

## Review (Narrative)

# COVID-19

## Facts and Recommendations from A to Z

BASE Medicine Task Force

### SUMMARY

Since the first case of COVID-19 was reported in the late 2019, the virus has been filling almost every corner of the earth. The world suddenly woke up in a hurry, and began to surround and control SARS-CoV-2 on a large scale. Since then, the world has entered a state of lockdown. This task force reviewed from every aspect involved in the occurrence, development and treatment of COVID-19. Although no effective treatments exist and many areas require further study at length regarding the virus and the diseases caused by it, all the medical care implemented currently reflects the compassionate control of the disease. Whether it is the development of effective drugs or vaccines, the occurrence of COVID-19 pandemic sounded the alarm for humans. It is time to seriously think about the disease prevention system we have built so far and the next catastrophic epidemic that may come in the near future. While the virus is rapidly mutating, whether the development of medical science is catching up fast enough and finding effective countermeasures is a question worthy of serious consideration. ■

### KEYWORDS

SARS-CoV-2; COVID-19; Human catastrophe; Medical system; Future

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## OUTLINE

- Introduction
- Origin of SARS-CoV-2
- Structure of SARS-CoV-2
- Epidemiology of COVID-19
- Clinical Manifestations of COVID-19
- Diagnosis of COVID-19
- Virus Detection of SARS-CoV-2
  - Nucleic Acid Specimen Collection
  - Nucleic Acid Test Procedures
  - Serum Virus Antibody Detection
  - Virus Isolation and Culture
- Cytokine Storm of COVID-19
- Imaging Study of COVID-19
- Bronchoscopy in COVID-19
- Classification of COVID-19
- Treatment of COVID-19
  - General Management
  - Anti-viral Therapeutics
    - Lopinavir-Ritonavir (Kaletra®)
    - Arbidol
    - Chloroquine or Hydroxychloroquine
    - Favipiravir (Avigan®)
    - Remdesivir
    - Darunavir/Cobicistat (Prezcobix; Rezolsta)
    - Interferon
  - Anti-Shock Therapies of COVID-19
    - Indications for Corticosteroids Use
    - Application of Corticosteroids
    - Special Consideration during Corticosteroids Treatment
  - Oxygen Therapy for COVID-19
    - Oxygen Therapy
    - Mechanical Ventilation
    - Prone Position Ventilation
  - Extracorporeal Membrane Oxygenation Support
    - Timing of ECMO
    - Methods of Catheterization
    - Mode Selection
    - Flux Set-value and Target Oxygen Supply
    - Ventilation Setting
    - Anti-Coagulation and Bleeding Prevention
  - Antioxidant Treatment for COVID-19
    - Vitamin C
    - Vitamin E
    - Glutathione
    - N-acetyl-L-cysteine (NAC)
    - Melatonin
  - Traditional Chinese Medicine for COVID-19
    - Single Herbs
    - Chinese Patent Formulas
    - Chinese Herbal Compounds
  - Vaccine for COVID-19
  - Fluid Management
  - Food Therapy for COVID-19
- Discharge Criteria of COVID-19
- Perspectives
- References

## INTRODUCTION

SINCE the outbreak of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in Wuhan, Hubei Province of China (1), the pneumonia caused by the virus was designated as COVID-19 by the World Health Organization (2). With the rapid spreading of the virus, the COVID-19 confirmed cases have been overwhelmingly reach each corner of the world and reach 1,282,931 until April 7, 2020 (3). The global lockdown by the virus has been causing the world deep into a worrisome situation. All the people are asking the same questions as: Where did the virus come from? How can we prevent or control it? Do we have effective therapeutics to COVID-19? Will the virus disappear or stay with our human being all the time to come? Can we make efficient vaccine to conquer it? etc.

With evidence emerging quickly, this Task Force will review and update the recognition of the virus and COVID-19, and give recommendations for medical care and individual prevention and control.

## ORIGIN OF SARS-COV-2

Since the first report of the infectious disease, the origin of the virus has been becoming an attractive topic. Initially, it was considered as an animal-derived virus, especially bats and pangolins are the intermediate hosts (4). But cumulating evidence did not prove this link because the viruses from both types of animals did not show a big identity with less than 85% (5).

However, a natural evolution is regarded as the most likely possibility of the virus origin. Through analyzing the genomic sequence of SARS-CoV-2 and potentially related viruses, no solid evidence supports the declaration of the virus's origin as an engineered one for any reasons (6). Given the big disease spectrum caused by the Coronaviruses such as 2003 Severe Acute Respiratory Syndrome (SARS) in China and 2012 Middle East Respiratory Syndrome (MERS) in Saudi Arabia, this time, SARS-CoV-2 emerged as a new one causing serious illness with different severity (7). So far, two features of the virus suggest that it came from a natural selection, but not genetic engineering.

First, the receptor binding domain (RBD) of the virus spike glycoprotein has evolved to bind to a molecule called angiotensin-converting enzyme 2 (ACE<sub>2</sub>) that is

located on the human cell membranes with regulating function of blood pressure (8). This RBD mutation is exactly an indicator for the natural evolution. Second, generally, the engineered pathologic virus would have an identical backbone with the mother virus. Nevertheless, SARS-CoV-2 has a totally different backbone from those of already known coronaviruses such as SARS-CoV, MERS-CoV, and viruses found in bats and pangolins (9). Although the viral originality was concluded as a result of natural selection, how human being was infected becomes the key question.

As SARS-CoV and MERS-CoV had their intermediate hosts as civets and camels, respectively, no documented cases exist to indicate a bat-human transmission. However, theoretically, SARS-CoV-2 would have evolved in two parts to realize its animal-human and human-human transmission ability: the RBD portion of spike protein and cleavage site to open the virus up. In another situation, the virus evolved directly within human host to be pathogenic after getting into human body. No matter the RBD or cleavage site, SARS-CoV-2 might quickly get evolved to be a virulent one in human cells and then kicked off the current pandemic (10). For these two possibilities, the first one is much more dangerous than the second one because if the virus entered human host with its current pathogenic property from an intermediate animal host, it still would be possible for a future outbreak; but if the virus first got into humans without pathogenic ability, so the chance of a future outbreak is lower because the circulating viruses are non-illness-causing strain.

## STRUCTURE OF SARS-COV-2

In general, coronaviruses are a large family of viruses. Because this type of virus shapes spherically with protrusions like a spiky crown, so they are collectively named as coronaviruses. The diameter of coronaviruses are ranging from 75 to 160 nm, and the virus genome is a continuous linear single-stranded RNA ((ss)-RNA). The coronavirus genome can encode spike glycoprotein (S), envelope protein (E), membrane protein (M), and nucleoprotein (N protein) (11).

SARS-CoV-2 belongs to the beta genera of the Coronaviridae family. It has ~70% sequence identity with SARS-CoV and ~40% sequence identity with MERS CoV (12). Among the encoded viral proteins, S protein is the most pivotal surface membrane protein of

coronavirus. Given the binding of S proteins to cellular membrane receptors is the first step for the virus' vigilance, so S protein has been becoming the target for most studies to find corresponding therapeutic drugs and neutralizing vaccines. Primarily, S protein has two tasks that assist host infection: (i) aid in the attachment between the virus and host cell surface receptor ACE<sub>2</sub>, and (ii) facilitate virus enter into the host cell through helping the fusion process of the viral and host cell membranes (13). S protein structure is being extensively studies and different models were used to predict its crystal structure (14) (Table 1).

The N protein, as a structural protein, binds to the RNA genome so as to create capsid that encloses the nucleic acid. Furthermore, N protein also plays an essential role in: (i) viral assembly by interacting with the viral membrane protein; (ii) RNA synthesis and folding; (iii) virus budding, and (iv) host cell cycle and translation (15). Beside these two structural proteins, SARS-CoV-2 also encodes several non-structural proteins as showed in Table 2.

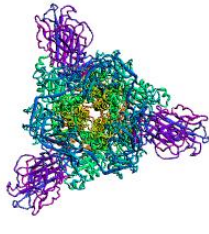
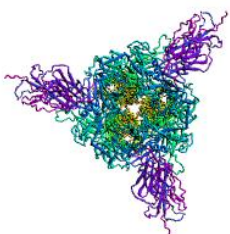
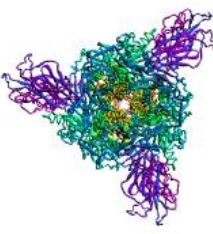
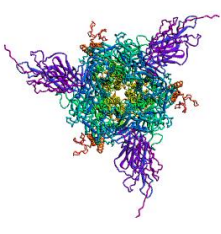
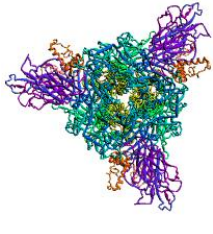
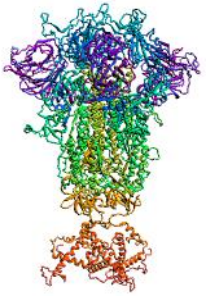
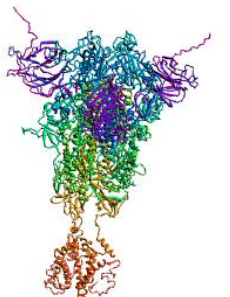
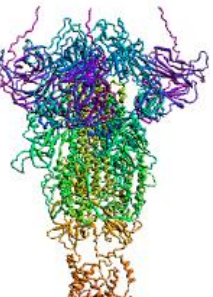
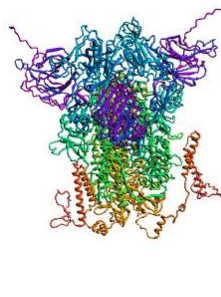
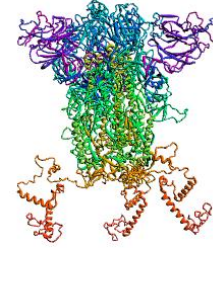
## EPIDEMIOLOGY OF COVID-19

The underlying cause of COVID-19 is the pathogenic coronavirus designated as SARS-CoV-2. Patients with symptoms after the infection are the major source of transmission. However, asymptomatic patients are also contagious and more dangerous than the symptom-positive patients in spreading the virus (16) because you don't know the person next to you is a virus carrier.

Transmission of SARS-CoV-2 is majorly via respiratory droplets and close contact. There is the possibility of aerosol transmission in a relatively closed environment for a long-time exposure to high concentrations of virus (17). As the virus was isolated in feces and urine, so special attention need to be paid to feces- or urine-contaminated items that may result in feces-oral transmission (18).

The susceptible people for SARS-CoV-2 include all aged population. However, the COVID-19 morbidity does some age-related difference. Although the youngest confirmed case was an infant and who died in Illinois (19), the virus looks like have a preference to senior population due to several reasons: (i) older populations generally have more underlying health conditions like diabetes, heart disease, and other chronic illnesses; (ii) with aging, the immune system gradually loses its resili-

Table 1. S protein Crystal Structures in Different Models.

	Model 1	Model 2	Model 3	Model 4	Model 5
Top View					
Side View					

Note: Modified from Reference #14.

ency that makes the elderly more susceptible to infection; (iii) aged people may be more likely undergoing ACE<sub>2</sub> inhibitor treatment for cardiovascular issues, which causes upregulation of SCE<sub>2</sub> expression in tissue (20) although population-based study did not show age-related difference of ACE<sub>2</sub> expression (21) and animal study showed that younger adults had much higher ACE<sub>2</sub> levels than the elderly comparisons (22).

Even though the first case of COVID-19 was appeared in Wuhan of China, it does not mean the virus has a racial preference (23). As COVID-19 was defined as a pandemic by the WHO, it almost reaches every corner of the world (3). Until April 3, 2020, a total of 206 countries, areas or territories have reported COVID-19 cases (3).

There is not huge difference of the COVID-19 morbidity between males and females. The WHO found that men make up a 51% of the confirmed cases over the 49% of female patients (24). But an early study from China showed a little bit greater difference, of which 58% were males with 42% were females (25).

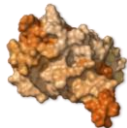
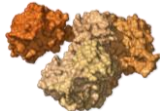
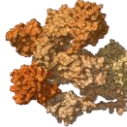
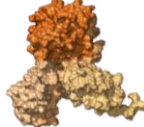
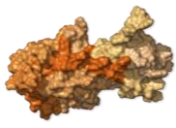
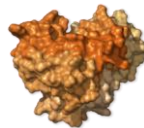
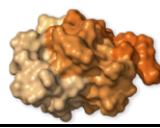
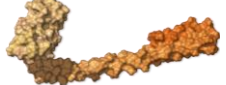
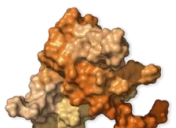
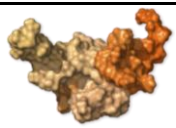
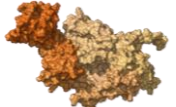
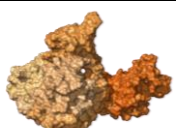
Regarding the mortality of COVID-19, different data were reported by various countries (3). The death

rate ranges from 0.1% to 12% in different countries and areas, and the overall death from the WHO data was approximately 5.67% on April 7, 2020 without considering the age, gender, and pre-existing conditions (3), but this figure is changing on a daily basis. Of course, many factors would influence this figure, such as (i) the ratio of aged patients; (ii) medical conditions especially intensive care settings where the patients enrolled in; (iii) basic conditions of the reported patients like nutrient status, smoking, and underlying medical diseases etc; and (iv) political consideration for special concerns. The estimated mortality of COVID-19 is shown in **Table 3**, in which we show the age-, gender-, and pre-existing condition-based mortalities.

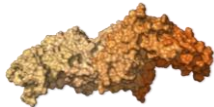
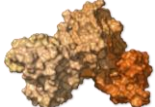
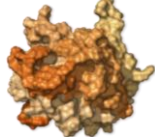
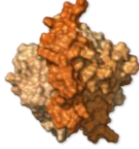


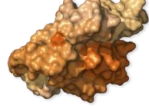
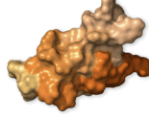
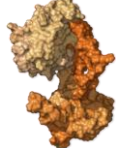


### CLINICAL MANIFESTATIONS OF COVID-19

Mostly, the incubation period for COVID-19 varies from 1 to 14 days, on an average, the time duration before the symptomatic manifestation is 3-7 days (26). For the clinical manifestations of COVID-19 in adults, fever, fatigue, and dry cough are three major ones that presented in most diagnosed cases, but it does not mean

**Table 2. SARS-CoV-2 Proteins and Potential Functions.**

Protein	Structure	Function
NSP1		Slow down the infected cell's production of its own proteins that could stop the virus.
NSP2		Not sure. May help move endosomes around the cell.
NSP3		<ol style="list-style-type: none"> <li>1. Cut and loose other viral proteins to help them do their own tasks.</li> <li>2. Remove tag proteins that help for destruction as an antiviral mechanism.</li> </ol>
NSP4		Help to build fluid-filled bubbles within infected cells.
NSP5		Cut and free other NSPs to carry out their own tasks.
NSP6		Work with NSP3 and NSP4 to make viral bubbles.
NSP7		Help NSP12 make new copies of the RNA genome.
NSP8		
NSP9		Infiltrate tiny channels in the infected host cell nucleus to hold host genome.
NSP10		Work with NSP16 to camouflage the virus's genes to avoid being attacked by human antiviral proteins.
NSP11	N/A	Not sure.
NSP12		Assemble genetic letters into new virus genomes. May be therapeutic target of Remdesivir.
NSP13		Unwind the intricate viral RNA twists and turns to help other proteins read its sequence and make new copies.



NSP14		Help correct wrong readings of the sequence by cutting them outs.
NSP15		Chop up leftover virus RNA to hide from the antiviral defense.
NSP16		Works with NSP10 to help hide viral genes from proteins that chop up viral RNA.
ORF3a		<ol style="list-style-type: none"> <li>1. Poke a hole in the infected host cell membrane to make it easier for new viruses to escape.</li> <li>2. Trigger inflammatory responses.</li> </ol>
ORF6		Block immuno-signaling pathways and virus-fighting proteins in the infected host cell.
ORF7a		<ol style="list-style-type: none"> <li>1. Cuts down tetherin supply to let more of the viruses to escape.</li> <li>2. Trigger infected cells to commit suicide that causes lung damage.</li> </ol>
ORF8		Not sure.
ORF10		Not sure.
S	See Table 1.	See in the text.
N		See in the text.
E		<ol style="list-style-type: none"> <li>1. Form the oily bubble of the virus</li> <li>2. Latch onto proteins to help turn host genes on and off</li> </ol>
M		Form part of the outer coat of the virus.

Note: Modified from Corum J, Zimmer C. Bad News Wrapped in Protein: Inside the Coronavirus Genome. April 3, 2020. Available at: <https://www.nytimes.com/interactive/2020/04/03/science/coronavirus-genome-bad-news-wrapped-in-protein.html>. Last accessed: April 3, 2020.

**Table 3. Mortality of COVID-19.**

	Mortality in Confirmed Cases	Mortality in All Cases
<b>Gender</b>		
Male	4.7%	2.8%
Female	2.8%	1.7%
<b>Age</b>		
> 80 yr	21.9%	14.8%
70-79 yr		8.0%
60-69 yr		3.6%
50-59 yr		1.3%
40-49 yr		0.4%
30-39 yr		0.2%
20-29 yr		0.2%
10-19 yr		0.2%
0-9 yr		0.1%
<b>Pre-Existing Condition</b>		
Cardiovascular Disease	13.2%	10.5%
Diabetes	9.2%	7.3%
Chronic Respiratory Disease	8.0%	6.3%
Hypertension	8.4%	6.0%
Cancer	7.6%	5.6%
No Pre-Existing Conditions		0.9%
*Mortality = (# of deaths / # of cases) = probability of dying if infected by the virus (%). The percentages do not have to add up to 100%, as they do not represent share of deaths by age, sex, and pre-existing condition.		

they all manifest simultaneously in one patient (27). In addition, runny nose, nasal congestion, sore throat, shortness of breath (SOB), myalgia and diarrhea are reported in some cases (27). For severe cases, dyspnea and/or hypoxemia may happen, and then metabolic acidosis, acute respiratory distress syndrome (ARDS), septic shock, coagulopathy, and multiple organ failure will ensue (28). For the severe or critically ill patients, fever may not be noticed.

For neonatal and children, COVID-19 may only show mild and atypical symptoms, such as gastrointestinal symptoms like vomiting and diarrhea, or low energy and SOB (29). For pregnant women, the clinical course is similar to that of patients with the same age (30).

In general, when you are in an emergency condition because of COVID-19, some warning signs should be the alerts for seeking medical attention immediately. The emergency warning signs include but not limited to: (i) trouble breathing; (ii) persistent pain or pressure in the chest; (iii) new confusion or inability to arouse;

or/and (iv) bluish lips or face. If you have one or more of these signs, you need to consult your medical provider or visit the emergency room (31).

## DIAGNOSIS OF COVID-19

For a confirmed COVID-2019 case, following diagnostic criteria must be met: (i) epidemiological history including cluster transmission; (ii) clinical manifestations (see above); (iii) lung CT imaging, and (iv) positive results of SARS-CoV-2 nucleic acid detection and/or serum-specific antibodies (32).

For COVID-19, as for all the other infectious diseases, early diagnosis, treatment and isolation are of great importance to have better outcomes. To confirmed cases, dynamic monitoring of lung CT imaging, oxygenation index and plasma cytokine levels are three essential steps to help determine whether the patient would develop into severe and critically ill condition (32).

Currently, a positive result of the nucleic acid of SARS-CoV-2 is still the gold standard for COVID-19 diagnosis, whereas the characteristic signs in CT imaging for those suspected cases can be treated as confirmed cases even if the nucleic acid test is negative because of the possibility of false negative in nucleic acid detection. So, isolation and continuous tests of multiple specimens should be carried out in such cases (33).

COVID-19 needs to be differentiated from upper respiratory tract infections (URI) caused by other viruses such as influenza virus, adenovirus, and respiratory syncytial virus. Generally, methods such as rapid antigen detection and multiplex PCR nucleic acid detection can be adopted for excluding common respiratory pathogens.

## VIRUS DETECTION OF SARS-COV-2

### Nucleic Acid Specimen Collection

The specimen quality is critical for improving the positive detection of viral nucleic acid test (NAT). The types of specimen for SARS-CoV-2 include: (i) upper airway samples such as pharyngeal swabs, nasal swabs, and nasopharyngeal secretions; (ii) lower airway samples like sputum, airway secretions, and bronchoalveolar lavage fluid; (iii) blood; (iv) feces; (v) urine; and (vi) conjunctival secretions.

SARS-CoV-2 preferentially proliferates in type II alveolar cells and the viral shedding peaks at the 3rd to 5th day after the onset of disease (34). Therefore, repeated sample collections and tests on the subsequent days are necessary if the NAT is negative at the beginning. In comparison, lower respiratory tract samples have a high positive rate of NATs and are preferred specimens.

### Nucleic Acid Test Procedures

NAT is the preferred means for diagnosing COVID-19. Generally, the testing procedures are follows with a little bit difference in different detection kits: (i) pre-process specimens, and lyse the virus to extract nucleic acids; (ii) amplify the three specific genes of SARS-CoV-2, i.e. ORF1a/b, N, and E genes using real-time quantitative PCR; (iii) detect the amplified genes based on fluorescence intensity. Criteria of positive NAT are: positive ORF1a/b gene, and/or positive N gene/E genes (35).

The dual or triple detection of nucleic acids from multiple types of specimens can substantially improve the diagnostic sensitivity. In patients with NAT positive respiratory tract, ~30%-40% of them have NAT positive blood and ~50%-60% of NAT positive feces. However, the NAT positive urine is quite low (36). Therefore, it is helpful for improving the diagnostic accuracy, monitoring treatment efficacy, and providing reference for post-discharge isolation when the combined NATs were used.

### Serum Virus Antibody Detection

As an invader, SARS-CoV-2 infection will evoke host immune system to produce antibodies, so serum antibody detection plays an essential role in diagnosing COVID-19. However, this method will delay the diagnosis to some contents because the production of special antibodies needs time. Of course, this method may be inversely used at least in part as an indicator of the emergence of individual immunity to the virus even it is still under research and discussion because we do not know how long this immunity will last. In general, the detection means for serum antibodies includes: enzyme-linked immunosorbent assay (ELISA), colloidal gold-based immunochromatography assay (GICA), and chemiluminescence immunoassay (CLIA), etc. Positive serum-specific IgM or specific IgG antibody titer in the recovery phase is  $\geq 4$  times higher than that in the acute phase. During the follow-up monitoring, IgM is detectable 10 days and IgG is detectable 12 days after the onset of the symptoms (37). With the increase of serum antibody levels, the viral load gradually decreases (38). On April 2, 2020, FDA approved the 1st SARS-CoV-2 antibody test kit (39), this will help to confirm the infectious status of the suspected cases.

### Virus Isolation and Culture

If a laboratory wants to isolate and culture the SARS-CoV-2, they need to be qualified with requirements of Biosafety Level 3 (BSL-3). The procedure is briefly described below: (i) obtain fresh specimens (sputum, feces, etc.); (ii) inoculate on Vero-E6 cells; (iii) measure the cytopathic effect (CPE) after 96 hours; (iv) detect viral nucleic acid in the culture medium as an indicator of successful culture; (v) measure virus titer by diluting the virus stock concentration with a factor of 10 in series, and then the median tissue culture infectious dose



(TCID<sub>50</sub>) is determined by the micro-cytopathic method; (vi) otherwise, viral viability is determined by plaque forming unit (PFU) (40).

## CYTOKINE STORM OF COVID-19

Cytokine storm depicts a vivid image in which an immune system over-reactivated and an inflammatory response flared out of control (41). According to the diagnosis criteria of cytokine storm syndrome (CSS), COVID-19 patients with severe conditions show up CSS based on the reports available: (i) fever and confusion; (ii) laboratory results such as elevated C-reactive protein (CRP), hyperferritinemia, hypofibrinogenemia, lymphopenia, prolonged prothrombin time, and elevated lactate dehydrogenase, interleukin (IL) 6, and soluble CD25; (iii) anemia; (iv) thrombocytopenia and neutropenia (42-46).

In confirmed COVID-19 cases, detecting the levels of C-reactive protein, procalcitonin, ferritin, D-dimer, lymphocytes, IL-1 $\beta$ , IL-4, IL-6, IL-10, TNF- $\alpha$ , INF- $\gamma$ , etc, can help evaluate clinical progress, alert clinical severity and tendency, and provide reference for potential therapeutic strategies. Both significantly elevated D-dimer and low total number of lymphocytes at the beginning of the infection are indicators for poor prognosis. The levels of IL-6 and IL-10 in severe patients are increased substantially suggesting that monitoring their levels is of help to evaluate the progression and prognosis (47). Elevated troponin is seen in some critically ill patients while most patients have elevated CRP and erythrocyte sedimentation rate and normal procalcitonin.

These overproduced inflammatory factors in COVID-19 patients indicate a state of host super reaction to the virus, and suggest that immunosuppression may take a part in improving the mortality. Therefore, corresponding therapeutic options such as steroids, intravenous immunoglobulin, and selective cytokine blockade like anakinra or tocilizumab and Janus kinase (JAK) inhibition (48).

## IMAGING STUDY OF COVID-19

Chest X-ray and high-resolution CT are two imaging modalities for COVID-19. They possess great value in the diagnosis, monitoring of therapeutic efficacy, and the discharge assessment. CT scanning for baseline evaluation is usually performed on the day of admission, and

can be re-performed 2 to 3 days after admission if an ideal therapy was not achieved, but it can be reviewed 5-7 days post admission if symptoms are stable or improved after treatment. Portable chest X-rays are valuable for critically ill immobile patients, and it is recommended to do on daily basis for critically ill patients.

On CT imaging, COVID-19 lungs at the early stage oftentimes presents with multifocal patchy shadows or ground glass opacities that are generally located in the periphery, subpleural area, and both lower lobes. The long axis of the lesion is mostly parallel to the pleura. Interlobular septal and intralobular interstitial thickening showing as subpleural reticulation is observed in some ground glass opacities. Some cases show solitary, local nodular/ patchy lesion distributed in agreement with bronchus with peripheral ground glass opacities. With the progression of the infection, the density of the lesions enlarges and increases compared with the baseline images, and consolidated lesions show air bronchogram sign generally after 7-10 days. Critical cases can present further expanded consolidation, with the whole lungs showing as “white lungs” both CT and plain X-ray (49-51).

As the condition gradually relieves, the ground glass opacities may be completely absorbed, but some consolidation lesions will leave fibrotic stripes or subpleural reticulation. In patients with multiple lobular involvements, especially those with expanded lesions need to be watched carefully for disease exacerbation. Those with typical CT imaging should be isolated and undergo continuous NATs if the early NAT was negative.

COVID-19 lungs show special signs on CT imaging and the progression of the disease is strongly associated with the development of the pulmonary manifestations. In **Table 4**, we summarize the typical presentations of CT signs and characteristics (52).

## BRONCHOSCOPY IN COVID-19

In mechanically ventilated COVID-19 patients, flexible bronchoscopy is a versatile, easy to use, and well tolerated method to be performed for (53):

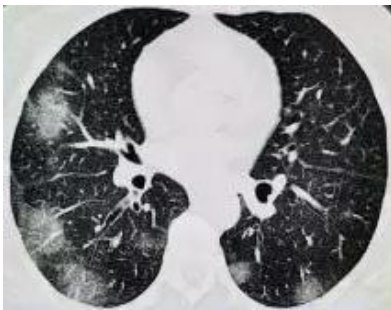
- (i) Collecting respiratory specimens from the lower respiratory tract, i.e. sputum, endotracheal aspirate, and bronchoalveolar lavage for SARS-CoV-2;
- (ii) Localizing the site of bleeding, cessation of hemop-

Table 4. CT Signs and Characteristics of COVID-19.

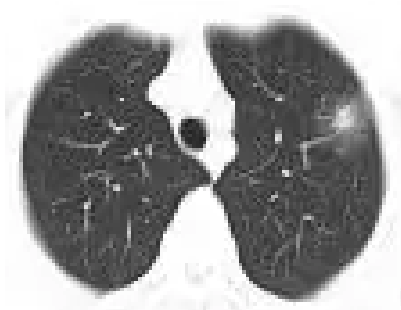
Characteristic	
Distribution	Subpleura, Subsegment, Segment, Lobar, Multi-Lobar, Inter-Lobar, Bilateral
Development	The lesion develops from the lung parenchyma in the lower periphery to the lung interstitium in the center, and the virus directly reaches the alveoli and lung lobules and completely occupies them indicating that it is extremely contagious and sinister.
Shape	Triangular, Spherical, Trapezoidal, Rectangular, Fan-Shaped, Ring-Shaped Distribution, Ground-Glass Opacity, Grid-Like, Strip-Shaped, and Vascular Bundle.
Stage	Early: Prickly Pear Sign, Hale Nodule Sign Middle: Grey Snow Sign, Gypsum Sign Late: Bat Wing Sign

Special Sign

Rosa Roxburghii Sign



Hale Nodule Sign



Grey Snow Sign



Gypsum Sign



Bat Wing Sign



White Lung Sign



Bronchus & Vascular Bundle Sign



- tysis, sputum or blood clots removal;
- (iii) Injecting cold saline, epinephrine, vasopressin, or fibrin as well as laser treatment locally;
  - (iv) Assisting the establishment of artificial airways by guiding tracheal intubation or percutaneous tracheotomy;
  - (v) Administering medicines such as  $\alpha$ -interferon and N-acetylcysteine.

Through bronchoscopy, we can view the extensive bronchial mucosal hyperemia, swelling, mucus-like secretions in the lumen and jelly-like sputum blocking the airway in critically ill COVID-19 patients (**Table 5**).

## CLASSIFICATION OF COVID-19

The classification of COVID-19 majorly depends on the severity, and correspondingly divided into four types as showed in **Table 6**.

## Treatment of COVID-19

So far, no effective therapeutic methods are available clinically to COVID-19. All listed therapeutic strategies and maneuvers only can be used with cautiousness at this stage because no solid clinical evidence exists to support their viability and reliability. All our listed therapeutic methods are only based on sporadic cases with successful therapies. No matter whatever treatment will be used, the eventual outcome of the individual patient will strongly depend on patient's personal immune status and potential response to the virus. We do not recommend, but suggest that healthcare professionals consider these potentially useful therapeutic strategies if conditions permit and are feasible.

## General Management

For suspected and mild confirmed cases, isolation in designated areas is required. Close observation is extremely important. Basically, thermometer, finger oximeter, and oxygen compressor should be available in the isolation environment to guarantee continuous measuring of temperature, pulse oxygen saturation, providing O<sub>2</sub> once in need.

## Anti-viral Therapeutics

For moderate to critically ill patients, anti-viral therapies can be administered as early as possible even no strong evidence exists.

### *Lopinavir-Ritonavir (Kaletra®)*

Controversial results exist regarding lopinavir-ritonavir (400 mg and 100 mg, respectively) in treating severe COVID-19 patients (54-56). However, this combined medication can be given to patients as a basic regimen. It can be applied twice a day for 14 days. Even we do not know whether it has an optimal dosage for COVID-19, it is completely acceptable for a trial with higher doses.

### *Arbidol*

The therapeutic efficacy of single use of arbidol, one of Russia's most popular OTC flu medicines, for COVID-19 has not been thoroughly studied. There were case reports on its combined use with lopinavir-ritonavir and some traditional Chinese medicine in COVID-19 patients, and showed favorable results (57, 58). Therefore, arbidol 200 mg can be applied twice day for 14 days.

### *Chloroquine or Hydroxychloroquine*


Chloroquine phosphate can be used on adults between 18-65 years old based on the weight: (i) if wt  $\geq$  50 kg, 500 mg bid for less than 7 days; (ii) weight < 50 kg, 500 mg bid for first two days, and then 500 mg once daily for following five days (53). Given the severe side effects of chloroquine (59), we strongly suggest that it can be given carefully with weighing its benefits over the risks.

Hydroxychloroquine sulfate was observed and found that hydroxychloroquine 200 mg three times a day produced an effective therapeutic role in the viral load reduction/disappearance in COVID-19 patients with an enforced effect by azithromycin (500 mg on day 1 followed by 250 mg per day for 4 days) (60). So we suggest that hydroxychloroquine plus azithromycin can be an alternative to chloroquine.

### *Favipiravir (Avigan®)*

Favipiravir, marketed as an anti-influenza drug by Fujifilm, have shown "obvious efficacy" against COVID-19.

Table 5. Bronchoscopic Views of COVID-19.

Bronchial mucosa swelling and congestion	Large amount of mucus secretions in the lumen
	

A clinical trial presented on medRxiv showed that favipiravir 1,600 mg twice a day followed with 600 mg twice a day for 7-10 days displayed superior to arbidol in COVID-19 treatment (61). Although these results need to be evaluated further, we can try to give favipiravir if it is clinically available.

Remdesivir

Remdesivir, developed by Gilead Sciences Inc., is a broad-spectrum antiviral medicine that inhibits viral replication via terminating RNA transcription prematurely. Cumulating evidence showed that remdesivir is the most promising medication for COVID-19 (62-64), and it is considered as a therapeutic option by CDC (65). The suggested doses of remdesivir for COVID-19 are 200 mg on day 1, and then 100 mg once daily for 4 to 9 days.

Darunavir/Cobicistat (Prezcobix; Rezolsta)

Darunavir/cobicistat has some degree of antiviral activity in viral suppression test in vitro, based on the treatment experience of HIV/AIDS patients. For COVID-19 patients who are intolerant to lopinavir/ritonavir, darunavir/cobicistat (800 mg and 150 mg, respectively) once daily is an alternative option after the ethical review even no clinical evidence exists to support its use (66). Simultaneous use of three or more antiviral drugs is not recommended. We are waiting for the results of the clinical trial of darunavir/ cobicistat on COVID-19 (67).

Interferon

In a typical scenario, a virus-infected cell will release interferons that cause nearby cells to enhance their anti-viral activities. This becomes the basis for interferon use for COVID-19 treatment. However, we strongly suggest that the administration of interferon should be thoroughly assessed because it is a strong suppressor of the immune system. If it is considered necessary for interferon in COVID-19 patients, we recommend that it should be applied in negative-pressure wards due to the possibility of aerosol transmission.

Anti-Shock Therapies of COVID-19

SARS-CoV-2 infection associated death is not because of the virus itself, but the virus-related inflammation-associated complications such as ARDS, septic shock, and multiple organ failure. Considering of the cytokine storm happened during the progression of COVID-19, so appropriate and short-term use of corticosteroids can be considered to inhibit cytokine cascade for patients with severe COVID-19. However, a high dose of corticosteroids should be avoided due to potential severe adverse events and complications.

Indications for Corticosteroids Use

- (i) Severe and critically ill stage;
- (ii) Persistent high fever > 39°C;
- (iii) Patchy ground-glass or > 30% area of the lungs are involved on CT imaging;



- (iv) Rapid progression with > 50% area involved in chest CT images within 48 hours;
- (v) IL-6  $\geq$  5 ULN.

### **Application of Corticosteroids**

- (i) Initially, methylprednisolone 0.75-1.5 mg/kg i.v. once a day is recommended;
- (ii) Methylprednisolone 40 mg every 12 hours can be considered for patients with falling body temperature or for patients with significantly increased cytokines under routine doses of steroid;
- (iii) Methylprednisolone 40-80 mg every 12 hours can be considered for critical cases;
- (iv) Closely monitor body temperature, OI, blood routine, CRP, cytokines, biochemical profile and lung CT every 2 to 3 days during the treatment;
- (v) Methylprednisolone should be halved every 3-5 days if medical conditions are improved, the body temperature normalized, or involved lesions on CT are significantly absorbed;
- (vi) Oral methylprednisolone once a day is recommended when the i.v. dose is reduced to 20 mg per day. The time course of corticosteroids is not defined, and it should be used on an individual basis.

### **Special Consideration during Corticosteroids Treatment**

- (i) Screen TB by T-SPOT assay, HBV and HCV by antibody assay before corticosteroid therapy;
- (ii) Consider proton pump inhibitors (PPIs) to prevent complications;
- (iii) Monitor blood glucose and treat high blood glucose with insulin if needed;
- (iv) Correct low serum potassium;
- (v) Monitor liver function closely;
- (vi) Give sedative-hypnotics temporarily for sleep difficulty.

### **Oxygen Therapy for COVID-19**

Frequently, COVID-19 causes hypoxemia due to impaired respiratory functions. Therefore, O<sub>2</sub> supplementation is necessary to correct hypoxemia, and relieve secondary organ damage resulted from respiratory distress and hypoxemia (53).

### **Oxygen Therapy**

- (i) Continual oxygen saturation monitoring during oxygen therapy to make sure SpO<sub>2</sub> > 92%;
- (ii) Oxygen therapy should be delivered as soon as possible if PaO<sub>2</sub>/FiO<sub>2</sub> < 300 mmHg;
- (iii) High-flow nasal cannula (HFNC) oxygen therapy is recommended if COVID-19 patients had:
  - SpO<sub>2</sub> < 93%;
  - PaO<sub>2</sub>/FiO<sub>2</sub> < 300 mmHg;
  - Respiratory rate > 25 bpm at bed;
  - Remarkable progression on chest X-ray;
  - Wear a surgical mask during HFNC treatment;
  - The airflow of HFNC oxygen therapy should start at a low level and gradually increased up to 40-60 l/min when PaO<sub>2</sub>/FiO<sub>2</sub> is between 200-300 mmHg;
  - An initial flow of at least 60 l/min should be given immediately for patients with obvious respiratory distress.
- (iv) Tracheal intubation for patients is dependent on disease progression, systemic status and complication of patients for those with stable situation but with a low OI < 100 mmHg (53).
  - Tracheal intubation should be performed as early as possible for patients with an OI < 150 mmHg;
  - Worsening symptoms of respiratory distress;
  - Multiple organ dysfunction within 1-2 hours after high-flow (60 l/min) and high-concentration (> 60%) HFNC oxygen therapy.
- (v) Patients > 60 years with more complications or PaO<sub>2</sub>/FiO<sub>2</sub> < 200 mmHg should be treated in ICU.

### **Mechanical Ventilation**

- (i) Noninvasive Ventilation (NIV)

NIV is not recommended in COVID-19 patients who fail to HFNC treatment. It can worsen ARDS, and cause intolerance to aspiration and worsen lung injury.

- (ii) Invasive Mechanical Ventilation

It is extremely critical to balance the benefits of ventilation and the risk of mechanical ventilation-related lung injury (53).

- Tidal volume to 4-8 ml/kg;
- Platform pressure < 30 cmH<sub>2</sub>O;



- Driving pressure  $< 15$  cmH<sub>2</sub>O;
- Set PEEP according to the institutional ARDS's protocol;
- Ventilation frequency: 18-25 times per minute;
- Moderate hypercapnia is allowed;
- Administer sedation, analgesia, or muscle relaxant if the variables like tidal volume, platform pressure and driving pressure are too high.

### (iii) Weaning of Ventilation

Sedatives is reduced and discontinued before awakening when  $\text{PaO}_2/\text{FiO}_2 > 150$  mmHg. The patient should be extubated as earlier as possible if the condition is permitted. HFNC or NIV is used for sequential respiratory support after extubation.

## Prone Position Ventilation

With a rapid improvement of oxygenation and lung mechanics, most critically ill patients with COVID-19 respond well to prone ventilation. Prone ventilation is recommended as a routine strategy for patients with  $\text{PaO}_2/\text{FiO}_2 < 150$  mmHg or with obvious imaging manifestations without contraindications. Time course recommended for prone ventilation is more than 16 hours each time. The prone ventilation can be ceased once  $\text{PaO}_2/\text{FiO}_2 > 150$  mmHg for more than 4 hours in the supine position (53).

Prone ventilation while awake may be attempted for patients who have not been intubated or have no obvious respiratory distress but with impaired oxygenation or have consolidation in gravity-dependent lung zones on lung images. Procedures for at least 4 hours each time is recommended. Prone position can be considered several times per day depending on the effects and tolerance.

## Extracorporeal Membrane Oxygenation Support

SARS-CoV-2 is a highly contagious virus primarily targeting pulmonary alveoli that results in respiratory failure. Extracorporeal membrane oxygenation (ECMO) is an alternative means for COVID-19 patients. When doing this, following attentions need to be paid to (53):

### Timing of ECMO

- Salvage ECMO: salvage ECMO intervention needs to be considered with the onset of one of the following conditions:
  - $\text{PaO}_2/\text{FiO}_2 < 80$  mmHg, regardless of PEEP level;
  - $\text{Pplat} \leq 30$  mmHg,  $\text{PaCO}_2 > 55$  mmHg;
  - The onset of pneumothorax, air leakage  $> 1/3$  tidal volume, duration  $> 48$  hours;
  - Circulation deterioration, the dosage of norepinephrine  $> 1 \mu\text{g}/(\text{kg} \times \text{min})$ ;
  - Cardio-pulmonary resuscitation.
- Replacement ECMO: ECMO replacement needs to be considered with the onset of one of the following conditions:
  - Decreased lung compliance. After the pulmonary recruitment maneuver, the compliance of the respiratory system  $< 10$  ml/cmH<sub>2</sub>O;
  - Persistent exacerbation of pneumomediastinum or subcutaneous emphysema, and the parameters of mechanical ventilation support cannot be reduced within 48 hours;
  - $\text{PaO}_2/\text{FiO}_2 < 100$  mmHg, and it cannot be improved by routine methods in 72 hours.
- Early Awake ECMO: For early awake ECMO, all the following conditions must be met:
  - Patient must be in a clear state of consciousness and is fully compliant;
  - Patient is not complicated with neuromuscular diseases;
  - Pulmonary damage score Murry  $> 2.5$ ;
  - Few pulmonary secretions. The time interval between the two airway suction procedures  $> 4$  hours;
  - Stable hemodynamics without assistance of vasoactive agents.

## Methods of Catheterization

Because the ECMO supporting time for most COVID-19 patients will be  $> 7$  days, the Seldinger wire technique should be used under the guidance of ultrasound, which reduces the bleeding damages and infection risks brought about by intravascular catheterization by venous angiotomy.

Intravascular catheterization by venous angiotomy may be considered only for the patients with bad blood vessel conditions, or the patients whose catheterization

**Table 6. Classification of COVID-19.**

Classification	Criteria
Mild Case	The clinical symptoms are mild and no pneumonia manifestations in imaging study.
Moderate Case	Patients have fever and respiratory tract symptoms, etc. and pneumonia manifestations in imaging study.
Severe Case	Adults who meet any of the following criteria: <ul style="list-style-type: none"> <li>● Respiratory rate <math>\geq 30</math> bpm;</li> <li>● Oxygen saturation <math>\leq 93\%</math> at a rest state;</li> <li>● Arterial partial pressure of oxygen (<math>\text{PaO}_2</math>)/oxygen concentration (<math>\text{FiO}_2</math>) <math>\leq 300</math> mmHg;</li> <li>● Patients with <math>&gt; 50\%</math> lesions progression within 24-48 hours in lung imaging should be treated as severe cases.</li> </ul>
Critical Case	Meeting any of the following criteria: occurrence of respiratory failure requiring mechanical ventilation; presence of shock; other organ failure that requires monitoring and treatment in the ICU. Critical cases are further divided into early, middle and late stages according to the oxygenation index and compliance of respiratory system.
Early Stage	<ul style="list-style-type: none"> <li>● <math>100 \text{ mmHg} &lt; \text{OI} \leq 150 \text{ mmHg}</math>;</li> <li>● Compliance of respiratory system <math>\geq 30 \text{ ml/cmH}_2\text{O}</math>;</li> <li>● Without organ failure other than the lungs.</li> <li>● The patient has a great chance of recovery through active antiviral, anti-cytokine storm, and supportive treatment.</li> </ul>
Middle Stage	<ul style="list-style-type: none"> <li>● <math>60 \text{ mmHg} &lt; \text{OI} \leq 100 \text{ mmHg}</math>;</li> <li>● <math>30 \text{ ml/cmH}_2\text{O} &gt; \text{compliance of respiratory system} \geq 15 \text{ ml/cmH}_2\text{O}</math>;</li> <li>● May be complicated by other mild or moderate dysfunction of other organs.</li> </ul>
Late Stage	<ul style="list-style-type: none"> <li>● <math>\text{OI} \leq 60 \text{ mmHg}</math>;</li> <li>● Compliance of respiratory system <math>&lt; 15 \text{ ml/cmH}_2\text{O}</math>;</li> <li>● Diffuse consolidation of both lungs that requires the use of ECMO;</li> <li>● Or failure of other vital organs.</li> <li>● The mortality risk is significantly increased.</li> </ul>

Note: OI: oxygenation index;

cannot be identified and selected by ultrasound, or the patients whose Seldinger method failed.

port is still needed and the Awake ECMO should be avoided.

### Mode Selection

- (i) The first choice should be the V-V mode. The V-A mode cannot be the first option with the consideration of possible circulation problems;
- (ii) For the respiratory failure patients complicated with cardiac impairment,  $\text{PaO}_2/\text{FiO}_2 < 100 \text{ mmHg}$ , the V-A-V mode ought to be selected with the total flux  $> 6 \text{ l/min}$  and  $\text{V/A} = 0.5/0.5$  is maintained by current limiting;
- (iii) For patients without severe respiratory failure but complicated with serious cardiovascular outcomes leading to cardiogenic shock, the V-A assisted by ECMO mode ought to be selected. But IPPV sup-

### Flux Set-value and Target Oxygen Supply

- (i) The initial flux  $> 80\%$  cardiac output (CO) with a self-cycling ratio  $< 30\%$ ;
- (ii)  $\text{SpO}_2 > 90\%$  is to be maintained.  $\text{FiO}_2 < 0.5$  is supported by mechanical ventilation or the other oxygen therapy;
- (iii) To ensure the target flux, 22 Fr (24 Fr) vein access canula is the first choice for the patient with a body weight below 80 kg.

### Ventilation Setting

- (i) The initial air flow is set to be Flow: sweep gas = 1:1. The basic target is to maintain  $\text{PaCO}_2 < 45 \text{ mmHg}$ .

For the patients complicated with COPD,  $\text{PaCO}_2 < 80\%$  basal level;

- (ii) The patient's spontaneous respiratory strength and respiratory rate (RR) should be maintained, with  $10 < \text{RR} < 20$  and without chief complaint of breathing difficulty from the patient;
- (iii) The sweep gas setup of the V-A mode needs to ensure the 7.35-7.45 pH value of the bloodstream out of the oxygenator membrane.

### **Anti-Coagulation and Bleeding Prevention**

- (i) For the patients without active bleeding, without visceral bleeding, and with platelet count  $> 50 \times 10^9/\text{L}$ , the recommended initial heparin dosage is 50 U/kg;
- (ii) For the patients complicated with bleeding or with platelet count  $< 50 \times 10^9/\text{L}$ , the recommended initial heparin dosage is 25 U/kg;
- (iii) Maintain the activated partial thromboplastin time (aPPT) at 40-60 seconds. The trend of D-dimer change should be considered at the same time.

### **Antioxidant Treatment for COVID-19**

Free radicals refer to any molecules capable of independent existence and contain unpaired electrons. They behave as oxidants or reductants by either donating an electron to or accepting an electron from other molecules. In many pathological conditions, especially infection-related inflammatory states, oxygen-containing free radicals are the major underlying mechanism for cellular injury (68). These  $\text{O}_2$ -related free radicals include hydroxyl radical, hydrogen peroxide, superoxide anion radical, hypochlorite, oxygen singlet, nitric oxide radical, and peroxynitrite radical. They are highly reactive species and can react to and damage DNA, proteins, carbohydrates, and lipids (68, 69).

SARS-CoV-2 infection would, theoretically, also evoke free radical-associated damage in the body via targeting to all kinds of molecules. Therefore, all therapeutic means that can alleviate free radicals can be applied to COVID-19 patients to conquer the inflammation-induced burst of free radicals. Furthermore, such potential therapeutics should be used as early as possible to prevent the disease from developing into late stage. For this, an antioxidant, a molecule that is stable enough to donate an electron to a rampaging free radical and neutralize it, can be applied to reduce the damage.

### **Vitamin C**

Vitamin C (Ascorbic acid) is a monosaccharide antioxidant. It is a reducing agent and can reduce and neutralize reactive oxygen species such as hydrogen peroxide. So a therapeutic dose of vitamin C of 3,000 mg once daily can be applied for COVID-19 patients.

### **Vitamin E**

Vitamin E, a collective name for a set of eight related tocopherols and tocotrienols, is a fat-soluble vitamin with strong antioxidant properties. It can remove free radical intermediates and prevent the propagation reaction from continuing. Therefore, a therapeutic dose of vitamin E of 1,000 IU once daily can be used for COVID-19 patients.

### **Glutathione**

Due to the thiol group in its cysteine moiety, glutathione possesses antioxidant properties. It is a reducing agent and can be reversibly oxidized and reduced. It has a high concentration and plays a central role in maintaining cell's redox state, as thus glutathione becomes one of the most pivotal cellular antioxidants. The possible dosage of glutathione in COVID-19 patients can reach 70 mg/kg per day.

### **N-acetyl-L-cysteine (NAC)**

NAC is a precursor of L-cysteine that increases biosynthesis of glutathione. It acts directly as a scavenger of free radicals, especially oxygen radicals. With combined administration of NAC and glutathione, the oxidative stress of patients with septic shock was significantly decreased (70). From this, the potential therapeutic dose of NAC for COVID-19 patients can be 75 mg/kg per day.

### **Melatonin**

Melatonin, N-acetyl-5-methoxytryptamine, is a naturally occurring hormone. It is a powerful antioxidant that can easily cross cell membranes and the blood-brain barrier. Melatonin can form several stable end-products

upon reacting with free radicals. In clinical setting, melatonin has been proposed to treat sepsis or septic shock (71, 72). Even the optimal dose in this setting has not been established (73), we suggest that it can be given at less than 50 mg orally per day for COVID-19 patients.

## Traditional Chinese Medicine for COVID-19

Traditional Chinese medicine (TCM) is an essential alternative means for western medicine in China. Particularly, herbal compounds are the major part of TCM. Cumulating evidence is becoming increasing in academic field on its potential effects in disease prevention and therapy. Given its property of multi-target and multi-signaling pathway intervention including anti-oxidative effect, herbal formulas may play a critical role in mitigating COVID-19-associated pathophysiological alterations (74, 75), and it can become a source of drug discovery against COVID-19 (76). We herein present some TCM herbs and herbal formulas for reference (77).

### Single Herbs

- Radix Isatidis
- Banlan Gen
- Small Bupleurum
- Coptis

### Chinese Patent Formulas

- Huoxiang Zhengqi capsules (pills, liquid, or oral solution)
- Jinhua Qinggan granules
- Lianhua Qingwen capsules (granules)
- Shufeng Jiedu capsules (granules)
- Fangfeng Tongsheng pills (granules)

### Chinese Herbal Compounds

- Ephedra 9 g, Zhigancao 6 g, Almond 9 g, Gypsum 15-30 g (fried first), Guizhi 9 g, Zixie 9 g, Zhuling 9 g, Baizhu 9 g, Zhiling 15 g, Bupleurum 16 g, Scutellaria baicalensis 6 g, and Pinellia 9 g, Ginger 9 g, aster 9 g, winter flower 9 g, shoot dry 9 g, asarum 6 g, yam 12 g, coriander fruit 6 g, tangerine peel 6 g, aquilegia 9 g. (One dose per day, twice in the morning and evening (forty minutes after a

meal), take with warm water, and three doses a course.)

- Raw ephedra 6 g, raw gypsum 15 g, almond 9 g, loquat 15 g, gardenia 15 g, Guanzhong 9 g, Dilon 15 g, Xu Changqing 15 g, Huoxiang 15 g, Peilan 9g, Cangzhu 15 g, Yunling 45 g, Atractylodes 30 g, Jiao Sanxian 9 g each, Magnolia officinalis 15 g, betel coconut 9 g, yarrow fruit 9 g, ginger 15 g. (One dose daily, boiled with 600ml water, take it three times at morning, noon and evening before meal.)
- Betel nut 10 g, apple 10 g, Magnolia 10 g, Zhimu 10 g, scutellaria baicalensis 10 g, Bupleurum 10 g, red peony 10 g, forsythia 15 g, artemisia annua 10 g (decocted later), 10 g of green leaves, 10 g of green leaves, 5 g of raw licorice. (One dose daily, boiled with 400 ml water, take it twice at morning and evening.)
- Raw ephedra 6 g, bitter almond 15 g, raw gypsum 30 g, raw coix seed 30 g, grass root 10 g, patchouli 15 g, artemisia annua 12 g, Polygonum cuspidatum 20 g, verbena 30 g, dried reed root 30 g, gardenia 15 g 15 g of orange red, 10 g of raw licorice. (One dose daily, boiled with 400 ml water, take it twice at morning and evening.)
- Atractylodes lancea 15 g, Chenpi 10 g, Magnolia 10 g, Aquilegia 10 g, grass fruit 6 g, raw ephedra 6 g, Zhihuo 10 g, ginger 10 g, betel nut 10 g. (One dose daily, boiled with 400 ml water, take it twice at morning and evening.)
- Raw ephedra 6 g, almond 9 g, raw gypsum 15 g, licorice 3 g, fragrant fragrant 10 g (back), Magnolia 10 g, atractylodes 15 g, grass fruit 10 g, pinellia 9 g, Poria 15 g, raw rhubarb 5 g (back) 10 g, gardenia 10 g, red peony 10 g. (One or two doses daily, boiled with 100-200 ml water, take it 2-4 times, oral or nasal feeding.)
- 30-60 g gypsum (fried first), 30 g of Zhimu, 30-60 g of raw land, 30 g of buffalo horn (fried first), 30 g of red sage, 30 g of black ginseng, 15 g of forsythia, 15 g of paeonia, 6 g of peony 12 g, gardenia 15 g, raw licorice 6 g. (One dose per day, decoction, first decoct gypsum and buffalo horn, then apply other pieces, 100-200 ml each time, 2-4 times a day, orally or nasally.)

### Vaccine for COVID-19

Although vaccine development needs time, we compassionate with the potential COVID-19 vaccine, because this is the only means that can effectively prevent and control even eradicate the virus. With the first mRNA vaccine mRNA-1573 was injected into the volunteers (78), we put the hope of conquering the virus on the vaccine, and we believe effective vaccine will be at the corner.

## Fluid Management

Pulmonary function is the key of COVID-19 patients. Excessive fluid burden will worsen the hypoxemia. In order to reduce pulmonary exudation and improve oxygenation, the amount of fluid should be strictly controlled while ensuring the patient's basic perfusion.

## Food Therapy for COVID-19

Food therapy is a supplementary method for COVID-19 treatment that should be on the basis of balanced nutrition supply. This is suitable for everyone including those sheltered in place due to the pandemic, and suspected and confirmed cases at different stages. When preparing foods, mostly, we can add foods with anti-oxidative ingredients as much as possible ensuring the nutrition balance.

We herein list the top foods with anti-oxidative role: Tomatoes, Oats, Green Tea, Ginseng, Blueberries, Dark Chocolate, Raspberries, Strawberries, Spinach, Oranges, Beans, Blackberries, Kale, Cranberries, Beets, Red Cabbage, Goji Berries, Artichokes, and Pecans.

## DISCHARGE CRITERIA OF COVID-19

If COVID-19 patients meet following criteria, they can be discharged home.

- (i) No fever  $\geq 3$  days;
- (ii) No need for  $O_2 > 48$  hours;

- (iii) Negative NAT twice consecutively with sampling interval at least 24 hours;
- (iv) Respiratory symptoms improve obviously;
- (v) Pulmonary imaging shows obvious absorption of inflammation;
- (vi) 14 days isolation and observation after discharge.

## PERSPECTIVES

The occurrence of COVID-19 is unavoidable. As the virus mutates, we cannot predict the next potentially more deadly virus. Even today, with the development of medical science to a certain degree, we are still suddenly at a loss when faced with tiny viruses that cannot be seen by the naked eye. Since the advent of penicillin, we have developed many antibacterial drugs. However, in an era when humans hurriedly mapped the entire human genome sequence, whereas we could not find a broad-spectral drug that can effectively fight against viruses. As we humans continue to move forward, should we pause for a moment to reexamine what we have done in science today. When the world shuts down because of COVID-19, should we slow down and review the path we have traveled. We seem to have enough power to leap into the vast universe to find the next so-called human resting place, but have we learned a little lesson from this global pandemic of COVID-19? We look up at the sky on earth, always thinking of printing our footprints on the surface of other planets. However, do we think about what we really should do? Obviously, the seemingly highly developed science and technology have numerous fatal flaws and loopholes. We believe that everyone who has experienced this COVID-19 disaster will seriously reflect on themselves and reposition themselves in the next step. We hope that after a certain period of time, we human being will no longer be that blind confident, but will be prepared for the next human crisis. ■

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