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Diagnosis and treatment for Novel Coronavirus Pneumonia (COVID-19): International Expert Opinions and Experience from China

Jafron Biomedical Co.,Ltd.

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Diagnosis and Treatment Scheme for Novel Coronavirus Pneumonia Edition VI

National Health Commission of the People's Republic of China 18 February 2020

Since December 2019, Wuhan City, Hubei Province (China) has found a number of novel coronavirus pneumonia patients, with the spread of the epidemic, other parts of China and abroad have also found such cases. As an acute respiratory infectious disease, the disease has been included in the Class B infectious disease stipulated in the Law of the People's Republic of China on the Prevention and Control of Infectious Diseases.With the deepening of understanding of the disease and the accumulation of experience in diagnosis and treatment, we revised the <u>Diagnosis</u> and <u>Treatment Scheme for Novel Coronavirus Pneumonia - Edition VI.</u>

1 Pathogenic characteristic

The novel coronavirus belongs to the coronavirus of the β genus, which has an envelope, round or oval particles, often polymorphic, with a diameter of 60-140 nm. Its gene characteristics are obviously different from those of SARS-C and MERSI-CoV. Recent studies have shown that the homology reaches up over 85% with SARS-like coronavirus (bat-SL-CoVZC45). When isolated and cultured in vitro, 2019-nCoV can be found in human airway epithelial cells in about 96 hours, while in Vero E6 and Huh-7 cell lines, it takes about 6 days to isolate and culture.

The understanding of physicochemical properties of coronaviruses comes from the study of SARSr-Cov and MERSr-Cov. The virus was sensitive to ultraviolet and heat. The virus could be inactivated by solvent such as ether, 75% ethanol, chlorine-containing disinfectant, peracetic acid and chloroform or while at 56 \degree C for 30 minutes.

2 Epidemiological characteristics

2.1 Source of infection

At present, the main source of infection is patients infected with novel coronavirus.



Asymptomatic infected patients may also become the source of infection.

2.2 Route of transmission

Respiratory droplets and close contact are the main routes of transmission. The possibility of aerosol transmission exists in the case of long-term exposure to high concentration aerosols in a relatively closed environment.

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2.3 Susceptible population

The population is generally susceptible

3 Clinical characteristics

3.1 Clinical manifestations

Based on the current epidemiological survey, the incubation period is 1-14 days, mostly 3-7 days. The main manifestations were fever, dry cough and fatigue. A small number of patients with nasal congestion, runny nose, sore throat, myalgia and diarrhea and other symptoms.

Mild patients only showed low fever, slight fatigue and so on, without symptoms of pneumonia. Most of the severe patients have dyspnea and/or hypoxemia one week after the onset of the disease, and the severe patients can rapidly progress to acute respiratory distress syndrome, septic shock, metabolic acidosis, bleeding and coagulation dysfunction and multiple organ failure. It is worth noting that severe and critical patients may have moderate to low fever or even no obvious fever in the course of the disease.

From the current treatment of cases, most patients have a good prognosis, a small number of patients in critical condition. The prognosis was poor in the elderly and those with chronic underlying diseases. The symptoms of child cases are relatively mild.

3.2 Laboratory examination

In the early stage of the disease, the total number of peripheral blood leucocytes was normal or decreased, the number of lymphocytes decreased, and some patients may have elevated liver enzymes, lactate dehydrogenase (LDH), muscle enzymes and myoglobin.Increased troponin was seen in some critical patients.C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR)



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were elevated and procalcitonin was normal in most patients.<u>In severe cases, D-dimer increased</u> and peripheral lymphocytes decreased progressively.Severe and critical patients often have elevated inflammatory factors.

The novel coronavirus nucleic acid can be detected from specimens with nasopharyngeal swabs, sputum or other lower respiratory tract secretions, blood, feces and others.

In order to improve the positive rate of nucleic acid detection, it is suggested that sputum should be collected as much as possible, lower respiratory tract secretions should be collected from patients with tracheal intubation if possible, and samples should be sent for examination as soon as possible after collection.

3.3 Chest imaging.

In the early stage, there are multiple small patches and interstitial changes, especially in the outer zone of lung. And then the development of bilateral lung multiple ground-glass shadow, infiltration shadow, severe cases may appear lung consolidation, pleural effusion cases are rare.

4 Diagnostic criteria

4.1 Suspected cases

Comprehensive analysis should combine the following epidemiological history and clinical manifestations, and if the patient has: 1) any one of the epidemiological history and together with any 2 of the clinical manifestations, or 2) with no clear epidemiological history, but with 3 of the clinical manifestations considered suspected patient.

4.1.1 Epidemiological history

A) History of travel or residence in Wuhan and surrounding areas, or other communities in which the case has been reported, within 14 days prior to onset of illness;

B) History of contact with a person infected with the novel coronavirus (who has a positive nucleic acid test) within 14 days prior to the onset of illness;



C) Contacted with a patient with fever or respiratory symptoms from Wuhan and surrounding areas, or from a community in which a case has been reported, in the 14 days prior to onset of illness;D) Cluster morbidity.

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4.1.2 Clinical manifestations

A) Fever and/or respiratory symptoms;

B) Having the imaging characteristics of the novel coronavirus pneumonia mentioned above;

C) In the early stage of onset, the total number of white blood cells is normal or reduced, and the number of lymphocytes is reduced.

4.2 Confirmed cases

Suspected cases with one of the following etiological evidence:

A. A positive result of real-time fluorescent RT-PCR detection of novel coronavirus nucleic acid positive;

B. Viral gene sequencing, which is highly homologous to the known novel coronavirus.

5 Clinical Classifications

5.1 Mild type

The clinical symptoms were mild, no imaging findings of pneumonia.

5.2 Common type

With fever, respiratory tract and other symptoms, radiological signs of novel coronavirus pneumonia can be detected.

5.3 Severe type

In accordance with any of the following:

A) Shortness of breath, RR \geq 30 times/min;

B) At rest, oxygen saturation \leq 93 %;

C) PaO2/FiO2 \leq 300 mmHg; (1 mmHg = 0.133 kPa)



Note:

1) At high altitudes (above 1000m), PaO2/FiO2 should be corrected according to the following formula: PaO2/FiO2×[atmospheric pressure (mmHg)/760];

2) Patients with pulmonary lesions progressing more than 50% within 24-48 hours were managed as severe cases.

5.4 Critical type

It meets one of the following conditions:

A) Respiratory failure occurs and requires mechanical ventilation;

B) Occurrence of shock;

C) Combined with other organ failure and required monitored and treated in ICU.

6 Differential diagnoses

A) The mild manifestations of novel coronavirus infection should be differentiated from upper respiratory tract infection caused by other viruses.

B) The novel coronavirus pneumonia is mainly distinguished from influenza virus, adenovirus, respiratory syncytial virus and other known viral pneumonia and mycoplasma pneumoniae infection, especially for suspected cases, methods including rapid antigen detection and multiplex PCR nucleic acid detection should be adopted as far as possible to detect common respiratory pathogens.

C) It should also be differentiated from non-infectious diseases, such as vasculitis, dermatomyositis and organizing pneumonia.

7 Treatments

7.1 Treatment place determination

A) Suspected and confirmed cases should be isolated and treated in designated hospitals with effective isolation conditions and protective conditions, suspected cases should be isolated and treated in a single ward, and confirmed cases can be treated in the same ward.

B) Critical cases should be treated in ICU as early as possible.



7.2 General treatment

A) Rest in bed, strengthen supportive treatment and ensure adequate calories; pay attention to the balance of water and electrolyte, and maintain the stability for hemostasis; closely monitor vital signs, finger oxygen saturation, etc.

B) Monitor blood routine, urine routine, CRP, biochemical indicators (liver enzymes, myocardial enzymes, renal function, etc.), coagulation function, arterial blood gas analysis, chest imaging, etc. Cytokine detection is feasible for those who have the medical conditions.

C) Prompt administration of effective oxygen therapy, including nasal cannula, mask oxygen administration and high flow oxygen therapy through the nose.

D) Antiviral therapy

a) Try Alpha-interferon (5,000,000 U or equivalent dose for adults, nebulized twice a day with 2ml sterile water for injection);

b) Lopinavir/Ritonavir (200 mg/50 mg/pill for adults, 2 pills each time, twice a day, for a course not exceeding 10 days);

c) Ribavirin (recommended in combination with Interferon or Lopinavir/Ritonavir; for adults 500 mg/time, intravenous infusion 2-3 times daily, for a course not exceeding 10 days);

d) Chloroquine phosphate (500 mg twice daily for adults, for a course not exceeding 10 days);

e) Arbidol (200 mg three times daily for adults, for a course not exceeding 10 days).

Note:

Attention should be paid to the adverse reactions of Lopinavir/Ritonavir related diarrhea, nausea, vomiting, liver damage and other drug interactions. In the clinical application of further evaluation of the efficacy of drugs currently on trial. It is not recommended to use three or more antiviral drugs at the same time, and the use of related drugs should be stopped when intolerable side effects occur.

E) Antibacterial therapy: <u>blind or inappropriate use of antibiotics should be avoided, especially the</u> <u>combination of broad-spectrum antibiotics.</u>



7.3 Treatment for severe and critical cases

A) Treatment principle

On the basis of symptomatic treatment, to actively prevent and treat complications, underlying diseases, secondary infection, and support organ function timely.

B) Respiratory support

a) Oxygen therapy: Severe patients should receive nasal cannula or mask oxygen, and timely evaluation of whether the respiratory distress and/or hypoxemia are resolved.

b) High-flow nasal tube oxygen therapy or non-invasive mechanical ventilation: When the respiratory distress and/or hypoxemia can not be alleviated after standard oxygen therapy, high-flow nasal tube oxygen therapy or non-invasive mechanical ventilation can be considered. If there is no improvement or even deterioration in a short time (1-2 hours), tracheal intubation and invasive mechanical ventilation should be carried out in time.

c) Invasive mechanical ventilation: Lung protective ventilation strategy was used, namely, low tidal volume (4-8 ml/kg ideal body weight) and low inspiratory pressure (Plateau pressure < 30 cm H2O) to reduce ventilator-associated lung injury. Most patients have patient-ventilator asynchrony, then sedation and muscle relaxants should be used in time.

d) Rescuing therapy: <u>For patients with severe ARDS, lung recruitment is recommended. In the case of adequate human resources, more than 12 hours of prone ventilation should be carried out every day. If prone position ventilation is not effective, extracorporeal membrane oxygenation (ECMO) should be considered as early as possible.</u>

C) Circulatory support

On the basis of adequate fluid resuscitation, use vasoactive drugs for microcirculation improvement, and monitor the hemodynamic if necessary.

D) Treatment with plasma of convalescents

It is suitable for patients with rapid progression, severe and critical diseases. The usage and dosage are referred to the *Clinical Therapeutic Scheme of convalescents' Plasma for Patients with Novel Coronavirus Pneumonia (Edition I).*

E) Other treatment measures



a) For patients with progressive deterioration of oxygenation indicators, rapid medical imaging progress, and excessive activation of the body's inflammatory response, may conduct appropriate and short-term (3-5 days) use of glucocorticoids with the suggested dosage not exceeding 1-2 mg/kg/day equivalent to methylprednisolone; and it should be noted that larger doses of glucocorticoids will delay the clearance of coronavirus due to the immunosuppressive effect.

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b) Intestinal micro-ecological modulators can be used to maintain intestinal microecological balance and prevent secondary bacterial infection.

c) For critically ill patients with a high inflammatory response, the use of plasma exchange, plasma adsorption, hemoperfusion/hemoadsorption, hemofiltration/plasma filtration and other extracorporeal organ support technology should be considered.

Note:

Since patients are always under anxiety and fear status, psychological counseling should be strengthened.

8 Attentions

8.1 Release criteria

Those who meet the following conditions may be released from isolation and discharged:

A) The body temperature returns to normal for more than 3 days;

B) The symptoms of respiratory tract are obviously improved;

C) Acute exudative lesions in the lungs were markedly improved on medical imaging;

D) Two consecutive negative nucleic acid tests of respiratory tract specimens (sampling time interval of at least 1 day).

8.2 Attentions after release

A) Designated hospitals should make good contact with basic medical institutions in the patient's residence, to share medical records, and to timely deliver the information of discharged patients to the relative basic medical and health institutions.



B) After the patient is discharged from hospital, due to the low immune function of the body during the recovery period and the risk of infection with other pathogens, it is suggested that he/she should continue to carry out self-health monitoring for 14 days, wear medical mask, live in a single room with good ventilation, reduce close contact with the family, eat separately, do a good job of hand hygiene, and avoid outdoor activities.

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C) It is also suggested that follow-up and re-examination should be carried out in the 2nd and the 4th week after discharge.



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Expert consensus



Application of Artificial Liver Blood Purification System in the Treatment of Severe and Critical Pneumonia Caused by Novel Coronavirus

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At present, the prevention and treatment of novel coronavirus pneumonia has entered a critical stage, the effective treatment of severe and critical patients is the key to reduce the mortality of the disease. The clinical features and disease process of acute severe respiratory infectious diseases have common characteristics: rapid progress of pulmonary inflammation, severe hypoxemia and multiple organ failure, the ultimate cause of death is respiratory failure, shock and other multiple organ failure and late uncontrollable secondary infection. Studies have shown that severe cases of SARS, H5N1 and H7N9 virus infection all present "cytokine storm", which is the main deterioration factor of severe disease. Therefore, blocking the "cytokine storm" is the key link in the treatment of shock, hypoxemia and multiple organ failure previous. Studies revealed that artificial liver blood purification system (ALBPS) could eliminate inflammatory factors, block the "cytokine storm", thus reducing the tissue injury due to the inflammatory response to the body's injury, and has important value for the treatment of severe and critical patients. Practice shows that Li's artificial liver has played a huge role in the treatment of severe patients infected with H7N9 avian influenza, and achieved good results. After discussion by the expert team, the following consensus was concluded on the principle, indications, relative contraindications, monitoring indicators and efficacy evaluation of artificial liver support for severe and critical novel coronavirus pneumonia patients.

Chinese Journal of Clinical Infectious Diseases, 2020, 13 (00): E003-E003.

1. Basic principle

Artificial liver and blood purification system integrates plasma exchange, plasma adsorption, hemoadsorption/hemoperfusion, blood/plasma filtration and other technologies, which can be used to remove inflammatory mediators, endotoxin and middle and small molecular harmful toxins, supplement albumin, coagulation factors and other beneficial substances, regulate water and electrolyte, acid-base balance. It can block the "cytokine storm", reduce lung inflammation and improve respiratory function; At the same time, it is helpful to restore the immune homeostasis, improve the metabolic spectrum disorder, help the precise management of capacity, improve the function of liver, kidney and other organs, so as to improve the success rate of treatment for severe and critical novel coronavirus pneumonia patients and reduce the mortality rate.

2. Indication

Artificial liver support is indicated for the patients who match the criteria (1) + (2), or just criteria (3) as below:

(1) The concentration of inflammatory factors, such as interleukin-6 (IL-6) in blood is \geq 5 folds of the upper limit of normal, or the daily rising rate is > 1 fold;

(2) Pulmonary imaging progressed rapidly, and the percentage of lung involvement showed by CT or X-ray progressed $\geq 10\%$ daily;

(3) Patients with underlying diseases requiring artificial liver treatment.

3. Relative contraindications

In the rescue of critically ill patients, there are no absolute contraindications, but the following situations should be considered cautiously: (1) Severe active hemorrhage or disseminated intravascular coagulation (DIC); (2) Severe hypersensitivity to blood products or drugs, such as plasma, heparin and protamine used in the course of treatment; (3) Acute cerebrovascular accident or severe craniocerebral injury; (4) Chronic cardiac insufficiency, with cardiac function grade III or above; (5) Uncorrected hypotension and shock; (6) Severe Arrhythmia.

4. Choice of treatment mode

After fully evaluating the patients, choose the appropriate treatment mode:

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(1) When plasma is available, plasma exchange combined with plasma adsorption or Double Plasma Molecule Adsorption System (DPMAS), hemoadsorption/hemoperfusion and hemofiltration are recommended; the volume of plasma exchange (L) = body mass (kg)×(1/13)× (1- Hct/100). In case of plasma shortage, the volume of plasma exchange should be more than 2,000 mL.

(2) When plasma is unavailable or < 2,000 mL, combination with plasma adsorption or DPMAS (Double Plasma Molecule Adsorption System), hemoadsorption/hemoperfusion and hemofiltration are recommended. If the patient is combining with renal insufficiency, sequential combination with hemodialysis and/or CVVH should be conducted.

5. Indicators Monitoring

5.1 Indicators before treatment

(1) Clinical symptoms and signs: vital signs, pulmonary manifestations and so on; Oxygen supply mode, flow rate and concentration; (2) Blood type, blood routine, C-reactive protein (CRP), procalcitonin (PCT), coagulation function, biochemical set, immunoglobulin, arterial blood gas analysis & lactic acid, peripheral blood IL-6, Partial arterial oxygen pressure (PaO2)/ Fraction of inspired oxygen (FiO2), lung imaging (X-ray or CT) examination; (3) Conditional units can detect cytokines such as IL-8, IL-10, tumor necrosis factor- α (TNF- α) and peripheral blood lymphocyte subsets; (4) PSI score (Pneumonia Severity Index).

5.2. Indicators after treatment

(1) Daily recording of clinical symptoms and signs: vital signs, lung performance and so on; Oxygen supply mode, flow rate and concentration; (2) Blood routine, CRP, PCT, coagulation function, biochemistry set, arterial blood gas analysis & lactic acid, peripheral blood IL-6, Partial arterial oxygen pressure (PaO2)/ Fraction of inspired oxygen (FiO2), were monitored every day; and IL-8, IL-10 and TNF- α if available; (3) Daily assessment of Pneumonia severity index (PSI score); (4) Immunoglobulin monitoring (every 3 days), and lymphocyte subsets monitoring if available; (5) Lung radiological (X-ray or CT) examination, every 3 days.

6. Efficacy evaluation

It is divided into the evaluation of each treatment and the evaluation of overall survival rate.

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(1) For each treatment: the evaluation standard of each treatment was the change of monitoring index before and after treatment, and the main indexes were the change of cytokines (IL-6, etc.) And PSI score. (2) Evaluation of survival rate: to evaluate the 28-days and 12-weeks survival rate.

7. End of treatment

In addition to the need for continued treatment of the underlying disease, any of the following tips $(1) + (2) \sim (5)$ can be considered as the end point of treatment:

(1) The body temperature is normal for 3 days, and obviously improved of respiratory symptoms;

(2) The level of inflammatory factors (such as IL-6) decreased to < 2 folds of the normal value and lasted for 3 days;

(3) Weaning from ventilator support;

(4) Blood lactate concentration < 2.0 mmol/L and lasted for 3 days;

(5) One week later, obviously improved of radiological lesions of the lungs (with > 30% absorption of the lung lesions);

Final words

It should be noted that at present, the application of artificial liver to the rescue and treatment of severe and critical novel coronavirus pneumonia patients is based on the experience of several centers in Zhejiang, Hubei, Henan and Shaanxi provinces in China. Under the severe epidemic situation of novel coronavirus pneumonia, this operation manual is formulated for the reference of all units to carry out rescue and treatment work and make a modest contribution to reduce the mortality rate!

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Chinese Journal of Clinical Infectious Diseases, 2020, 13 (00): E003-E003.

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Expert consensus



Diagnosis and treatment of acute kidney injury associated with novel coronavirus infection

Chinese Society of Nephrology

Abstract

Novel coronavirus disease 2019 (COVID-19) is a newly discovered class B infectious diseases. It is characterized by virus infected pneumonia, accompanying with multiple organ damage including kidney, heart, blood, and nerve system. Since its outbreak in China in December 2019, COVID-19 has now spread to more than 20 countries and regions all over the world, and WHO has declared it as a public health emergency of international concern.COVID-19, like severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS), are all caused by coronavirus. And acute kidney injury (AKI) is one of the important complications of the disease. Timely prevention and treatment of AKI is critical for patients with COVID-19. Here the Chinese Society of Nephrology organized a group of experts in nephrology to summarize the features of COVID-19 related AKI including epidemiological and clinical characteristics, specifically, the suggestions on diagnosis and treatment was given. It is our hope to raise clinical concern about management of AKI so as to improve the outcome of patients with COVID-19.

Foreword

The novel coronavirus disease 2019 (COVID-19) is a newly discovered SARS-CoV-2 virus-induced acute infectious diseases which mainly manifest as acute respiratory disease and also affected

multiple organs or system such as the kidney, cardiovascular, digestive, blood and nerves systems. The disease is highly infectious, and the clinical manifestations are complex and diverse, with the main feature of respiratory disease. Apart from the lung, the kidney is one of the vital organs involved, which shows a very important impact on the prognosis of patients. It is very important to know more about the acute kidney injury (AKI) of COVID-19 in order to improve the success in rescuing patients with COVID-19.

1. Epidemiology

In December 2019, a novel coronavirus pneumonia (NCP) broke out in Wuhan, Hubei Province, China. NCP spread rapidly to the whole country and even abroad, and was listed as a class B infectious disease managed by the state with class A standards ^[1], then the pathogenic virus was named COVID-19 by WHO on February 11, 2020 ^[2]. The viral gene shows over 85% homology with bat-SARS-like coronavirus, and the virus is mainly transmitted by respiratory droplets and contact, but may also be transmitted by aerosols and fecal-oral routes.

The population is generally susceptible and the disease presents a cluster outbreak. The incubation period was similar to that of SARS (severe acute respiratory syndrome, with an average incubation period of 4.6 days, 95% CI: 3.8-5.8 days) and MERS (Middle East respiratory syndrome, with the incubation period of 2-14 days) ^[1, 3-4]. According to the NCP epidemic data in China, as of February 19, 2020, the cumulative confirmed cases in mainland China were 74679, of which the severe cases were 11864 (accounting for 15.9%), with 2122 deaths in total and a mortality rate of 2.8%. The basic reproductive number (R0) of covid-19 also fluctuated, up to January 24, 2020, it was 2.2-3.6^[5-8], showing a stronger infectivity than SARS (R0: 0.9-2.7) and MERS (R0: 2-3).

AKI caused by coronavirus infection is not rare, mainly manifested as renal tubular injury. Among 536 SARS cases analyzed by Chu et al, AKI patients accounted for 6.7% (36/536), with a high mortality rate of 91.7% (33/36) ^[9-10]. MERS-CoV cases reported a 67% mortality rate with AKI ^[11]. In addition, in report of 99 patients with NCP, 7 patients (7%), different degrees of renal injury occurred, accompanied by elevated Serum Creatinine (SCr) and/or Blood Urea Nitrogen (BUN) ^[8];

in another report, 5 of 138 patients developed AKI (3.6%), and 2 underwent renal replacement therapy ^[12].Recently, Guan et al reported that the incidence of AKI was 0.5% in 1099 patients with NCP, and in 173 critically ill patients, AKI occurred in 5 patients (2.9%) ^[13]. Cheng et al ^[14] showed that the incidence of AKI in 710 consecutive COVID-19 patients in a single-center was 3.2%. These data above may be related to sample size and patient bias, but the overall incidence of AKI seems to be lower than that of SARS and MERS. The exact incidence of AKI remains to be confirmed with larger sample size in the future.

2. Pathogenesis of AKI

The mechanism of AKI caused by coronavirus infection is still unclear. According to the existing research, it may be directly mediated by virus, or indirectly caused by cytokines and other factors released by abnormal immune response.

2.1 Direct viral mediation

Organ-targeted injury of coronavirus is mainly determined by the binding ability of receptor-binding protein and cell surface receptor. Two major coronavirus functional receptors have been identified: (1) Angiotensin converting enzyme 2 (ACE2): it can bind to the S1 domain of the SARS coronavirus spike protein. Therefore, it is suggested that ACE2 is a functional receptor of SARS-CoV ^[15]. ACE2 is mainly expressed in lung, kidney, heart, ileum and other tissues, and is strongly expressed in the proximal tubule of the kidney, while weak expression in the glomerulus ^[16]. SARS-CoV was detected by polymerase chain reaction (PCR). SARS-CoV has also been found in renal tissue of infected patients ^[17]. In addition, the whole genome sequence of the virus in COVID-19 shares 79.5% homology with SARS virus, ACE2 is a cell targeted receptor of both viruses ^[18]. The binding affinity of ACE2 protein to novel coronavirus is 10-20 times higher than that of SARS virus ^[19]. Therefore, it is speculated that COVID-19 may also infects ACE2 or other receptors and mediate AKI, but the specific mechanism remains to be further clarified.

(2) Dipeptidyl Peptidase 4 (DDP4), which is considered as a functional receptor of MERS-CoV [20], is highly expressed in kidney, small intestine and lung, and is also one of the renal tubular brush

border membrane proteins ^[21], as well as in glomerular podocytes and capillaries. Therefore, it cannot be ruled out that it has a direct targeted attack on kidney tissue.

2.2 Immune activation mediation

The immune activation caused by infection and the release of a large number of pro-inflammatory factors may also be one of the important reasons leading to AKI. SARS-CoV and MERS-COV infection can lead to significant up-regulation of inflammatory cytokines and chemokines ^[4], mainly through the release of chemokines, pro-inflammatory cytokines and inducible nitric oxide synthase from macrophages M1 subtype, forming cytotoxic peroxynitrite, which mediates kidney injury. In addition, dendritic cells release TNF- α to further promote inflammatory response ^[22]. Recently, cytokine Storm Syndrome (cytokine storm syndrome, CSS) has been found to play an important role in various infection-mediated multiple organ failure. It promotes cytokine activation cascade reaction through the body's immune response out of control, and releases a large number of cytokines, which can cause systemic inflammation, methemoglobinemia, hemodynamic imbalance, shock, disseminated intravascular coagulation and multiple organ failure. CSS is also important triggering factor of Acute Respiratory Distress Syndrome and multiple organ failure ^[5].TNF-a, II-l, IL-6, IL-12 and IFN-a were significantly increased in patients with COVID-19, suggesting that there may be a phenomenon of CSS. Chen Lei ^[23] reported that IL-6 and GM-CSF were significantly increased in a group of 29 patients with NPC. The mechanism may be that COVID-19 activates T cells to release IL-6, while GM-CSF activates monocytes to further release inflammatory factors, amplifying the immune effect and leading to AKI.

2.3 Other factors

Severe and critical COVID-19 patients often have hypotension, dehydration caused by loss of fluid in digestive tract, hypoxemia, electrolyte acid-base disturbance, cardiac insufficiency and so on. Norepinephrine, the use of a variety of antiviral drugs and antibiotics, as well as the basic diseases such as diabetes, hypertension, and old age, these factors may induce AKI.

3. Clinical manifestations

3.1 General manifestations

COVID-19 infection mainly causes respiratory, cardiovascular, digestive, urinary, nervous and other diseases ^[5]. The main clinical manifestations were fever, dry cough and fatigue. A small number of patients are with nasal congestion, runny nose, sore throat, myalgia and diarrhea and other symptoms. Severe patients are with high fever, shortness of breath, shortness of breath, cyanosis, hypoxemia, and hypotension and so on.

3.2 Renal manifestations

The main manifestations of the patients are proteinuria, hematuria, oliguria, BUN, SCr elevation and renal imaging changes, and some patients develop AKI ^[8].Elevated BUN and SCr can be seen in the laboratory examination, and CT indicates the size or structural changes of the kidney ^[24]. A study consisted of 59 early stage patients with COVID-19 infection ^[25] found that 34% had proteinuria on the first day of admission; during the course of the disease, 63% of the patients had proteinuria. The serum BUN level was elevated in 27% of the patients, the serum BUN level was higher in 2/3 of the patients who died, and the SCr level was higher than 200µmol/L in 3 patients who died. CT Hounsfield value of kidney in 27 cases was lower than normal (35HU), which may be related to kidney inflammation and edema. In addition, a group of literatures reported that about 3.6% of COVID-19 patients had AKI and the proportion of patients receiving CRRT was 1.45%, while the proportion of patients receiving CRRT in ICU was as high as 5.56% ^[12]. Cheng et al ^[14] reported 710 COVID-19 inpatients in a single-center, 44% of them had proteinuria and 26.9% had hematuria, while 14.1% had elevated SCr on admission, the incidence of AKI was 3.2%. AKI was considered as an independent risk factor for death.

3.3 Cytokine Storm Syndromes (CSS)

The manifestations are persistent fever, hepatosplenomegaly and lymphadenopathy, hemodynamic instability, shock, rash, DIC and multiple organ failure, and the condition often progresses rapidly.

3.4 Laboratory examination

In the early stage of onset, the total number of peripheral blood leukocytes is normal or reduced, the number of lymphocytes is reduced, some patients may have liver dysfunction, lactate dehydrogenase, creatase s and myoglobin are high; increased troponin was seen in some critical patients. C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were elevated and procalcitonin was normal in most patients. In severe cases, D-dimer increased and peripheral lymphocytes decreased progressively. <u>Severe and critical patients often have elevated inflammatory factors.</u>

Imaging examination showed multiple small patches and interstitial changes in the early stage, and then developed into multiple ground-glass opacities and infiltrates in both lungs, lung consolidation in severe cases, pleural effusion was rare. The main laboratory abnormalities of CSS were: increased CRP, methemoglobinemia, leukocytopenia, thrombocytopenia, hemophagocytosis in bone marrow, increased cytokines (IL-2, IL-6, IL-10, IL-17, GSCF, IP10, MCP-1, and TNF-α) in blood.

4. Diagnosis

The diagnosis of novel coronavirus infection is mainly based on clinical manifestations, epidemiological history and laboratory tests (including hemogram, chest CT and etiological analysis). The main diagnostic criteria are real-time fluorescent RT-PCR detection of novel coronavirus nucleic acid positive, or related virus gene sequencing shows high homology with known novel coronavirus ^[1]. However, the current detection method has a certain rate of false negative, which may be related to the low sensitivity of sampling and detection reagents, and more sensitive molecular detection technology still needs to be developed.

The diagnostic of COVID-19 with AKI is mainly referred to KDIGO criteria ^[5]. Based on the diagnosis of novel coronavirus infection, AKI was diagnosed and staged according to the level of serum creatinine and/or urine output, that is, the level of Scr increased or exceeded 26.5 μ mol/L within 48 hours. Scr increased more than 1.5 folds than baseline, confirmed or presumed to occur within 7 days; Urine volume < 0.5 ml/ (kg h) and lasting more than 6 hours (with one of the above conditions can diagnose AKI)^[26].

5. Treatment

The treatment of COVID-19 combined with AKI includes general treatment, antiviral therapy, renal and other supportive treatment.

5.1 General treatment

All COVID-19 patients should be isolated and treated in designated hospitals with good isolation and protection conditions, and <u>critically ill patients should be admitted to ICU as early as possible.</u>

General treatment mainly includes rest, symptomatic and nutritional support, maintaining the hemostasis and vital signs, timely laboratory monitoring, and oxygen inhalation when necessary. Fever is a common symptom in patients with COVID-19, when nonsteroidal anti-inflammatory drugs (NSAIDS) used as antipyretic therapy, the indications should be strictly controlled, the frequency and dosage of use should be reduced, more water should be drunk, and the effective circulation blood volume of patients should be observed to avoid further damage to renal function. Severe and critical cases should actively prevent and treat complications, maintain organ function and circulation support, prevent secondary infection, and give high-flow oxygen therapy, mechanical ventilation and lung re-expansion treatment when necessary. In patients with severe ARDS, extracorporeal membrane oxygenation (ECMO) should be considered as early as possible.

In addition, to stabilize the patient's emotion, timely psychological assessment, psychological counseling to alleviate patient anxiety and to establish confidence to overcome the disease is necessary.

5.2 Antiviral treatment

At present, there is no effective antiviral drug for COVID-19. Potentially effective options include: α - interferon nebulization inhalation, Lopinavir/Ritonavir, the latter two drugs are human immunodeficiency virus-1 (HIV-1) protease inhibitors, and their therapeutic value in COVID-19 infection needs to be evaluated (ChiCTR 2000029308). Dose adjustment is not required for patients because of low renal clearance of Lopinavir and Ritonavir and renal insufficiency. Both drugs have strong protein binding capacity, so hemodialysis or peritoneal dialysis will not significantly affect

their clearance. Furthermore, as a novel nucleotide prodrug (GS-5734), Remdesivir can effectively inhibit the replication of coronavirus through nsp14-ExoN, and is effective in the treatment of MERS and SARS coronavirus infection ^[27], but its efficacy in COVID-19 patients is also being studied clinically (NCT04252664; NCT04257656). It is not recommended to use three or more antiviral drugs at the same time, and the use of related drugs should be stopped when intolerable side effects occur.

5.3 Blood purification therapy

It is very important to carry out blood purification and other renal replacement therapy in time for patients with severe coronavirus pneumonia complicated with AKI, SIRS, MODS, and CSS and so on. Blood purifications include plasma exchange, plasma adsorption, hemoadsorption/hemoperfusion, hemofiltration, especially continuous renal replacement therapy (CRRT). It has played an important role in the rescue and treatment of SARS, MERS and other sepsis in the past ^[28-29]. The study demonstrated that treatment with high-volume hemofiltration (HVHF) for sepsis for 6 hours resulted in a significant decrease in IL-6 levels (P=0.025). The improvement of the estimated score of systemic organ failure (SOFA score)^[30] indicated that CRRT may play a very important role in the rescue of patients with severe infection in COVID-19. Diagnosis and Treatment Scheme for Novel Coronavirus Pneumonia (Edition VI) by National Health Commission Suggested that, for the critically ill patients with high inflammatory reaction, plasma exchange, plasma adsorption, hemoadsorption/hemoperfusion, hemofiltration and other extracorporeal blood purification techniques can be considered when conditions permit ^[1]. We believe that SIRS, ARDS, CSS are associated with the release of a great number of cytokines, and the clinical processes are under critical conditions, which come be an important mechanism of disease progression. According to the principle of blood purification technology, early active start to remove cytokines with the use of plasma exchange, immunoadsorption or CRRT may be of great significance to rescue some severe patients, which is worth exploring in clinical practice.

5.4 Other therapies

Early use of convalescent plasma therapy in patients with SARS-CoV infection can reduce mortality ^[31]. However, the acquisition of convalescent plasma and the timing of collection are in the process of groping, if there is no high titer of neutralizing antibodies, it cannot ensure the efficacy ^[32]. Some of the patients with severe COVID-19 disease have achieved preliminary curative effect, but the relevant experience still needs to be further accumulated.

Chloroquine phosphate was mainly used for the treatment of malaria, connective tissue diseases and photosensitive diseases. Recently, it was found that chloroquine phosphate has some effect on NCP, but the exact mechanism is not clear.

Monoclonal antibodies have been validated in the treatment of MERS-CoV infections ^[33]. However, the monoclonal antibody against COVID-19 is still under development. As a monoclonal antibody to IL-6 receptor, Tocilizumab is undergoing pre-clinical trials (ChiCTR2000029765) and needs to be verified.

The current guidelines recommend the use of glucocorticoids for 3-5 days according to the degree of dyspnea and the progress of chest imaging, equivalent to the dose of methylprednisolone < 1-2 mg (kg d) ^[1]. Although corticosteroids have been shown to reduce mortality and length of hospital stay in SARS patients ^[34], glucocorticoid may inhibit virus clearance and prolong the duration of viremia ^[35]. There is a lack of strict designed trials in the literature to assess the exact efficacy of glucocorticoids in the treatment of NCP, so caution should be taken in clinical use.

6. Conclusion

COVID-19 is the third disease caused by coronavirus infection in this century, which has brought a major threat to public health security to human society. COVID-19 combined with AKI is a clinical problem that we need to pay active attention to, which not only increases the mortality of patients, but also may lead to further development of chronic kidney disease. For COVID-19 complicated with AKI, both the basic pathogenesis and clinical diagnosis and treatment research have just begun,

more unknown is needed to be actively explored, multi-disciplinary collaboration to tackle key problems are still undergoing.

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Published online February 6, 2020 https://doi.org/10.1016/S2213-2600(20)30060-6

International Experts Opinion

-- From Prof. Claudio Ronco & Prof. Jean-Louis Vincent

Coronavirus epidemic: preparing for extracorporeal organ support in intensive care

Zoonotic viral infections are more frequently crossing species to infect human populations. In 2003, the severe acute respiratory syndrome (SARS) virus was transmitted to humans from exotic animals in wet markets in China, and in 2015, the Middle East respiratory syndrome (MERS) virus was transmitted from camels in Saudi Arabia. In both cases, and with the 2019 coronavirus outbreak in China, the original host of the virus is likely to be bats.

The 2019 coronavirus (2019-nCoV) was identified as such with the use of electron microscope analysis, to determine its shape, and genomic sequencing. The virus causes an aspecific respiratory syndrome and a generalised inflammatory response in humans. Patient zero was likely to have been infected by 2019-nCoV at a seafood market in Wuhan (Hubei province, China)-WHO has provided the case definition. Although the information surrounding the current situation is changing on a daily basis, transparency and consistent data through official channels for the international scientific community is highly recommended. Experts provide their opinion based on experience and current information, but the basic reproduction number (R_0) —ie, the number of cases generated by one case—is presently unclear, and data about mortality are inconsistent. Both in Europe and the USA, close attention is being paid to the problem despite the apparent low risk of an immediate epidemic diffusion.

What has been confirmed is that some infected individuals have developed acute respiratory distress syndrome (ARDS), which requires mechanical ventilation and, in the most severe cases, extracorporeal membrane oxygenation (ECMO).

Transmission of 2019-nCoV is likely to occur through large droplets, which could provide an explanation for the initial infection at the wet fish market in Wuhan, although contact by aerosols cannot be excluded. In recent reports, the median time from onset of symptoms to first hospital admission was 7.0 days (minimum to maximum 4.0-8.0), to shortness of breath was 8.0 days (5.0-13.0), to ARDS was 9.0 days (8.0-14.0), to mechanical ventilation was 10.5 days (7.0-14.0), and to intensive care unit (ICU) admission was 10.5 days. Beyond the classic prevention measures, strict adherence to suggested precautions should also be followed to prevent transmission. Despite specific sanitary measures at airports and frontiers, we must be able to respond appropriately to the international public health emergency declared by WHO. From our past experience of treating viral infections in critically ill patients, we know the level of severity of illness in which might indicate, in the most severe forms, the need for venous-arterial ECMO support.

Extracorporeal CO₂ removal (ECCO2R) is a technique that can be performed in more ICUs due to the much lower level of complexity than is required for ECMO, but ECCO2R is not really helpful for severely hypoxaemic patients who actually need full ECMO treatment. Acute kidney injury in these patients is not common, but it might result from a systemic inflammatory syndrome involving combined myocardial and kidney function. In these cases, continuous renal replacement therapies by haemofiltration and haemodiafiltration can contribute to resolution of organ failure. Liver dysfunction can also rarely occur in patients with severe viral infection and it might require extracorporeal blood purification techniques to support the patient until hepatocyte recovery occurs. Finally, a sepsis-like syndrome might occur frequently due to the virus itself or to a superimposed bacterial infection and in this case, since pharmacological approaches have shown poor results, new extracorporeal organ support therapies including haemoadsorption and haemoperfusion, with

patients infected by coronavirus depends on the presence of comorbidities and immune status of the host. On the one hand, anergic patients are likely to develop a severe clinical response: on the other hand, an excessive immune response might also add to severity through a generalised inflammatory status. In both cases, immune dysregulation can lead to a progressive cascade of pathophysiological events leading to critical illness with multiple organ dysfunction.

Because it is not possible to anticipate the extent of the epidemic and the consequent number of patients who require intensive care management, intensive care clinicians must be prepared to provide specific organ support treatments and to consider that this type of treatment might be necessary for a large number of patients. Extracorporeal therapies can be helpful to support different organs, such as the lungs, heart, kidneys, and liver, through the application of specific devices. Venovenous ECMO is a complex and sophisticated support for treatment of the most severe forms of acute hypoxaemic respiratory failure; it is performed in specialised, experienced referral centres that are commonly organised into networks, serving large regions or whole countries. The number of critically ill individuals who are infected with 2019-nCoV and who will require ECMO is unknown. In some regions, more than in others, a shortness of ECMO devices could occur and might impose choices that come with important ethical questions. Without predefined criteria to guide the decision on who will get the treatment and in what order, this will lead unavoidably to a first-come-first-serve approach. Clinical presentation, comorbidities, age, number of days of mechanical ventilation before indication for ECMO, and risk for complications are all factors influencing a potentially favourable outcome. 2019-nCoV might also cause severe myocarditis resulting in acute heart failure,



new sorbent cartridges designed to remove cytokines and other circulating mediators, should be considered.

However the 2019-nCoV epidemic evolves, ICH personnel must be prepared and trained to apply early and optimal interventions. Extracorporeal organ support therapies might represent an important part of the response and clinicians and other health-care professionals need to be familiar with this sophisticated therapy. A call to action should be made to raise awareness of the different extracorporeal techniques, each with specific criteria and modalities of prescription, delivery, and monitoring.

We declare no competing interests

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uncet Respir Med 2020 Published Online February 6, 2020 https://doi.org/10.1016/ S2213-2600(20)30060-6 For more on 2019-nCoV global surveillance see https://

who.int/health-topics/ coronavirus For more on the first cases of

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HA330/HA380 for novel coronavirus

1. Principle of work

As we know, novel coronavirus infections can rapidly develop into respiratory distress syndrome, septic shock, metabolic acidosis, and coagulopathy. Cytokine storm plays an important role in the progression of disease.

The HA380/HA330 disposable hemoperfusion cartridges are specially developed for critically ill patients. The adsorbent inside the cartridges is neutral macro-porous adsorption resin. Due to its large amount of neutral porous structures and high specific surface area, it can adsorb excessive inflammatory factors and oxidative metabolites in the blood through different interaction forces, down-regulate the intensity of inflammatory response and restore the body's immunity, thereby controlling the disease progression and reducing important organ damage and its complications.



2. Operation mode

- 1) The "2-1-1" therapy is recommended for novel coronavirus infection, which is 2 times of treatment per 24 hours, followed by once each day for two days
- 2) Anticoagulant: Heparin or Citrate
- 3) Compatible with various blood purification device, such as CRRT or ECMO



DPMAS for novel coronavirus

1. Principle of work

Novel coronavirus infections can rapidly develop into respiratory distress syndrome, septic shock, metabolic acidosis, and coagulopathy. As Prof. Jean-Louis Vincent mentioned ^[1], liver dysfunction can also occur in patients with severe viral infection and it might require extracorporeal blood purification techniques to support the patient until hepatocyte recovery occurs.

Chinese academician Li Lanjuan, who is the leading expert in the field of infectious disease and artificial liver support system, proposed the "Four-Anti-Two-Balance" treatment principle, namely: antiviral therapy, anti-hypoxemia and multiple organ failure, anti-shock therapy, anti-infection therapy; Maintain water-electrolyte-acid-base balance and regulate human micro-ecological balance. If the bilirubin is significantly increased during the progress of the disease, the use of DPMAS artificial liver technology can be considered.

DPMAS (Double Plasma Molecular Adsorption System) is a blood purification system, combination of BS330 and HA330-II adsorption cartridge. BS330 cartridge specifically adsorbs bilirubin and bile acid, while HA330-II removes other middle molecular toxins induced by liver disorder, such as inflammatory mediators, ammonia, phenol, mercaptan, etc.



Anion-exchange Resin





Neutro-macroporous Resin

2. Three recommended guidelines for DPMAS

- 1) Guidelines for Non-biological Artificial Liver support system in treatment of liver failure, Edition :2016^[2]
- 2) Guideline for diagnosis and treatment of liver failure (2018), Edition: 2018^[3]
- 3) Guidelines for the Diagnosis and Treatment of Cirrhosis and Hepatic Encephalopathy, Edition: 2018^[4]

3. Operation mode

- 1) Treatment frequency: 2-5 times per week for the first two weeks, and 1-2 times per week for the next weeks.
- 2) Treatment mode: a) DPMAS; b) DPMAS+PE; c) DPMAS+CVVH; d) DPMAS+ECMO
- 3) Anticoagulant: Heparin, Low molecular weight heparin, or Citrate



DPMAS- Double Plasma Molecular Adsorption System

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Jafron is taking actions during SARS-CoV-2 Epidemic

At the critical moment of fighting against the novel coronavirus epidemic, as a leading national enterprise in the field of blood purification, Jafron takes the social responsibilities without hesitation, not only provides cash, medical device and consumables, commercial insurance for medical staff worth 2,500,000 USD for the epidemic areas, but also pays close attention to the epidemic situation by providing help to doctors and patients in time, and working side by side with hundreds and thousands of compatriots on the way to fight the epidemic.

Experts Team and Supplies at Wuhan

Jafron Adsorption Therapy on Patients with Cytokine Storm