# COVID-19

## NOVEL INTERVENTIONS FOR A NOVEL VIRUS

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**Novel Coronavirus 2019 (SARS-CoV-2) is very closely related to the SARS virus (SARS-CoV) that caused the SARS epidemic of 2003.**

**There are some very important differences that make this novel virus and its clinical disease presentation unique to anything we've ever seen before.**

**None of the following information should be considered to be medical advice for anyone with whom I have not established a physician-patient relationship as required by law and medically ethical practice guidelines**

# DEFINITIONS

**SARS-CoV is the SARS virus of the 2003 SARS epidemic.**

**SARS-CoV-2 is the current “coronavirus” which is a SARS coronavirus that is closely related to the SARS virus of 2003.**

**COVID-19 is the disease caused by SARS-CoV-2.**

# TRANSMISSIBILITY OF SARS-CoV-2

**This virus contains furin cleavage sites on its external spike proteins.**

**These furin cleavage sites are also part of other viruses such as HIV-1, avian influenza virus A, Ebola, Hepatitis B and papillomavirus.**

**The presence of the furin cleavage site on SARS-CoV-2 makes this virus 1000 times more transmissible than SARS-CoV.[1]**

**The virus enters the host cells via the ACE2 receptor.**

**ACEIs and ARBs upregulate ACE2 receptors. ACE2 is on epithelial cells of the lung, intestine, kidney and blood vessels.**

**NSAIDS and Selenium also have been found to upregulate ACE2.**

**Fang, L., Karakiulakis, G., Roth, M. Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? *Lancet Respir Med 2020.* Published online March 11, 2020.[3]**

## MECHANISMS OF ACTION OF SARS-CoV-2 IN THE INFECTED HOST - REPLICATION

**After the virus has entered the cell, it works like many viruses do, by “hijacking” the host cell’s components to allow itself to replicate.**

**SARS-CoV-2 uses the enzyme mTOR (mammalian target of rapamycin) in order to replicate. mTOR is a central controller of cell growth in the cell.**

**After SARS-CoV-2 takes control of mTOR, it can replicate rapidly, until filling the cell, at which time the cell bursts, releasing many more viral copies to infect other cells.**

# MECHANISMS OF ACTION OF SARS-CoV-2 IN THE INFECTED HOST– ILLNESS AND DEATH

**Inflammation promotes healing by bringing beneficial growth factors and white blood cells to the site of injury to kill infection and regenerate the damaged tissue.**

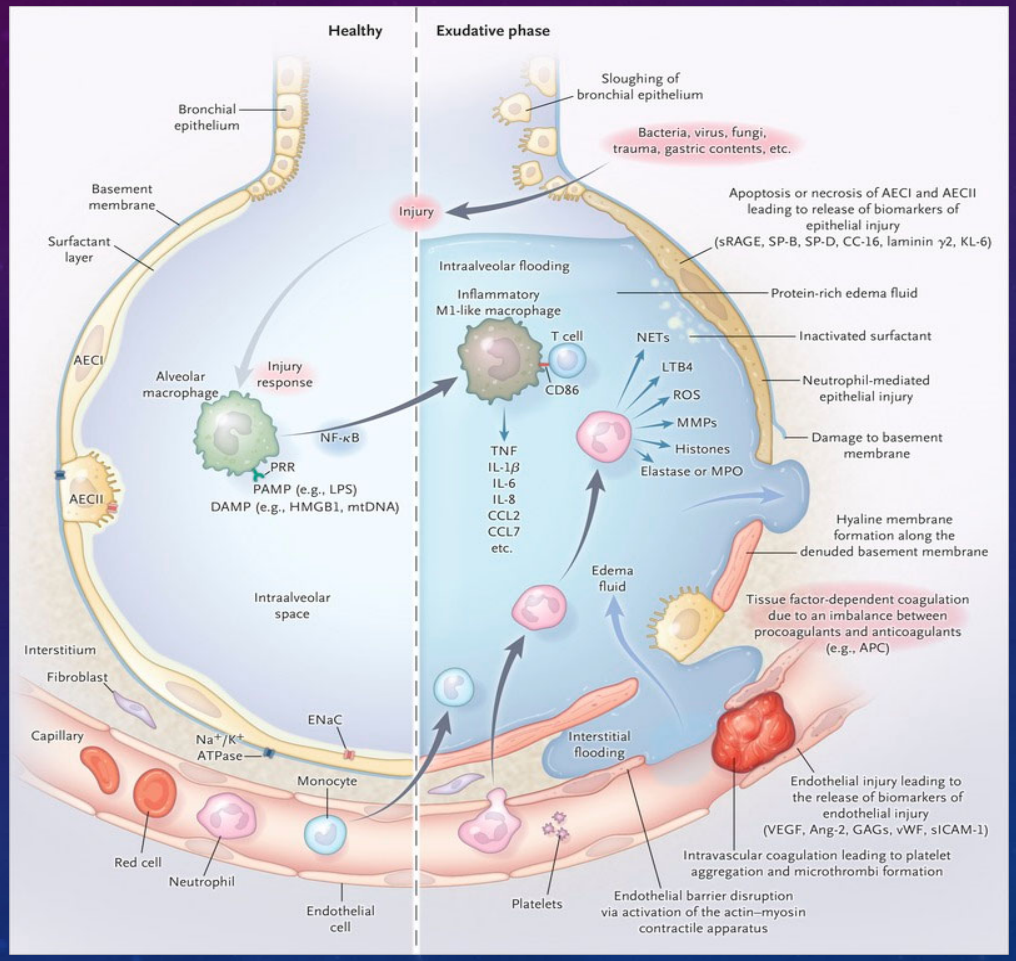
**On the other hand, chronic inflammation is the cause of many chronic diseases.**

**In the case of many viruses, including SARS-CoV-2, the virus itself targets specific processes in the cell to drive the immune response, therefore causing even more damage to the host.**

**The specific site of the damage resulting from COVID-19 is the lungs.**

**The overwhelming majority of deaths from COVID-19 are as a result of respiratory failure, specifically via a process called Adult Respiratory Distress Syndrome (ARDS).**

**The pathogenesis of ARDS is via the host immune response. This is why ARDS is so difficult to treat once it has begun. Below is a depiction of the damage caused by ARDS to the lungs.**



The main inducers/mediators of the immune response are cytokines.

One type of cytokines, called interleukins, specifically IL-1B, has been implemented as the key cause of ARDS.[6]

SARS-CoV-2 uses viroporins to induce immune responses in the infected host.

Studies have linked the viroporin E protein of SARS-CoV-2 with pulmonary edema and death.

In one study, deletion of the E protein in SARS-CoV reduced lung damage via reduced IL-1B activity.[5]

Viroporins induce IL-1B production by direct activation of NOD-, LRR- and pyrin domain-containing protein 3 (NLRP3), which is an intracellular sensor.

When activated, NLRP3 activates the NLRP3 inflammasome, which releases IL-1B and IL-18.[8]

Two recent studies identify the NLRP3 inflammasome as key to the induction of ARDS.[8,9]

# EPIDEMIOLOGY OF INJURY AND DEATH

**The following table shows death rate by age and was published from two sources:**

- **The *Report of the WHO-China Joint Mission* published on Feb. 28 by WHO, which is based on 55,924 laboratory confirmed cases.**
- **A paper by the Chinese CCDC released on Feb. 17, which is based on 72,314 confirmed, suspected, and asymptomatic cases of COVID-19 in China as of Feb. 11, and was published in the Chinese Journal of Epidemiology.**

| AGE | DEATH RATE* |
|---|---|
| 80+ years old | 14.8% |
| 70-79 years old | 8.0% |
| 60-69 years old | 3.6% |
| 50-59 years old | 1.3% |
| 40-49 years old | 0.4% |
| 30-39 years old | 0.2% |
| 20-29 years old | 0.2% |
| 10-19 years old | 0.2% |
| 0-9 years old | no fatalities |

https://www.worldometers.info/coronavirus/coronavirus-age-sex-demographics/

# PROPOSED TARGETS OF PREVENTION AND INTERVENTION

**TRANSMISSION** via blocking furin cleavage and attachment

**CELL INVASION** via down-regulating ACE2 sites and blocking

**VIRAL REPLICATION** via blocking the action of mTOR

**PATHOGENESIS AND INFLAMMATION** via blocking NLRP3 inflammasome and IL-1B

# VITAMIN C

One important finding in the patients who were in critical condition in Wuhan was that the patients who could still produce lymphocytes in the third week of infection generally could eventually recover from the infection. Those who could not, usually died.[21]

T-lymphocytes are particularly important in fighting infection. Vitamin C has been found to be very important in the production and maturation of T-lymphocytes.[22,23]

Natural killer cells (NK) are another type of lymphocyte that is very important in fighting viral infections. Vitamin C also helps in the production and activation of NK cells.[24]

Vitamin C prevents stabilization of hypoxia inducible factor 1a (HIF-1a). Stabilization of HIF-1a is an important step in the expression of furin molecules. This is an important reason why Vitamin C helps to prevent COVID-19 transmission.[25]

Vitamin C also increases production of nitric oxide (NO), thereby inhibiting the production of NLRP3 inflammasomes.

# NITRIC OXIDE (NO)

**Nitric oxide directly inhibits the production of NLRP3 inflammasomes, thereby decreasing production of IL-1B and protecting against ARDS.[27]  As above, Vitamin C helps nitric oxide accomplish this.**

**Many supplements and foods can boost nitric oxide, including arginine, citrulline, beet root extract, pine bark extract and black pepper.  There are many commercially available products that boost nitric oxide, however, many of these are preworkout supplements that contain large amounts of caffeine.**

# ZINC

Zinc has been recognized for its antiviral effects for decades and is generally accepted as useful in treating the common cold and cold sores. There have been studies showing that zinc can help fight many viruses, including HIV, H1N1, papillomavirus, herpes virus and even coronavirus SARS-CoV (SARS 2003).[27,28]

Many forms of zinc are available as supplements. It is generally accepted that zinc citrate or zinc gluconate are well absorbed and these are the most commonly available forms. A 1987 study looked at zinc levels in hair, urine, erythrocytes and serum after supplementation with either citrate, gluconate or picolinate forms. They concluded that zinc picolinate showed the best absorption overall.[29] Chelated zinc is the same as zinc picolinate.

# VITAMIN D3

**There is a plethora of evidence for the use of Vitamin D3 for the prevention of many diseases, including viral infections. This isn't as clear when looking at vitamin D and SARS-CoV-2.**

**Studies looking at how vitamin D and the vitamin D receptor (VDR) interact with NLRP3 are somewhat contradictory. There are some studies showing that vitamin D inhibits activation of NLRP3 inflammasomes and excretion of IL-1B, and a couple that show that it can increase IL-1B.[29-33] For now, it is wise to use D3 with caution and to consider stopping it if symptoms arise.**

# SELENIUM

Much like vitamin D, selenium has been shown to be beneficial in general prevention and also the treatment of many conditions, including viral infections.  But, like vitamin D, when it comes to SARS-CoV-2, its benefit vs risk isn't so clear.

In 1998, Forceville, et al. published a study in Critical Care Medicine, showing that ICU patients with viral illnesses resulting systemic inflammatory response syndrome (SIRS) had a rapid drop in their selenium levels and that these patients had a much higher rate of morbidity than patients who were not selenium deficient.[34]

A 2015 study showed that in selenium deficiency, benign strains of Coxsackie and influenza viruses can mutate to highly pathogenic strains.[35]  These, and another study by Beck, et al. in 2003 show poor outcomes in patients with selenium deficiency.[36]

I have not found any evidence that selenium supplementation in individuals without deficiency has any benefit.

# SELENIUM

Recently, selenium was found to be a potent inhibitor of angiotensin converting enzyme ACE.[37] Previous studies have looked at the benefits of selenium on the cardiovascular system, but this is the first time this mechanism has been found.

Because the prescription medication classes of ACEIs and ARBs have been found to upregulate the expression of ACE2, it can be postulated that selenium can do the same by the same mechanism.

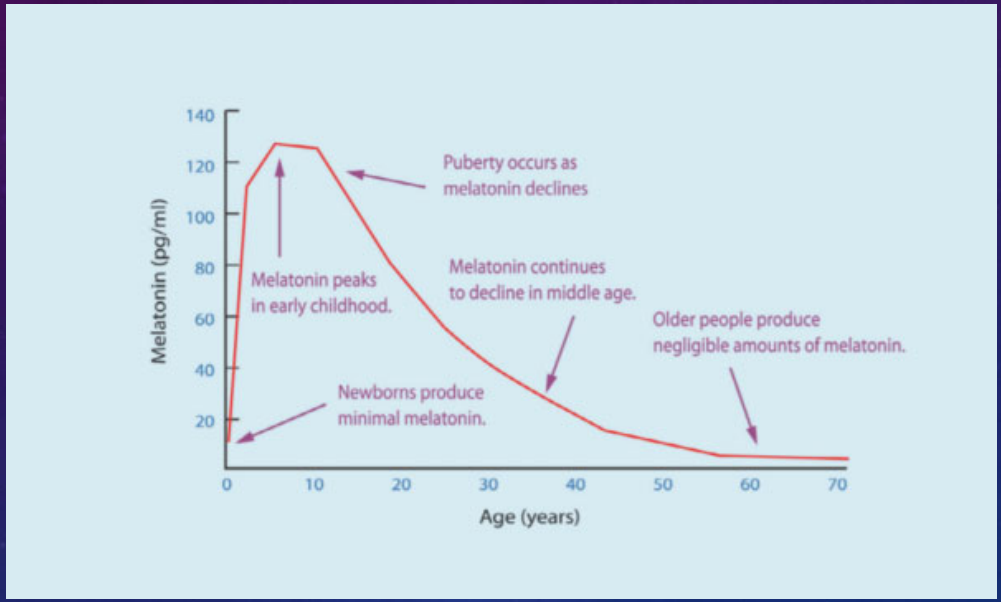
There is uncertainty surrounding the potential risk of upregulation of the ACE2 receptor.

There is overwhelming evidence for an increase in mortality from selenium deficiency in patients with viral induced systemic inflammatory illness.

For now, the balance of the evidence seems to favor selenium supplementation in high risk individuals, especially after they begin to show signs of respiratory distress.

# MELATONIN

**Below is a table showing the age-associated production of melatonin.**




**Grivas TB, Savvidou OD. Melatonin the "light of night" in human biology and adolescent idiopathic scoliosis. Scoliosis. 2007;2:6. Published 2007 Apr 4. doi:10.1186/1748-7161-2-6**

# MELATONIN

**In looking at the biochemistry of melatonin as it pertains to in inflammatory cascade, the association between the two images above appears to be much more than just a coincidental association.**

**Melatonin targets the NLRP inflammasomes directly. Melatonin has been shown to limit damage in animal models of sepsis by this mechanism.[10,11,12,13]**

**In mice, studies have shown that supplemental melatonin reduces damage from acute lung injury, ARDS and mechanical ventilation.[14,15,16]**

**A study by Huang, et. al. in 2019 showed that mice infected with H1N1 had markedly increased survival when given melatonin plus an antiviral drug as compared to the antiviral drug alone. [17]**

# MELATONIN

**In another twist, none of the pregnant mothers in Wuhan who were infected with SARS-CoV-2 developed severe pneumonia or died.**

**If the hypothesis of the protective effect of melatonin is true, then it is likely that pregnant women have better survival rates because they produce significantly more melatonin for their age than non-pregnant women.[18]**

**In the melatonin table, one cannot help but see that newborns do not produce melatonin. Then why don't they succumb from COVID-19 like older people?**

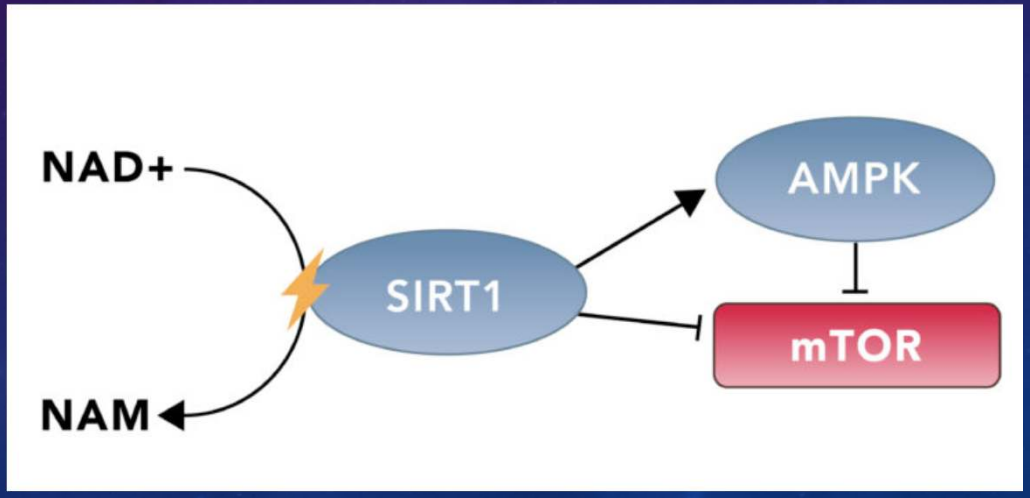
**Because newborns produce a large amount of nitric oxide. Infants have been found to produce as much nitric oxide in their paranasal sinuses as healthy adults.[38] And, as seen above, nitric oxide is a potent inhibitor of NLRP3 inflammasomes, much like melatonin.**

## NAD+, RESVERATROL, QUERCETIN AND METFORMIN – ALL ABOUT mTOR

**One of the actions of NAD is as a coenzyme in the production and activation of SIRT1, one of many sirtuin proteins involved in cellular processes.**

**As previously discussed, SARS-CoV-2 replicates by using mTOR in the host cell.**

**SIRT1 blocks the action of mTOR by two mechanisms. It directly inhibits mTOR, and it also activates adenosine monophosphate-activated protein kinase (AMPK), which also blocks mTOR.**



Although supplementation with NAD might seem like a good idea, it isn't that simple. Another mechanism that immune cells use to combat the virus is to kill off infected cells via a surface protein called CD38 by depleting their NAD supply. Supplementing with NAD could undo that process.[40,41,42]

It is unclear whether pro-NAD supplements such as resveratrol and quercetin would block mTOR without adversely affecting CD38s ability to kill infected cells.

# NSAIDS

**There isn't enough evidence one way or the other to formulate a strong, evidence-based opinion on the use of NSAIDS in the context of potential COVID-19 infection. Fang, et al. postulated that NSAIDS increase expression of ACE2.[3]**

**Many medical societies have said that there is not a reason to stop NSAIDS.**

**On March 17, WHO officially recommended that patients infected with or at risk for COVID-19 refrain from using NSAIDS.**

# The End