COVID-19

NOVEL INTERVENTIONS FOR A NOVEL VIRUS

Kenneth D. Wilgers, M.D.

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.

This article will be limited in scope to the unique pathophysiology of the disease process of the SARS-CoV-2 virus (COVID-19) and some yet unproven, but biochemically sound interventions that could save many lives. Everything presented in this narrative is absolutely reasonable considering the plethora of evidence from known biochemical pathways and published research related to how these pathways function. The potential interventions proposed herein are also reasonable and scientifically sound, coming from the same evidence.

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. This is merely my best attempt to help other healthcare providers to understand the information that I have found on this subject and to give them an avenue to begin their own research on the subject, in order to help the most patients in the shortest amount of time, given the complete lack of available medically tested interventions at the time of this writing.

Many medical experts might disagree with my opinions on this, which is to be expected. Much of this information is not available for easy access to most physicians. Medical professionals and patients are encouraged to seek out the trusted opinions of experts as they see fit.

Following are some clarifications of the nomenclature as used in this article.

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

SARS-CoV-2 has one very unique characteristic that was not shared by the SARS virus of 2003 that enhances its ability to be transmitted and also its ability to infect cells. 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 function of the furin cleavage site on a virus is to interact with furin enzymes on the surface of host cells, thereby gaining access to the cell. Furin proteins are present on every cell line in the human body. This is why the viruses that contain these cleavage sites are so easily transmissible. The presence of the furin cleavage site on SARS-CoV-2 makes this virus **1000 times more transmissible** than SARS-CoV.[1] The presence of furin enzymes on the surface of SARS-CoV-2 is also the reason why many people who are infected with the virus show signs of encephalopathy and central nervous system dysfunction. This was described by doctors at Beijing Ditan Hospital in early March 2020.[2]

There have been reports of an increased risk for patients with preexisting cardiovascular disease and diabetes, both in their susceptibility to catching the virus and having a poor outcome, including death. There are many sites on the internet that are attributing this in part to the frequent use of certain classes of drugs in these patients. Some are calling for these patients to discontinue the use of **angiotensin converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs)**. This comes from the finding that the SARS-CoV-2 virus gains access to cell entry, in part, via the **ACE2** receptor.

In theory, which has been supported in the past by many scientific studies, because these two classes of medications block **ACE** receptors, including **ACE2**, there is an

upregulation of these receptors by the cells. This is a phenomenon we see with many medications.

> *For example, men who use Viagra and Cialis, which work by blocking the receptor for **phosphodiesterase 5 (PDE5)**, often find that, over time, the medications become less effective than they were at the onset of use. This is because, when the receptors are blocked, the body adapts to this by making more receptors.*

This is also seen in some patients taking **ACEIs** and **ARBs**. Since SARS-Cov-2 gains access to the cell via these **ACE2** receptors, in theory, the upregulation of the receptors by these classes of medications could increase susceptibility to this virus in the patients who are taking these classes of medications. Because these **ACE** receptors are found on epithelial cells of the lung, intestine, kidney and blood vessels, these are the main sites of damage from the virus. Fang, et. al. published a short but well thought out review of the literature regarding this online recently. [3]

Many medical professional societies are warning patients not to stop their medications based on the information that is circulating regarding this topic. I also do not recommend that patients make any medication changes without consulting a licensed healthcare professional, preferably the one who prescribed their medications. Healthcare providers who are reading this article should exercise caution and go above and beyond to educate themselves from as many sources as possible before making recommendations regarding this issue. There will be more about this later in the article, including recommendations.

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.

> *Before going any further, it is important to point out that viruses are unique to anything else on the planet, in that there is great debate regarding the status of viruses as “living” or not. Viruses are essentially tiny packets of either DNA or RNA. They have the ability to transcribe their genetic material and produce proteins for building their structure and for basic*

functions of attaching to host cells and gaining access. What they cannot do is replicate without a host, nor can they survive without host interaction for very long. Each virus is unique in this capacity and that is not the focus of this article.

After SARS-CoV-2 gains access to the host cell, it uses the enzyme **mTOR (mammalian target of rapamycin)** in order to replicate. mTOR is a central controller of cell growth in the cell. It plays a key role in development and aging and it has been studied as one of the reasons why cancer cells can grow and replicate so well. 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.

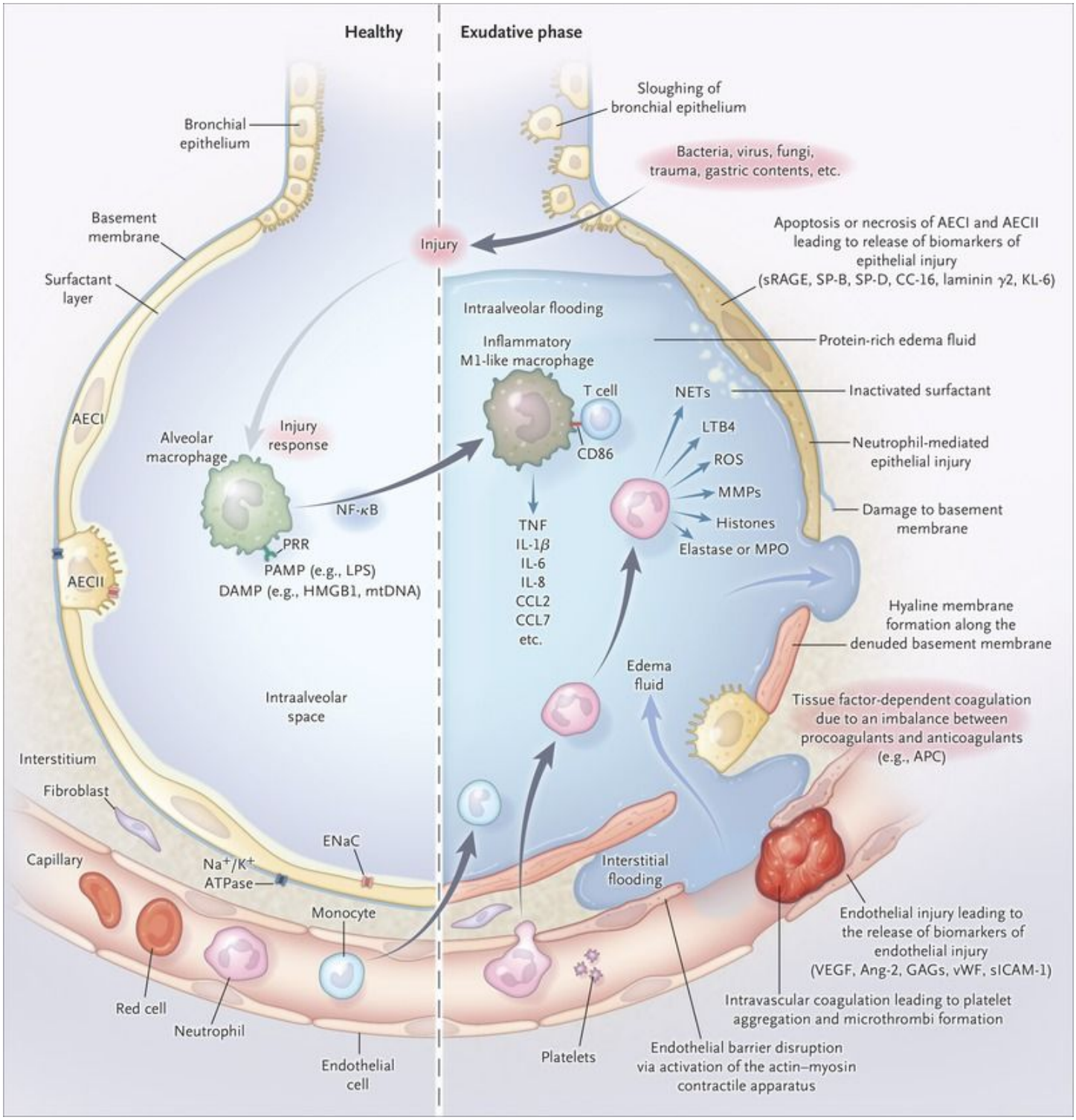
MECHANISMS OF ACTION OF SARS-CoV-2 IN THE INFECTED HOST– ILLNESS AND DEATH

The inflammatory response in the human body is a double-edged sword. On one hand, 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 such as arthritis and autoimmune disease, and has been more recently postulated to play a major part in cardiovascular disease and dementia.

In viral infection, the host cells will mount an immune response in order to try to kill the virus. 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. This is why cough, shortness of breath and fever are essential positives on the screening exam, while runny nose and congestion are not. 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)**. Until the 1990s, death rates from ARDS exceeded 70%. Since then, death rates have decreased to about 40%, due in large part to a better understanding of the pathophysiology of sepsis, advances in antibiotic therapies and improvements in mechanical lung ventilation.

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



N Engl J Med 2017; 377:562-572 DOI: 10.1056/NEJMra1608077

As can be seen, the inflammatory response is very complicated and multifactorial. The main inducers/mediators of the immune response are the **cytokines**. There are many,

many cytokines that have been discovered, including **interleukins**. Interleukins are involved in many beneficial inflammatory processes, as well as many disease processes, including ARDS. Specifically, one interleukin, **interleukin 1 beta (IL-1B)** has been found to be the main inducer of ARDS.[6] A current NIH-funded study is being conducted at the University of Pennsylvania looking at a genetic variant that codes for an antagonist to the IL-1B receptor. Subjects with this variant appear to be protected from ARDS. There was also a study published in 2018 showing benefit of a recombinant IL-1B antagonist.[4]

This is all very important when considering the clinical course of COVID-19. SARS-CoV-2 uses **viroporins** to induce immune responses in the infected host. Viroporins are specific proteins produced by viruses that play critical roles in viral replication and pathogenesis. Two specific viroporins are produced by SARS-CoV, a **viroporin envelope protein (E) and viroporin ORF3a**. Studies have linked the 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]

The mechanism by which the SARS-CoV-2 viroporins induce IL-1B production is by direct activation of **NOD-, LRR- and pyrin domain-containing protein 3 (NLRP3)**, which is an intracellular sensor that detects a broad range of microbial motifs, endogenous danger signals and environmental irritants, resulting in the formation and activation of the NLRP3 inflammasome.[7] When activated, NLRP3 activates the **NLRP3 inflammasome**, which releases IL-1B and IL-18. 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/

As shown above, there seems to be a clear age-related influence on the death rate of COVID-19.

PROPOSED METHODS OF PREVENTION AND INTERVENTION

There are currently many avenues of treatment being explored by health officials worldwide, from new vaccines, to new medications, to novel uses of existing medications. Many of them seem promising, but time is of the essence. It is clear that the novel use of existing treatments would be the option that would provide the quickest results. A comprehensive review of the potential for repurposing existing pharmaceutical agents was published in Cell Discovery in the last few weeks.[19]

The purpose of this article is to offer a well thought out, thoroughly researched opinion on possible options for prevention of and methods of decreasing injury from infection with SARS-CoV-2. As stated in the introduction, this is not medical advice. Also, the proposed interventions are not endorsed by any medical authority, including the CDC, FDA nor are they recommended by any medical society or advisory board.

VITAMIN C

Vitamin C has been used for prevention of infection and treatment of the common cold for decades and even centuries. Grandmothers all over the globe would agree. But is this more than just legend?

Trials are currently underway in China, looking at the benefits of Vitamin C in patients infected with COVID-19.[20] They are using up to 24,000 mg daily.

One important finding in the patients who were in critical condition in Wuhan was that the patients who could still produce lymphocytes (one beneficial line of white blood cells) 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]

50 tons of Vitamin C were sent to Wuhan to help citizens combat COVID-19. This is why.

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.

NEONOX© by NeoGen Nutrition is an all-natural supplement that helps with production of nitric oxide. https://www.neogenstemcell.com/product/neonox/

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. For now, it is wise to use D3 with caution and to consider stopping it if symptoms arise.[29-33]

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] Since then, there has been a focus of much research surrounding selenium deficiency as a risk factor for poor outcomes in viral infections. 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[36] show poor outcomes in patients with selenium deficiency. There has not been any evidence that selenium supplementation in individuals without deficiency has any benefit whatsoever.

As mentioned earlier in this article, there has been some debate surrounding the ACE2 receptor and two classes of medications, ACEIs and ARBs. The mode of cell entry by SARS-CoV-2 via ACE2 is also a consideration when making the decision whether or not to recommend selenium supplementation for protection against COVID-19.

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. A further discussion of ACE2 follows in the next section.

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.

ACE2 – THE DOUBLE EDGED SWORD OF ACEIs AND ARBs

As stated earlier in the article, Fang, et al. published an opinion in Lancet last week. This was a very thorough and very scientifically sound examination of the biochemistry and the available evidence. Their conclusion was that patients taking this medications were at a higher risk for infection. They fell short of recommending that these medications be stopped. They likely did this because they are not medical professionals and that they felt that such a recommendation would be inappropriate. This was very appropriate and admirable. They also reviewed the class of antihypertensives known as calcum channel blockers and concluded that this class of medications did not have the same effect on ACE2. They proposed this class as an alternate therapy to the other two.

Six days later, on March 17, 2020, an article was published on the COVID-19 Resource Center website, in what seems to be a rebuttal of Fang, et al. This was a synopsis of statements from multiple medical societies, including The American Heart Association, The Heart Failure Society of America, The American College of Cardiology, The European Society of Cardiology and the Nephrology Journal Club. This article had no scientific references, except the Fang, et al. article. There was not one critique of any of the scientific findings in the Lancet article. There were no scientific mechanisms offered to back up any of the advice in the article. Robert Harrington, MD, the president of the American Heart Association stated, “We have reviewed the latest research – the evidence does not confirm the need to discontinue ACE inhibitor or angiotensin receptor blockers, and we strongly recommend all physicians to consider the individual needs of each patient before making any changes to ACE inhibitor or angiotensin receptor blocker treatment regimens.” The Nephrology Journal Club called the conclusions of Fang, et al. “speculation”. Richard Kovacs, the president of The American College of Cardiology urged “urgent, additional research”.

It is clear that the scientific evidence shows that patients on ACEIs or ARBs are already at an increased risk of becoming infected and having poorer outcomes because of their underlying conditions. It would do them a disservice not to improve their chances by whatever means necessary. Whenever possible, these patients should be changed over to another class of medication at their healthcare provider’s discretion.

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

Understanding that association does not prove causation, this table appears to show the inverse of the table presented earlier. That is, that it shows an association between melatonin production and death rate, when correlated by age.

Melatonin has long been known to be involved in promoting sleep. There are many other proposed benefits of melatonin, which will not be addressed here. In looking at the biochemistry of this molecule 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]

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

Nicotinamide adenine dinucleotide (NAD), is a critical coenzyme found in every cell in the body. NAD+ levels decline with age and for that reason it has been targeted as a means to slow aging. Multiple forms of NAD are available as supplements.

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. The inhibition of mTOR has been shown to be a novel treatment for many cancers. As registered in clinicaltrials.gov, there are more than 80 clinical trials for **mTOR inhibitor** monotherapy in **cancer** patients.[39] Blocking mTOR could markedly inhibit the ability of SARS-CoV-2 to replicate, making it much less lethal.

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 would 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.

Alternative methods of blocking mTOR would work much better. The prescription medication **metformin** works very well for this. Many of the cancer studies use metformin to block mTOR. Its mechanism of action is not dependent on SIRT1 or NAD.

NSAIDS

There isn't enough evidence one way or the other to formulate an 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] Other sources are scarce and inconsistent on this.

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