

Review (Narrative)

Facts and Recommendations of SARS-CoV-2 and COVID-19

An Update

The BASE Medicine Task Force

SUMMARY

Since the first SARS-CoV-2 infection was officially reported at the end of 2019, COVID-19 has quickly swept the world like a terrifying demon. The whole world is like entering a biological terrorist attack. Everyone seeks all kinds of useful or useless self-protection amidst extreme panic and uncomfortable sadness. The shutdown of the world has brought the entire pandemic crisis into an unprecedented level of confusion. In this process, various forces wrestled with each other, and even science and politics were mixed and strangled. This jumbled together of fish and dragons has cast a shadow of uncertainty over the entire atmosphere of fighting the pandemic. This updated task force provides the latest information on the SARS-CoV-2 and COVID-19 from its occurrence, development, therapeutics, and prevention. Over several months, although the scientific community has spared no effort in searching for effective drugs that can effectively fight against SARS-CoV-2, the facts are not satisfactory. This task force provides potentially useful therapeutic information after careful identification and screening. It is hoped that it will play a meaningful role in the entire process of the siege of SARS-CoV-2. Simultaneously, this task force makes a more detailed comment on the development of the SARS-CoV-2 vaccine. In the face of the global pandemic, various forces should work together to find useful medical methods to control SARS-CoV-2 as soon as possible instead of mutual condemnation. We cannot control the virus's mutation, whereas we will never lose our confidence in defeating the virus and taking off the masks to return to normal. ■

KEYWORDS

SARS-CoV-2; COVID-19; Human Catastrophe; Public Health; Pandemic

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INTRODUCTION

SINCE the outbreak of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in Wuhan, Hubei Province of China (1), 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 had been overwhelmingly reaching each corner of the world and reach 30,055,710 until September 18, 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 beings all the time to come? Can we make an efficient vaccine to conquer it? etc.

With evidence emerging quickly, we updated the prior version of the Task Force (4) to recognize 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 virus's origin has become an attractive topic. It was initially considered an animal-derived virus, especially bats, and pangolins are the intermediate hosts (5). Nevertheless, cumulating evidence did not prove this link because the viruses from both types of animals did not show a prominent identity with less than 85% (6).

However, a natural evolution is regarded as the most likely possibility of virus origin. Through analyzing the genomic sequence of SARS-CoV-2 and potentially related viruses, no substantial evidence supports the declaration of the virus's origin as an engineered one for any reason (7). 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 (8).

First, the receptor-binding domain (RBD) of the virus spike glycoprotein has evolved to bind to a molecule called angiotensin-converting enzyme 2 (ACE2) that is located on the human cell membranes with regulating

the function of blood pressure (9). This RBD mutation is precisely an indicator of natural evolution. Second, generally, the engineered pathologic virus would have an identical backbone with the mother virus. Nevertheless, SARS-CoV-2 has a different backbone from those of already known coronaviruses such as SARS-CoV, MERS-CoV, and viruses found in bats and pangolins (10).

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 the human host to be pathogenic after getting into the 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 (11). For these two possibilities, the first one is much more dangerous than the second one because if the virus entered a human host with its current pathogenic property from an intermediate animal host, it still would be possible for a future outbreak. However, if the virus first got into humans without pathogenic ability, a future outbreak is lower because the circulating viruses are a non-illness-causing strain.

The accumulation of the above evidence does not currently provide a definite answer to the source of SARS-CoV-2. It seems that the currently available information cannot deny that SARS-CoV-2 was a genetic engineering product from the laboratory, but this possibility still exists. Today we cannot conclude this, but we believe that the truth of the facts will be revealed one day. In the face of speculation and discussion about the virus's source, the existing scientific evidence cannot yet give a 100% answer, and only the virus itself knows its identity best. Let us wait and see the day when the truth and facts are disclosed.

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 coronaviruses. The coronaviruses' diameter ranges 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), an envelope protein (E), membrane protein (M), and nucleoprotein (N protein) (12).

SARS-CoV-2 belongs to the beta genera of the Coronaviridae family. It has a ~70% sequence identity with SARS-CoV and ~40% sequence identity with MERS CoV (13). 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's vigilance, S protein has become the target for most studies to find corresponding therapeutic drugs and neutralize vaccines. Primarily, S protein has two tasks that assist host infection: (i) aid in the attachment between the virus and host cell surface receptor ACE2, and (ii) facilitate virus enter into the host cell through helping the fusion process of the viral and host cell membranes (14). S protein structure is being extensively studied, and different models were used to predict its crystal structure (15) (Table 1).

As a structural protein, the N protein binds to the RNA genome to create a capsid containing 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 (16). Besides these two structural proteins, SARS-CoV-2 also encodes several non-structural proteins, as shown in Table 2.

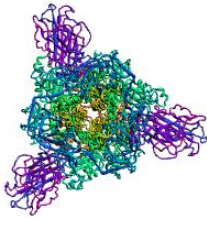
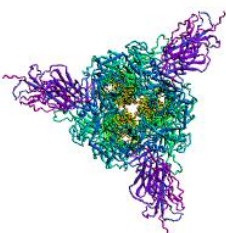
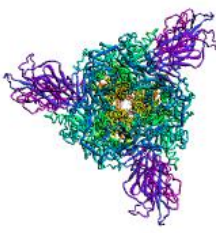
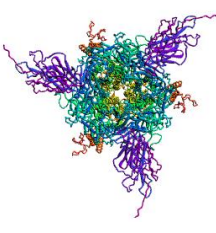
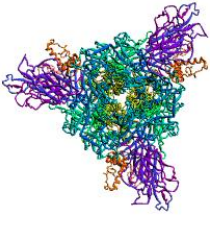
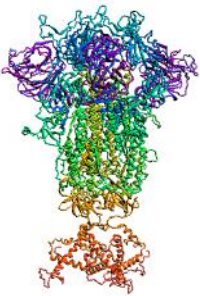
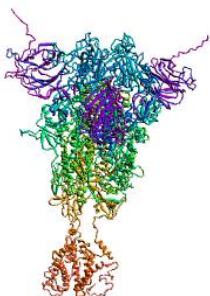
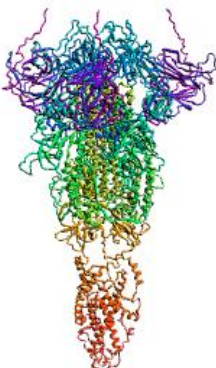
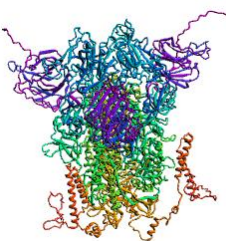
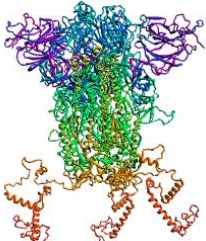
EPIDEMIOLOGY OF COVID-19

The underlying cause of COVID-19 is the pathogenic coronavirus designated as SARS-CoV-2. Patients with symptoms after the infection are the primary source of transmission. However, asymptomatic patients are also contagious and more dangerous than the symptom-positive patients in spreading the virus (17) because you do not know the person next to you is a virus carrier.

Transmission of SARS-CoV-2 is central via respiratory droplets and close contact. There is the possibility of aerosol transmission in a relatively closed environment for a long-time exposure to the high virus (18). As the virus was isolated in feces and urine, so special attention needs to be paid to feces- or urine-contaminated items that may result in feces-oral transmission (19).

The susceptible people for SARS-CoV-2 include all

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 #15.

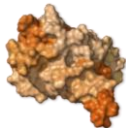
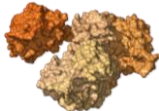
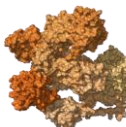
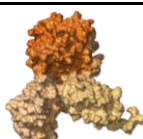
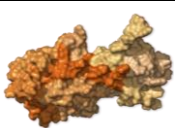
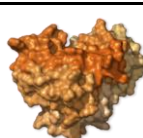
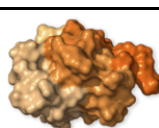
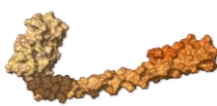
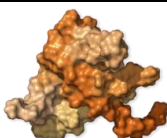
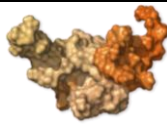
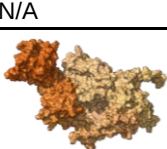
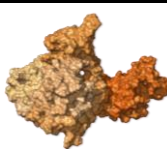
aged population. However, COVID-19 morbidity makes some age-related differences. Although the youngest confirmed case was an infant and who died in Illinois (20), the virus looks like have a preference to the senior population due to several reasons: (i) older populations generally have more underlying health conditions like diabetes, heart disease, and other chronic illnesses; (ii) with aging, the immune system gradually loses its resiliency that makes the elderly more susceptible to infection; (iii) aged people may be more likely undergoing ACE2 inhibitor treatment for cardiovascular issues, which causes upregulation of ACE2 expression in tissue (21) although the population-based study did not show an age-related difference of ACE2 expression (22) and an animal study showed that younger adults had much higher ACE2 levels than the elderly comparisons (23).

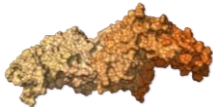
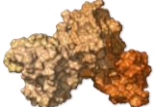
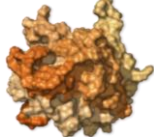
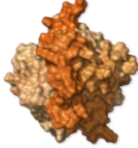
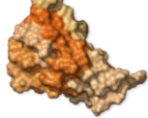
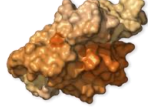
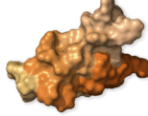
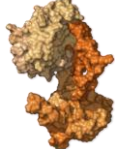
Even though the first case of COVID-19 appeared in Wuhan of China, it does not mean the virus has a racial preference (24). As COVID-19 was defined as a pandemic by the WHO, it almost reaches every corner of the world (3). Until September 18, 2020, all the countries, areas, or territories have reported COVID-19 cases (3).

There is not a vast difference in the CCOVID-19 morbidity between males and females. The WHO found that men make up 51% of the confirmed cases over 49% of female patients (25). However, an early study from China showed a little more significant difference, of which 58% were males, with 42% were females (26).

Regarding the mortality of COVID-19, different data were reported by various countries (3). The death rate ranges from 0.0% to 12% in different countries and areas, and the overall death from the WHO data was approximately 3.14% on September 18, 2020, without considering the age, gender, and pre-existing conditions (3), but this figure is changing daily. Of course, many factors would influence this figure, such as (i) the ratio of aged patients; (ii) medical conditions, incredibly intensive care settings where the patients enrolled in; (iii) primary conditions of the reported patients like nutrient status, smoking, and underlying medical diseases, etc.; and (iv) political consideration for particular 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.

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		1. Cut and loose other viral proteins to help them do their own tasks. 2. Remove tag proteins that help for destruction as an antiviral mechanism.
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		1. Poke a hole in the infected host cell membrane to make it easier for new viruses to escape. 2. Trigger inflammatory responses.
ORF6		Block immuno-signaling pathways and virus-fighting proteins in the infected host cell.
ORF7a		1. Cuts down tetherin supply to let more of the viruses to escape. 2. Trigger infected cells to commit suicide that causes lung damage.
ORF8		Not sure.
ORF10		Not sure.
S	See Table 1.	See in the text.
N		See in the text.
E		1. Form the oily bubble of the virus 2. Latch onto proteins to help turn host genes on and off
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. September 18, 2020. Available at:

<https://www.nytimes.com/interactive/2020/04/03/science/coronavirus-genome-bad-news-wrapped-in-protein.html>. Last accessed: September 18, 2020.

Table 3. Mortality of COVID-19.

	Mortality in Confirmed Cases	Mortality in All Cases
Gender		
Male	4.7%	2.8%
Female	2.8%	1.7%
Age		
> 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%
Pre-Existing Condition		
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.		

CLINICAL MANIFESTATIONS OF COVID-19

Mostly, the incubation period for COVID-19 varies from 1 to 14 days; on average, the time duration before the symptomatic manifestation in 3-7 days (27). The clinical manifestations of COVID-19 in adults, fever, fatigue, and dry cough are three major ones presented in most diagnosed cases, but it does not mean they all manifest simultaneously in one patient (28). Besides, runny nose, nasal congestion, sore throat, shortness of breath (SOB), myalgia, and diarrhea are reported (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 (29). For 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 (30). For pregnant women, the clinical course is similar to that of patients of the same age (31).

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 are 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 (32).

DIAGNOSIS OF COVID-19

For a confirmed COVID-2019 case, the 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 (33).

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 determine whether the patient would develop into severe and critically ill conditions (33).

A positive result of the nucleic acid of SARS-CoV-2 is still the gold standard for COVID-19 diagnosis. In contrast, CT imaging's characteristic signs for those suspected cases can be treated as confirmed cases even if the nucleic acid test is negative because of the possibility of a false negative in nucleic acid detection. So, isolation and continuous tests of multiple specimens should be carried out in such cases (34).

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 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 (35). Therefore, repeated sample collections and tests on the subsequent days are necessary if the NAT is negative initially. 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 followed with a little bit different 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 (36).

The dual or triple detection of nucleic acids from multiple specimens can substantially improve the diagnostic sensitivity. In patients with NAT positive respiratory tract, about 30%-40% of them have NAT positive blood and about 50%-60% of NAT positive feces. However, NAT positive urine is relatively low (37). Therefore, it improves the diagnostic accuracy, monitors treatment efficacy, and provides a reference for post-discharge isolation when the combined NATs.

Serum Virus Antibody Detection

As an invader, SARS-CoV-2 infection will evoke the 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 of some contents because the production of unusual 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 ≥ 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 (38). With the increase of serum antibody levels, the viral load gradually decreases (39). On April 2, 2020, the FDA approved the 1st SARS-CoV-2 antibody test kit (40); this will help confirm the suspected cases' infectious status.

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 thriving 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 (TCID₅₀) is determined by the micro-cytopathic method; (vi) otherwise, viral viability is determined by plaque-forming unit (PFU) (41).

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 (42). 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 (43-47).

In confirmed COVID-19 cases, detecting C-reactive protein levels, procalcitonin, ferritin, D-dimer, lymphocytes, IL-1 β , IL-4, IL-6, IL-10, TNF- α , INF- γ , etc., can help evaluate clinical progress, alert clinical severity and tendency, and provide a reference for potential therapeutic strategies. Both significantly elevated D-dimer and the 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 (48). Elevated troponin is seen in critically ill patients, while most patients have elevated CRP and erythrocyte sedimentation rates 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 improve the mortality. Therefore, corresponding therapeutic options such as steroids, intravenous immunoglobulin, and selective cytokine blockades like

anakinra or tocilizumab and Janus kinase (JAK) inhibition (49).

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 a definitive 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 daily for critically ill patients.

On CT imaging, COVID-19 lungs at the early stage frequently present 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 infection's progression, the lesions' density enlarges and increases compared with the baseline images, and consolidated lesions show air bronchogram signs 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 (50-52).

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

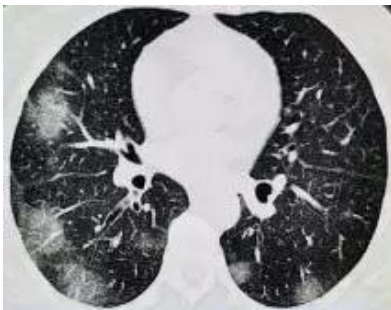
COVID-19 lungs show unique signs on CT imaging, and the progression of the disease is strongly associated with the development of the pulmonary manifestations. In **Table 4**, we summarize the typical presentations of CT signs and characteristics (53).

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

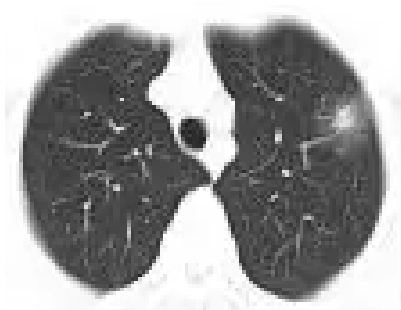
Characteristic	
Distribution	Subpleura, Subsegment, Segment, Lobar, Multi-Lobar, Inter-Lobar, Bilateral
Development	The lesion develops from the lung parenchyma in the lower periphery to the lung interstitium in the center, and the virus directly reaches the alveoli and lung lobules and completely occupies 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



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 (54):

- (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 hemoptysis, 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 tracheostomy;
- (v) Administering medicines, such as α -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 shown 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 substantial 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 individual patient's eventual outcome will strongly depend on the patient's 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 fundamental. A thermometer, finger oximeter, and oxygen compressor should be available in the isolation environment to guarantee continuous measuring of temperature, pulse oxygen saturation, and providing O₂.

Anti-viral Therapeutics

For moderate to critically ill patients, antiviral therapies can be administered as early as possible, even no firm evidence exists.

Lopinavir-Ritonavir (Kaletra®)

Controversial results exist regarding lopinavir-ritonavir (400 mg and 100 mg, respectively) in treating severe COVID-19 patients (55-57). 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 entirely 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 (58, 59). Therefore, arbidol 200 mg can be applied twice a 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 q.d. for following five days (54). Given the severe side effects of chloroquine (60), we strongly suggest that it be administered carefully by weighing its benefits over the risks.

Table 5. Bronchoscopic Views of COVID-19.

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

Hydroxychloroquine sulfate was observed and found that hydroxychloroquine 200 mg three times a day produced an influential 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 four days) (61). So we suggest that hydroxychloroquine plus azithromycin can be an alternative to chloroquine.

Favipiravir (Avigan®)

Favipiravir, marketed as an anti-influenza drug by Fujifilm, has shown “obvious efficacy” against COVID-19. 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 (62). Although these results need to be evaluated further, we can try to give favipiravir 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 (63-65), and it is considered a therapeutic option by CDC (66). 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 (67). Simultaneous use of three or more antiviral drugs is not recommended. We are waiting for the clinical trial of darunavir/ cobicistat on COVID-19 (68).

Interferon

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

Anti-Shock Therapies of COVID-19

SARS-CoV-2 infection-associated death is not because of the virus itself but by virus-related inflammation-associated complications such as ARDS, septic shock, and multiple organ failure. Considering 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 corti-

costeroids should be avoided due to potentially severe adverse events and complications.

Indications for Corticosteroids Use

- (i) Severe and critically ill stage;
- (ii) Persistent high fever $> 39^{\circ}\text{C}$;
- (iii) Patchy ground-glass or $> 30\%$ area of the lungs are involved in CT imaging;
- (iv) Rapid progression with $> 50\%$ area involved in chest CT images within 48 hours;
- (v) IL-6 ≥ 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 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 is recommended once a day when the i.v., the 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_2 supplementation is necessary to correct hypoxemia and relieve secondary organ damage resulted from respiratory distress and hypoxemia (54).

Oxygen Therapy

- (i) Continual oxygen saturation monitoring during oxygen therapy to make sure $\text{SpO}_2 > 92\%$;
- (ii) Oxygen therapy should be delivered as soon as possible if $\text{PaO}_2/\text{FiO}_2 < 300$ mmHg;
- (iii) High-flow nasal cannula (HFNC) oxygen therapy is recommended if COVID-19 patients had:
 - $\text{SpO}_2 < 93\%$;
 - $\text{PaO}_2/\text{FiO}_2 < 300$ mmHg;
 - Respiratory rate > 25 bpm at the 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 $\text{PaO}_2/\text{FiO}_2$ is between 200-300 mmHg;
 - An initial flow of at least 60 l/min should be given immediately for patients with apparent respiratory distress.
- (iv) Tracheal intubation for patients is dependent on disease progression, systemic status, and complication of patients for those with a stable situation but with a low OI < 100 mmHg (54).
 - 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 $\text{PaO}_2/\text{FiO}_2 < 200$ 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 exceptionally critical to balance the benefits of ventilation and the risk of mechanical ventilation-related lung injury (54).

- Tidal volume to 4-8 ml/kg;
- Platform pressure < 30 cmH₂O;
- Driving pressure < 15 cmH₂O;
- 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 are reduced and discontinued before awakening when PaO₂/FiO₂ > 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 PaO₂/FiO₂ < 150 mmHg or obvious imaging manifestations without contraindications. The time course recommended for prone ventilation is more than 16 hours each time. The prone ventilation can be ceased once PaO₂/FiO₂ > 150 mmHg for more than 4 hours in the supine position (54).

Prone ventilation while awake may be attempted for patients who have not been intubated or have no apparent 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, the following attentions need to be paid to (54):

Timing of ECMO

- (i) Salvage ECMO: salvage ECMO intervention needs to be considered with the onset of one of the following conditions:
 - PaO₂/FiO₂ < 80 mmHg, regardless of PEEP level;
 - P_{plat} ≤ 30 mmHg, PaCO₂ > 55 mmHg;
 - The onset of pneumothorax, air leakage > 1/3 tidal volume, duration > 48 hours;
 - Circulation deterioration, the dosage of norepinephrine > 1 µg/(kg×min);
 - Cardio-pulmonary resuscitation.
- (ii) 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/cmH₂O;
 - Persistent exacerbation of pneumomediastinum or subcutaneous emphysema, and the parameters of mechanical ventilation support cannot be reduced within 48 hours;
 - PaO₂/FiO₂ < 100 mmHg, and routine methods cannot improve it in 72 hours.
- (iii) Early Awake ECMO: For early awake ECMO, all the following conditions must be met:
 - The patient must be in a clear state of consciousness and is fully compliant;
 - The 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;

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: ● Respiratory rate ≥ 30 bpm; ● Oxygen saturation $\leq 93\%$ at a rest state; ● Arterial partial pressure of oxygen (PaO_2)/oxygen concentration (FiO_2) ≤ 300 mmHg; ● Patients with $> 50\%$ lesions progression within 24-48 hours in lung imaging should be treated as severe cases.
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	● $100 \text{ mmHg} < \text{OI} \leq 150 \text{ mmHg}$; ● Compliance of respiratory system $\geq 30 \text{ ml/cmH}_2\text{O}$; ● Without organ failure other than the lungs. ● The patient has a great chance of recovery through active antiviral, anti-cytokine storm, and supportive treatment.
Middle Stage	● $60 \text{ mmHg} < \text{OI} \leq 100 \text{ mmHg}$; ● $30 \text{ ml/cmH}_2\text{O} > \text{compliance of respiratory system} \geq 15 \text{ ml/cmH}_2\text{O}$; ● May be complicated by other mild or moderate dysfunction of other organs.
Late Stage	● $\text{OI} \leq 60 \text{ mmHg}$; ● Compliance of respiratory system $< 15 \text{ ml/cmH}_2\text{O}$; ● Diffuse consolidation of both lungs that requires the use of ECMO; ● Or failure of other vital organs. ● The mortality risk is significantly increased.

Note: OI: oxygenation index;

- Stable hemodynamics without the 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 ultrasound guidance, which reduces the bleeding damages and infection risks brought about by intravascular catheterization by venous angiomy.

Intravascular catheterization by venous angiomy may be considered only for the patients with terrible blood vessel conditions, or the patients whose catheterization cannot be identified and selected by ultrasound, or the patients whose Seldinger method failed.

Mode Selection

- 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;
- For the respiratory failure patients complicated with cardiac impairment, $\text{PaO}_2/\text{FiO}_2 < 100$ mmHg, the V-A-V mode ought to be selected with the total flux > 6 l/min and $\text{V/A} = 0.5/0.5$ is maintained by current limiting;
- For patients without severe respiratory failure but complicated with serious cardiovascular outcomes leading to cardiogenic shock, the V-A assisted by ECMO mode should be selected. However, IPPV support is still needed, and awake ECMO should be avoided.

Flux Set-value and Target Oxygen Supply

- (i) The initial flux > 80% cardiac output (CO) with a self-cycling ratio < 30%;
- (ii) SpO₂ > 90% is to be maintained. FiO₂ < 0.5 is supported by mechanical ventilation or the other oxygen therapy;
- (iii) To ensure the target flux, 22 Fr (24 Fr) vein access cannula is the first choice for the patient with a bodyweight below 80 kg.

Ventilation Setting

- (i) The initial airflow is set to be Flow: sweep gas = 1:1. The primary target is to maintain PaCO₂ < 45 mmHg. For the patients complicated with COPD, PaCO₂ < 80% basal level;
- (ii) The patient's spontaneous respiratory strength and respiratory rate (RR) should be maintained, with 10 < 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 > 50×10⁹/l, the recommended initial heparin dosage is 50 U/kg;
- (ii) For the patients complicated with bleeding or with platelet count < 50×10⁹/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 significant underlying cellular injury (69). These O₂-related free radicals include hydroxyl radicals, hydrogen peroxide, superoxide anion radicals,

hypochlorite, oxygen singlet, nitric oxide radical, and peroxynitrite radicals. They are highly reactive species and can react to and damage DNA, proteins, carbohydrates, and lipids (69, 70).

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 to 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 to prevent the disease from developing into a late-stage as early as possible. For this, an antioxidant, a stable enough molecule to donate an electron to a rampaging free radical and neutralize it, can be applied to reduce the damage.

Zinc

Zinc (Zn) is everywhere in human cells. It is one of the necessary elements for cells to maintain their normal functions. Existing knowledge has proven that Zn plays an irreplaceable role through multiple channels: (i) Zn blocks of the virus entry into the cell via stabilizing the cell membrane. (ii) Zn directly inhibits viral replication by changing the proteolytic processing of replicase polyproteins and RNA-dependent RNA polymerase and diminishing the RNA-synthesizing activity. (iii) Zn balances the immune response by enhancing both innate and humoral antiviral activities, restoring the depleted immune cell function, and improving normal immune cell function, particularly in immunocompromised or elderly patients. (iv) Zn acts synergistically with the standard antiviral therapy like hydroxychloroquine when co-administered. Based on this, Zn may also have a strong inhibitory effect on SARS-CoV-2 infection. The proper use of Zn in COVID-19 patients will be very beneficial (71, 72).

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 D

Vitamin D modulates innate and adaptive immune responses. Supplement of vitamin D can help reduce the autoimmunity as well as susceptibility to infection. Cumulative evidence indicated that vitamin D functions as an antiviral agent by inducing cathelicidins and defensins that lower viral replication rates and reducing concentrations of pro-inflammatory cytokines (73). Thus, the potential use of vitamin is to raise 25(OH)D concentrations above 40-60 ng/mL or 100-150 nmol/L.

Vitamin E

Vitamin E, a collective name for a set of eight related tocopherols and tocotrienols, is a fat-soluble vitamin with potent 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 the 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 the biosynthesis of glutathione. It acts directly as a scavenger of free radicals, especially oxygen radicals. With the combined NAC administration and glutathione administration, the peroxidative stress of patients with septic shock was significantly decreased (74). 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 the clinical setting, melatonin has been proposed to treat sepsis or septic shock (75, 76). Even the optimal dose in this setting has not been established (77), 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. Mainly, herbal compounds constitute a significant part of TCM. Cumulating evidence is becoming increasing in the academic field on its potential effects on disease prevention and therapy. Given its property of multi-target and multi-signaling pathway intervention, including antioxidative effect, herbal formulas may play a critical role in mitigating COVID-19-associated pathophysiological alterations (78, 79), and it can become a source of drug discovery against COVID-19 (80). Although there is no direct clinical evidence to prove that TCM formula can inhibit SARS-CoV-2 or have a significant therapeutic effect on COVID-19, in the spirit of humanity and compassionate comfort, we provide possible TCM formulations (81) here for reference only. If you can obtain the relevant TCM formula, please consult your physician and get reliable usage advice.

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, Dilong 15 g, Xu Changqing 15 g, Huoxiang 15 g, Peilan 9 g, Cangzhu 15g, Yunling 45g, Atractylodes 30g, 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 in 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 in 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 in morning and evening.)
- Raw ephedra 6 g, almond 9 g, raw gypsum 15 g, licorice 3 g, 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) 10g, 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.)

Vaccine for COVID-19

After SARS-CoV-2 disrupted the world's normal order, the supposedly orderly medical system became complicated and unpredictable under the amalgamation of various factors. Although vaccine development needs time, we are compassionate with the potential COVID-19 vaccine because this is the only means to prevent and control, even eradicate the virus effectively. Countries all over the world are doing their best to develop the SARS-CoV-2 vaccine. However, there are different opinions on vaccine development (82-84). With the first mRNA vaccine, mRNA-1573 was injected into the volunteers (85), different SARES-CoV-2 vaccines are being developed using different biotechnology. Clinical trials in different phases have also begun to be carried out in full swing. Before effective methods appear, we must be confident that we have enough wisdom to deal with and eliminate SARS-CoV-2.

Fluid Management

Pulmonary function is the key to COVID-19 patients. The excessive fluid burden will worsen the hypoxemia. To reduce pulmonary exudation and improve oxygenation, the fluid amount should be strictly controlled while ensuring the patient's essential perfusion.

Food Therapy for COVID-19

Food therapy is a supplementary method for COVID-19 treatment that should be based on a 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, we can mostly add foods with anti-oxidative ingredients as much as possible, ensuring the nutrition balance.

We herein list the top foods with the anti-oxidative role: Garlic, 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 the following criteria; they can be discharged home.

- (i) No fever ≥ 3 days;
- (ii) No need for O₂ > 48 hours;
- (iii) Negative NAT twice consecutively with sampling interval at least 24 hours;
- (iv) Respiratory symptoms improve obviously;
- (v) Pulmonary imaging shows apparent absorption of inflammation;
- (vi) Fourteen days of 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 other planets' surface. However, do we think about what we really should do? The seemingly highly advanced 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. Regardless of political or cultural reasons, regardless of a difference in ethnicity or personal values, regardless of regional or spatial differences, we can undoubtedly be unable to avoid its potential interference. Today, the SARS-CoV-2 attack on our humans is precisely the result of these mixed factors. Some people hide the facts, but some reveal secrets; some do not care about safety, but some are cautious. The COVID-19 outbreak is like a magic mirror revealing the hidden characteristics of various characters. We hope that we human beings will no longer be that blind confident after a certain period, but will be prepared for the next human crisis.■

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