D-dimer level continues to increase, the underlying cause should be determined, and the anticoagulation strategies should be adjusted in a timely manner.[1,80]

Throughout the entire period of COVID-19 diagnosis and treatment, thrombolytic therapy or other therapies for cardiopulmonary support (such as ECMO) can be initiated with full informed consent from the patient. This would be appropriate in cases where the condition suddenly worsens and high-risk factors for PTE, such as hypotension or sudden cardiac arrest, are present. Additionally, bedside echocardiography can identify the new onset of increased right-ventricular load or pulmonary arterial hypertension that cannot be explained by the

primary pneumonia. Shock or sudden cardiac arrest caused by other conditions should also be excluded.

VII Rehabilitation and health management for patients with COVID-19

1 Rehabilitation

Respiratory rehabilitation guidance can be provided for patients in quarantine through audio, video, brochures, or remote consultations. Discharged patients who are released from isolation can be provided with various forms of comprehensive rehabilitation treatment appropriate to the types of dysfunction experienced by the patient.[81] Evaluation and monitoring should be performed throughout the rehabilitation period, and indications and contraindications should be strictly followed.

(1) Patients with mild COVID-19 have mild clinical symptoms that may be accompanied by psychological problems such as fear and anxiety.[1,82] Relevant knowledge about the prevention and control of COVID-19 should be actively shared with patients. Countermeasures and ways of asking for help if the condition worsens[30] should be explained, and patients who smoke should be encouraged to quit smoking. Psychological interventions should be provided using manuals, audio, and video for psychological counseling.[82] Patients should be instructed to perform low-intensity exercise, preferably at an intensity that does not induce fatigue the following day.[81]

(2) Patients with general COVID-19 have decreased muscle strength, sputum clearance disorder,[81] and increased risk of thrombosis[79] owing to reduced activity; these patients can also experience psychological problems such as anxiety and depression.[83] It is important to ensure that the airway remains unobstructed during rehabilitation interventions, and thoracic expansion exercises can support sputum clearance. The intensity of daily exercise should be maintained between rest [1.0 metabolic equivalents (METs)] and light physical activity (<3.0 METs) with a duration of 15–45 min; intermittent exercise can also be performed.[81] The types of rehabilitation, such as respiratory rehabilitation exercises or simple Taijiquan or Baduanjin, can be based on the patient's preference. Because COVID-19 may become severe in 3–5% of patients, any changes in vital signs during rehabilitation should be carefully monitored, and rehabilitation intervention and suspension guidelines should be strictly followed[2, 84].

(3) Respiratory and physical dysfunction may occur in critically ill patients. In such cases, the underlying causes of hypoxia and physical injury should be determined. Early rehabilitation can help reduce complications, prevent and improve dysfunction, reduce disability, and improve patient's quality of life. Refer to the "Respiratory Rehabilitation Guidance for 2019 Novel Coronavirus Pneumonia (Second Edition)" for appropriate timing of rehabilitation interventions. SARS-CoV-2 can attack multiple organs, systems, and tissues, causing varying degrees of lung consolidation, mucus, and mucus plug formation in the bronchial cavity.[1] Critically ill patients often develop systemic infection, shock, and multiple organ dysfunction syndrome owing to extremely low or progressively reduced immunity.[10]

There are four primary rehabilitation measures: (i) Airway clearance management[81]: Use intra-airway vibration or oscillatory-positive expiratory pressure. (ii) Postural management and early activities[85]: Implement anti-gravity posture and progressive active and passive activities. For patients with ARDS, ventilate in a prone position for more than 12 h per day. (iii) Muscle retraining[86]: Use neuromuscular electrical stimulation, peripheral muscle strength training, and respiratory muscle strength training. (iv) Prevention of venous thrombosis of the lower limbs: Use compression socks, ankle pump exercises, etc. During the respiratory rehabilitation process, ensure the safety of pipelines, circuits, and equipment, and prevent adverse events such as falls.

(4) There are several rehabilitation considerations for patients after discharge. Patients recovering from severe disease may experience a certain degree of cognitive, mental, and physical dysfunction[87] and may find it difficult to adapt to family and social life. A personalized rehabilitation plan should be developed based on a comprehensive assessment of the patient's respiratory function, exercise ability, activities of daily living (ADL), anxiety, depression, cognitive abilities, and other key factors. The plan should include aerobic training, skeletal muscle strength training (peripheral and respiratory muscles), guidance for performing ADL, and nutrition and psychological support. Remote online management may be used.

2 Health management

Patients with COVID-19 should be kept in isolation for 14 days of medical observation, with careful health management and rehabilitation after recovery and discharge.[88] Short-term

health management should address typical symptoms, including fever, cough, sputum, shortness of breath, chest tightness, and activity tolerance. For formerly critically ill patients with significant residual pulmonary fibrosis lesions, daily monitoring of oxygen levels using a pulse oximeter is recommended, especially during physical activity. If the patient had hypoxemia, oxygen therapy should be administered. If the patient has chronic diseases, ensure that the underlying diseases are stabilized.

Mid- and long-term health managements primarily target recovered patients with severe and critical pneumonia and recovered COVID-19 patients with chronic diseases such as diabetes mellitus, hypertension, chronic obstructive pulmonary disease, asthma, bronchiectasis, and cancer. Careful follow-up and management of such patients can improve rehabilitation results. Quality of life assessment and lung function and chest imaging examinations can be performed to determine potential lung injury caused by severe COVID-19.

The implementation of a health management plan requires the close cooperation of specialized public health institutions, such as designated hospitals, isolation locations, medical rehabilitation institutions, centers for disease prevention and control, and primary medical institutions.[89] Exploring monitoring and follow-up options with an online-offline integration and linkage of medical institutions at all levels is necessary to cope with short-term increases in health management medical service needs.

VIII Prevention of COVID-19

SARS-CoV-2 is highly infectious, and preventing healthcare-associated infections caused by SARS-CoV-2 in medical institutions is critical for protecting patients and medical workers and eventually ending the pandemic. Infection prevention and control in medical facilities should begin with controlling the source of infection, cutting off transmission routes, and protecting susceptible populations.[90]

1 Controlling the source of infection

The primary known source of SARS-CoV-2 infection is patients with COVID-19. Asymptomatic cases can also be a source of infection. Early detection, early reporting, early isolation, and early treatment of the source of infection (referred to as the "four earlies") are key strategies

to reduce the outbreak of healthcare-associated infections. Medical institutions should carefully adhere to the "Administrative Measures for the Pre-examination and Triage of Infectious Diseases in Medical Institutions" guidelines.

First, the entrance of patients to medical institutions should be controlled, and standardized pre-examination triage points should be established in outpatient and emergency departments. Imaging and laboratory testing of suspected COVID-19 cases should be performed as early as possible; this can be achieved by focusing on relevant clinical manifestations, epidemiological history, and temperature monitoring. Screening time and diagnosis of suspected patients should be expedited, isolation measures should be implemented quickly, and the time between diagnosis and hospitalization should be shortened to achieve the "four earlies."

Medical institutions that are second-tier and above should establish independent fever clinics and observation areas, with obvious signs to distinguish these areas from ordinary outpatient and emergency departments. Fever clinics should be divided into three areas: clean area, potentially polluted area and/or buffer zone, and polluted area. The doctor-patient channel should be organized separately, and the area should be well ventilated. A one-way flow from the clean area to the polluted area should be maintained, air cleaning and disinfection facilities should be provided, and negative pressure wards should be arranged if possible.

Second, patient admission to hospitals and the management of inpatients, escorts, and visitors should be improved. Medical institutions should formulate screening procedures for patient admission during the pandemic in accordance with the risk level of the country and region. Routine blood tests, chest CT screening, and screening for the novel coronavirus nucleic acid with nasopharyngeal swabs should be performed if necessary. Screening of confirmed cases, suspected cases, patients with fever symptoms, and close contacts should be strengthened, and a transition ward can be set up for newly admitted patients. Patients should be treated in a single room before SARS-CoV-2 infection is ruled out, after which they should be transferred to a conventional ward for further hospitalization. A space of more than one meter should be maintained between beds in the general ward to reduce the potential risk of cross-infection in the hospital. Escorts and visitors should also be screened and managed as necessary.

Third, proactive monitoring of nosocomial infections in hospitalized patients is essential, as is establishing health monitoring and a mandatory reporting system for all members of the hospital personnel (including all medical, nursing, management, logistics, cleaning, security, delivery, and other staff). Active monitoring of fever, respiratory symptoms, and chest imaging can promptly detect cases of sporadic infections, clustered infections, and suspected infections, allowing for appropriate and timely investigations and preventive measures.

2 Preventing transmission

SARS-CoV-2 may have several transmission routes, and the current understanding of these routes continues to evolve. Initially, the virus was understood to be transmitted via respiratory droplets and close contacts. Since then, the possibility of aerosol transmission via prolonged exposure to high concentrations of virus aerosols in a relatively closed environment has been discovered. As stated in "Novel Coronavirus Pneumonia Diagnosis and Treatment Plan (Trial Version 7)", SARS-CoV-2 can be isolated from fecal and urine samples, and thus, the possibility of aerosol or contact transmission from environmental pollution caused by feces and urine should be further investigated. A key strategy for controlling nosocomial infection is to take all necessary measures to reduce droplet spray, avoid contact between infectious and clean sources, and prevent airborne transmission. In general, the highest level of prevention and control should be applied when a novel infectious disease with unknown origin appears.

The easiest, most effective, most convenient, and most economical method for controlling hospital infections is hand hygiene. Every person who enters a medical institution, regardless of who they are or their purpose, must adhere to appropriate hand hygiene practices. Medical institutions should be equipped with adequate hand hygiene facilities, including sinks, non-contact faucets, hand sanitizers, and hand drying facilities. Fast-acting alcohol and hydrogen peroxide-based hand disinfectants should be widely available during the COVID-19 pandemic. Medical staff in particular must improve hand hygiene compliance. It is important to note that wearing gloves cannot replace hand hygiene.[91]

Daily cleaning and disinfection of environmental surfaces must be enforced, particularly in terms of disinfection frequency of high-frequency contact surfaces (i.e., handles, computer

keyboards, instrument panels). According to the "Technical Specifications for Disinfection of Medical Institutions (WA / T367.2019)," an appropriate disinfectant should be selected, and the product instructions for concentration and contact time should be adhered to. Indoor ventilation and mechanical ventilation should be reinforced if necessary. 'No-touch' disinfection methods, such as ultraviolet light devices or hydrogen peroxide systems, can be implemented to reduce the cleaning workload of hospital staff. In principle, centralized air conditioning and ventilation systems should be suspended during an epidemic for increased prevention and control. If it is necessary to open the centralized air conditioning ventilation system, the air return valve should be completely closed, and the fresh air valve should be completely opened to increase the fresh air volume in the system. The corresponding exhaust system should also be turned on, and the air return port should be equipped with a nanometer or high-intensity ultraviolet lamp and other disinfection devices for centralized air conditioning ventilation systems. All components of the centralized air conditioning ventilation system should be regularly cleaned and disinfected, and components should be replaced once per month and again after the pandemic has ended.

The proper use of masks plays a very important role in preventing the spread of droplets. Each person entering a medical institution must wear a mask. Confirmed or suspected COVID-19 patients should not wear masks with exhalation valves. In addition, respiratory hygiene/cough etiquette and maintaining a safe social distance are important measures to prevent droplet transmission.

During the pandemic, hospitals should strengthen management, inspection, and operation of activities that may generate aerosol and droplets. For example, pulmonary function tests should be avoided as much as possible. Portable lung function testing machines can help reduce cross-infection and are also convenient for the online diagnosis and treatment of patients in their home. The cleaning and disinfection of pipes, valves, and interfaces of lung function instruments should be performed in accordance with the specifications outlined in the "Technical Specifications for Disinfection of Medical Institutions (WA / T367.2019)." Bronchoscopy should only be performed when strictly necessary; if it is not urgently needed, the operation should be postponed. Cough relief and sedatives should be used during examinations to reduce droplet spray.

It is mandatory that the hospital logistics department strictly implements sewage system

disinfection measures in accordance with relevant national regulations. Directly discharging sewage or discharging sewage without meeting national standards is strictly forbidden. Disposing or dumping solid infectious waste and various chemical waste liquids into the sewer is strictly forbidden.[20] The treatment of medical waste should also be carefully managed during the epidemic. Medical waste generated by patients diagnosed with or suspected to have COVID-19, including the domestic waste of these patients, should be managed as infectious medical waste and strictly disposed in accordance with relevant regulations.[21]

3 Protecting susceptible populations

COVID-19 is a novel infectious disease, and thus, all populations are susceptible. However, the susceptible populations that are protected by hospital infection prevention and control measures in this epidemic are atypical. In addition to patients presenting to the hospital for treatment and hospitalization, medical staff are also at a high risk of infection, especially front-line personnel who have close contact with patients and patient body fluids, secretions, and excreta. Each medical institution should formulate emergency plans and operating procedures according to real-world conditions of their hospitals and national laws, regulations, industry norms, and guidelines during the epidemic. In addition to areas such as fever clinics and isolation wards, personalized diagnosis/treatment procedures and emergency plans should be developed for all clinical departments and imaging medicine, ultrasound, radiotherapy, and hemodialysis departments.

While medical institutions routinely conduct active surveillance of nosocomial infections, the prevention of infections in key populations is of particular importance. Such populations include pregnant women, patients in emergency departments, critically ill patients, patients with acute cardiovascular and cerebrovascular diseases, patients on hemodialysis, and patients with malignant tumors. Vigilance is especially important in invasive procedures, such as surgery and endoscopic diagnosis and treatment.

Medical institutions should strengthen resource allocation and institutional capabilities for developing specialized and part-time personnel in infection control. Funding of infection control should be ensured at all levels, management of infection control should be implemented at all levels, and all medical staff should become an infection control

practitioner. The layout and workflow of key departments should meet the requirements of relevant technical standards and specifications, and all departments should be equipped with the necessary safeguards to provide medical staff with a safe working environment and good personal hygiene conditions.

Training on infection control knowledge and occupational protection for all members of the hospital should be provided, and no medical staff should be allowed to work without training qualifications. All medical personnel should strictly implement standard prevention measures, particularly regarding bi-directional protection. Medical personnel should select protective equipment that is appropriate for the inherent risks of diagnostic and treatment operations. In any situation where medical staff may come into contact with patients' blood, body fluids, or secretions or situations in which aerosols may be generated, protective equipment (e.g., goggles, protective face shields, isolation clothing, and medical protective masks) should be worn. Additionally, medical staff should master the method and sequence of putting on and removing protective equipment. Medical institutions should establish a special working group for material management, referring to relevant national standards[92] such as the "Technical Guide of Protection for Medical Staff during the Novel Coronavirus Pneumonia Epidemic (Trial)" (National Health Office Medical Letter (2020) No. 155) and should rationally allocate resources, formulate protection level requirements according to exposure risks, and ensure that the quality and quantity of protective equipment are maintained throughout the hospital.

To reduce risks inherent to gatherings of medical staff and occupational exposure, medical institutions should implement the use of modern information methods, such as remote consultation, cloud imaging, and video conferencing. Medical staff should minimize social interactions, and work hours should be organized to avoid infection caused by decreased immunity from overwork. Medical institutions should implement interventions to support the physical and mental health care of medical personnel involved in key activities, such as those working in fever clinics, triage and admission of suspected and confirmed patients, and observation wards; additionally, living arrangements close to the hospital should be arranged for medical staff.

IX Integrated Chinese and Western medical treatment

COVID-19 belongs to the "epidemic disease" category of traditional Chinese medicine. The syndrome elements are "wet, poison, cold, heat, stasis, and deficiency." The pathogenic characteristics of wet evil are prominent, and the main disease characteristics are observed in the "lung" and "spleen". The treatment is different according to the incubation period, disease period (mildly, moderately, severely and critically ill), and recovery period. Disease differentiation and syndrome differentiation (including cold-damp constraint in the lung pattern, damp-heat accumulation in the lung pattern, epidemic toxin blocking the lung pattern, internal blockage and external desertion pattern, lung-spleen qi deficiency pattern, deficiency of both qi and yin patterns) should be combined in the treatment.[1,93-97] Traditional Chinese medicine injections, which can be used in combination, should be used according to the patients' situation.

X Medical treatment systems and social mobilization

When an epidemic occurs, the entire society must be mobilized to create a complete and efficient medical treatment system. Of vital importance to the coordinated response for emerging and rapidly spreading respiratory infections is the activation of the primary medical system; improvement of the comprehensive prevention and treatment capacities of county hospitals; and mobilization of a coordinated system for the respiratory and critical care medicine department, the infectious disease department, the clinical microbiology department, and a comprehensive critical care department.

Grass-roots medical institutions are the front-line defense in an epidemic and play a joint role in prevention and control. These institutions are the most effective defense against external anti-input and internal anti-proliferation. In the prevention and control of the COVID-19 epidemic, primary-level medical institutions must consider overall planning. In addition to epidemic prevention and control, these institutions must successfully manage daily diagnosis and treatment, family doctor contracting, and basic public health services, among other roles, to ensure the continuity of basic health services for urban and rural residents, as well as to play the dual role of "gatekeepers" of residents' health and "net bottom" of the COVID-19 epidemic.[98]

The role of grass-roots medical institutions includes (1) strengthening outpatient pre-screening and triage screening and perform early detection, early reporting, and isolation referral for patients with fever, suspected patients, and clustered cases of families; (2) organizing grid-based carpet-style management of urban and rural communities, including follow-up and isolated medical observations of close contacts of patients, as well as follow-up of discharged patients; and (3) attending to the basic health and medication needs of key populations in the relevant jurisdiction, particularly those of pregnant women, children, elderly adults, and patients with chronic diseases, such as hypertension, chronic obstructive pulmonary disease, diabetes mellitus, etc., and for these populations, health education, health management, prevention, rehabilitation, and psychological counseling should be provided. Follow-up services can be provided through several communication modes such as telephone, text messages, WeChat, video, or regional health cloud app. For patients with chronic diseases, policies such as long-term prescriptions and extended prescriptions should be implemented.[99-101]

County-level hospitals are another frontier and an important battlefield in the prevention and control of the COVID-19 epidemic, playing a vital role in disease prevention at the county level. However, the deficiencies of county-level hospitals are particularly prominent, including the lack of discipline system construction, a talent shortage in the departments of respiratory and critical medicine and infectious diseases, and a limited capacity to respond to infectious disease outbreaks. Through platform organizations, such as the National Medical Union for Respiratory Diseases, the National Telemedicine and Internet Healthcare Center, and the Chinese Alliance for Respiratory Disease in Primary Care, it is possible to open communication and resource channels between county-level hospitals and provincial and national hospitals. For early detection and diagnosis of severely and critically ill patients, it is necessary to leverage the advantages of internet medical care, to refine the consultation network between provincial designated hospitals and municipal designated hospitals, and to achieve full coverage of city-level expert consultations for confirmed cases and provincial expert consultation for severe cases. In addition, an efficient clinical microbiology department must be developed to provide technical support for rapid diagnosis, timely

admission, and isolation.[99]

XI Fangcang Shelter Hospital

Fangcang shelter hospitals ("Fangcang hospitals") are temporary hospitals located in large public facilities (i.e., exhibition centers, stadiums) that can provide isolation, monitoring of disease progression, and medical care or other services for patients with mild-to-moderate COVID-19. The construction of Fangcang hospitals can alleviate medical pressure from designated treatment hospitals and can allow for rapid admission and treatment of confirmed cases.[102] The establishment of these hospitals is a key move in compliance with China's strategic policy of "leaving no patients unattended" and "leaving no patients untreated" and has played a vital role in combating the COVID-19 outbreak.

The main functions of Fangcang hospitals are as follows: (1) Isolation: Interpersonal contact with COVID-19 patients can result in community transmission.[103,104] Admitting confirmed patients into Fangcang hospitals can significantly reduce community transmission. (2) Treatment: Medical care that conforms to the disease characteristics can be administered to the admitted patients (patients with mild and moderate COVID-19).[105] (3) Monitoring: Fangcang hospitals can admit and treat patients with mild-to-moderate COVID-19, closely monitoring each patient's condition, providing early identification of patients with complications or disease progression, and transferring such patients to designated hospitals for further treatment.

There are several required features of Fangcang hospitals: (1) Large capacity: Fangcang hospitals are converted from large public facilities such as exhibition centers and stadiums and can accommodate a large number of beds to quickly admit and treat confirmed COVID-19 patients. (2) High speed: The construction of Fangcang hospitals can be efficiently completed in a very short time; the construction steps include creating wards, dividing infection control areas into separate zones (polluted zone, buffer zone, clean zone), and establishing basic medical facilities. (3) Low cost: Fangcang hospitals make full use of existing resources using large public facilities. Additional required resources include bedplates,

partitions, bedside tables, and other basic items, as well as resources for establishing basic facilities such as temporary toilets and wash basins. Other costs are also lower or at least are not higher than costs of ordinary hospitals. (4) Clinical function zones: The functional zones include a ward department, radiological examination department, laboratory examination department, and viral nucleic acid detection department. Each Fangcang hospital can organize clinical functional zones according to the surrounding medical resources and specific needs of each hospital.

There are several basic operating rules of Fangcang hospitals.

(1) Admission criteria: (i) Confirmed COVID-19 case (mild or moderate); (ii) ability to walk and live independently; (iii) no serious chronic diseases, including hypertension, diabetes, coronary heart disease, malignancy, structural lung disease, pulmonary heart disease, or immunosuppression; (iv) no history of mental health disorders; (v) age <65 years; (vi) no influenza virus infection; and (vii) SpO_2 >93% and respiratory rate <30 breaths/min in a resting state.

(2) Monitoring and transfer: Patients' vital signs and SpO_2 should be closely monitored to identify potential severely and critically ill patients at an early stage. If a patient's disease condition progresses rapidly or fulfills the diagnostic criteria for severely or critically ill patients, the patient should be transferred to a designated hospital for appropriate and timely treatment.

(3) Prevention of cross-infection: All patients in Fangcang hospitals must wear masks; staff members must wear comprehensive personal protective equipment in the ward environment.

(4) Community management: Fangcang hospitals are essentially a small community of patients with mild-to-moderate COVID-19. Considering the large number of patients gathered in one location, it is necessary to monitor patients' psychological conditions to prevent potential conflict. In addition, to enrich patients' quality of life, designated spaces such as reading corners and television areas can be established, and cultural activities can be organized.

The Fangcang hospital is a new model for responding to public health emergencies. The

promotion of this model will support the modernization of China's health care system and capacity for governance.

XII Focus of future research

1. The traceability of viruses, evolution of mutations, biological characteristics, and transmission routes should be investigated to provide a theoretical basis for the prevention and control of infectious diseases, vaccines, and drug development.

2. The mechanism by which SARS-CoV-2 damages target organs, including the mechanisms for the attack on immune cells and the reduction of lymphocytes, should be elucidated. As the lung is the first and main target organ of SARS-CoV-2, changes that occur in the pathology and pathophysiology of the lung should be assessed. In addition to studies of the lungs, research is needed on the pathogenesis of other important organs, including myocardial damage, liver and kidney damage, thrombocytopenia, and even the pathogenesis of viral encephalitis.

3. The law of disease progression for COVID-19, including risk factors specific to patients who progress from mild to severe and critical illness, risk factors for death, and related predictive disease models should be clarified.

4. Intervention measures and timing of implementation, including the efficacy of antiviral drugs, side effects, course of treatment, applicable population, timing, dosage course and adverse reactions of glucocorticoid use, and the timing, indications, and benefits of invasive mechanical ventilation and ECMO administration need to be clarified.

5. Research and development of antiviral drugs is needed, as well as the formulation of guidelines for conducting standardized, well-structured, clinical drug trials in emergency situations. New anti-coronavirus drugs should be developed based on an understanding of the biological characteristics of the virus. Existing drugs include lopinavir/ritonavir, radixivir, arbidol, chloroquine, and hydroxychloroquine. The efficacy and mechanism of traditional Chinese medicines against SARS-CoV-2 should also be clarified.

6. The shortcomings and risk points of the existing system should be elucidated, including investigations on how to improve the sensitivity and efficiency of the existing infectious disease reporting system and how to improve a coordinated ability to respond to major public health emergencies. Epidemic prevention and control are not limited to medical and

health systems but also require a comprehensive response. For example, stadiums and soccer fields that have been converted to medical treatment facilities, known as "Fangcang shelter hospitals," have played an important role in fighting against the COVID-19 epidemic. Planning ahead and integrating disaster preparedness into urban design and construction, such as anticipating a future need to transform large venues into temporary hospitals, are needed.

COVID-19 Chinese Thoracic Society (CTS) and Chinese Association of Chest Physician (CACP) Task Force:

Consultant committee:

Nan-Shan Zhong (Department of Pulmonary and Critical Care Medicine, the First Affiliate Hospital of Guangzhou Medical University, Guangzhou, Guangdong, China; Guangzhou Institute of Respiratory Diseases, Guangzhou, Guangdong, China; State key Laboratory of Respiratory Diseases, Guangzhou, Guangdong, China),

You-Ning Liu (Department of Pulmonary and Critical Care Medicine, The General Hospital of People's Liberation Army, Medical School of Chinese People's Liberation Army, Beijing, China);

Rong-Chang Chen (Shenzhen Institute of Respiratory Diseases, Shenzhen, Guangdong, China)

Writing committee (listed in alphabetic order by surname):

Bin Cao (Department of Pulmonary and Critical Care Medicine, China-Japan Friendship Hospital, Beijing, China),

De-Chang Chen (Department of Critical Care Medicine, Ruijin Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China),

Rong-Chang Chen (Shenzhen Institute of Respiratory Diseases, Shenzhen, Guangdong, China) ,

Hua-Ping Dai (Department of Pulmonary and Critical Care Medicine, China-Japan Friendship Hospital, Beijing, China),

Rong-Hui Du (Wuhan Pulmonary Hospital, Wuhan, Hubei, China),

Yi Hu (Department of Pulmonary and Critical Care Medicine, The General Hospital of Wuhan, Wuhan, Hubei, China),

Yi Huang (Department of Pulmonary and Critical Care Medicine, Changhai Hospital, Navy

Medical University, Shanghai, China),

Yang Jin (Department of Pulmonary and Critical Care Medicine, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei, China),

Qing-Quan Liu (Beijing Hospital of Traditional Chinese Medicine, Capital Medical University, Beijing, China),

Qing Miao (Xiyuan Hospital, China Academy of Chinese Medical Sciences, Beijing, China),

Zhi-Yong Peng (Department of Critical Care Medicine, Zhongnan Hospital of Wuhan University, Wuhan, Hubei, China),

Jie-Ming Qu (Department of Pulmonary and Critical Care Medicine, Ruijin Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China),

Yuan-Lin Song (Department of Pulmonary and Critical Care Medicine, Zhongshan Hospital, Shanghai Medical College, Fudan University, Shanghai, China),

Chao-Fu Wang (Department of Pathology, Ruijin Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China),

Chen Wang (Department of Pulmonary and Critical Care Medicine, Center of Respiratory Medicine, China-Japan Friendship Hospital, Beijing, China; National Clinical Research Center for Respiratory Diseases, Beijing, China; Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China; Institute of Respiratory Medicine, Chinese Academy of Medical Sciences, Beijing, China; Department of Respiratory Medicine, Capital Medical University, Beijing, China),

Jian-Wei Wang (NHC Key Laboratory of Systems Biology of Pathogens and Christophe Merieux Laboratory, Institute of Pathogen Biology, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China),

Yi-Min Wang (Department of Pulmonary and Critical Care Medicine, China-Japan Friendship Hospital, Beijing, China),

Jin-Fu Xu (Department of Respiratory and Critical Care Medicine, Shanghai Pulmonary Hospital, Tongji University School of Medicine, Shanghai, China),

Ting Yang (Department of Pulmonary and Critical Care Medicine, China-Japan Friendship Hospital, Beijing, China),

Zhen-Guo Zhai (Department of Pulmonary and Critical Care Medicine, China-Japan Friendship Hospital, Beijing, China),

Qing-Yuan Zhan (Department of Pulmonary and Critical Care Medicine, China-Japan Friendship Hospital, Beijing, China),

Ding-Yu Zhang (Wuhan Jinyintan Hospital, Wuhan, Hubei, China),

Jing Zhang (Department of Pulmonary and Critical Care Medicine, Zhongshan Hospital, Shanghai Medical College, Fudan University, Shanghai, China),

Wen-Hong Zhang (Department of Infectious disease, Huashan Hospital, Shanghai Medical College, Fudan University, Shanghai, China),

Hong-Mei Zhao (Department of Pulmonary and Critical Care Medicine, China-Japan Friendship Hospital, Beijing, China),

Jian-Ping Zhao (Department of Pulmonary and Critical Care Medicine, Tongji Hospital, Tongji Medical College of Huazhong University of Science and Technology, Wuhan, Hubei, China),

Min Zhou (Department of Pulmonary and Critical Care Medicine, Ruijin Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China),

Advisory committee (listed in alphabetic order by surname):

Chun-Xue Bai (Department of Pulmonary and Critical Care Medicine, Zhongshan Hospital, Shanghai Medical College, Fudan University, Shanghai, China),

Liang-An Chen (Department of Pulmonary and Critical Care Medicine, The General Hospital of People's Liberation Army, Medical School of Chinese People's Liberation Army, Beijing, China)

Jian Kang (The First Hospital of China Medical University, Shenyang, Liaoning, China)

Shi-Yue Li (Department of Pulmonary and Critical Care Medicine, The First Affiliated Hospital of Guangzhou Medical University, Guangzhou, Guangdong, China; Guangzhou Institute of Respiratory Diseases, Guangzhou, Guangdong, China)

Wei-Min Li (Department of Pulmonary and Critical Care Medicine, West China Hospital, Sichuan University, Chengdu, Sichuan, China)

Jiang-Tao Lin (Department of Pulmonary and Critical Care Medicine, China-Japan Friendship Hospital, Beijing, China)

Chun-Tao Liu (Department of Pulmonary and Critical Care Medicine, West China Hospital, Sichuan University, Chengdu, Sichuan, China)

Hua-Hao Shen (Department of Pulmonary and Critical Care Medicine, The Second Affiliated Hospital of Zhejiang University School of Medicine, Hangzhou, Zhejiang, China)

Yong-Jian Xu (Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei, China)

Secretary:

Xiao-Ying Gu (Department of Pulmonary and Critical Care Medicine, China-Japan Friendship Hospital, Beijing, China)

Yi-Hui Zuo (Department of Pulmonary and Critical Care Medicine, Zhongshan Hospital, Shanghai Medical College, Fudan University, Shanghai, China)

Conflicts of interest

None.

References

1. Novel Coronavirus Pneumonia Diagnosis and Treatment Plan (Trial Version 7). Beijing: National Health Commission of the People's Republic of China, 2020. Available from: http://www.nhc.gov.cn/yzygj/s7653p/202003/46c9294a7dfe4cef80dc7f5912eb1989/files/ce3e694 5832a438eaae415350a8ce964.pdf. [Accessed on March 3, 2020].

2. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395:497-506. doi: 10.1016/S0140-6736(20)30183-5.

3. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020;395:1054-1062. doi: 10.1016/S0140-6736(20)30566-3.

4. Notice of the National Health Commission on Amending the English Naming of New Coronavirus Pneumonia. Beijing: National Health Commission of the People's Republic of China,

2020. Available from:

http://www.nhc.gov.cn/yzygj/s7653p/202002/33393aa53d984ccdb1053a52b6bef810.shtml.

[Accessed on February 22, 2020].

5. Ren LL, Wang YM, Wu ZQ, Xiang ZC, Guo L, Xu T, et al. Identification of a novel coronavirus causing severe pneumonia in human: a descriptive study. Chin Med J (Engl) 2020; doi: 10.1097/CM9.0000000000000722.

6. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med 2020;382:727-733. doi: 10.1056/NEJMoa2001017.

7. Zhou P, Yang XL, Wang XG, Hu B, Zhang L, Zhang W, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature 2020;579:270-273. doi: 10.1038/s41586-020-2012-7.

8. Coronaviridae Study Group of the International Committee on Taxonomy of Viruses. The species Severe acute respiratory syndrome-related coronavirus: classifying 2019-nCoV and naming it SARS-CoV-2. Nat Microbiol 2020;5:536-544. doi: 10.1038/s41564-020-0695-z.

9. Ou X, Liu Y, Lei X, Li P, Mi D, Ren L, et al. Characterization of spike glycoprotein of SARS-CoV-2 on virus entry and its immune cross-reactivity with SARS-CoV. Nat Comm 2020;11:1620. doi: 10.1038/s41467-020-15562-9.

10. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med 2020. doi: 10.1056/NEJMoa2002032.

11. Xie C, Jiang L, Huang G, Pu H, Gong B, Lin H, et al. Comparison of different samples for 2019 novel coronavirus detection by nucleic acid amplification tests. Int J Infect Dis 2020;93:264-267. doi: 10.1016/j.ijid.2020.02.050.

12. Wang W, Xu Y, Gao R, Lu R, Han K, Wu G, et al. Detection of SARS-CoV-2 in Different Types of Clinical Specimens. JAMA 2020;doi: 10.1001/jama.2020.3786.

13. Special Expert Group for Control of the Epidemic of Novel Coronavirus Pneumonia of the Chinese Preventive Medicine Association. An update on the epidemiological characteristics of novel coronavirus pneumonia (COVID-19) (in Chinese). Chin J Epidemiol 2020;41:139-144. doi: 10.3760/cma.j.issn.0254-6450.2020.02.002.

14. Shanghai Clinical Treatment Expert Group for Coronavirus Disease 2019. Comprehensive treatment and management of coronavirus disease 2019: expert consensus statement from Shanghai (in Chinese). Chin J Infect Dis 2020;38. doi: 10.3760/cma.j.issn.1000-6680.2020.0016.

15. Wu C, Chen X, Cai Y, Xia J, Zhou X, Xu S, et al. Risk Factors Associated with Acute Respiratory Distress Syndrome and Death in Patients with Coronavirus Disease 2019 Pneumonia in Wuhan, China. JAMA Intern Med ,2020. doi: 10.1001/jamainternmed.2020.0994.

16. Lu J, Hu S, Fan R, Liu Z, Yin X, Wang Q, et al. ACP risk grade: a simple mortality index for patients with confirmed or suspected severe acute respiratory syndrome coronavirus 2 disease (COVID-19) during the early stage of outbreak in Wuhan, China. MmedRxiv 2020. doi: 10.1101/2020.02.20.20025510.

17. National Health Commission of the People's Republic of China. Protocol for diagnosis and treatment of influenza (2018 revised version) (in Chinese). Chin J Clin Infect Dis 2019;12:1-5. doi: 10.3760/cma.j.issn.1674-2397.2019.01.001.

18. Chinese Thoracic Society. Guidelines for the diagnosis and treatment of community-acquired pneumonia in Chinese adults (2016 edition) (in Chinese). Chin J Tubere Respir Dis 2016;39:253-279. doi: 10.3760/cma.j.issn.1001-0939.2016.04.005.

19. Coronavirus disease (COVID-2019) R&D. Geneva: World Health Organization, 2020. Available from: http://www.who.int/blueprint/priority-diseases/key-action/novel-coronavirus/en/. [Accessed on February 14, 2020].

20. Sheahan TP, Sims AC, Graham RL, Menachery VD, Gralinski LE, Case JB, et al. Broad-spectrum antiviral GS-5734 inhibits both epidemic and zoonotic coronaviruses. Sci Transl Med 2017;9. pii: eaal3653. doi: 10.1126/scitranslmed.aal3653.

21. Sheahan TP, Sims AC, Leist SR, Schäfer A, Won J, Brown AJ, et al. Comparative therapeutic efficacy of remdesivir and combination lopinavir, ritonavir, and interferon beta against MERS-CoV. Nat Commun 2020;11:222. doi: 10.1038/s41467-019-13940-6.

22. Mulangu S, Dodd LE, Davey RT Jr, Tshiani Mbaya O, Proschan M, Mukadi D, et al. A Randomized, Controlled Trial of Ebola Virus Disease Therapeutics. N Engl J Med 2019;381:2293-2303. doi: 10.1056/NEJMoa1910993.

23. Chen F, Chan KH, Jiang Y, Kao RY, Lu HT, Fan KW, et al. In vitro susceptibility of 10 clinical isolates of SARS coronavirus to selected antiviral compounds. J Clin Virol 2004;31:69-75. doi: 10.1016/j.jcv.2004.03.003.

24. Wu CY, Jan JT, Ma SH, Kuo CJ, Juan HF, Cheng YS, et al. Small molecules targeting severe acute respiratory syndrome human coronavirus. Proc Natl Acad Sci U S A 2004;101:10012-10017. doi: 10.1073/pnas.0403596101.

25. Chu CM, Cheng VC, Hung IF, Wong MM, Chan KH, Chan KS, et al. Role of lopinavir/ritonavir in the treatment of SARS: initial virological and clinical findings. Thorax 2004;59:252-256. doi: 10.1136/thorax.2003.012658.

26. Arabi YM, Alothman A, Balkhy HH, Al-Dawood A, AlJohani S, Al Harbi S, et al. Treatment of

Middle East Respiratory Syndrome with a combination of lopinavir-ritonavir and interferon-β1b

(MIRACLE trial): study protocol for a randomized controlled trial. Trials 2018;19:81. doi:

10.1186/s13063-017-2427-0.

27. Cao B, Wang Y, Wen D, Liu W, Wang J, Fan G, et al. A Trial of Lopinavir-Ritonavir in Adults

Hospitalized with Severe Covid-19. N Engl J Med 2020;doi: 10.1056/NEJMoa2001282.

28. Wang M, Cao R, Zhang L, Yang X, Liu J, Xu M, et al. Remdesivir and chloroquine effectively

inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Res 2020;30:269-271.

doi: 10.1038/s41422-020-0282-0.

29. Stevens MP, Patel PK, Nori P. Involving antimicrobial stewardship programs in COVID-19

response efforts: All hands on deck. Infect Control Hosp Epidemiol 2020;1-2. doi:

10.1017/ice.2020.69.

30. Clinical management of severe acute respiratory infection (SARI) when COVID-19 disease is

suspected: interim guidance, 13 March 2020. Geneva: World Health Organization, 2020.

Available   from:

https://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection

-when-novel-coronavirus-(ncov)-infection-is-suspected. [Accessed on March 13, 2020].

31. Yu J , Liu W , Chen W , Zhang XM, Wan Z, Wang AP, et al. Experts opinion on the laboratory

diagnosis and treatment of invasive fungal infection secondary to severe novel coronavirus

pneumonia (in Chinese). Chin J Mycology ,2020;15:1-5.

32. Chen RC, Tang XP, Tan SY, Liang BL, Wan ZY, Fang JQ, et al. Treatment of severe acute

respiratory syndrome with glucosteroids: the Guangzhou experience. Chest 2006;129:1441-1452.

doi: 10.1378/chest.129.6.1441.

33. Ni Q, Ding C, Li YT, Zhao H, Liu J, Zhang X, et al. Retrospective study of low-to-moderate dose glucocorticoids on viral clearance in patients with novel coronavirus pneumonia (in Chinese). Chin J Clin Infect Dis 2020;13. doi: 10.3760/cma.j.cn115673-20200225-00072.

34. Zhao JP, Hu Y, Du RH, Chen ZS, Jin Y, Zhou M, et al. Expert consensus on the use of corticosteroid in patients with 2019-nCoV pneumonia (in Chinese). Chin J Tubere Respir Dis 2020;43:183-184. doi: 10.3760/cma.j.issn.1001-0939.2020.03.008.

35. Zumla A, Hui DS, Azhar EI, Memish ZA, Maeurer M. Reducing mortality from 2019-nCoV: host-directed therapies should be an option. Lancet 2020;395:e35-35e36. doi: 10.1016/S0140-6736(20)30305-6.

36. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 2020;395:507-513. doi: 10.1016/S0140-6736(20)30211-7.

37. Riegler LL, Jones GP, Lee DW. Current approaches in the grading and management of cytokine release syndrome after chimeric antigen receptor T-cell therapy. Ther Clin Risk Manag 2019;15:323-335. doi: 10.2147/TCRM.S150524.

38. Shimabukuro-Vornhagen A, Gödel P, Subklewe M, Stemmler HJ, Schlößer HA, Schlaak M, et al. Cytokine release syndrome. J Immunother Cancer 2018;6:56. doi: 10.1186/s40425-018-0343-9.

39. Miettunen PM, Narendran A, Jayanthan A, Behrens EM, Cron RQ. Successful treatment of severe paediatric rheumatic disease-associated macrophage activation syndrome with interleukin-1 inhibition following conventional immunosuppressive therapy: case series with 12 patients. Rheumatology (Oxford) 2011;50:417-419. doi: 10.1093/rheumatology/keq218.

40. van Vollenhoven RF, Fleischmann R, Cohen S, Lee EB, García Meijide JA, Wagner S, et al. Tofacitinib or adalimumab versus placebo in rheumatoid arthritis. N Engl J Med 2012;367:508-519. doi: 10.1056/NEJMoa1112072.

41. Broglie L, Pommert L, Rao S, Thakar M, Phelan R, Margolis D, et al. Ruxolitinib for treatment of refractory hemophagocytic lymphohistiocytosis. Blood Adv 2017;1:1533-1536. doi: 10.1182/bloodadvances.2017007526.

42. Plasma clinical treatment plan for convalescent patients with new coronary pneumonia (trial second version). National Health Commission of the People's Republic of China, 2020. Available from: http://www.nhc.gov.cn/yzygj/s7658/202003/61d608a7e8bf49fca418a6074c2bf5a2/files/a5e00234 915344c6867a3e6bcfac11b7.pdf. [Accessed on March 4, 2020].

43. Ortiz LA, Dutreil M, Fattman C, Pandey AC, Torres G, Go K, et al. Interleukin 1 receptor antagonist mediates the antiinflammatory and antifibrotic effect of mesenchymal stem cells during lung injury. Proc Natl Acad Sci U S A 2007;104:11002-11007. doi: 10.1073/pnas.0704421104.

44. Shen Q, Chen B, Xiao Z, Zhao L, Xu X, Wan X, et al. Paracrine factors from mesenchymal stem cells attenuate epithelial injury and lung fibrosis. Mol Med Rep 2015;11:2831-2837. doi: 10.3892/mmr.2014.3092.

45. Matthay MA, Calfee CS, Zhuo H, Thompson BT, Wilson JG, Levitt JE, et al. Treatment with allogeneic mesenchymal stromal cells for moderate to severe acute respiratory distress syndrome (START study): a randomised phase 2a safety trial. Lancet Respir Med 2019;7:154-162. doi: 10.1016/S2213-2600(18)30418-1.

46. Clinical Research of Stem Cell Therapy for the Treatment of Novel Coronary Pneumonia.

National Health Commission of the People's Republic of China, 2020. Available from: http://www.gov.cn/xinwen/gwylflkjz60/mobile.htm. [Accessed on March 17, 2020]

47. Expert Guidance on Clinical Research and Application of Stem Cells for the Treatment of New Coronavirus Pneumonia (COVID-19). Society of Infectious Diseases of Chinese Medical Association, Stem Cell Biology Branch of Chinese Society of Cell Biology, 2020. Available from: http://med.china.com.cn/content/pid/164626/tid/1026. [Accessed on March 10, 2020].

48. Keyaerts E, Vijgen L, Maes P, Neyts J, Van Ranst M. In vitro inhibition of severe acute respiratory syndrome coronavirus by chloroquine. Biochem Biophys Res Commun 2004;323:264-268. doi: 10.1016/j.bbrc.2004.08.085.

49. Vincent MJ, Bergeron E, Benjannet S, Erickson BR, Rollin PE, Ksiazek TG, et al. Chloroquine is a potent inhibitor of SARS coronavirus infection and spread. Virol J ,2005;2:69. doi: 10.1186/1743-422X-2-69.

50. Gao J, Tian Z, Yang X. Breakthrough: Chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies. Biosci Trends 2020;14:72-73. doi: 10.5582/bst.2020.01047.

51. Hulseberg CE, Fénéant L, Szymańska-de Wijs KM, Kessler NP, Nelson EA, Shoemaker CJ, et al. Arbidol and Other Low-Molecular-Weight Drugs That Inhibit Lassa and Ebola Viruses. J Virol 2019;93. pii: e02118-e02188. doi: 10.1128/JVI.02185-18.

52. Khamitov RA, Loginova SY, Shchukina VN, Borisevich SV, Maksimov VA, Shuster AM. Antiviral activity of arbidol and its derivatives against the pathogen of severe acute respiratory syndrome in the cell cultures (in Russian). Vopr Virusol 2008;53:9-13.

53. Wang Z, Yang B, Li Q, Wen L, Zhang R. Clinical features of 69 cases with coronavirus

disease 2019 in Wuhan, China. Clin Infect Dis 2020. pii: ciaa272. doi: 10.1093/cid/ciaa272.

54. He R, Forman M, Mott BT, Venkatadri R, Posner GH, Arav-Boger R. Unique and highly selective anticytomegalovirus activities of artemisinin-derived dimer diphenyl phosphate stem from combination of dimer unit and a diphenyl phosphate moiety. Antimicrob. Agents Chemother 2013;57:4208-4214. doi: 10.1128/AAC.00893-13.

55. Clinical management of severe acute respiratory infection when novel coronavirus (2019-nCoV) infection is suspected: interim guidance, 28 January 2020. World Health Organization, 2020.

Available from: https://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection -when-novel-coronavirus-(ncov)-infection-is-suspected. [Accessed on January 28, 2020]

56. O'Driscoll BR, Howard LS, Earis J, Mak V, British Thoracic Society Emergency Oxygen Guideline Group, BTS Emergency Oxygen Guideline Development Group. BTS guideline for oxygen use in adults in healthcare and emergency settings. Thorax 2017;72:ii1-ii90. doi: 10.1136/thoraxjnl-2016-209729.

57. Frat JP, Thille AW, Mercat A, Girault C, Ragot S, Perbet S, et al. High-flow oxygen through nasal cannula in acute hypoxemic respiratory failure. N Engl J Med 2015;372:2185-2196. doi: 10.1056/NEJMoa1503326.

58. Arabi YM, Al-Omari A, Mandourah Y, Al-Hameed F, Sindi AA, Alraddadi B, et al. Critically Ill Patients with the Middle East Respiratory Syndrome: A Multicenter Retrospective Cohort Study. Crit Care Med 2017;45:1683-1695. doi: 10.1097/CCM.0000000000002621.

59. Critical Care Medicine Group of Chinese Thoracic Society. Guidelines for Mechanical

Ventilation in Patients with Acute Respiratory Distress Syndrome (Trial) (in Chinese). Natl Med J China 2016;96:404-424. doi: 10.3760/cma.j.issn.0376-2491.2016.06.002.

60. Kangelaris KN, Ware LB, Wang CY, Janz DR, Zhou H, Matthay MA, et al. Timing of Intubation and Clinical Outcomes in Adults with Acute Respiratory Distress Syndrome. Crit Care Med 2016;44:120-129. doi: 10.1097/CCM.0000000000001359.

61. Fan E, Del Sorbo L, Goligher EC, Hodgson CL, Munshi L, Walkey AJ, et al. An Official American Thoracic Society/European Society of Intensive Care Medicine/Society of Critical Care Medicine Clinical Practice Guideline: Mechanical Ventilation in Adult Patients with Acute Respiratory Distress Syndrome. Am J Respir Crit Care Med 2017;195:1253-1263. doi: 10.1164/rccm.201703-0548ST.

62. Gattinoni L, Caironi P, Cressoni M, Chiumello D, Ranieri VM, Quintel M, et al. Lung recruitment in patients with the acute respiratory distress syndrome. N Engl J Med 2006;354:1775-1786. doi: 10.1056/NEJMoa052052.

63. Guérin C, Reignier J, Richard JC, Beuret P, Gacouin A, Boulain T, et al. Prone positioning in severe acute respiratory distress syndrome. N Engl J Med 2013;368:2159-2168. doi: 10.1056/NEJMoa1214103.

64. Writing Group for the Alveolar Recruitment for Acute Respiratory Distress Syndrome Trial (ART) Investigators, Cavalcanti AB, Suzumura ÉA, Laranjeira LN, Paisani DM, Damiani LP, et al. Effect of Lung Recruitment and Titrated Positive End-Expiratory Pressure (PEEP) vs Low PEEP on Mortality in Patients With Acute Respiratory Distress Syndrome: A Randomized Clinical Trial. JAMA 2017;318:1335-1345. doi: 10.1001/jama.2017.14171.

65. Combes A, Hajage D, Capellier G, Demoule A, Lavoué S, Guervilly C, et al. Extracorporeal

Membrane Oxygenation for Severe Acute Respiratory Distress Syndrome. N Engl J Med 2018;378:1965-1975. doi: 10.1056/NEJMoa1800385.

66. Bein T, Weber-Carstens S, Goldmann A, Müller T, Staudinger T, Brederlau J, et al. Lower tidal volume strategy (≈3 ml/kg) combined with extracorporeal CO2 removal versus 'conventional' protective ventilation (6 ml/kg) in severe ARDS: the prospective randomized Xtravent-study. Intensive Care Med 2013;39:847-856. doi: 10.1007/s00134-012-2787-6.

67. Rozencwajg S, Guihot A, Franchineau G, Lescroat M, Bréchot N, Hékimian G, et al. Ultra-Protective Ventilation Reduces Biotrauma in Patients on Venovenous Extracorporeal Membrane Oxygenation for Severe Acute Respiratory Distress Syndrome. Crit. Care Med 2019;47:1505-1512. doi: 10.1097/CCM.0000000000003894.

68. Crotti S, Bottino N, Spinelli E. Spontaneous breathing during veno-venous extracorporeal membrane oxygenation. J Thorac Dis 2018;10:S661-661S669. doi: 10.21037/jtd.2017.10.27.

69. Kurihara C, Walter JM, Singer BD, Cajigas H, Shayan S, Al-Qamari A, et al. Extracorporeal Membrane Oxygenation Can Successfully Support Patients with Severe Acute Respiratory Distress Syndrome in Lieu of Mechanical Ventilation. Crit Care Med 2018;46:e1070-e1073. doi: 10.1097/CCM.0000000000003354.

70. Yang XH, Sun RH, Zhao MY, Chen EZ, Liu J, Wang HL, et al. Expert advice on the treatment process of blood purification in patients with severe COVID-19 (in Chinese). Natl Med J China 2020. doi: 10.3760/cma.j.cn 112137-20200224-00420.

71. Chinese Society of Critical Care Medicine , Critical Care Physicians Group of Chinese Medical Doctor Association, Committee of Critical Care Medicine of Chinese Society of Pathology and Physiology. Recommendations from experts in the management of severe new coronavirus

pneumonia (in Chinese). Chin J Crit Care Med 2020. doi: 10.3877/cma.j.issn.2096-1537.2020.0026.

72. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. JAMA 2020;doi: 10.1001/jama.2020.1585.

73. Khwaja A. KDIGO clinical practice guidelines for acute kidney injury. Nephron Clin Pract 2012;120:c179-c184. doi: 10.1159/000339789.

74. Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. Intensive Care Med 2017;43:304-377. doi: 10.1007/s00134-017-4683-6.

75. Singer P, Blaser AR, Berger MM, Alhazzani W, Calder PC, Casaer MP, et al. ESPEN guideline on clinical nutrition in the intensive care unit. Clin Nutr 2019;38:48-79. doi: 10.1016/j.clnu.2018.08.037.

76.Nutritional recommendations for prevention and treatment of new coronavirus pneumonia. Chinese Society for Parenteral and Enteral Nutrition (CSPEN), 2020. Available from: http://med.china.com.cn/content/pid/158173/tid/1015. [Accessed on February 1, 2020].

77. Jin YH , Cai L, Cheng ZS, Cheng H, Deng T, Fan YP, Fang C, et al. A rapid advice guideline for the diagnosis and treatment of 2019 novel coronavirus (2019-nCoV) infected pneumonia (standard version). Med J Chin PLA 2020;45:1-20. doi: 10.11855/j.issn.0577-7402.2020.01.01.

78. Diagnosis and Treatment Protocol for Severe and Critically Ill COVID-19 Cases (Trial Second Version). National Health Commission of the People's Republic of China, 2020. Available from: http://www.nhc.gov.cn/yzygj/s7653p/202004/c083f2b0e7eb4036a59be419374ea89a/files/0f4be6

a0f4f0419cae3ab6b6efd7cead.pdf.[Accessed on April 1, 2020]

79. Pulmonary Embolism and Pulmonary Vascular Disease Group of Chinese Thoracic Society, Pulmonary Embolism and Pulmonary Vascular Disease Working Committee of Chinese Medical Doctor Association , National Collaborative Group on Prevention and Treatment of Pulmonary Embolism and Pulmonary Vascular Disease, National Office of Capacity Building for the Prevention and treatment of Pulmonary embolism and Deep Venous Thrombosis. Recommendations for prevention and treatment of venous thromboembolism associated with new coronavirus pneumonia (Trial) (in Chinese). Natl Med J China 2020:E7. doi: 10.3760/cma.j.issn.0376-2491.2020.0007.

80. Pulmonary Embolism and Pulmonary Vascular Disease Group of Chinese Thoracic Society , Pulmonary Embolism and Pulmonary Vascular Disease Working Committee of Chinese Medical Doctor Association , National Collaborative Group on Prevention and Treatment of Pulmonary Embolism and Pulmonary Vascular Disease. Guidelines for diagnosis, treatment and prevention of pulmonary thromboembolism (in Chinese). Natl Med J China 2018;1060-1087. doi: 10.3760/cma.j.issn.0376-2491.2018.14.007.

81. Chinese Association of Rehabilitation Medicine, Respiratory rehabilitation committee of Chinese Association of Rehabilitation Medicine, Cardiopulmonary rehabilitation Group of Chinese Society of Physicai Medicine and Rehabilitation. Recommendations for respiratory rehabilitation of COVID-19 in adult (in Chinese). Chin J Tuberculosis Respir Dis 2020;43:E029. doi: 10.3760/cma.j.cn112147-20200228-00206.

82. Notice on the Guiding Principles of Emergency Psychological Crisis Intervention for New Coronavirus Pneumonia. National Health Commission of the People's Republic of China, 2020.

Available from: http://www.gov.cn/zhengce/zhengceku/2020-01-27/content_5472433.htm. [Accessed on January 26, 2020].

83. de Voogd JN, Sanderman R, Postema K, van Sonderen E, Wempe JB. Relationship between anxiety and dyspnea on exertion in patients with chronic obstructive pulmonary disease. Anxiety Stress Coping 2011;24:439-449. doi: 10.1080/10615806.2010.520081.

84. Zhou L, Liu HG. Early detection and disease assessment of patients with novel coronavirus pneumonia (in Chinese). Chin J Tuberculosis Respir Dis 2020;43:167-170. doi: 10.3760/cma.j.issn.1001-0939.2020.03.003.

85. Green M, Marzano V, Leditschke IA, Mitchell I, Bissett B. Mobilization of intensive care patients: a multidisciplinary practical guide for clinicians. J Multidiscip Healthc 2016;9:247-256. doi: 10.2147/JMDH.S99811.

86. Jang MH, Shin MJ, Shin YB. Pulmonary and Physical Rehabilitation in Critically Ill Patients. Acute Crit Care 2019;34:1-13. doi: 10.4266/acc.2019.00444.

87. Sommers J, Engelbert RH, Dettling-Ihnenfeldt D, Gosselink R, Spronk PE, Nollet F, et al. Physiotherapy in the intensive care unit: an evidence-based, expert driven, practical statement and rehabilitation recommendations. Clin Rehabil 2015;29:1051-1063. doi: 10.1177/0269215514567156.

88. COVID-19 rehabilitation program for discharged patients (trial). National Health Commission of the People's Republic of China, 2020. Available from: http://www.nhc.gov.cn/yzygj/s7653pd/202003/d4558d2cc35e44d5b9adb. [Accessed on March 4, 2020].

89. Notice on doing a good job in the follow-up of discharged COVID-19 patients. National Health

Commission of the People's Republic of China, 2020. Available from:

http://www.nhc.gov.cn/yzygj/s7653p/202002/0572eef930d5441c96181c44a1fca878.shtml.

[Accessed on February 19, 2020].

90. Notice of the General Office of the National Health Commission on Further Strengthening the

Prevention and Control of Infections in Medical Institutions During the Epidemic Situation.

National Health Commission of the People's Republic of China, 2020. Available from:

http://www.nhc.gov.cn/xcs/zhengcwj/202003/0c85996bb762437581e98317365fa01c.shtml.

[Accessed on March 13, 2020].

91. Standard for hand hygiene of medical staff. National Health Commission of the People's

Republic of China, 2019. Available from:

http://www.nhc.gov.cn/wjw/s9496/202002/dbd143c44abd4de8b59a235feef7d75e/files/6a3e2bf3d

82b4ee8a718dbfc3cde8338.pdf. [Accessed on November 26, 2019].

92. Technical Guide for the Protection of Medical Staff During the Epidemic of COVID-19 (Trial).

National Health Commission of the People's Republic of China, 2020. Available from:

http://www.nhc.gov.cn/xcs/zhengcwj/202003/0c85996bb762437581e98317365fa01c.shtml.

[Accessed on March 13, 2020].

93. Tong XL, Huang LQ, Liu QQ, Zhang ZD, Miao Q, Wang YG. Interpretation of prevention and

treatment strategies of traditional Chinese medicine in "New Coronavirus Infection Pneumonia

Diagnosis and Treatment Program (Trial Version 4)". Journal of Traditional Chinese Medicine

2020.

94.Gao SM, Ma Y, Yang FW, Zhang JH, Yu CQ. ZHANG Boli: traditional Chinese medicine plays

a role in the prevention and treatment on novel coronavirus pneumonia. Tianjin J Tradit Chin

Med ,2020,37:121-124. doi: 10.11656/j.issn.1672-1519.2020.02.01.

95. Liu QQ, Xia WG, An CQ, Li XC, Wang YG, Miao Q, et al. Thoughts on the effect of combination of traditional Chinese and Western Medicine in the treatment of COVID-19 (in Chinese). Journal of Traditional Chinese Medicine 2020;61:463-464. doi: 10.13288/j.11-2166/r.2020.06.002.

96. Miao Q, Cong XD, Wang B, Wang YG, Zhang ZD. Understanding and thinking of Novel coronavirus pneumonia in traditional Chinese Medicine (in Chinese). Journal of Traditional Chinese Medicine 2020;61:286-288. doi: 10.13288/j.11-2166/r.2020.04.003.

97. Huang DH, Feng CL, Cai JX. Clinical Observation on 111 Cases of New Coronavirus Pneumonia Treated by Traditional Chinese Medicine. Journal of Beijing University of Traditional Chinese Medicine 2020. doi: 10.3969/j.issn.1006-2157.2020.06.12.

98. Chinese Thoracic Society, Chinese Society of General Practice, Chinese Association of Chest Physician, Chinese Medical Doctor Association General Practitioners Sub-Association, Chinese Society of Infectious Disease, Chinese Alliance for Respiratory Diseases in Primary Care, et al. Expert recommendations for the prevention and control of novel coronavirus infections in primary care (First Edition) (in Chinese). Chin J Gen Pract 2020. doi: 10.3760/cma.j.issn.1671-7368.2020.0001.

99. Notice of the General Office of the National Health Commission on carrying out national remote consultation of critically ill COVID-19 patients in the National Telemedicine and Internet Medical Center. National Health Commission of the People's Republic of China, 2020. Available from:

http://www.nhc.gov.cn/xcs/zhengcwj/202002/69b24672365043eebc379c8bab30c90d.shtml.

[Accessed on February 21, 2020].

100. Guidelines for Primary Medical and Health Institutions to Provide Medical and Health Services for Elderly Patients with Chronic Diseases during the Prevention and Control of New Coronavirus Pneumonia Outbreak (Trial). National Health Commission of the People's Republic of China, 2020. Available from:

http://www.nhc.gov.cn/xcs/zhengcwj/202002/e7307a4c19a14a6fb16603d16dcf9854.shtml.

[Accessed on February 24, 2020].

101. Notice of the General Office of the National Health Commission on the accurate classification and doing well of primary medical and health institutions in the prevention and control of COVID-19 epidemic situation. National Health Commission of the People's Republic of China, 2020. Available from:

http://www.nhc.gov.cn/xcs/zhengcwj/202003/8331518df21448729983580e427046db.shtml.

[Accessed on March 2, 2020].

102. Chen S, Zhang Z, Yang J, Wang J, Zhai X, Bärnighausen T, et al. Fangcang shelter hospitals: a novel concept for responding to public health emergencies. Lancet 2020. doi: 10.1016/S0140-6736(20)30744-3.

103. Chan JF, Yuan S, Kok KH, To KK, Chu H, Yang J, et al. A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. Lancet 2020;395:514-523. doi: 10.1016/S0140-6736(20)30154-9.

104. Li Q, Guan X, Wu P, Wang X, Zhou L, Tong Y, et al. Early Transmission Dynamics in Wuhan, China, of Novel Coronavirus-Infected Pneumonia. N Engl J Med 2020;382:1199-1207. doi: 10.1056/NEJMoa2001316.

105. Manual for working in Fangcang shelter hospitals (3rd ed; in Chinese). National Health Commission of the People's Republic of China, 2020. Available from: https://mp.weixin.qq.com/s/va9vs4HuP8wRQM5fALQcrg. [Accessed on February 22, 2020].
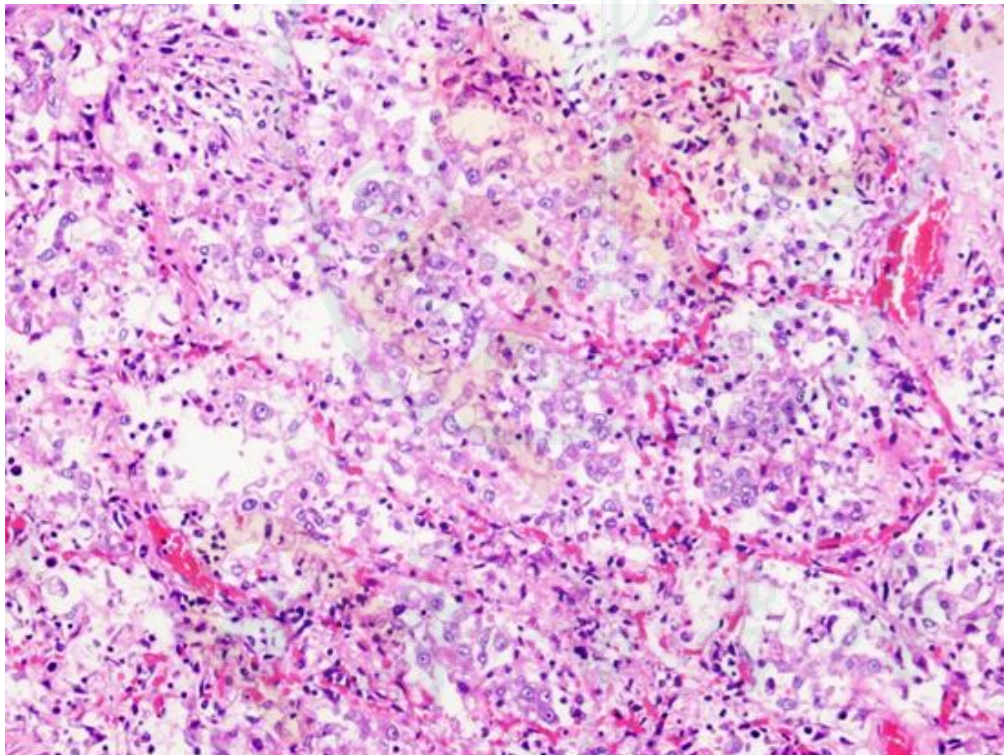
Figure legends

Figure 1: Exudation of a large number of macrophages in the alveolar cavity and a small amount of lymphocyte infiltration in the alveolar septum (hematoxylin & eosin staining; original magnification ×200)
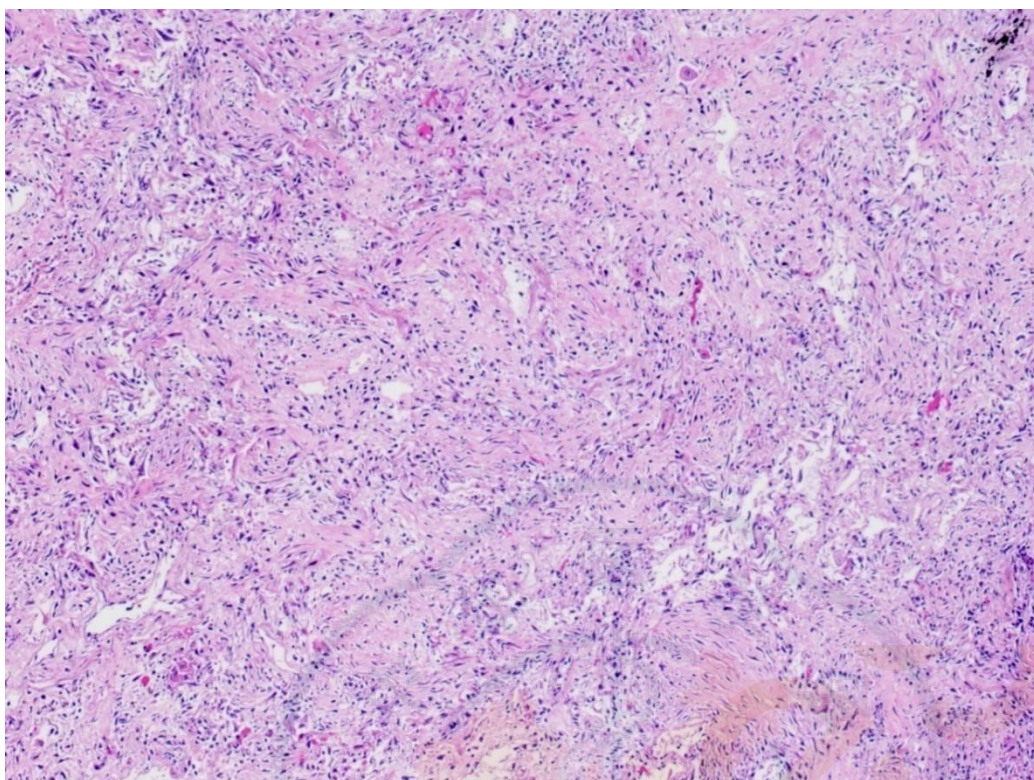
Figure 2: Significant fibrotic proliferation and lung consolidation (hematoxylin & eosin staining; original magnification ×100)
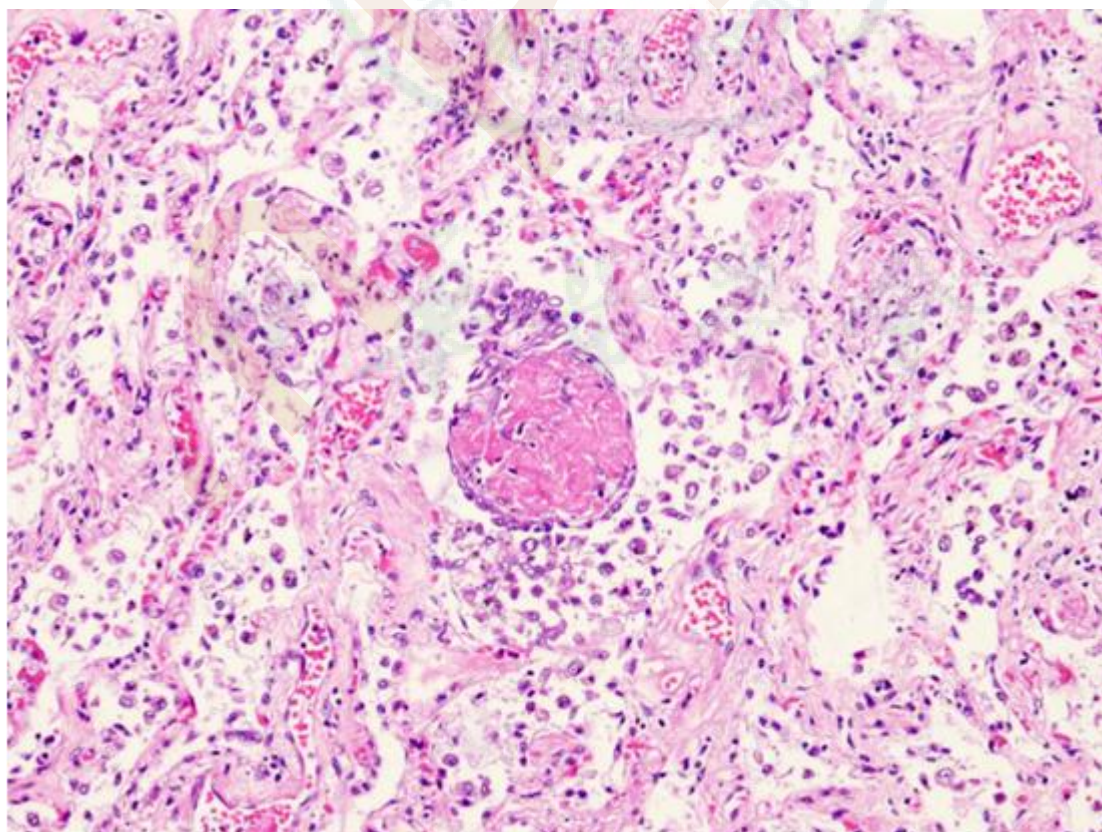
Figure 3: Widening of the alveolar septum with fibrotic proliferation (hematoxylin & eosin staining; original magnification ×100)