**NAME: JONATHAN WISDOM OVUNDAH**

**MATRIC NUMBER: 16/MHS03/016**

**COURSE CODE: ANA 404**

**COURSE TITLE: INTRODUCTION TO HISTOPATHOLOGY**

**LECTURER: MR. EDEM, Edem Ekpenyong**

**ASSIGNMENT**

Write a comprehensive review of the aetiology of COVID-19, its pathogenesis, histopathological features and the current potential therapies to address it. Also, comment on the future of COVID-19 on public health.

VIROLOGY

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a previously unknown betacoronavirus that was discovered in bronchoalveolar lavage samples taken from clusters of patients who presented with pneumonia of unknown cause in Wuhan City, Hubei Province, China, in December 2019 (Ren *et al*., 2020) Coronaviruses are a large family of enveloped RNA viruses, some of which cause illness in people (e.g., common cold, severe acute respiratory syndrome [SARS], Middle East respiratory syndrome [MERS]), and others that circulate among mammals and birds. Rarely, animal coronaviruses can spread to humans and subsequently spread between people, as was the case with SARS and MERS.

SARS-CoV-2 belongs to the *Sarbecovirus* subgenus of the *Coronaviridae* family, and is the seventh coronavirus known to infect humans. The virus has been found to be similar to SARS-like coronaviruses from bats, but it is distinct from SARS-CoV and MERS-CoV (Zhu *et al.,* 2020; Lu *et al.,* 2020) The full genome has been determined and published in GenBank.

A preliminary study suggests that there are two major types (or strains) of the SARS-CoV-2 virus in China, designated L and S. The L type was found to be more prevalent during the early stages of the outbreak in Wuhan City and may be more aggressive (although this is speculative), but its frequency decreased after early January. The relevance of this finding is unknown at this stage and further research is required (Tang *et al.,* 2020)

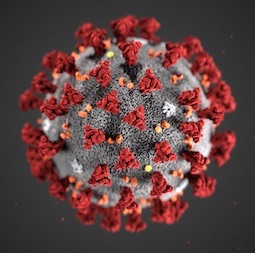


Illustration revealing ultra-structural morphology exhibited by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) when viewed with electron microscopically *Centers for Disease Control and Prevention*

ORIGIN OF VIRUS

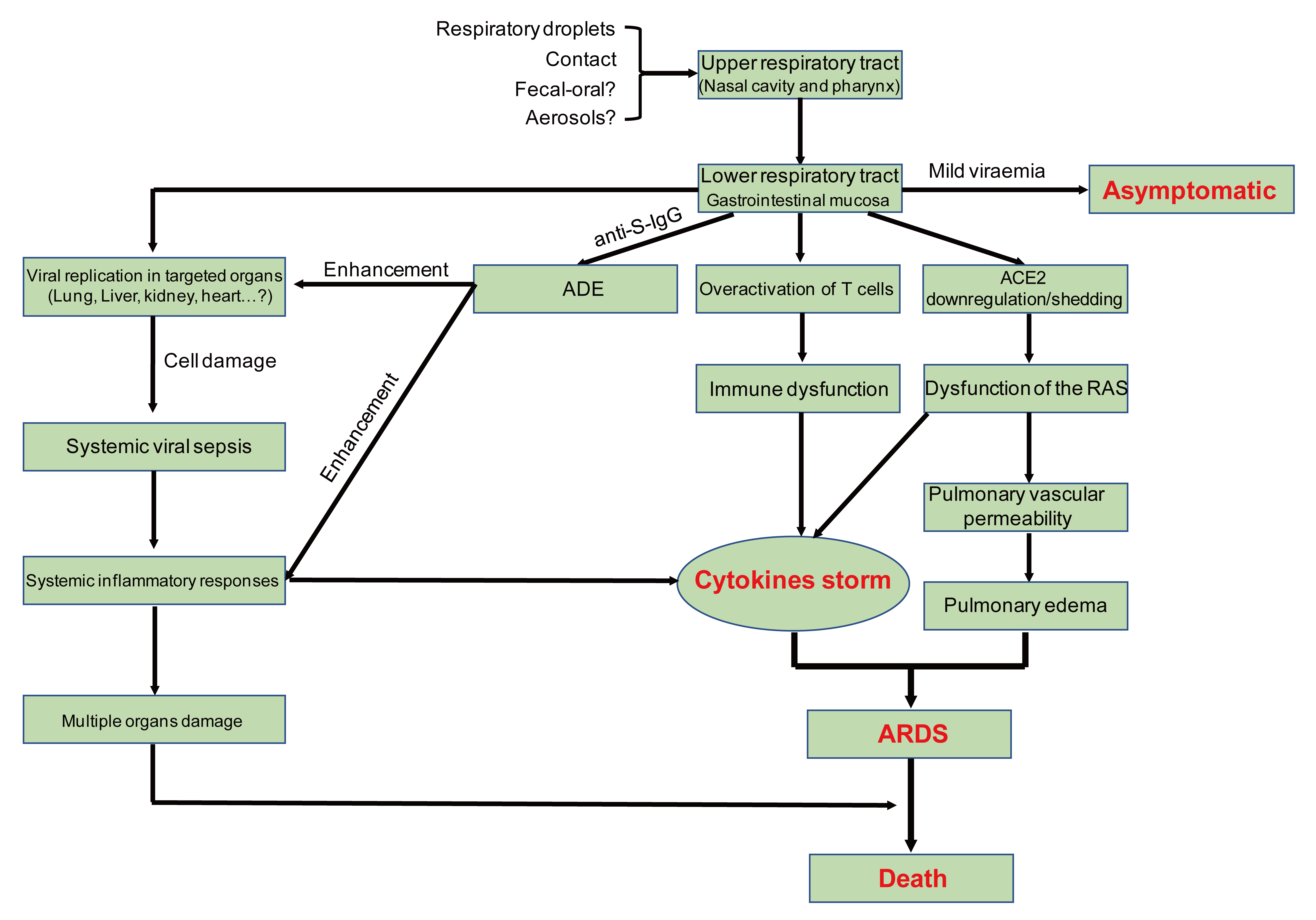
A majority of patients in the initial stages of this outbreak reported a link to the Huainan South China Seafood Market, a live animal or "wet" market, suggesting a zoonotic origin of the virus (Huang *et al.,* 2020; Chen *et al.,* 2020; Li *et al.,* 2020).

While the potential animal reservoir and intermediary host(s) are unknown at this point, studies suggest they may derive from a recombinant virus between the bat coronavirus and an origin-unknown coronavirus; however, this is yet to be confirmed (Zhu *et al.,* 2020; Lu *et al.,* 2020;Paraskevis *et al.,* 2020; Ji *et al.,* 2020). Pangolins have been suggested as an intermediate host as they have been found to be a natural reservoir of SARS-CoV-2-like coronaviruses (Zhang, Wu, Zhang Z, 2020; Lam *et al.,* 2020).

PATHOGENESIS OF COVID-19

**Virus Entry and Spread**

SARS-CoV-2 is transmitted predominantly via respiratory droplet, contact, and potential in fecal-oral. Primary viral replication is presumed to occur in mucosal epithelium of upper respiratory tract (nasal cavity and pharynx), with further multiplication in lower respiratory tract and gastrointestinal mucosa (Xiao *et al.,* 2020) giving rise to a mild viremia. Few infections are controlled at this point and remain asymptomatic. Some patients have also exhibited non-respiratory symptoms such as acute liver and heart injury, kidney failure, diarrhea (Huang *et al.,* 2020; Cheng *et al.,*2020; Guan *et al.,*2020; Wang *et al.,* 2020) implying multiple organ involvement. ACE2 is broadly expressed in nasal mucosa, bronchus, lung, heart, esophagus, kidney, stomach, bladder, and ileum, and these human organs are all vulnerable to SARS-CoV-2 (Zou *et al.,* 2020) Recently, potential pathogenicity of the SARS-CoV-2 to testicular tissues has also been proposed by clinicians, implying fertility concerns in young patients (Fan *et al.,* 2020). The postulated pathogenesis of SARS-CoV-2 infection is graphed in below.



Postulated pathogenesis of SARS-CoV-2 infection. Antibody-dependent enhancement (ADE); ACE2: angiotensin-converting enzyme 2; RAS: renin-angiotensin system; ARDS: acute respiratory distress syndrome. Red words represent the important turning points in SARS-CoV-2 infection.

**Pathological Findings**

The first report (Xu *et al.,* 2020) of pathological findings from a severe COVID-19 showed pulmonary bilateral diffuse alveolar damage with cellular fibromyxoid exudates. The right lung showed evident desquamation of pneumocytes and hyaline membrane formation, indicating acute respiratory distress syndrome. The left lung tissue displayed pulmonary edema with hyaline membrane formation, suggestive of early-phase acute respiratory distress syndrome (ARDS). Interstitial mononuclear inflammatory infiltrates, dominated by lymphocytes, could be observed in both lungs. Multinucleated syncytial cells with atypical enlarged pneumocytes characterized by large nuclei, amphophilic granular cytoplasm, and prominent nucleoli were identified in the intra-alveolar spaces, indicating viral cytopathic-like changes. These pulmonary pathological findings extremely resemble those seen in SARS (Ding *et al.,* 2003) and MERS (Ng *et al.,* 2016). Moderate microvascular steatosis and mild lobular and portal activity were observed in liver biopsy specimens, which might be caused by either SARS-CoV-2 infection or drug use. In addition, only a few interstitial mononuclear inflammatory infiltrates were found in the heart tissue, which means that SARS-CoV-2 might not directly impair the heart (Xu *et al.,* 2020). Massive mucus secretion in both lungs was found in death cases with COVID-19, which was different from SARS and MERS (Liu *et al.,* 2020).

**Acute Respiratory Distress Syndrome (ARDS)**

ARDS is a life-threatening lung condition that prevents enough oxygen from getting to the lungs and into the circulation, accounting for mortality of most respiratory disorders and acute lung injury (Thompson, Chambers, Liu, 2017). In fatal cases of human SARS-CoV, MERS-CoV, and SARS-CoV-2 infections, individuals exhibit severe respiratory distress requiring mechanical ventilation, and the histopathology findings also support ARDS (Xu *et al.,* 2020; Ding *et al.,* 2020; Ng *et al.,* 2020) Previous studies have found that genetic susceptibility, and inflammatory cytokines were closely related to the occurrence of ARDS. More than 40 candidate genes including ACE2, interleukin 10 (IL-10), tumor necrosis factor (TNF), and vascular endothelial growth factor (VEGF) among others have been considered to be associated with the development or outcome of ARDS (Meyer and Christie 2013). Increased levels of plasma IL-6 and IL-8 were also demonstrated to be related to adverse outcomes of ARDS (Thompson, Chambers, Liu, 2017). The above biomarkers suggest both a molecular explanation for the severe ARDS and a possible treatment for ARDS followingSARS-CoV-2 infection.

**Cytokine Storm**

Clinical findings showed exuberant inflammatory responses during SARS-CoV-2 infection, further resulting in uncontrolled pulmonary inflammation, likely a leading cause of case fatality. Rapid viral replication and cellular damage, virus-induced ACE2 down regulation and shedding, and antibody dependent enhancement (ADE) are responsible for aggressive inflammation caused by SARS-CoV-2, as concluded in a recently published review article (Fu, Cheng and Wu 2020). SARS-CoV-2 hijacks the same entry receptor, ACE2, as SARS-CoV for infection, suggesting the likelihood of the same population of cells being targeted and infected (Gu *et al.,* 2005) The initial onset of rapid viral replication may cause massive epithelial and endothelial cell death and vascular leakage, triggering the production of exuberant pro-inflammatory cytokines and chemokines (Yang, 2020). Loss of pulmonary ACE2 function has been proposed to be related to acute lung injury (Imai, Kuba and Penninger 2008) because ACE2 downregulation and shedding can lead to dysfunction of the renin-angiotensin system (RAS), and further enhance inflammation and cause vascular permeability. For SARS-CoV, one confusing issueis that only a few patients, particularly those who produce neutralizing antibodies early, experience persistent inflammation, ARDS, and even sudden death, while most patients survive the inflammatory responses and clear the virus (Fu, Cheng and Wu 2020). The above phenomenon also exists in SARS-CoV-2 infection. A possible underlying mechanism of antibody-dependent enhancement (ADE) has been proposed recently (Fu Cheng and Wu 2020). ADE, a well-known virology phenomenon, has been confirmed in multiple viral infections (Takada and Kawaoka 2003). ADE can promote viral cellular uptake of infectious virus–antibody complexes following their interaction with Fc receptors (FcR), FcγR, or other receptors, resulting in enhanced infection of target cells (Takada and Kawaoka 2003) The interaction of FcγR with the virus-anti-*S* protein-neutralizing antibodies (anti-*S*-IgG) complex may facilitate both inflammatory responses and persistent viral replication in the lungs of patients (Fu, Cheng, and Wu 2020).

**Immune Dysfunction**

Peripheral CD4 and CD8 T cells showed reduction and hyperactivation in a severe patient. High concentrations of proinflammatory CD4 T cells and cytotoxic granules CD8 T cells were also determined, suggesting antiviral immune responses and overactivation of T cells ( Xu *et al.,* 2020) Additionally, several studies have reported that lymphopenia is a common feature of COVID-19 (Zhu *et al.,* 2020; Huang *et al.,* 2020) suggestive of a critical factor accounting for severity and mortality.

**Potential Therapeutics**

Currently, there are no specificantiviral drugs or vaccines for the control of SARS-CoV-2. Symptomatic treatment strategies are recommended for clinical practice. Here are the potential therapeutics available for the treatment of SARS-CoV-2.

**Type I IFNs**

Type I IFNs are antiviral cytokines that induce a large range of proteins that can impair viral replication in targeted cells. Previous studies have reported that IFN-β was superior against SARS-CoV compared to IFN-α (Scagnolari *et al.,* 2004). Synergistic effects of leukocytic IFN-α with ribavirin (Chen *et al.,* 2004) and IFN-β with ribavirin (Morgenstern, Michaelis, Baer, Doerr, and Cinatl 2005) against SARS-CoV were demonstrated in vitro.

**Potential Antiviral Compounds**

Ribavirin. During the outbreak of SARS in Hong Kong, ribavirin was broadly used for patients with or without concomitant use of steroids (Wenzel and Edmond 2003). Ribavirin and IFN-β could synergistically inhibit SARS-associated CoV replication in vitro (Morgenstern, Michaelis, Baer, Doerr, and Cinatl 2005). Due to adverse reactions, the proper dose of ribavirin in clinical application should be given carefully.

Lopinavir/ritonavir. The combination of lopinavir/ritonavir is widely used in the treatment of HIV infection. It has been reported that the use of lopinavir/ritonavir with ribavirin has a good therapeutic effect in SARS (Chu *et al.,* 2004) and MERS (Kim *et al.,* 2016). Lopinavir/ritonavir has been recommended for clinical treatment for COVID-19.

Remdesivir. Remdesivir (RDV) was previously reported to restrain SARS-CoV in vivo (Agostini *et al.,* 2018) and the antiviral protection of RDV and IFN-β was found to be superior to that of lopinavir/ritonavir-IFN-β against MERS-CoV in vitro and in vivo. In addition, remdesivir was used in the treatment of the first COVID-19 patient in the United States (Hoehl *et al*., 2020) and was shown to have antiviral activity against SARS-CoV-2 in vitro (Wang *et al.,* 2020) However, its effectiveness and safety have not been verified in clinica/89l trials yet.

Nelfinavir. Nelfinavir is a selective inhibitor of HIV protease, which has been shown to have a strong inhibition of SARS-CoV (Yamamoto *et al.,* 2004) implying a possible therapeutic for COVID-19.

Arbidol. Arbidol, a broad-spectrum antiviral compound, is able to block viral fusion against influenza viruses. In addition, arbidol and its derivative, arbidolmesylate, have been reported to have antiviral activity against SARS-CoV in vitro (Khamitov *et al.,* 2008) The antiviral activity of arbidol against SARS-CoV-2 has been confirmed in vitro and recommended for clinical treatment.

Chloroquine. Chloroquine has many interesting biochemical properties including antiviral effect (Savarino *et al.,* 2003). It has been found to be a potent inhibitor of SARS-CoV through interfering with ACE2 (Yamamoto *et al.,* 2004). Chloroquine can effectively inhibit SARS-CoV-2 in vitro (Wang *et al.,* 2020) and is recommended for the clinical control of viral replication

**Convalescent Plasma**

Recently, convalescent plasma has been widely recommended to be used for COVID-19 (Li, Wang, Xu, and Cao, 2020), but the effect of convalescent plasma cannot be discerned from the effects of patient comorbidities, stage of illness, or effect of other treatments.

**Protective Monoclonal Antibody**

It has been reported that the monoclonal antibody (mAb) can efficiently neutralize SARS-CoV and inhibit syncytia formation between cells expressing the *S* protein and those expressing the SARS-CoV receptor ACE2 (Duan *et al.,* 2005) However, mAbs can only recognize a single epitope, and the anti-infective effect may be limited. In addition, the development of mAbs requires a certain period of time, which is difficult to achieve in clinical application in a short time.

**Others**

Based on the virology of SARS-CoV-2, blocking the binding of *S* protein to ACE2 is important for the treatment of virus infection. ACE2 is an important component of the renin-angiotensin system (RAS). RAS inhibitors, ACEI and AT1R, may be potential therapeutic tools for COVID-19. Additionally, intravenous transplantation of ACE2-mesenchymal stem cells (MSCs), blocking of FcR with immunoglobulin (IVIG), and systemic anti-inflammatory drugs to reduce cytokine storm are also potential therapeutic strategies for severe COVID-19 (Fu, Cheng, and Wu 2020; Leng *et al.,* 2020) Traditional Chinese medicines have also been found to have potential anti-SARS-CoV-2 activity (Zhang *et al.,* 2020).

**Covid-19: What is next for Public Health?**

Non-pharmaceutical interventions remain central for management of COVID-19 because there are no licensed vaccines or coronavirus antivirals. If the situation changes towards much wider community transmission with multiple international foci, the WHO strategy of containment for elimination could need to be adjusted to include mitigation strategies combined with the following activities currently recommended by STAG-IH on the WHO website.

First, close monitoring is needed of changes in epidemiology and of the effectiveness of public health strategies and their social acceptance.

Second, continued evolution is needed of enhanced communication strategies that provide general populations and vulnerable populations most at risk with actionable information for self-protection, including identification of symptoms, and clear guidance for treatment seeking.

Third, continued intensive source control is needed in the epicentre in China—ie, isolation of patients and persons testing positive for COVID-19, contact tracing and health monitoring, strict health facility infection prevention and control, and use of other active public health control interventions with continued active surveillance and containment activities at all other sites where outbreaks are occurring in China.

Fourth, continued containment activities are needed around sites outside China where there are infected people and transmission among contacts, with intensive study to provide information on transmissibility, means of transmission, and natural history of infection, with regular reporting to WHO and sharing of data.

Fifth, intensified active surveillance is needed for possible infections in all countries using the WHO-recommended surveillance case definition.

Sixth, preparation for resilience of health systems in all countries is needed, as is done at the time of seasonal influenza, anticipating severe infections and course of disease in older people and other populations identified to be at risk of severe disease.

Seventh, if widespread community transmission is established, there should then be consideration of a transition to include mitigation activities, especially if contact tracing becomes ineffective or overwhelming and an inefficient use of resources. Examples of mitigation activities include cancelling public gatherings, school closure, remote working, home isolation, observation of the health of symptomatic individuals supported by telephone or online health consultation, and provision of essential life support such as oxygen supplies, mechanical ventilators and extracorporeal membrane oxygenation (ECMO) equipment.

Eighth, serological tests need to be developed that can estimate current and previous infections in general populations.

Finally, continued research is important to understand the source of the outbreak by study of animals and animal handlers in markets to provide evidence necessary for prevention of future coronavirus outbreaks.

**REFERENCES**

Agostini, M.L.; Andres, E.L.; Sims, A.C.; Graham, R.L.; Sheahan, T.P.; Lu, X.; Smith, E.C.; Case, J.B.; Feng, J.Y.; Jordan, R.; et al. Coronavirus Susceptibility to the Antiviral Remdesivir (GS-5734) Is Mediated by the Viral Polymerase and the Proofreading Exoribonuclease. *MBIO* **2018**, *9*.

Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020 Feb 15;395(10223):507-13.

Chen, F.; Chan, K.H.; Jiang, Y.; Kao, R.Y.; Lu, H.T.; Fan, K.W.; Cheng, V.C.; Tsui, W.H.; Hung, I.F.; Lee, T.S.; et al. In vitro susceptibility of 10 clinical isolates of SARS coronavirus to selected antiviral compounds. *J. Clin. Virol. Off. Publ. Pan. Am. Soc. Clin. Virol.* **2004**, *31*, 69–75

Cheng, Y.; Luo, R.; Wang, K.; Zhang, M.; Wang, Z.; Dong, L.; Li, J.; Yao, Y.; Ge, S.; Xu, G. Kidney impairment is associated with in-hospital death of COVID-19 patients. *medRxiv* **2020**.

Chu, C.M.; Cheng, V.C.; Hung, I.F.; Wong, M.M.; Chan, K.H.; Chan, K.S.; Kao, R.Y.; Poon, L.L.; Wong, C.L.; Guan, Y.; et al. Role of lopinavir/ritonavir in the treatment of SARS: Initial virological and clinical findings. *Thorax* **2004**, *59*, 252–256.

Ding, Y.; Wang, H.; Shen, H.; Li, Z.; Geng, J.; Han, H.; Cai, J.; Li, X.; Kang, W.; Weng, D.; et al. The clinical pathology of severe acute respiratory syndrome (SARS): A report from China. *J. Pathol.* **2003**, *200*, 282–289.

Duan, J.; Yan, X.; Guo, X.; Cao, W.; Han, W.; Qi, C.; Feng, J.; Yang, D.; Gao, G.; Jin, G. A human SARS-CoV neutralizing antibody against epitope on S2 protein. *Biochem. Biophys. Res. Commun.* **2005**, *333*, 186–193.

Fan, C.; Li, K.; Ding, Y.; Lu, W.L.; Wang, J. ACE2 Expression in Kidney and Testis May Cause Kidney and Testis Damage After 2019-nCoV Infection. *medRxiv* **2020**.

Fu, Y.; Cheng, Y.; Wu, Y. Understanding SARS-CoV-2-Mediated Inflammatory Responses: From Mechanisms to Potential Therapeutic Tools. *Virol. Sin.* **2020**.

General Office of National Health Commission; General Office of National Administration of Traditional Chinese Medicine. *Diagnostic and treatment protocol for Novel Coronavirus Pneumonia*; (Trial version 6).

Global surveillance for human infection with novel coronavirus (2019-nCoV)

https://www.who.int/publications-detail/global-surveillance-for-human-infection-with-novel-coronavirus-(2019-ncov)

Gu, J.; Gong, E.; Zhang, B.; Zheng, J.; Gao, Z.; Zhong, Y.; Zou, W.; Zhan, J.; Wang, S.; Xie, Z.; et al. Multiple organ infection and the pathogenesis of SARS. *J. Exp. Med.* **2005**, *202*, 415–424.

Guan, G.W.; Gao, L.; Wang, J.W.; Wen, X.J.; Mao, T.H.; Peng, S.W.; Zhang, T.; Chen, X.M.; Lu, F.M. Exploring the mechanism of liver enzyme abnormalities in patients with novel coronavirus-infected pneumonia. *Chin. J. Hepatol.* **2020**, *28*, E002.

Hoehl, S.; Berger, A.; Kortenbusch, M.; Cinatl, J.; Bojkova, D.; Rabenau, H.; Behrens, P.; Böddinghaus, B.; Götsch, U.; Naujoks, F.; et al. Evidence of SARS-CoV-2 Infection in Returning Travelers from Wuhan, China. *N. Engl. J. Med.* **2020**.

Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020 Feb 15; 395(10223):497-506.

Huang, C.; Wang, Y.; Li, X.; Ren, L.; Zhao, J.; Hu, Y.; Zhang, L.; Fan, G.; Xu, J.; Gu, X.; et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet (Lond. Engl.)* **2020**, *395*, 497–506

Imai, Y.; Kuba, K.; Penninger, J.M. The discovery of angiotensin-converting enzyme 2 and its role in acute lung injury in mice. *Exp. Physiol.* **2008**, *93*, 543–548.

Ji W, Wang W, Zhao X, et al. Cross-species transmission of the newly identified coronavirus 2019-nCoV. J Med Virol. 2020 Apr;92(4):433-40.

Khamitov, R.A.; Loginova, S.; Shchukina, V.N.; Borisevich, S.V.; Maksimov, V.A.; Shuster, A.M. Antiviral activity of arbidol and its derivatives against the pathogen of severe acute respiratory syndrome in the cell cultures. *Vopr. Virusol.* **2008**, *53*, 9–13

Kim, U.J.; Won, E.J.; Kee, S.J.; Jung, S.I.; Jang, H.C. Combination therapy with lopinavir/ritonavir, ribavirin and interferon-alpha for Middle East respiratory syndrome. *Antivir. Ther.* **2016**, *21*, 455–459.

Lam TT, Shum MH, Zhu HC, et al. Identifying SARS-CoV-2 related coronaviruses in Malayan pangolins. Nature. 2020 Mar 26.

Leng, Z.; Zhu, R.; Hou, W.; Feng, Y.; Liu, H.; Jin, R.; Jin, K.; Zhao, R.C. Transplantation of ACE2- mesenchymal stem cells improves the outcome of patients with COVID-19 pneumonia. *Aging Dis.* **2020**, *11*, 216–228.

Li Q, Guan X, Wu P, et al. Early transmission dynamics in Wuhan, China, of novel coronavirus-infected pneumonia. N Engl J Med. 2020 Mar 26;382(13):1199-207.

Li, H.; Wang, Y.M.; Xu, J.Y.; Cao, B. Potential antiviral therapeutics for 2019 Novel Coronavirus. *Chin. J. Tuberc. Respir. Dis.* **2020**, *43*, E002.

Liu, Q.; Qu, G.; Wang, Y.; Liu, P.; Zhu, Y.; Fei, G.; Ren, L.; Zhou, Y.; Liu, L. Anatomy of a COVID-19 Death Corpse System. *J. Forensic Med.* **2020**, *36*, 21–23.

Lu R, Zhao X, Li J, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. Lancet. 2020 Feb 22;395(10224):565-74.

Lu, R., Zhao, X., Li, J., Niu, P., Yang, B., Wu, H., & Bi, Y. (2020). Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. *The Lancet*, *395*(10224), 565-574.

Meyer, N.J.; Christie, J.D. Genetic heterogeneity and risk of acute respiratory distress syndrome. *Semin. Respir. Crit. Care Med.* **2013**, *34*, 459–474.

Morgenstern, B.; Michaelis, M.; Baer, P.C.; Doerr, H.W.; Cinatl, J., Jr. Ribavirin and interferon-beta synergistically inhibit SARS-associated coronavirus replication in animal and human cell lines. *Biochem. Biophys. Res. Commun.* **2005**, *326*, 905–908

Ng, D.L.; Al Hosani, F.; Keating, M.K.; Gerber, S.I.; Jones, T.L.; Metcalfe, M.G.; Tong, S.; Tao, Y.; Alami, N.N.; Haynes, L.M.; et al. Clinicopathologic, Immunohistochemical, and Ultrastructural Findings of a Fatal Case of Middle East Respiratory Syndrome Coronavirus Infection in the United Arab Emirates, April 2014. *Am. J. Pathol.* **2016**, *186*, 652–658.

Paraskevis D, Kostaki EG, Magiorkinis G, et al. Full-genome evolutionary analysis of the novel corona virus (2019-nCoV) rejects the hypothesis of emergence as a result of a recent recombination event. Infect Genet Evol. 2020 Jan 29;79:104212.

Ren, L. L., Wang, Y. M., Wu, Z. Q., Xiang, Z. C., Guo, L., Xu, T., ... & Li, H. (2020). Identification of a novel coronavirus causing severe pneumonia in human: a descriptive study. *Chinese medical journal*.

Savarino, A.; Boelaert, J.R.; Cassone, A.; Majori, G.; Cauda, R. Effects of chloroquine on viral infections: An old drug against today’s diseases? *Lancet Infect. Dis.* **2003**, *3*, 722–727.

Scagnolari, C.; Vicenzi, E.; Bellomi, F.; Stillitano, M.G.; Pinna, D.; Poli, G.; Clementi, M.; Dianzani, F.; Antonelli, G. Increased sensitivity of SARS-coronavirus to a combination of human type I and type II interferons. *Antivir. Ther.* **2004**, *9*, 1003–1011

Takada, A.; Kawaoka, Y. Antibody-dependent enhancement of viral infection: Molecular mechanisms and in vivo implications. *Rev. Med. Virol.* **2003**, *13*, 387–398.

Tang X, Wu C, Li X, et al. On the origin and continuing evolution of SARS-CoV-2. Nat Sci Review. 2020 Mar 3.

Thompson, B.T.; Chambers, R.C.; Liu, K.D. Acute Respiratory Distress Syndrome. *N. Engl. J. Med.* **2017**, *377*, 562–572.

Wang, D.; Hu, B.; Hu, C.; Zhu, F.; Liu, X.; Zhang, J.; Wang, B.; Xiang, H.; Cheng, Z.; Xiong, Y.; et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. *JAMA* **2020**.

Wang, M.; Cao, R.; Zhang, L.; Yang, X.; Liu, J.; Xu, M.; Shi, Z.; Hu, Z.; Zhong, W.; Xiao, G. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. *Cell Res.* **2020**.

Wenzel, R.P.; Edmond, M.B. Managing SARS amidst uncertainty. *N. Engl. J. Med.* **2003**, *348*, 1947–1948.

Xiao, F.; Tang, M.; Zheng, X.; Li, C.; He, J.; Hong, Z.; Huang, S.; Zhang, Z.; Lin, X.; Fang, Z.; et al. Evidence for gastrointestinal infection of SARS-CoV-2. *medRxiv* **2020.**

Xu, Z.; Shi, L.; Wang, Y.; Zhang, J.; Huang, L.; Zhang, C.; Liu, S.; Zhao, P.; Liu, H.; Zhu, L.; et al. Pathological findings of COVID-19 associated with acuterespiratory distress syndrome. *Lancet Respir. Med.* **2020**.

Yamamoto, N.; Yang, R.; Yoshinaka, Y.; Amari, S.; Nakano, T.; Cinatl, J.; Rabenau, H.; Doerr, H.W.; Hunsmann, G.; Otaka, A.; et al. HIV protease inhibitor nelfinavir inhibits replication of SARS-associated coronavirus. *Biochem. Biophys. Res. Commun.* **2004**, *318*, 719–725.

Yang, M. Cell Pyroptosis, a Potential Pathogenic Mechanism of 2019-nCoV Infection. *SSRN* **2020**

Zhang T, Wu Q, Zhang Z. Probable pangolin origin of SARS-CoV-2 associated with the COVID-19 outbreak. Curr Biol. 2020 Apr 6;30(7):1346-51.

Zhang, D.; Wu, K.; Zhang, X.; Deng, S.; Peng, B. In silico screening of Chinese herbal medicines with the potential to directly inhibit 2019 novel coronavirus. *J. Integr. Med.* **2020**.

Zhu N, Zhang D, Wang W, et al. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med. 2020 Feb 20;382(8):727-33.

Zhu, N., Zhang, D., Wang, W., Li, X., Yang, B., Song, J. & Niu, P. (2020). A novel coronavirus from patients with pneumonia in China, 2019. *New England Journal of Medicine*.

Zhu, N.; Zhang, D.; Wang, W.; Li, X.; Yang, B.; Song, J.; Zhao, X.; Huang, B.; Shi, W.; Lu, R.; et al. A Novel Coronavirus from Patients with Pneumonia in China, 2019. *N. Engl. J. Med.* **2020**.

Zou, X.; Chen, K.; Zou, J.; Han, P.; Hao, J.; Han, Z. The single-cell RNA-seq data analysis on the receptor ACE2 expression reveals the potential risk of different human organs vulnerable to Wuhan 2019-nCoV infection. *Front. Med.* **2020**, 1–8.