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Might COVID-19 Respond to EtOH *in vivo*?

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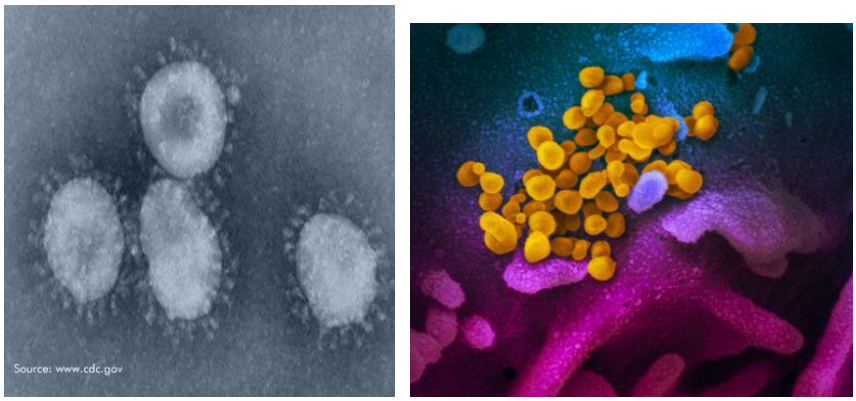
Introduction

The respiratory illness called COVID-19 caused by SARS-CoV-2 [Severe Acute Respiratory Syndrome coronavirus] is an emergent serious pandemic threat because of its high transmission rate (contagion factor, r_0 = ~ 2.2), its multiple pathways around the globe leading to pandemic, its relatively high fatality rate compared to both the common coronaviruses and influenza viruses, its shift of increased affinity for the human receptors in the lung and heart, the longer viability of the virus in the air and on surfaces, and the very existence of long-term super-spreaders with the absence of signs or symptoms. First appearing in Wuhan, Hubei Province, China, it has inexorably spread [1,2,3]. While the world anxiously awaits a vaccine expected next year and increased testing kits, in the interim, the increased prevalence is an opportunity to review new findings, possible palliation(s) and diagnostic signs, and to reconsider where medical advantages can be taken, and as this short review suggests, that may include use of antihypertensive change, or ethanol and/or other GRAS (generally recognized as safe) materials, in vivo.

What are Coronaviruses?

Coronaviruses are medium-sized (~125 nm) enveloped spherical positive-single stranded RNA Nidovirales viruses (**(+)**ssRNA virus) which replicate using nested messenger RNAs [mRNAs ("nido-" for "nest")] and are classified as type IV under the Baltimore classification. Coronavirus RNA has the largest known viral RNA genome size, and is surrounded by a nucleocapsid and a membrane carrying a characteristic “crown”-like appearance of glycoprotein spikes for which they are named. First seen in early electron micrographs, the coronavirus "crown" spike are due to a protein which is glycosylated, trimeric, and controls receptor binding to the next victim cell.



Human coronaviruses – (left) Four coronavirus showing crown on transmission electron microscopy; (right) A cluster of coronaviruses leaving a host cell observed by SEM.

The viral genome of SARS-CoV-2 has been sequenced and made available online. It is 75-80% identical to SARS-CoV and very similar to bat coronaviruses. RNA viruses are genetically error-prone due to their RNA-dependent RNA polymerases. A benefit of the high mutation rates is their ability to shift their structure for new host tissues and ecosystems. Coronaviruses have been shown to have as high as a 25% frameshift rate in vitro which may increase their effective protein repertoire and mutation rate, and are well known for their ability to change tropism [4,5].

SARS-CoV mutated during the 2002–2004 epidemic as it increased binding to the human receptor which enhanced virulence. SARS-CoV-2 has already mutated. Two strains, L and S have appeared. L is the most aggressive, and has become less prevalent since early January. To some extent these divergent strains can also be used to classify the transmission times between population cohorts to trace spread of this virus.

Origin of the Deadly Coronoviruses

Hypotheses for their origin include SARS-CoV's emergence from bats to infected animals sold in live-animal exotic wet-markets which also enable direct contact to large human crowds. MERS-CoV is believed to have passed from camels to humans. This group of viral illnesses are termed 'epizootics' and their fatal human "spillover" occurs from many types of viruses including poultry-derived influenza viruses (labeled H5N1 and H7N9) and the three coronavirus infections transmitted to humans in the last 3 decades.

Diseases Coronoviruses produce

Human coronaviruses account for ~7 percent of all acute upper respiratory tract infections in adults, with seasonal increases to circa 30 percent. Specifically the common types 229E, NL63, OC43, and HKU1 cause mild to moderate upper-respiratory tract diseases such as the common cold. Although symptoms and signs are usually cough, runny/stuffy nose, fever, sore throat, headache, and diarrhea; pneumonia and death less frequently. However, there are at least three more lethal types including Severe Acute Respiratory Syndrome coronavirus (SARS-CoV), Middle East Respiratory Syndrome coronavirus (MERS-CoV) and the newly identified coronavirus disease 2019 (COVID-19). These are the types that currently cause the most concern around the world. The MERS-CoV (Middle East Respiratory Syndrome) coronavirus in 2012 had a high mortality rate of 45% in 9 countries [6].

Pathology Enabling Targeting of the Human Victim's Cell

Coronaviruses enter human cells after their glycoproteins bind to cell surface proteins. The angiotensin-converting enzyme 2 (hACE2) site on human cells is the receptor for the S-protein in SARS-CoV, coronavirus NL63, and SARS-CoV-2. Angiotensin converting enzyme 2 (ACE2) is expressed in human airway epithelia and lung parenchyma, which may explain in part why both SARS-CoV and MERS-CoV infect intrapulmonary epithelial cells more than cells of the upper airways. It has now been shown that ACE2 is the entry point for SARCoV[7]. Undifferentiated

cells expressing very small amounts of ACE2 were poorly infected with SARS-CoV, as opposed to well-differentiated cells fully expressing ACE2 were readily infected [8].

ACE2 is a monocarboxypeptidase which converts angiotensin II into angiotensin 1–7 (Ang 1–7) which counter-regulates angiotensin II, protecting against heart failure while preserving ejection fraction [9]. ACE2 forms a homo-dimer which docks with two of the S protein trimers of the coronavirus through polar residues [10]. SARS-CoV-2 binds tightly to the site with higher affinity possibly explaining why it is more contagious than previous viruses. In fact, 2019-nCoV grows better in primary human airway epithelial cells than in standard tissue-culture cells.
Thereafter, when coronaviruses (Nidovirales viruses) take over the host, their replication of new viral RNA uses a unique pathway where the RNA polymerase establishes multiple locations along the nucleic acid being copied for new virus mRNA molecules to be growing (nesting) simultaneously.

Transmission of Coronavirus

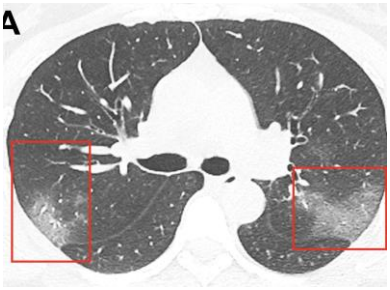
Transmission of SARS-CoV, MERS-CoV and 2019-nCoV occurs to a large extent by means of superspreading events. Superspreading transmission includes person-to-person contact and by contact of contaminated surfaces. 2019-nCoV spreads by both large droplets, direct contact, aerosols and fomites, similar to SARS-CoV and MERS-CoV. [11]. Strain 229E of MERS-CoV survives more than three hours after drying [12]. Severe Acute Respiratory Syndrome (SARS) coronavirus, Middle East Respiratory Syndrome (MERS) coronavirus or endemic human coronaviruses (HCoV) can persist on inanimate surfaces like metal, glass or plastic for up to 9 days. Some disinfectant agents effectively reduce coronavirus infectivity within 1 minute such 62%–71% ethanol, 0.5% hydrogen peroxide or 0.1% sodium hypochlorite.][13].

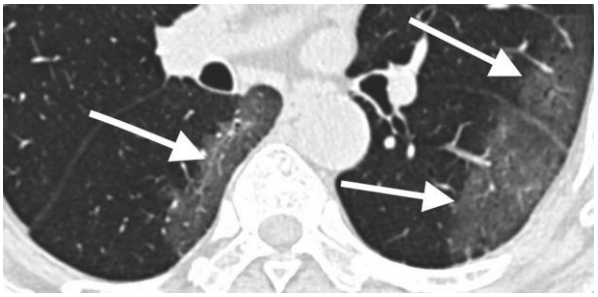
What is the Clincal Medical Result/Outcome?

As of January 24, 2020, there were more than 800 reported cases, with a mortality rate of ~3% [1,2,14]. The median age of the patients was 47 years. 56-58% of the patients were male. There were no cases in children younger than 15 years of age; perhaps heralding that differentiation and an adult milieu may have a role. The median incubation period was 4 days (interquartile range, 2 to 7), and Li et al. report a mean interval of 9.1 to 12.5 days between the onset of illness and hospitalization. Zoonotic SARS coronaviruses replicate in the lungs and intestine with an infection that resembles viral pneumonia [fever (43.8% on admission and 88.7% during hospitalization), cough (67.8%), shortness of breath, fatigue, and myalgias]. Some reports state that diarrhea was uncommon (3.8%), although other reports state 40% of patients get diarrhea -- including with SARS-CoV genomic material detectable in stool for more than 10 weeks after onset of the initial illness [15]. Lymphocytopenia was present in 83.2% of the patients on admission.

Radiologic Signs of 2019-nCoV

2019-nCoV typically manifests on non-contrast CT scans with diffuse bilateral confluent multifocal patchy ground-glass opacities in the lower lobes with a peripheral distribution, occasionally with consolidative pulmonary opacities. On admission, this ground-glass opacity was the most common radiologic finding on chest computed tomography (CT) (56.4%). No radiographic or CT abnormality was found in 157 of 877 patients (17.9%) with nonsevere disease and in 5 of 173 patients (2.9%) with severe disease. [16]. Other radiographic signs include nodular opacities, "crazy-paving pattern". Lung cavitation, discrete pulmonary nodules without the opacities, pleural effusions and lymphadenopathy are characteristically absent in cases of 2019-nCoV [17,18].





Medical Therapies

Therapy currently consists of supportive care. Investigational therapies include antivirals: lopinavir–ritonavir, interferon-1β, the RNA polymerase inhibitor remdesivir, chloroquine, and a variety of traditional Chinese medicine products, and as obtainable globulin from recovered individuals, and monoclonal antibodies.

Differences in outcome

The seriousness, susceptibility, signs, symptoms, and outcome of 2019-nCoV/SARS-CoV-2 infection is obviously multifactorial, and it involves age, high blood pressure (HPB), and ACE2 levels, and maybe human ACE2 variants.

1. The first factor is likely the strain of the virus encountered. As mentioned earlier, there are two main strains at this time, with two different levels of aggressiveness.
2. High blood pressure appears to be a major death risk, about 50% of the fatalities had hypertension in Wuhan [19].
3. This might be related to the ACE2 binding site. Asian males may have higher expression of ACE26. However, there is not yet evidence supporting that 1700 variants of ACE2 mutants have different susceptibility to SARS-CoV-2 [20].
4. Normal differences of age, susceptibility, nutritional and immunologic status.
5. Secondary illnesses.
6. History of treatment. Almost half of the patients requiring mechanical ventilation die of their disease, and those who recover were ventilated early.
7. Age and Ageism. Patients over 65 "are not even assessed" at some locations.

Could Ethanol have a Role?

Alcohol is a major coronavirus disinfectant. Could it have a "protective" role when applied in low quantities in vivo? Alcohol has been shown to have similar activity against HCoV-229E in a cultured cell system. In addition, human coronaviruses, including CoV-229E and SARS-CoV, are reportedly highly susceptible to 70% ethanol, with a reduction of viability by greater than 1/1000 within seconds, albeit with in vitro data. Propanol (100% and 70%) and ethanol (78%) demonstrated reduction of SARS-CoV to levels below detection in 30 seconds; 60 seconds were required for wine vinegar [21,22].

Whether due to personal preference, customs, economics or law, alcohol consumption can vary considerably worldwide. On March 10, 2020, it was reported that more than 20 Iranians died after imbibing industrial-strength alcohol (methanol and antifreeze) amid rumors that it would protect them [23]. In such Moslem countries, drinking, selling or buying alcohol is general prohibited perhaps consistent with the fact that MERS-CoV (coronavirus in 2012 had a high mortality rate of 45% in 9 countries where alcohol is strictly controlled [1] although more research is needed to determine if there are other links.

There are medical roles of alcohol throughout medicine, obstetrics and surgery. Given the roles of fear [24] and terror in the latest coronavirus pandemic there are, then, perhaps more than one reason to consider small amounts of ethanol in a controlled study.

However, one matter that must be considered is that ethanol quickly also inactivates hydroxyl radical which is used throughout the human immune system. Another effect that should be determined and evaluated is the concern that potential inhibitors of ACE2 may lead to its later upregulation and the potential for increased future susceptibility. However, it has also been observed that at least one type of SARS actually down-regulates ACE2, and so both competing roles must be measured and sorted out [24]. Yet another issue is that larger intakes of alcohol are linked to increases in hypertension [25] – an attribute already described as a possible indicator for concern during treatment. Nevertheless, for this deadly illness, every antidote, therapy, and approach needs to be on the table given the potential panic and economic destruction it can cause.

Researchers and medical providers should take a closer look at better/alternate controls of hypertension, especially in the elderly and alcohol use. Sought is clinical significance before statistical significance given the velocity at which this disease is propagating; sometimes, what we need, might be right at our fingertips.

References

[1] Clinical Characteristics of Coronavirus Disease 2019 in China [Wei-jie Guan, Ph.D., Zheng-yi Ni, M.D., Yu Hu, M.D., Wen-hua Liang, Ph.D., Chun-quan Ou, Ph.D., Jian-xing He, M.D., Lei Liu, M.D., Hong Shan, M.D., Chun-liang Lei, M.D., David S.C. Hui, M.D., Bin Du, M.D., Lan-juan Li, M.D., Guang Zeng, M.Sc., Kwok-Yung Yuen, Ph.D., Ru-chong Chen, M.D., Chun-li Tang, M.D., Tao Wang, M.D., Ping-yan Chen, M.D., Jie Xiang, M.D., Shi-yue Li, M.D., Jin-lin Wang, M.D., Zi-jing Liang, M.D., Yi-xiang Peng, M.D., Li Wei, M.D., Yong Liu, M.D., Ya-hua Hu, M.D., Peng Peng, M.D., Jian-ming Wang, M.D., Ji-yang Liu, M.D., Zhong Chen, M.D., Gang Li, M.D., Zhi-jian Zheng, M.D., Shao-qin Qiu, M.D., Jie Luo, M.D., Chang-jiang Ye, M.D., Shao-yong Zhu, M.D., and Nan-shan Zhong, M.D.]
https://www.nejm.org/doi/full/10.1056/NEJMoa2002032
[2] https://www.nejm.org/doi/full/10.1056/NEJMe2002387
Covid-19 — Navigating the Uncharted Anthony S. Fauci, M.D., H. Clifford Lane, M.D., and Robert R. Redfield, M.D.
[3] open source site: https://www.cambridge.org/core/browse-subjects/medicine/coronavirus-free-access-collection
[4] Fehr, Anthony R, and Stanley Perlman. "Coronaviruses: an overview of their replication and pathogenesis." Methods in molecular biology (Clifton, N.J.) vol. 1282 (2015): 1-23. doi:10.1007/978-1-4939-2438-7_1
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4369385/
[5] R.J.G. Hulswit, C.A.M. de Haan, B.-J. Bosch, Chapter Two - Coronavirus Spike Protein and Tropism Changes, Advances in Virus Research, Academic Press, Volume 96, 2016, Pages 29-57, ISSN 0065-3527, ISBN 9780128047361, https://doi.org/10.1016/bs.aivir.2016.08.004. (http://www.sciencedirect.com/science/article/pii/S0065352716300434)
[6] Penttinen, P. et al. 2013. Taking stock of the first 133 MERS coronavirus cases globally – is the epidemic changing? Euro Surveillance. 18: 1-5].
[7] Hoffmann et al., SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor, Cell (2020), https://doi.org/10.1016/j.cell.2020.02.052
[8] Hong Peng Jia,1 Dwight C. Look,2 Lei Shi,2 Melissa Hickey,1 Lecia Pewe,1 Jason Netland,1 Michael Farzan,3 Christine Wohlford-Lenane,1 Stanley Perlman,1 and Paul B. McCray, Jr1,*, ACE2 Receptor Expression and Severe Acute Respiratory Syndrome Coronavirus Infection Depend on Differentiation of Human Airway Epithelia, J Virol. 2005 Dec; 79(23): 14614–14621, doi: 10.1128/JVI.79.23.14614-14621.2005,
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1287568/
[9] Vaibhav B. Patel, Jiu-Chang Zhong, Maria B. Grant, and Gavin Y. Oudit, Circulation Research, 118, 8, Role of the ACE2/Angiotensin 1–7 Axis of the Renin–Angiotensin System in Heart Failure, 15 Apr 2016
https://doi.org/10.1161/CIRCRESAHA.116.307708Circulation Research. 2016;118:1313–1326
https://www.ahajournals.org/doi/full/10.1161/CIRCRESAHA.116.307708
[10] Structural basis for the recognition of the SARS-CoV-2 by full-length human ACE2, Renhong Yan1,2, Yuanyuan Zhang1,2,*, Yaning Li3,*, Lu Xia1,2, Yingying Guo1,2, Qiang Zhou1,2,†, Science 04 Mar 2020: DOI: 10.1126/science.abb2762
https://science.sciencemag.org/content/early/2020/03/03/science.abb2762?rss=1].
[11]Editorial January 24, 2020, NEJM.org.
https://www.nejm.org/doi/full/10.1056/NEJMe2001126]

[12] Wang, X-W., et al. 2005. Study on the resistance of severe acute respiratory syndrome-associated coronavirus. Journal of Virological Methods. 126: 171-177.].
[13] Potential role of inanimate surfaces for the spread of coronaviruses and their inactivation with disinfectant agents GünterKampf https://doi.org/10.1016/j.infpip.2020.100044Get rights and content
[14] Qun Li, Xuhua Guan, Peng Wu, et. al. Early Transmission Dynamics in Wuhan, China, of Novel Coronavirus–Infected Pneumonia. New England Journal of Medicine. Published online Jan. 29, 2020. DOI: 10.1056/NEJMoa2001316. Accessed Jan. 31, 2020.
[15] Leung, W. et al. 2003. Enteric involvement of severe acute respiratory syndrome-associated coronavirus infection. Gastroenterology. 125: 1011-1017.].
[16] Radiological Society of North America] Ct https://www.itnonline.com/content/radiologists-describe-coronavirus-ct-imaging-features Computed Tomography (CT) | February 05, 2020 Radiologists Describe Coronavirus CT Imaging Features].
[17] Radiological Presentation of Coronavirus on CT Imaging, Coronavirus Patient CT Scans Reveal Imaging Features February 10, 2020 https://www.itnonline.com/article/ct-imaging-2019-novel-coronavirus-2019-ncov-pneumonia, Computed Tomography (CT) | January 31, 2020
[18] Junqiang Lei, Junfeng Li, Xun Li, Xiaolong Qi. CT Imaging of the 2019 Novel Coronavirus (2019-nCoV) Pneumonia. Radiology 2020 https://doi.org/10.1148/radiol.2020200236 Accessed Jan 31, 2020
[19] March 09, 2020 20:39 Bloomberg].
[20] Yanan Cao, Lin Li, Zhimin Feng, Shengqing Wan, Peide Huang, Xiaohui Sun, Fang Wen, Xuanlin Huang, Guang Ning & Weiqing Wang Cell Discovery volume 6, Article number: 11 (2020)]
[21] [Rabenau, H. et al. 2005. Stability and inactivation of SARS coronavirus. Medical Microbiology and Immunology. 194: 1-6.
[22] Rabenau, H. et al. 2005. Efficacy of various disinfectants against SARS coronavirus. Journal of Hospital Infection. 61: 107-111.
[23] Dozens in Iran die from drinking bootleg alcohol to prevent coronavirus infection: reports Danielle Wallace, Fox News, March 10, 2020].
https://www.foxnews.com/world/iran-coronavirus-dozens-die-bootleg-alcohol-poisoning
[24] Another Decade, Stanley Perlman, M.D., Ph.D., A striking feature of the SARS epidemic was that fear played a major role in the economic and social consequences
[25] Ilona Glowacka, Stephanie Bertram, Petra Herzog, Susanne Pfefferle, Imke Steffen, Marcus O. Muench, Graham Simmons, Heike Hofmann, Thomas Kuri, Friedemann Weber, Jutta Eichler, Christian Drosten, Stefan Pöhlmann, Differential Downregulation of ACE2 by the Spike Proteins of Severe Acute Respiratory Syndrome Coronavirus and Human Coronavirus NL63, Journal of Virology Dec 2009, 84 (2) 1198-1205; DOI: 10.1128/JVI.01248-09
https://jvi.asm.org/content/84/2/1198.abstract?site=JVirol&utm_source=TrendMDJVirol&utm_medium=TrendMDJVirol&utm_campaign=trendmdalljournals_0
[26] Husain, Kazim et al. "Alcohol-induced hypertension: Mechanism and prevention." World journal of cardiology vol. 6,5 (2014): 245-52. doi:10.4330/wjc.v6.i5.245
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4038773/