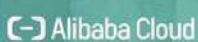




Handbook of COVID-19 Prevention and Treatment

*The First Affiliated Hospital, Zhejiang University School of Medicine
Compiled According to Clinical Experience*





Editor's Note:



Faced with an unknown virus, sharing and collaboration are the best remedy.

The publication of this Handbook is one of the best ways to mark the courage and wisdom our healthcare workers have demonstrated over the past two months.

Thanks to all those who have contributed to this Handbook, sharing the invaluable experience with healthcare colleagues around the world while saving the lives of patients.

Thanks to the support from healthcare colleagues in China who have provided experience that inspires and motivates us.

Thanks to Jack Ma Foundation for initiating this program, and to AliHealth for the technical support, making this Handbook possible to support the fight against the epidemic.

The Handbook is available to everyone for free. However, due to the limited time, there might be some errors and defects. Your feedback and advice are highly welcomed!

Prof. Tingbo LIANG

Editor-in-Chief of the Handbook of COVID-19 Prevention and Treatment
Chairman of The First Affiliated Hospital, Zhejiang University School of Medicine

A stylized handwritten signature in black ink, consisting of three main characters: '梁廷波' (Liang Tingbo).

Foreword

This is an unprecedented global war, and mankind is facing the same enemy, the novel coronavirus. And the first battlefield is the hospital where our soldiers are the medical workers.

To ensure that this war can be won, we must first make sure that our medical staff is guaranteed sufficient resources, including experience and technologies. Also, we need to make sure that the hospital is the battleground where we eliminate the virus, not where the virus defeats us.

Therefore, the Jack Ma Foundation and Alibaba Foundation have convened a group of medical experts who have just returned from the frontlines of fighting the pandemic. With the support of The First Affiliated Hospital, Zhejiang University School of Medicine (FAHZU), they quickly published a guidebook on the clinical experience of how to treat this new coronavirus. The treatment guide offers advice and reference against the pandemic for medical staff around the world who are about to join the war.

My special thanks goes out to the medical staff from FAHZU. While taking huge risks in treating COVID-19 patients, they recorded their daily experience which is reflected in this Handbook. Over the past 50 days, 104 confirmed patients have been admitted to FAHZU, including 78 severe and critically ill ones. Thanks to the pioneering efforts of medical staff and the application of new technologies, to date, we have witnessed a miracle. No staff were infected, and there were no missed diagnosis or patient deaths.

Today, with the spread of the pandemic, these experiences are the most valuable sources of information and the most important weapon for medical workers on the frontline. This is a brand-new disease, and China was the first to suffer from the pandemic. Isolation, diagnosis, treatment, protective measures, and rehabilitation have all started from scratch. WE hope that this Handbook can provide doctors and nurses in other affected areas valuable information so they don't have to enter the battlefield alone.

This pandemic is a common challenge faced by mankind in the age of globalization. At this moment, sharing resources, experiences and lessons, regardless of who you are, is our only chance to win. The real remedy for this pandemic is not isolation, but cooperation.

This war has just begun.

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Part One Prevention and Control Management

I. Isolation Area Management

1 Fever Clinic

1.1 Layout

- (1) Healthcare facilities shall set up a relatively independent fever clinic including an exclusive one-way passage at the entrance of the hospital with a visible sign;
- (2) The movement of people shall follow the principle of “three zones and two passages” : a contaminated zone, a potentially contaminated zone and a clean zone provided and clearly demarcated, and two buffer zones between the contaminated zone and the potentially contaminated zone;
- (3) An independent passage shall be equipped for contaminated items; set up a visual region for one-way delivery of items from an office area (potentially contaminated zone) to an isolation ward (contaminated zone);
- (4) Appropriate procedures shall be standardized for medical personnel to put on and take off their protective equipment. Make flowcharts of different zones, provide full-length mirrors and observe the walking routes strictly;
- (5) Infection prevention and control technicians shall be assigned to supervise the medical personnel on putting on and removing protective equipment so as to prevent contamination;
- (6) All items in the contaminated zone that have not been disinfected shall not be removed.

1.2 Zone Arrangement

- (1) Set up an independent examination room, a laboratory, an observation room, and a resuscitation room;
- (2) Set up a pre-examination and triage area to perform preliminary screening of patients;
- (3) Separate diagnosis and treatment zones: those patients with an epidemiological history and fever and/or respiratory symptoms shall be guided into a suspected COVID-19 patient zone; those patients with regular fever but no clear epidemiological history shall be guided into a regular fever patient zone.

1.3 Patient Management

- (1) Patients with fevers must wear medical surgical masks;
- (2) Only patients are allowed to enter the waiting area in order to avoid overcrowding;
- (3) The duration of the patient’s visit shall be minimized so as to avoid cross infections;
- (4) Educate patients and their families about early identification of symptoms and essential preventative actions.

II. Staff Management

1 Workflow Management

- (1) Before working in a fever clinic and isolation ward, the staff must undergo strict training and examinations to ensure that they know how to put on and remove personal protective equipment. They must pass such examinations before being allowed to work in these wards.
- (2) The staff should be divided into different teams. Each team should be limited to a maximum of 4 hours of working in an isolation ward. The teams shall work in the isolation wards (contaminated zones) at different times.
- (3) Arrange treatment, examination and disinfection for each team as a group to reduce the frequency of staff moving in and out of the isolation wards.
- (4) Before going off duty, staff must wash themselves and conduct necessary personal hygiene regimens to prevent possible infection of their respiratory tracts and mucosa.

2 Health Management

- (1) The front-line staff in the isolation areas – including healthcare personnel, medical technicians and property & logistics personnel – shall live in an isolation accommodation and shall not go out without permission.
- (2) A nutritious diet shall be provided to improve the immunity of medical personnel.
- (3) Monitor and record the health status of all staff on the job, and conduct health monitoring for front-line staff, including monitoring body temperature and respiratory symptoms; help address any psychological and physiological problems that arise with relevant experts.
- (4) If the staff have any relevant symptoms such as fever, they shall be isolated immediately and screened with an NAT.
- (5) When the front-line staff including healthcare personnel, medical technicians and property & logistics personnel finish their work in the isolation area and are returning to normal life, they shall first be NAT tested for SARS-CoV-2. If negative, they shall be isolated collectively at a specified area for 14 days before being discharged from medical observation.

III. COVID-19 Related Personal Protection Management

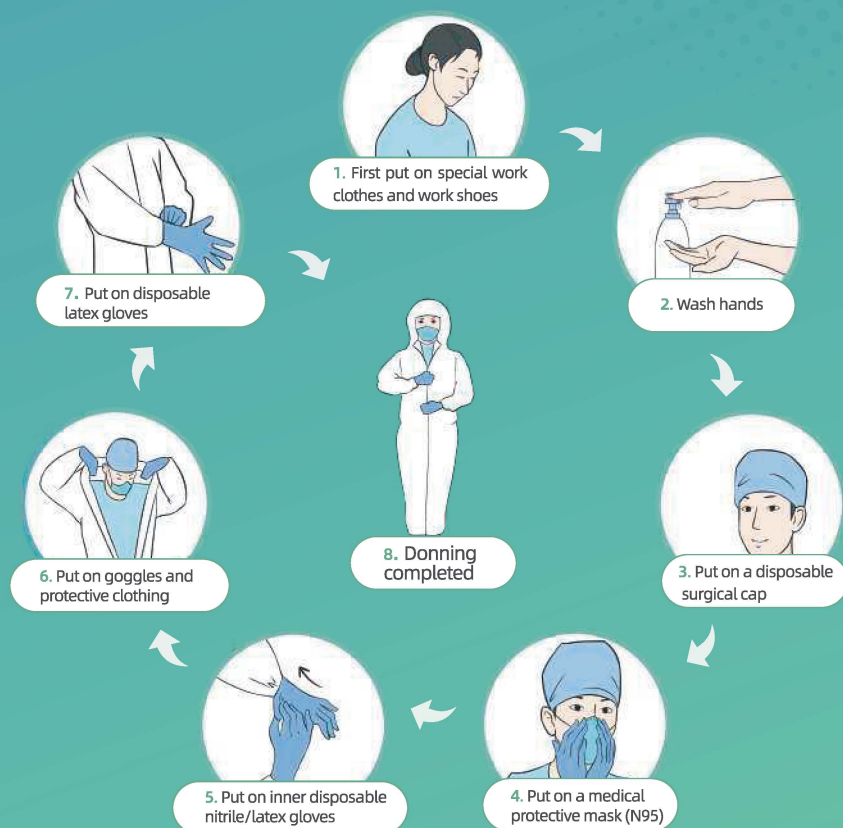
| Protection Level | Protective Equipment | Scope of Application |
|-----------------------------|--|--|
| Level I protection | <ul style="list-style-type: none"> • Disposable surgical cap • Disposable surgical mask • Work uniform • Disposable latex gloves or/and disposable isolation clothing if necessary | <ul style="list-style-type: none"> • Pre-examination triage, general outpatient department |
| Level II protection | <ul style="list-style-type: none"> • Disposable surgical cap • Medical protective mask (N95) • Work uniform • Disposable medical protective uniform • Disposable latex gloves • Goggles | <ul style="list-style-type: none"> • Fever outpatient department • Isolation ward area (including isolated intensive ICU) • Non-respiratory specimen examination of suspected/confirmed patients • Imaging examination of suspected/confirmed patients • Cleaning of surgical instruments used with suspected/confirmed patients |
| Level III protection | <ul style="list-style-type: none"> • Disposable surgical cap • Medical protective mask (N95) • Work uniform • Disposable medical protective uniform • Disposable latex gloves • Full-face respiratory protective devices or powered air-purifying respirator | <ul style="list-style-type: none"> • When the staff performs operations such as tracheal intubation, tracheotomy, bronchofibroscope, gastroenterological endoscope, etc., during which, the suspected/confirmed patients may spray or splash respiratory secretions or body fluids/blood • When the staff performs surgery and autopsy for confirmed/suspected patients • When the staff carries out NAT for COVID-19 |

Notes:

1. All staff at the healthcare facilities must wear medical surgical masks;
2. All staff working in the emergency department, outpatient department of infectious diseases, outpatient department of respiratory care, department of stomatology or endoscopic examination room (such as gastrointestinal endoscopy, bronchofibroscopy, laryngoscopy, etc.) must upgrade their surgical masks to medical protective masks (N95) based on Level I protection;
3. Staff must wear a protective face screen based on Level II protection while collecting respiratory specimens from suspected/confirmed patients.

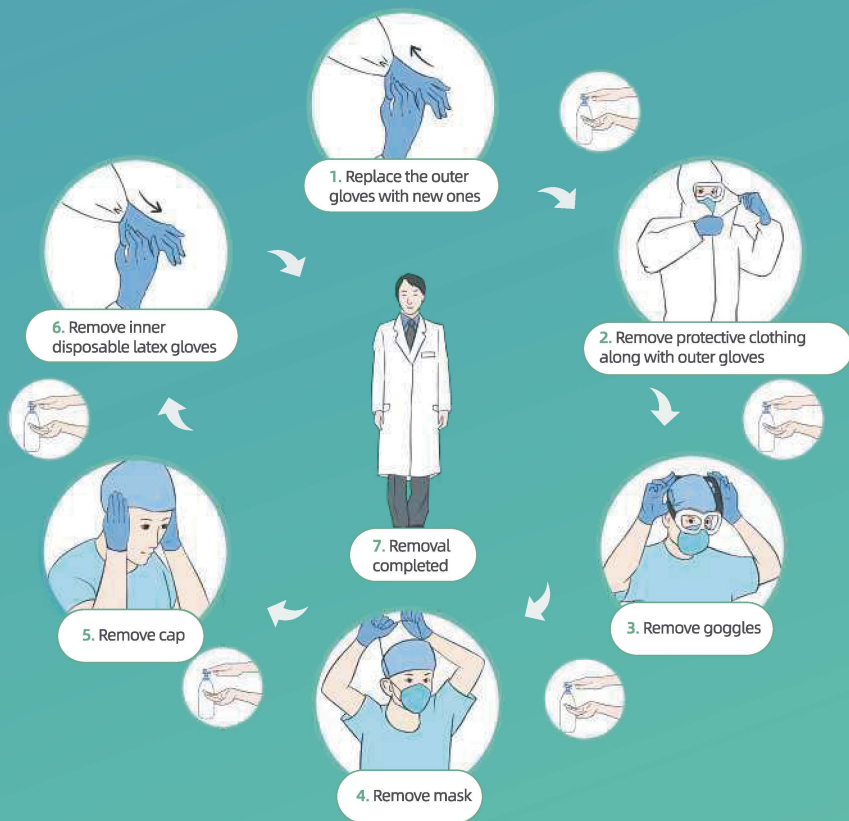
IV. Hospital Practice Protocols during COVID-19 Epidemic

1 Guidance on Donning and Removing Personal Protective Equipment (PPE) to manage COVID-19 Patients



Protocol for Donning PPE:

Put on special work clothes and work shoes → Wash hands → Put on disposable surgical cap → Put on medical protective mask (N95) → Put on inner disposable nitrile/latex gloves → Put on goggles and protective clothing (note: if wearing protective clothing without foot covers, please also put on separate waterproof boot covers), put on a disposable isolation gown (if required in the specific work zone) and face shield/powered air-purifying respirator(if required in the specific work zone) → Put on outer disposable latex gloves



Protocol for Removing PPE:

Wash hands and remove visible bodily fluids/blood contaminants on the outer surfaces of both hands → Wash hands replace outer gloves with new gloves → Remove powered air-purifying respirator or self-priming filter-type full-face mask/mask (if used) → Wash hands → Remove disposable gowns along with outer gloves (if used) → Wash hands and put on outer gloves → Enter Removal Area No. ① → Wash hands and remove protective clothing along with outer gloves (for gloves and protective clothing, turn inside out, while rolling them down) (note: if used, remove the waterproof boot covers with clothing) → Wash hands → Enter Removal Area No. ② → Wash hands and remove goggles → Wash hands and remove mask → Wash hands and remove cap → Wash hands and remove inner disposable latex gloves → Wash hands and leave Removal Area No. ② → Wash hands, take a shower, put on clean clothes and enter the clean area

2 Disinfection Procedures for COVID-19 Isolation Ward Area

2.1 Disinfection for Floor and Walls

- (1) Visible pollutants shall be completely removed before disinfection and handled in accordance with disposal procedures of blood and bodily fluid spills;
- (2) Disinfect the floor and walls with 1000 mg/L chlorine-containing disinfectant through floor mopping, spraying or wiping;
- (3) Make sure that disinfection is conducted for at least 30 minutes;
- (4) Carry out disinfection three times a day and repeat the procedure at any time when there is contamination.

2.2 Disinfection of Object Surfaces

- (1) Visible pollutants should be completely removed before disinfection and handled in accordance with disposal procedures of blood and bodily fluid spills;
- (2) Wipe the surfaces of objects with 1000 mg/L chlorine-containing disinfectant or wipes with effective chlorine; wait for 30 minutes and then rinse with clean water. Perform disinfection procedure three times a day (repeat at any time when contamination is suspected);
- (3) Wipe cleaner regions first, then more contaminated regions: first wipe the object surfaces that are not frequently touched, and then wipe the object surfaces that are frequently touched. (Once an object surface is wiped clean, replace the used wipe with a new one).

2.3 Air Disinfection

- (1) Plasma air sterilizers can be used and continuously run for air disinfection in an environment with human activity;
- (2) If there is no plasma air sterilizers, use ultraviolet lamps for 1 hour each time. Perform this operation three times a day.

2.4 Disposal of Fecal Matter and Sewage

- (1) Before being discharged into the municipal drainage system, fecal matter and sewage must be disinfected by treating with chlorine-containing disinfectant (for the initial treatment, the active chlorine must be more than 40 mg/L). Make sure the disinfection time is at least 1.5 hours;
- (2) The concentration of total residual chlorine in the disinfected sewage should reach 10 mg/L.

3 Disposal Procedures for Spills of COVID-19 Patient Blood/Fluids

3.1 For spills of a small volume (< 10 mL) of blood/bodily fluids:

(1) Option 1: The spills should be covered with chlorine-containing disinfecting wipes (containing 5000 mg/L effective chlorine) and carefully removed, then the surfaces of the object should be wiped twice with chlorine-containing disinfecting wipes (containing 500 mg/L effective chlorine);

(2) Option 2: Carefully remove the spills with disposable absorbent materials such as gauze, wipes, etc., which have been soaked in 5000 mg/L chlorine-containing disinfecting solution.

3.2 For spills of a large volume (> 10 mL) of blood and bodily fluids:

(1) First, place signs to indicate the presence of a spill;

(2) Perform disposal procedures according to Option 1 or 2 described below:

① Option 1: Absorb the spilled fluids for 30 minutes with a clean absorbent towel (containing peroxyacetic acid that can absorb up to 1 L of liquid per towel) and then clean the contaminated area after removing the pollutants.

② Option 2: Completely cover the spill with disinfectant powder or bleach powder containing water-absorbing ingredients or completely cover it with disposable water-absorbing materials and then pour a sufficient amount of 10,000 mg/L chlorine-containing disinfectant onto the water-absorbing material (or cover with a dry towel which will be subjected to high-level disinfection). Leave for at least 30 minutes before carefully removing the spill.

(3) Fecal matter, secretions, vomit, etc. from patients shall be collected into special containers and disinfected for 2 hours by a 20,000 mg/L chlorine-containing disinfectant at a spill-to-disinfectant ratio of 1:2.

(4) After removing the spills, disinfect the surfaces of the polluted environment or objects.

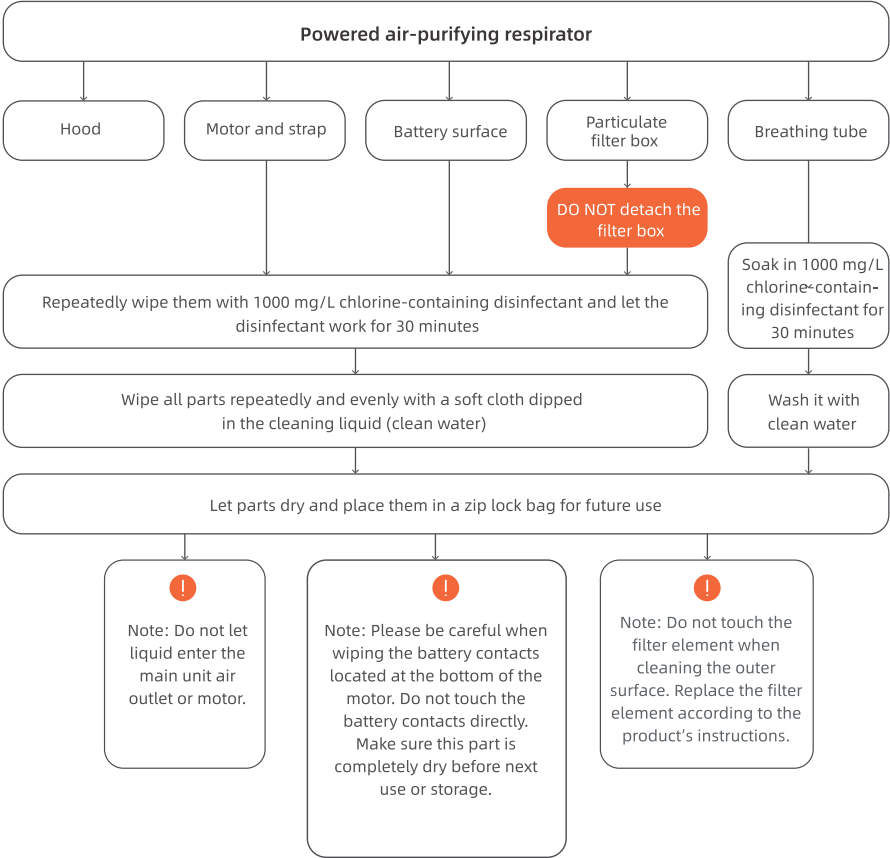
(5) The containers that hold the contaminants can be soaked and disinfected with 5,000 mg/L active chlorine-containing disinfectant for 30 minutes and then cleaned.

(6) The collected pollutants should be disposed of as medical waste.

(7) The used items should be put into double-layer medical waste bags and disposed of as medical waste.

4 Disinfection of COVID-19 Related Reusable Medical Devices

4.1 Disinfection of powered air-purifying respirator



Note: The disinfection procedures for protective hood described above are only for reusable protective hoods (excluding disposable protective hoods).

4.2 Cleaning and Disinfection Procedures for Digestive Endoscopy and Bronchofibroscopy

- (1) Soak the endoscope and reusable valves in 0.23% peroxyacetic acid (confirm the concentration of the disinfectant before use to make sure it will be effective);
- (2) Connect the perfusion line of each channel of the endoscope, inject 0.23% peroxyacetic acid liquid into the line with a 50 mL syringe until fully filled, and wait for 5 minutes;
- (3) Detach the perfusion line and wash each cavity and valve of the endoscope with a disposable special cleaning brush;
- (4) Put the valves into an ultrasonic oscillator containing enzyme to oscillate it. Connect the perfusion line of each channel with the endoscope. Inject 0.23% peroxyacetic acid into the line with a 50 mL syringe and flush the line continuously for 5 minutes. Inject air to dry it for 1 minute;
- (5) Inject clean water into the line with a 50 mL syringe and flush the line continuously for 3 minutes. Inject air to dry it for 1 minute;
- (6) Perform a leakage test on the endoscope;
- (7) Put in an automatic endoscopic washing and disinfection machine. Set a high level of disinfection for treatment;
- (8) Send the devices to the disinfection supply center to undergo sterilization with ethylene oxide.

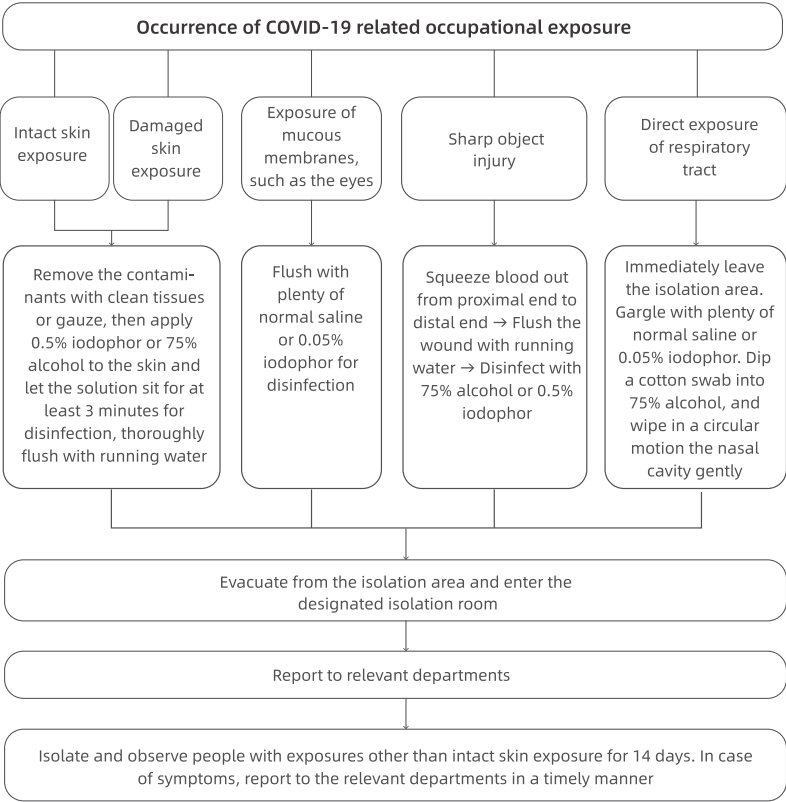
4.3 Pre-treatment of Other Reusable Medical Devices

- (1) If there are no visible pollutants, soak the device in 1000 mg/L chlorine-containing disinfectant for at least 30 minutes;
- (2) If there are any visible pollutants, soak the device in 5000 mg/L chlorine-containing disinfectant for at least 30 minutes;
- (3) After drying, pack and fully enclose the devices and send them to the disinfection supply center.

6 Disposal Procedures for COVID-19 Related Medical Waste

- (1) All waste generated from suspected or confirmed patients shall be disposed of as medical waste;
- (2) Put the medical waste into a double-layer medical waste bag, seal the bag with cable ties in a gooseneck fashion and spray the bag with 1000 mg/L chlorine-containing disinfectant;
- (3) Put sharp objects into a special plastic box, seal the box and spray the box with 1000 mg/L chlorine-containing disinfectant;
- (4) Put the bagged waste into a medical waste transfer box, attach a special infection label, fully enclose the box and transfer it;
- (5) Transfer the waste to a temporary storage point for medical waste along a specified route at a fixed time point and store the waste separately at a fixed location;
- (6) The medical waste shall be collected and disposed of by an approved medical waste disposal provider.

7 Procedures for Taking Remedial Actions against Occupational Exposure to COVID-19



- (1) Skin exposure: The skin is directly contaminated by a large amount of visible bodily fluids, blood, secretions or fecal matter from the patient.
- (2) Mucous membrane exposure: Mucous membranes, such as the eyes and respiratory tract are directly contaminated by visible bodily fluids, blood, secretions or fecal matter from the patient.
- (3) Sharp object injury: Piercing of the body by sharp objects that were directly exposed to the patient's bodily fluids, blood, secretions or fecal matter.
- (4) Direct exposure of respiratory tract: Falling off of a mask, exposing the mouth or nose to a confirmed patient (1 meter away) who is not wearing a mask.

8 Surgical Operations for Suspected or Confirmed Patients

8.1 Requirements for Operation Rooms and Staff PPE

- (1) Arrange the patient in a negative pressure operating room. Verify the temperature, humidity and air pressure in the operation room;
- (2) Prepare all required items for the operation and use disposable surgical items if possible;
- (3) All surgical personnel (including surgeons, anesthesiologists, hand-washing nurses, and charge nurses in operating room) should put on their PPE in the buffer room before entering the operating room: Put on double caps, medical protective mask (N95), medical goggles, medical protective clothing, boot covers, latex gloves, and powered air-purifying respirator;
- (4) The surgeons and the hand-washing nurses should wear disposable sterile operating clothes and sterile gloves in addition to the PPE as mentioned above;
- (5) Patients should wear disposable caps and disposable surgical masks according to their situation;
- (7) The charge nurses in the buffer room are responsible for delivering items from the buffer area to the negative pressure operating room;
- (8) During the operation, the buffer room and the operating room shall be tightly closed, and the operation must be carried out only if the operation room is under negative pressure;
- (9) Irrelevant personnel shall be excluded from entering the operating room.

8.2 Procedures for Final Disinfection

- (1) Medical waste shall be disposed of as COVID-19 related medical waste;
- (2) Reusable medical devices shall be disinfected according to the disinfection procedures of SARS-CoV-2 related reusable medical devices;
- (3) Medical fabrics shall be disinfected and disposed of according to the disinfection procedures for SARS-CoV-2 related infectious fabrics;
- (4) Surfaces of objects (instruments and devices including device table, operating table, operating bed, etc.);
 - ① Visible blood/bodily fluid pollutants shall be completely removed before disinfection (handled in accordance with disposal procedures of blood and bodily fluid spills).
 - ② All surfaces shall be wiped with a disinfectant containing 1000 mg/L active chlorine and allowed to sit for 30 minutes with the disinfectant.
- (5) Floors and walls:
 - ① Visible blood/bodily fluid pollutants shall be completely removed before disinfection (handled in accordance with disposal procedures of blood and bodily fluid spills).
 - ② All surfaces shall be wiped with a disinfectant containing 1000 mg/L active chlorine and allowed to sit for 30 minutes with the disinfectant.
- (6) Indoor air: Turn off the fan filter unit (FFU). Disinfect the air by irradiation by ultraviolet lamp for at least 1 hour. Turn on the FFU to purify the air automatically for at least 2 hours.

9 Procedures for Handling Bodies of Deceased Suspected or Confirmed Patients

- (1) Staff PPE: The staff must make sure they are fully protected by wearing work clothes, disposable surgical caps, disposable gloves and thick rubber gloves with long sleeves, medical disposable protective clothing, medical protective masks (N95) or powered air purifying respirators (PAPRs), protective face shields, work shoes or rubber boots, waterproof boot covers, waterproof aprons or waterproof isolation gowns, etc.
- (2) Corpse care: Fill all openings or wounds the patient may have, such as mouth, nose, ears, anus and tracheotomy openings, by using cotton balls or gauze dipped in 3000-5000 mg/L chlorine-containing disinfectant or 0.5% peroxyacetic acid.
- (3) Wrapping: Wrap the corpse with a double-layer cloth sheet soaked with disinfectant, and pack it into a double-layer, sealed, leak-proof corpse wrapping sheet soaked with chlorine containing disinfectant.
- (4) The body shall be transferred by the staff in the isolation ward of the hospital via the contaminated area to the special elevator, out of the ward and then directly transported to a specified location for cremation by a special vehicle as soon as possible.
- (5) Final disinfection: Perform final disinfection of the ward and the elevator.

[FAHZU Internert + Hospital - A Model for Online Healthcare]

Since the outbreak of COVID 19, FAHZU Internet+ Hospital quickly shifted to offer online healthcare through Zhejiang's Online Medical Platform with 24-hour free online consultation, providing telemedicine service to patients in China and even around the world. Patients are provided access to the first-rate medical services of FAHZU at home, which reduces the chances of transmission and cross infection as a result of their visits to the hospital. As of March 14, over 10,000 people have used the FAHZU Internet+ Hospital online service.

• Instructions for Zhejiang Online Medical Platform:

- ① Download Alipay app;
- ② Open Alipay (China Version) and find "Zhejiang Provincial Online Medical Platform" ;
- ③ Choose a hospital (The First Affiliated Hospital, Zhejiang University School of Medicine);
- ④ Post your question and wait for a doctor to respond;
- ⑤ A notification will pop up when a doctor replies. Then open Alipay and click Friends;
- ⑥ Click Zhejiang Online Medical Platform to see more details and start your consultation.

[Establishing the International Medical Expert Communication Platform of the First Affiliated Hospital, Zhejiang University School of Medicine]

Due to the spread of the COVID-19 epidemic, the First Affiliated Hospital, Zhejiang University School of Medicine (FAHZU) and Alibaba jointly established the International Medical Expert Communication Platform of FAHZU with an aim to improve the quality of care and treatment and promote the sharing of global information resource. The platform allows medical experts all over the world to connect and share their invaluable experience in the fight against COVID-19 through instant messaging with real-time translation, remote video conferencing, etc.

• Instructions on the International Medical Expert Communication Platform of The First Affiliated Hospital, Zhejiang University School of Medicine

- ① Visit www.dingtalk.com/en to download DingTalk app.
- ② Sign up with your personal information (Name and Phone Number) and log in.
- ③ Apply to join the International Medical Expert Communication Platform of FAHZU:
 Method 1: Join by team code. Select "Contacts" > "Join Team" > "Join by Team Code", then enter the Input ID: 'YQDK1170'.
 Method 2: Join by scanning the QR code of the International Medical Expert Communication Platform of FAHZU.
- ④ Fill out your information to join. Enter your name, country and medical institution.
- ⑤ Join the FAHZU group chat after the admin has approved.
- ⑥ After joining the group chat, medical staff can send instant messages assisted by AI translation, receive remote video guidance, and access to medical treatment guidelines.



Part Two Diagnosis and Treatment

I. Personalized, Collaborative and Multidisciplinary Management

FAHZU is a designated hospital for COVID-19 patients, especially severe and critically ill individuals whose condition changes rapidly, often with multiple organs infected and requiring the support from the multidisciplinary team (MDT). Since the outbreak, FAHZU established an expert team composed of doctors from the Departments of Infectious Diseases, Respiratory Medicine, ICU, Laboratory Medicine, Radiology, Ultrasound, Pharmacy, Traditional 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 them to determine scientific, integrated and customized treatment strategies for every severe and critically ill patient.

Sound decision-making is the key to MDT discussion. During the discussion, experts from different departments focus on issues from their specialized fields as well as critical issues to diagnoses and treatment. The final treatment solution is determined by experienced experts through various discussions of different opinions and advice.

Systematic analysis is at the core of MDT discussion. Elderly patients with underlying health conditions are prone to becoming critically ill. While closely monitoring the progression of COVID-19, the patient's basic status, complications and daily examination results should be analyzed comprehensively to see how the disease will progress. It is necessary to intervene in advance to stop the disease from deteriorating and to take proactive measures such as antivirals, oxygen therapy, and nutritional support.

The goal of MDT discussion is to achieve personalized treatment. The treatment plan should be adjusted to each person when considering the differences among individuals, courses of disease, and patient types.

Our experience is that MDT collaboration can greatly improve the effectiveness of the diagnosis and treatment of COVID-19.

II. Etiology and Inflammation Indicators

1

Detection of SARS-CoV-2 Nucleic Acid

1.1 Specimen Collection

Appropriate specimens, collection methods and collection timing are important to improve detection sensitivity. Specimen types include: upper airway specimens (pharyngeal swabs, nasal swabs, nasopharyngeal secretions), lower airway specimens (sputum, airway secretions, bronchoalveolar lavage fluid), blood, feces, urine and conjunctival secretions. Sputum and other lower respiratory tract specimens have a high positive rate of nucleic acids and should be collected preferentially. SARS-CoV-2 preferentially proliferates in type II alveolar cells (AT2) and peak of viral shedding appears 3 to 5 days after the onset of disease. Therefore, if the nucleic acid test is negative at the beginning, samples should continue to be collected and tested on subsequent days.

1.2 Nucleic Acid Detection

Nucleic acid testing is the preferred method for diagnosing SARS-CoV-2 infection. The testing process according to the kit instructions is as follows: Specimens are pre-processed, and the virus is lysed to extract nucleic acids. The three specific genes of SARS-CoV-2, namely the Open Reading Frame 1a/b (ORF1a/b), nucleocapsid protein (N), and envelope protein (E) genes, are then amplified by real-time quantitative PCR technology. The amplified genes are detected by fluorescence intensity. Criteria of positive nucleic acid results are: ORF1a/b gene is positive, and/or N gene/E gene are positive.

The combined detection of nucleic acids from multiple types of specimens can improve the diagnostic accuracy. Among patients with confirmed positive nucleic acid in respiratory tract, about 30% - 40% of these patients have detected viral nucleic acid in the blood and about 50% - 60% of patients have detected viral nucleic acid in feces. However, the positive rate of nucleic acid testing in urine samples is quite low. Combined testing with specimens from respiratory tract, feces, blood and other types of specimens is helpful for improving the diagnostic sensitivity of suspected cases, monitoring treatment efficacy and the management of post-discharge isolation measures.

2

Virus Isolation and Culture

Virus culture must be performed in a laboratory with qualified Biosafety Level 3 (BSL-3). The process is briefly described as follows: Fresh samples of the patient's sputum, feces, etc. are obtained and inoculated on Vero-E6 cells for virus culture. The cytopathic effect (CPE) is observed after 96 hours. Detection of viral nucleic acid in the culture medium indicates a successful culture. Virus titer measurement: After diluting the virus stock concentration by a factor of 10 in series, the TCID₅₀ is determined by the micro-cytopathic method. Otherwise, viral viability is determined by plaque forming unit (PFU).

3 Detection of Serum Antibody

Specific antibodies are produced after SARS-CoV-2 infection. Serum antibody determination methods include colloidal gold immunochromatography, ELISA, chemiluminescence immunoassay, etc. Positive serum-specific IgM, or specific IgG antibody titer in the recovery phase ≥ 4 times higher than that in the acute phase, can be used as diagnostic criteria for suspected patients with negative nucleic acid detection. During follow-up monitoring, IgM is detectable 10 days after symptom onset and IgG is detectable 12 days after symptom onset. The viral load gradually decreases with the increase of serum antibody levels.

4 Detecting Indicators of Inflammatory Response

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

Most patients with COVID-19 have a normal level of procalcitonin with significantly increased levels of C-reactive protein. A rapid and significantly elevated C-reactive protein level indicates a possibility of secondary infection. D-dimer levels are significantly elevated in severe cases, which is a potential risk factor for poor prognosis. Patients with a low total number of lymphocytes at the beginning of the disease generally have a poor prognosis. Severe patients have a progressively decreased number of peripheral blood lymphocytes. The expression levels of IL-6 and IL-10 in severe patients are increased greatly. Monitoring the levels of IL-6 and IL-10 is helpful to assess the risk of progression to a severe condition.

5 Detection of Secondary Bacterial or Fungal Infections

Severe and critically ill patients are vulnerable to secondary bacterial or fungal infections. Qualified specimens should be collected from the infection site for bacterial or fungal culture. If secondary lung infection is suspected, sputum coughed from deep in the lungs, tracheal aspirates, bronchoalveolar lavage fluid, and brush specimens should be collected for culture. Timely blood culture should be performed in patients with high fever. Blood cultures drawn from peripheral venous or catheters should be performed in patients with suspected sepsis who had an indwelling catheter. It is recommended that they take blood G test and GM test at least twice a week in addition to fungal culture.

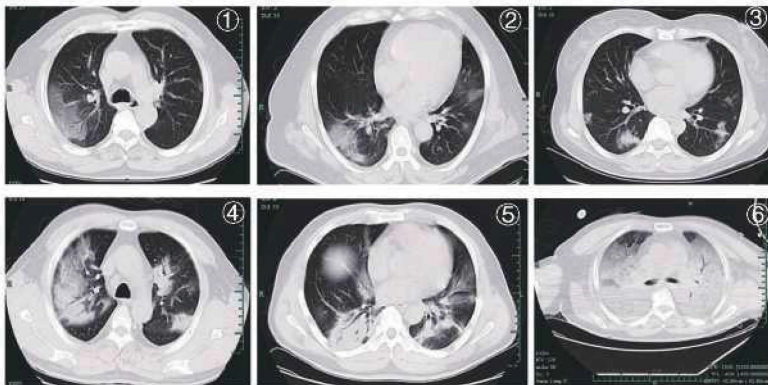
6 Laboratory Safety

Biosafety protective measures should be determined based on different risk levels of experimental process. 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. Personal protection in accordance with BSL-2 laboratory protection requirement should be carried out for biochemical, immunological tests and other routine laboratory tests. Specimens should be transported in special transport tanks and boxes that meet biosafety requirements. All laboratory waste should be strictly autoclaved.

III. Imaging Findings of COVID-19 Patients

Thoracic imaging is of great value in the diagnosis of COVID-19, monitoring of therapeutic efficacy, and patient discharge assessment. A high-resolution CT is highly preferable. Portable chest X-rays are helpful for critically ill patients who are immobile. CT for baseline evaluation of patients with COVID-19 is usually performed on the day of admission, or if ideal therapeutic efficacy is not reached, it can be re-performed after 2 to 3 days. If symptoms are stable or improved after treatment, the chest CT scan can be reviewed after 5 to 7 days. Daily routine portable chest X-rays are recommended for critically ill patients.

COVID-19 at the early stage often presents with multifocal patchy shadows or ground glass opacities located in the lung periphery, subpleural area, and both lower lobes on chest CT scans. The long axis of the lesion is mostly parallel to the pleura. Interlobular septal thickening and intralobular interstitial thickening, displaying as subpleural reticulation namely a "crazy paving" pattern, is observed in some ground glass opacities. A small number of cases may show solitary, local lesions, or nodular/ patchy lesion distributed consistent with bronchus with peripheral ground glass opacities changes. Disease progression mostly occurs in the course of 7-10 days, with enlarged and increased density of the lesions compared with previous images, and consolidated lesions with air bronchogram sign. Critical cases may show further expanded consolidation, with the whole lung density showing increased opacity, sometimes known as a "white lung". After the condition is relieved, the ground glass opacities can be completely absorbed, and some consolidation lesions will leave fibrotic stripes or subpleural reticulation. Patients with multiple lobular involvement, especially those with expanded lesions should be observed for disease exacerbation. Those with typical CT pulmonary manifestations should be isolated and undergo continuous nucleic acid tests even if the nucleic acid test of SAR-CoV-2 is negative.



Typical CT features of COVID-19 :

Figure 1, Figure 2: patchy ground glass opacities;

Figure 3: nodules and patchy exudation;

Figure 4, Figure 5: multifocal consolidation lesions;

Figure 6: diffuse consolidation, "white lung".