Are we treating Covid-19 the wrong way?

A Deep Dive Into SARS-CoV-2:
Understanding the virus and its effect on the respiratory system.

SARS, MERS, and SARS-Cov-2 all share similar properties. They cause rapid onset ARDS and have varying differences in animal hosts, infectivity, virulence, and mortality. We all know that the virus enters cells via the ACE2 receptor, then spreads throughout the body. We have been using evidence-based practices which have worked in every critical care unit across the world to care for these severe ARDS patients. This disease is moving faster than we ever imagined. People may think the strain on hospital systems is just a failure of public health but I have a different theory. Is it the fault of the virus, or our lack of understanding on how it works?

One of the most exciting things about working in critical care is that our job is to come up with a presumed diagnosis, an evidence-based treatment plan, act, and see how the body reacts in real time. This is hypothesis testing that we all learned in basic science. We knew this disease was coming for quite a while and thought we were prepared. This preparation has been too little and too late. The Doctors in countries hit first by this virus gave us all the information we needed: the epidemiological data, the lab characteristics, and the treatments that worked for them. They threw the whole toolbox at these patients to see what worked!
One of my frustrations is that the only measure to control the spread of this virus is absolute quarantine in the community. This is out of our control since this responsibility lays in the hands of our elected officials.

The research done on SARS and MERS gave us extensive information about this type of virus. Studies from cardiology journals, lab research, and genetic databases have given us all the information we need about ACE2 receptors in the human body. Sadly, this disease is moving like wildfire and we don't have the time to type the right words into Pubmed®. By the time it burns through our country, someone will have the same ideas we have below. We are not unique, we are just interested fellows who saw the covid-19 tsunami warning, saw the water level drop before the wave hit, and now we have some time to compile this while you are all trying to tread water while taking care of critically ill patients.

Hypothesis:
The reason SARS/MERS/SARS-CoV-2 cause ARDS is because of which cells they preferentially infect in the lung, the effect on the depletion of those cells, and the immune response to this infection. *This assumes that the SARS literature also applies to SARS-CoV-2*.

1) Which cells does this virus really care about? It's a virus, all it cares is that you have an ACE2 enzyme on your surface and you are a cell. In a study from 2007 on SARS, researchers found that ACE2 was present in high concentrations on the following tissues: lung alveolar epithelial cells (type II pneumocytes -T2P) and enterocytes of the small intestine[1]. Yes, you read that right, a paper from ***2007.***
2) What is the function of the T2P? production of surfactant, ion transport, proliferation and differentiation into type l cells after cellular injury for damage repair.

3) Why is surfactant so important in the lung? "High surface tension at the air–liquid interface has important effects on the alveolar micro-architecture and leads to a reduction in alveolar surface area by causing **collapsibility of airspaces**. This is counteracted by the intra-alveolar surfactant through **reduction of surface tension at end-expiration**[2]"
4) Does SARS (and possibly SARS-CoV-2) preferentially infect T2P? Yes! "SARS-CoV replicates in primary human alveolar type II cell cultures but not in type I-like cells[3]"
5) What is the effect on depletion of the T2P? Loss of surfactant with a resultant increase of surface tension during end-expiration and alveolar collapse[2] (atelectotrauma). "Cyclical recruitment and derecruitment of lung parenchyma (R/D) remains a serious problem in ALI/ARDS patients, defined as atelectotrauma[4]"
6) In an autopsy review from SARS cases in Singapore, they noted injury to bronchiolar and alveolar epithelium [diffuse alveolar damage], and type II pneumocyte multinucleation[5]." Although the authors stated it was unclear which was the causative agent.
7) What is the effect of the immune response at this level? In two autopsies done on Covid-19 patients in china, "edema, proteinaceous exudate, focal reactive hyperplasia of pneumocytes with patchy inflammatory cellular infiltration [diffuse alveolar damage], and multinucleated giant cells [T2P][6]" was seen on one of those patients. There were even suspected viral inclusions in these type 2 pneumocytes (Fig 2D).
8) Why do some people have no or mild disease while others have severe disease? "the expression of [ACE2], the receptor for SARS-CoV, was quite variable among different individuals, and **cells from different donors differed in their susceptibility to SARS-CoV infection**[7]"
9) Possible reason older patients have higher mortality?
    a. "SARS-CoV enters the host; infects the BASCs [stem cells] of the lungs and controls its developmental stages via the molecular switches-miRNAs. Co-option of host miRNAs by viruses reveal their intelligent plan to control their replication in order to evade immune elimination until they undergo successful transmission and establish a strong infection. Thereafter, they undergo rapid mutation to maximize the target-miRNA mismatches and enhance their replication before the cell reaches at a fully differentiated state. On successful replication, the virus infects resident, infiltrating, and circulating immune cells. The circulating immune cells carry the virus to other organs and causes damages to the immune cells of spleen, peripheral and central lymph nodes and other lymphoid tissues. The immune defense being weakened significantly, leads to rapid deterioration of the pneumonia[8]" I suspect that is why we see such marked lymphopenia in these covid-19 patients[9].
    b. "possible involvement of lung stem/progenitor cells, in addition to pneumocytes, in severe acute respiratory syndrome coronavirus infection, accounting for the continued deterioration of lung tissues and apparent loss of capacity for lung repair[10]"

c. *Younger patients may have more pulmonary stem cells and can repair the damage done by the virus. Just have to beat the clock of the infection and inflammation phases and go to the repair phase* - conjecture

More to come on implications for therapy? **Below are my own opinions regarding what I have learned about the mechanisms of this disease.** They have not been tested in a randomized controlled fashion, but involve minimal risk to the patient and potential avoidance of intubation. I call upon you to do the research on your own patients.

Want a Hint? Look at the Huff cough from CF literature (https://youtu.be/8UKd-GRNUFk) to clear trapped air (low frequency cough) from panbronchiolitis during the exudative phase, mobilize small airways debris to the larger airways to clear it (high frequency cough), an inspiratory hold, high flow devices, or even some form of positive flow for PEEP and recruit alveolar units. It may only take low flow nasal cannula to prevent atelectotrauma.
Proper chest physiotherapy with proning for postural drainage.

Listening to the patient's chest you may hear an absent expiratory phase because the small airways are obstructed. You will not hear wheezing because these are the small airways. You will hear air trapping if you ask them to take a deep breath, hold it, and exhale completely. Repeat this maneuver after the high frequency cough and the air trapping should be GONE.

Want to see the effect of de-recruitment? - https://youtu.be/oKH7CtsEgHw

Try having a stable Covid-19 patient sing while on oxygen supplementation[11]

If a patient is acutely short of breath and dyspneic, try applying NRB for nitrogen washout and relief of trapped air then prone the non-intubated and awake patient for manual percussive chest PT. They don't need to be intubated for chest PT. You will be very underwhelmed by the amount of secretions, so trust your patient if they feel better.

Wear proper protection if concerned about exposure risk, and have the patient wear a mask.

Try metered dose inhaler bronchodilators (suspected bronchiolitis) and inhaled corticosteroids. A small pre-print article of 26 patients from china showed significant improvement on duration of oxygen use, and improved radiographic findings[11], which conflicts with data from SARS/MERS.

1. Hamming I, Timens W, Bulthuis ML, Lely AT, Navis G, van Goor H. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. *J Pathol*. 2004;203(2):631–637. doi:10.1002/path.1570
2. Knudsen L, Ochs M. The micromechanics of lung alveoli: structure and function of surfactant and tissue components. *Histochem Cell Biol*. 2018;150(6):661–676. doi:10.1007/s00418-018-1747-9
3. Mossel EC, Wang J, Jeffers S, et al. SARS-CoV replicates in primary human alveolar type II cell cultures but not in type I-like cells. *Virology*. 2008;372(1):127–135. doi:10.1016/j.virol.2007.09.045
4. Shi C, Boehme S, Hartmann EK, Markstaller K. Novel technologies to detect atelectotrauma in the injured lung. *Exp Lung Res*. 2011;37(1):18–25. doi:10.3109/01902148.2010.501402
5. Franks, T. J., Chong, P. Y., Chui, P., Galvin, J. R., Lourens, R. M., Reid, A. H., Selbs, E., Mcevoy, C. P. L., Hayden, C. D. L., Fukuoka, J., Taubenberger, J. K., & Travis, W. D. (2003). Lung pathology of severe acute respiratory syndrome (SARS): a study of 8 autopsy cases from Singapore. Human Pathology, 34(8), 743–748. https://doi.org/10.1016/s0046-8177(03)00367-8
6. Tian S, Hu W, Niu L, Liu H, Xu H, Xiao SY. Pulmonary Pathology of Early-Phase 2019 Novel Coronavirus (COVID-19) Pneumonia in Two Patients With Lung Cancer [published online ahead of print, 2020 Feb 28]. *J Thorac Oncol*. 2020;S1556-0864(20)30132-5. doi:10.1016/j.jtho.2020.02.010
7. Qian Z, Travanty EA, Oko L, et al. Innate immune response of human alveolar type II cells infected with severe acute respiratory syndrome-coronavirus. *Am J Respir Cell Mol Biol*. 2013;48(6):742–748. doi:10.1165/rcmb.2012-0339OC
8. Mallick, B., Ghosh, Z., & Chakrabarti, J. (2009). MicroRNome Analysis Unravels the Molecular Basis of SARS Infection in Bronchoalveolar Stem Cells. PLoS ONE, 4(11), e7837. https://doi.org/10.1371/journal.pone.0007837
9. Guan, W., Ni, Z., Hu, Y., Liang, W., Ou, C., He, J., Liu, L., Shan, H., Lei, C., Hui, D. S. C., Du, B., Li, L., Zeng, G., Yuen, K.-Y., Chen, R., Tang, C., Wang, T., Chen, P., Xiang, J., … Zhong, N. (2020). Clinical Characteristics of Coronavirus Disease 2019 in China. New England Journal of Medicine. https://doi.org/10.1056/nejmoa2002032
10. Ling TY, Kuo MD, Li CL, et al. Identification of pulmonary Oct-4+ stem/progenitor cells and demonstration of their susceptibility to SARS coronavirus (SARS-CoV) infection in vitro. *Proc Natl Acad Sci U S A*. 2006;103(25):9530–9535. doi:10.1073/pnas.0510232103
11. Salomoni S, van den Hoorn W, Hodges P. Breathing and Singing: Objective Characterization of Breathing Patterns in Classical Singers. *PLoS One*. 2016;11(5):e0155084. Published 2016 May 9. doi:10.1371/journal.pone.0155084
12. Wang Y, Jiang W, He Q, Wang C, Wang B, Zhou P, Dong N, Tong Q, (2020) Early, low-dose and short-term application of corticosteroid treatment in patients with severe COVID-19 pneumonia: single-center experience from Wuhan, China. medRxiv: 2020.2003.2006.20032342