Virology, epidemiology, pathogenesis, treatment and nursing care of patients with Covid-19: Review article

Islam Ali [*1], Amel Hassan[2], Amal Hamid[3]

[1]Associate Professor of Pathology, Faculty of Medical Technical Sciences, Alzaiem Alazhari University, Khartoum North, Sudan
[2]Assistant Professor of Community Health Nursing, Faculty of Medical Technical Sciences, Alzaiem Alazhari University, Khartoum North, Sudan
[3]Assistant Professor of Obestetrics & Gynecological Nursing, Faculty of Medical Technical Sciences, Alzaiem Alazhari University, Khartoum North, Sudan

Corresponding author: Islam Ali (BVSc, MVSc, PhD) PO box 1432, Khartoum North, Code 13311, Sudan. Email: islam@aau.edu.sd; islam_siddig333@hotmail.com

Abstract

Coronavirus disease (COVID-19) which is caused by SARS-COV2 represent great global public health concern, was reported in Wuhan, China.

Severe acute respiratory syndrome coronavirus (SARSCoV) and the Middle East respiratory syndrome coronavirus (MERS-CoV) consensus guideline to understand the epidemiology and pathogenesis of SARS-Cov2 This review provide comperhensive summary to explain current status and development of therapeutics to treat patient with covid 19 infection and clinical skills consensus guideline on nursing care holistic of patients with severe COVID-19.

Key Words: Pathogenesis; SARS-CoV-2; COVID-19; Therapeutic; Nursing Care

{**Citation**: Islam. Ali, Amel. Hassan, Amal. Hamid. Virology, epidemiology, pathogenesis, treatment and nursing care of patients with Covid-19: Review article. American Journal of Research Communication, 2020, Vol8(8): 1-23} www.usa-journals.com, ISSN: 2325-4076.

Introduction

Coronavirus disease (COVID-19) is a fetal viral pneumonia with an unusual outbreak in Wuhan, China, in December 2019 ,and great public highly pathogenic (Zhou *et al* , 2020) (Chan *et al*, 2020) (Huang *et al*, 2020). It is highly pathogenic coronavirus afte r the severe acute respiratory syndrome coronavirus (SARSCoV) and the Middle East respiratory syndrome coronavirus (MERS-CoV). WHO listed it as the Public Health E mergency of International Concern (PHEIC).

Person-to-person transmission of COVID-19 infection led to the isolation of patients. In Washington the community transmission was detected in February 2020 and hypo xemic respiratory failure and hypotension cause ICU admission leading to mechanical ventilation and vasopressor treatment respectively leading to high mortality.(Bhatraju *et al*, 2020)To face this pandemic and overcome the limitation of healthcare system, Americans pay attention to transition to remote working and other digital solutions to continue functioning. (Sirina Keesara and Kevin Schulman, 2020).

Elderly people children, and health care providers should have special care (Rothan a nd Byrareddy, 2020).

Pathogenesis

The main pathogenesis of COVID-19 infection as respiratory system targeting virus w as severe pneumonia, RNAaemia, combined with the incidence of ground-glass opacit ies, and acute cardiac injury (Huang *et al,* 2020) (Shi *et al,* 2020).

Clinical manifestations including fever, nonproductive cough, dyspnea, myalgia, fati gue, normal or decreased leukocyte counts, and radiographic evidence of pneumonia

(Huang *et al*, 2020). which are similar to the symptoms of SARS-CoV and MERS-C oV infections (J.S.M Peiris, 2003) .

From patients with laboratory-confirmed Covid-19 from 552 hospitals in 30 provincs, China through January 29, 2020, data were extracted and found that the most common symptoms were fever (43.8% on admission and 88.7% during hospitalization) and co ugh (67.8%). Diarrhea was uncommon (3.8%). The patients often presented without f ever, and many did not have abnormal radiologic findings (Guan *et al*, 2020).

Observational database from hospitalized Covid-19 patients in Asia, Europe, and Nort h America who were admitted between December 20, 2019, and March 15, 2020, use d to study the relationship of cardiovascular disease and drug therapy with in-hospital death confirm that cardiovascular disease is associated with in-hospital death among h ospitalized patients with Covid-19 (Mehra *et al*, 2020) .

Although the pathogenesis of COVID-19 is still unclear, but the similar mechanisms o f SARSCoV and MERS-CoV can facilitate study of the pathogenesis of SARS-CoV-2 infection of COVID-19.

Virus replication

The virus entry into host cells facilitate by S protein (De Wit *et al,* 2016) envelope spi ke.

glycoprotein binds to its cellular receptor, ACE2 for SARS-CoV (Kuhn *et al,* 2004) a nd SARS-CoV-2(Wu *et al*, 2020) by direct membrane fusion between the virus and p lasma membrane (Simmons *et al*, 2004) .

Viral infection occur through binding of a host cells receptor to the virus followed by fusion with the cell membrane. Lung epithelial cells are the primary target of the virus. Thus, several studies reported that hman-to-human transmissions of SARS-CoV occu

rs 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) recep tor suggesting that the entry COVID-19 into the host cells is most likely via the ACE2 receptor.(Wan *et al*, 2020) (Jaimes *et al*, 2020) .

After entry to the cells, the viral RNA genome is released into the cytoplasm and is translated into two polyproteins and structural proteins, after which the viral genome begins to replicate (Perlman and Netland, 200 9). The envelope glycoproteins are inserted into the membrane of the endoplasmic reti culum or Golgi and form vesicles containing the virus particles, which fuse with the plasma membrane and release the virus (De Wit *et al,* 2016) .

The virus antigen will be presented to the antigen presenting cells (APC).

major histocompatibility complex (MHC; or human leukocyte antigen (HLA) in huma ns) will present Antigenic peptides which recognized by virus-specific cytotoxic T ly mphocytes (CTLs). MHC I molecules and MHC II contributes to SARS-CoV presenta tion (Liu *et al*, 2010) .

Although COVID-19 pathogenesis is still unclear, previous researches on SARS-CoV and MERS-CoV can give us some guidance.

Immunity

Humoral and cellular immunity triggered by antigen presentation, which are mediated by virus-specific B and T cells. IgM and IgG antibodies act against SARS-CoV virus production (Li, Chen, and Xu, 2003).

Latest studies show that SARS-CoV-2-infected patients CD4+ and CD8+ T cells signi ficantly is reduced.(Xu et al, 2020) . In SARS-CoV there is severe decrease of CD4+ T and CD8+ T cells and in recovered individuals, CD4+ and CD8+ memory T cells ca n persist for four years and then DTH response and production of IFN- (Fan *et al*, 200 9) . Also specific T-cell memory responses to the SARS-CoV S peptide library persist Six years post SARS-CoV infection in 14 of 23 recovered SARS patients (Tang *et al*, 2011) .

Cytokines Storm

ARDS as the main cause of death of COVID-19 is the common immunopathological event for SARS-CoV-2, SARS-CoV and MERS-CoV infections (Xu *et al,* 2020) .

Uncontrolled systemic inflammatory response which cause excessive release of cytok ines play important role in ARDS mechanisms leading to release of large amounts of pro-inflammatory cytokines (IFN-a, IFN-g, IL-1b, IL-6, IL-12, IL-18, IL-33, TNF-a, TGFb, etc.) and chemokines (CCL2, CCL3, CCL5, CXCL8, CXCL9, CXCL10, etc.) by immune effector cells in SARS-CoV infection (Anne Kimball *et al*, 2020; Willia ms and Chambers, 2014).

Also elevated levels of IL-6, IFN-a, and CCL5, CXCL8, CXCL-10 in serum occur in MERS-CoV severe infection (Min *et al*, 2016) .

Microbial structures called pathogen-associated molecular patterns (PAMPs) can be r ecognized by pattern recognition receptors (PRRs).

Production of double-membrane vesicles that lack PRRs that induced by SARS-CoV and MERS-CoV replicate in these vesicles, thereby avoiding the host detection of thei r dsRNA (Snijder *et al*, 2006) .

During SARS-CoV and MERS-CoV infection IFN-I (IFN-a and IFN-b) has a protecti ve role but the IFN-I pathway is inhibited in infected mice (Rudragouda Channappana var, 2016; Channappanavar *et al*, 2019). In addition induction of IFN may block ME RSCoV.

ORF4a, ORF4b, ORF5, and membrane proteins of MERSCoV inhibit nuclear transpo rt of IFN regulatory factor 3 (IRF3) and activation of IFN b promoter(Y. Yang *et al*, 2013) . Corona virus can affect antigen presentation (Menachery *et al,* 2018) .

Comparative Pathogenesis between Covid-19, SARS-CoV and MERS-CoV

In severe cases of Covid 19, bilateral lung involvement with ground-glass opacity is t he most common chest computed tomography (CT) finding (Shi *et al,* 2020) . Similar ly to the 2002/2003 outbreak of SARS, the severity of COVID-19 disease is associate d with increased age and/or a comorbidity, although severe disease is not limited to th ese risk groups (Perlman and Netland, 2009) . However, despite the large number of cases and deaths, limited information is available on the pathogenesis of this virus inf ection. Two reports on the histological examination of the lungs of three patients sho wed bilateral diffuse alveolar damage (DAD), pulmonary edema and hyaline membra ne formation, indicative of acute respiratory distress syndrome (ARDS), as well as ch aracteristic syncytial cells in the alveolar lumen (Xu *et al,* 2020; Sufang Tian *et al*, 20 20) , similar to findings during the 2002/2003 outbreak of SARS-CoV (John M Nicho lls *et al*, 2003) .

SARS-CoV-2 infection was characterized in the same animal model for SAR S-CoV infection where aged animals develop disease.(Rockx *et al,* 2020; Fe i Xiao *et al*, 2020) and compared with infection with MERS-CoV and historical

data on SARS-CoV (Fei Xiao *et al*, 2020;*Kuiken et al,* 2003), (Haagmans *et al*, 2004) .

Higher levels of SARS-CoV-2 RNA were detected in nasal swabs of aged animals compared with young animals.

The autopsy in this model. Showed foci of pulmonary consolidation in the lungs.

The main histological lesion in the consolidated pulmonary tissues of animals involved the alveoli and bronchioles and consisted of areas with acute or more advanced DAD filled with protein-rich edema fluid, fibrin, and cellular debris, alveolar macrophages, and fewer neutrophils and lymphocytes. There was epithelial necrosis with extensive loss of epithe-lium from alveolar and bronchiolar walls. Hyaline membranes were present in a few damaged alveoli. In areas with more advanced lesions, the alveolar walls were moderately thickened and there is type II pneumocyte hyperplasia, and the alveolar lumina were empty. Alveolar and bronchiolar walls were thickened by edema fluid, mononuclear cells, and neutrophils. There were aggregates of lymphocytes around small pulmonary vessels. Moderate numbers of lymphocytes and macrophages were present in the lamina propria and submucosa of the bronchial walls, and a few neutrophils in the bronchial epithelium. Regeneration of epithelium occur in some bronchioles, visible as an irregular layer of squamous to high cuboidal epithelial cells with hyperchromatic nuclei. There were occasional multinucleated giant cells (syncytia) free in the lumina of bronhioles and alveoli.

Severity of infection with SARS-CoV-2 compared with MERS-CoV, animals inoculated Intra Nasal (IN) and Intra Throught (IT) with MERS-CoV revealed presence of MERS-CoV specific antibodies in their sera by ELISA. MERS-CoV RNA was detected in nasal and throat swabs. (Rockx *et al,* 2020).

autopsy of four animals at day 4 p.i., three animals had foci of pulmonary consolidatio n, characterized by slightly depressed areas in the lungs Similar to SARS-CoV-2 infec tion in both young and aged animals, on day 4 p.i., MERS-CoV RNA was primarily d etected in the respiratory tract of inoculated animals. Infectious virus titers were com parable to SARS-CoV-2, but lower compared to SARS-CoV infection of young anima ls.

Histopathological changes characteristic for DAD were observed in the lungs of inocu lated animals including alveolar and bronchiolar epithelial necrosis, alveolar edema, h yaline membrane formation, and accumulation of neutrophils, macrophages and lymp hocytes. (Rockx et al. 2020). Similarly pathological analyses of human COVID-19 ca ses (Xu *et al,* 2020; Sufang Tian *et al*, 2020) .

Presence of syncytia in the lung lesions is characteristic of respiratory coronavirus inf ections. Whereas MERS-CoV primarily infects type II pneumocytes both SARS-CoV and SARS-CoV-2 also infect type Ipneumocytes which result in pulmonary edema, an d formation of hyaline membranes (Matthay, Ware, and Zimmerman, 2012), which may explain why hyaline membrane formation is a hallmark for SARS and COVID-1 9 (Kuiken *et al*, 2003) (Sufang Tian *et al*, 2020), but not frequently reported for ME RS (Dianna L. Ng *et al*, 2016; Shieh *et al*, 2005) .

productive infection in the absence of overt clinical signs occur due to inoculation of young and aged animals with a low passage clinical isolate of SARS-CoV-2, and Rec ent studies in human cases have shown that presymptomatic and asymptomatic cases can also shed virus (Anne Kimball *et al*., 2020 ; Lai *et al*., 2020). Increased age did n ot affect disease outcome, but there was prolonged viral shedding in the upper respirat

ory tract of aged animals. Prolonged shedding has been observed in both SARS-CoV-2 and SARS-CoV patients (Lirong Zou *et al*., 2020 ; Peiris *et al*., 2003).

Also, SARS-CoV-2 antigen was detected in ciliated epithelial cells of nasal mucosae in the inoculated animals, which was not seen for SARS-CoV (Kuiken *et al,* 2003) or MERS-CoV infections (Rockx *et al*, 2020) SARS-CoV-2 was primarily detected in tissues of the respiratory tract, however SARS-CoV-2 RNA was also detectable in other tissues such as intestines (Rockx *et al*, 2020; Fei Xiao *et al*, 2020).

Comparative Pathogenesis between Covid-19 and influenza A(H1N1) infection

A recent study compare between lung autopsy from patients who died from Covid-19 and one from patients who died from acute respiratory distress syndrome (ARDS) secondary to influenza A(H1N1)19 using immunohistochemical analysis, micro–computed tomographic imaging, scanning electron microscopy, corrosion casting, and direct multiplexed measurement of gene expression. revelead that presence of diffuse alveolar damage but the lungs from patients with Covid-19 also showed severe endothelial injury associated with the presence of intracellular virus and disrupted cell membranes triggering widespread blood clotting. In addition the study found that formation of new vessel growth by intussusceptive angiogenesis mechanim in lungs from patients with Covid-19 higher than the lungs from patients with influenza (Ackermann *et al,* 2020).

Therapeutics

Although several therapeutic agents have been evaluated, none have yet been proven effective for the treatment of coronavirus disease 2019 (Covid-19)

Hydroxychloroquine

Chloroquine phosphate, an old drug for treatment of malaria, is shown to have potent efficacy and acceptable safety in treating patients with COVID-19 pneumonia in more than 10 hospitals in different cities in China.(Gao, Tian, and Yang, 2020) .

Other observational study target hospitalized patients with Covid-19 in NEW YORL city and compare outcomes in patients who received hydroxychloroquine with those in patients who did not reveals that hydroxychloroquine administration was not associated with either a greatly lowered or an increased risk of the composite end point of intubation or Death.(Geleris *et al*, 2020).

Lopinavir–Ritonavir

Hospitalized adult patients with confirmed SARS-CoV-2 infection, which causes the respiratory illness Covid-19 receive either lopinavir–ritonavir (400 mg and 100 mg, respectively) twice a day for 14 days in addition to standard care, or standard care alone no benefit was observed with lopinavir–ritonavir treatment beyond standard care (Cao *et al*, 2020).

Remdesivir

Remdesivir as a treatment has a potent antiviral activity and efficacy against coronavirus disease 2019 (Covid-19) refer to its action as RNA polymerase inhibitor.

Remdesivir show an evidence potency in shortening the time to recovery in adults hospitalized with Covid-19 and evidence of lower respiratory tract infection who receive remdesivir.(Beigel *et al*, 2020) .

Also hospitalized patients with confirmed SARS-CoV-2 infection randomly receive intravenous remdesivir for either 5 days or 10 days imply no significant difference between a 5-day course and a 10-day course of Remdesivir(Goldman *et al*, 2020) .

Nursing care of patient with covid-19

At the end of 2019, an outbreak of Coronavirus disease 2019 (COVID-19) was report ed in Wuhan, China. As the epidemic continued to spread, the World Health Organiza tion (WHO) as a Public Health Emergency of International Concern listed it, and Chin a initiated a first-level response. Due to the disease's high infectivity and Pathogenicit y and the high mortality rate of severely affected patients (Hui Wang *et al*, 2020) (X. Yang *et al*, 2020) .

Nursing care of critically ill patients with COVID-19 is extremely difficult and requir es high standards. Thus, The Chinese Government has proposed establishing a holistic nursing system for severe and critical patients to provide patient centered care followi ng modern nursing concepts, and utilizing nursing procedures as a fundamental frame work and guide for clinical nursing care and nursing management. To standardize and guide holistic care of patients with COVID-19 in severe and critical condition and to effectively preserve their physical and mental health, an expert consensus panel on Ho listic Care of COVID-19 Patients in Severe and Critical Condition (hereafter "Consen sus") was jointly developed, led by the Chinese Nursing Association, and involving th e Nursing Department of Tongji Hospital Affiliated with Tongji Medical College of H uazhong University of Science and Technology, the Nursing Department of the Pekin g Union Medical College Hospital of the Chinese Academy of Medical Sciences, and nursing experts dispatched by the Intensive Care Professional Committee of the Chine se Nursing Association to assist Wuhan.

The Centers for Medicare & Medicaid Services (CMS) and the Centers for Disease C ontrol and Prevention (CDC) are issuing new recommendations to State and local gov ernments and long-term care facilities (also known as nursing homes) to help mitigate the spread of the 2019 Novel Coronavirus (COVID-19). Long-term care facilities are

a critical component of America's healthcare system. They are unique, as they serve a s both healthcare providers and as full-time homes for some of the most vulnerable A mericans (Centers for Medicare & Medicaid Services, 2020).

Nursing is the main active partners in any primary and secondary infectious disease pr evention efforts. In every country, regardless of their socio-economic development, n ursing is considered to be the top first line dedicated profession in the prevention from diseases and alleviation of suffering during and after a treatment of any disease,

including the COVID-19. Nurses were and still are the pioneers in developing all the best practices in relevant to patient management and clinical safety. Their capacity an d effectiveness thrive more during crisis, wars, disaster and even in infectious disease pandemics, as the COVID-19.

Florence Nightingale is one of the earliest nurses and the pioneers who dealt with epid emics through the principles of hygiene and sanitation. Nightingale showed the relatio n between infection control and hand washing (World Economic Forum, 2020). The l essons of Florence Nightingale's nursing practice during the Crimean War are still bei ng applied today during the COVID-19 pandemic essential hand washing, maintainin g standards of cleanliness, learning from the data, and more. The World Health Organ ization, Department of Pandemic and Epidemic Diseases (WHO-PED) develops strate gies, initiatives, and mechanisms to address emerging and re-emerging epidemic disea ses to reduce the impact on affected populations and limit international spread. Part of the policies and protocols are focused on the role of the healthcare team led by the nu rses on how to deal with diseased patients.

Nurses are central force team for preventing and responding to any pandemic, includi ng the COVID-19. This is due to nursing being the most significant healthcare profess

ion in the entire sector in any country. For example, in the United States, the number of nurses reaches approximately4 million nurses, while today; there are more than 20 million nurses worldwide. Nurses were and still are the most important service provid er and the front-line care professional that stand near the patients' journey when they f ace a complex disease that requires hospitalization and even intensive critical care, as the COVID-19 (Buheji and Buhaid , 2020) .

Professional nurses historically bring compassionate competent care to disaster respon se but are challenged to provide care when the nature of their work puts them at increa sed risk. Nurses struggle with feeling physically unsafe in the response situation, such as in times of scarce resources where supplies of such items as personal protective eq uipment (PPE) may be inadequate. Nurses are concerned about professional, ethical, a nd legal protection when asked to provide care in such high-risk situations, such as th eCOVID-19 pandemic (American Nurses Association, 2019).

Long-term care facilities (LTCFs), such as nursing homes and rehabilitative centers, a re facilities that care for people who suffer from physical or mental disability, some of who are of advanced age. The people living in LTCF are vulnerable populations who are at a higher risk for adverse outcome and for infection due to living in close proxim ity to others. Thus, LTCFs must take special precautions to protect their residents, em ployees, and visitors. Note that infection prevention and control (IPC) activities may a ffect the mental health and well-being of residents and staff, especially the use of PPE and restriction of visitors and group activities (World Health Organization , 2020).

References:

Ackermann, Maximilian, Stijn E. Verleden, Mark Kuehnel, Axel Haverich, Tobias W elte, Florian Laenger, Arno Vanstapel, et al. 2020. “Pulmonary Vascular Endothe

lialitis, Thrombosis, and Angiogenesis in Covid-19." *New England Journal of M edicine*, NEJMoa2015432. https://doi.org/10.1056/NEJMoa2015432.

American Nurses Association. 2019. "NURSES , ETHICS AND THE RESPONSE T O THE COVID – 19 COVID-19 PANDEMIC," 1–3.

Anne Kimball, ; Kelly M. Hatfield; Melissa Arons; Allison James; Joanne Taylor; Ke vin Spicer; Ana C. Bardossy; Lisa P. Oakley; Sukarma Tanwar; Zeshan Chisty; J eneita M. Bell Mark Methner; Josh Harney; Jesica R. Jacobs; Christina M. Carls on; Heather P. McL; Libby C. Pag, and PhD; Sujan C. Reddy; John A. Jernigan; Public Health – Seattle & King County; CDC COVID-19 Investigation Team Jes sica Gant; Jeffrey S. Duchin; Thomas A. Clark; Margaret A. Honein. 2020. "Asy mptomatic and Presymptomatic SARS-CoV-2 Infections in Residents of a Long-Term Care Skilled Nursing Facility —." *Morbidity and Mortality Weekly Report Summary, CDC* 69 (13): 377–81.

Beigel, John H, Kay M Tomashek, Lori E Dodd, Aneesh K Mehta, Barry S Zingman, Andre C Kalil, Elizabeth Hohmann, et al. 2020. "Remdesivir for the Treatment o f Covid-19 - Preliminary Report." *The New England Journal of Medicine*, 1–12. https://doi.org/10.1056/NEJMoa2007764.

Bhatraju, Pavan K., Bijan J. Ghassemieh, Michelle Nichols, Richard Kim, Keith R. Je rome, Arun K. Nalla, Alexander L. Greninger, et al. 2020. "Covid-19 in Criticall y Ill Patients in the Seattle Region — Case Series." *New England Journal of Med icine*, 2012–22. https://doi.org/10.1056/nejmoa2004500.

Buheji, Mohamed, and Nawal Buhaid. 2020. "Nursing Human Factor During COVID -19 Pandemic," no. April. https://doi.org/10.5923/j.nursing.20201001.02.

Cao, B., Y. Wang, D. Wen, W. Liu, Jingli Wang, G. Fan, L. Ruan, et al. 2020. "A Tri al of Lopinavir-Ritonavir in Adults Hospitalized with Severe Covid-19." *New En gland Journal of Medicine* 382 (19): 1787–99. https://doi.org/10.1056/NEJMoa2 001282.

Centers for Medicare & Medicaid Services. 2020. "COVID-19 Long-Term Care Facil ity Guidance," 2–4.

Chan, Jasper Fuk Woo, Shuofeng Yuan, Kin Hang Kok, Kelvin Kai Wang To, Hin Ch u, Jin Yang, Fanfan Xing, et al. 2020. "A Familial Cluster of Pneumonia Associa ted with the 2019 Novel Coronavirus Indicating Person-to-Person Transmission: A Study of a Family Cluster." *The Lancet* 395 (10223): 514–23. https://doi.org/1 0.1016/S0140-6736(20)30154-9.

Channappanavar, Rudragouda, Anthony R. Fehr, Jian Zheng, Christine Wohlford-Len ane, Juan E. Abrahante, Matthias Mack, Ramakrishna Sompallae, Paul B. McCra y, David K. Meyerholz, and Stanley Perlman. 2019. "IFN-I Response Timing Re lative to Virus Replication Determines MERS Coronavirus Infection Outcomes." *Journal of Clinical Investigation* 129 (9): 3625–39. https://doi.org/10.1172/JCI1 26363.

Dianna L. Ng,* Farida Al Hosani, y M. Kelly Keating,* Susan I. Gerber, z Tara L. Jo nes,* Maureen G. Metcalfe,* Suxiang Tong, X, Xx Ying Tao, x Negar N. Alami, {k Lia M. Haynes,** Mowafaq Ali Mutei, yy Laila Abdel-Wareth, zz Timothy M. Uyeki, and kk and Sherif R. Zaki* David L. Swerdlow,{{ Maha Barakat. 201 6. "Clinicopathologic, Immunohistochemical, and Ultrastructural Findings of a F atal Case of Middle East Respiratory Syndrome Coronavirus Infection in the Uni ted Arab Emirates, April 2014." *The American Journal of Pathology* 186 (Januar

y): 652e658.

Fan, Yan Ying, Zi Tong Huang, Li Li, Man Hui Wu, Tao Yu, Richard A. Koup, Robe rt T. Bailer, and Chang You Wu. 2009. "Characterization of SARS-CoV-Specific Memory T Cells from Recovered Individuals 4 Years after Infection." *Archives of Virology* 154 (7): 1093–99. https://doi.org/10.1007/s00705-009-0409-6.

Fei Xiao, Meiwen Tang, Xiaobin Zheng, Ye Liu, Xiaofeng Li, and Hong Shan. 2020. "Evidence for Gastrointestinal Infection of SARS-CoV-2." *Gastroenterology* 15 8 (February 2019): 1831–1833.

Gao, Jianjun, Zhenxue Tian, and Xu Yang. 2020. "Breakthrough: Chloroquine Phosp hate Has Shown Apparent Efficacy in Treatment of COVID-19 Associated Pneu monia in Clinical Studies." *BioScience Trends* 14 (1): 1–2. https://doi.org/10.558 2/BST.2020.01047.

Geleris, Joshua, Yifei Sun, Jonathan Platt, Jason Zucker, Matthew Baldwin, George H ripcsak, Angelena Labella, et al. 2020. "Observational Study of Hydroxychloroq uine in Hospitalized Patients with Covid-19." *New England Journal of Medicine*, 1–8. https://doi.org/10.1056/nejmoa2012410.

Goldman, Jason D, David C B Lye, David S Hui, Kristen M Marks, Raffaele Bruno, Rocio Montejano, Christoph D Spinner, et al. 2020. "Remdesivir for 5 or 10 Day s in Patients with Severe Covid-19." *The New England Journal of Medicine*, 1–1 1. https://doi.org/10.1056/NEJMoa2015301.

Guan, W., Z. Ni, Yu Hu, W. Liang, C. Ou, J. He, L. Liu, et al. 2020. "Clinical Charact eristics of Coronavirus Disease 2019 in China." *New England Journal of Medici ne* 382 (18): 1708–20. https://doi.org/10.1056/NEJMoa2002032.

Haagmans, Bart L., Thijs Kuiken, Byron E. Martina, Ron A.M. Fouchier, Guus F. Rimmelzwaan, Geert Van Amerongen, Debby Van Riel, et al. 2004. "Pegylated Interferon-α Protects Type 1 Pneumocytes against SARS Coronavirus Infection in Macaques." *Nature Medicine* 10 (3): 290–93. https://doi.org/10.1038/nm1001.

Huang, Chaolin, Yeming Wang, Xingwang Li, Lili Ren, Jianping Zhao, Yi Hu, Li Zhang, et al. 2020. "Clinical Features of Patients Infected with 2019 Novel Coronavirus in Wuhan, China." *The Lancet* 395 (10223): 497–506. https://doi.org/10.1016/S0140-6736(20)30183-5.

Hui Wang , Tieying Zeng , Xinjuan Wu, Hong Sun. 2020. "Holistic Care for Patients with Severe Coronavirus Disease 2019: An Expert Consensus." *International Journal of Nursing Sciences* 7: 128–34. https://doi.org/10.1016/j.ijnss.2020.03.010.

J.S.M Peiris. 2003. "Severe Acute Respiratory Syndrome (SARS)." *Journal of Clinical Virology* 28 (January): 245–47. https://doi.org/10.1016/S1386-6532(03)00250-6.

Jaimes, Javier A., Jean K. Millet, Alison E. Stout, Nicole M. André, and Gary R. Whittaker. 2020. "A Tale of Two Viruses: The Distinct Spike Glycoproteins of Feline Coronaviruses." *Viruses* 12 (1): 1–14. https://doi.org/10.3390/v12010083.

John M Nicholls, Leo L M Poon, Kam C Lee, Wai F Ng, Sik T Lai, Chung Y Leung, Chung M Chu, Pak K Hui, Kong L Mak, Wilina Lim, Kin W Yan, Kwok H Chan, Ngai C Tsang, Yi Guan, Kwok Y Yuen, J S Malik Peiris. 2003. "Lung Pathology of Fatal Severe Acute Respiratory Syndrome." *THE LANCET* 361: 1773–78.

Kuhn, J. H., W. Li, H. Choe, and M. Farzan. 2004. "Angiotensin-Converting Enzyme 2: A Functional Receptor for SARS Coronavirus." *Cellular and Molecular Life S*

ciences 61 (21): 2738–43. https://doi.org/10.1007/s00018-004-4242-5.

Kuiken, Thijs, Ron A.M. Fouchier, Martin Schutten, Guus F. Rimmelzwaan, Geert V an Amerongen, Debby Van Riel, Jon D. Laman, et al. 2003. "Newly Discovered Coronavirus as the Primary Cause of Severe Acute Respiratory Syndrome." *Lanc et* 362 (9380): 263–70. https://doi.org/10.1016/S0140-6736(03)13967-0.

Lai, Chih Cheng, Yen Hung Liu, Cheng Yi Wang, Ya Hui Wang, Shun Chung Hsueh, Muh Yen Yen, Wen Chien Ko, and Po Ren Hsueh. 2020. "Asymptomatic Carrie r State, Acute Respiratory Disease, and Pneumonia Due to Severe Acute Respirat ory Syndrome Coronavirus 2 (SARS-CoV-2): Facts and Myths." *Journal of Micr obiology, Immunology and Infection* 2 (xxxx). https://doi.org/10.1016/j.jmii.2020. 02.012.

Li, Gang, Xuejuan Chen, and Anlong Xu. 2003. "Profile of Specific Antibodies to the SARS-Associated Coronavirus [6]." *New England Journal of Medicine* 349 (5): 508–9. https://doi.org/10.1056/NEJM200307313490520.

Lirong Zou, M.Sc. Feng Ruan, M.Med, Mingxing Huang, Ph.D.Lijun Liang, Ph.D, H uitao Huang, B.Sc, Zhongsi Hong, M.D. Jianxiang Yu, B.Sc. Min Kang, M.Sc. Yingchao Song, B.Sc., Jinyu Xia, M.D. Qianfang Guo, M.Sc. Tie Song, M.Sc.H ui-Ling Yen, Ph.D. Malik Peiri, Ph.D., and B.Sc. Jianfeng He. 2020. "SARS-Co V-2 Viral Load in Upper Respiratory Specimens of Infected Patients." *New Engl and Journal of Medicine* 382 (12): 1175–77. https://doi.org/10.1056/NEJMc2000 231.

Liu, Jun, Peng Wu, Feng Gao, Jianxun Qi, Ai Kawana-Tachikawa, Jing Xie, Christop her J. Vavricka, Aikichi Iwamoto, Taisheng Li, and George F. Gao. 2010. "Nove

l Immunodominant Peptide Presentation Strategy: A Featured HLA-A*2402-Restricted Cytotoxic T-Lymphocyte Epitope Stabilized by Intrachain Hydrogen Bonds from Severe Acute Respiratory Syndrome Coronavirus Nucleocapsid Protein." *Journal of Virology* 84 (22): 11849–57. https://doi.org/10.1128/jvi.01464-10.

Matthay, Michael A, Lorraine B Ware, and Guy A Zimmerman. 2012. "The Acute Respiratory Distress Syndrome Find the Latest Version : Review Series The Acute Respiratory Distress Syndrome." *The Journal of Clinical Investigation* 122 (8): 2731–40. https://doi.org/10.1172/JCI60331.on.

Mehra, Mandeep R., Sapan S. Desai, SreyRam Kuy, Timothy D. Henry, and Amit N. Patel. 2020. "Cardiovascular Disease, Drug Therapy, and Mortality in Covid-19." *New England Journal of Medicine*, 1–8. https://doi.org/10.1056/nejmoa2007621.

Menachery, Vineet D., Alexandra Schäfer, Kristin E. Burnum-Johnson, Hugh D. Mitchell, Amie J. Eisfeld, Kevin B. Walters, Carrie D. Nicora, et al. 2018. "MERS-CoV and H5N1 Influenza Virus Antagonize Antigen Presentation by Altering the Epigenetic Landscape." *Proceedings of the National Academy of Sciences of the United States of America* 115 (5): E1012–21. https://doi.org/10.1073/pnas.1706928115.

Min, Chan Ki, Shinhye Cheon, Na Young Ha, Kyung Mok Sohn, Yuri Kim, Abdimadiyeva Aigerim, Hyun Mu Shin, et al. 2016. "Comparative and Kinetic Analysis of Viral Shedding and Immunological Responses in MERS Patients Representing a Broad Spectrum of Disease Severity." *Scientific Reports* 6 (May): 1–12. https://doi.org/10.1038/srep25359.

Peiris, J. S.M., C. M. Chu, V. C.C. Cheng, K. S. Chan, I. F.N. Hung, L. L.M. Poon, K.

I. Law, et al. 2003. “Clinical Progression and Viral Load in a Community Outbr eak of Coronavirus-Associated SARS Pneumonia: A Prospective Study.” *Lancet* 361 (9371): 1767–72. https://doi.org/10.1016/S0140-6736(03)13412-5.

Perlman, Stanley, and Jason Netland. 2009. “Coronaviruses Post-SARS: Update on R eplication and Pathogenesis.” *Nature Reviews Microbiology* 7 (6): 439–50. https: //doi.org/10.1038/nrmicro2147.

Rockx, Barry, Thijs Kuiken, Sander Herfst, Theo Bestebroer, Mart M. Lamers, Bas B. Oude Munnink, Dennis de Meulder, et al. 2020. “Comparative Pathogenesis of COVID-19, MERS, and SARS in a Nonhuman Primate Model.” *Science* 7314 (A pril): eabb7314. https://doi.org/10.1126/science.abb7314.

Rothan, Hussin A., and Siddappa N. Byrareddy. 2020. “The Epidemiology and Patho genesis of Coronavirus Disease (COVID-19) Outbreak.” *Journal of Autoimmunit y* 109 (February): 102433. https://doi.org/10.1016/j.jaut.2020.102433.

Rudragouda Channappanavar, Anthony R. Fehr, Rahul Vijay, Matthias Mack, Jincun Zhao, David K. Meyerholz, Stanley Perlman, and Correspondence. 2016. “Dysre gulated Type I Interferon and Inflammatory Monocyte-Macrophage Responses C ause Lethal Pneumonia in SARS-CoV-Infected Mice.” *Cells Host&mMicrobe* 19: 181–193.

Shi, Heshui, Xiaoyu Han, Nanchuan Jiang, Yukun Cao, Osamah Alwalid, Jin Gu, Yan qing Fan, and Chuansheng Zheng. 2020. “Radiological Findings from 81 Patient s with COVID-19 Pneumonia in Wuhan, China: A Descriptive Study.” *The Lanc et Infectious Diseases* 20 (4): 425–34. https://doi.org/10.1016/S1473-3099(20)30 086-4.

Shieh, Wun Ju, Cheng Hsiang Hsiao, Christopher D. Paddock, Jeannette Guarner, Cy nthia S. Goldsmith, Kathleen Tatti, Michelle Packard, et al. 2005. "Immunohisto chemical, in Situ Hybridization, and Ultrastructural Localization of SARS-Assoc iated Coronavirus in Lung of a Fatal Case of Severe Acute Respiratory Syndrom e in Taiwan." *Human Pathology* 36 (3): 303–9. https://doi.org/10.1016/j.humpat h.2004.11.006.

Simmons, Graham, Jacqueline D. Reeves, Andrew J. Rennekamp, Sean M. Amberg, Andrew J. Piefer, and Paul Bates. 2004. "Characterization of Severe Acute Respi ratory Syndrome-Associated Coronavirus (SARS-CoV) Spike Glycoprotein-Med iated Viral Entry." *Proceedings of the National Academy of Sciences of the Unite d States of America* 101 (12): 4240–45. https://doi.org/10.1073/pnas.0306446101.

Sirina Keesara, M.D., Andrea Jonas, M.D., and Kevin Schulman, M.D. 2020. "Covid-19 and Health Care's Digital Revolution." *New England Journal of Medicine* 38 2 (1). https://doi.org/DOI: 10.1056/NEJMp2009027.

Snijder, Eric J., Yvonne van der Meer, Jessika Zevenhoven-Dobbe, Jos J. M. Onderw ater, Jannes van der Meulen, Henk K. Koerten, and A. Mieke Mommaas. 2006. "Ultrastructure and Origin of Membrane Vesicles Associated with the Severe Ac ute Respiratory Syndrome Coronavirus Replication Complex." *Journal of Virolo gy* 80 (12): 5927–40. https://doi.org/10.1128/jvi.02501-05.

Sufang Tian, MD, PhD, Weidong Hu, MD, b Li Niu, MD, PhD, Huan Liu, MS, a Hai bo Xu, MD, PhD, Shu-Yuan Xiao, MD. 2020. "Pulmonary Pathology of Early-P hase 2019 Novel Coronavirus (COVID-19) Pneumonia in Two Patients With Lu ng Cancer Including This Research Content - Immediately Available in PubMed Central and Other Publicly Funded Repositories , Such as the WHO COVID Dat

aba." *Journal of Thoracic Oncology Vol.* 15: 700–704.

Tang, Fang, Yan Quan, Zhong-Tao Xin, Jens Wrammert, Mai-Juan Ma, Hui Lv, Tian-Bao Wang, et al. 2011. "Lack of Peripheral Memory B Cell Responses in Recove red Patients with Severe Acute Respiratory Syndrome: A Six-Year Follow-Up St udy." *The Journal of Immunology* 186 (12): 7264–68. https://doi.org/10.4049/jim munol.0903490.

Wan, Yushun, Jian Shang, Rachel Graham, Ralph S. Baric, and Fang Li. 2020. "Rece ptor Recognition by the Novel Coronavirus from Wuhan: An Analysis Based on Decade-Long Structural Studies of SARS Coronavirus." *Journal of Virology* 94 (7). https://doi.org/10.1128/jvi.00127-20.

Williams, Andrew E., and Rachel C. Chambers. 2014. "The Mercurial Nature of Neut rophils: Still an Enigma in ARDS?" *American Journal of Physiology - Lung Cell ular and Molecular Physiology* 306 (3). https://doi.org/10.1152/ajplung.00311.2 013.

Wit, Emmie De, Neeltje Van Doremalen, Darryl Falzarano, and Vincent J. Munster. 2 016. "SARS and MERS: Recent Insights into Emerging Coronaviruses." *Nature Reviews Microbiology* 14 (8): 523–34. https://doi.org/10.1038/nrmicro.2016.81.

World Health Organization. 2020. "Infection Prevention and Control Guidance for Lo ng-Term Care Facilities in the Context of COVID-19," no. March: 1–5.

Wu, Fan, Su Zhao, Bin Yu, Yan Mei Chen, Wen Wang, Zhi Gang Song, Yi Hu, et al. 2020. "A New Coronavirus Associated with Human Respiratory Disease in Chin a." *Nature* 579 (7798): 265–69. https://doi.org/10.1038/s41586-020-2008-3.

Xu, Zhe, Lei Shi, Yijin Wang, Jiyuan Zhang, Lei Huang, Chao Zhang, Shuhong Liu, e

t al. 2020. “Pathological Findings of COVID-19 Associated with Acute Respirat ory Distress Syndrome.” *The Lancet Respiratory Medicine* 8 (4): 420–22. https:// doi.org/10.1016/S2213-2600(20)30076-X.

Yang, Xiaobo, Yuan Yu, Jiqian Xu, Huaqing Shu, Jia Xia, Hong Liu, Yongran Wu, et al. n.d. “Clinical Course and Outcomes of Critically Ill Patients with SARS-CoV -2 Pneumonia in Wuhan , China : A Single-Centered , Retrospective , Observatio nal Study.” *The Lancet Respiratory* 8 (5): 475–81. https://doi.org/10.1016/S2213 -2600(20)30079-5.

Yang, Yang, Ling Zhang, Heyuan Geng, Yao Deng, Baoying Huang, Yin Guo, Zheng dong Zhao, and Wenjie Tan. 2013. “The Structural and Accessory Proteins M, O RF 4a, ORF 4b, and ORF 5 of Middle East Respiratory Syndrome Coronavirus (MERS-CoV) Are Potent Interferon Antagonists.” *Protein and Cell* 4 (12): 951– 61. https://doi.org/10.1007/s13238-013-3096-8.

Zhou, Peng, Xing Lou Yang, Xian Guang Wang, Ben Hu, Lei Zhang, Wei Zhang, Ha o Rui Si, et al. 2020. “A Pneumonia Outbreak Associated with a New Coronavir us of Probable Bat Origin.” *Nature* 579 (7798): 270–73. https://doi.org/10.1038/s 41586-020-2012-7.