Translation: Management of coronavirus disease 2019 (COVID-19): experience in Zhejiang province, China
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Abstract
The current epidemic situation of coronavirus disease 2019 (COVID-19) still remains severe. As the National Clinical Research Center for Infectious Diseases, The First Affiliated Hospital of the Zhejiang University School of Medicine is the primary medical care center for COVID-19 in Zhejiang Province. Based on the present expert consensus carried out by the National Health Commission and National Administration of Traditional Chinese Medicine, our team summarized and established an effective treatment strategy centered on “Four-Anti and Two-Balance” for clinical practice. The “Four-Anti and Two-Balance” strategy includes antivirus, anti-shock, anti-hypoxemia, and anti-secondary infection, and maintaining of water, electrolyte and acid/base balance and microecological balance. Simultaneously, an integrated multidisciplinary personalized treatment is recommended to improve therapeutic effects. The importance of early viral detection, dynamic monitoring of inflammatory indexes and chest radiographs has been emphasized in clinical decision-making. Sputum was observed with the highest positive rate by RT-PCR. Viral nucleic acids could be detected in 10% of the patients’ blood samples at the acute phase and 50% of patients had positive RT-PCR results in their feces. We also isolated live viral strains from feces, indicating potential infectiousness of feces. Dynamic cytokine detection was necessary to timely identify cytokine storms and for the application of the artificial liver blood purification system. The “Four-Anti and Two-Balance” strategy effectively increased cure rates and reduced mortality. Early antiviral treatment alleviated disease severity and prevented illness progression. We found that lopinavir/ritonavir combined with abidol showed antiviral effects against COVID-19. Shock and hypoxemia were usually caused by cytokine storms. The artificial liver blood purification system was able to rapidly remove inflammatory mediators and block the cytokine storm. Moreover, it also contributed to the balance of fluids, electrolytes and acids/bases and thus improved treatment efficacy during critical illness. For cases of severe illness, early and also short periods of moderate glucocorticoid administration was supported. Patients with an oxygenation index below 200 mmHg were transferred to the intensive care unit. Conservative oxygen therapy was preferred and noninvasive ventilation was not recommended. Patients with mechanical ventilation were strictly supervised with cluster ventilator-associated pneumonia prevention strategies. Antimicrobial prophylaxis was prescribed rationally and was not recommended, except for patients with a long course of disease, repeated fever and elevated procalcitonin (PCT), similarly secondary fungal infections were of concern. Some patients with COVID-19 showed intestinal microbial dysbiosis with decreased genus such as Lactobacillus and Bifidobacterium. Nutritional and gastrointestinal function should therefore be assessed for all patients. Nutritional support and application of probiotics or probiotics were suggested to regulate the balance of intestinal microbiota and reduce the risk of secondary infections due to bacterial translocation. Anxiety and fear were common in patients with COVID-19. Therefore, we established a dynamic assessment and warning for psychological crises. We also integrated Chinese medicine in the treatment to promote rehabilitation. We optimized nursing processes for severe patients to promote their rehabilitation. Since viral clearance patterns after SARS-CoV-2 infections remained unclear, two weeks quarantine for discharged patients was required, and a regular follow-up was also needed. These Zhejiang experiences and suggestions have been implemented in our center and achieved good results. However, since COVID-19 was a newly emerging disease, more work is warranted to further improve strategies of prevention, diagnosis and treatment for COVID-19.

Keywords: Coronavirus disease 2019; Severe acute respiratory syndrome coronavirus 2; Novel coronavirus infection; Severe; Critical illness; Clinical treatment; Multi-disciplinary team

Editor: Stijn van der Veen
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Author contributions: Conceived and designed by Lanjuan Li and Tingbo Liang. Organized and summarized by Kaijin Xu and Honglui Cai. Written and approved by all authors.

Founding: Supported by Zhejiang Provincial Key Research and Development Program (2020C03123).
Conflict of interest: The authors declared no conflicts of interest.
This article has been translated with permission from the original publication in Journal of Zhejiang University (Medical Sciences) February 2020, Volume 49, Issue 2. doi:10.3785/j.issn.1008-9292.2020.02.02
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The current epidemic situation of novel coronavirus pneumonia is still progressing, and has already led to hundreds of thousands of infections and thousands of deaths after its first outbreak was discovered in Wuhan in December 2019. By Jan 7, 2020, Chinese scientists had isolated a novel coronavirus (CoV) from respiratory tract samples from patients in Wuhan and finished whole genome sequencing. By Jan 20, 2020, experts of the Chinese Center for Disease Control and Prevention (CDC) had successfully detected nucleotides of the coronavirus and isolated the novel coronavirus from environmental samples of a seafood market in Wuhan. On Feb 7, 2020, the pneumonia caused by the novel coronavirus was named Novel Coronavirus Pneumonia (NPC) by the National Health Commission of the People’s Republic of China. On Feb 11, 2020, the coronavirus was named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by the International Committee on Taxonomy of Viruses. On the same day, the disease caused by this coronavirus was named coronavirus disease 2019 (COVID-19) by the World Health Organization.

Since Jan 20, 2020, COVID-19 has been included in the Class B infectious diseases described in the Law of the People’s Republic of China on Prevention and Treatment of Infectious Diseases, and managed as an infectious disease of Class A. The National Health Commission of the People’s Republic of China has released the document: Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia to standardize the diagnosis and treatment of COVID-19. The incubation period of COVID-19 lasts from one to 14 days, commonly three to seven days, and mainly manifests as fever, fatigue, and dry cough. Severe patients develop dyspnea and/or hypoxemia after one week and may progress rapidly to acute respiratory distress syndrome, septic shock, refractory metabolic acidosis, coagulopathy, and other symptoms.

Since the first case of COVID-19 in Zhejiang Province was reported on Jan 17, 2020, a total of 1162 cases have been confirmed, with no recorded deaths. By 17 o’clock, Feb 14, 2020, The First Affiliated Hospital of Zhejiang University School of Medicine (FAHZU), as the only designated provincial level medical care center for COVID-19 in Zhejiang Province, has provided remote guidance and consultations to hospitals all over the province. A total of 99 patients with non-mild symptoms, with an average age of 52.8 years (range 13-96, 8 cases over 80 years), were admitted and treated in this hospital, among which there were 31 critical cases (31.3%), 43 severe cases (43.4%) and 25 moderate cases (25.3%). By the end of data collection, 47 cases (47.5%) showed improvement and 43 cases have been cured. In order to strengthen the diagnostic accuracy rate of the disease and improve the cure rate, we concluded the experience of management of COVID-19 in Zhejiang province for our peers’ reference and further research.

1 Personalized, collaborative and multidisciplinary management

COVID-19 patients admitted to FAHZU are mostly severe and critically ill individuals whose conditions change rapidly, often with multiple organs infected and in need of the support from the multidisciplinary team (MDT). Since the outbreak, FAHZU has established an expert team that integrates doctors from the Departments of Infectious Diseases, Respiratory Medicine, ICU, Laboratory Medicine, Radiology, Ultrasound, Pharmacological Treatment, Chinese Medicine, Psychology, Respiratory Therapy, Rehabilitation, Nutrition, Nursing, etc. A comprehensive multidisciplinary diagnosis and treatment mechanism has been established in which doctors both inside and outside the isolation wards can discuss patients’ conditions every day via video conference. This allows for the determination of scientific, integrated and customized treatment strategies for each patient according to their individual conditions.

Scientific decision-making is the key to MDT discussion. During the discussion, experts from different departments take maximum advantage of their expertise and focus on critical issues for diagnoses and treatment. The final treatment solution is determined by experienced experts after integrating various opinions and advice.

Systematic analysis is at the core of MDT discussion. Elderly patients and patients with underlying health conditions are prone to become critically ill. While closely monitoring the progression of COVID-19, the patient’s baseline condition, comorbidity and complications, and daily examination results should be analyzed comprehensively to predict how the patient’s condition will progress. Intervention measures including antivirals, oxygen therapy, and nutritional support should be taken accordingly in advance to stop the disease from deteriorating.

The goal of MDT discussion is to achieve personalized treatment. The treatment plan should be personalized and precisely adjusted to each patient according to the differences between individuals, courses of disease, and patient types.

To our experience, the MDT mechanisms can extensively improve the effectiveness of diagnosis and treatment of COVID-19.

2 Correct etiological and inflammatory detection supports clinical treatment decision-making

The novel coronaviruses belong to the β-genus. They have envelopes, and the virus particles are round or oval. Current research shows that they share more than 85% identity with bat SARS-like coronaviruses (bat-SL-CoVZC45). FAHZU makes full use of the advantages of new techniques and methods established in the State Key Laboratory of Diagnosis and Treatment of Infectious Diseases, including pathogen isolation, culture and clinical detection, inflammatory mediators and cytokines storm monitoring, and intestinal microecological analysis, to support the clinical diagnosis and treatment of COVID-19. The following experiences are summarized.

2.1 Specimen collection protocol

Appropriate specimen collection methods and collection timing are important to improve detection sensitivity. Among the airway specimens, sputum showed the highest positive rate of SARS-CoV-2 nucleic acids, followed by nasal swabs and pharyngeal swabs. Therefore, sputum specimens should be collected preferentially to avoid false negative samples or patients being missed. SARS-CoV-2 preferentially proliferates in type II alveolar cells (AT2) and peaks of viral shedding appear 3 to 5 days after the onset of disease. Therefore, if the nucleic acid tests are negative in the beginning, specimen collection and testing should continue on subsequent days. The results of radiology shows that SARS-CoV-2 infected lesions are often located in the lung periphery and both lower lobes, far away from the airway. The main manifestation is dry cough with quite different amounts of virus excretion in each sputum sample. Therefore, patients should be instructed to perform a deep cough 3-5 times and try their best to cough up deep sputum. Samples should be taken multiple times continuously when necessary to improve the positive rate of detection.

2.2 Virus isolation and culture

The isolation and culture of clinical samples, including
sputum, pharyngeal swabs, bronchoalveolar lavage fluid, and feces are very important in pathogen screening, traceability and infectivity assessment, and antiviral efficacy analysis. African green monkey kidney cells (Vero) are virus sensitive cells and can be used to inoculate and culture the virus. By combining cytopathic effects and culture gene sequencing, the pathogen and its molecular characteristics can be identified.

2.3 Nucleic acid detection

Nucleic acid testing is the primary method for diagnosing SARS-CoV-2 infections. Real-time quantitative PCR is adopted to detect the three specific genes of SARS-CoV-2, namely orf1a/b (ORF1a/b) and the genes encoding nucleocapsid protein (N), and envelope protein (E). Among these, orf1a/b has the highest specificity and should therefore be considered as the confirmation target. To ensure the sensitivity, accuracy and laboratory biosafety of nucleic acid detection, special attention should be paid to the specimen collection scheme, multi-specimen combined detection and specimen collection protection.

2.4 Combined detection of nucleic acids from multiple types of specimens

Among the patients with confirmed positive nucleic acids in the sputum, only 10% have detectable viral nucleic acids in the blood during the acute phase, with weak positivity, therefore it can be inferred that patient's blood is less infectious. On the other hand, about 50% of the patients have detectable viral nucleic acids in the feces, with some strongly positive results, and three strains of the virus have been cultured and isolated. So it is necessary to be aware of the potential risk of infectiousness of the patients' feces. The combined detection of respiratory tract specimens, feces, blood and other types of specimens is important to improve the diagnostic sensitivity of suspected cases and to monitor the curative effect. Detection of specific IgM/IgG in peripheral blood is also helpful for the diagnosis of disease. Fecal virus nucleic acids should be tested before a patient is discharged. If the feces continuously show high levels of positive nucleic acids, virus cultivation will be helpful to confirm. Then post-discharge isolation management measures can be made accordingly.

2.5 Indicators of inflammatory response

It is recommended to monitor indicators of inflammation and immune status, such as C-reactive protein, procalcitonin, ferritin, D-dimer, total and subpopulations of lymphocytes, IL-4, IL-6, IL-10, TNF-α, and INF-γ, which is helpful to evaluate clinical progress, alert tendencies of severe and critical conditions, and provide a basis for the formulation of treatment strategies.

2.6 Laboratory safety

Biosafety protective measures should be determined based on different risk levels of experimental processes, to achieve the purpose of both effective protection and resource conservation. Personal protection should be taken in accordance with BSL-3 laboratory protection requirements for respiratory tract specimen collection, nucleic acid detection and virus culture operations. However, the protection requirements for routine blood tests can be reduced appropriately. It is emphasized to operate without opening the cover or after opening the cover in the biosafety cabinet, to avoid the generation of aerosols.

3 Imaging findings of COVID-19 patients to alert the deterioration of disease

Pulmonary/thoracic imaging is of great value for COVID-19 diagnosis, monitoring of therapeutic efficacy, and patient discharge assessment. A high-resolution CT is preferable, while portable chest X-rays are helpful for critically ill patients who are immobile. A chest CT scan is usually performed on patients with COVID-19 on the day of admission for baseline evaluation. It can be re-performed after 2 to 3 days if therapeutic efficacy is not ideal. It can be reviewed after 5 to 7 days if symptoms are stable or improved after treatment. Portable chest X-rays should be performed for critically ill patients on a daily basis.

Chest CT scans of patients at the early stage of COVID-19 often show multifocal patchy shadows or ground glass opacities located in the lung periphery, subpleural area, and both lower lobes. A small number of cases may show single, local lesions, which can progress to both lungs within a short period. Individual cases show lesion distribution consistent with the bronchus, with peripheral ground nodular or patchy glass opacities. In the middle and later stages of the disease, there may be lung consolidation, or interstitial changes, including ground glass opacities and reticulation and local fibrosis, with rare pleural effusion.

Disease progression mostly occurs in patients with expanded lesions, and with enlarged ground glass opacities and increased density lesions, especially prompted after dynamic re-examination.

4 Early diagnosis and early detection of severely and critically ill patients

The standard of diagnosis and treatment follows the Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia. Early diagnosis, treatment and isolation should be carried out as soon as possible. Patients who are prone to become severely and critically ill can be identified by dynamic monitoring of lung imaging, oxygenation index and cytokine levels. A positive result of the nucleic acid test for SARS-CoV-2 is the gold standard for diagnosis of COVID-19. However, considering the possibility of false negatives in nucleic acid tests, suspected cases with characteristic manifestations in CT scans should be treated as confirmed cases in isolation with multiple specimens continuously tested even if the nucleic acid tests are negative.

5 Effective treatment strategy centered on “Four-Anti and Two-Balance” can increase cure rate and reduce mortality

Treatment should center on the “Four-Anti and Two-Balance” strategy, which includes antiviral, anti-shock, anti-hypoxemia, and anti-secondary infections, and maintaining of water, electrolyte and acid/base balance and microecological balance. Treatment strategy centered on “Four-Anti and Two-Balance” was summarized and established by FAHZU for the treatment of H7N9 Avian Influenza, and can also be applied for clinical treatment of COVID-19.

5.1 Antiviral treatment for timely elimination of pathogens

An early antiviral treatment can prevent COVID-19 from progressing to severe and critical cases. There is no clinical evidence for effective antiviral drugs. Currently, the antiviral strategies are based on the characteristics of SAR-CoV-2 and are adopted according to Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia.

5.1.1 Antiviral treatment
Lopinavir/ritonavir (2 capsules, po q12h) combined with arbidol (200 mg po tid) were applied as the basic regimen. From the treatment experience of 49 patients in our hospital, the average time to achieve a first-time negative viral nucleic acid test was 12 days (95% CI: 8-15 days). The duration of negative nucleic acid test results (negative for more than 2 times consecutively with an interval ≥ 24 h) was 13.5 days (95% CI: 9.5 - 17.5 days).

Interferon nebulization is recommended in Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia. We recommend that it should be performed in negative-pressure wards rather than general wards due to the possibility of aerosol transmission.

5.1.2 Side effects and treatment of adverse reactions

Adverse reactions to lopinavir/ritonavir include gastrointestinal symptoms, such as nausea, poor appetite, diarrhea, etc. It can also interfere with lipid metabolism and cause hyperlipidemia. Liver and kidney dysfunctions may occur to some patients. Lopinavir/ritonavir tablets need to be metabolized by the liver P450 enzyme, which may interfere with the metabolism of many drugs, including voriconazole, tacrolimus, rifamycin, and atorvastatin. The main adverse reactions of abidol include low heart rate, nausea, diarrhea, etc. It is necessary to avoid administration in combination with metoprolol, propranolol and other beta-antagonists. It is recommended to stop taking abidol when the heart rate is lower than 60 times/min. Symptomatic treatment will be the main choice to gastrointestinal symptoms. Darunavir/cobicistat has some level of antiviral activity in in vitro viral suppression tests, based on the treatment experience of AIDS patients, and adverse events are relatively mild. For patients who are intolerant to lopinavir/ritonavir, darunavir/cobicistat (1 tablet qd) or favipiravir (starting dose of 1600 mg, followed by 600 mg tid) is an alternative option after ethical review.

5.1.3 Course of treatment

The optimal course of treatment has not yet been determined. Antiviral drugs should be stopped after administration for two weeks, or if nucleic acid test results from sputum specimens remain negative for more than 3 times.

5.2 Anti-shock and anti-hypoxemia treatment

During the progression from the severely to the critically ill stage, patients may experience severe hypoxemia, cytokine storm and severe infections that might develop into shock, tissue perfusion disorders, and even multiple organ failure. Treatment is aimed to remove triggers and recover fluid balance. The artificial liver support system (ALSS) and blood purification can rapidly remove inflammatory mediators, eliminate cytokine storm and prevent shock, hypoxemia and respiratory distress syndrome.

5.2.1 Artificial liver treatment for suppression of cytokine storm

Integrating techniques, including plasma exchange, adsorption, perfusion and filtration, ALSS can remove inflammatory mediators, endotoxins and small or medium-molecular harmful metabolic substances, provide beneficial substances, including serum albumin and coagulation factors, and balance fluid volume, electrolytes and acid/base ratios. ALSS can block the cytokine storm, correct shock, reduce lung inflammation, and improve respiratory function. It can contribute to the recovery of immune homeostasis and the improvement of metabolic disorder, which can help to improve multiple organ functions, including the liver and kidney, and subsequently increase treatment success and reduce the mortality of severe patients.

a) Concentrations of serum inflammatory indicator (such as IL-6, etc.) are greater than or equal to 5 upper limit of normal (ULN), or the rising rate is ≥1 time per day.
b) Rapid progressing in pulmonary imaging, involved area of pulmonary CT or X-ray images ≥10% progression per day.
c) Artificial liver support system is required for the treatment of patients with basic diseases.

Patients meeting a) + b), or patients meeting c).

2) Contra-indications

For the treatment of critically ill patients, there are no absolute contra-indications. However, ALSS should be used with caution in the following patients:

- Patients with severe bleeding or disseminated intravascular coagulation.
- Patients who are highly allergic to blood products or drugs used in the treatment process, such as plasma, heparin, protamine, etc.
- Patients with acute cerebrovascular diseases or severe head injury.
- Patients with chronic cardiac failure, cardiac functional classification ≥ grade III.
- Patients with uncontrolled hypotension and shock.
- Patients with severe arrhythmia.

Plasma exchange combined with plasma adsorption or dual plasma molecular adsorption, perfusion, and filtration is recommended. The plasma exchange volume should be 2000 mL during when ALSS is performed. Detailed operating procedures are described in Expert Consensus on the Application of Artificial Liver Blood Purification System in the Treatment of Severe and Critical COVID-19.

Up to Feb 12, 2020, the time that critically ill patients stay in the ICU of FAHZU after receiving ALSS has been significantly reduced. Typically, the levels of serum cytokines such as IL-2/IL-4/IL-6/TNF-α have been remarkably decreased, accompanied by breathing improvement and rising oxygen saturation.

5.2.2 Usage of glucocorticoids

Appropriate and short-term use of corticosteroids to inhibit cytokine storm and to prevent disease progression should be considered for patients with severe and critical COVID-19 as early as possible. It can shorten the course of the disease and avoid adverse reactions and complications caused by long-term and large use of glucocorticoids.

1) Indications

a) Use early for those in the severe and critically ill stage.
b) Patients with persistent high fever (temperature above 39°C).
c) Those showing CT-demonstrated patchy ground-glass attenuation or more than 30% area of the lungs are involved.
d) Those whose CT demonstrated rapid progression (more than 50% area involved in pulmonary CT images within 48 hours).
e) Patients with IL-6 ≥ 5 ULN.

2) Instruction

Initial routine methylprednisolone at a dose of 0.75-1.5 mg/kg intravenously once a day (nearly 40 mg once or twice a day) is recommended according to the degree of inflammatory damage. Closely monitor blood routine, C-reactive protein, cytokines, biochemical profile, blood glucose and lung CT every 2 to 3 days during the treatment as necessary. The dosage of methylprednisolone should be halved every 3 to 5 days if medical conditions of patients are improved and the body temperature normalizes. Oral methylprednisolone (Medrol) once a day is recommended when the intravenous dose is reduced to
20 mg per day. The detailed course depends on patients’ conditions.

3) Special considerations during treatment
   a) Screening of TB by T-SPOT assay, and HBV and HCV by antibody assays should be performed prior to treatment to prevent activation of potential infections during hormone therapy.
   b) Proton pump inhibitors and calcium should be considered to prevent complications.
   c) Blood glucose should be monitored and insulin could be injected subcutaneously to control blood sugar when necessary.
   d) Monitor serum potassium and correct when necessary.
   e) Closely monitor the liver function and perform liver protection when necessary.
   f) Traditional Chinese herbal medicine may be considered for patients who are sweating.
   g) Sedative-hypnotics can be administered temporarily for patients with erethism and sleep disorder.

5.2.3 Oxygen therapy for hypoxemia

1) Continual oxygen saturation monitoring during oxygen therapy.

2) Controlled oxygen therapy such as Venturi masks and High-flow nasal cannula (HFNC) oxygen therapy are preferred for their advantages in PaO2/FiO2 evaluation.

3) Oxygen therapy is not necessary for patients with oxygen saturation (SpO2) of more than 93% or for patients without obvious symptoms of respiratory distress without oxygen treatment. Otherwise oxygen therapy is strongly recommended.

4) HFNC oxygen therapy is recommended for patients with the following conditions: SpO2 < 93%; PaO2/FiO2 < 300 mmHg (1 mmHg = 0.133 kPa); respiratory rate > 25 times per min at bed; or remarkable progression on X-ray imaging. Patients should receive sufficient education before the treatment. The airflow of HFNC oxygen therapy should start at a low level at 30 L/min and 34°C with oxygen concentration set according to PaO2. Afterwards the airflow can be increased to the highest value that the patient can tolerate.

5) For patients without obvious symptoms of respiratory distress and with stable hemodynamics, or patients with chronic type II respiratory failure, the treatment goal of oxygen therapy can be set at 88%-92%. The target value of SpO2 should be increased appropriately for some patients because the oxygen concentration fluctuates greatly during low-intensity daily activities.

6) Patients with an oxygenation index less than 200 mmHg should be admitted to ICU.

7) When treated with HFNC oxygen therapy, if the patient shows symptom relief in respiratory distress syndrome, continuing use of HFNC oxygen therapy is recommended. If the patient shows hemodynamic instability, respiratory fatigue, hypoxemia persists despite oxygen therapy, deterioration of consciousness, the respiratory rate > 40 breaths per minute continuously, obvious acidosis, or significant amounts of sputum, invasive mechanical ventilation should be performed when necessary.

5.2.4 Mechanical ventilation

1) Noninvasive ventilation (NIV) is not strongly recommended in COVID-19 patients who fail HFNC treatment. A short-term (less than 2 hours) use of NIV should be closely monitored to make sure intubation can be performed as early as possible when necessary.

2) Under a conservative oxygen therapy strategy, the target value of SpO2 can be set at 88%-92%. It can be adjusted according to the real-time SpO2 value.

3) Strictly implement strategies to prevent ventilator-associated pneumonia.
   a) Select appropriate type of endotracheal tube.
   b) Use an endotracheal tube with subglottic suction (once every 2 hours, aspirated with 20 mL empty syringe each time).
   c) Make sure the endotracheal tube is in the correct position and depth (imaging evaluation) and properly fixed to avoid pulling.
   d) Maintain the airway pressure at 30-35 cmH2O (1 cmH2O = 0.098 kPa) and monitor once every 4 hours.
   e) Monitor the airbag pressure and deal with water condensates when the position changes (dumping and pouring the water condensates with two people into a capped container containing a pre-made disinfectant chlorine solution). Deal with the secretions accumulated in the airbag.
   f) Clean-up secretions from the mouth and nose timely.
   g) Use a closed sputum suction system, including closed disposable collection bags.
   h) Adjust the endotracheal tube’s position (up to 2 cm) according to the severity of acute respiratory distress syndrome (mild: 5<7 cmH2O; moderate: 8-12 cmH2O; severe: at least 12 cmH2O). Or use a titration method to adjust the PEEP according to the reaction of the patients, such as oxygenation and lung compliance.
   i) The lung recruitment maneuver is not routinely recommended. The assessment of lung expandability should be performed prior to the application.
   j) When the patient’s PaO2/FiO2 is more than 150 mmHg, sedatives should be reduced and discontinued and intubation withdrawal should be performed.
   k) Hospital infection prevention and control measures should be strictly followed.

5.3 The rational use of antibiotics to prevent secondary infection

COVID-19 is a viral infectious disease. Antibacterial agents are not recommended to prevent bacterial infection in mild or ordinary patients. A prudent decision about prophylactic use of antibiotics in severely ill patients should be made based on their conditions. Antibiotics can be used with discretion in patients who have the following conditions: extensive lung lesions; excess airway secretions; chronic airway diseases with a pathogen colonization history in the lower respiratory tract; taking glucocorticoids with a dosage ≥ 20 mg × 7d (in terms of prednisone), etc. The options of antibiotics include quinolones, second or third generation cephalosporins, β-lactamase inhibitor compounds, etc. Prophylactic use of antibacterial agents, such as carbapenems, β-lactamase inhibitor compounds, linezolid and vancomycin, may be considered in severely and critically ill patients according to the individual risk factors, especially those...
receiving invasive mechanical ventilation.

The symptoms, signs, blood routine, C-reactive protein and procalcitonin should be closely monitored during the treatment. Clinical comprehensive judgment is required for the occurrence of disease changes. Qualified specimens should be collected for testing by smear preparation, cultivation, nucleic acids, antigens and antibodies if a secondary infection cannot be ruled out, in order to identify the infectious agent as early as possible. Antibiotics can be empirically used in the following conditions: 1) Elevated expectoration, darker sputum color, especially yellow pus sputum. 2) Increased temperature, which is not due to exacerbation of the primary disease. 3) Significantly increased numbers of white blood cells and/or neutrophils. 4) Procalcitonin ≥ 0.5 ng/mL. 5) Exacerbation of oxygenation index and/or circulatory disturbance that could not be caused by the viral infection. 6) Other suspicious conditions caused by bacterial infections.

Some COVID-19 patients are at the risk of secondary fungal infections due to decreased cellular immunity caused by viral infections and the use of glucocorticoid and/or broad-spectrum antibiotics. It is necessary to perform respiratory secretion microbiological detections, such as smear preparation and cultivation, for critically ill patients and provide timely D-Glucose (G-test) and galactomannan (GM-test) of blood or bronchoalveolar lavage fluid for suspected patients. It is necessary to be vigilant with possible invasive candidiasis infection and anti-fungal therapy. Fluconazole or echinocandin can be used in the following conditions: 1) Patients are given broad-spectrum antibiotics for seven days or more. 2) Patients have parenteral nutrition. 3) Patients have invasive examination or treatment. 4) Patients have positive candida culture in the specimen obtained from two body parts or more. 5) Patients have significantly increased results for G-tests. It is necessary to be vigilant with possible invasive pulmonary aspergillosis. Anti-fungal therapies such as voriconazole, posaconazole, or echinocandin are considered to be used in the following conditions: 1) Patients are given glucocorticoid for seven days or more. 2) Patients have agranulocytosis. 3) Patients have chronic obstructive pulmonary disease and aspergillus cultures are tested positive in the specimen obtained from the airway. 4) Patients have significantly increased results by GM-tests.

5.4 Maintaining of water, electrolyte and acid/base balance and promoting stability of the internal environment

Some of the COVID-19 patients suffer from diarrhea, which can also be caused by lopinavir/ritonavir administration. It is necessary to be vigilant with risk of fluid and electrolyte imbalance, especially hypokalemia and hyponatremia. The blood electrolytes of patients with severe conditions should be monitored and corrected timely. Hypoxemia is prone to lead to secondary metabolic acidosis and tissue perfusion disorder, causing increased lactic acid level, which should be corrected in time to halt disease progression. Continuous renal replacement therapy or artificial liver therapy should be used when necessary.

5.5 Maintaining of intestinal microecology and prevention of bacterial translocation and infection

Some COVID-19 patients suffer from gastrointestinal symptoms (such as abdominal pain and diarrhea) due to direct viral infection of the intestinal mucosa or antiviral and anti-infective drugs. Intestinal microecological imbalance has been detected in patients with COVID-19, which was manifested as a significant reduction in Lactobacillus, Bifidobacterium and other beneficial bacteria in the intestinal tract. Intestinal microecological imbalance may lead to bacterial translocation and secondary infections. Therefore, it is important to maintain the balance of intestinal microecology by microecological modulators and nutritional support. 5.5.1 Microecologics can increase the dominant bacterium by reducing bacterial translocation and secondary infections. It can inhibit intestinal bacteria, reduce toxins and lower the infection risks caused by gut microflora dysbiosis. Medical experience in the treatment of H7N9 avian influenza severe pneumonia suggests that the risk of secondary infections in patients treated with microecological agents is greatly reduced. 5.5.2 Microecological modulators can improve the gastrointestinal symptoms of patients. It can reduce water in the feces, improve fecal character and defecation frequency and reduce diarrhea by inhibiting intestinal mucosal atrophy. 5.5.3 Institutes or hospitals with sufficient conditions could analyze the intestinal flora and detect the intestinal flora disturbance as early as possible. Thus antimicrobial drugs and probiotics can be administrated as soon as possible to reduce the occurrence of intestinal flora translocation and enterogenic infections. 5.5.4 Nutritional support is an important means to maintain intestinal microecological balance, which could timely implement nutritional support on the basis of effective assessment of nutritional risk, gastrointestinal function and risk of aspiration. 1) Oral feeding is preferred. For patients with tracheal intubation or at high aspiration risks, intestinal nutrition tube indwelling is recommended to provide nutritional support, nourish intestines, improve intestinal mucusal barrier and intestinal immunity, and maintain intestinal microecology. 2) Energy supply: 25-30 kcal per kg body weight, the target protein content is 1.2-2.0 g/kg daily. For patients with good intestinal functions, whole-protein preparations with relatively high calories can be selected. For patients with severe conditions, predigested short peptide preparations are recommended. For hyperglycemia patients, nutritional preparations, which are beneficial to glycemic controlling, are recommended. For patients with strict requirements of volume control (e.g., patients with heart failure), high-energy preparations may be considered.

6 Psychological interventions to reduce the pressure of COVID-19 patients

6.1 Establishing a dynamic mechanism for evaluation and warning of psychological crisis

Patients’ mental states (individual psychological stress, mood, sleep quality, and pressure) should be monitored when admitted, 1 week and 2 weeks after admission and before discharge. The self-rating tools include: Self-Reporting Questionnaire 20 (SRQ-20), Patient Health Questionnaire 9 (PHQ-9) and Generalized Anxiety Disorder 7 (GAD-7). The peer-rating tools include: Hamilton Depression Rating Scale (HAM-D), Hamilton Anxiety Rating Scale (HAMA), Positive and Negative Syndrome Scale (PANSS). Among 89 patients evaluated by FAHZU, 52% showed no symptoms, 35% showed mild symptoms, and 13% showed moderate to severe symptoms. 6.2 Intervention and treatment based on the assessment
7 Traditional Chinese medicine (TCM) classification therapy to improve curative efficacy

7.1 Classification and stage

COVID-19 can be divided into early, middle, critical and recovery stages. At the early stage, the disease shows two main types: “wet lungs” and “external cold and internal heat.” The middle stage is manifested as “intermittent cold and heat.” The critical stage is mainly manifested as “internal block of epidemic toxin.” The recovery stage is manifested as “qi deficiency in lung-spleen.” The disease initially belongs to wet lung syndrome, so consideration is given to both cold and heat due to having a fever. In the middle stage, cold, dampness, and heat coexist, belonging to a “cold-heat mixture” type in terms of TCM. Both cold and heat therapy should be considered. According to the theory of TCM, heat should be treated with cold drugs, but cold drugs impair Yang and lead to a deficiency-cold spleen and stomach and cold-heat mixture in the middle-Jiao. Therefore, in this stage both cold and heat therapies should be considered. Because cold-heat symptoms are commonly seen in COVID-19 patients, the cold-heat therapy is better than other approaches.

7.2 Syndrome differentiation and treatment

1) Wet lungs
It is advisable to dispel cold and dissipate dampness, and relieve exterior syndrome with aromatic herbs.
- Ephedra Herb 6 g, Semen Armeniacae Amarum 10 g, Coix Seed 30 g, Liquoric Root 6 g, Baical Skullcap Root 15 g, Huoxiang 10 g, Reed Rhizome 30 g, Cytotrimon Rhizome 15 g, Indian Buead 20 g, Chinese Atractylodes Rhizome 12 g, Officinal Magnolia Bark 12 g.

2) External cold and internal heat
It is advisable to clear lung heat and relieve the exterior syndrome with drugs pungent in flavor and cool in property.
- Herba Ephedrae 9 g, Raw Gypsum Fibrosum 30 g, Semen Armeniacae Amarum 10 g, Liquoric Root 6 g, Baical Skullcap Root 15 g, Periparatum Trichosanthis 20 g, Fructus Aurantii 15 g, Officinal Magnolia Bark 12 g, Tripterospermum Cordifolium 20 g, White Mulberry Root-bark 15 g, Pinellia Tuber 12 g, Indian Buead 20 g, Platycodon Root 9 g.

3) Intermittent cold-heat
It is advisable to regulate the cold and heat, and dissipate the damp and heat.
- Pinellia Tuber 12 g, Baical Skullcap Root 15 g, Golden Thread 6 g, Dried Ginger 6 g, Chinese Date 15 g, Kudzuvine Root 30 g, Costustooot 10 g, Indian Buead 20 g, Thunberg Fritillary Bulb 15 g, Coix Seed 30 g, Liquoric Root 6 g.

4) Internal block of epidemic toxin
Use cheongsimhwan for treatment.

5) Qi deficiency of lung and spleen
It is advisable to strengthen spleen and replenish lung, and tonify qi and secure exterior.
- Membranous Milkvetch Root 30 g, Pilose Asiabell Root 20 g, Roasted Largehead Atractylodes Rhizome 15 g, Indian Buead 20 g, Fructus Amomi 6 g, Siberian Solomonseal Rhizome 15 g, Pinellia Tuber 10 g, Tangerine Peel 6 g, Wingde Yan Rhizome 20 g, Semen Nelumbinis 15 g, Chinese Date 15 g.

Select the corresponding prescription for different patients according to the classification and stage. Boil the medicine in water, one dose per day and take it every morning and evening.

8 Optimizing nursing care for severely ill patients to promote their rehabilitation

8.1 Nursing care for patients with mechanical ventilation

8.1.1 Analgesia and sedation management
For patients with PEEP of at least 10 cmH₂O when protective ventilation is applied with small tidal volume, deep analgesia and sedation should be applied following the doctor’s advice. For patients with gradually improved oxygenation and reduced PEEP, shallow sedation should be applied following the doctor's advice. Determine the target pain management goal every day after multidisciplinary rounds, and titrate the infusion rate of analgesics and sedatives.

8.1.2 Operating strategy for prevention of Ventilator-Associated Pneumonia (VAP)

Raise the tilt angle of the patient’s bed to 30-45°. Perform oral care every 4 to 6 hours with chlorhexidine by using a disposable oral mucus extractor. Maintain endotracheal tube (ETT) cuff pressure at 30-35 cmH₂O every 4 hours. Use washable tracheal tubes for continuous subglottic suctioning combined with syringe suctioning every 1 to 2 hours, and adjust the suctioning frequency according to the actual amount of secretions. Monitor once every 4h after nasogastric tube feeding. Follow the doctor's daily wake-up plan and evaluate in time for ventilator removal.

8.1.3 Nursing care for the prone position ventilation (PPV)
Use the ICU prone ventilation checklist operated by the same person. Check each link of before, during and after prone position, and handle unexpected events to finish the treatment.

8.2 High-flow nasal cannula (HFNC) oxygen therapy

1) Adjust the length of fastening habenula on neck and leave proper activity for nasal catheter. Avoid stretch of the nasal catheter after cough and activities, which could compromise the efficacy of oxygen therapy.
2) Maintain the water level in the humidifier chamber.
3) Avoid device-related pressure injuries on the facial skin by using non-adhesive foam plaster to keep patient comfort and prevent the occurrence of instrument-related stress injury on the face.

8.3 Aspiration Prevention

1) Gastric retention monitor: perform intermittent feeding and small residue feeding to reduce gastroesophageal reflux. Evaluate gastric motility and gastric retention with ultrasound to prevent aspiration.
2) Evaluate gastric residual volume (GRV) every 4 hours. Re-infuse the aspirate if the GRV is < 100 mL; otherwise, report to the attending physician for a decision.
3) Prevention of aspiration during transportation: before transportation, stop nasal feeding, aspirate the gastric residues and connect the gastric tube to a negative pressure bag; during transportation, keep the patient’s head up to 30°.
4) Prevention of aspiration in patients treated with HFNC: Check the humidifier every 4 hours to avoid excessive or insufficient humidification. Remove any water accumulated
Discharge standards and follow-up plan for COVID-19 patients

9.1 Discharge standards
1) Body temperature remains normal for at least 3 days (ear temperature is lower than 37.5 °C).
2) Respiratory symptoms improved significantly.
3) Nucleic acids for respiratory tract pathogens turned and stays negative twice consecutively (sampling interval more than 24 hours). Nucleic acid tests of stool samples can be performed at the same time if possible.
4) Lung imaging shows obvious improvement in lesions.
5) There are no other comorbidities or complications requiring hospitalization.
6) SpO₂ > 93% without assisted oxygen inhalation.
7) Discharge approved by multi-disciplinary medical team.

9.2 Medication after discharge
Generally, antiviral drugs are not necessary after discharge. Treatments for symptoms can be applied if patients have mild cough, poor appetite, thick tongue coating, etc.

9.3 Home isolation
Patients must continue two weeks of isolation after discharge. Home isolation conditions are recommended as follows:
1) Independent living area with frequent ventilation and disinfection.
2) Avoid contacts at home with infants, the elderly and people with weak immune functions.
3) Patients and their family members must wear masks and wash hands frequently.
4) Take body temperature twice a day (in the morning and evening) and pay close attention to any changes in the patient’s condition.

9.4 Follow-up
A specialized doctor should be arranged to follow-up each patient discharged from the hospital. They should finish the first follow-up phone call within 48 hours after discharge. The outpatient follow-up will be carried out 1 week, 2 weeks, and 1 month after discharge. Examinations include liver and kidney functions, blood test, nucleic acid test of sputum and stool samples, and pulmonary function test or lung CT scan should be reviewed according to the patient’s condition. Follow-up phone calls should be made 3 and 6 months after discharge.

Since COVID-19 is a newly emerging infectious disease, more fundamental and clinical issues are to be further studied and the preventing and treatment methods and strategies for COVID-19 are still being explored and improved.

Acknowledgement
We thank Jianrong Huang, Nanping Wu, Xiaowei Xu, Hong Zhao, Yongtao Li, Yanfei Chen, Jun Liu, Junwei Su, Yimin Zhang, Guojun He, Wenqiao Yu, Qibin Pu, Yun Zhang, Tong Li, Jun Xu, Hua Zhou, Jie Wang, Ning Wei, Jianbo Hu, Xuehong Zhao, Jianhua Wei, Chunhua Gao, Feng Chen and Wenrui Wu from the First Affiliated Hospital of the Zhejiang University School of Medicine for the help with writing and revision of the manuscript.

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