



Clinical Treatment of COVID-19

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4.1 Management of COVID-19 Patients in Fever Clinics

Peng Sun

Fever clinic provides a window for screening and treatment of infectious diseases. Management at fever clinics is of the utmost importance.

The layout of fever clinics shall strictly follow the principle of “three zones and two passages.” Managing patients to track where they come from and where they go.

During the visiting, the medical institution distributes patient notifications and information forms, which are to be signed and filled out by the patient or a family member, along with the cover page of the medical record. The patient’s information is then entered into a computer system by the triage nurse.

A nurse measures the patient’s temperature (T), heart rate (P/HR), respiration (R), blood pressure (BP), and fingertip oxygen saturation (SaO₂).

A doctor fills in the clinic medical record in a standard way, noting related epidemiological history, underlying diseases, and any special patient status such as maternity or renal dialysis. According to the patient’s BP, P, HR, RR, SaO₂, and overall condition, the severity of the disease can be quickly determined, and patients are classified for placement in different treatment areas accordingly [1].

During the initial visit, the necessary examinations, diagnosis of exclusion, biochemical parameters related to underlying diseases, and imaging of implicated organs need to be completed.

For patients paying a subsequent visit, inquire and record the examination results and main treatment plans related to the disease. Follow up on any examination items that are required as well as any changes in the condition that needs to be monitored dynamically, in order to evaluate the treatment effect.

Re-evaluate the patient’s condition and classify the diagnosis according to the results of their examination, and admit the patient for treatment based on the severity of the disease. Determine whether to fill out an infectious disease card, and whether to request an epidemiological investigation by the Center for Disease Control (CDC).

Patient Triage [2, 3]:

1. Mild and moderate cases are assigned by health care workers under the corresponding government jurisdiction to either centralized isolation sites for observation, designated hospitals to receive treatment in isolation, or mobile cabin hospitals [4].

2. Severe suspected or confirmed cases are hospitalized or placed under observation. Treatment includes antivirals, anti-infective, and symptomatic support, giving equal weight to Chinese and Western approaches [5].
3. Critical suspected or confirmed cases are immediately placed under observation and treated promptly in accordance with routine rescue intervention. Patients are hospitalized once their conditions are stable. Treatment includes antivirals, anti-infective, and symptomatic support, giving equal weight to Chinese and Western medical approaches. Rehabilitation method also includes plasma therapy and ECMO support [6].
4. Regarding the transfer of patients within or between designated hospitals at different levels, utilize the designated transport tools and routes and follow the related processes.

Doctors fill out the examination and condition assessment results in the appropriate columns of the patients' information card and patients are triaged accordingly. Doctors write information about patients under observation on the observation board for turnover between shifts.

During or after the epidemic, potential sources of infection are needed to be continuously screened, including assay of COVID-19 serum IgM/IgG antibodies from discharged patients, and interpretation of the results of two COVID-19 nucleic acid and serum IgM/IgG antibody tests (at least 24 h apart). According to the discharge and release standards in the seventh version of the Diagnosis and Treatment Plan [1], patients with or without fever and those rehabilitated are classified for treatment, and then further triaged based on the items on the checklist [1, 4].

Outpatient services related to mass travel and work resumption are provided in due time. The National Security Department implements citizen health codes to establish status classifications and revise classification procedures.

The most stringent measures for the prevention and control of infectious diseases are adopted based on changes in imported and output cases. Increased control over entry and exit is being enforced, and measures and procedures are formulated for the transfer, diagnosis, and treatment of patients with fever at fever clinics.

4.2 Diagnosis and Clinical Typing

Jianchu Zhang

COVID-19 diagnostic criteria include epidemiological history (including clustered onset), clinical symptoms (fever and respiratory symptoms), pulmonary imaging, SARS-CoV-2 nucleic acid testing, and serum-specific antibodies.

4.2.1 Diagnostic Criteria

4.2.1.1 Suspected Cases

Comprehensive analysis of the following epidemiological history and clinical manifestation.

4.2.1.1.1 Epidemiological History

History of travel or residence in Wuhan or surrounding areas, or other communities with case reports, within 14 days prior to onset of illness.

History of contact with a COVID-19 infected person (positive nucleic acid testing) within 14 days prior to onset of illness.

Contact with patients with fever or respiratory symptoms from Wuhan and surrounding areas, or communities with case reports, within 14 days prior to onset of illness.

Clustered onset (two or more cases of fever and/or respiratory symptoms in 2 weeks within a small population, such as a home, office, and school).

4.2.1.1.2 Clinical Manifestation

1. Having fever and/or respiratory symptoms.
2. Having characteristic imaging of COVID-19 as described above.
3. Showing normal or decreased total white blood cell count and normal or decreased lymphocyte count in the early stages of onset.

Exhibiting any one item of epidemiological history and any two items of clinical picture; No explicit epidemiological history, but exhibiting three items of clinical picture.

4.2.1.2 Confirmed Cases

Suspected cases are those who have one of the following etiologies or serological signs:

1. Showing positive for COVID-19 nucleic acid testing by real-time fluorescent RT-PCR.
2. Showing highly homologous to known COVID strains in viral gene sequencing.
3. Result of serum testing is positive for COVID-19-specific IgM and IgG antibodies; result of serum testing for COVID-19-specific IgG antibodies changes from negative to positive, or is four or more times higher in the recovery period than in the acute phase.

Positive for SARS-CoV-2 nucleic acid is the gold standard for COVID-19 diagnosis, but false negatives do occur. Therefore, even if the nucleic acid test is negative, patients highly suspected for COVID-19 upon lung CT, can still be treated in isolation as if clinically diagnosed, and repeatedly tested for SARS-CoV-2.

4.2.2 Clinical Typing

1. Mild: Showing mild clinical symptoms, no pneumonia manifestations on imaging.
2. Moderate: Having fever and respiratory symptoms, with pneumonia manifestations on imaging.

It is recommended that patients with any one of the following factors be treated as a severe case: age ≥ 65 years, with underlying diseases (coronary heart disease, severe hypertension, insulin-dependent diabetes, COPD, rheumatic autoimmune disease, other infectious diseases, etc.), received immunosuppressive therapy, organ transplant, dialysis, radiotherapy or chemotherapy of active tumors, etc. [7].

3. Severe: Adults with any of the following should be treated as severe cases: respiratory rate ≥ 30 times/min; resting fingertip oxygen saturation $\leq 93\%$; arterial partial pressure of oxygen (PaO_2)/fraction of inspired oxygen (FiO_2) ≤ 300 mmHg; pulmonary imaging shows significant progression of lesions $>50\%$ within 24–48 h.
4. Critical: Anyone with one of the following conditions: respiratory failure and on mechanical ventilation; shock; ICU monitoring and treatment in combination with other organ failures.

It is recommended that COVID-19 patients who are elderly (≥ 75 years old) and have organ dysfunction or poorly controlled underlying diseases, be treated as critical cases.

The goal is to achieve early diagnosis, early isolation, and early treatment. In order to discover the patient early who is suffering from severe or critical illness, some clinical parameters should be dynamically monitored during diagnosis and treatment, including oxygenation index, pulmonary imaging, and the levels of plasma cytokines.

4.3 Early Warning and Treatment of Severe COVID-19 Cases

Fanjun Cheng

Preliminary observations indicate that age ≥ 65 years, CRP ≥ 20 mg/L, lymphocyte count $\leq 800/\mu\text{L}$, eosinophil deficiency ($\leq 100/\mu\text{L}$), pulmonary consolidation involving internal bands, and abnormal DIC screening may be independent prognostic factors, which are warning signs of a worsening condition [8–10]. Patients with three or more conditions above should be treated as soon as possible to reduce the risk of deterioration, ultimately improve overall efficacy and reduce mortality rate.

Retrospective studies have found that elevated neutrophils and non-elevated or decreased lymphocytes, with or without an associated decrease in eosinophils, also predicts a poor prognosis in addition to indicating a concomitant bacterial infection [8].

Damage to the respiratory system, as well as cardiovascular system, liver, and kidneys is common. Important causes include ischemia, hypoxia, and pharmaceuticals in addition to viral infections [11].

It is recommended to list the elderly (≥ 65 years old), or patients with underlying diseases (bronchitis, COPD, coronary heart disease, severe hypertension, insulin-dependent diabetes, rheumatic autoimmune disease, other infectious diseases,

tumors, etc.) or patients receiving immunosuppressive therapy, organ transplant, dialysis, and radiotherapy or chemotherapy as independent risk factors. Patients with the above conditions combined with SARS-CoV-2 infection can be admitted to intensive care.

It is recommended that COVID-19 patients of advanced age (≥ 75 years old), who have any organ dysfunction, or poorly controlled underlying diseases be admitted to intensive care for critical cases.

It is recommended that patients who have been sick for more than a week and who have not seen significant improvement during initial treatment should be treated as potential severe/critical cases, and be placed under enhanced clinical observation and given more frequent auxiliary examinations. If the condition is getting worse, empirical first response treatment is implemented immediately according to the standards for severe cases.

4.4 Multidisciplinary Collaborative and Personalized Therapy

Yong Gao

A multidisciplinary team (MDT) [12–15] is an important hospital management strategy to improve the quality of clinical diagnosis and treatment, and has played an important role in the treatment of critical COVID-19 patients. COVID-19 can affect multiple organs and systems in the human body. At the same time, elderly patients often suffer from several underlying comorbidities. Cases can turn severe rapidly, often involving multiple organs, resulting in failure of multiple organs, and requiring multidisciplinary assistance. In order to effectively treat severe and critical cases, and prevent mild cases from becoming severe, hospitals should establish a multidisciplinary collaborative treatment and early warning system. General hospitals take advantage of multiple departments, integrating respiratory medicine, the ICU, anesthesia, general surgery, cardiology, hematology, neurology, obstetrics and gynecology, orthopedics, endocrinology, vascular surgery, neurosurgery. Traditional Chinese Medicine, laboratories, interventional radiology, ultrasound, pharmacy, psychiatry, rehabilitation, and nursing to form a COVID-19 team of experts, and establish a complete multidisciplinary collaborative diagnosis and treatment (MDT) mechanism, conduct daily workshops, and allow doctors in isolated ward areas to participate in daily video conferences over the Internet, coordinate diagnosis and treatment, formulate scientific, systematic, and individualized treatment plans for each severe and critical patient, and provide multidisciplinary consultations as needed. At the same time, a multidisciplinary surgical team from obstetrics and gynecology, orthopedics, general surgery, neurosurgery, vascular surgery, radiological intervention, critical care medicine, anesthesia, and the OR is established to make surgical procedures more accessible and provide 24-h ensure for emergency surgery for COVID-19 patients. In order to complete treatment goals in different periods, tracheal intubation teams, pulmonary response teams, cardiac response

teams, brain care teams, venous catheterization teams, VTE prevention and treatment teams, and bone-building teams are established. Attention is paid to the treatment needs of COVID-19 patients in different periods to further refine the treatment goals of different types of patients.

Ensuring the quality of MDT is the core of MDT. Discussion should rely on expertise from the various disciplines, as well as focus on key issues in diagnosis and treatment. The various opinions and suggestions of experts who understand the overall situation and have extensive experience must be combined to determine the final treatment plan.

Improving the organizational efficiency of MDT is the key to MDT. The doctor submitting an MDT application should emphasize on the difficulties with diagnosis and treatment, which helps experts to quickly clarify the purpose of the MDT and pay attention to the evolution of the disease, while also conducting a comprehensive analysis of the patient's underlying comorbidities, complications, and daily test and examination results in order to determine the direction of the disease, make early intervention, prevent disease progressing, and take measures such as antivirals, oxygen therapy, and nutritional support.

Individualized diagnosis and treatment are the outcomes of MDT. The treatment plan should be based on individual and precise strategies, and fully take into account the differences in the treatment of different individuals, different disease courses, and different types of patients.

Multidisciplinary collaborative personalized treatment provides comprehensive, standardized, individualized diagnosis, and treatment programs for COVID-19 patients. At the same time, seminars also provide a platform for all subspecialties to learn and communicate, while also creating conditions for further improving medical staff's knowledge and ability regarding diagnosis and treatment of COVID-19.

The core concept of a multidisciplinary comprehensive treatment team is actually patient centered. It is to provide timely and effective treatment plans, to make treatment more reasonable, and discussions more complete. In the event of a major public health emergency, general hospitals are temporarily converted to infectious disease hospitals. In order to ensure the success rate of treatment, a new, multiparty treatment system must be promptly built based on the original operation system to make the transition from a nonemergency state to a wartime state. In the process of accomplishing this goal, how to take full advantage of the multidisciplinary diagnostic and treatment strengths of a general hospital in order to reduce the mortality rate of patients, especially critical patients, is always the most important consideration during epidemic prevention and control.

General hospitals possess established MDT modes and teams. The inherent advantages of an organizational, and functional medical management structure based on a scientific management mode, and wartime medical service make MDT work easier to promote. During the treatment of COVID-19, MDT has played an important comprehensive treatment function. At the same time, it must be acknowledged that due to the short time frame of the diagnosis and treatment of COVID-19 patients being carried on by multidisciplinary collaboration under this special management model, patients' follow-up still needs to be further improved, and

evaluation of the efficacy of MDT diagnosis and treatment plans also requires long-term experience and analysis.

4.5 Symptomatic and Supportive Treatment

Jianchu Zhang

Initial symptoms of COVID-19 include fever, cough, and fatigue. Treatment principles include antiviral therapy, general symptomatic therapy, respiratory and circulatory support, management of acute kidney injury, and renal replacement therapy [16].

Antipyretic treatment: Fever is generally controlled by physical cooling and oral rehydration. Antipyretic medicine can be used in patients with high fever. Paracetamol (acetaminophen) is recommended. Glucocorticoid is not recommended for a fever [17]. It can be cautiously used after weighing the pros and cons. When using antipyretic medicine, we should pay attention to the patient's sweating status, balancing the water and electrolytes.

Cough and expectoration: We found that most patients complained of cough but with less expectoration during managing the COVID-19 patients. Autopsy of COVID-19 found that distal airways were blocked by mucus plugs, so the use of apophlegmatisant is very important. Ambroxol hydrochloride and acetylcysteine are commonly used during practice [18]. If the patient suffers severe cough, an antitussive can be appropriately added.

Fatigue: In the early stages, fatigue is pronounced due to fever, poor appetite, and low oral intake. Proper nutritional support can be administered while paying attention to the rest.

Respiratory support: The most obvious manifestation of respiratory impairment is hypoxemia in COVID-19 patients. When hypoxemia is effectively corrected, it can significantly mitigate multiorgan damage and dysfunction due to hypoxia, and significantly improve the prognosis of disease. For related content, see Chap. 7 of Part IV.

Circulatory support: When COVID-19 turns from severe to critical, we should pay more attention to circulation problems. Patients in the critical stages of the disease are likely to suffer from shock. Tissue perfusion disorders and even multiple organ failures may occur. Early rapid fluid resuscitation can improve the prognosis of shock. We should pay more attention to fluid balance strategies, avoiding excess or insufficient fluid resuscitation. If necessary, vasoactive medicine may be considered. See the following sections for more details.

Electrolyte imbalance and nutritional support: Many patients were complicated with hypokalemia, hypocalcemia, hyponatremia, and significant weight loss during admission. Interventional methods can be taken by dietitian support or related medications.

Treatment of Acute Renal Injury and Renal Replacement Therapy: Critical patients are vulnerable to acute kidney injury. It is necessary to investigate the

causes of AKI for intervention. CRRT can be considered for cases of renal failure which shows: (1) hyperkalemia; (2) acidosis; (3) pulmonary edema or excessive fluid load; and (4) multiple organ dysfunction during fluid management.

Symptomatic treatment of inflammatory cytokines storm: For the early-middle stages of cytokine storm in severe and critical patients, blood purification techniques can be used to clear inflammatory factors and block the cytokine storm, thereby reducing damage to the body caused by the inflammatory response. Low-dose, short-course glucocorticoids can be used with caution in the following cases: early intervention for severe and critical patients with a progressively deteriorating oxygenation index, or rapidly progressing pulmonary imaging with a significant increase in the affected area (review of lung CT at 48 h indicates progression of more than 50%) [19].

Broad-spectrum protease inhibitors can be considered [20]. For patients with significantly elevated IL-6 in the blood, the use of IL-6R monoclonal antibodies can be taken into account (See related sections) [21].

Deep venous thrombosis prophylaxis: Incidence of deep venous thrombosis is high in severe and critical patients. D-dimer is also an indicator of poor prognosis. After fully assessing the risk of bleeding, anticoagulation can be used as an early preventive treatment [21].

4.6 Antiviral Treatment

Jianchu Zhang

Early antiviral therapy can reduce viral replication and shorten viral clearance times, as well as reduce the incidence of severe and critical illnesses. Antiviral drugs with clearly demonstrated clinical efficacy against COVID-19 are lacking. However, there are a few that have received initial clinical validation.

Currently available drugs for clinical trial: Arbidol tablets [21, 22] (200 mg, po, q8h), or Favipiravir [19] (1600 mg, q12h on the first day, 600 mg, q12h thereafter), or Lopinavir/Ritonavir Tablets [21] (400/100 mg, po, q12h), α -interferon (5 million IU in 2 mL normal saline for inhalation, bid). If initial efficacy is poor, hydroxychloroquine sulfate (200 mg, po, q12h) or chloroquine phosphate can be used [23], (chloroquine phosphate can be used in adults aged 18–65 years. For those weighing more than 50 kg, give 500 mg, q12h; for less than 50 kg, give 500 mg, q12h for the first 2 days, then 500 mg, qd on Day 3–7).

For patients who are intolerant to Lopinavir/Ritonavir, consider giving oral Darunavir/Cobicistat (800 mg/150 mg, qd) instead. We have recently tried this clinically in a small number of patients over 70 years of age and achieved good clinical results and tolerance.

In mild/moderate cases, single-agent therapy is the main treatment. In severe/critical cases, combination therapy may be considered, such as Arbidol Tablets combined with Lopinavir/Ritonavir, or Hydroxychloroquine sulfate, or chloroquine phosphate. Lopinavir/ritonavir and hydroxychloroquine sulfate/chloroquine phosphate should be cautiously in combination due to their QT interval prolongation

effects and other adverse reactions [24]. Concurrent use of three or more antiviral drugs is not recommended [21].

Course of antiviral therapy: Chloroquine phosphate for no more than 7 days; other drug regimens are generally 10 days, or until viral nucleic acid tests are negative for three or more times [21].

In addition, patients with severe and critical COVID-19 who have a positive respiratory virus test, or non-severe/critical patients with rapid disease progression, or underlying with immunosuppression, maybe also considered the use of plasma therapy during recovery stage (see relevant chapters for details).

4.7 Countering Hypoxemia

Zhaohui Fu

Hypoxemia is the most prominent feature of impaired respiratory function due to COVID-19. Timely and effective correction of hypoxemia and alleviation of secondary organ damage and dysfunction caused by respiratory distress and hypoxia are of great significance for improving patient prognosis.

4.7.1 Nasal Cannula

Oxygen therapy should be considered immediately in the following circumstances: $\text{SPO}_2 < 93\%$, respiratory distress ($\text{RR} > 24$ bpm). Adjust the oxygen flow to 2–5 L/min according to blood oxygen saturation (connect to a humidifier bottle).

4.7.2 Face Mask Oxygen

If the oxygen saturation with the nasal cannula therapy is still $< 93\%$, the patient is in respiratory distress, or the patient's initial SPO_2 is $< 85\%$, give oxygen by face mask (flow 5–10 L/min) to correct the hypoxia as soon as possible. If available, other forms of respiratory support such as high-flow nasal cannula can be used.

4.7.3 High-Flow Nasal Cannula

High-flow nasal cannula (HFNC) is used to provide patients with a high flow of oxygen (up to 60–80 L/min) at a relatively constant concentration (21–100%), temperature (31–37 °C) intranasally. Its applications to COVID-19 are as follows:

4.7.3.1 Indications

Condition not indicated for urgent tracheal intubation; mild-to-moderate type I respiratory failure ($150 \text{ mmHg} \leq \text{P/F} < 300 \text{ mmHg}$); mild respiratory distress (respiratory rate > 24 bpm); intolerance to traditional oxygen therapy or noninvasive

positive pressure ventilation or with contraindications; assistance with withdrawal of ventilator and extubation (P/F: arterial oxygen partial pressure/fractional inspired oxygen concentration).

4.7.3.2 Contraindications

Severe type I respiratory failure, ventilatory disorder ($\text{pH} < 7.30$); paradoxical breathing; poor airway protection, high risk of aspiration; unstable hemodynamics, requiring vasoactive drugs; inability to wear HFNC due to facial or upper respiratory surgery; severely blocked nasal cavity; HFNC intolerance.

4.7.3.3 Clinical Operation of HFNC

4.7.3.3.1 Temperature Settings

The temperature for non-tracheotomy patients is set to 31 or 34 °C, and then adjusted according to comfort and sputum viscosity. For tracheotomy patients, the temperature is set to 37 °C.

4.7.3.3.2 Flow Rate

Set initially to 35–45 L/min and titrate the inhaled oxygen concentration to maintain blood oxygen saturation above 93%. Combine with blood gas analysis to dynamically adjust the flow rate and oxygen concentration.

4.7.3.4 HFNC Withdrawal Criteria

After the primary disease is controlled, gradually reduce the HFNC parameters. If $\text{HFNC} < 25 \text{ L/min}$ and $\text{FiO}_2 < 30\%$ can be achieved, oxygen can be given by nasal cannula.

4.7.3.5 Precautions

(1) Fully communicate with the patient before placing them on the machine. Explain the purpose of treatment and obtain the patient's consent. (2) Posture: The semi-recumbent position is recommended. (3) Choose a suitable model of nasal stopper. A nasal cannula less than 50% of the inner diameter of the nostril is recommended. (4) Advise patients who breathe with an open mouth to close their mouth. If they are not able to do so, change to a face mask. (5) Avoid excessive and insufficient humidification. Observe airway secretions closely and suck sputum as needed. (6) Pay attention to water accumulation in the pipeline. (7) Carefully observe vital signs, breathing patterns, and changes in blood gas analysis during use to avoid delayed intubation. (8) Carefully adjust the tightness of the nasal stoppers. (9) Pay attention to various alarms during use and deal with them promptly.

4.7.3.6 Monitoring

After beginning HFNC therapy (within 2–4 h), the response to treatment should be closely monitored. If the following conditions persist, a different support method should be utilized: respiratory rate $>35 \text{ bpm}$; $\text{SpO}_2 < 90\%$; chest and abdominal paradoxical breathing; combined $\text{PCO}_2 > 45 \text{ mmHg}$; $\text{pH} < 7.35$; unstable circulation and other situations.

4.7.4 Noninvasive Positive Pressure Ventilation

Common modes of noninvasive positive pressure ventilation (NPPV) include continuous positive airway pressure (CPAP) and bi-level positive pressure ventilation (BiPAP). Noninvasive positive pressure ventilation requires attention to the details of treatment when treating hypoxic respiratory failure.

4.7.4.1 Mode Selection

Because CPAP has better human–machine synchronization than BiPAP, the CPAP mode is preferred; BiPAP may be considered for patients who cannot tolerate CPAP, or have COPD.

4.7.4.2 Initial Pressure Setting

(1) Set CPAP to 5 cm H₂O FiO₂ 100%, and perform an arterial blood gas analysis after 30–60 min to evaluate the ARDS severity. (2) Adjust pressure gradually until reaching 8–10 cm H₂O.

4.7.4.3 Contraindications

Excessive airway secretions or obstructed expectoration; severe infection; extreme nervousness; severe hypoxemia PaO₂ < 45 mmHg; severe acidosis pH < 7.20; recent upper abdominal surgery; severe obesity; upper airway mechanical obstruction. Heartbeat or breathing cessation, weak spontaneous breathing, coma; high possibility of aspiration; concomitant organ failure (hemodynamic instability, severe brain disease, gastrointestinal bleeding or perforation); trauma, surgery or malformation related to the face; uncooperative.

4.7.4.4 Precautions

(1) Communicate and discuss the process with the patient before placing them on the machine. Address concerns to improve cooperation. (2) Posture: semi-recumbent position, bed raised 30–45°. (3) Give patient water every 2 h. (4) The mask should not be worn for more than 4–6 h to avoid pressure ulcers. (5) Choose a face mask suited to the patient's face. (6) Make sure the mask is fixed in place and not too loose or tight. (7) Instruct the patient to close their mouth and breathe through their nose as much as possible. (8) If the patient's gastrointestinal bloating is obvious, consider inserting a gastric tube for gastrointestinal decompression. (9) Carefully observe vital signs, changes in breathing patterns, and blood gas analysis, to identify high-risk factors for failure, and avoid delayed intubation.

Common high-risk factors for failure of noninvasive positive pressure therapy in hypoxemic respiratory failure: shock; multiple organ failure; high APACHEII score; P/F < 147 mmHg; VTe > 9.5 mL/kg; high RR; high minute ventilation; imaging improves after NIV therapy; increased PaCO₂.

4.7.4.5 Withdrawal

After the patient's primary disease is controlled and the condition is stable, the following methods can be adopted: (1) Gradually reduce the pressure. (2) Gradually reduce the ventilation time (first during the day, then at night).

4.7.5 Invasive Positive Pressure Ventilation

Early tracheal intubation and invasive ventilation should be considered immediately to avoid the risk of death due to delayed intubation if the respiratory failure has still not been corrected after 2 h of HFNC or NPPV therapy; the respiratory distress is progressively getting worse; with hypoxemia, altered consciousness; become hemodynamically unstable, or with elevated PaCO₂.

4.7.5.1 Mechanical Ventilation Mode

A/C is preferred. If the patient has strong respiration, consider the PSV + PEEP mode.

4.7.5.2 Ventilation Strategies

1. Tidal volume: Small tidal volume (4–8 mL/kg).
2. Plateau pressure: Control P_{plat} < 30 mm H₂O.
3. PEEP: High PEEP level (>12 cm H₂O); PEEP can be adjusted according to the resilience of the lung. There is currently no standard for setting individualized PEEP levels.
4. Ventilation with prone position: Can be implemented routinely, no less than 12 h each time.
5. Muscle relaxant drugs: Patients with severe respiratory distress and difficulty adjusting to the machine, difficulty executing low tidal volume during respiratory driving, or severe ARDS, can be considered for administration but not routinely recommended.
6. Pulmonary recruitment maneuver: It is mainly used as a remedy for patients with refractory hypoxemia and cannot be routinely applied to patients with ARDS.

4.7.5.3 Management of Artificial Airway

(1) Use a closed suction tube to drain airway secretions. (2) Aspirate sputum only as needed in order to reduce the risk of choking. (3) Avoid or reduce bedside fiberoptic bronchoscopy. (4) A tracheal tube with subglottic suction is recommended during intubation, as well as continuous negative pressure for subglottic drainage. (5) Test the balloon pressure and maintain at 25–30 cm H₂O to avoid air leakage and pressure ulcers. (6) Avoid physical therapy on the chest. (7) Carefully monitor the patient and avoid unplanned extubation. (8) Perform tracheotomies with caution.

4.7.5.4 Precautions

(1) Daily assessment to see if able to extubate; (2) checking the vital signs, blood gas, and adjusting the corresponding parameters of the ventilator; (3) observing complications related to the ventilator: pneumothorax, poor drainage, displacement of tracheal tube, etc.; (4) Pay close attention to various alarms during ventilation and deal with them in time; (5) Be cautious to prevent VAP.

4.7.5.5 Alveolar Recruitment

Alveolar recruitment may improve the heterogeneity of the lung in patients with ARDS, but can be concomitant with severe respiratory and circulatory complications. We do not recommend the routine use of alveolar recruitment. If it is necessary, first assess the expandability of the lung.

4.7.5.6 Prone Position Ventilation

Most of critical COVID-19 patients respond well to prone ventilation. Oxygenation and lung mechanics can be significantly improved in a short time. We recommend routine prone ventilation for patients with $\text{PaO}_2/\text{FiO}_2 < 150$ mmHg or serious imaging findings without contraindication. Each session should last 16 h or more. When the $\text{PaO}_2/\text{FiO}_2$ of a patient in the supine position for more than 4 h is still greater than 150 mmHg, use of the prone position can be suspended.

Prone ventilation may be attempted in patients awake who have not been intubated and have no significant respiratory distress, but with poor oxygenation and imaging showing consolidation in a gravity-dependent portion of the lung. Each session should last at least 4 h. Depending on the efficacy and tolerance, the prone position can be used many times a day.

4.7.5.7 Prevention of Reflux Aspiration

Gastric residual volume and gastrointestinal function should be routinely evaluated and appropriate enteral nutrition given as soon as possible. An indwelling nasogastric tube is recommended for jejunal nutrition and a gastric tube for continuous decompression. Enteral nutrition should be discontinued prior to the patient's transport. Aspirate with a 50-mL syringe. Use a 30° semi-seated position if not contraindicated.

4.7.5.8 Management of Fluids

Excessive fluid infusion can significantly worsen hypoxemia in patients with COVID-19. In cases where the patient's circulatory perfusion is being maintained, the influx of fluid should be strictly controlled. This positively reduces pulmonary exudation and improves oxygenation.

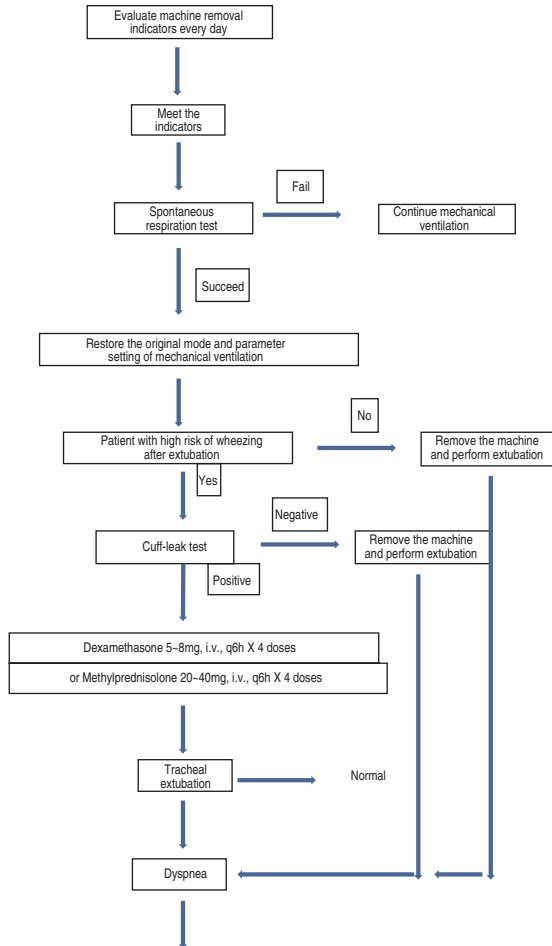
4.7.5.9 Strategies for Prevention of Ventilator-Associated Pneumonia

The prevention and management strategy for clustered ventilator-associated pneumonia (VAP) should be strictly implemented: (1) Select the appropriate type of tracheal intubation. (2) Use tracheal intubation with subglottic suction (aspirate every 2 h with a 20-mL syringe). (3) Ensure the tube is positioned correctly at an appropriate depth and properly fixed, and avoid pulling. (4) Maintain the pressure of the airbag at 30–35 cm H₂O (1 cm H₂O = 0.098 kPa) and check every 4 h. (5) When repositioning the patient, monitor airbag pressure monitoring and remove condensate water (inline to one side using two people and pour into a covered container of chlorinated disinfectant), and dispose of secretions on the airbag. (6) Clear the patient's mouth and nose secretions.

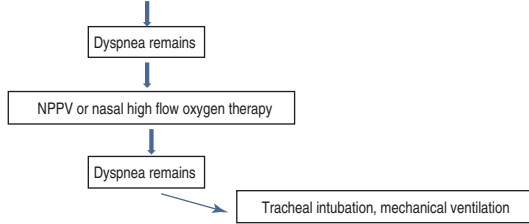
4.7.5.10 Timing and Strategies for Ventilator Withdrawal

It is reasonable to begin to reduce sedatives and awake the patient as the $\text{PaO}_2/\text{FiO}_2$ is >150 mmHg. If it is allowed, the patient can be extubated as soon as possible. HFNC or NIV is used for continuous respiratory support after extubation.

Procedure for Ventilator Withdrawal and Extubation of COVID-19 Patients



Cause	Laryngeal edema	Bronchospasm	Obstruction of airway by secretions	Vocal cord paralysis	Residual muscle relaxant
Handling	Epinephrine 0.3mg+saline 3ml, aerosol inhalation	Bronchodilator	Sputum suction, supervise expectoration, dilute sputum by nebulization, expectorate by vibration, assist in expectoration	Recurrent laryngeal nerve injured?	muscle relaxant antagonist



4.8 Nutritional Support and Intestinal Microbiomic Balance

Shi Liu

Common digestive symptoms in patients with COVID-19, including loss of appetite, nausea and vomiting, diarrhea, and abdominal pain, especially the high proportion of diarrhea, may be related to the viral infections involving the intestine. Antibiotics, antivirals, and other medications are also common cause of gastrointestinal symptoms. Enterovirus infection and the use of antibiotics can cause imbalances of intestinal microbiota, which may be the important mechanism involved in COVID-19 intestinal symptoms. The homeostasis of the intestinal microbiome, that is, the health and integrity of the intestinal flora, plays an important role in maintaining the well-being of the human body. The imbalances of intestinal microbiome may destroy the mucosal barrier, and cause the immune disturbances of the mucosa, or ectopic colonization of intestinal bacteria, which can induce secondary infections and aggravate systemic inflammation. Therefore, more attention should be paid to establish the therapeutic effect of intestinal microbiomic balance and enteral nutrition in COVID-19 patients.

4.8.1 Microbiotic Preparations

Microbiotic regulators include probiotics, prebiotics, and synbiotics, which can correct imbalances in the intestinal microbiome, increase the ratio of beneficial gut bacteria, repair the intestinal mucosal barrier, improve inflammation of the intestinal mucosa, and reduce bacterial translocation and secondary infections [25]. Commonly used microbiotic preparations include active bacteria such as Golden Bifid and ZhengChangSheng, and deactivated bacteria such as Mamiai and Lactéol Fort.

Microbiotic preparations can be given to patients with gastrointestinal symptoms such as diarrhea, bloating, or indigestion. Active bacterial preparations of *Bifidobacterium* and *Lactobacillus* are recommended. A mixture of multiple species and strains is ideal and should be taken for at least 2 weeks [25, 26].

For patients on antibiotics who cannot discontinue usage, fungal probiotic preparations such as *Saccharomyces boulardii*, or deactivated bacteria are advised to be used, but the efficacy requires further evaluation [27].

For patients with diarrhea, stool culture and enterovirus testing are recommended. If possible, an intestinal flora analysis can be conducted, in order to adjust utilization of antibacterial medicine and give targeted microbiotic preparations according to the patient's particular intestinal flora profile [27].

Note: Concomitant administration of probiotics and adsorbents such as activated carbon or astringents such as tannin and bismuth subcarbonate is contraindicated. Microbiotic preparations should be stored in a cool and dry place, and be taken with warm water less than 40 °C.

4.8.2 Nutritional Support

Enteral nutritional support is an important means to maintain the balance in the intestinal microbiome, and also the key to improving the high risk and poor prognosis associated with malnutrition in COVID-19 patients. All patients should be evaluated for nutritional risk and gastrointestinal function, and enteral nutrition support should be implemented as early as possible.

4.8.2.1 Enteral Nutrition

Enteral nutrition is preferred and should begin as soon as possible. It aids in restoring intestinal function, balancing intestinal microbiota, and improving intestinal mucosal barrier and intestinal immune function [28].

4.8.2.1.1 Modalities of Enteral Nutrition

Oral feeding is preferred. For patients who cannot eat independently, an indwelling nasogastric tube may be considered. For severe and critical patients with frequent acute gastrointestinal dysfunction and tracheal intubation, post-pyloric feeding is recommended with a jejunal tube [28, 29].

4.8.2.1.2 Selection of Nutrient Solution

For patients with acceptable gastrointestinal function, intact protein with high-calorie is recommended, e.g., Nutrison with fiber, Supportan, RuiDai, or RuiSu without fiber. For patients with gastrointestinal damage and poor digestive function, short peptide preparations that are predigested and directly absorbed are recommended, e.g., Peptisorb. For diabetic patients, blood glucose must be monitored, and a low-glucose nutritional solution suitable for blood glucose controlling should be selected, e.g., RuiDai [29].

4.8.2.1.3 Daily Caloric Intake

Daily dosage should be calculated according to the patient's weight and nutritional status [29, 30]. For non-cachectic patients, 25–30 kcal/kg/day is recommended. For cachectic patients, the recommended dosage is 40–50 kcal/kg/day, and the target protein amount is 1.2–2.0 g/kg/day. When administering medication via a feeding tube, dosage should be gradually increased from a small one. The drip rate on the first day is about 20 mL/h, and then gradually increased by 20 mL/h/day. The maximum drip rate is 100 mL/h. The nutrient solution should be heated moderately (about 35 °C). The semi-recumbent position is recommended during tube feeding to prevent accidental aspiration.

4.8.2.2 Parenteral Nutrition

For patients with significant intestinal failure, bloating, or other conditions that require fasting, and high risk of aspiration, temporary parenteral nutrition may be considered. Pay attention to the ratio of various nutrients in the nutrient solution such as amino acids, fat emulsion, glucose, vitamins, and trace elements. At the same time, pay attention to electrolyte and liquid balance, and then gradually transition to enteral nutrition or autonomous diet after the condition improves.

4.9 Early Respiratory Rehabilitation

Qingtang Zhu

4.9.1 Purposes of Respiratory Rehabilitation in Severe Cases

1. Alleviate respiratory difficulties.
2. Increase lung ventilation and improve hypoxemia.
3. Promote sputum evacuation and reduce sputum retention.
4. Restore patients' exercise tolerance and achieve functional independence.
5. Reduce anxiety and depression, and increase confidence in fighting diseases.
6. Avoid long-term bed rest, which causing systemic complications.

4.9.2 Principles of Respiratory Rehabilitation for Severe Patients

4.9.2.1 Safety Principle

Before rehabilitation, an evaluation should be conducted to rule out contraindications, and relevant indicators should be monitored throughout the treatment to ensure the safety of the patient. The safety of the therapist should also be ensured.

4.9.2.2 Effectiveness Principle

Through evaluation, the main problems of the patient are identified. The appropriate intervention measures are selected according to the problem, and there should be an evaluation method to evaluate the treatment effect.

4.9.2.3 Individualization Principle

The most severe patients are the elders, and may have multiple underlying conditions. Respiratory rehabilitation measures should be selected according to the patient's specific condition. Appropriate intensity, frequency, and duration of treatments as well as the monitoring and evaluation of treatment efficacy and timely feedback and correction are made to ensure maximal benefits.

4.9.3 Contraindications for Respiratory Rehabilitation of Severe Patients

1. Fraction of inspired oxygen (FiO_2) >0.6 , blood oxygen saturation (SpO_2) $<90\%$, or respiratory rate >40 breaths/min.
2. In patients with mechanically assisted ventilation, the positive end-expiratory pressure is greater than 10 cm H_2O , or there is a patient incompatibility with the ventilator or unsafe airway risk.
3. Systolic pressure >180 mmHg or <90 mmHg; or mean arterial pressure <65 mmHg or >110 mmHg.

4. Heart rate <40 bpm or >120 bpm.
5. Malignant arrhythmia or severe myocardial ischemia.
6. Recent unstable deep vein thrombosis and pulmonary embolism.
7. Coma or significant restlessness and inability to cooperate with active rehabilitation.
8. Presentation with intracranial hypertension or monitoring shows intracranial pressure >20 cm H₂O.
9. Clinical conditions such as active hemorrhage, progressive liver and kidney failure, severe acid–base imbalance or electrolyte disturbance, severe edema, or abdominal distension that may be aggravated by activity.
10. Body temperature <35 °C or >38.5 °C.

4.9.4 Respiratory Rehabilitation of Severe Patients

Routine procedure for respiratory rehabilitation of severe patients: First, rule out contraindications. Second, assess patient's dysfunction based on the patient's specific condition, generally including dyspnea, decreased ventilatory function, decreased airway clearance, and decreased exercise tolerance. Most patients may have multiple dysfunctions, but one or two are pronounced, or there may be other dysfunctions caused by underlying conditions, e.g., decreased physical activity. Next, an appropriate combination of respiratory rehabilitation treatment techniques is selected for intervention based on the patient's functional issues. The entire intervention should be monitored, so the treatment method and intensity can be adjusted or revised at any time according to the patient's clinical picture. Assessment should be carried out prior to each treatment session. At the end of each treatment, it is necessary to evaluate its efficacy and safety, as well as adjust and optimize the intervention based on the outcome.

The pre-treatment procedure is shown in Fig. 4.1.

4.9.5 Precautions During Respiratory Rehabilitation

Prior to each treatment, the patient's consciousness, vital signs, oxygen saturation, vasoactive drug use, symptoms, and extremity condition must be evaluated.

During treatment, attention must be paid to the patient's subjective symptoms, so as not to induce dyspnea, pain, or obvious strain.

If the patient shows a decrease in SaO₂ to less than 90%, or a decrease of more than 4% from the baseline (e.g., the original SaO₂ of 95% decreased to 91%), treatment should be suspended and the doctor should be informed.

If the patient's respiratory rate \geq 40 breaths/min, SBP decreases to \leq 90 mmHg, or SBP \geq 180 mmHg, heart rate \leq 40 bpm or \geq 120 bpm, suspend treatment, observe and inform the doctor.

If the patient has poor awareness, indifference, decreased speech, uncoordinated limb movements, or restlessness, immediately stop treatment and inform the doctor.

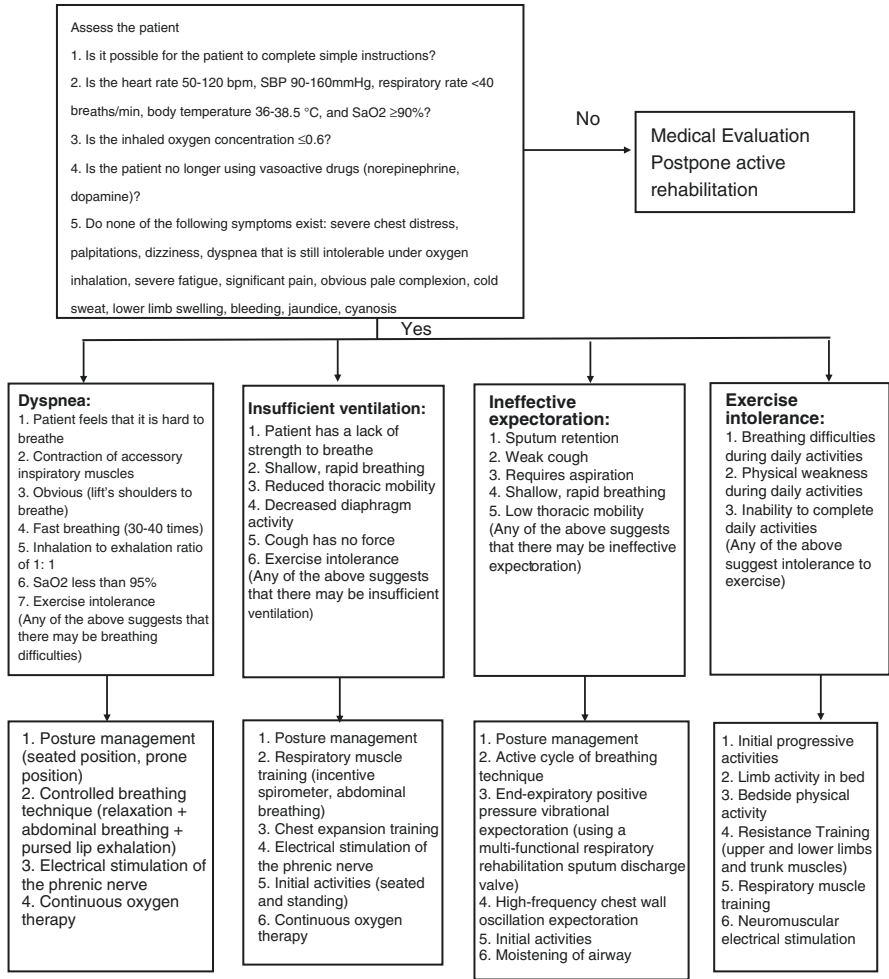


Fig. 4.1 Procedure for respiratory rehabilitation of hospitalized patients with severe COVID-19

If the patient experiences dizziness, faintness, palpitations, chest pain, chest tightness, weakness in extremities, palor, clammy skin, severe pain, vomiting, the treatment should be stopped immediately, and the doctor should be informed.

It is recommended to give oxygen throughout the treatment and monitor finger pulse oxygen saturation. Choose ECG and blood pressure monitoring according to the patient’s condition.

Therapists should protect themselves and avoid direct exposure to the patient’s exhaled airflow and coughed secretions.

4.9.6 Respiratory Rehabilitation Techniques

4.9.6.1 Posture Management

Improving posture helps to avoid sputum retention, as well as prevent and improve atelectasis and dyspnea. During semi-recumbent management, the patient assumes a supine position, raises the knee joint 10–15° or places a small pillow under the knee. Raising the head of the patient's bed to 30–45° allows the patient to adapt for a short period of time and gradually transition to 60°. During lateral position management, the patient turns over and changes to a side lying position with the help of the therapist. The head and back are supported with pillows. The arms lie freely and the legs are positioned as if taking a step. Change the position every 20–120 min according to the patient's vital signs and/or subjective tolerance. The forward tilt position can reduce breathing effort and relieve symptoms of dyspnea. When the patient is seated in or on the bed, keep the torso tilted forward 20–45°, and provide a small table to help the patient maintain a comfortable sitting position. The forearms are supported on the table, elbow joints flexed at 80–110°, or a pillow can be placed on the table for the patient to rest their head. If their feet do not reach the ground, support such as a low stool should be given, and the therapist or nurse should watch over them.

4.9.6.2 Controlled Breathing Techniques

Controlled breathing helps patients establish normal breathing patterns and learn how to breathe while relaxed. The patient assumes a seated, semi-seated, or side lying position, and is encouraged to relax the shoulders and upper chest. The therapist puts one hand on the patient's shoulder to prompt the patient to relax and puts the other hand on the patient's upper abdomen to enhance sensory input. The patient inhales smoothly through the nose and exhales through the mouth. The therapist gently presses inward and upward during exhalation to guide breathing. The patient breathes tidally at their own speed and depth for 1–3 min. Note that the abdomen should expand on inhalation and contract on exhalation. The shoulders should not rise during inhalation.

4.9.6.3 Chest Expansion Training

The purpose of chest expansion training is to improve thoracic mobility, increase lung capacity, and strengthen respiratory muscles. The patient is placed in a semi-recumbent position and the therapist or patient's hands are placed bilaterally on the eighth ribs. Using proprioceptive stimulation, make two breath adjustments from shallow to deep. For the third time of breathing, the patient is encouraged to take a deeper breath and hold it for 2–3 s. Exhalation should be through the mouth. During the exercise, the therapist or patient presses or vibrates the ribs with both hands. This further promotes chest expansion and increases ventilation and chest wall movement in this part of the lung. This step is done 5–10 times/min for 1–3 min. Make sure to prompt the patient to feel the air reaching the corresponding lung segment and then slowly exhale.

The patient's active thoracic expansion is also called a respiratory rehabilitation exercise. During training, you can take a sitting position or a semi-recumbent position to relax. When inhaling, both hands are raised forward or horizontally abducted at the same time, with the torso extended. Each action is repeated 10–20 times, and the exercise is done 2–3 times a day.

4.9.6.4 Respiratory Muscle Training (Using an Incentive Spirometer)

During the respiratory training with an incentive spirometer, the slight increase in inhalation resistance and sustained post-inhalation can increase the respiratory muscle strength and endurance of patients with reduced respiratory muscle function, improve atelectasis, and increase lung ventilation. The patient assumes a comfortable position, first takes 3–4 slow natural breaths, and on the fourth, exhales slowly and deeply. Then the spirometer is placed in the mouth, and the maximum inhalation is taken through the spirometer. The colored ball inside the device should be kept afloat for at least several seconds. When it can no longer be maintained, the spirometer can be removed and the patient can take several normal, relaxed breaths. The airflow with each inhalation can be observed visually and can increase the patient's desire to train. This step can be done in 5–7 sets per day, 8–10 times per set. This method of training should not continue for too long to prevent fatiguing the inspiratory muscles.

4.9.6.5 Active Cycle of Breathing Technique

This technique can effectively clear bronchial secretions and improve lung function, while not aggravating hypoxemia or airflow obstruction. This technique consists of three stages of ventilation chosen according to the patient's condition and repeated in cycles: breathing control (BC), thoracic expansion exercise (TEE), and forced expiratory technique (FET). FET entails huffing and breathing control (BC). Breathing control is a rest interval between two active parts: the patient is encouraged to relax the shoulders and upper chest. The therapist puts one hand on the patient's abdomen to enhance sensory input, and the other hand rests on the patient's shoulder, encouraging the patient to relax the upper chest and shoulders, and take tidal breaths according to their own speed and depth. In order to prevent airway spasm, breathing control must be carried out between stages.

4.9.6.6 End-Expiratory Positive Pressure Vibratory Expectorator (Using Multifunctional Respiratory Rehabilitation Sputum Discharge Valve)

The multifunctional respiratory rehabilitation sputum discharge valve is composed of three parts: a spirometer, a bacterial filter, and a nebulizer. The oscillating positive pressure generated in the airway loosens sputum to facilitate discharge. Assemble the three parts before use. Inject normal saline or nebulizer inhalation solution into the nebulizer and connect it with a high-flow oxygen breathing tube. Adjust the resistance knob of the multifunctional respiratory rehabilitation sputum discharge valve, turn it to green, and hand it to the patient. The therapist first demonstrates a strong and rapid exhalation after deep inhalation. Instruct the patient to

hold the device tightly in their mouth, inhale deeply through the mouth, and then exhale strongly and quickly. If the spirometer makes a popping sound when exhaling, or if the patient feels the airflow vibrating in the oral cavity, then the technique is effective. If the patient can blow and produce a shrill sound, it indicates the airway is expanding, secretions are being cleared of the respiratory tract, and expiratory muscles are being exercised. After repeating this step 2–5 times, instruct the patient to rest or cough to expectorate the sputum. Continue the next cycle after a 1-min break. Each set should be done 10–15 times. If the patient feels the green resistance position is less strenuous, adjust the resistance valve to the blue resistance position, and finally the red resistance position. Generally, the blue resistance level suffices for sputum expectoration. The technique is performed in 2–3 sets per day, and can be divided into different periods. Except during the demonstration, the therapist should stand in a position that avoids exposure to the patient's exhaled air flow.

4.9.6.7 High-Frequency Chest Wall Oscillation System

The patient assumes a lateral position. The machine vibrates at 20–35 Hz. The therapist places the tapping head over areas of heavy sputum accumulation for about 30 s, then lifts the instrument and places it on another area, moving inferior to superior, and lateral to medial. It promotes the excretion of sputum, and can improve the blood circulation of the lungs, prevent venous stasis, relax the respiratory muscles, improve the muscle tone of the whole body, and strengthen respiratory muscles to produce a cough reflex. Patients who have a weak cough or are physically frail should be aspirated with a sputum suction device.

4.9.6.8 Active Limb Movement

Exercising the limbs in bed is suitable for severe bedridden patients. Exercises can be carried out on the condition that the patient's vital signs and blood oxygenation are stable and he or she can actively cooperate. The goal is to use physical training to increase muscle strength, promote respiratory function, and improve limb movement when patients can tolerate exercise.

Bedside limb exercises are suitable for severe patients whose pneumonia are stabilized, but have reduced cardiopulmonary function and physical activity. The goal is to use physical training to increase muscle strength and limb movement, and improve cardiopulmonary function when patients are tolerant to exercise. Select exercises that activate the joints, step training, etc.

Walk Training Once the patient is able to stand and balance, and has completed bedside step training, he or she can begin walk training with support 2–3 times per day, 5–10 min per session.

Balance training, including standing on one leg, cross-walking, horizontal walking, and others, can be alternated with walking training.

4.9.6.9 Resistance Exercise

Resistance training is suitable for mild cases or severe cases in remission with stabilized pneumonia but with an obvious decline in muscle strength. Low-intensity resistance training can be used during hospitalization, and self antigravity training

such as sitting and standing, wall squats, wall pushes, or resistance training with elastic bands. Repeat each exercise 10–15 times for 2–3 sets, as long as the patient does not have dyspnea, pain, or severe fatigue. Blood oxygen needs to be monitored the entire time, and exercises requiring straining while holding the breath should be avoided.

4.10 Clinical Pharmacy Services for Hospitalized Patients

Yu Zhang, Yuyong Su and Xuefeng Cai

Pharmaceutical intervention is a key component of COVID-19 treatment. Most severe and critical COVID-19 patients have underlying comorbidities and complicated medication regimens. Therefore, integrated pharmaceutical services are very important to ensure the safety of patients' medication in a comprehensive and timely manner during the epidemic.

4.10.1 Ensuring the Supply of Medications During the Epidemic

When responding to COVID-19 public health emergencies, ensuring the supply of medications is of great importance to improve medical treatment capabilities and support epidemic prevention and control. Drug supply is mainly ensured by drawing up a drug catalog based on diagnosis and treatment scheme and guidelines relevant to COVID-19, to maintain a timely, effective, and sufficient supply to meet the needs of clinical diagnosis and treatment.

4.10.2 Clinical Pharmacy Services for COVID-19 Diagnosis and Treatment

During the epidemic, clinical pharmacists rely on information technology to offer clinical pharmacy services, including prescription confirmation, medication consultations, pharmacy ward rounding, pharmacy consultation, and pharmaceutical care.

4.10.2.1 Examination and Verification of Prescription

Clinical pharmacists formulate prescription review standards for pharmaceuticals usage in COVID-19's diagnosis and treatment based on the drug instructions, COVID-19 related diagnosis and treatment scheme, evidence-based medical data, and so forth. The clinical pharmacists keep the rules for updated review in a software database for reasonable usage of the medications, warn clinicians about reasonable use of medications when medical orders are issued, and promptly intercept medical orders which call for unreasonable use of medication. Clinical pharmacists review medical orders that have already been issued mainly for drug interactions, duplicate medications, and use in special populations. During the epidemic, an

online system for communicating about unreasonable medical orders should be established to ensure that communication between doctors and pharmacists is timely and efficient. Clinical pharmacists keep records of unreasonable medical orders upon review, and give feedback to clinicians by summarizing frequent problems.

4.10.2.2 Medication Consultation

4.10.2.2.1 Clinical Drug Usage Consultations

Antiviral drugs used during the epidemic are not standard stock medicines in hospitals, and some clinicians lack experience with using them. Clinical pharmacists can provide consultation for clinicians in terms of usage, dosage, indication, mechanism, and usage in special groups. Nurse inquiries mainly entail a drug's administration, compatibility, infusion rate, infusion stability, and storage. In order to reduce contact between personnel, inquiries can be made via Internet, phone, or video. Clinical pharmacists should summarize high-frequency inquiries, and write up the usage information for clinical reference.

4.10.2.2.2 Medication Consultation for Patients

Most hospitalized COVID-19 patients suffer from underlying diseases, and their drug regimens are specialized. Providing patients with specific medication consultations can ensure medication usage safe and effective. Inquiries may include medication usage, precautions, adverse reactions, and food–drug interactions. Clinical pharmacists should respect patients, protect patients' privacy, help patients articulate their inquiries patiently and meticulously and use plain language to answer patients' questions correctly during the medication consultation. The hospital's online consultation program can be used to provide patients with medication consultation, as well as WeChat, telephone, or other means.

4.10.2.3 Pharmacy Ward Rounds

Clinical pharmacists should participate in pharmacy ward rounding with protective gear. Pharmacy ward rounds include pharmaceutical consultation, evaluation of patients' compliance with a drug regimen, evaluation of medication efficacy, patient drug education, and monitoring of adverse reactions. Clinical pharmacists evaluate treatment efficacy based on the patient's examination indicators and posttreatment symptoms and signs if with improvement then formulate a monitoring plan, provide doctors with timely advice on the adjustment of the drug treatment plan. Communicate with nurses, about administration methods (such as drip rate). Drug storage (such as keep away from light), the order of drug administrating, and so on. Records are kept for clinical references.

4.10.2.4 Pharmacological Diagnostic Consultation and MDT Discussion

About 10% of COVID-19 patients have secondary infections during hospitalization, and most patients receive empirical antibacterial therapy [31]. Clinical pharmacist

participation in anti-infective pharmaceutical diagnostic consultations can promote the rational use of antibacterial drugs and enhance the effectiveness of anti-infective treatments. During consultations regarding anti-infective pharmaceuticals, clinical pharmacists must determine whether there is a bacterial infection, find the source of the secondary infection, and recommend suitable antibacterial drugs based on the infection site, common pathogens, patient status, medication history, high-risk factors for drug resistance, etc., to formulate a dosing regimen based on antimicrobial PK/PD modeling. Clinical pharmacists and clinicians form an MDT team to improve drug treatment plans for difficult and critical COVID-19 cases.

4.10.2.5 Pharmaceutical Care

Pharmaceutical care of COVID-19 patients includes observation of medication efficacy, safety monitoring, evaluation of drug interactions, and adjustment of drug regimen for special populations. The major special populations are children, pregnant women, the elderly, mechanically ventilated patients, patients with liver and kidney dysfunction, patients undergoing extracorporeal membrane oxygenation or renal replacement therapy, and other patients whose physiological characteristics and pharmaceutical combinations will alter a drug's pharmacokinetics and affect the efficacy. Therefore, clinical pharmacists must make recommendations to personalize treatment based on the patients' special physiological characteristics and medication risks.

Inhibition of viral replication is the key to control the development of COVID-19. Drugs for this purpose are the most frequently utilized in treatment. See Attachment 1 for the main points of pharmaceutical care of drugs in this class [32–38]. In the present, there is no drug confirmed to be effective against COVID-19. As progress is made in COVID-19 research, clinical trials of drugs for COVID-19 are also continuously adjusted. The latest version of the diagnosis and treatment plan developed by the National Health Commission of the People's Republic of China [39] mainly recommends the use of α -interferon, Lopinavir/Ritonavir, Ribavirin, Chloroquine Phosphate, and Arbidol. The plan also states that the use of three or more antiviral drugs concurrently is not recommended.

4.10.3 Adverse Reaction Monitoring

In the treatment of COVID-19, attention should be paid to adverse drug reactions, especially those of clinical trial and clinical research medication. Pharmacists should pay attention to identify symptoms of the disease, and use proper judgment on the causes and effects of adverse drug reactions. According to the circumstances, pharmacists should report adverse reactions, actively monitor pharmaceutical applications, issue early clinical warnings, pay attention to the prognosis of adverse reactions, analyze drug safety information, offer clinical feedback, and ensure the safety of clinical drug regimens.

Attachment 1. Essentials of Antiviral Drug Use and Monitoring

1. α -Interferon (Nebulization)

- (a) Possible mechanism of action: By inhibiting the synthesis of viral RNA and protein, cells are induced to produce antiviral proteins, thereby exerting antiviral effects.
- (b) Metabolic pathway: Catabolism in the lungs.
- (c) ADR: Aerosol inhalation has fewer adverse reactions, though low fever is seen occasionally.
- (d) Precautions: Ultrasonic nebulization is not recommended, but jet nebulizers may be considered. Care should be taken to avoid contact with eyes during nebulization. Nebulization in a negative pressure ward is recommended in order to avoid aerosol induction.
- (e) Drug interactions: Reduction in the clearance rate of theophylline can result in theophylline poisoning. It is necessary to monitor the blood concentration of theophylline and adjust the dose. Combination with antiepileptic drugs, antituberculosis drugs, and other drugs that have an impact on liver function poses a potential risk of liver poisoning. Take care to check liver function in people with a history of liver disease. Combination with Zidovudine can increase the incidence of adverse reactions.
- (f) Contraindications for combined use: Do not nebulize simultaneously with chymotrypsin, acetylcysteine, or ipratropium bromide.
- (g) Adjustment of drug regimen: Use of ultrasonic nebulization should be avoided in patients on mechanical ventilation. It is not necessary to adjust drug dosage while patients are receiving ECMO and RRT.
- (h) Contraindications: Known allergies to interferon products; history of angina pectoris, myocardial infarction, or other serious cardiovascular diseases; serious conditions those do not tolerate this drug's side effects; epilepsy and other central nervous system dysfunction.

2. Lopinavir/Ritonavir

- (a) Possible mechanism of action: Inhibition of the 3CLpro's protease activity of SARS-Cov.
- (b) Metabolic pathways and metabolic enzymes: Liver CYP3A enzyme metabolism.
- (c) ADR: Diarrhea, nausea and vomiting, hypertriglyceridemia, impaired liver function, etc.
- (d) Precautions: The tablets can be taken before or after meals. The tablets should be swallowed in total, not be chewed, broken, or crushed. The oral solution contains ethanol and propylene glycol and should be taken together with food. Oral liquid can be used for tube-fed patients with PVC and silicone tubes. Polyurethane tubes cannot be used for the tube-fed patients.
- (e) Drug interactions: Lopinavir/Ritonavir co-administered with drugs metabolized via CYP3A (such as dihydropyridine, calcium channel blockers, HMG-CoA reductase inhibitors, immunosuppressants, and PDE5 inhibi-

tors) can lead to increased plasma concentrations of these drugs. Combination of Lopinavir/Ritonavir with voriconazole may reduce the blood drug concentrations of voriconazole.

- (f) Contraindication for combinational usage: It is contraindicated to be used together with medications such as Amiodarone, Fusidic Acid, Colchicine, Cisapride, Quetiapine, Lovastatin, Simvastatin, Midazolam, Triazolam, and Ergot Alkaloids.
- (g) Adjustment of drug regimen: Oral liquid can be selected for patients on mechanical ventilation. The dosage should be increased when using ECMO. There is no need to adjust the dosage while on RRT.
- (h) Contraindications: Allergy to Lopinavir, Ritonavir, or any excipients; severe liver dysfunction.

3. Favipiravir

- (a) Possible mechanism of action: Selective inhibition of RNA polymerase associated with viral replication.
- (b) Metabolic pathway: Metabolized by the liver.
- (c) ADR: Increased blood uric acid, diarrhea, decreased neutrophil count, increased AST and ALT, etc.
- (d) Precautions: Reproductive toxicity. Can pass through the placenta and breast milk. Lactating women should discontinue breastfeeding.
- (e) Drug interactions: Theophylline can increase the bioavailability of Favipiravir. Favipiravir can increase the bioavailability of acetaminophen by 1.79 times, with elevated uric acid level in the blood when combined with pyrazinamide, and increased blood concentration of repaglinide that can induce risk of hypoglycemia.
- (f) Adjustment of drug regimen: Not necessary in mechanically ventilated patients.
- (g) Contraindications: Pregnancy or possible pregnancy; allergic to favipiravir

4. Ribavirin

- (a) Possible mechanism of action: Inhibition of viral RNA polymerase and mRNA guanosine transferase.
- (b) Metabolic pathway: Intrahepatic metabolism.
- (c) ADR: Can cause hemolytic anemia and heart damage. There are also reports of low electrolyte disturbances and central nervous system toxicity.
- (d) Precautions: Ribavirin has reproductive toxicity, can pass through the placenta and breast milk. Men and women taking this product should use contraception prior to starting, while taking, and at least 6 months after discontinuing the medication. Lactating women should discontinue breastfeeding.
- (e) Drug interactions: Combination with Zidovudine can lead to increased drug toxicity. Combination with nucleoside reverse transcriptase inhibitors can lead to increased risk of adverse reactions related to mitochondrial poisoning (lactic acidosis, pancreatitis, and liver failure).

- (f) Adjustment of drug regimen: Not necessary for patients on mechanical ventilation and those using ECMO. Hemodialysis patients should be administered 1/2 the original dose. No adjustment required in CRRT patients.
- (g) Contraindications: Pregnancy, autoimmune hepatitis, allergy to ribavirin.

5. Chloroquine Phosphate

- (a) Possible mechanism of action: Inhibition of coronavirus binding to ACE2 receptors in human cells; inhibition of interferon and interleukin-6 production and release.
- (b) Metabolic pathway: Liver metabolism.
- (c) ADR: Arrhythmia, adverse gastrointestinal reactions, blood cell decline, rash, and impaired vision. The most serious ADR is cardiotoxicity, which can cause cardiac arrest. Long-term or large doses can cause irreversible retinopathy.
- (d) Precautions: Electrocardiogram must be normal before starting the treatment. Pay close attention to adverse reactions after administration. Discontinue immediately in case of intolerable toxic side effects. Pay attention to changes in the patient's vision during treatment. Observe the patient's mental state for psychological abnormalities, depression, etc.
- (e) Drug interactions: Monitor liver function closely when combined with Lopinavir/Ritonavir, Ribavirin, Arbidol, Favipiravir, as these drugs all exhibit hepatotoxicity. Closely monitor adverse cardiac reactions when used with Arbidol.
- (f) Contraindications for combined use: Moxifloxacin, azithromycin, and other drugs may cause prolonged Q-T interval.
- (g) Adjustment of drug regimen: Not required in patients on mechanical ventilation. RRT patients can be partially cleared by hemodialysis.
- (h) Contraindications: Pregnancy; known allergy to 4-aminoquinine compounds; arrhythmia (such as conduction block), chronic heart disease; end-stage chronic liver and kidney disease; known retinal disease, diminished hearing, or hearing loss; known mental disorder; skin disease (rash, dermatitis, psoriasis); glucose-6-phosphate dehydrogenase deficiency.

6. Arbidol

- (a) Possible mechanism of action: Inhibition of fusion of viral lipid membranes with human cells; induction of interferon production in human cells, which in turn induces production of multiple antiviral proteins.
- (b) Metabolic pathways and metabolic enzymes: Through liver CYP3A4 enzyme metabolism.
- (c) ADR: Mainly nausea, diarrhea, dizziness, and elevated serum transaminase.
- (d) Precautions: Safety in patients over 65 years of age has not been established.
- (e) Drug interactions: Possible interactions between CYP3A4 and UGT1A9 substrates, inhibitors, and inducers. Monitor carefully if used with Propofol and Zidovudine. Liver enzymes and jaundice may increase when used with Lopinavir.
- (f) Adjustment of drug regimen: Not necessary in mechanically ventilated patients.
- (g) Contraindications: Allergic to arbidol.

4.11 Psychological Intervention to Patients

Jian Luo

4.11.1 Psychological Reaction and Psychiatric Symptoms of COVID-19 Patients

After diagnosis with COVID-19, patients often feel annoyed, self-blame, anxiety, fear, have insomnia, nightmares, sadness and despration, sensitivity, paranoia, irritability and quickness to anger, and may become aggressive [40]. Suspected patients often face unknown fear and helplessness while isolating and waiting for test results [41]. Psychological evaluation in the isolation ward shows that about 48% of COVID-19 patients have psychological reactions at the beginning of admission, most of which are emotional reactions under stress [42]. Deliration occurs in a high proportion of critical patients. One case of encephalitis caused by COVID-19 infection was reported, accompanied by symptoms such as unconsciousness and irritability.

4.11.2 Establishing Dynamic Psychological Assessment and Early Warning

All patients undergo dynamic psychological assessments weekly after admission and before discharge. Mental health self-assessment tools: Mental health self-assessment (SRQ-20), depression screening (PHQ-9), generalized anxiety screening (GAD-7). Mental health scale: Hamilton Depression Scale (HAM-D), Hamilton Anxiety Scale (HAMA), Positive and Negative Syndrome Scale (PANSS) in the special environment of the isolation ward, patients are advised to complete the self-assessment questionnaire on a mobile phone under guidance. You can also conduct interviews and assessments in person or via voice connection. For patients who have breathing difficulties or difficulty completing the self-assessment questionnaire on a mobile phone, we recommended using the four-question method of the PHQ-9 (If there are two or more positive answers, further psychological assessment is required). For in-person screening, use the GAD-7 four-question method (if the answers are all positive, further psychological assessment is required). The patient can answer by simply nodding or shaking their head [43].

4.11.3 Counseling Intervention

4.11.3.1 Intervention Principles

For patients with positive psychological assessment results, non-pharmacological psychological interventions are recommended. Relaxation breathing, mindfulness, meditation, music therapy, and so on can be used for psychological self-regulation [44]. If conditions permit, psychological counselors can offer individualized

one-on-one counseling. Commonly used psychological counseling methods include progressive whole-body muscle relaxation, cognitive transformation therapy, experiential transformation, and existential purpose therapies. For patients in whom non-pharmacological intervention is not efficacious, use of drugs in combination with psychological intervention is recommended [42]. New antidepressants and anxiolytics, as well as benzodiazepines can be given to improve mood and sleep problems [40]. Second-generation antipsychotic drugs such as Olanzapine and Quetiapine improve hallucinations, delusions, and other psychotic symptoms [40].

4.11.3.2 Precautions When Using Psychotropic Drugs [40]

COVID-19 has a high incidence in middle-aged and elderly populations, and is often accompanied by underlying physical diseases such as hypertension and diabetes. Therefore, when selecting psychotropic drugs, drug interactions, and effects on respiration must be fully considered. Citalopram and Escitalopram are recommended for depression and anxiety, benzodiazepines such as Estazolam and Alprazolam for anxiety and sleep quality, and Olanzapine and Quetiapine for psychotic symptoms. Use psychotropic drugs with caution for patients who have dyspnea or respiratory failure.

4.12 Discharge Criteria and Patient Follow-Up

Ying Su

4.12.1 Discharge Criteria

According to the COVID-19 Diagnosis and Treatment Plan (Trial Version 7) issued by the National Health Commission of the People's Republic of China, the discharge criteria for COVID-19 patients are as follows:

1. Body temperature has returned to normal for more than 3 days.
2. Respiratory symptoms have improved significantly.
3. Lung imaging shows a significant improvement in acute exudative lesions.
4. Two consecutive sputum, nasopharyngeal swabs, or other respiratory tract specimens test negative for nucleic acid testing (sampling time at least 24 h apart).

Those who meet the above conditions can be discharged.

4.12.2 Medical Advice and Precautions for Hospital Discharge [45]

14-Day isolation and health monitoring are required for all patients discharged from the hospital.

It is recommended that patients return to the nearest hospital on the second and fourth weeks after discharge. The treatment hospital conducts a telephone follow-up interview one week after the patient is discharged to keep updating about the patient's physical and mental healthy status and make sure to remind the patient back to the hospital for follow-up examinations.

4.12.3 Home Isolation Precautions [46]

In general, all recovered and discharged patients should be transferred to a rehabilitation station in the jurisdiction of their home address for 2 weeks of isolation and observation. In special circumstances, such as older age, inability to take care of oneself, mental disorder, pregnancy, or other conditions not suitable for independent living in a rehabilitation station, home isolation can be applied for. The following precautions should be taken during home isolation:

1. Enhance health awareness, exercise properly, and ensure sufficient and early sleep to improve immunity.
2. If conditions permit, stay in a well-ventilated single room, and reduce close contact with family members.
3. Eat meals by dishes separately, maintain hand hygiene, and avoid outside activities.
4. Maintain good personal hygiene. Cover your mouth and nose with a tissue, your sleeve, or your elbow when coughing or sneezing. Wash your hands thoroughly, and do not touch your eyes, nose, or mouth with dirty hands.
5. If possible, avoid close contact with people who have symptoms of respiratory diseases (such as fever, cough, and sneezing).
6. Avoid crowded and confined spaces as much as possible. If unable to do so, wear a mask.
7. Avoid contact with wild animals, poultry, and livestock.
8. Adhere to safe eating habits. Meat and eggs should be fully cooked.
9. Pay close attention to symptoms such as fever and cough, and check your body temperature twice a day (morning and evening). If you have these symptoms, seek medical treatment immediately.

4.12.4 Follow-Up

The hospital arranges the physician for a telephone follow-up for the first week after discharge. The patient is instructed to go to the nearest hospital for an outpatient follow-up 2 and 4 weeks after discharge. Liver and kidney function tests and a blood routine test are recommended during the follow-up examination, as well as sputum or nasopharyngeal swab for viral nucleic acid testing, lung function assessment, and lung CT. At the third and sixth month after discharge, follow-up is conducted on the hospital's official WeChat platform.

Content of the first follow-up telephone interview is as follows:

4.12.4.1 Assessment of Clinical Symptomology

After discharge, ask if the patient has fever, cough, expectoration, dyspnea, shortness of breath after activity, fatigue, diarrhea, muscle aches, decreased muscle strength, etc.

4.12.4.2 Mental Health Assessment

Assessment based on the self-rating depression scale (SDS), self-rating anxiety scale (SAS), and Pittsburgh sleep questionnaire, etc.

4.12.5 Handling of Repeat Positive Patients

For the patients meeting discharge criteria, but positive with nucleic acid test again on follow-up which might be related to the retention of initial specimens and the detection of false negatives, we recommend:

1. Isolate according to the standards for patients diagnosed with COVID-19.
2. Decide whether to continue initially effective antiretroviral therapy according to clinical symptoms and lung CT findings.
3. Discharge after lung imaging further improved, and the sputum and nasopharyngeal swab are nucleic acid negative for three times (24 h apart).
4. Observe discharged patients according to the above isolation method and follow-up requirements.

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