**A TERM PAPER**

**BY**

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**ON**

**A COMPREHENSIVE REVIEW OF THE AETIOLOGY OF COVID-19, ITS PATHOGENESIS, HISTOPATHOLOGICAL FEATURES, THE CURRENT POTENTIAL THERAPIES TO ADDRESS IT AND THE FUTURE OF COVID-19 ON PUBLIC HEALTH.**

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**INTRODUCTION**

Coronaviruses are a family of viruses that can cause illnesses such as the common cold, severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS). In 2019, a new coronavirus was identified as the cause of a disease outbreak that originated in China.

The virus is now known as the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The disease it causes is called coronavirus disease 2019 (COVID-19). In March 2020, the World Health Organization (WHO) declared the COVID-19 outbreak a pandemic.

Public health groups, including the U.S. Centres for Disease Control and Prevention (CDC) and WHO, are monitoring the pandemic and posting updates on their websites. These groups have also issued recommendations for preventing and treating the illness.

The COVID-19 virus spreads primarily through droplets of saliva or discharge from the nose when an infected person coughs or sneezes, so it’s important that you also practice respiratory etiquette (for example, by coughing into a flexed elbow).

On 31st December 2019, 27 cases of pneumonia of unknown aetiology were identified in Wuhan City, Hubei province in China. Wuhan is the most populous city in central China with a population exceeding 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 (Tang Y. *et al.,* 2020). The causative agent was identified from throat swab samples conducted by the Chinese Centre for Disease Control and Prevention (CCDC) on 7th January 2020 and was subsequently named Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). The disease was named COVID-19 by the World Health Organization (WHO).

The COVID-19 virus affects different people in different ways. COVID-19 is a respiratory disease and most infected people will develop mild to moderate symptoms and recover without requiring special treatment. People who have underlying medical conditions and those over 60 years old have a higher risk of developing severe disease and death.

Signs and symptoms may appear two to fourteen days after exposure and can include;

* Fever
* Cough
* Shortness of breath

Other symptoms can include;

* Tiredness
* Aches
* Runny nose
* Sore throat
* Headache
* Vomiting
* Diarrhea
* Loss of smell or taste
* Nausea

Risk factors for COVID-19 are;

* Recent travel from or residence in an area with ongoing community spread of COVID-19.
* Close contact with someone who has the disease such as when a family member or health care worker takes care of an infected person.

Complications of COVID-19 can include pneumonia in both lungs, organ failure in several organs or in some cases death.

The following precautions are recommended to prevent/avoid COVID-19;

* Avoid large events and mass gatherings.
* Avoid close contact (within about 6 feet, or 2 meters) with anyone who is sick or has symptoms.
* Keep distance between yourself and others if COVID-19 is spreading in your community, especially if you have a higher risk of serious illness.
* Wash your hands often with soap and water for at least 20 seconds or use an alcohol-based hand sanitizer that contains at least 60% alcohol.
* Cover your mouth and nose with your elbow or a tissue when you cough or sneeze. Throw away the used tissue.
* Avoid touching your face.
* Avoid sharing dishes, glasses, bedding and other household items if you're sick.
* Clean and disinfect high touch surfaces daily.
* Stay home from work, school and public areas if you're sick, unless you're going to get medical care. Avoid taking public transportation if you're sick.
* Refrain from smoking and other activities that weaken the lungs.

**AETIOLOGY OF COVID-19**

SARS-CoV-2 is the causative pathogen of COVID-19, identiﬁed as the seventh type of coronavirus to infect humans (Zha N, *et al.,* 2019). Six other kinds of coronaviruses are known to cause human disease, including severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) with high mortality rate (Su S, *et al.,* 2016). According to the genome characteristics, coronavirus is separated into four genera: α-CoV, β-CoV, γ-CoV, and δ-CoV (Su S, *et al.,* 2016). Deep sequencing revealed that this novel coronavirus isolated from lower respiratory tract samples of patient with COVID-19 belongs to β-CoV (Zha N, *et al.,* 2019).

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 (Forni D, *et al.,* 2017). All coronaviruses share the same genome organization and expression pattern, with two large overlapping reading frames (ORF1a/b) which encode 16 non-structural proteins, followed by ORFS for four major structural proteins: spike (S), envelope (E), membrane (M), and nucleocapsid (N) (Forni D, *et al.,* 2017). The SARS-CoV-2 protein also contains eight accessory proteins (Wu A, *et al.,* 2020).

Coronaviruses are enveloped single-stranded RNA viruses that are zoonotic in nature and cause symptoms ranging from those similar to the common cold to more severe respiratory, enteric, hepatic, and neurological symptoms (Zhu N, *et al.,* 2019).

Other than SARS-CoV-2, there are six known coronaviruses in humans: HCoV-229E, HCoV-OC43, SARS-CoV, HCoVNL63, HCoV-HKU1, and MERS-CoV (Li Q, *et al.,* 2020). Coronavirus has caused two large-scale pandemics in the last two decades: SARS and MERS (Zhou P, *et al.,* 2020).

The binding of a receptor expressed by host cells is the first step of viral infection followed by fusion with the cell membrane. It is reasoned that the lung epithelial cells are the primary target of the virus. Thus, it has been reported that human-to-human transmissions of SARS-CoV occurs by the binding between the receptor-binding domain of virus spikes and the cellular receptor which has been identified as angiotensin-converting enzyme 2 (ACE2) receptor. Importantly, the sequence of the receptor-binding domain of COVID-19 spikes is similar to that of SARS-CoV. This data strongly suggests that entry into the host cell is most likely via the ACE2 receptor (Wan Y, *et al.,* 2020).

World Health Organisation (WHO) has classified COVID-19 as a β CoV of group 2B. Ten genome sequences of COVID-19 obtained from a total of nine patients exhibited 99.98% sequence identity. Another study showed there was 99.8–99.9% nucleotide identity in isolates from five patients and the sequence results revealed the presence of a new beta-CoV strain (Ren L, *et al.,* 2020). The genetic sequence of the COVID19 showed more than 80% identity to SARS-CoV and 50% to the MERSCoV, and both SARS-CoV and MERS-CoV originate in bats (Cui J, *et al.,* 2019).

Thus, the evidence from the phylogenetic analysis indicates that the COVID-19 belongs to the genus beta-coronavirus, which includes SARSCoV, that infects humans, bats, and wild animals (Zhu N, *et al.,* 2019).

COVID-19 represents the seventh member of the coronavirus family that infects humans and has been classified under the *Orthocoronavirinae* subfamily. The COVID-19 forms a clade within the subgenus sarbecovirus. Based on the genetic sequence identity and the phylogenetic reports, COVID-19 is sufficiently different from SARS-CoV and it can thus be considered as a new beta coronavirus that infects humans (Zhu N, *et al.,* 2019).

The COVID-19 most likely developed from bat origin coronaviruses. Another piece of evidence that supports the COVID-19 is of bat origin is the existence of a high degree of homology of the ACE2 receptor from a diversity of animal species, thus implicating these animal species as possible intermediate hosts or animal models for COVID-19 infections (Wan Y, *et al.,* 2020).

Moreover, these viruses have a single intact open reading frame on gene 8, which is a further indicator of bat-origin CoVs. However, the amino acid sequence of the tentative receptor-binding domain resembles that of SARS-CoV, indicating that these viruses might use the

same receptor (Ren L, *et al.,* 2020).

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.

Common human CoVs: HCoV-OC43, and HCoV-HKU1 (beta-CoVs of the A lineage); HCoV-229E, and HCoV-NL63 (alpha-CoVs). 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 (beta-CoVs 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 beta-CoVs 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. 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.

To detect the infection source of COVID-19, China CDC researchers collected 585 environmental samples from the Huanan Seafood Market in Wuhan, Hubei Province, China on 1 January and 12 January 2020. They detected 33 samples containing SARS-CoV-2 and indicated that it originated from wild animals sold in the market. Then, researchers used the lung fluid, blood, and throat swab samples of 15 patients to conduct laboratory tests. These laboratory tests found that the virus-specific nucleic acid sequences in the sample are different from those of known human coronavirus species. Laboratory results also indicated that SARSCoV-2 is similar to some of the beta (β) coronaviruses genera identified in bats, which is situated in a group of SARS/SARS-like CoV.

**PATHOGENESIS OF COVID-19**

The severe symptoms of COVID-19 are associated with an increasing numbers and rate of fatalities specially in the epidemic region of China. On January 22, 2020, the China National Health Commission reported the details of the first 17 deaths and on January 25, 2020 the death cases increased to 56 deaths (Wang W. *et al.,* 2020). The percentage of death among the reported 2684 cases of COVID-19 was approximately 2.84% as of Jan 25, 2020 and the median age of the deaths was 75 (range 48–89) years (Wang W. *et al.,* 2020). Patients infected with COVID-19 showed higher leukocyte numbers, abnormal respiratory findings, and increased levels of plasma pro-inflammatory cytokines.

One of the COVID-19 case reports showed a patient at 5 days of fever presented with a cough, coarse breathing sounds of both lungs, and a body temperature of 39.0 °C. The patient's sputum showed positive real-time polymerase chain reaction results that confirmed COVID-19 infection (Lei J, *et al.,* 2020). The laboratory studies showed leukopenia with leukocyte counts of 2.91 × 10^9 cells/L of which 70.0% were neutrophils. Additionally, a value of 16.16 mg/L of blood C-reactive protein was noted which is above the normal range (0–10 mg/L). High erythrocyte sedimentation rate and D-dimer were also observed (Lei J, *et al.,* 2020). The main pathogenesis of COVID-19 infection as a respiratory system targeting virus was severe pneumonia, RNAaemia, combined with the incidence of ground-glass opacities, and acute cardiac injury (Huang C. *et al.,* 2020). Significantly high blood levels of cytokines and chemokines were noted in patients with COVID-19 infection that included IL1-β, IL1RA, IL7, IL8, IL9, IL10, basic FGF2, GCSF, GMCSF, IFNγ, IP10, MCP1, MIP1α, MIP1β, PDGFB, TNFα, and VEGFA. Some of the severe cases that were admitted to the intensive care unit showed high levels

of pro-inflammatory cytokines including IL2, IL7, IL10, GCSF, IP10, MCP1, MIP1α, and TNFα that are reasoned to promote disease severity (Huang C. *et al.,* 2020).

CoVs are enveloped, positive-stranded RNA viruses with nucleocapsid. Pathophysiology and virulence mechanisms of CoVs, and therefore also of SARS-CoV-2 have links to the function of the non-structural proteins (nsps) and structural proteins. Among functions of structural proteins, the envelope has a crucial role in virus pathogenicity as it promotes viral assembly and release.

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 W, *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.

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 labelled 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 (Song W, *et al.,* 2018).

**HISTOPATHOLOGICAL FEATURES OF COVID-19**

Pulmonary changes are the most outstanding, even though non-specific. Findings of diffuse alveolar damage corresponding to the phase of disease;

* Exudative phase; hyaline membrane formation, desquamation of pneumocytes, cellular or proteinaceous exudates, alveolar haemorrhage, fibrinoid necrosis of small vessels
* Organizing phase; interstitial and intra-alveolar proliferation of fibroblasts, lymphocytic infiltration, type II pneumocyte hyperplasia, fibrin deposition.
* Findings representing the fibrotic phase (e.g. dense collagen fibrosis, architectural remodelling) are not reported so far.

Viral infection changes are as follows;

* Multinucleated enlarged pneumocytes with large nuclei, amphophilic cytoplasm and prominent nucleoli in alveolar spaces
* Intranuclear inclusions

Extrapulmonary changes; various levels of cell injury and microvascular disorders in parenchymal organs

Pathological findings are primarily based on minimally invasive autopsies

The pathophysiological features of COVID-19 greatly resembles those seen in SARS and Middle Eastern respiratory syndrome (MERS) coronavirus infection (Ding Y, *et al.,* 2003)

**CURRENT POTENTIAL THERAPIES TO ADDRESS COVID-19**

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 COVID-19 infection for potential therapy of humans. The best prevention is to avoid being exposed to the virus. The treatment is symptomatic, and oxygen therapy represents the major treatment intervention for patients with severe infection. Mechanical ventilation may be necessary in cases of respiratory failure refractory to oxygen therapy, whereas hemodynamic support is essential for managing septic shock.

Another option available is using broad-spectrum antiviral drugs like Nucleoside analogues and also HIV-protease inhibitors that could attenuate virus infection until the specific antiviral becomes available.

Another report showed that the broad-spectrum antiviral remdesivir and chloroquine are highly effective in the control of 2019-nCoV 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.

On January 28, 2020, the WHO released a document summarizing WHO guidelines and scientific evidence derived from the treatment of previous epidemics from HCoVs. This document addresses measures for recognizing and sorting patients with severe acute respiratory disease; strategies for infection prevention and control; early supportive therapy and monitoring; a guideline for laboratory diagnosis; management of respiratory failure and ARDS; management of septic shock; prevention of complications; treatments; and considerations for pregnant patients.

Below are the strategies recommended for addressing respiratory failure, which includes protective mechanical ventilation and high-flow nasal oxygen (HFNO) or non-invasive ventilation (NIV).

**Intubation and protective mechanical ventilation**

Special precautions are necessary during intubation. The procedure should be executed by an expert operator who uses personal protective equipment (PPE) such as FFP3 or N95 mask, protective goggles, disposable gown long sleeve raincoat, disposable double socks, and gloves. If possible, rapid sequence intubation (RSI) should be performed. Preoxygenation (100% O2 for 5 minutes) should be performed through the continuous positive airway pressure (CPAP) method. Heat and moisture exchanger (HME) must be positioned between the mask and the circuit of the fan or between the mask and the ventilation balloon.

Mechanical ventilation should be with lower tidal volumes (4 to 6 ml/kg predicted body weight, PBW) and lower inspiratory pressures, reaching a plateau pressure (Pplat) < 28 to 30 cm H2O. PEEP must be as high as possible to maintain the driving pressure (Pplat-PEEP) as low as possible (< 14 cmH2O). Moreover, disconnections from the ventilator must be avoided for preventing loss of PEEP and atelectasis. Finally, the use of paralytics is not recommended unless PaO2/FiO2 < 150 mmHg. The prone ventilation for > 12 hours per day, and the use of a conservative fluid management strategy for ARDS patients without tissue hypoperfusion (strong recommendation) are emphasized.

**Non-invasive ventilation**

Concerning HFNO or non-invasive ventilation (NIV), the experts' panel, points out that these approaches performed by systems with good interface fitting do not create widespread dispersion of exhaled air, and their use can be considered at low risk of airborne transmission (Hui DS, *et al.,* 2019). Practically, non-invasive techniques can be used in non-severe forms of respiratory failure. However, if the scenario does not improve or even worsen within a short period of time (1–2 hours) the mechanical ventilation must be preferred.

Furthermore, there are a number of other compounds that are in development. 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. 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 COVID-19 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.

**Continuous renal replacement therapy (CRRT)**

For critical patients, CRRT can support organ function, reduce cytokine storms and maintain internal environment stability. Three clinical studies showed that the incidence of AKI in patients with COVID-19 was 3% to 7%, and 7% to 9.0% were treated with CRRT. In ICU, the rate of CRRT application was 5.6% to 23.0% and reached as high as 66.7% to 100% in patients with AKI (Chen N., *et al.,* 2020). CRRT is recommended for patients who exhibit AKI indications (hyperkalaemia, acidosis, pulmonary oedema, severe sodium ion disorders) or patients with CKD who have not undergone haemodialysis.

 During septic shock, CRRT can effectively remove inﬂammatory mediators and signiﬁcantly improve hemodynamic. When ARDS appears in combination with multiple organ dysfunction syndrome (MODS), early CRRT is recommended (Trager K., *et al.,* 2016). CRRT combined with the treatment of ECMO may remove cytokines, reduce the activity of macrophages and monocytes, and better preserve lung parenchyma.

**Anticoagulant**

In clinical practice, nearly 20% of patients with COVID-19 are found to have abnormal coagulation function, and almost all severely and critically ill patients presented coagulation disorders (Wang D., *et al.,* 2020). In view of no relevant experience for reference, anticoagulation should be given with great caution in patients with DIC though micro-thrombosis 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 analogues.

**FUTURE OF COVID-19 ON PUBLIC HEALTH**

Extensive measures to reduce person-to-person transmission of COVID-19 are required to control the current outbreak. Special attention and efforts to protect or reduce transmission should be applied in susceptible populations including children, health care providers, and elderly people. A guideline was published for the medical staff, healthcare providers, and, public health individuals and researchers who are interested in the 2019-nCoV. The early death cases of COVID-19 outbreak occurred primarily in elderly people, possibly due to a weak immune system that permits faster progression of viral infection (Li Q., *et al.,* 2020).

The public services and facilities should provide decontaminating reagents for cleaning hands on a routine basis. Physical contact with wet and contaminated objects should be considered in dealing with the virus, especially agents such as faecal and urine samples that can potentially serve as an alternative route of transmission.

China and other countries including the US have implemented major prevention and control measures including travel screenings to control further spread of the virus. Epidemiological changes in COVID-19 infection should be monitored considering potential routes of transmission and subclinical infections, in addition to the adaptation, evolution, and virus spread among humans and possible intermediate animals and reservoirs.

There remains a considerable number of questions that need to be addressed. These include, but are not limited to, details about who and how many have been tested, what proportion of these turned positive and whether this rate remains constant or variable. Very few paediatric cases have so far been reported; is this due to lack of testing or a true lack of infection/susceptibility? Of the ones that have so far been tested, how many have developed severe disease and how many were tested positive but showed no clinical sign of disease? There are some basic questions that would provide a framework for which more specific and detailed public health measures can be implemented.

**CONCLUSION**

The recent COVID-19 outbreak has been deemed a global health emergency. In this review, we gave an overview of the history, aetiology, pathogenesis, histopathological features of COVID-19 and discussed the latest advancements in the treatment and therapies to address it. We also addressed the possible future of the disease. This novel virus spreads mainly through respiratory droplets and close personal contact. A series of complications tend to develop during disease progression, especially in critically ill patients. Apart from supportive care, no speciﬁc treatment has been established for COVID-19. The efﬁcacy of some promising antivirals, anticoagulants, non-invasive methods and CRRT needs to be further validated by ongoing clinical trials.

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