中华医学会器官移植分会

Chinese Guidance on Organ Donation and Transplantation during COVID-19 epidemic

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2020.02.23

Preface

01

In December 2019, a novel coronavirus pneumonia outbroke in Hubei province and spread rapidly to many provinces even overseas.

02

On January 20th, 2020, the novel coronavirus pneumonia was classified as a Category B infectious disease but managed as Category A according to the China's "National Infectious Diseases Law"

03

On January 31st, the World Health Organization (WHO) declared that the 2019-nCoV outbreak constitutes a "Public Health Emergency of International Concern". The novel coronavirus pneumonia has been named "COVID-19".

Preface

04

The English name of the novel coronavirus pneumonia was revised to "COVID-19 " on February 21st, 2020, being consistent with WHO suggested. But the Chinese name remains unchanged.

05

Organ transplantation in China is in the stage of development with high quality. During the severe epidemic, it is of great significance to manage organ donation and transplantation activities scientifically and disciplined, as well as to summarize and analyze the clinical characteristics of transplant recipients with COVID-19 and the prevention strategies accordingly.

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The risk for organ donation during the outbreak of COVID-19

The risk of donors

1. The donor is in critically ill caused by primary diseases, and COVID-19 cross infection is easy to occur in the rescue process. Medical staffs and transplant recipients could be infected through donors.

2. The gathering and mobility of donor's family could have caused cluster infection and cross infection easier.

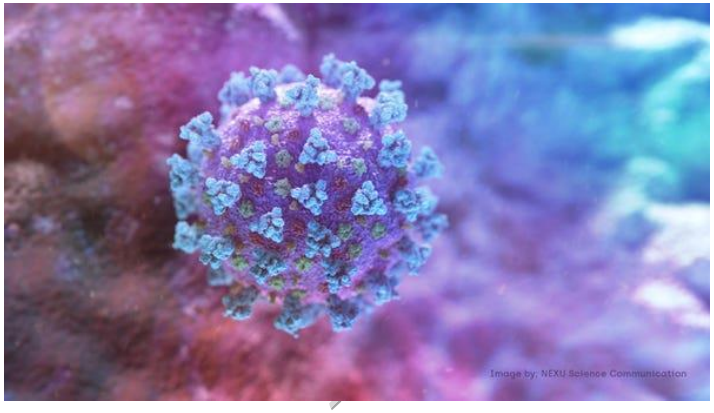
3. The area, type, epidemic situation, prevention and control of the donor hospitals are diverse and complex, which is not conducive to the epidemiological survey of the donor as well as his/her screening, prevention and control of COVID-19.

4. The donor could be a latent asymptomatic infector

The risk for organ donation during the outbreak of COVID-19

The risks facing by coordinators

The Coordinators have a wide range of activities in publicity for promoting organ donation and for identifying potential donors, with many contacts, which increases the difficulty of prevention and control with high risk of cross infection.



The prevention and control measures for organ donation during the outbreak of COVID-19

Contraindications of donation

In addition to the usual contraindications of donation, the following contraindications should also be included :,

- Patients with COVID-19 diagnosed or suspected or clinically diagnosed.
- Within 14 days before the onset of the disease, there was a clear epidemiological history of COVID-19 or contact history of the person with epidemiological history (donation can be considered only after 14 days of isolation and observation without onset).
- Due to the risk of unknow COVID-19 exposure of donors, organ donation should be suspended in high prevalence areas or hospitals with COVID-19 cases within 14 days.

The prevention and control measures for organ donation during the outbreak of COVID-19

Potential donor management

To reduce the risk of transmission to potential donors and their families during the outbreak:

- A rigorous epidemiological survey should be conducted among potential donors and their families.
- Detailed medical history of potential donors should be collected, and chest CT and lab tests should be conducted for screening of COVID-19 accordingly .
- Attention should be paid to the investigation of suspected and clinically diagnosed cases. When COVID-19 is suspected, consultation with the expert group and two viral nucleic acid tests must be done.
- During the maintenance of potential donors, there should be no confirmed or suspected patients with COVID-19 at the surrounding environment。Potential donor should be managed in single medical unit, as well as reducing the number of medical staff participating in the maintenance with fixed personnel, so as to avoid cross infection.

The prevention and control measures of organ donation during the outbreak of COVID-19

Recommendation for Coordinators

- Strengthen the self-protection awareness of the coordinator.
- The frequency of daily visit in donation hospitals need to be reduced, and the contact with donation hospitals could be strengthened through telephone, wechat, video communication, etc.
- Protection measures shall be taken according to the protection level required by the donation hospital when entering different areas of donation hospital
- Coordinator shall keep a distance of more than 1.5m when communicating with the family members.
- Entering to the emergency and ICU managing epidemic prevention activities are not recommended. Entering to the COVID-19 isolated observation ward, isolated ward or isolated intensive care area is prohibited .

The prevention and control measures for organ donation during the outbreak of COVID-19

Organ evaluation and procurement management

Measures are taken to reduce the risk of transmission in the organ assessment and procurement process:

- Self-protective measures for medical staffs participating in organ evaluation and procurement, careful selection of OR with appropriate protective level should be provided based on the current situation and environment for organ procurement. protective mask, goggles, protective clothing (operating clothes) should be worn and the protective packaging of the required equipment and material should be performed.
- It is forbidden to access the observation, isolation, diagnosis, treatment area for COVID-19.
- The environment of organ procurement such as operating room should be evaluated before procurement.
- After organ procurement, the protective layer of the external package of the carried equipment shall be stored in a centralized manner, treated as infectious waste. The external parts of the organ preservation device, refrigerator and other equipment shall be disinfected.

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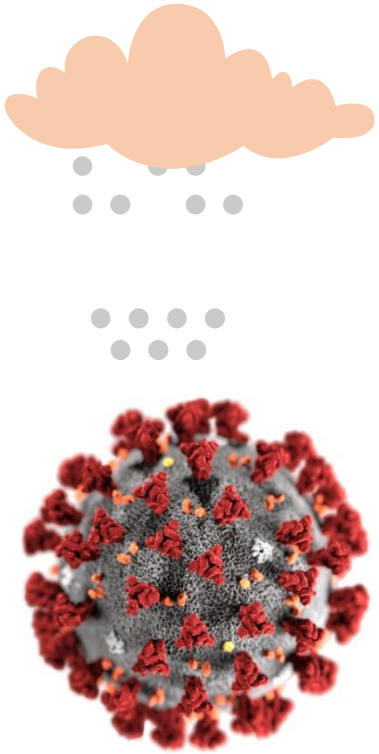
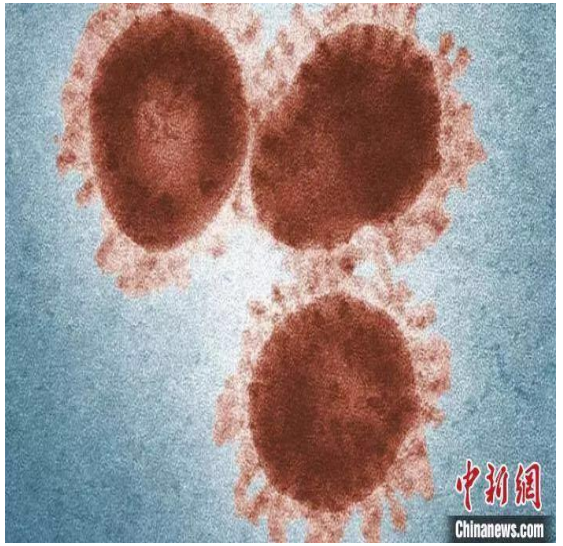
Donor Risk factors

Missed diagnosis of COVID -19 in donor could cause infection to the recipients and medical staffs through organ transplantation.



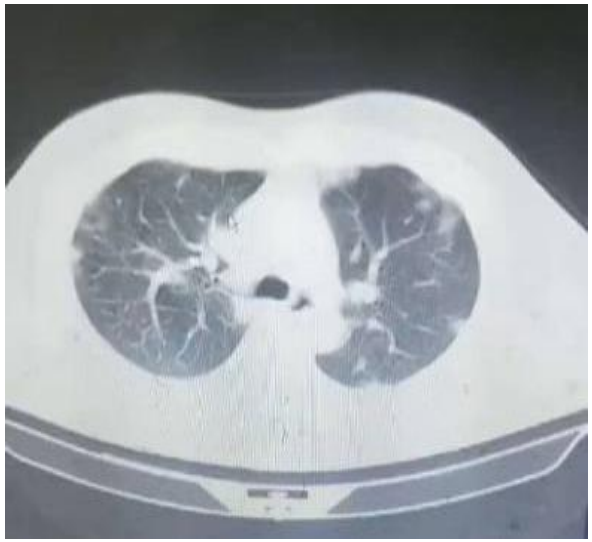
Recipients Risk factors

- High （+/ epidemiological）risk factors of COVID-19 cross infection in transplant candidates due to their frequent person-person contact in the treated unit.
- In order to receive transplantation as soon as possible, the waiting recipients may deliberately conceal the epidemiological history, resulting in the missed diagnosis of COVID-19.
- Latent asymptomatic COVID-19 could be the source of infection in transplant candidates and recipients in perioperative stage.



Risk factor of recipients

- The unrecognized COVID-19 transplant candidate could become severely infected after transplantation, which is life-threatening.
- The clinical symptoms and imaging manifestations of common pulmonary infection after transplantation are sometimes difficult to differentiated from COVID-19, which may delay the early diagnosis of COVID-19.



The prevention and control measures of organ transplantation during the outbreak of COVID-19

01

Enhance the management of transplant recipients

- The transplant recipients and their families should be informed and educated about the epidemic situation of COVID-19 via online education.
- In the process of sequential management of transplant candidates, the physician in charge should be aware of the status of the recipients, including information regarding their residence, contact history, clinical symptoms, recent travel history etc. in a timely and accurate manner.

02

Contraindications of organ transplantation

- In addition to the general contraindications of transplantation, candidates with the following patterns should not be considered for organ transplant:

  * Candidates confirmed or suspected with COVID-19.

* Of whom with epidemiological history of COVID-19 or contact history with patient exposure to the diseases (transplantation can be considered only when no disease occurred after 14 days of isolated observation).

* Because of the unknown risk of COVID-19 exposure in organ transplant recipients, it is recommended that organ transplantation should not be performed in areas with high incidence of disease.

03

The management of transplant candidates

- The candidate and their close contacts should be investigated and observed for **epidemiology and relevant symptoms**. They should be informed that the adverse consequences caused by deliberately concealing the epidemiological history and symptoms are of their own responsibility or to bear legal duty.
- **Before transplantation,** results of blood routine test, lung CT and C-reactive protein must be known. Related tests for COVID-19 should be carried out for virus screening and informed consent should be signed.
- The medical staffs should strengthen the propaganda regarding the epidemic protection for the recipients and their families. Pre-transplant evaluation and family approach should be carried out according to the hospital's regulations during the outbreak of COVID-19.

The prevention and control measures of organ transplantation during the outbreak of COVID-19

04

The management of post-transplant recipients

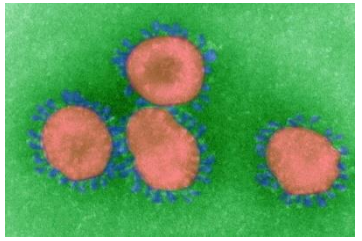
- Sterilization Isolation System in **the ward** for the perioperative period need to be implemented strictly. The distance between beds in the same ward should be more than 1.2m with good environmental ventilation.
- During the perioperative period of transplantation, recipients with **suspected symptoms** of COVID-19 should be isolated in a single room immediately. Medical staffs in contact of such recipients should receive isolated observation. Cases like this should be reported to the responding departments of the hospital in a timely manner and seek for consultation with the COVID-19 expert group.
- **P**atient should be transferred to the designated hospital once being diagnosed as a **suspected case** of COVID-19; those excluded from the suspected cases of COVID-19 can continue to be treated in the transplant ward and observed carefully.

The prevention and control measures of organ transplantation during the outbreak of COVID-19

05

The protection of medical staffs

Based on the principle of standard prevention and depend on the risk of transmission caused by different clinical operations, medical staffs should take measures accordingly for the prevention of hospital infection. Such actions include physical protection, hand hygiene, ward management, environmental ventilation, cleaning and disinfection of object surface and medical waste management.



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Clinical characteristics and diagnosis of organ transplant recipients with COVID-19

The clinical characteristics and diagnosis with COVID-19 in transplant recipients are **similar** to those from general population

Etiology and epidemiology of coronavirus

Clinical characteristics and diagnosis of COVID-19 in general population

Refer to *Guidance on the Novel Coronavirus Diagnosis and Treatment* issued by NHC P.R.C.

Clinical characteristics and diagnosis of organ transplant recipients with COVID-19

- **At present, there are few confirmed cases of COVID-19 in transplant recipients, no sufficient evidence exist to systematically summarize the clinical characteristics.**
- **Because of taking immunosuppressant for a long time, clinical characteristics in transplant recipients have its particularity, in addition to the common characters found in general population.**

Due to its **atypical clinical manifestations**, it is difficult to make early diagnosis of COVID-19 in transplant recipients. Transplant physician should be alert to their patients' uncomfortable symptoms.

- **For recipients coming from infected area:** the most important evidence for early clinical diagnosis is occurrence of symptoms such as fever, shortness of breath with/without chest tightness, and the characteristic pathological changes in chest CT

*** For recipients coming outside the infect area:**

the history of exposure to diseased needs to be interrogated carefully. Virus nucleic acid testing can be used as a clinical reference.

01 Clinical characteristics

* The main manifestations were symptoms like fever, dry cough, fatigue, chest tightness and shortness of breath in transplant recipients. However, **no fever or slight fever can be seen** in confirmed case; some patients have dry cough as the primary symptom; some patients only show diarrhea and digestive tract symptoms in the early stage. Lung image often lags behind the clinical manifestations and missed diagnosis may occur due to atypical clinical manifestations .

* Because of the immunosuppression of transplant recipients, **rapid progression** may occur once infecting from COVID-19, and ARDS may occur in critical ill patients.

02 General laboratory examination

- As a result of long-term use of immunosuppressants, **the number of leukocytes and lymphocytes** in peripheral blood of transplant recipients is often lower than that of normal people before the onset of the disease. And the number of lymphocytes in peripheral blood of tx patients with COVID-19 may be even significantly lower than that of the general population.

- It is necessary to go through the past history carefully, and to analyze and **longitudinally compare** the results of peripheral blood routine examination.

03 Etiological examination

* **RT-PCR** appeared high specificity and sensitivity, which can distinguish virus types and his subtypes in a fast manner.

- The sensitivity of the test may vary among samples (throat swab, sputum, secretion of lower respiratory tract, blood and feces) , and **the false negative rate** of the test using throat swab is relatively high. In order to improve the positive rate of nucleic acid test, it is recommended to keep **sputum** as much as possible ; **collect secretion of lower respiratory tract** for patients with intubation; samples should be sent for examination **right after the collection.**
- The diagnosis of COVID-19 depends on the real-time RT-PCR nucleic acid test positive; a negative test result can not completely exclude infection. For highly suspected COVID-19, **dynamic monitoring** of pathogen should be considered.

04 Imaging features

Most of the lung image findings of COVID-19 in transplant recipients are of the same as those of the general population:

- **In early stage,** most lesions are close to pleura, patchy shadowing, subsegmental or segmental ground-glass opacity, with or without interlobular septal thickening.
- **In advanced stage,** the lesions increased and expanded, evidenced by multilobar lesions, part of which were solid, ground-glass opacity and consolidation or coexistence of cords.
- **In severe stage,** there were diffuse lesions in both lungs, a few of which were "white lung", mainly with consolidation and ground-glass opacity, often with cord shadowing, air bronchus, rare pleural effusion or lymphadenopathy.

04 Imaging features

Imaging features of lung in renal transplant recipients with COVID-19

05 Imaging screening

- At present, the data from patients with COVID-19 in the general population indicates that imaging screening may be of higher sensitivity.
- Transplant recipients with high suspicion of COVID-19 should have lung image exam and dynamic monitoring as early as possible, and **chest CT** should be the first choice.

06 Tracheoscopy

* The tracheoscopy specialist should pay attention to the isolation and protection measures.

* **Suspected cases:** first of all, RT-PCR with respiratory tract sample should be used in detection of the Nucleic Acid of COVID-19 , the tracheoscopy can only be performed for infective-free recipients ; during the detection process, alveolus lavage fluid or lung tissue should be taken and sent for new coronavirus nucleic acid detection to rule out COVID-19.

* **Confirmed case**: In the absence of special protective measures, it is not allowed to repeat the use of tracheoscope .

Clinical characteristics and diagnosis of organ transplant recipients with COVID-19

The clinical symptoms of immunosuppressive host associated pneumonia after transplantation, such as CMV pneumonia and PJP pneumonia, are similar to those of COVID-19 and need to be differentiated, especially for transplant recipients 2-6 months after transplantation

	Clinical characteristics	Chest CT Lesion distribution	Chest CT Early manifestations	Chest CT Advanced stage	laboratory examination
CMV pneumonia	Mild symptom at early Dyspnea after pulmonary progression	Diffused, disseminated, asymmetric distribution	Military nodules with disseminated characteristics	Interstitial change with small nodule and consolidation	Positive CMV-DNA in blood and urine
PJP pneumonia	Rapid progress Progressive dyspnea and hypoxemia	Bilateral upper lung and hilus are distributed symmetrically, and subpleural area is "empty"	Diffused ground glass opacity with mosaic-like changes	Interstitial change, sometimes combined with consolidation	Positive G test in blood
COVID-19	Slow progress of symptoms at early Dyspnea in advanced stage	Subpleural distribution	Patchy or nodular ground-glass shadowing	Lesion fusion, interstitial change of fine reticular opacity, with consolidation	Positive COVID-19 nucleic acid in respiratory tract sample

Clinical characteristics and diagnosis of organ transplant recipients with COVID-19

Other common respiratory virus infections after transplantation are: influenza virus, adenovirus, parainfluenza virus, respiratory syncytial virus, rhinovirus, human metapneumovirus, etc.

Identification points:

- The virulence of viruses mentioned above are relatively weak.
- The incidence of these viral pneumonia is relatively low.
- The diagnosis mainly depends on RT-PCR in airway secretion due to non-speicific manifestation.

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Treatment of organ transplant recipients with COVID-19

The therapeutic principle are consistent with those applied to the general population

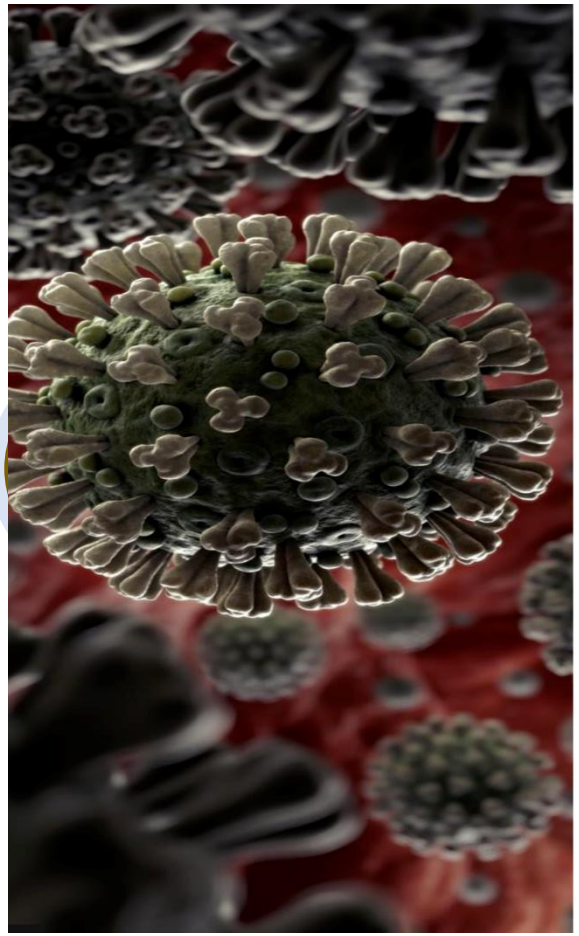
adjustment of immuno suppressive agent should be performed in a real time manner. Rejection should be avoided while anti-infection.

For those who have significant dysfunction of transplanted organs, special care should be taken, and the loss of graft function will cause more serious consequences.

Treatment of organ transplant recipients with COVID-19

* Based on factors such as age, the type of transplantation, the clinical characteristics, the severity of respiratory failure, the progress of the course of disease, the immune status, and the during after the transplant etc.

* Organize MDT consultation (with infection disease department, transplantation department, respiratory department, pharmaceutical department, etc.) to discuss and decide the treatment plan.



Treatment of organ transplant recipients with COVID-19

01 Determine the treatment site according to the severity of the disease

- The transplant physicians should carefully decide whether immunocompromised patient with mild symptoms could be isolated treated at home.

- Patients with suspected exposure history of COVID-19 and relevant symptoms should be screened with chest CT. Dynamic monitoring should be carried out to avoid missing the best time for treatment; if the result of lung CT shows positive or suspicious manifestations, patients should be hospitalized immediately.

Treatment of organ transplant recipients with COVID-19

02

Proper application of glucocorticoids in the treatment

- Methylprednisolone (MP) can alleviate the systemic inflammatory response of an infected patient, reduce the interstitial exudation of lung, control body temperature, and prevent graft rejection when reducing the dosage or stop using other immunosuppressants. It is suggested to use MP properly in the early stage.
- Overuse of hormone will further lower the body's immunity, affect the virus clearance, which is not conducive to the recovery from pneumonia, and may bring long-term complications.

Treatment of organ transplant recipients with COVID-19

02 Proper application of glucocorticoids in the treatment

Recommendation:

- In early stage of COVID-19, if lung CT shows typical ground-glass patchy shadowing, with or without fever, **MP 20 mg QD** can be injected intravenously. Dose can be increased according to the change of condition.
- If high fever occurs, bilateral multilobular flaky or large ground-glass opacity, **MP 40 mg Bid** can be injected intravenously; Dose **should not exceed 80 mg / d**.
- If the body temperature control fails, a small dosage of **dexamethasone** can be given intermittently.
- Attention should be paid to prevent the side effects when treated with glucocorticoids .

Treatment of organ transplant recipients with COVID-19

03 Dose adjustment of immunosuppressant

- For the confirmed cases **without positive result from lung CT** but with mild symptoms, we do not need to adjust immunosuppressant or to reduce the dosage.

- **For those with positive Lung CT result or highly suspicious manifestations, i**t is recommended to stop using antimetabolic drugs, and to reduce CNI drugs or rapamycin appropriately. Monitor closely the blood concentration of immunosuppressant during the reduction process and pay attention to drug interaction.

Treament of organ transplant recipients with COVID-19

03 Dose adjustment of immunosuppressant

For patient with severe condition and typical and extensive positive CT results

- All other immunosuppressants should be stopped immediately when MP (≥ 40mg / day) is applied.
- Whether to retore the usage of immunosuppressant should be determined by the improvement of CT and clinical symptoms. Lower dosage of CNI drugs can start first.
- It is suggested to control tacrolimus trough concentration to 4-6ng / ml and cyclosporine trough concentration to 50-80ng / ml in early stage of rehabilitation and adjust the target blood concentration gradually according to the recovery situation.

Treatment of organ transplant recipients with COVID-19

04 Respiratory support

- **Oxygen therapy**

It includes nasal catheter, mask for oxygen supply or high flow oxygen storage mask.

For patients with heart rate increased (> 100 BPM) and no hypoxemia, oxygen therapy can be started. It is suggested that oxygen therapy should be done in time if SpO2 < 95%.

The oxygen therapy method and flow rate shall be determined according to the specific situation, to make sure SpO2 ≥ 95%.

Treatment of organ transplant recipients with COVID-19

04 Respiratory support

- Transnasal high flow oxygen therapy (hfno) or noninvasive mechanical ventilation (NIV)

When respiratory distress and / or hypoxemia cannot be relieved after standard oxygen therapy, hfno or NIV should be used to maintain SpO2 > 90% .

Hfno and NIV systems do not produce extensive exhalation diffusion, so the risk of airborne transmission should be low.

If the condition does not improve or even worsen in a short time (1-2 hours), invasive mechanical ventilation should be carried out immediately.

Treament of organ transplant recipients with COVID-19

04 Respiratory support

- Invasive mechanical ventilation

Using lung protective ventilation strategy, low tidal volume (4-8ml / kg ideal body weight) and low inspiratory pressure (platform pressure < 30cmH_2O) to reduce ventilator-related lung injury.

Treament of organ transplant recipients with COVID-19

05 Anti-viral therapy

The latest recommendation by NHC:

- **α - interferon** (5 million U or equivalent dose per time for adults, 2ml of sterile water for injection, bid, atomized inhalation).
- **Lopinavir / ritonavir** (2 capsules (200 mg / 50 mg / capsule), bid ribavirin intravenous injection (500 mg each time for adults, twice a day, course of treatment no more than 10 days).
- Ribavirin (it is recommended to be used in combination with alpha interferon or lopinavir / ritonavir, 500mg for adults, twice to three times a day, with a course of no more than 10 days).

Treatment of organ transplant recipients with COVID-19

05 Antiviral therapy

- Chloroquine phosphate (adult 500mg, bid, course of treatment no more than 10 days).
- Abidol (adult 200mg, TID, course of treatment no more than 10 days).
- **Attention** should be paid to the adverse reactions such as diarrhea, nausea, vomiting and liver function damage related to lopinavir / ritonavir, as well as the interaction with other drugs; transplant recipients often have different degrees of hyperlipidemia, and when combined with lopinavir / ritonavir, attention should be paid to the severe hyperlipidemia-induced pancreatitis.

It is not recommended to use three or more antiviral drugs at the same time.

Treatment of organ transplant recipients with COVID-19

06

Supportive treatment and immune reconstitution

- Ensure sufficient energy supply, maintain water, electrolyte, **acid-base balance and homeostasis.**
- For critical ill patients, high dose **IVIG** can increase the resistance of human body to pathogens without increasing the risk of rejection. The recommended dose is 0.1-0.3 g / kg / D and the total dose is 1-2 g / kg.
- Due to the high metabolic consumption in the whole course of COVID-19, most of the patients will develop hypoproteinemia. **Timely supplementation of albumin and appropriate diuretics** are helpful to the absorption of pulmonary interstitial exudation.
- **Thymosin** could be used in severe patients when the absolute value of peripheral blood T cells are significantly decreased

Treatment of organ transplant recipients with COVID-19

07 TCM Treatment

- This disease is classified as the category of epidemic disease in traditional Chinese medicine. TCM as treatment can be considered based on the patient's condition, local climate characteristics and protocol proposed by theNational Health Commission .
- Due to the particularity of transplant recipients and complexity of combined medication, the effect of some Chinese herbal medicine or proprietary Chinese medicine on the concentration of immunosuppresants and the poor tolerance of gastrointestinal tract, it is necessary to be cautious when receiving the treatment **of TCM.** Pay attention to the influence of TCM on the metabolism of immunosuppressant, and closely monitor the concentration of immunosuppressants.

Treatment of organ transplant recipients with COVID-19

08 Other treatments

- **To protect the liver and kidney function,** we should avoid the use of drugs that damage the liver and kidney function, such as NSAIDs and some antibiotics.

- Because the pathogenesis of COVID-19 is likely to be a series of cascade reactions caused by the combination of new coronavirus and ACE2 in human respiratory tract and lung tissue, transplant recipients with COVID-19 using ACEI or ARB should balance the advantages and disadvantages, **stop using ACEI / ARB and switch them to CCB**.

- **Ambroxol** as an expectorant, may also be a therapeutic drug targeting new coronavirus receptor ACE2, which could be a solution for transplant recipients.

Treatment of organ transplant recipients with COVID-19

08 Other treatments

- There is no experience in the use of **plasma therapy** in transplant patients.
- The **intestinal microecological regulator** can maintain the intestinal microecological balance and prevent the secondary bacterial infection.
- **Blood purification technology**: plasma exchange, immune adsorption, perfusion, hemofiltration, etc.

Contents

Follow up management of organ transplant recipients during the outbreak of COVID-19

01 Scientific protection measures

- Transplant recipients are of susceptible population of COVID-19 due to their decreased resistance of to various pathogens.
- At present, there is no specific medication for COVID-19
- It is an effective way to reduce the incidence rate by strengthening the protection of SOT recipients in a scientific manner.
- Refer to *protection Guidelines for public regarding Novel Coronavirus Pneumonia*.

Follow up management of organ transplant recipients during the outbreak of COVID-19

02 Strengthen health management

- Prepare sufficient drugs, reduce the frequency of going out for medicine, and take drugs as prescribed. Do not adjust dosage without advice from the doctors or replace medication.
- Prevention of CMV and PJP pneumonia should be emphasized in early stage after transplantation.
- Make self-monitoring records.
- Online activities of NCP and transplant-related education instead of on-site ones.

Follow up management of organ transplant recipients during the outbreak of COVID-19

02 Strengthen health management

- Transplant patient recovering form COVID-19 should keep in touch with transplant physician. COVID-19 and organ function should be both followed up , to ensure the proper use of immunosuppressant.

- The transplant recipients are more sensitive to fever and pulmonary infection than others. They could easily get nervous and anxious. Psychological counseling should be strengthened. If necessary, psychiatrists should be consulted to give professional guidance.

Follow up management of organ transplant recipients during the outbreak of COVID-19

03 Follow up measures

- To avoid visiting transplant hospitals in epidemic areas.
- Follow-up can postpone according to the postoperative period. Based on the Lab results and the self-monitoring of the patients, follow up can be done through the internet.
- Patients with unstable condition can visit their doctors on the premise of keeping a good physical protection.
- Recipients can send their lab results obtained from local hospital to their transplant hospital through the internet for follow-up.

Follow up management of organ transplant recipients during the epidemic

03 Follow up measures

- Hospital with post-transplant clinic should strictly implement the disinfection policy in each department and ensure the protective measures to be taken for medical staff during follow-up.
- " 1 doctor,1 room for 1 patient" should be guaranteed in the transplant clinic.
- All follow-up transplant recipients and their companions should be re-checked and epidemiological investigated by the outpatient doctors.
- Guide the transplant recipient to carry out sufficient personal protection when visiting the clinics. Inform them not to access any fever clinic or emergency area, and to leave the hospital immediately after the visit.

Conclusion

During the outbreak of COVID-19, all transplant hospitals should manage their organ donation and transplantation activities in an orderly manner. At the same time, the hospital should strengthen the health management and follow-up measures for transplant recipients. Working together, these efforts will be beneficial for healthy development of organ transplantation in China in a long run.

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We are determined to fight and win this battle with united effort. Stay strong, Wuhan!