**A COMPREHENSIVE REVIEW OF THE AETIOLOGY OF COVID-19, ITS PATHOGENESIS, HISTOPATHOLOGICAL FEATURES AND CURRENT POTENTIAL THERAPIES.**

**BY**

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**INTRODUCTION**

According to World Health Organization (WHO), viral diseases continue to develop and signify a stern problem to public health. In the last twenty years, numerous viral epidemics such as the severe acute respiratory syndrome coronavirus (SARS-CoV) in 2002 to 2003 and H1N1 influenza in 2009 have been recorded. Most recently, the Middle East respiratory syndrome coronavirus (MERS-CoV) was first known in Saudi Arabia in 2012. Currently, coronavirus disease 2019 (COVID-19) poses a signiﬁcant risk to global health (Cascella *et al*., 2020). On 31st December 2019, 27 cases of pneumonia of unknown origin were recognized in Wuhan City, Hubei province in China (Lu *et al*., 2020). Wuhan is a densely inhabited city in central China with a population more than 11 million. These patients most notably presented with clinical symptoms of dry cough, dyspnea, fever, and bilateral lung infiltrates on imaging. Cases were all linked to Wuhan's Huanan Seafood Wholesale Market, which trades in fish and a variety of live animal species including poultry, bats, marmots, and snakes (Lu *et al*., 2020). The causative agent was known from throats swabs samples conducted by the Chinese Centre for Disease Control and Prevention (CCDC) on 7th of January 2020 and was subsequently named Severe Acute Respiratory Syndrome Coronavirus2(SARS-CoV-2). The World Health Organization named the disease COVID-19 (WHO, 2020). World Health Organization (WHO) has stated this outbreak as a “public health emergency of international concern” on January 31, 2020. Within the ﬁrst two months of the outbreak, the epidemic spread swiftly around the country and the world. As of March 8, 2020, a total of 80, 868 conﬁrmed cases and 3,101 deaths had been reported in Chinese mainland by National Health Commission of China, and 90 other countries are affected. COVID-19 as a developing disease, has exceptional biological characteristics, clinical symptoms, and imaging manifestations, though significant improvement has been made on the clinical management (Zhou *et al*., 2020).

**Virologic characteristics of SARS-CoV-2**

SARS-CoV-2 is the causative pathogen of COVID-19, known as the seventh type of coronavirus to infect humans (Zhu *et al*., 2020). Six other kinds of coronaviruses are known to be the origin to human disease, including severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) with high death rate. According to the genome characteristics, coronavirus is divided into four genera: α-CoV, β-CoV, γ-CoV, and δ-CoV (Su *et al*., 2016). Deep sequencing exposed that this novel coronavirus isolated from lower respiratory tract samples of patient with COVID-19 belongs to β-CoV (Zhu *et al*., 2020). Coronavirus has the appearance of crown under electron microscopy. They are enveloped viruses with a single strand, positive-sense RNA genome, which is the largest known genome for an RNA virus. All coronaviruses share the same genome organization and expression pattern, with two large overlapping reading frames (ORF1a/b) which encode 16 nonstructural proteins, followed by ORFS for four major structural proteins: spike (S), envelope (E), membrane (M), and nucleocapsid (N) (Forni *et al*., 2017). The SARS-CoV-2 protein also contains eight accessory proteins (Wu *et al*., 2020). Spike protein plays a vital role in binding to receptors and is critical for determining host tropism and transmission capacity. It is functionally divided into S1 domain and S2 domain, responsible for receptor binding and cell membrane fusion respectively. The receptor binding domain (RBD) of β-CoV is commonly located in the C-terminal domain of S1 (Lu *et al*., 2020). A team analyzed the cryogenic electron microscopy(CryoEM) structure of the SARS-CoV-2 spike protein and found that it has 10 to 20-fold higher binding afﬁnity to human angiotensin-converting enzyme 2 (ACE2) than SARSCoV does (Wrapp *et al*., 2020). Phylogenetic analysis of the evolution history exhibited that SARS-CoV-2 shared a closer sequence homology toward the genomes of SARS-CoV than to that of MERS CoV (Xu *et al*., 2020). SARS-CoV-2 is highly similar to a bat coronavirus RaTG13, with an overall genome sequence identity of 96.2% (Zhou *et al*., 2020), indicating that bat, which was discovered to be the natural reservoir host of various SARS-related coronaviruses (de Wit *et al*., 2016), may also be the original host of SARS-CoV-2. The intermediate host in the process of transmission remains uncertain.



Figure 1: Showing the structure of SARS-CoV-2 (Cascella *et al*., 2020)

**Symptoms of COVID-19**

The symptoms of COVID-19 infection appear after a gestation period of approximately 5.2 days (Li *et al*., 2020). The period from the start of COVID-19 symptoms to death ranged from 6 to 41 days with a median of 14 days. This period is reliant on the age of the patient and status of the patient's immune system. It was smaller amongst patients>70-years old compared with those under the age of 70 (Wang *et al.*, 2020). The most common symptoms at beginning of COVID-19 illness are fever, cough, and fatigue, while other symptoms include sputum production, headache, haemoptysis, diarrhoea, dyspnoea, and lymphopenia (Ren *et al*., 2020; Huang *et al*., 2020; Wang *et al*., 2020; Carlos *et al*., 2020). A chest CT scan revealed some clinical features presented as pneumonia, however, there were abnormal features such as RNAaemia, acute respiratory distress syndrome, acute cardiac injury, and incidence of grand-glass opacities that led to death (Huang *et al*., 2020). In some cases, the multiple peripheral ground-glass opacities were detected in subpleural regions of both lungs that likely induced both systemic and localized immune response that led to increased inﬂammation. Regrettably, treatment of some cases with interferon inhalation presented no clinical eﬀect and instead seemed to worsen the condition by progressing pulmonary opacities (Lei *et al*., 2020). It is vital to note that there are similarities in the symptoms between COVID-19 and earlier betacoronavirus such as fever, dry cough, dyspnea, and bilateral ground-glass opacities on chest CT scans (Huang *et al*, 2020). However, COVID-19 showed some exceptional clinical features that include the targeting of the lower airway as evident by upper respiratory tract symptoms like rhinorrhea, sneezing, and sore throat (Assiri *et al*., 2013; Lee *et al*., 2003). Furthermore, based on results from chest radiographs upon admission, some of the cases show an inﬁltrate in the upper lobe of the lung that is associated with increasing dyspnea with hypoxemia (Phan *et al*., 2020). Importantly, whereas patients infected with COVID-19 developed gastrointestinal symptoms like diarrhea, a low percentage of MERS-CoV or SARS-CoV patients experienced similar GI distress. Hence, it is important to test fecal and urine samples to exclude a potential alternative route of transmission, speciﬁcally through health care workers, patients etc. (Assiri *et al*., 2013; Lee *et al*., 2003). Therefore, development of approaches to identify the various modes of transmission such as fecal and urine samples are urgently warranted in order to develop strategies to inhibit and/or minimize transmission and to develop therapeutics to control the disease.

**AETIOLOGY**

CoVs are positive-stranded RNA viruses with a crown-like appearance under an electron microscope (coronam is the Latin term for crown) due to the presence of spike glycoproteins on the envelope. The subfamily Orthocoronavirinae of the Coronaviridae family (order Nidovirales) classifies into four genera of CoVs: Alpha coronavirus (alphaCoV), Beta coronavirus (betaCoV), Delta coronavirus (deltaCoV), and Gamma coronavirus (gammaCoV). Furthermore, the betaCoV genus divides into five sub-genera or lineages (Chan *et al*., 2013). Genomic characterization has shown that probably bats and rodents are the gene sources of alphaCoVs and betaCoVs. On the contrary, avian species seem to represent the gene sources of deltaCoVs and gammaCoVs.

Members of this large family of viruses can cause respiratory, enteric, hepatic, and neurological diseases in different animal species, including camels, cattle, cats, and bats. To date, seven human CoVs (HCoVs) — capable of infecting humans — have been identified. Some of HCoVs were identified in the mid-1960s, while others were only detected in the new millennium.

In general, estimates suggest that 2% of the population are healthy carriers of a CoV and that these viruses are responsible for about 5% to 10% of acute respiratory infections (Chen *et al*., 2020).

Common human CoVs: HCoV-OC43, and HCoV-HKU1 (betaCoVs of the A lineage); HCoV-229E, and HCoV-NL63 (alphaCoVs). They can cause common colds and self-limiting upper respiratory infections in immunocompetent individuals. In immunocompromised subjects and the elderly, lower respiratory tract infections can occur.

Other human CoVs: SARS-CoV, SARS-CoV-2, and MERS-CoV (betaCoVs of the B and C lineage, respectively). These cause epidemics with variable clinical severity featuring respiratory and extra-respiratory manifestations. Concerning SARS-CoV, MERS-CoV, the mortality rates are up to 10% and 35%, respectively.

Thus, SARS-CoV-2 belongs to the betaCoVs category. It has round or elliptic and often pleomorphic form, and a diameter of approximately 60–140 nm. Like other CoVs, it is sensitive to ultraviolet rays and heat. Furthermore, these viruses can be effectively inactivated by lipid solvents including ether (75%), ethanol, chlorine-containing disinfectant, peroxyacetic acid and chloroform except for chlorhexidine.

In genetic terms, Chan *et al*. (2020) have proven that the genome of the new HCoV, isolated from a cluster-patient with atypical pneumonia after visiting Wuhan, had 89% nucleotide identity with bat SARS-like-CoVZXC21 and 82% with that of human SARS-CoV. For this reason, the new virus was called SARS-CoV-2. Its single-stranded RNA genome contains 29891 nucleotides, encoding for 9860 amino acids. Although its origins are not entirely understood, these genomic analyses suggest that SARS-CoV-2 probably evolved from a strain found in bats. The potential amplifying mammalian host, intermediate between bats and humans, is, however, not known. Since the mutation in the original strain could have directly triggered virulence towards humans, it is not certain that this intermediary exists.

**Transmission**

Because the first cases of the CoVID-19 disease were linked to direct exposure to the Huanan Seafood Wholesale Market of Wuhan, the animal-to-human transmission was presumed as the main mechanism. Nevertheless, subsequent cases were not associated with this exposure mechanism. Therefore, it was concluded that the virus could also be transmitted from human-to-human, and symptomatic people are the most frequent source of COVID-19 spread. The possibility of transmission before symptoms develop seems to be infrequent, although it cannot be excluded. Moreover, there are suggestions that individuals who remain asymptomatic could transmit the virus. This data suggests that the use of isolation is the best way to contain this epidemic.

As with other respiratory pathogens, including flu and rhinovirus, the transmission is believed to occur through respiratory droplets from coughing and sneezing. Aerosol transmission is also possible in case of protracted exposure to elevated aerosol concentrations in closed spaces. Analysis of data related to the spread of SARS-CoV-2 in China seems to indicate that close contact between individuals is necessary. The spread, in fact, is primarily limited to family members, healthcare professionals, and other close contacts.

Based on data from the first cases in Wuhan and investigations conducted by the China CDC and local CDCs, the incubation time could be generally within 3 to 7 days and up to 2 weeks as the longest time from infection to symptoms was 12.5 days (95% CI, 9.2 to 18) (Li *et al*., 2020). This data also showed that this novel epidemic doubled about every seven days, whereas the basic reproduction number (R0 - R naught) is 2.2. In other words, on average, each patient transmits the infection to an additional 2.2 individuals. Of note, estimations of the R0 of the SARS-CoV epidemic in 2002-2003 were approximately 3 (Bauch *et al*., 2005).

It must be emphasized that this information is the result of the first reports. Thus, further studies are needed to understand the mechanisms of transmission, the incubation times and the clinical course, and the duration of infectivity.

**PATHOGENESIS**

Based on the published literature and clinical observations of COVID-19 patients, a proposed, reasonable, hypotheses about the pathogenesis of SARS-CoV-2 infection in humans. The virus might pass through the mucous membranes, especially nasal and larynx mucosa, then enters the lungs through the respiratory tract. The early most common symptoms of infection are fever and cough (Guan *et al*., 2020). The virus may enter the peripheral blood from the lungs, causing viremia. Then the virus would attack the targeting organs that express ACE2, such as the lungs, heart, renal, gastrointestinal tract (Dan *et al*., 2002; Letko *et al*., 2020). The SARS-CoV-2 detected in the fecal samples (Wang *et al*., 2020) is more likely because the virus enters the blood from the lungs and then travels from the blood to the intestines which supports our hypothesis. Dawei Wang *et al* (2020) found that the median time from symptom onset to ARDS was about 8 days. We speculate that in this way, the virus begins a second attack, causing the patient’s condition to aggravate around 7 to 14 days after onset. During the infection process, the white blood cell count in peripheral blood in the early stage of the disease is normal or slightly low (Guan *et al*.,2020), and lymphopenia is observed in patients (Wang *et al*., 2020). We speculate that B lymphocyte reduction may occur early in the disease, which may affect antibody production in the patient. In severe type patients, lymphocytes were significantly reduced (Wang *et al*., 2020). We speculate that lymphocytes in patients with COVID-19 might gradually decrease as the disease progress. But the mechanism of significant lymphocyte reduction in severe type patients remains unclear. Besides, the inflammatory factors associated with diseases mainly containing IL-6 (Wan *et al*., 2020) were significantly increased, which also contributed to the aggravation of the disease around 7 to 14 days after onset. Non-survivors had higher levels of neutrophils, D-Dimer, blood urea nitrogen, and creatinine than the survivors (Wang *et al*., 2020). Based on the above assumptions, the clinical phase is divided into three: the viremia phase, the acute phase (pneumonia phase) and the recovery phase. If the immune function of patients in the acute phase (pneumonia phase) is effective, and no more basic diseases, the virus can be effectively suppressed then enter the recovery phase. If the patient is older, or in an immune impaired state, combined with other basic diseases such as hypertension and diabetes, the immune system cannot effectively control the virus in the acute phase (pneumonia phase), the patient will become severe or critical type. As we mentioned etin our hypothesis, T cells, B cells were further reduced, while inflammatory cytokines and D-Dimer continued to increase in severe type patients. To enhance the immune function of patients and inhibit the formation of inflammatory factor storms, we proposed the following two therapeutic measures. COVID-19 does not have specific antiviral drug treatment currently, so the treatment of the disease is mainly focused on symptomatic treatment and oxygen therapy. Inflammatory factors and lymphocyte subsets are recommended to be monitored during the disease. We suggest that IVIg and low molecular weight heparin (LMWH) anticoagulant therapy could be given as early as possible when T cells, B cells, inflammatory cytokines, and D-Dimer show the following trends: T lymphocytes and B lymphocytes in peripheral blood are significantly lower than before; inflammatory cytokines such as IL-6 are increased significantly; coagulation parameters such as D-Dimer increased abnormally; Chest CT indicates the expansion of lung lesions. In our recommendation, high-dose IVIg at 0.3-0.5g per kg weight per day could be given for 5 days, which can interrupt the storm of inflammatory factors at an early stage, enhance immune function. A randomized controlled clinical trial of IVIg in patients with severe SARS-CoV-2 infection has been initiated (NCT 04261426). Although IVIG has shown efficacy in the treatment of patients with influenza (Liu *et al*., 2016) and SARS (Ho *et al*., 2004), we need more clinical data of COVID-19 patients as evidence. LMWH anticoagulation therapy is especially recommended in the early stage of the disease. Infection is a common cause of disseminated intravascular coagulation. Inflammation, infection and other factors can lead to excessive activation of coagulation. We have observed in clinical that COVID-19 patients with severe type may develop disseminated intravascular coagulation (DIC). In COVID-19 patients with severe type, ischemic changes may occur in the fingers and toes. Anticoagulation therapy is recommended for COVID-19 patients when the D-Dimer value is 4 times higher than the normal upper limit, except for patients with anticoagulant contraindications. The recommended dose of LMWH is 100U per kg weight per 12 hours by subcutaneous injection for 3-5 days. Clinicians should closely monitor the indicators of laboratory examination of patients to be alert for side effects after anticoagulant treatment. In conclusion, the current treatment of COVID-19 patients with severe type and critical type is the key to controlling the rising number of deaths. We recommend early initiation of IVIg and LMWH anticoagulant therapy, which is effective in improving the prognosis of severe and critical type patients

**PATHOPHYSIOLOGY**

CoVs are enveloped, positive-stranded RNA viruses with nucleocapsid. For addressing pathogenetic mechanisms of SARS-CoV-2, its viral structure, and genome must be considerations. In CoVs, the genomic structure is organized in a +ssRNA of approximately 30 kb in length — the largest known RNA viruses — and with a 5′-cap structure and 3′-poly-A tail. Starting from the viral RNA, the synthesis of polyprotein 1a/1ab (pp1a/pp1ab) in the host is realized. The transcription works through the replication-transcription complex (RCT) organized in double-membrane vesicles and via the synthesis of subgenomic RNAs (sgRNAs) sequences. Of note, transcription termination occurs at transcription regulatory sequences, located between the so-called open reading frames (ORFs) that work as templates for the production of subgenomic mRNAs. In the atypical CoV genome, at least six ORFs can be present. Among these, a frameshift between ORF1a and ORF1b guides the production of both pp1a and pp1ab polypeptides that are processed by virally encoded chymotrypsin-like protease (3CLpro) or main protease (Mpro), as well as one or two papain-like proteases for producing 16 non-structural proteins (nsps). Apart from ORF1a and ORF1b, other ORFs encode for structural proteins, including spike, membrane, envelope, and nucleocapsid proteins (Perlman and Netland, 2009). and accessory proteic chains. Different CoVs present special structural and accessory proteins translated by dedicated sgRNAs.

Pathophysiology and virulence mechanisms of CoVs, and therefore also of SARS-CoV-2 have links to the function of the nsps and structural proteins. For instance, research underlined that nsp is able to block the host innate immune response (Lei *et al*., 2018). Among functions of structural proteins, the envelope has a crucial role in virus pathogenicity as it promotes viral assembly and release. However, many of these features (e.g., those of nsp 2, and 11) have not yet been described.

Among the structural elements of CoVs, there are the spike glycoproteins composed of two subunits (S1 and S2). Homotrimers of S proteins compose the spikes on the viral surface, guiding the link to host receptors (Song *et al*., 2018). Of note, in SARS-CoV-2, the S2 subunit — containing a fusion peptide, a transmembrane domain, and cytoplasmic domain — is highly conserved. Thus, it could be a target for antiviral (anti-S2) compounds. On the contrary, the spike receptor-binding domain presents only a 40% amino acid identity with other SARS-CoVs. Other structural elements on which research must necessarily focus are the ORF3b that has no homology with that of SARS-CoVs and a secreted protein (encoded by ORF8), which is structurally different from those of SARS-CoV.

In international gene banks such as GenBank, researchers have published several Sars-CoV-2 gene sequences. This gene mapping is of fundamental importance allowing researchers to trace the phylogenetic tree of the virus and, above all, the recognition of strains that differ according to the mutations. According to recent research, a spike mutation, which probably occurred in late November 2019, triggered jumping to humans. In particular, Angeletti *et al*. (2020) compared the Sars-Cov-2 gene sequence with that of SARS-CoV. They analyzed the transmembrane helical segments in the ORF1ab encoded 2 (nsp2) and nsp3 and found that position 723 presents a serine instead of a glycine residue, while the position 1010 is occupied by proline instead of isoleucine. The matter of viral mutations is key for explaining potential disease relapses. Research will be needed to determine the structural characteristics of SARS-COV-2 that underlie the pathogenetic mechanisms. Compared to SARS, for example, initial clinical data show less extra respiratory involvement, although due to the lack of extensive data, it is not possible to draw definitive clinical information. The pathogenic mechanism that produces pneumonia seems to be particularly complex. Clinical and preclinical research will have to explain many aspects that underlie the particular clinical presentations of the disease. The data so far available seem to indicate that the viral infection is capable of producing an excessive immune reaction in the host. In some cases, a reaction takes place which as a whole is labeled a 'cytokine storm'. The effect is extensive tissue damage. The protagonist of this storm is interleukin 6 (IL-6). IL-6 is produced by activated leukocytes and acts on a large number of cells and tissues. It is able to promote the differentiation of B lymphocytes, promotes the growth of some categories of cells, and inhibits the growth of others. It also stimulates the production of acute phase proteins and plays an important role in thermoregulation, in bone maintenance and in the functionality of the central nervous system. Although the main role played by IL-6 is pro-inflammatory, it can also have anti-inflammatory effects. In turn, IL-6 increases during inflammatory diseases, infections, autoimmune disorders, cardiovascular diseases and some types of cancer. It is also implicated into the pathogenesis of the cytokine release syndrome (CRS) that is an acute systemic inflammatory syndrome characterized by fever and multiple organ dysfunction.

**HISTOPATHOLOGY**

Tian *et al*. (2020) and others reported histopathological data obtained on the lungs of two patients who underwent lung lobectomies for adenocarcinoma and retrospectively found to have had the infection at the time of surgery. Apart from the tumors, the lungs of both 'accidental' cases showed edema and important proteinaceous exudates as large protein globules. The authors also reported vascular congestion combined with inflammatory clusters of fibrinoid material and multinucleated giant cells and hyperplasia of pneumocytes.

**Therapeutics/treatment options**

The person-to-person transmission of COVID-19 infection led to the isolation of patients that were administered a variety of treatments. At present, there are no speciﬁc antiviral drugs or vaccine against COVID19 infection for possible treatment of humans. Antiviral drugs like Nucleoside analogues and also HIV-protease inhibitors are the only choice available that could attenuate virus infection until the speciﬁc antiviral becomes available (Lu, 2020). The treatment that have so far been tried exhibited that 75 patients were administrated current antiviral drugs. The course of treatment included twice a day oral administration of 75 mg oseltamivir, 500 mg lopinavir, 500 mg ritonavir and the intravenous administration of 0·25 g ganciclovir for 3–14 days (Chen *et al*., 2020). Another report presented that the broad-spectrum antiviral remdesivir and chloroquine are very eﬀective in the control of 2019nCoV infection in vitro. These antiviral compounds have been used in human patients with a safety track record. Thus, these therapeutic agents can be considered to treat COVID-19 infection (Wang *et al*., 2020). Furthermore, there are a number of other compounds that are in progress. These include the clinical candidate EIDD-2801 compound that has shown high therapeutic potential against seasonal and pandemic inﬂuenza virus infections and this represents another potential drug to be considered for the treatment of COVID-19 infection (Toots *et al*., 2019). Along those lines, until more speciﬁc therapeutics become available, it is reasonable to consider more broad-spectrum antivirals that provide drug treatment options for COVID-19 infection include Lopinavir/Ritonavir, Neuraminidase inhibitors, peptide (EK1), RNA synthesis inhibitors. It is clear however, that more research is urgently needed to identify novel chemotherapeutic drugs for treating COVID-19 infections. In order to develop pre-and post-exposure prophylaxis against COVID-19, there is an urgent need to establish an animal model to replicate the severe disease currently observed in humans. Several groups of scientists are currently working hard to develop a nonhuman primate model to study COVID19 infection to establish fast track novel therapeutics and for the testing of potential vaccines in addition to providing a better understanding of virus-host interactions.

**Corticosteroids**

According to current WHO interim guidance on COVID19 management (2020), corticosteroids were not suggested as routine therapy unless indicated for another reason, because potential harms and higher risk of mortality attributed to corticosteroids therapy have been identiﬁed by studies on other coronaviruses and inﬂuenza. An epidemiological study conducted in Wuhan observed a larger percentage of patients receiving corticosteroids in ICU groups when compared with non-ICU groups (6 (46%) vs. 3 (11%); P = 0.013), while we still cannot determine the effects of corticosteroids due to the limited sample size. According to the latest rules issued by National Health Commission of China (version 7) (2020) and the interim guidance of WHO (2020), when SARS-CoV2 infection is suspected, corticosteroids should be recommended to use with caution. New Coronavirus Infection Diagnosis and Treatment Scheme (Trial Version) published by Military Support Hubei Medical Team also put forward that for mild to moderate COVID-19 patients, corticosteroids should not be given mainly and high dose corticosteroid pulse therapy was not optional. Only patients presenting ongoing deterioration in oxygenation index, or rapid progression of radiological ﬁndings, or excessive activation of immune responses, will be considered to use short-term corticosteroid therapy within 10 days of illness onset. Seven designated hospitals in Zhejiang Province gave patients corticosteroids when they showed increased resting respiratory rate (> 30 breaths/ minute), drop in oxygen saturation (< 93%) on room air, or multi-lobular progression (> 50%) on imaging within 48h (Xu *et al*., 2020). To prevent severe patients from developing ARDS, timely and appropriate use of corticosteroids combined with ventilator support should be considered (Xu *et al*., 2020).

**Anticoagulant**

In clinical practice, nearly20% ofpatientswithCOVID-19 are found to have abnormal coagulation function, and almost all severely and critically ill patients presented coagulation disorders (Chen *et al*., 2020; Huang *et al*., 2020; Wang *et al*., 2020). In view of no relevant experience for reference, anticoagulation should be given with great caution in patients with DIC though microthrombosis was observed in lung, liver, and other organs by autopsy. When patients exhibit a bleeding tendency or when surgical treatment is needed, platelet transfusion or administration of fresh-frozen plasma is recommended to correct coagulopathies analogs (Nishida *et al*., 2018).

**Oxygen therapy**

For mild to moderate patients with hypoxemia, nasal catheters and masks and even high-ﬂow nasal cannula oxygen therapy (HFNC) are advised. While for severe and critical patients with respiratory distress, HFNC, non-invasive mechanical ventilation(NIV)or invasive mechanical ventilation, and even ECMO should be considered.

**HFNC**

HFNC can provide accurate oxygen concentration and a certain positive airway pressure to promote alveolar expansion to improve oxygenation and respiratory distress (Lee *et al*., 2015). However, according to expert consensus on the use of HFNC for COVID-19, patients with cardiac arrest, weak spontaneous breathing, PaO2/FiO2 < 100 mmHg, PaCO2 > 45 mmHg and pH < 7.25 and upper airway obstruction are contraindicated.

NIV or invasive mechanical ventilation

For severe patients with respiratory distress or hypoxemia that cannot be alleviated after standard oxygen therapy, NIV can also be considered with close surveillance (Guan *et al*., 2020; Wang *et al*., 2020). Dangers *et al.* (2018) considered that changes in dyspnea could be used as a variable to predict the failure of noninvasive ventilation. If the patient continuously deteriorates or the respiratory rate cannot be improved after a short time (about 1–2 h), timely tracheal intubation and invasive ventilation are required (Fan *et al*., 2017). Notably, patients with hemodynamic instability, multiple organ failure or abnormal mental status should not receive noninvasive ventilation. Lung protection ventilation strategies (small tidal volume, limited plateau pressure, and permissive hypercapnia) are suggested to be adopted in invasive mechanical ventilation to reduce ventilator-related lung injury (Fan *et al*., 2018). Compared with NIV, invasive mechanical ventilation can more effectively improve the pulmonary ventilation function and respiratory mechanics of patients with acute respiratory failure. It can effectively increase the SaO2 level and is more conducive to lower the plasma BNP level (Yang and Zhou, 2010). However, invasive mechanical ventilation requires tracheotomy, or oral/nasal tracheal intubation to establish an artiﬁcial airway, which is very likely to cause damage to patients, such as mediastinal emphysema, ventilator related lung injury, and other related complications, such as reduced swallowing function, gastroesophageal reﬂux, infections, etc. What’s more, invasive mechanical ventilation also increases the risk of secondary infections transmitted by aerosol particles (Hui, 2013).

The current pandemic, COVID-19, is going to have a great effect on public health if necessary precautions are not taken. Precautions like provision of protective gear for health personal and professionals and it being disposed immediately after use and properly, extensive measures to reduce person-to-person transmission of COVID-19 are required to control the current outbreak and use of decontaminating agents such as alcohol sanitizers. Special attention and eﬀorts to protect or reduce transmission should be applied in susceptible populations including children, health care providers, and elderly people. Hence, the future of COVID-19 might be bleak if we all do our part by maintaining good hygiene and staying indoors.

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