**A REVIEW OF THE AETIOLOGY OF COVID-19, PATHOGENESIS, HISTOPATHOLOGICAL FEATURES AND POTENTIAL THERAPIES & TREATMENT**

**BY**

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The pneumonia caused by novel corona virus (SARS-CoV-2) in Wuhan, China in December

2019 is a highly contagious disease. The World Health Organization (WHO) has declared the

Ongoing outbreak as a global public health emergency. Currently, the research on novel corona virus is still in the primary stage.

In late December 2019, a case of unidentified pneumonia was reported in Wuhan, Hubei Province, People's Republic of China (PRC). Its clinical characteristics are very similar to those of viral pneumonia. After analysis on respiratory samples, PRC Centers for Disease Control (CDC) experts declared that the pneumonia, later known as novel corona virus pneumonia (NCP), was caused by novel corona virus (Huang C .,*et al* 2019). WHO officially named the disease COVID-19.

International Committee on Taxonomy of Viruses (ICTV) named the virus severe acute respiratory syndrome corona virus 2 (SARS-CoV-2). This virus belongs to β – corona virus, a large class of viruses prevalent in nature. Similar to other viruses, SARS-CoV-2 has many potential natural hosts, intermediate hosts and final hosts. This poses great challenges to prevention and treatment of virus infection. Compared with SARS and MERS, this virus has high transmissibility and infectivity, despite of low mortality rate (Liu Y., *et al* 2020)

Genome analysis of novel corona virus sequences revealed that the complete genome sequence recognition rates of SARS-CoV and bat SARS corona virus (SARSr-CoV-RaTG13) were 79.5% and 96% respectively (Organization WH 2019). It implies that the corona virus might originate from bat.

**Genetic structure**

Corona virus (COV) is a single strand RNA virus with a diameter of 80-120nm. It is divided

into four types: α-corona virus (α-COV), β-corona virus (β-COV), δ-corona virus (δ-COV) and

γ - corona virus (γ-COV) (Zhu N., *et al* 2013). Six corona viruses were previously known to cause disease in humans, SARS-CoV-2 is the seventh member of the corona virus family that infects human beings after SARS-CoV and MERS-CoV (Zhu N., *et al* 2019). SARS-CoV-2, like SARS-CoV and MERS-CoV, belongs to β-corona virus. The genome sequence homology of SARS-CoV-2 and SARS is about 79%, the 2019-nCoV is closer to the SARS-like bat CoVs (MG772933) than the SARS-CoV (Wu A., *et al* 2020), which is descended from SARS-like bat CoVs Interestingly, for high similarity of receptor-binding domain (RBD) in Spike-protein, several analyses reveal that SARS-CoV-2 uses angiotensin-converting enzyme 2 (ACE2) as receptor, just like as SARS-CoV (Hoffmann M., *et al* 2019). Corona virus mainly recognizes the corresponding receptor on the target cell through the S protein on its surface and enters into the cell, then causing the occurrence of infection. A structure model analysis shows that SARS-CoV-2 binds ACE2 with above 10 folds higher affinity than SARS-CoV, but higher than the threshold required for virus infection (Wrapp D., *et al* 2019).

**Most susceptible**

Elderly male citizens are more susceptible to this coronavirus as compared with other groups, and this virus is more likely to affect elderly male citizens with chronic underlying diseases (diabetes, hypertension, heart disease, etc.) (Chen N., *et al* 2020).

**Transmission of SARS-CoV-2**

Previous epidemiological studies have proved that there are three conditions for wide spread of virus, i.e. the source of infection, route of transmission, and susceptibility (Barreto ML., *et al* 2006). There is no exception for SARS-CoV-2.

Bats are considered to be the natural hosts of SARS-CoV-2, while pangolins and snakes are thought to be the intermediate hosts. Studies of Institute Pasteur of Shanghai showed that bats might be the natural hosts of SARS-CoV-2.

Study from wuhan institute of virology showed that the similarity of gene sequence between SARS-CoV-2 and bat corona virus is as high as 96.2% by sequencing technology (Zhou P., *et al* 2020) This also implied that bats are the possible source of SARS-CoV-2.

(Xu X., *et al* 2020) showed that the similarity of SARS-CoV-2 isolated from pangolin and the virus strains currently infecting humans is as high as 99% using macrogenomic sequencing, molecular biological detection and electron microscopic analysis. The team also observed the typical novel coronavirus granules and revealed that pangolin is the potential intermediate host of the SARS-CoV-2.

Transmission and close contact are the most common ways of transmission for SARS-CoV-2.

Aerosol transmission might also be a way of transmission. In addition, researchers also detected SARS-CoV-2 in the samples of stool, gastrointestinal tract, saliva and urine.

Based on bioinformatics evidence indicated that digestive tract might be a potential route of SARS-CoV-2 infection (Wang J., *et al* 2020). Consistently, SARS-CoV-2 RNA was also detected in gastrointestinal tissues from COVID-19 patients (Xiao F., *et al* 2020).

**Viral latency**

Zhong. *et al.* found that, based on clinical features of 1,099 COVID-19 patients, the median incubation period was 3.0 days (range, 0 to 24.0), the median time from the first symptom to death was 14 days (Guan W., *et al*) (Wang W., *et al* 2019). For SARS, the median latency of SARS is 4 days, the average duration of first symptoms to hospital admission was 3.8 days, and admission to death was 17.4 days for casualties (Lessler J., *et al* 2009), and the median latency of MERS is 7 days (Cho SY., *et al* 2016). From the median incubation period, COVID-19 is shorter than SARS and MERS. However, the maximum latency of SARS-CoV-2 currently observed is as high as 24 days, which may increase the risk of virus transmission. Moreover, it also found that people 70 years or older had shorter median days (11.5 days) from the first symptom to death than those with ages below 70 years (20 days), demonstrating that elderly people have faster disease progression than younger people (Wang W., *et al* 2019).

**Clinical characteristics of SARS-CoV-2 infection**

COVID-19 produces an acute viral infection in humans with median incubation period was 3.0 days (Guan W., *et al*), which is similar to the SRAS with an incubation period ranging from 2–10 days (Chan PK., *et al* 1979).The presenting features of COVID-19 infection in adults are pronounced. The presenting features in adults are pronounced. The most common clinical symptoms of SARS-CoV-2 infection were fever (87.9%), cough (67.7%), fatigue (38.1%), whereas diarrhea (3.7%) and vomiting (5.0%) were rare (Guan W., *et al*) (Yang Y., *et al* 2019), which were similar to others corona virus.

Most patients had some degree of dyspnoea at presentation, because the time from onset of symptoms to the development of acute respiratory distress syndrome (ARDS) was only 9 days among the initial patients with COVID-19 infection (Huang C .,*et al* 2019). Moreover, severe patients are prone to a variety of complications, including acute respiratory distress syndrome, acute heart injury and secondary infection (Chen N., *et al* 2019). There are already some evidences that COVID-19 can cause damage to tissues and organs other than the lung. In a study of 214 COVID-19 patients, 78 (36.4%) patients had neurological manifestations (Mao L., *et al* 2020). In addition, there is already evidence of ocular surface infection in patients with COVID-19, and SARS-CoV-2 RNA was detected in eye secretions of patient (Ai T., *et al* 2019). Some COVID-19 patients have arrhythmia, acute heart injury, impaired renal function, and abnormal liver function (50.7%) at admission (Li Z., *et al* 2020) (Wang D., *et al* 2020). A case report of the pathological manifestations of a patient with pneumonia showed moderate micro vesicular steatosis in his liver tissue (Xu Z., *et al* 2020). Besides, tissue samples of stomach, duodenum, and rectal mucosa were confirmed positive for SARS-CoV-2 RNA (Xiao F., *et al* 2020).

In general, the radio graphical features of coronavirus are similar to those found in community-acquired pneumonia caused by other organisms (Wong KT., *et al* 2003). Chest CT scan is important tool to diagnose this pneumonia. Nevertheless, several typical imaging features are frequently observed in COVID-19 pneumonia, including the predominant groundglass opacity (65%), consolidations (50%), smooth or irregular interlobular septal thickening (35%), air bronchogram (47%), and thickening of the adjacent pleura (32%), with predominantly peripheral and lower lobe involvement (Shi H., *et al* 2020). A recent study reported that most patients (90%) had bilateral chest CT findings and the sensitivity of chest CT to suggest COVID-19 was 97% (Ai T., *et al* 2019). Combining chest CT imaging features with clinical symptom and laboratory test could facilitate early diagnosis of COVID-19 pneumonia. Laboratory examination revealed that 82.1% of patients was lymphopenia and 36.2% of patients was hrombocytopenia. Most patients had normal leukocytes, but leukopenia was observed in 33.7% of patients. In addition, most patients demonstrated elevated levels of C-reactive protein, lactate dehydrogenase and creatinine kinase, but minority of patients had elevated transaminase, abnormal myocardial enzyme spectrum, or elevated serum creatinine (Guan W-j., *et al* 2020). As compared with bacterial pneumonia, patients withSARS-CoV-2 showed lower oxygenation index. Cytokine release syndrome is a vital factor that aggravates disease progression. A higher levels of IL-6 and IL-10, and lower levels of CD4+T and CD8+T are observed in COVID-19 patients parallel with the severity of the disease (Wan S., *et al* 2020).

**Diagnosis of SARS-CoV-2**

The detection of viral nucleic acid is the standard for noninvasive diagnosis of COVID-19.

However, the present detection of SARS-CoV-2 nucleic acid was high in specificity and low

in sensitivity, so that there might be false negatives and the testing time could be relatively

long. The Novel Coronavirus Pneumonia Diagnosis and Treatment Plan (5th trial version) took

“suspected cases with pneumonia imaging features” as the clinical diagnostic criteria in Hubei Province (PRC NHC 2020). But the sixth edition of diagnostic criteria eliminates the distinction between Hubei and other provinces outside Hubei (PRC NHC 2020). One reason might be to distinguish the flu from the COVID-19.

A research group of Peking University claimed to have developed a new method for rapid construction of transcriptome sequencing library of SHERRY, which is helpful for rapid sequencing of SARS-CoV-2 (Feng Zhang OOA., *et al* 2020).

**Treatment of SARS-CoV-2**

**Antiviral western medicine treatment**

At present, the treatments of patients with SARS-CoV-2 infection are mainly symptomatic treatments. Remdesivir was recently reported as a promising antiviral drug against a wide array of RNA viruses. Holshue *et al*. for the first time reported that treatment of a patient with COVID-19 used remdesivir and achieved good results [(Holshue ML., *et al* 2020)]. Then, Xiao *et al.* findings reveal that remdesivir effectively in the control of 2019-nCoV infection in vitro. Meanwhile, also found that chloroquine has an immune-modulating activity and could effectively inhibit in this virus in vitro [Wang M., *et al* 2020]. Clinical controlled trials have shown that Chloroquine was proved to be effective in the treatment of patients with COVID-19 [Gao J., *et al* 2020]. Remdesivir is undergoing a large number of clinical trials in several hospitals, and the final efficacy of the drug is uncertain. Arbidol, a small indole derivative molecule, was found to block viral fusion against influenza A and B viruses and hepatitis C viruses (Boriskin YS., *et al* 2008) and confirmed to have antiviral effect on SARS-CoV in cell experiment (Khamitov RA., *et al* 2008), so that it might be a choice for COVID-19 treatment.

The randomized controlled study on treatment of novel coronavirus by Arbidol and Kaletra undertaken at present showed that Arbidol had better therapeutic effect than Kaletra did and could significantly reduce the incidence of severe cases.

Apart from the above, lopinavir/ritonavir, nucleoside analogues, neuraminidase inhibitors, remdesivir, and peptide EK1 could also be the choices of antiviral drugs for COVID-19 treatment (Lu H 2020).

**Chinese medicine treatment**

Chinese medicine also played an important role in the treatment of SARS-CoV-2 infection.

Local governments and medical institutions published a number of traditional Chinese medicine prescriptions. The Novel Corona virus Pneumonia Diagnosis and Treatment Plan (6th trial version) suggested to use clearing lung and detoxification decoction in the clinical treatment [PRC NHC 2020]. A joint study made by Shanghai Institute of Materia Medica and Wuhan Institute of Virology. CAS found that Shuanghuanglian oral liquid could inhibit SARS-CoV-2.

Previous studies have proved that baicalin, chlorogenic acid and forsythin in Shuanghuanglian oral liquid have certain inhibitory effects on a variety of viruses and bacteria (Li W., *et al* 2002, Lu HT., *et al* 2000]. The mechanism might be that these components played a therapeutic role by effectively reducing the inflammatory response of the body caused by viruses and bacteria (Chen X., *et al* 2002)]. Lianhuaqingwen capsule has been proven to have a wide-spectrum effect on a series of influenza viruses, including H7N9, and could regulate the immune response of the virus, reducing the level of inflammatory factors in the early stage of infection (Ding ., *et al* 2017).

**Immunoenhancement therapy**

Synthetic recombinant interferon α has proven to be effective in treatment of SARS patients

in clinic trials (Loutfy MR., *et al* 2003). Pulmonary X-ray abnormal remission time was reduced by 50% in the interferon-treated group compared with the glucocorticoid-treated group alone. Interferon was also found to be an effective inhibitor of MERS-CoV replication (Mustafa S., *et al* 2018). Those findings suggested that interferon could be used in the treatment of COVID-19. Intravenous immunoglobulin might be the safest immunomodulator for long-term use in all ages, and could help to inhibit the production of pro inflammatory cytokines and increase the production of anti-inflammatory mediators (Gilardin L., *et al* 2015). Moreover, Thymosin alpha-1 (Ta1) can be an immune booster for SARS patients, effectively controlling the spread of disease (Kumar V., *et al* 2013). Intravenous immunoglobulin and Ta1 may also be considered as therapeutics for COVID-19.

**Convalescent plasma therapy**

When there are no sufficient vaccines and specific drugs, convalescent plasma therapy could

be an effective way to alleviate the course of disease for severely infected patients (Mair-Jenkins J., *et al* 2015). In a retrospective analysis, convalescent plasma therapy is more effective than severe doses of hormonal shock in patients with severe SARS, reducing mortality and shortening hospital stays (Soo YO., *et al* 2004). A prospective cohort study by Hung and colleagues showed that for patients with pandemic H1N1 influenza virus infection in 2009, the relative risk of death was significantly lower in patients treated with convalescent plasma (Hung IF., *et al* 2004). Moreover, from the perspective of immunology, most of the patients recovered from COVID-19 would produce specific antibodies against the SARS-CoV-2, and their serum could be used to prevent re-infection. At the same time, antibodies can limit the virus reproduction in the acute phase of infection and help clear the virus, which is conducive to the rapid recovery of the disease (GR K. 1996). Theoretically, viremia peaks during the first week of most viral infections, and it should be more effective to give recovery plasma early in the disease (Cheng Y., *et al* 2005). Therefore, the plasma of some patients recovered from COVID-19 could be collected to prepare plasma globulin specific to SARS-CoV-2.

**Auxiliary blood purification treatment**

At present, extracorporeal blood purification technology in the treatment of severe NCP patients (PRC NHC 2020). According to the latest studies (Li Z., *et al* 2020), ACE2, the key receptor of SARS-CoV-2, is highly expressed in human kidney (nearly 100 times higher than that in lung). Kidney might be main target of attack for novel corona virus. Early continuous blood purification treatment could reduce renal workload and help to promote the recovery of renal function (Zarbock A., *et al* 2016). Most of the severe patients with novel corona virus might suffer from cytokine storm. The imbalance of pro-inflammatory factors and anti-inflammatory factors might cause immune damage.

Therefore, blood purification technology could be used to remove inflammatory factors, eliminate cytokine storm, correct electrolyte imbalance, and maintain acid-base balance, to control patient’s capacity load in an effective manner (Lim CC., *et al* 2015). In this logic, the patient's symptoms could be improved and the blood oxygen saturation could be increased.

In summary, the drug treatment for COVID-19 mainly comprised four ways, i.e., antiviral Western medicine, Chinese medicine, immunoenhancement therapy, and viral specific plasma globulin. Machines could be used as auxiliary therapy. However, randomized double-blind large sample clinical trial should be served as the standard to determine whether the antiviral drugs could be used in clinical practice.

**Prevention of SARS-CoV-2**

So far, there are no specific antiviral treatments or vaccines for SARS-CoV-2. And the clinical treatment of COVID-19 has been limited to support and palliative care until now. Therefore, it is urgent to develop a safe and stable COVID-19 vaccine. Dr. Tedros, director-general of WHO, said that novel coronavirus vaccine was expected to be ready in 18 months. In addition, SARS-CoV-2 is an RNA virus. RNA virus related vaccines, including measles, polio, encephalitis B virus and influenza virus, could be the most promising alternatives. And interpersonal transmission of the virus could be prevented by immunizing health care workers and non-infected population (Zhang L., *et al* 2020).

Prevention of infectious diseases by traditional Chinese medicine has been recorded for a long time in Chinese history, and there have been previous studies on the prevention of SARS by traditional Chinese medicine (Lau JT., *et al* 2005). The present principles on prevention of COVID-19 are to tonify body energy to protect outside body, dispel wind, dissipate heat, and dissipate dampness with aromatic agent. The six most commonly used Chinese herbal medicines are astragalus, liquorice, fangfeng, baizhu and honeysuckle. However, the decoction is not suitable for long-term use, and the best period is one week only (Luo H., *et al* 2020). Studies have shown that vitamin C may prevent the susceptibility of lower respiratory tract infection under certain conditions (Hemila H 1997), while COVID-19 may cause lower respiratory tract infection. Therefore, a moderate amount of vitamin C supplementation may be a way to prevent COVID-19. In addition, the decrease in vitamin D and vitamin E levels in cattle could lead to the infection of bovine coronavirus (Nonnecke BJ., *et al* 2014). This suggests that proper supplementation of vitamin D and vitamin E may enhance our resistance to SARS-CoV-2. Patients with primary basic diseases, especially those with chronic diseases such as hypertension, diabetes, coronary heart disease and tumor, are more susceptible to SARS-CoV-2 and their risk of poor prognosis will increase significantly after infection, because they have low systemic immunity as a result of the disease itself and treatments (Liang W., *et al* 2020). Therefore, it is particularly important to enhance self-resistance. The main way to boost personal immunity is to maintain personal hygiene, a healthy lifestyle and adequate nutritional intake (High KP 2001, Simpson RJ., *et al* 2015). For individuals, taking protective measures can effectively prevent SARS-CoV-2 infection, including improving personal hygiene, wearing medical masks, adequate rest and good ventilation (Guan W-j., *et al* 2020).

**Physiotherapy management principles – respiratory care**

Examples of physiotherapy-led respiratory interventions (or chest physiotherapy) are provided below.

Airway clearance techniques

Airway clearance techniques include positioning, active cycle of breathing, manual and/or ventilator hyperinflation, percussion and vibrations, positive expiratory pressure therapy (PEP) and mechanical insufflation-exsufflation.

Non-invasive ventilation and inspiratory positive pressure breathing

Physiotherapists may use inspiratory positive pressure breathing (eg, for patients with rib fractures). Non-invasive ventilation may be applied as part of airway clearance strategies in the management of respiratory failure or during exercise.

Techniques to facilitate secretion clearance

Techniques to facilitate secretion clearance include assisted or stimulated cough manoeuvres and airway suctioning.

Physiotherapists prescribe exercise and assist patients to mobilize. Physiotherapists also play an integral role in the management of patients with a tracheostomy.

COVID-19 poses significant considerations for respiratory physiotherapy interventions due to their aerosol-generating procedures.

Many respiratory physiotherapy interventions are potentially aerosol-generating procedures. While there are insufficient investigations confirming the aerosol generating

potential of various physiotherapy interventions, the combination with cough for airway clearance makes all techniques potentially aerosol-generating procedures.

These include:

* Cough-generating procedures (e.g., cough during treatment or huff) Positioning or gravity assisted drainage techniques and manual techniques (e.g., expiratory vibrations, percussion and manual assisted cough) that may trigger a cough and sputum expectoration.
* Use of positive pressure breathing devices (eg, inspiratory positive pressure breathing), mechanical insufflation-exsufflation devices, intra/extra pulmonary high-frequency oscillation devices (eg, The Vest, MetaNeb, Percussionaire)
* PEP and oscillating PEP devices
* Bubble PEP
* Nasopharyngeal or oropharyngeal suctioning
* Manual hyperinflation
* Open suction
* Saline instillation via an open-circuit endotracheal tube
* Inspiratory muscle training, particularly if used with patients who are ventilated and disconnection from a breathing circuit is required
* Sputum inductions any mobilization or therapy that may result in coughing and expectoration of mucus.

Physiotherapists are responsible for providing musculoskeletal, neurological and cardiopulmonary rehabilitation tasks, as outlined below.

Range of motion exercises

Passive, active-assisted, active or resisted joint range of motion exercises may be performed to maintain or improve joint integrity, range of motion and muscle strength.

Mobilization and rehabilitation

Examples of mobilization and rehabilitation include bed mobility, sitting out of bed, sitting balance, sit to stand, walking, tilt table, standing hoists, upper/lower limb ergometry and exercise programs.

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