COVID-19, Nearly A Year in the Making White Paper

By

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Outline

- Introduction
- Real Numbers and Demographics
- Biology of SARS-CoV-2
- Effects of SARS-CoV-2/COVID-19
- Early Symptoms of COVID-19
- Predictive Biomarkers of COVID-19
- Testing for COVID-19
- Prevention of COVID-19
- Potential Treatment Options for COVID-19
- Vaccine Therapy for COVID-19
- Lessons learned
- Resources

Introduction

The purpose of this COVID-19 White Paper is to inform and empower the public. It is written with great respect for all healthcare workers, our essential workforce, and all non-profit organizations caring for those in need. For the next 1-2 years, short of COVID-19 disappearing, we all need to understand the lessons the virus is teaching us about our state of health and how best to maintain it going forward. This virus is a wake-up call from nature that has afforded us unprecedented insight into our vulnerabilities and how to better prevent being infected by it as well as how to deal with a Covid-19 infection. This paper contains the kind of deeper public health knowledge that will improve all our lives now and in the post-COVID world to come.

The crucial challenge now is to find a balanced way to minimize the impact of COVID, particularly in high-risk populations, as well as "collateral damage" to our school age children, our economy, our essential workforce and our overall health care system. This task is complicated by the fact arbitrary guidelines and restrictions have been forced upon the majority of us. The justification or scientific basis for these measures is oftentimes summed up with the authoritative phrase "this is science"; something which has been so abused as to make the term both condescending and almost meaningless.

One very fundamental aspect of all this is to educate the public in healthy lifestyle practices, those that are protective but which go beyond wearing masks and social distancing. People want to get back to living their lives in familiar, customary ways, which includes less of "don't do this and don't do that," and more of "if you want to do more, and you are willing to accept some risk, then here are very practical ways to lower your risk of serious illness should you get exposed to the virus."

The Price of Freedom

We here in America are getting used to seeing or hearing about Covid-19 deaths in the thousands each and every day. We also harbor a shared love of being free to make choices about what we say, what we do, where we go and how we behave. Our country has fought many wars to uphold our liberty and rights, but have lost sight of the fact that sometimes bad choices can harm others in our orbit. We are, in fact, now   paying a heavy price for letting our personal freedom entitle us to act in ways that endanger others. President Trump fueled this particular fire   by placing the individual's right to do or behave as he or she wishes above concerns for the common good. And even if it turns out the pandemic crisis is overblown and mismanaged beyond what he could control while in office, the fact remains that he failed to have the medical experts who cared for him during his Covid-19 infection explain how he was treated. In addition, the former President and his administrations did fund studies that would have helped address public health concerns such as whether children should stay in school, as they have in many countries around the world.

It is clear that masks do help stem the tide of COVID infections. As such there should have been a mandatory mask use policy across the country early on in the pandemic.

Compared to developed countries in Asia, like Japan and Korea, the USA had more than 2-5 times more deaths each day than they saw in the last year. We must learn from this tragic situation and the mistakes and blunders that led to it, not only to inform our actions now but also to help us in laying the groundwork for now to deal decisively and effectively with future catastrophic pandemics.

While I am exceedingly optimistic about people being able to resume many "normal" activities as early as the summer, the new administration and the scientific experts we are relying on must fully understand what drives health and what fuels the inflammation that produces the cytokine storm responsible for the majority of COVID-19 deaths. As part of this we must enact a nationwide campaign to educate everyone concerning the risk factors that predispose so many of us to develop catastrophic complications from a COVID-19 infection. Also, we must have an honest discussion about risks linked to the FDA approved COVID-19 vaccines.

Below is a summary of where we stand in terms of the pandemic. For readers in healthcare professions or scientific research, we have attached an 80+ page "deep dive" into the science and treatments of COVID-19. With 500 references, it is comprehensive and thus will prove a powerful tool for making informed treatment decisions, for open discussion and debate, and for stimulating new treatment approaches.

Multiple COVID-19 Surges in the United States

1

Surge 1: March – June: The first 3 months of the pandemic primarily in the Northeast states. Through the heroics of our first responders in our initial hotspots and all of our essential workforces, we successfully flattened the COVID19 curve. The primary purpose of the Northeast lockdown was to manage the risk of overwhelming our hospital systems.

Surge 2: July – August: With the early summer holiday and travel season, the second surge of hospitalizations and high mortality rates emerged in many new hot spots, primarily focused in the South which brought about lockdowns that impacted local and state economies.

Surge 3: September – Present: A third surge of hospitalizations throughout most states but concentrated in the Midwest and South are driving up hospitalizations and also a death rate that grew from approximately 1,000 Americans per day to 3,500+ deaths per day.

Today, we are reaping the whirlwind! We devastated our economy, but did not, as a nation contain the virus. We remain obsessed with the number of new cases, yet we remain "consistently inconsistent" in our approach on what to do with this data. The result is unnecessary fear and distrust.

We have no choice but to act collectively to get the local surges under control. Simply waiting for vaccines to reach everyone is NOT a sound strategy. It remains a promising addition to our public health toolbox but not one that we can definitively count on to end the pandemic overnight. Understanding the basic science behind this pandemic is the foundation of how both

our Public Health officials can make informed decisions and also how we can individually maintain our health, now and moving forward.

What do we mean by a basic understanding of the science? It includes such questions as:

- What is the true COVID-19 fatality rate?
- How does this virus produce the damage that it does?
- Why are people with hypertension, obesity, diabetes, and heart disease more likely to develop serious symptoms than others?
- How do we keep the economy viable and robust, at least for all low-risk populations?
- If the serious complications from COVID19 are inflammatory in nature, how do we protect ourselves?
- What do the laboratory biomarkers that predict severe illness in the hospital tell us about who is most at risk?
- What therapies reduce serious complications and death, and what can these early results teach us about how to be more strategic in protecting ourselves and our families?
- What does a positive PCR test mean in asymptomatic persons? They are certainly not infectious.
- How do we get and keep schools open?
- Essentially, how does one begin to live more freely in a post-COVID world? What is my risk, so I can make more informed decisions about how I can best live my life?
- What is the relevance of COVID-19 variants currently in the news worldwide?

Unless we properly answer these questions and address their underlying issues, we cannot improve outcomes and will remain in this state of heightened fear needlessly for at least the 6-12 more months with our schools and younger populations trapped in the middle by our national paralysis.

In a condition that will likely kill over 500,000 people in the USA before the end of February (2021) according to CDC projections, our Public Health Service men and women, as well as physicians, need to focus on educating the public on how to identify and improve our risk factors, how to modulate our immune systems, how to practice stress reduction and the importance of diet and exercise to all this and more. Public Health 101 has never been more needed or important.

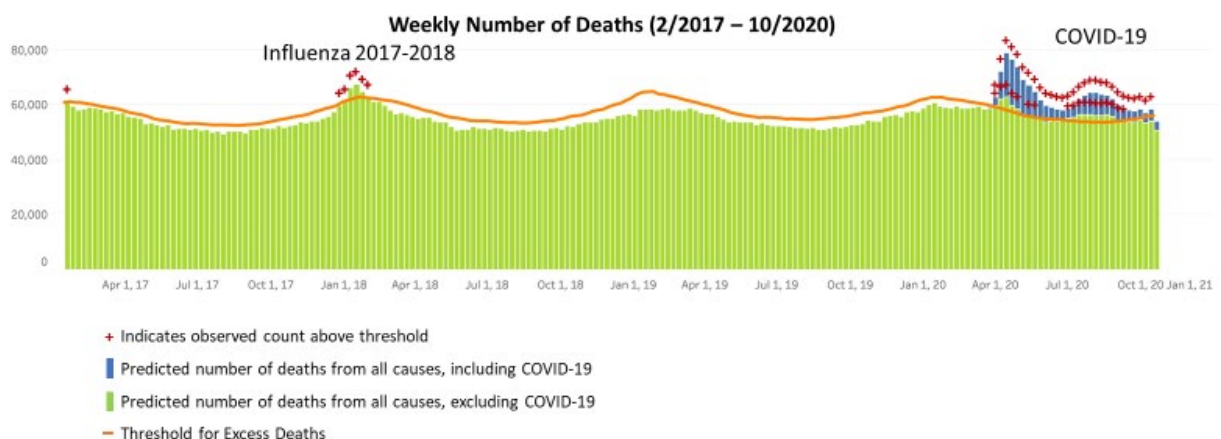## Difficult Questions Regarding Vaccine Candidates

- We don't know anything about the long-term consequences of mRNA vaccines.
- Prior animal studies on coronavirus vaccines raised some very complex safety issues. One CANNOT do long term animal toxicology studies (1-2 years) if one approves a vaccine after only a few months of clinical testing.
- We don't know much if anything about the short-term safety for the "general population". We have to ask ourselves: how many patients with serious chronic illness were included in the trials. The answer: NONE. I am particularly worried about persons with drug allergies and autoimmune disorders. Did you know that 3 patients experienced

anaphylaxis in the Pfizer trial and 1 nurse suffered an anaphylactic reaction after receiving her first dose in Alaska?
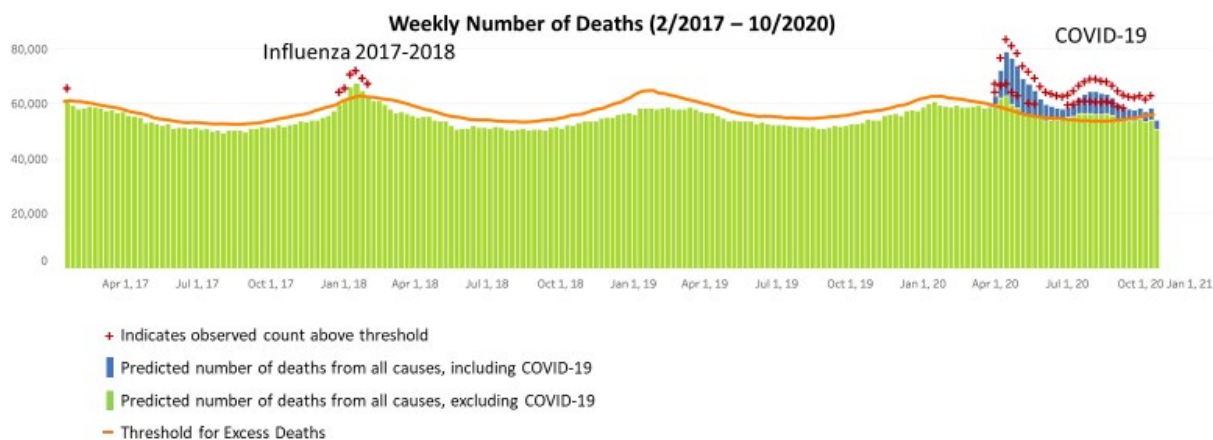
- Why vaccinate any more than is deemed necessary from a risk-benefit analysis perspective?
- After vaccinating nursing home and assisted living persons and workforce personnel, as well as hospital-based staff at high risk, and people in state and federal prisons…. why vaccine ANYONE under the age of 55 without pre-existing conditions? I don't see the risk benefit here for our younger "healthy" population, since overwhelmingly, they remain asymptomatic. This point is underscored by the fact that >94% of Americans hospitalized with COVID have had pre-existing conditions, with an average of 2.6 conditions!
- Asymptomatic persons are <1% likely to be infectious… At least by standards set by our current PCR testing, which identifies more than 100 asymptomatic persons for every 1 that is infectious. So, the "casedemic" argument is valid.

On the other hand, I disagree with the argument that this is not a true pandemic, at least in the USA, EU and South America. Unless CDC data is falsified, we have more deaths due to CV disease and dementia with the total number rivaling the 400K+ deaths we are currently reporting due to COVID. Is this possible to falsify? Anything is possible, but, unlikely. By the mechanism of action of this virus, it is CLEAR who is at risk. The youngsters are largely spared, unlike with the flu; people without pre-existing conditions are by-and-large spared; people with adequate to high active serum Vit D levels are typically spared, at any age. People in Asia have infection rates well below the US, EU and South America. (In Japan most citizens received the BCG vaccine at a young age. There is an argument that this confers cross reactive immunity to other viruses including Coronaviruses). People in India and Africa have been hit but the drop in the number of infected seems more rapid than in the West. God knows, we need to look more intensely into why.

Comparing Excess Deaths Including/Excluding COVID-19 (USA)

Weekly Number of Deaths (2/2017 – 10/2020)

+ Indicates observed count above threshold

█ Predicted number of deaths from all causes, including COVID-19

█ Predicted number of deaths from all causes, excluding COVID-19

— Threshold for Excess Deaths

https://www.cdc.gov/nchs/nvss/vsrr/covid19/excess_deaths.htm

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Excess Deaths Attributed to COVID-19 [2]
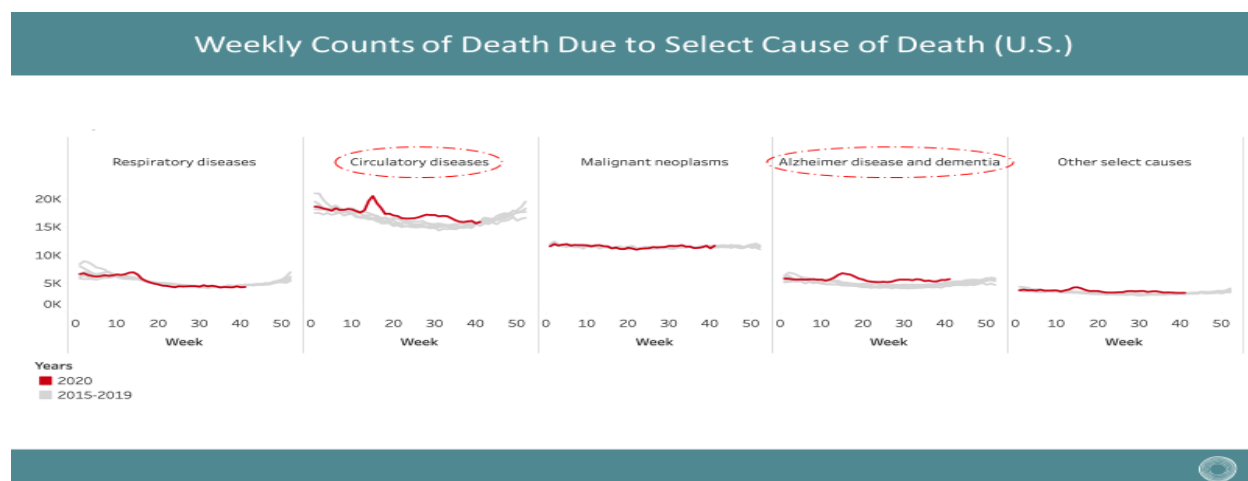
Real Numbers and Demographics

Our Real Numbers

Perspective: COVID-19 Statistics in the USA- December 16, 2020 [3–6]

- **Number of Positive Cases:** 17,352,881
- **Number of Deaths:** 314,162
  - Roughly 10.8% of our total annual death rate of 2.9 million
  - **Cumulative death rate:** approximately 949 deaths per 1 million population
- **Number of Current Hospitalizations:** 112,814
- **Calculated Fatality Rate:** 1.8%
- **Estimated True Fatality Rate:** 0.25-0.5%
- Last year, COPD, pneumonia & flu caused 8% of our total annual death rate (226,000 deaths)
- 23% of annual deaths are from Cardiovascular disease, 21% from Cancer
- COVID-19 deaths will go up by end of 2020 and may rise to >10% of all deaths

I have only heard lip service given to the low risk of death that the population under 55 has from COVID-19, and the extraordinary low risk for those under 25.

Center of Disease Control Age Group Data: 2/1/2020-12/12/2020 [7]

Group:	Age:	Number of Deaths	% of Total Deaths
I	≤24	553	0.2%
II	25-54	2,0650	7.5%
III	55-64	33,378	12.1%
IV	≥65	218,480	79.1%

Perspective-based on the data shown above

- 99.8% of COVID-19 deaths are ≥25 years old
- There is an approximate 11-fold lessened risk of dying from COVID-19 in 25-54 years of age vs. ≥65 years
- There is an approximate 396-fold less risk of dying from COVID-19 in ≤24 years of age vs. ≥65 years

CDC COVID Data Tracker

The media relentlessly focuses on fear of the virus and reliance on a vaccine. We need to instead ⸺weigh the situation in light of the realistic or actual COVID fatality rate which has been inaccurately publicized. The discrepancies in the fatality rate statistics stem from a miscalculation of COVID cases in the first wave of the pandemic: we weren't counting the number of infected people who were not admitted to the hospital who were experiencing mild or no symptoms at all. This oversight resulted in a much higher case fatality rate. This inaccurate picture early on in the pandemic set the tone for public health policies and is what continues to influence decision-making and media-driven fear mongering.

What should we have learned from the pandemic?

- For all people under the age of 55, COVID-19 has a lower death rate than the last severe influenza flu outbreak in 2017-2018.
- For people less than 24 years of age, COVID-19 has ten times lower death rate than the flu.
- For individuals less than 15 years of age, only 1 in every 2,800 COVID deaths occurred in this age group.
- 80% of all deaths are in the 65 and older population
- 94% of all deaths have occurred in people with pre-existing conditions. Of these, the average number of conditions was almost 3 (2.6 – see previously shared data).

If we take the U.S. death rate from COVID-19 from the median age of Americans which is 38, the total number of deaths would still be lower than the 2017-18 influenza season.

Since COVID-19 attaches to our bodies via the AE2 receptor, our younger population without abnormal ACE2 receptors is largely protected, and the great majority who wind up infected are asymptomatic and very unlikely to infect others. So, schools can and should remain open.

If we had fewer persons in the U.S. and the E.U. with metabolic syndrome (obesity, high blood pressure, diabetes, heart disease), we would have much lower death rates (This explains some of the enormous differences seen in Asia where metabolic syndrome is a rarity).

Lastly, due to the way we perform PCR testing, a positive result in an asymptomatic person does NOT mean they are infective. The overwhelming number of asymptomatic persons with positive PCR tests CANNOT transmit the disease to someone else (data presented previously).
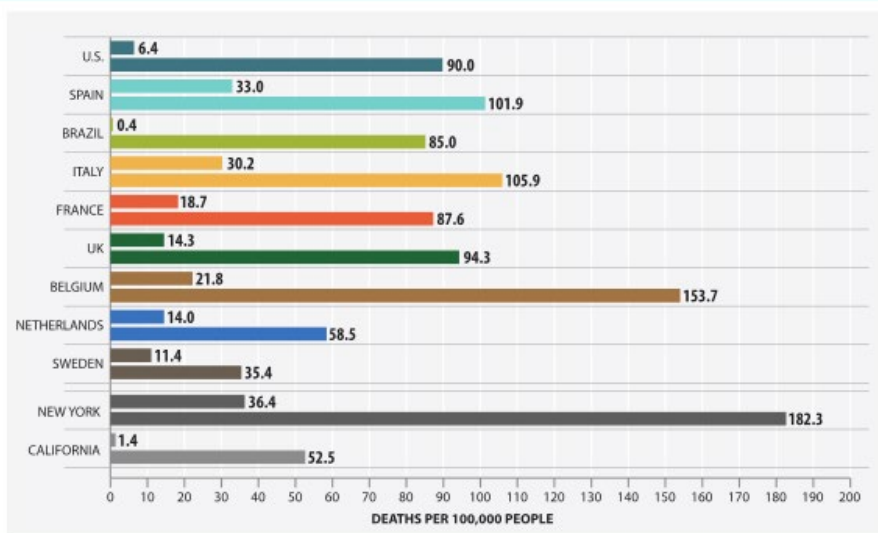
Let's consider what we know about the facts

COVID-19 Case Fatality Care (CFR) is flat and similar to that in the EU.

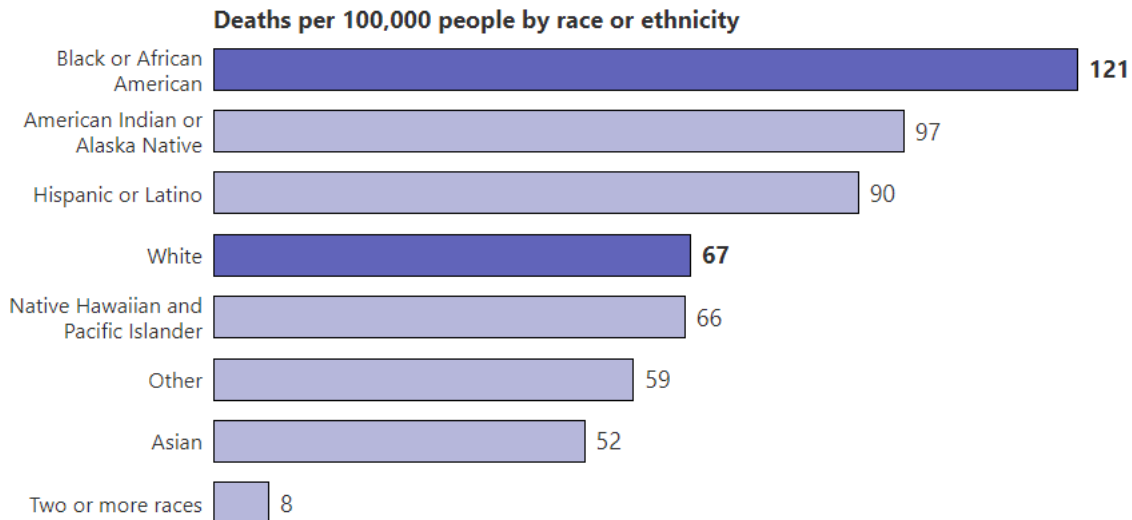U.S. COVID-19 Case Fatality Rate (One-Week Average)

COVID-19 Deaths per 100K People (4/9 vs 12/12)

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Demographics: Behind the Risk of COVID-19 Deaths

Ethnic demographic data

COVID-19 affects minority groups the most. In the US, black people are dying at 1.8 times the rate of white people as of 12/16/2020.

Deaths per 100,000 people by race or ethnicity

Race or ethnicity	Deaths per 100,000
Black or African American	121
American Indian or Alaska Native	97
Hispanic or Latino	90
White	67
Native Hawaiian and Pacific Islander	66
Other	59
Asian	52
Two or more races	8

8

Risk factors

We know that some people are more vulnerable to COVID-19, but what is considered a risk factor?

COVID-19 Relative Risk Factors

Relative risk of mortality is a function of:

- Age
- Pre-existing conditions (ACE 2 function)
- Region you live in
- Race and standard of living
- High-risk specific work/living environment (hospital, nursing home, assisted living, prison)
- True prevalence in the population
- Vitamin D level
- Obesity

Coronavirus Latching on to an ACE2 receptor (in Yellow)
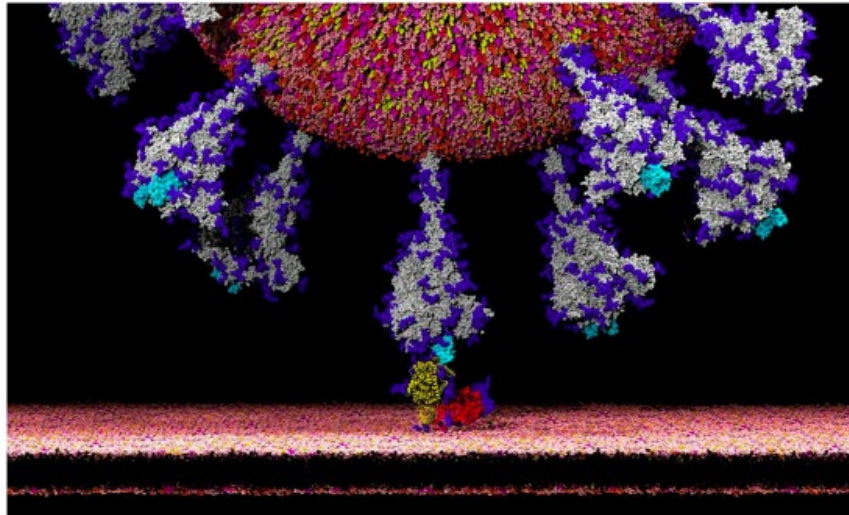
Lorenzo Casalino, Amaro Lab, U.C. San Diego.

ACE 2 Receptor

- ACE 2 has powerful anti-inflammatory and immune modulating effects
- When levels are reduced, these beneficial effects are lost
- COVID-19 causes low levels of ACE 2 and can produce a state of severe inflammation
- Pre-existing disease such as HTN, heart disease, DM, obesity, COPD, cancer, and immune suppression increase risk
- All these pre-existing conditions represent longstanding ACE 2 deficiencies
- So, COVID-19 makes all these disorders worse and many reach a tipping point that cannot be reversed

Not only are these risk factors at play, but others unique to people with pre-existing conditions lend them to be more vulnerable to COVID-19 than other population groups.

US CDC Data August 2020

- For 6% of the deaths, COVID-19 was the only cause mentioned

- For the remaining 94%, the average COVID deaths were associated with <u>2.6 additional conditions</u> or causes per death

https://www.cdc.gov/nchs/nvss/vsrr/covid_weekly/index.htm?fbclid=IwAR3-wrg3tTKK5-9tOHPGAHWFVO3DfsIkJ0KsDEPQpWmPbKtp6EsoVV2Qs1Q

Who is getting serious COVID-19 infections?

Certain conditions put people at a higher risk of contracting COVID-19. The data below is from July 2020, which includes chronic health conditions characterized by highly inflammatory risk factors that tend to compromise people's immune systems. Hypertension, cardiovascular disease and obesity are conditions that pose the greater risk to people in the current pandemic [5].

Laboratory-Confirmed COVID-19-Associated Hospitalizations in Adults
Preliminary cumulative rates as of Jul 18, 2020

- Hypertension 53.5%
- Obesity 49.8%
- Metabolic Disease 40.7%
- Cardiovascular Disease 31.3%
- Neurologic Disease 22.6%
- Chronic Lung Disease 18.9%

- Renal Disease 15.1%
- Asthma 12.2%
- No Known Condition 9.1%
- Immune Suppression 8.8%
- Other Disease 7.3%
- Gastrointestinal/Liver Disease 5.1%
- Autoimmune 2.8%

Metabolic syndrome

Why are we impacted with so many COVID deaths? Our country has more than 50 times more deaths than Japan, how are we so different? [9]

Cases & Deaths Comparison of Countries as of 10/13/2020

Country	Population	Cases	Deaths	Deaths per Million
US	330 Million	8,072,012	220,280	665
Japan	126.5 Million	89,673	1,634	13
Brazil	209.5 Million	5,105,033	150,772	708
India	1.35 Billion	7,236,995	110,617	80

50x

We are faced with a large number of people with metabolic syndrome, a group of conditions that may occur together and increase the risk of cardiac disease, stroke, diabetes, and hypertension.

Metabolic Syndrome

- A large waist circumference (obesity)

- Prediabetes or Type 2 Diabetes

- Prehypertension or hypertension (high blood pressure)

- High blood triglycerides

- Low HDL cholesterol

Metabolic Syndrome

- In 2016, NHANES published data revealed 87.8% of Americans are metabolically unhealthy, based on these 5 parameters

- In 2019, the U.S. Centers for Disease Control and Prevention (CDC) found, more than 122 million American adults have diabetes or prediabetes – conditions which have been shown to increase your changes of contracting and even dying from COVID-19

COVID-19 Long-Haulers

"Long-Hauler" is a term applied to people who haven't yet fully recovered from COVID-19 weeks or months after the onset of their symptoms. Practitioners tend to attribute this to the fact that SARS-CoV-2 impacts the immune-system long term. We're seeing people wrestling with a protracted post-viral syndrome, having mainly mild-moderate symptoms such as "fatigue, chills and sweats, body aches, headaches, brain fog, and gastrointestinal issues." While cough and fatigue seem to be the most commonly experienced symptoms, the more persistent and debilitating are "impaired memory and concentration, often with extreme fatigue." [10]

Chronic Complications from COVID Infection

- Permanent lung injury
- Malnutrition
- Deconditioning
- Need for extensive physical therapy
- Post-viral autoimmunity
  - Heart (myocarditis)
  - Brain (neuro-inflammation and cognitive decline)

The long-haulers often face medical gaslighting in response to their post-viral syndrome. These suffering patients not infrequently never had an actual laboratory confirmed active COVID-19 infection because they experienced mild-moderate symptoms and either didn't get tested or tested once their viral load decreased. Due to this lack of testing confirmation they have been greeted by skepticism on the part of mainly medical professionals and a belief that psychological influences on their symptoms are major contributors to them, Some practitioners contribute long-hauler complaints to "hysteria," and thus diagnose them as having anxiety, especially with respect to female patients [11].

(Note: Any experienced Integrative Medicine doctor can more easily explain why this chronic syndrome happens and how to correct it than other healthcare practitioners can!)

Lessons Learned: The Horizon is Looking Brighter

The over-reactive immune response to COVID-19 in infected people has been driving this virus' reported prevalence. If we can get ahead of the excessive inflammation that so profoundly impacts the infected in our nation, we will be better situated to help the uninfected bolster their immune systems so as to have an appropriate response to COVID exposure.

Vaccines should be a part of the public health response, though this really should not be our overriding or only focus.

We must emphasize the importance of reducing inflammation with diet, exercise, proper supplementation including Vitamin D and Zinc, along with stress and fear reduction. With these we can reduce our individual risk and pave the way for all of us to achieve a more balanced and empowered approach to life with COVID-19.

The pros and cons for each of the approved vaccines and a scientifically rigorous examination of them will be issues soon.

Please note that the materials above express my opinion and are not to be treated as a substitute for a formal medical consultation. The material in this document has not been reviewed or evaluated by the FDA.

Biology of SARS-CoV-2/COVID-19 – A Brief Review

Route of Entry: Viral Spike Protein and the ACE2 Doorway

The process of invading host cells is one of the first steps in the life cycle of most viruses. A common route of entry for many viruses involves a "lock and key scenario" where a protein on the surface of the virus interacts with an enzyme-receptor on the surface of host cells. This interaction at the cell surface opens the cellular doorway and allows the virus to enter the cell.

SARS-CoV-2, the virus that causes the disease COVID-19, has specific proteins on its surface called 'spike proteins' [12]. These viral proteins interact with angiotensin-converting enzyme 2 (ACE2), an enzyme-receptor found on cells throughout the human body [13] which acts as a cellular doorway for the virus to enter them [14].

ACE2 is found in many tissues but in especially high levels in the lung, hence the acute respiratory distress syndrome, pneumonia and lung injury which characterize so many COVID-19 cases. This is the same route of entry that was exploited by the SARS-CoV virus that caused the 2003 SARS outbreak [13].

In addition to using ACE2 as a doorway researchers have proposed that SARS-CoV-2 enters human cells by a separate, more effective means involving a special site on its outer surface called a furin cleavage site [15]. Furin enzymes on the surface of human cells interact with the furin cleavage site of SARS-CoV-2 and rapidly facilitate entry of the virus into the cell. Since almost all cell surfaces in the human body have furin enzymes on them, the furin cleavage site of SARS-CoV-2 significantly increases its ability to invade human cells and become activated [16]. Activation of SARS-CoV-2 allows it to effectively bind to ACE2 infecting more cells and causing additional damage. Interestingly, the presence of furin cleavage sites allows SARS-CoV-2 to invade human cells regardless of whether cells have low expression of the ACE2 receptor [17].

Understanding how the SARS-CoV-2 virus invades human cells is important for identifying viable preventative and treatment options. Furthermore, understanding the implications of SARS-CoV-2's effect on ACE2 is also important because ACE2 is not just a doorway into cells but may actually be protective in COVID-19.

A Brief Review of the Renin Angiotensin System (RAS)

The renin-angiotensin system (RAS) is an elaborate system that primarily regulates blood pressure as well as fluid and electrolyte balance. Angiotensin-converting enzyme 2 (ACE2) along with the angiotensin II converting enzyme (ACE) are key players in regulating blood pressure and work together to keep RAS balanced [18]. ACE2 is found in high numbers in lung tissue, gastrointestinal tissue and within the cardiovascular system. ACE converts Angiotensin I to Angiotensin II which increases blood pressure. In contrast, ACE2 reduces blood pressure by countering the effect of ACE and has other protective effects [18–20].

The Importance of ACE2 and a Balanced RAS

ACE2 has powerful anti-inflammatory and immune modulating effects but when levels are reduced these beneficial effects are lost. As COVID-19 progresses it causes a state of imbalance in the RAS with low levels of ACE2 due to viral particles binding to them along with high levels of ACE. Additionally, it is believed that SARS-CoV-2 can exacerbate this imbalance by directly reducing the number of ACE2 receptors on host cells by genetic downregulation [13].

The imbalance of ACE2/ACE can have severe consequences and various studies have shown the importance of ACE2 in regards to lung health and underlying conditions that increase the risk of severe COVID-19.

Low ACE2 is closely associated with acute respiratory disease syndrome (ARDS) which is prevalent in COVID-19 [21]. Low ACE2 and high ACE levels may exacerbate underlying cardiovascular conditions including high blood pressure, atherosclerosis, and heart failure, as well as kidney disease, serious lung injury, and others [13]. All of which are comorbidities associated with severe COVID-19 cases [22].

Disease models have demonstrated that the loss of ACE2 function can lead to increased neutrophils (a type of white blood cell) in the lung, exaggerated inflammation and lung injury [13]. ACE2 may also protect against the acute severe lung injury commonly seen in COVID-19 [23].

Although ACE2 has been identified as a doorway for SARS-CoV-2 to enter cells it also exerts a range of protective effects that may be beneficial in COVID-19.

Speculative Concerns about Increasing ACE2 in COVID-19

Considering the fact the SARS-Cov-2 virus uses ACE2 receptors to gain entry into cells, it follows that medications which increase ACE2 receptors such as Ibuprofen and blood pressure medication may have dire consequences in COVID-19 [24–26] .

Following a study published in The Lancet medical journal that hypothesized Ibuprofen's potentially negative impact on SARS-CoV-2/COVID-19 via increasing ACE2, the Health Minister of France warned that anti-inflammatory drugs could worsen COVID-19 [27]. His comments also seem to have been sparked by statements made by an infectious disease doctor in France who cited four cases of young COVID-19 patients who developed serious symptoms after using non-steroidal anti-inflammatory drugs (NSAIDS) in the early stages of their infection [25].

A recently published manuscript supports the hypothesis that blood pressure medications may negatively affect SARS-CoV-2/COVID-19 by increasing ACE2 receptors. The argument is that patients treated with blood pressure medications such as ACE inhibitors and angiotensin receptor blockers (ARBS) will have increased levels of ACE2 in their lungs which may increase the risk of infection and therefor severe disease due to COVID-19 [24].

Despite speculative concerns that Ibuprofen and blood pressure medications may increase the risk of SARS-CoV-2 infections and exacerbate existing COVID-19 via their effect on ACE2, clinical evidence to support this is lacking. As such, until more evidence is available experts and numerous medical authorities including the European Society of Cardiology, the American Heart Association and the American College of Cardiology have recommended continuing the use of standard blood pressure medications as prescribed [28].

Inflammation and Immune Response: Viroporins, NLRP3 inflammasome cytokine storm, NRF2 and 3 CL protease.

Viroporins

Viroporins are special ion channel proteins which play essential roles in viral replication, virulence and pathogenicity. These proteins are so essential that without them a virus would be unable to invade cells and replicate. Research has shown that the virus SARS-CoV in the SARS 2003 outbreak used specific viroporins (Viroporin ORF3a and E protein) [16]. The activity of

these viroporins triggers the activation of the NLRP3 inflammasome. As discussed below, NLRP3 causes an over production of inflammatory cytokines which can led to severe inflammation, a cytokine storm, and the development of ARDS and ALI [16].

Recently, SARS-CoV-2 has been shown to have these same viroporins which is thought to contribute to its high degree of virulence and pathogenicity [16].

The NLRP3 inflammasome

After SARS-CoV-2 is activated inside a human cell it releases NLRP3 inflammasomes which quickly initiates a cascade of largely uncontrolled immune reactions.

Inflammasomes are an important part of our innate immune system as they sense pathogens and other threats and respond by releasing a controlled amount of pro-inflammatory cytokines to defend host cells. However, cytokines are a double-edged sword. When controlled they support an appropriate immune response to defend host cells. When uncontrolled they can lead to a cytokine storm which can result in severe organ damage, organ failure and death [16].

The NLRP3 inflammasome and the inflammatory cytokines it releases has been linked with the development of acute respiratory distress syndrome (ARDS) and acute lung injury (ALI) [29–32]. NLRP3 also plays a critical role in the development of cytokine storms and multi-organ dysfunction [33].

In addition, the NLRP3 inflammasome is responsible for many negative effects on cardiovascular health. Inflammasomes have been clearly associated with the progression of atherosclerosis, heart attack and heart failure. These effects on cardiovascular health were also seen in SARS-CoV infected people in 2003 [34].

Cytokine storms

A cytokine storm is an excessive immune response due to infection, drugs or other external stimuli, that progresses rapidly leading to organ damage and oftentimes death [35,36].

Cytokine storms are considered one of the main causes of ARDS and multiple-organ failure and plays a significant role in disease aggravation [37]. The results from Animal models of SARS-CoV infection support the hypothesis that high viral loads and elevated inflammatory cytokines cause a cytokine storm which has negative effects on lung tissue [38].

Recent evidence shows that a portion of severe COVID-19 cases are closely linked to cytokine storms [35,37]. It is also is considered to be a one of the most important mechanisms underlying the severe deterioration seen in some patients [39] and a main cause of organ failure and death in critically-ill COVID-19 patients [40].

Nuclear Factor E2-Related Factor (Nrf2)

Nrf2 is a master transcription factor that regulates the expression of numerous protective genes [41]. Increasing the expression of these protective genes increases various antioxidant enzymes including superoxide dismutase, catalase and glutathione peroxidase which strongly protects against oxidative stress, something commonly seen in COVID-19 [42,43].

Emerging evidence indicates that Nrf2 and these antioxidant enzymes could also play a role in reducing viral induced inflammation and improving immune clearance of the virus [44–46].

Research suggests that activating Nrf2 with Nrf2 activating compounds inhibits the NLRP3 inflammasome, which is involved with causing ARDS, lung injury and cytokine storms, and inhibits the pro-inflammatory cytokine, IL-1Beta [47]. Researchers also suggest that the immunomodulatory effects of Nrf2 may also be beneficial in treating cytokine storms and in helping patients enter the recovery and repair phase of the inflammatory response [48].

In addition, to its role in modulating inflammation, research has shown that Nrf2 activation can inhibit viral cell entry and replication. Furthermore, Nrf2 activating compounds such as sulforaphane found in broccoli and epigallocatechin gallate (EGCG) found in green tea have been shown to significantly decrease viral entry and replication of Influenza A in human cells [44].

Researchers at the University of Colorado and Pathways Bioscience have recently demonstrated that a potent Nrf2 activator reduces the receptors that SARS CoV-2 uses to invade cells and suggest that it may reduce the ability of the virus to bind to host cells [48].

3CL protease
Once inside human cells the process of cellular take over begins and the virus starts to replicate. The virus also begins damaging cells by producing an enzyme called 3CL Protease. This enzyme not only damages cells and causes inflammation but it also allows the virus to spread to other nearby cells [49,50].

Effects of SARS CoV-2/COVID-19
"The CDC is actively working to learn more about the whole range of short- and long-term health effects associated with COVID-19" [51]. It is clear that COVID-19 negatively affects multiple organ systems of the body including the lungs, heart, coagulation, the immune system and others. Furthermore, COVID-19 can have long term effects and protracted symptoms after recovery.

Lung Health
Severe cases of COVID-19 are mainly represented by two processes, viral pneumonia caused by the SARS CoV-2 virus and progression to acute respiratory distress syndrome (ARDS) [52]. ARDS is a syndrome comprised of different pathological lung features and is not only due to COVID-19. It is in fact the end result of a variety of diseases or injury to the lung. For the most part, lung damage from ARDS due to COVID-19 is almost identical to lung damage from other causes such as sepsis, vaping, etc. [53].

One of the most common pathological changes in COVID-19 is a pattern of lung damage called diffuse alveolar damage (DAD) which is comprised of injury to lung cells, namely alveolar epithelial cells as well as type II pneumocytes with signs of fibrosis [54]. The latest postmortem studies confirm this showing that the most common finding in patients who have died from COVID-19 is DAD [54,55]. Other pathological changes include dilated pulmonary vessels, the

formation of small pulmonary thrombi (blood clots due to coagulation dysfunction), multi-organ dysfunction and others [52].

Coagulation dysfunction is common in COVID-19 and can lead to widespread thrombosis. In fact, most deaths from ARDS in COVID-19 show evidence of thrombotic disseminated intravascular coagulation (DIC). This may explain atypical features seen in the lung such as dilated pulmonary vessels which is rare in non-COVID-19 ARDS [52].

COVID-19 patients who develop ARDS and survive may not be totally out of danger. In April 2020, the Pulmonary Fibrosis Foundation stated that some COVID-19 patients with ARDS may be at risk for developing fibrosis of the lung which could be permanent. One study found that 17% of severe COVID-19 patients had signs of fibrosis in chest CT scans [56]. Post ARDS fibrosis does not progress but can be severe and take approximately one year to recover from although residual deficits will likely remain [53].

ARDS due to COVID-19 appears to be more deadly than ARDS from other causes with a mortality range of 26% to 61.5% for those in ICU settings and 65.7% to 94% for those who received mechanical ventilation. The majority of deaths from COVID-19 ARDS are due to respiratory failure, respiratory failure with heart failure and myocardial damage and circulatory failure [52].

Cardiovascular Health

Cardiovascular complications of COVID-19
Cardiovascular complications of viral infections including myocarditis, acute heart attack and exacerbation of heart failure have been documented in past epidemics and greatly contribute to mortality [57,58]. Coronavirus outbreaks such as SARS, MERS and SARS-CoV-2 have also been associated with significant cardiovascular complications and have been shown to directly cause damage to the heart [59,60].

Recent clinical studies on COVID-19 have shown that cardiac injury is more common in critically ill patients [61]. One study showed that 23% of critically ill patients developed cardiac injury [62] while a similar study showed that around 37% of COVID-19 patients experienced cardiovascular injury [63]. Another study revealed that 33% of patients developed cardiomyopathy [64].

In addition to direct heart damage acute ST segment elevation indicating potential heart attack has also been associated with COVID-19. In COVID-19 cases, heart attack could be due to various causes including plaque rupture, a cytokine storm, hypoxic injury, coronary spasm, microthrombi or direct endothelial or vascular injury [65].

Long term cardiovascular effects from COVID-19
Long term follow-up data on survivors of respiratory virus epidemics is scarce but what there is indicates there are long term cardiovascular effects. After becoming infected with the H7N9 influenza virus survivors had cardiac abnormalities present for a year before returning to normal [66]. Twelve years after clinical recovery, SARS survivors were shown to have cardiovascular system abnormalities, significant cholesterol disorders, and glucose metabolism disorders [67].

There are also long term effects from pneumonia with an increased risk of cardiovascular disease up to 10 years following an episode [68].

In a study of 100 patients who recently recovered from COVID-19, cardiac MRI performed on average of 71 days after diagnosis showed cardiac involvement in 78% and on-going myocardial inflammation in 60% of patients [69]. Myocardial inflammation and myocardial injury was observed in 46% of post COVID-19 patients, up to 53 days after initial diagnosis [70].

Although we can use recent data and extrapolate from published reports on similar previous epidemics, the current COVID-19 outbreak underscores the need for greater understanding of the potential long-term implications of viral infection on cardiovascular health.

Coagulation

Although most patients infected with SARS-CoV-2 primarily have symptoms of respiratory tract infection and other mild symptoms some patients progress to more severe, systemic disease such as ARDS and multiple organ dysfunction. Severe COVID-19 patients have also been shown to have coagulation abnormalities including disseminated intravascular coagulation (DIC), thrombotic microangiopathy (blood clots in small blood vessels), pulmonary embolism, and other thromboembolic complications, which are associated with an increased risk of death [71].

The most common laboratory finding in patients with COVID-19 coagulopathy is an increased D-dimer level, a modest decrease in total platelet count and a prolonged prothrombin time. Other lab findings relevant to abnormal coagulation include increased lactate dehydrogenase (LDH) and extremely high levels of ferritin. Various inflammatory cytokines including TNF-alpha and IL-1beta are also important when present as they can initiate coagulation activation and suppress anticoagulant pathways [71].

In critically ill COVID-19 patients the incidence of thromboembolic complications ranges from 5-15% and up to 35-45% in cohort studies [71]. Alarmingly, most deaths from COVID-19 ARDS show evidence of DIC [52]. Additionally, some experts suggest that pulmonary embolism could be involved with the rapid respiratory deterioration seen in some critically ill patients with ARDS [71].

Although DIC related to COVID-19 has been shown to be clinically different from other causes such as sepsis, the available evidence suggests that the coagulation abnormalities in COVID-19 are a combination of low grade DIC and local pulmonary thrombotic microangiopathy [71].

However, referencing pathological evidence from a series of autopsies, other researchers believe that the major mechanism underlying the coagulation abnormality is 'pulmonary intravascular coagulopathy' (PIC), a term first coined by McGonagle et al, which describes a kind of immune thrombosis distinct from classical DIC [72].

Regardless of the name given the specific mechanism, patients need to be treated accordingly and anticoagulation therapy has proven useful. A study done in China has shown that patients with severe COVID-19 associated coagulopathy who received heparin, an anticoagulant medication, had lower rates of mortality than patients who didn't receive this drug [73]. Another

clinical trial is underway investigating the use of tissue plasminogen activator (tPA), an FDA approved drug used to dissolve blood clots in COVID-19 patients [74].

Tissue plasminogen activator (tPA) treatment for COVID-19 associated acute respiratory distress syndrome (ARDS): A case series - PubMed (nih.gov)

Impaired fibrinolysis in critically ill COVID-19 patients - PubMed (nih.gov)

Multisystem Inflammatory Syndrome

In addition to causing negative effects on the cardiovascular, pulmonary and coagulation systems, COVID-19 has been associated with the development of a previously unseen inflammatory condition primarily in children that effects multiple organs of the body called multisystem inflammatory syndrome in children (MIS-C) [75].

Although MIS-C is rare, and most children who have it eventually get better, it can be life threatening. Common symptoms include fever, severe fatigue, vomiting, diarrhea, stomach pain, rash, fast heart beat and others. Emergency warning signs include severe stomach pain, difficulty breathing, bluish lips or face, previously unseen onset of confusion, and inability to wake up or stay awake [76].

A systematic review of 39 observational studies involving over 600 pediatric patients with MIS showed that 71% of them were admitted to the ICU, 22.2% required mechanical ventilation and only 1.7% died. MIS-C was also associated with depressed ejection fraction. Fever, abdominal pain or diarrhea and vomiting were the most commonly reported symptoms [75].

Many other studies investigating MIS-C have been published [76–81].

Recently, MIS has also been reported to occur in adults. Sixteen cases of multisystem inflammatory syndrome in adults (MIS-A) originating in the US and the UK have been reported. In addition, three published case series involving a total of eleven patients reported MIS-A [82].

Despite telltale common symptoms and laboratory biomarkers in reported MIS cases, the pathophysiology of MIS in children and adults is not fully understood. However, data from the aforementioned reports suggest that MIS may represent a post-infectious process as the majority of MIS-A and MIS-C patients had negative PCR and positive antibody results [82].

Stem Cells

Experimental studies have demonstrated negative effects of the SARS coronavirus on stem cells which may contribute to the development and progress of COVID-19.

A recent experimental study has demonstrated that stem cells lose their ability to transform into heart cells after being exposed to the SARS-CoV-2 virus. Researchers found that the structure and speed of growth of stem cells was significantly changed after two weeks of being exposed to the virus. They also found that the stem cells lost their ability to transform into heart cells while some stem cells unexpectedly turned into fibroblast cells which produce collagen and

fibrotic tissue. Although collagen is important for the integrity and health of the skin, it can be dangerous at certain levels in the lungs and other organs [83].

The loss of the ability to repair or renew heart cells in the face of infection, inflammation and tissue damage could be detrimental for COVID-19 patients especially those with underlying cardiovascular disease. Furthermore, having excess collagen and fibrotic tissue especially in the lungs could potentially exacerbate ALI and ARDS.

Another experimental study showed that the 2003 SARS coronavirus (SARS-CoV) negatively affected lung stem cells. Researchers found that lung stem cells also have ACE2 on their cell surface and are the target cells for SARS coronavirus infection in cell cultures. Furthermore, like other host cells, lung stem cells are used by the virus for viral replication and can become damaged and then destroyed [84].

The findings of these two experimental studies demonstrate the negative effects of SARS-CoV and SARS-CoV-2 on stem cells and provide new insight into the possible cause of the heart and lung damage commonly seen in severe COVID-19.

Other Long-Term Effects: Long COVID-19

"The CDC is actively working to learn more about the whole range of short- and long-term health effects associated with COVID-19" [51].

Depending on the severity of illness people who have been infected with SARS-CoV-2 typically recover within 2 to 6 weeks. However, regardless of the severity, COVID-19 can sometimes result in prolonged illness both in children and adults who do not have underlying medical conditions. These patients are often referred to as 'COVID long haulers' and have 'long covid' symptoms that can linger or recur for weeks or months following the initial onset of illness [85]. In a multi-state telephone survey 35% of symptomatic COVID-19 patients reported that they had not returned to their usual level of health 2-3 weeks after infection [86]. Aside from the aforementioned long-term effects of COVID-19 on the cardiovascular and pulmonary systems, many others have been reported [86–94].

Neurological

In addition to causing a prolonged loss of smell and loss of taste, the most common long-term neurological symptoms associated with COVID-19 are headache and vertigo [87]. Encephalitis, seizures and other neurologically associated conditions such as mood swings, confusion and brain fog have also been reported up to 2 to 3 months after the initial onset of illness [88].

Fatigue

Many 'COVID long haulers' report severe fatigue and have many symptoms characteristic of chronic fatigue syndrome. A small study performed in a hospital in Rome found that 53% of discharged COVID-19 patients reported fatigue up to 2 months after their symptoms first appeared [89]. A second study done in China, not only found that COVID-19 patients continued to have abnormal lung function 3 months after the initial onset of symptoms but 16% still reported fatigue [90]. A New York Times article published on October 22, 2020 reported on three patients

all under 21 years old who are now considered 'COVID long haulers' due to complaints of protracted post COVID-19 symptoms. Their symptoms primarily included severe, debilitating fatigue [91]. A similar report accounting for symptoms in 'COVID-19 long haulers' including chronic fatigue was published in Nature [89].

Cognitive impairment

Long term cognitive effects of COVID-19 have been predicted and are now being observed post-COVID-19. A study on patient survivorship after an intensive care unit (ICU) stay showed that new or worsening cognitive impairment is common among survivors of such stays. One year after ICU hospitalization, 33% of survivors of acute respiratory failure or shock experienced cognitive impairment with neuropsychological test scores consistent with traumatic brain injury (TBI) [92]. Data from a recently published study in the Journal of Psychiatric Research found that cognitive impairments were present in patients who recovered from COVID-19 and may possibly be linked with inflammation [93].

Autoimmunity

Autoimmunity has recently been identified as a common clinical feature in patients with severe COVID-19. A retrospective study based in Atlanta, Georgia assessed various laboratory markers of autoimmune disease including ANA (antinuclear antibody) and Rheumatoid Factor, commonly used to diagnosis Rheumatoid Arthritis, in 31 critically ill COVID-19 patients with no known history of autoimmunity. Their results revealed that of the 31 participants, nearly half of them had positive levels of ANA. Furthermore, of the positive ANA tests, 81% displayed titers greater than 1:160, a level seen in less than 5% of the normal population. Other autoimmune markers were also seen in the participants. In addition, the results of this study demonstrate that the presence of autoimmunity is highly correlated with increasing inflammation. Overall, their study indicates a correlation between severe COVID-19 and the possible development of autoimmunity. The authors concluded that "the immunological environment of serious COVID-19 infection, including TLR7 activation by SARS-CoV2 ssRNA, is sufficient to drive de novo autoreactivity against a variety of self-antigens" [94]. Note, this preprint article reports new research and has not yet been peer reviewed.

Early Symptoms, Predictive of Underlying Conditions and Biomarkers of COVID-19

Early Symptoms

Loss of smell and taste

A number of new studies have appeared demonstrating that loss of smell (anosmia) and/or loss of taste (dysgeusia) are common among COVID-19 patients. Although, these two symptoms may be less common than fever, dry cough and fatigue, they have been added to the World

Health Organization's (WHO) list of COVID-19 symptoms and are becoming recognized as initial symptoms and predictors of disease [95,96].

A survey from UC San Diego showed that 68% of COVID-19 patients reported impairment in smell and 71% reported impairment in taste. This is in sharp contrast to COVID-19 negative patients in which 16% had loss of smell and 17% had loss of taste [97]. One of the authors of this survey stated that these results indicate that "if you have loss of smell and taste you are 10 times more likely to have COVID-19 than other causes of infection" [96]. In a study reviewing 237 cases, profound loss of smell was found in 73% of people prior to COVID-19 diagnosis and was the initial symptom in 27% of these people [97]. A recent systematic review of 19 studies showed that SARS-CoV-2 viral shedding is highest from the nose and therefore acts as a major source for transmission of the virus. The authors concluded that loss of smell without nasal obstruction may be a highly specific predictor of COVID-19 [98].

Many organizations worldwide have begun collecting symptom reports and have linked the sudden loss of smell and taste as likely indicators of COVID-19. A report from the CDC involving 5000 healthcare workers found that prior to diagnosis 16% indicated they experienced loss of smell or taste [99]. Results from a preprint study that used RADAR COVID-19, a symptom tracking system showed that 59% of 579 UK residents with COVID-19 reported loss of smell compared to 18% of COVID-19 negative patients [100]. Similarly, results from a study that used the COVID-19 Symptom Tracker, a joint effort among Massachusetts General Hospital, Stanford University and King's College of London, showed that nearly 65% of 6,400 UK residents and 67% of 726 US residents who tested positive for the virus reported loss of smell and taste [101].

Predictive underlying conditions

The vast majority of hospitalized COVID-19 patients have been shown to have underlying medical conditions also known as comorbidities [102]. The most common comorbidities among COVID-19 patients include hypertension, cardiovascular disease, and chronic lung disease. In addition, obesity and type 2 diabetes are major contributors to the COVID-19 pandemic and may predict severe COVID-19 and death [102–105]. Considering 60% of COVID-19 patients report gastrointestinal symptoms, the microbiome of the gut may also be involved in predicting disease [106].

Underlying cardiovascular conditions and SARS CoV-2

Patients with underlying heart conditions appear to be more susceptible to coronavirus infection, have more complications and are more at risk of death.

According to the National Health Commission of China (NHC) 35% of patients with SARS-CoV-2 infection had a history of hypertension and 17% had a history of coronary heart disease [107]. One study showed that COVID-19 patients with underlying hypertension had 3 times the risk of death compared to those without hypertension [108]. Another study showed that among COVID-19 patients with severe symptoms 58% had hypertension, 25% had heart disease and 44% had a heart arrhythmia [109]. A meta-analysis of multiple studies showed that COVID-19 patients with hypertension were more at risk of having severe disease requiring intensive care unit (ICU) care

compared to those without hypertension [110]. The largest case series data with close to 45,000 confirmed COVID-19 cases in China reported that patients with cardiovascular disease had a fatality rate of 10.5% and those with hypertension had a fatality rate of 6%, both higher than the overall fatality rate of 2.3% [111].

Coronary artery disease has also been associated with an increased risk of death and an increased risk of severe disease requiring ICU care in COVID-19 patients [108,110]. Patients with coronary artery disease may be more at risk for complications due to the risk of coronary plaque rupture as a result of virally induced inflammation. In addition, systemic inflammation may increase coagulation and the likelihood of microvascular thrombi, stent thrombosis and other complications [68].

It is speculated that the relationship between cardiovascular disease and death from COVID-19 could be due to the fact that patients with a history of cardiovascular disease may have an impaired ability to adapt to new changes, and the COVID-19 infection may increase myocardial demand leading to worsening ischemia or increase metabolic demands leading to heart failure and death [112].

Obesity

A study of 5700 patients hospitalized with COVID-19 showed that 41.7% were obese, the second most common comorbidity after hypertension [104] while a separate study of 3615 COVID-19 patients showed that 36% were obese [113].

Obesity can restrict ventilation by increasing pressure on the diaphragm, is highly inflammatory, induces oxidative stress and leads to blood sugar dysregulation and diabetes [114,115]. Obesity also impairs normal immune system functioning and has been shown to delay and hinder the response of the immune system to viral infections including the influenza virus [114,116].

Although older adults are most at risk for severe COVID-19, the younger population is also at risk considering obesity is a serious problem for children and adolescents, particularly in the US where the prevalence is 18.5% for those aged 2-19 years [117]. A study published in The Lancet found that younger individuals admitted to the hospital for COVID-19 were more likely to be obese. The researchers concluded that in areas with a high prevalence of obesity, COVID-19 will affect younger populations more than what has been previously reported [103]. Based on data collected by the newly established COVID-19-Associated Hospitalization Surveillance Network (COVID-NET), obesity was the most common condition seen in young adults with COVID-19, with a prevalence of 59% in those aged 18-59 years [102].

Not only is obesity a common comorbidity it also associated with increased risk of severe COVID-19 and death. A study from France found a high prevalence of obesity in COVID-19 patients indicating that nearly half of the patients admitted to ICU were obese and patients with severe obesity had the worst prognosis. The researchers also found that the need for invasive mechanical ventilation was correlated with the body mass index (BMI) of obese patients and that 85.7% of patients with severe obesity needed ventilation [118].

A study of over 3500 COVID-19 patients showed that obese and severely obese patients were two and 3.5 times more likely, respectively, to be admitted to acute and critical care compared to overweight and normal weight patients [113]. According to two studies published in Diabetes Care, obese patients were nearly 3 times more likely to develop severe COVID-19 compared to those with normal weight [119,120]. The obese patients were also more inflamed as they presented to the hospital with higher levels of the inflammatory marker, C-reactive protein (CRP) than non-obese patients [120]. This finding isn't surprising as inflammation is very common in obesity and has been shown to increase as the degree of obesity increases [121–123].

Obesity which is a growing problem worldwide is the single most important risk factor for type 2 diabetes, which is one of the most common comorbidities and a major risk factor for severe COVID-19 and related death [124].\

[Obesity and clinical severity in patients with COVID-19: a scoping review protocol - PubMed (nih.gov)](#)

Diabetes

Even though the exact overall prevalence of diabetes in COVID-19 is difficult to ascertain, many studies indicate that it is between 10-20% of cases [125,126]. A recent report from China showed that diabetes was a comorbidity in 16.2% of severe COVID-19 patients while a separate study showed that 12% of hospitalized patients with COVID-19 had diabetes [127,128].

Patients with diabetes have an increased susceptibility to infections in general due to alterations in immune activation and an internal environment that favors immune system dysfunction [129–132]. Furthermore, people with diabetes are six times more likely to be hospitalized during influenza epidemics [133]. However, based on available data researchers conclude that diabetes may not increase the risk of SARS-CoV-2 infection but can worsen outcomes leading to severe COVID-19 and an increased risk of death [125].

A small study showed that among 32 non-survivors with severe COVID-19 diabetes was the most common comorbidity [62]. A study from China of nearly 72,000 cases of COVID-19 found that diabetes nearly tripled the rate of death (2.3% to 7.3%) [111].

The impact of obesity and diabetes in COVID-19 has been reported in numerous studies and clearly shows an increased risk of morbidity and death. This is particularly concerning considering the high prevalence of these two conditions throughout the world. Since inflammation is shared player in these conditions, strategies to reduce inflammation and support the immune system should be beneficial for prevention.

The gut microbiome

In addition to other predictors such as obesity and diabetes, the gut microbiome may also predict the severity of COVID-19 and explain the differences in susceptibility.

Although much of the focus has been on lung injury, the SARS CoV-2 virus also affects the intestines. More than 60% of patients with COVID-19 report gastrointestinal symptoms and patients with such symptoms often have more severe/critical disease. SARS CoV-2 negatively

affects the intestines primarily due to its impact on ACE2. Found in higher amounts in the small and large intestine than in the lung, ACE2 is an important regulator of intestinal inflammation and has a significant effect on the composition of the gut microbiome [106].

After identifying a series of blood-based and protein-based biomarkers that closely correlated with predictive markers seen in COVID-19 and predicted progression of severe COVID-19, researchers investigated if the gut microbiome could do the same. They found that the gut microbiome is highly predictive of their set of biomarkers and therefore is also predictive of severe COVID-19. Their findings suggest that the disruption of the microbiome may predispose individuals to gut inflammation and increase the risk of severe COVID-19 [134].

This study also determined that specific metabolites from stool samples including amino acids, fatty acids and bile acids were significantly associated with microbiome activity and features. This association suggests that these metabolic pathways, modulated by diet and host bacteria populations may also affect inflammation and susceptibility to COVID-19 [134].

Furthermore, the function of ACE2 in regulating amino acid levels after dietary intake and the gut microbiome's role in synthesizing essential amino acids might be another link between the gut and inflammation in predicting COVID-19 as amino acids are essential in reducing inflammation and maintaining a healthy immune system [106,135]. The researchers conclude that the gut microbiome is highly predictive of the biomarkers they identified and may underlie the predisposition of some individuals to severe COVID-19 [134].

Predictive Biomarkers

Studies have revealed that several biomarkers are associated with COVID-19 and can predict severity of disease, progression of disease and death [136].

Such biomarkers are useful in stratifying a patient's risk and triaging patients to the most appropriate care. We will review a selection of commonly reported biomarkers that may provide insights into patients with COVID-19.

Vitamin D

Low levels of vitamin D and frank vitamin D deficiency have been linked to COVID-19.

An observational study comparing outcomes from various countries revealed a statistically significant correlation between low vitamin D levels and death from COVID-19. They also demonstrated the prevalence of vitamin D deficiency in Europe and its relationship to the severity of COVID-19 and death [137].

Similarly, after analyzing patient data from 10 countries researchers at Northwestern University showed in a preprint study that Vitamin D deficiency was associated with disease severity as the risk of severe COVID-19 among patients with vitamin D deficiency was 17.3%. They also showed strong correlations between severe deficiency and mortality rates [138,139].

An observational study of 212 COVID-19 cases also reported a link between vitamin D status and COVID-19. Their data showed that serum vitamin D levels were statistically significant in

clinical outcomes and that vitamin D levels were lowest in critical cases. The study also found that the majority of COVID-19 patients had insufficient serum vitamin D with an average level of 23.8 ng/ml [140].

A preprint study from the University of Chicago involving over 4,000 COVID-19 patients demonstrated that up to 25% were likely to be vitamin D deficient and that testing positive for COVID-19 was associated with such a deficiency. Predictive rates of COVID-19 also support this finding as the rate in the vitamin D deficient group was 21.6% compared to 12.2% in the sufficient group [141].

C-Reactive Protein (CRP)

C-Reactive Protein (CRP), a common marker of inflammation has been widely used in the laboratory assessment of COVID-19. It has been shown to be associated with severe disease and death and may be used to predict aggravation of disease.

A small study showed that patients with severe disease had higher levels of CRP than those with mild disease and that CRP was positively associated with the CT severity score. The results suggest that CRP values were significantly increased in the initial disease stage which came to light prior to CT findings indicating it may serve as a predictor of early severe COVID-19 [142]. Similarly, another study reported that CRP levels were positively correlated with lung lesions in the early stage of COVID-19 [143].

In a study investigating disease progression from non-severe to severe COVID-19 CRP was shown to be significantly associated with aggravation in non-severe COVID-19 patients. Their results suggest that CRP could be used to anticipate the possibility of aggravation and progression disease [144].

CRP has also been shown to be positively correlated with the severity of COVID-19 pneumonia and longer hospital stays. Their findings confirm that of other studies and also suggest that CRP may be useful as an earlier indicator of severe disease [145].

A study reporting the clinical characteristics of 25 death cases due to COVID-19 showed that 85% of patients had an elevated level of CRP before death confirming the presence of a severe inflammatory cascade in patients with severe COVID-19 [146].

Ferritin

Ferritin, a marker for the storage of iron and an inflammatory biomarker, has been shown to be associated with COVID-19, cytokine storms and may also predict severity of disease and death [147,148].

A study published in The Lancet analyzed the clinical characteristics of 99 COVID-19 patients and showed that 63% of patients in the study had ferritin levels above normal with an average level of 808.7 ng/ml, over 3 times the upper normal limit [149].

Baseline levels of ferritin have been shown to be closely related to the severity of COVID-19 [150]. Ferritin has also been shown to be markedly elevated in very severe COVID-19 patients and is associated with a poor clinical prognosis [151].

In regards to death, significantly increased ferritin levels were observed in non-survivors and higher serum levels were associated with a greater likelihood of dying. Patients who died from COVID-19 had elevated ferritin levels upon hospital admission and throughout their stay [108].

Ferritin is also among the inflammatory markers that are elevated in cytokine storms which has been associated with critical illness and death in COVID-19 [35].

D-dimer

D-dimer, a marker of coagulation has been associated with COVID-19 and correlates with poor prognosis and death. A retrospective study observed that 74.6% of patients had elevated D-dimer levels [152] while results from a separate study showed that a coagulation abnormality was present in 69% of patients and that all severe cases showed a coagulation abnormality [153]. An early study from China showed that 71.4% of non-survivors met the criteria for disseminated intravascular coagulation (DIC) and that non-survivors had significantly higher levels of D-dimer [154]. Similarly, another study from China demonstrated a higher incidence of death in patients with elevated D-dimer levels. This study also showed that an elevated D-dimer level (>2.0μg/mL) was predictive of in-hospital mortality [155]. Other studies corroborated previous findings that linked elevated D-dimer with the severity of disease, poor prognosis and death [146,152,153].

Lactate Dehydrogenase (LDH)

Lactate Dehydrogenase (LDH), an enzyme involved with glucose metabolism and a marker of tissue breakdown and necrosis of cell membranes has been linked to severe COVID-19 and can predict severity of disease and death.

The results from multiple studies have clearly demonstrated that elevated LDH levels are common in patients with severe COVID-19 and are associated with death [127,146,156–158]. A study reporting the clinical characteristics of 25 cases of COVID-19 which ended in death showed that 100% of these had an increased level of LDH before death compared to baseline [146].

LDH along with lymphocyte count and high sensitivity-CRP, were identified as biomarkers that predict COVID-19 mortality with more than a 90% accuracy. Elevated levels of LDH alone helps in identifying cases that require immediate care [159]. LDH has also been identified as a predictor of need for ICU care in COVID-19 patients in two large studies [160,161].

Cardiac Troponin

Cardiac troponin, a biomarker associated with heart attacks and damage to the heart has been investigated as a biomarker in COVID-19 due to the high prevalence of cardiac injury seen in COVID-19 patients.

A systematic review of 34 relevant studies revealed that elevated cardiac troponin levels are significantly higher in patients with severe complications of COVID-19 [156]. It has also been

shown that patients who required mechanical ventilation have significantly higher levels compared to those who didn't require ventilation. [162].

Regarding death from COVID-19, cardiac troponin has also been shown to be significantly higher in non-survivors compared to survivors [108]. A small study of patients with COVID-19 pneumonia identified elevated cardiac troponin as one of four risk factors in COVID-19 and was predictive of death [163].

Although, elevated levels of cardiac troponin are common in hospitalized patients, it can be used to identify early heart damage seen in COVID-19 and aid in appropriate triage for care [156].

Interleukin 6 (IL-6)

IL-6, an inflammatory cytokine has been shown to be positively correlated with COVID-19 severity and subsequent death.

A retrospective preprint study of 69 patients with severe COVID-19 found that IL-6 was significantly increased in severe cases compared to non-severe cases. Baseline IL-6 values were also correlated with increased levels of CRP, LDH, ferritin and D-dimer [164].

Similar results from a study of patients with mild and severe COVID-19 revealed that IL-6 values were closely related to the occurrence of severe COVID-19. When combined with d-dimer values, the ability to predict the severity of COVID-19 was increased (specificity = 93.3% and sensitivity = 96.4%) [165]. IL-6 has also been reported to be significantly increased in non-survivors [166].

Other COVID-19 relevant interleukin markers include IL-1Beta, IL-1RA, IL-2, IL-7, IL-8 and IL-10 [136].

Procalcitonin (PCT)

Procalcitonin is produced by many different cells typically in response to a bacterial infection or tissue injury and has been used as a biomarker for sepsis, in-hospital death and to distinguish bacterial infection from other causes [167–169].

Procalcitonin has also been associated with severe COVID-19 and subsequent death. A meta-analysis which reviewed four studies demonstrated that elevated PCT levels were associated with an almost five times higher risk of severe infection [170].

A study reporting the clinical characteristics of 25 death cases from COVID-19 showed that 90.5% of patients had an elevated level of PCT indicating that bacterial infections may play a role in increasing mortality [146].

Other biomarkers

Many other markers have been associated with COVID-19 including hematologic markers (total WBC count, neutrophil count, platelet count, etc.), biochemical markers (ALT, AST, total bilirubin, blood urea nitrogen, etc.) [136], and cytokines and other factors (IFN-gamma, monocyte chemoattractant peptide (MCP)-1, macrophage inflammatory protein (MIP)-1A, MIP-1B, granulocyte-colony stimulating factor (G-CSF), and tumor necrosis factor-alpha (TNF-alpha) [171].

Potential new biomarkers have also been proposed including homocysteine, Angiotensin II, neutrophil-lymphocyte ration, and others. [136].

Testing For SARS-CoV-2/COVID-19

Currently, the FDA had authorized two different types of tests for the SARS-CoV-2 virus, polymerase chain reaction (PCR) testing and antibody testing [172].

Polymerase Chain Reaction (PCR)

The PCR test is used for diagnosis as it can quickly indicate if a patient with COVID-19 symptoms has been infected with the SARS-CoV-2 virus. The results of the PCR test are qualitative, in that they give a positive or negative result [172].

Polymerase chain reaction (PCR) is a commonly used testing method that is able to detect the faintest amount of genetic material, usually RNA, from all types of bacteria, fungi and viruses in a given sample. Although all PCR tests use similar chemicals each requires a specific probe in order to detect different organisms. Thus, a PCR test had to be specifically developed to detect the SARS-CoV-2 virus [173].

Many companies have developed PCR tests for SARS-CoV-2 with the primary difference between them being which coronavirus gene each test targets. For instance, CDC approved tests target coronavirus genes that are responsible for creating the envelope that houses its genetic material. The PCR tests also have different levels of accuracy and precision as each have different performance characteristics [174].

The accuracy of PCR testing for SARS-CoV-2

Recently concerns regarding the diagnostic accuracy of the available PCR tests for SARS-CoV-2 have emerged. It is well known that the ability of the PCR test to accurately identify patients with a given disease is problematic depending on when the test is done. If done too soon the PCR test may not detect shedding RNA and if performed too late it may continue to detect RNA of a virus that is not alive or viable [175]. This means that the PCR test does not discern between inactive or "dead" viruses and active or "live" ones. It merely identifies the presence of genetic material, specifically RNA. This means that a positive PCR test result may not mean a person is still infectious or indicate clinically meaningful disease.

Another major diagnostic issue regarding the PCR test is how it's used to measure viral RNA load and how to interpret that in terms of infectiousness. The viral RNA load is expressed as the cycle threshold (Ct) and is sometimes referred to as amplification. The Ct value is the point at which the PCR test first detects viral genetic material in a specimen. There is a strong inverse correlation between the Ct value and the amount of viral genetic material, also known as viral load [176]. The higher the Ct value the lower the viral load. The lower the viral load, the less contagious someone is.

A cycle threshold or amplification of 24 or less has been shown to be accurate in identifying SARS-CoV-2 and active COVID-19 cases. Bullard et al have reported that patients were not

contagious with a positive PCR test at a Ct >25 because the virus load was too low and was not detectable in culture above this number [177].

A recent study published in Clinical Infectious Disease correlated Ct values of PCR testing for SARS-CoV-2 and the results of viral culturing from nasal swabs of nearly 180,000 patients. Their data shows that at a Ct value of 25, 70% of PCR tests remained positive in viral culture, but when the Ct value was increased to 30 the positive culture result dropped to 20%. When the Ct value was increased to 35, the culture result was reduced still further to less than 3%. The authors conclude that high Ct values are mostly correlated with low positive culture results and with low viral loads [178].

An article in the New York Times reported that in a data compiled by health officials from Massachusetts, New York and Nevada that included Ct values , up to 90% of people who had a positive SARS-CoV-2 PCR test had low viral loads [179]. After reanalyzing the testing data, a New York state laboratory found that 43% of the positive results were eliminated by reducing the originally used Ct value of 40 to 35. The percentage of positive results was further reduced to 63% when the Ct value was reduced to 30 [180].

Unfortunately, many laboratories do not provide clear information on what specific test product they use and what Ct value they employ in their SARS-CoV-2 PCR test. However, manufactures of SARS-CoV-2 PCR tests have provided recommended Ct cutoff values which are almost all above 40 [181].

Yet, another issue with the PCR test for SARS-CoV-2 is the genetic probe used to identify viral RNA. Accurately identifying the presence of SARS-CoV-2 RNA also depends on the DNA probe and the length of its bases. The DNA probe used in CDC's PCR test kits are only 25 bases long which does not meet the viral diagnostic recommendations set forth by the FDA which is 100 bases [182].

Antibody Testing

The other testing method approved by the FDA is antibody testing also called serological testing. This test is used to diagnose a recent or past immune response to SARS-CoV-2 by detecting the presence of IgM, IgG and IgA antibodies [172].

Antibodies are produced by the immune system and are critically important to fight infection and clear the virus. This test only indicates an immune response to the virus and does not detect the presence of the virus like PCR based testing does.

Preliminary data suggests that it can take up to 11 days for most infected people to develop an antibody response that is detectable. For this reason, antibody testing is not typically done in patients who have shown symptoms for only a few days [183].

Antibody testing is not only important for clinical diagnosis but for public health experts as results from antibody tests will enable them to estimate how many people have been infected and provide information about the percentage of people who have not had COVID-19 and are

still at risk [174,184]. In addition, antibody testing is important for the development of vaccines in order to evaluate the immune systems response to the virus [183].

Despite the usefulness of this test in detecting an immune response, The World Health Organization (WHO) initially issued a warning saying that there is no evidence that antibody tests can show if a person has immunity to the virus or is no longer at risk of becoming infected. WHO officials stated that not all people who recover from COVID-19 have detectable antibodies which raised concern that such people may not have developed immunity and therefore may be at risk for a second infection [185].

Testing Recommendations from the CDC [172]

- The CDC recommends that laboratories rely on the PCR based test to diagnose the presence of SARS-CoV-2 infections and that a negative test result does not rule out infection. Negative results should be interpreted in light of exposure history and symptoms of the patient.
- The CDC recommends that antibody testing should not be used to diagnose or exclude SARS-CoV-2 infections or to provide information on infection status. Negative results from antibody testing do not rule our SARS-CoV-2 infection especially in those who have been exposed to the virus but are within the incubation period.
- Antibody testing for SARS-CoV-2 still needs to be validated and therefore positive results from antibody testing may be due to past or current infections with a coronavirus other than SARS-CoV-2.
- If antibody testing is done, the CDC recommends following up with PCR testing.

Prevention of SARS-CoV-2/COVID-19

Aside from the vaccine candidates discussed in detail below, there is currently no approved treatment to prevent SARS-CoV-2 infection/COVID-19. Therefore, various public health measures to prevent exposure and reduce the spread of SARS-CoV-2/COVID-19 have been recommended.

The CDC Recommendations

The CDC has reviewed the latest scientific findings and affirms that cloth masks are critical in the fight against COVID-19. The CDC director, Robert Redfield had said that "cloth face coverings are one of the most powerful weapons we have to slow and stop the spread of the virus - particularly when used universally within a community setting" [186]. Furthermore, states across the US have implemented mask ordinances to help prevent the spread of COVID-19.

The CDC recommends the following [187]:

- Clean and disinfect: Clean and disinfect frequently touched surfaces such as tables, doorknobs, light switches, etc., daily.
- Hand washing: Wash your hands often with soap and water for at least 20 seconds. If soap and water are not available use a hand sanitizer that contains at least 60% alcohol.

- Social distance: Avoid people who are sick. Maintain at least 6 feet of distance between yourself and others you don't live with.
- Face Covering: Cover your mouth and nose with a mask when around others. Always wear a mask in public settings and when around people who you don't live with.

The WHO has also published similar recommendations to prevent exposure and the spread of COVID-19 [188].

Face Masks

Among health care workers (HCW) at Mass General Brigham, the implementation of universal masking of both HCW and hospitalized patients was associated with a significant lower rate of SARS-CoV-2 infection. Universal masking was shown to reduced positivity rates from 14.65% to 11.46%. The authors conclude that their results "support universal masking as part of a multipronged infection reduction strategy in health care settings" [189].

In August 2020, an editorial published in JAMA discussed the most recent data about face coverings including the large-scale study among health care workers at Mass General Brigham. The authors of the editorial concluded that "at this critical juncture when COVID-19 is resurging, broad adoption of cloth face coverings is a civic duty, a small sacrifice reliant on a highly effective low-tech solution that can help turn the tide favorably in national and global efforts against COVID-19" [190].

An article in the Washington Post reported a collaboration between Carnegie Mellon's CovidCast, an academic project tracking real time COVID-19 statistics, and the social media platform used by almost 70% of Americans, Facebook. In the absence of a nationwide random digit dial survey which is typically used in public polling, these two groups have teamed up to survey tens of thousands of Americans across the country to help understand the relationship between mask wearing and the prevalence of COVID-19 symptoms in the US. To ensure that state level samples were representative of each state population and its demographics the researchers also utilized census bureau data. Survey data collected from all 50 states plus Washington DC, demonstrates the correlation between mask use and COVID-19 symptoms. Overall, their data showed that states with higher mask use reported fewer COVID-19 symptoms and that masks may reduce the transmission of the coronavirus and other respiratory illnesses [191].

Although cloth masks are suitable for public use, new research clearly shows that cloth masks should not be used by healthcare workers. Recently a study among healthcare workers in Vietnam showed a significant difference between the effectiveness of medical and cloth masks against contracting COVID-19. The results indicate that viral particle penetration of cloth masks was almost 97% compared to 44% of medical masks. In addition, healthcare workers who used a cloth mask were more likely to experience influenza like illness and test positive for SARS-COV-2. The authors suspect that moisture retention, reuse of cloth masks and poor filtration may result in increased risk of infection and thus they should not be recommended for healthcare workers [192].

Prophylaxis Treatment

Although there is no approved preventative strategy, additional measures to support the immune system should be taken, especially considering that most people in the US are likely to be exposed to SARS-CoV-2 over the next 12 months. Vitamins and minerals including vitamin D, vitamin C, and zinc, along with other natural compounds such as quercetin, melatonin and NAC may be useful as part of a preventative strategy. Advanced therapies such as ozone therapy, stem cell therapy and exosome therapy may provide additional support to the immune system in preventing SARS-CoV2 infections. The rationale and scientific evidence for using specific natural agents and advanced therapies can be found in the treatment section of this paper. Furthermore, many studies are being conducted to evaluate Hydroxychloroquine/chloroquine for prophylaxis treatment of SARS-CoV-2/COVID-19 [193–215]. Recently, a study published in JAMA in late September 2020 was terminated early because there was no significant difference in PCR confirmed SARS-CoV-2 cases between hydroxychloroquine and placebo [216].

EVMS Critical Care COVID-19 Management Protocol

Eastern Virginia Medical School (EVMS) has published a severity-based treatment protocol for the management of COVID-19 including recommendations for prophylaxis. The foundational components of their prophylaxis protocol include oral B complex vitamins, vitamin C, vitamin D, melatonin, quercetin, and zinc. Famotidine, an over-the-counter medication is also included. The authors note that while there is extremely limited data, their protocol may be useful in preventing COVID-19 [217].

Vaccine Therapy for COVID-19

As the search continues to identify safe and effective treatments options for COVID-19, the development of COVID-19 vaccines has resulted in many approved versions and some still in development.

Stages of Vaccine Development

Before a vaccine can be widely used in the United States, it must be rigorously evaluated for safety and effectiveness through multiple stages of development. The stages of development include the following [218].

- **Pre-clinical stage.** Scientists use lab tests and animal tests.
- **Clinical development stage.** Three-phase process of testing in humans which may last up to 15 years.
- **Regulatory review and approval.** The FDA and CDC review data of clinical trials
- **Manufacturing.** The FDA inspects the manufacturing factory and approves vaccine labels
- **Quality control.** Governmental authorities monitor the vaccine manufacturing process and the people who receive the vaccine.

However, due to the COVID-19 pandemic, governmental authorities have fast tracked some vaccines which in some instances have been tested in humans and FDA approved.

First Vaccine Use in the US

On March 16, 2020 the first person in the US received a COVID-19 vaccine in Seattle, Washington as part of a new clinical trial. Due to the COVID-19 pandemic the National Institute of Allergy and Infectious Diseases (NIAID) permitted the new vaccine to be fast-tracked to human studies, skipping the thorough testing done in animal models. This clinical study investigated the safety of the new vaccine and its ability to cause an immune response in healthy volunteers [219] and took place at Kaiser Permanente Washington Research Institute in Seattle, Washington.

Emerging & Approved Vaccines

Since March 2020, numerous pharmaceutical manufacturers such as Pfizer, Moderna, AstraZeneca and Johnson & Johnson have created and tested vaccine candidates which are now FDA approved.

Pfizer/BioNTech (BTN162b2)

One now approved COVID-19 vaccine was created by Pfizer and partner BioNTech. They developed BTN162b2, an mRNA vaccine given in two time-spaced doses by injection to protect against COVID-19.

Among the milestones along the way to approval:

On October 9, 2020 Pfizer and partner BioNTech reported that early analysis of their clinical trial showed that their vaccine candidate is 90% effective in preventing COVID-19 [221]. This was a significant achievement as the FDA requires vaccine manufactures to show 50% efficacy before requesting emergency use authorization (EUA) [222]. Phase 3 of this trial began in July 2020 and involved than enrolled 43,000 volunteers of which nearly 40,000 received the second and final dose of the vaccine [221].

On November 9, 2020 Pfizer/BioNTech announced that an analysis performed by an external, independent Data Monitoring Committee (DMC) on data from their phase 3 clinical trial provided further evidence that their vaccine has an efficacy rate over 90%. This rate was determined 7 days after the second injection and means that protection is achieved 28 days after the initial injection. The DMC also did not report any serious safety concerns at the time of its release [223].

On November 11, 2020 Pfizer submitted its EUA request to the FDA for its COVID-19 vaccine candidate [224]. One the same day the European Union announced that it has agreed to pay for 300 million doses of the coronavirus vaccine pending approval from the European Medical Agency [225].

Approximately, a week later on November 18, 2020 Pfizer/BioNTech concluded the analysis of their Phase 3 clinical trial and show their trial met all primary and secondary endpoints. The vaccine candidate was effective across age, gender, race and ethnicity and observed efficacy in adults over 65 years of age was over 94%. In addition, the vaccine appears to prevent severe

COVID-19, as 9 severe cases were reported in the placebo group and only 1 case was reported in the vaccine group. Furthermore, their safety data demonstrated that the vaccine was well tolerated across all populations with no serious safety concerns observed. Fatigue and headache were the most common non-serious adverse events experienced by participants [226].

With this analysis, the safety data requirements set forth by the FDA for Emergency Use Authorization (EUA) was achieved. Pfizer/BioNTech submitted safety data on over 40,000 participants who have been monitored for two months following the second dose of the vaccine. The participants included racially and ethnically diverse children and adults [224].

In December 2020, the Medicines & Health Products Regulatory Agency in the United Kingdom granted temporary emergency use for the Pfizer/BioNTech vaccine and announced plans to purchase a total of 40 million doses [227]. Those living in residential care homes and elderly people were designated to be the first to receive the Pfizer/BioNTech vaccine in the UK [228].

Following suit, a week later, Canada's health department also approved the Pfizer/BioNTech vaccine for emergency use and anticipated acquiring an initial supply of nearly 250,000 doses. At that time Canada expected vaccinations to before the end of December 2020 [229].

On December 11, 2020 the FDA "issued the first emergency use authorization (EUA) for a vaccine for the prevention of coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals 16 years of age and older. The emergency use authorization allows the Pfizer-BioNTech COVID-19 Vaccine to be distributed in the U.S."

This vaccine was authorized "For the prevention of 2019 coronavirus disease (COVID-19) for individuals 16 years of age and older".

According to the FDA "The most commonly reported side effects, which typically lasted several days, were pain at the injection site, tiredness, headache, muscle pain, chills, joint pain, and fever. Of note, more people experienced these side effects after the second dose than after the first dose, so it is important for vaccination providers and recipients to expect that there may be some side effects after either dose, but even more so after the second dose."

Moderna (mRNA-1273)

The biotech company, Moderna was one of the first developers to announce it had begun working on a COVID-19 vaccine at the start of the pandemic. Similarly to Pfizer/BioNTech, Moderna's vaccine candidate, mRNA-1273 is an mRNA based vaccine given in two injections [230].

In November 2020, Moderna similarly reported more than 94% efficacy of their vaccine candidate in an interim analysis of their Phase 3 clinical trial. The trial initially began in July 2020 and enrolled over 30,000 participants. Moderna's vaccine was shown to protect against severe cases of COVID-19. Their interim analysis of over 15,000 participants demonstrated that all of the 11 reported severe COVID-19 cases were in the unvaccinated group [231]. Furthermore, a

recent investigation published in the New England Journal of Medicine demonstrates that the Moderna vaccine produces neutralizing antibodies detectable at four months post initial vaccination.

In late November 2020, after reporting their interim analysis Moderna applied for FDA Emergency Use Authorization which was granted on December 18, 2020.

According to the CDC's Information about the Moderna COVID-19 Vaccine | CDC webpage:

- Based on evidence from clinical trials, the Moderna vaccine was 94.1% effective at preventing laboratory-confirmed COVID-19 illness in people who received two doses who had no evidence of being previously infected.

- The vaccine appeared to have high effectiveness in clinical trials (efficacy) among people of diverse age, sex, race, and ethnicity categories and among persons with underlying medical conditions.

- Although few people in the clinical trials were admitted to the hospital, this happened less often in the people who got the Moderna vaccine compared to people who got the saline placebo.

- CDC will continue to provide updates as we learn more about how well the Moderna vaccine works in real-world conditions.

Demographic information from clinical trials

Clinical trials for the Moderna vaccine included people from the following racial and ethnic categories:

- 79.4% White

- 20% Hispanic/Latino

- 9.7% African American

- 4.7% Asian

- <3% other races/ethnicities

Age and sex breakdown:

- 52.6% male

- 47.4% female

- 25.3% 65 years and older

Most people who participated in the trials (82%) were considered to have an occupational risk of exposure, with 25.4% of them being healthcare workers.

Among people who participated in the clinical trials, 22.3% had at least one high-risk condition, which included lung disease, heart disease, obesity, diabetes, liver disease, or HIV infection. Four percent (4%) of participants had two or more high-risk conditions.

AstraZeneca (AZD1222)

AstraZeneca and the University of Oxford developed, AZD1222, a COVID-19 vaccine. Unlike vaccine candidates from Pfizer/BioNTech and Moderna, AZD1222 is an adenoviral based vaccine given in two injections [234].

On December 8, 2020 AstraZeneca and the University of Oxford became the first vaccine developers to release their full-data in a peer reviewed journal, the British Medical Journal (BMJ). Their analysis confirmed that their vaccine candidate is 70% effective. An early analysis reported in the Lancet involving nearly 12,000 participants showed that the vaccine was 62% effective in protection against COVID-19 symptoms. Despite promising results, many questions came to light specifically regarding its efficacy in older adults as only 12% of trial participants were over 55 and only 4% were over 70 years old. These numbers are too small to provide a statistically significant answer regarding the effectiveness in older adults [235].

AstraZeneca's vaccine was also been shown to be safe and well tolerated among participants with no deaths, hospitalizations or severe disease reported 3 weeks after the first dose. Furthermore, their vaccine was reportedly easier to manufacture, transport and is significantly cheaper that other vaccine candidates [235].

On December 30 2020, the vaccine was approved for use in the UK's vaccination program, and the first vaccination was administered on January 4 2021.

And on January 29, 2021, the European Medicines Agency (EMA) recommended granting a conditional marketing authorization for the vaccine in people from 18 years of age.

The vaccine has also been approved by regulatory bodies for emergency use in Argentina, El Salvador, Indian, Mexico, Bangladesh, the Dominican Republic, Pakistan, the Philippines, Nepal, Brazil and Sri Lanka.

However, on February 7, 2021, the vaccine roll out in South Africa was suspended after University of Witwatersrand researchers stated in a prior-to-peer analysis that the vaccine "provided minimal protection against mild or moderate disease infection among young people. AstraZeneca is working to adapt the vaccine to target new variants of the coronavirus."

See Oxford–AstraZeneca COVID-19 vaccine - Wikipedia

Johnson & Johnson (JNJ-78436735)

Johnson & Johnson (J&J) also developed a COVID-19 vaccine that went through testing in clinical trials. Similar to AstraZeneca's candidate, JNJ-78436735 made by J&J, is also an adenoviral based vaccine.

Among the developmental milestones for this vaccine:

It was studied in two global Phase 3 clinical trials; the single dose study entitled ENSEMBLE and the two-dose study entitled ENSEMBLE 2.

The ENSEMBLE trial, which was a collaboration among the Biomedical Advanced Research and Development Authority (BARDA), Department of Health and Human Services (HHS), and the National Institute of Allergy and Infectious Disease (NIAID), began after interim results from J&J's Phase 1/2a trial demonstrated safety and an immunological response after a single dose. Its design involved the enrollment of up to 60,000 participants over the age of 18 [236].

The ENSEMBLE 2 (NCT04614948) trial is a randomized, double blind placebo-controlled trial designed to evaluate the safety and efficacy of two doses of the JNJ-78436735 vaccine in adults at risk for severe COVID-19. Participants will be enrolled in multiple countries and areas with high infection rates including Spain, Belgium, France, Germany and the United States [237,238].

According to a February 4th 2021 news item posted by Johnson & Johnson officials to the company's website:

"The Company's EUA submission is based on topline efficacy and safety data from the Phase 3 ENSEMBLE clinical trial, demonstrating that the investigational single-dose vaccine met all primary and key secondary endpoints. The Company expects to have product available to ship immediately following authorization.

'Today's submission for Emergency Use Authorization of our investigational single-shot COVID-19 vaccine is a pivotal step toward reducing the burden of disease for people globally and putting an end to the pandemic," said Paul Stoffels, M.D., Vice Chairman of the Executive Committee and Chief Scientific Officer at Johnson & Johnson. "Upon authorization of our investigational COVID-19 vaccine for emergency use, we are ready to begin shipping. With our submission to the FDA and our ongoing reviews with other health authorities around the world, we are working with great urgency to make our investigational vaccine available to the public as quickly as possible.'

The Company has initiated rolling submissions with several health agencies outside the U.S., and will submit a Conditional Marketing Authorization Application (cMAA) with the European Medicines Agency in the coming weeks."

J&J has agreed to manufacture and deliver 100 million doses to the United States, upon emergency use authorization from the FDA [236]. This authorization is expected to be granted during March (2021) according to Dr. Anthony Fauci, President Biden's top medical adviser on the COVID-19 pandemic.

Russian developed "Sputnik V"

In November 2020, developers of the Russian vaccine, Sputnik V announced positive results from their controversial phase 3 trial. The Gamaleya National Center of Epidemiology and Microbiology in Moscow, Russia reported that the interim analysis of 16,000 participants identified 20 COVID-19 cases and showed the vaccine to be 93% effective. Due to the small

number of cases reported in this trial there is less certainty regarding the true efficacy of the vaccine. Furthermore, no trial protocol has been published [239].

Long Term Protection

Despite promising results from recent analyses, the top vaccines and vaccine candidates have only been studied for a relatively short period of time and data on long term protection is limited. At least one study has demonstrated the presence of neutralizing antibodies 4 months post initial vaccination with Moderna's mRNA-1273 vaccine [232].

Therefore, at this time, it is not possible to accurately predict how long any vaccine may protect against SARS-CoV2 infection and the development of COVID-19. Long term monitoring will be necessary to demonstrate long term prevention of vaccine candidates.

Potential Issues with Vaccines for New Epidemics

Despite a global effort to produce safe, effective vaccines and bring them to the public, there are many potential issues with vaccines with respect to new epidemics [240,241].

- In the history of medicine, there has never been a vaccine developed fast enough to stop an on-going new epidemic. Successful vaccines today are only effective against existing infectious disease or a recurrent epidemic.
- Although many governmental authorities are fast tracking vaccines and have approved some, the development and evaluation process for a new vaccine normally takes many years to complete.
- Viruses frequently mutate and due to the delay in widely manufacturing any vaccine, the virus will have likely mutated which may reduce the effectiveness of the vaccine. COVID-19 virus variants already exist in Africa, the UK, the US and elsewhere, some of which appear to be especially infectious in nature and thus more easily spread than the original COVID-19 virus. In early February 2021, Science journal reported that use of AstraZeneca's vaccine had been suspended in South Africa because "a SARS-CoV-2 variant that can apparently dodge key antibodies has become widespread."
- A vaccine cannot be used to treat COVID-19, but only to prevent it.
- Vaccines for any disease can cause side effects. For example, in one of the worst pharmaceutical disasters in US history, in 1955 more than 200,000 children were injected with a polio vaccine that resulted in 200 children left with varying degrees of paralysis, 10 deaths and over 40,000 new polio cases arose.

In addition, safety concerns still exist in current trials. Various side effects from vaccine therapy have been reported and recently vaccine trials from leading manufactures were stopped due to adverse effects.

Side-Effects and Safety Concerns of Vaccine Trials

Multiple news reports have surfaced regarding patients who experienced side effects after being treated with COVID-19 vaccines from Moderna and Pfizer [242,243]. Other vaccine trials had to pause due to safety concerns [244,245].

Results from the phase 1, dose escalation trial of Moderna's vaccine candidate mRNA-1273, showed that adverse events such as fatigue, chills, headache, joint pain and pain at injection site occurred in more than half of the participants. Systemic adverse events were more common after the second injection, particularly in those who received the highest dose [230].

In early October 2020, Pfizer reported that some participants in their late phase trial experienced mild side effects such as fatigue, headache, chills, muscle pain and joint pain after receiving the first shot. Unlike the Moderna trial, Pfizer reported that fewer participants reported side effects after the second injection. No severe systemic adverse events were reported [246].

On October 12, 2020, Johnson & Johnson (J&J) announced it had paused the clinical trial of their candidate vaccine, JNJ-78436735, due to "unexplained illness" of one of the volunteers. The company did not reveal what the illness was but stated that volunteer's illness was being reviewed by an independent data safety monitoring [244].

Similarly, the final phase of testing of the vaccine candidate made by AstraZeneca was put on hold at one point in time in the US after a participant in England developed severe neurological symptoms consistent with transverse myelitis, a rare inflammatory condition of the spinal cord [245]. This was the second safety incident to stop the trial which was suspended worldwide in September 2020 [247]. However, in October 12, 2020 the FDA authorized their phase III trial to begin again in the US [248] which was carried out. The vaccine has yet to receive FDA emergency use approval (February 2021) and had its use in South Africa suspended because a SARS-CoV-2 variant there was found to "apparently dodge key antibodies" and had "become widespread."

Vaccine Trial Design Concerns

In September 2020, an article appeared in Forbes Magazine which included an in-depth review of the clinical trials of the then forerunner vaccine candidates and revealed that "these trials seem designed to prove their vaccines work, even if the measure effects are minimal." The author of this article William Haseltine, a former professor at Harvard Medical School, highlighted numerous concerns including the very small numbers of participants that were being evaluated for interim analysis of safety and efficacy.

Efficacy of a vaccine is typically demonstrated with large clinical trials involving tens of thousands of people over several years. Although some vaccine manufactures did enroll tens of thousands of participants, vaccine trials often rely on a similar protocol where very small numbers of participants are being evaluated. For example, at one point in time the J&J interim analysis was set up to include the results of 77 vaccine recipients, Moderna to include 53 recipients, AstraZeneca 50 recipients and Pfizer just 32 vaccine recipients. Considering that interim analysis success requires 70% efficacy and these analyses designs included such small numbers of patients, it follows that the results from very few patients are used to demonstrate success [250].

Another concern highlighted by Haseltine was the mild range of symptoms due to contracted COVID-19 set forth in these trials. The minimum requirement for a case of COVID-19 was

given as a positive PCR test and one or two mild symptoms such as headache, cough, fever, of mild nausea. Although the J&J trial assessed the efficacy of their vaccine to prevent COVID-19 using criteria from the CDC and the University of Oxford, Haseltine voiced a fear that the diagnostic requirements of these trials are far from adequate and stated that the "vaccine trials are testing to prevent common cold symptoms" [250].

Beyond inadequate numbers of participants for interim analysis and inadequate diagnostic criteria for COVID-19, none of the aforementioned trials emphasized the prevention of overall infection, hospitalization and death; the primary goals of vaccine therapy. Vaccine protocols from Moderna, Pfizer and AstraZeneca primarily assessed prevention of mild symptoms such as cough or headache and did not require that their vaccine prevent serious disease. In fact, the ability of the vaccine to prevent severe illness and death were only secondary objectives in these trials [250].

Treatments for COVID-19: Medications, Natural Substances and Advanced Therapies

Anti-viral Medications

Hydroxychloroquine/Chloroquine
Chloroquine and its cousin hydroxychloroquine are medications that have been used for many decades to treat malaria all over the world. Previous studies done in the early 2000s, demonstrated that chloroquine was active against the SARS-CoV virus that caused the SARS outbreak in 2003 [252,253]. These anti-malarial medications have been considered for treating COVID-19 patients, however data regarding safety and effectiveness is mixed.

Two early studies confirmed that both chloroquine and hydroxychloroquine effectively inhibits the SARS-CoV-2 virus responsible for the current COVID-19 pandemic [254,255]. A study from France showed a significant reduction in viral loads of COVID-19 patients after being treated with hydroxychloroquine alone and when combined with azithromycin [256]. A study published in August 2020 from the Henry Ford Health System involving over 2,500 patients demonstrated that treatment with hydroxychloroquine alone and in combination with azithromycin was associated with a significant reduction in death among COVID-19 patients. The study found 13.5% of patients treated with hydroxychloroquine alone died and 20.1% of patients treated with hydroxychloroquine plus azithromycin died compared to 26.4% of patients not treated with either drug [257]. The Henry Ford Health System is also involved with a prophylactic study using hydroxychloroquine in COVID-19. This study entitled "Will Hydroxychloroquine Impede or Prevent COVID-19" (WHIP COVID-19) will involve 3,000 participants and investigate whether hydroxychloroquine prevents healthcare/frontline workers from developing COVID-19 [258].

This study was supposed to have been completed in December 2020 though no results have been posted as of February 8 2021.

Conversely, results from an early trial from China suggest that hydroxychloroquine is of no benefit in COVID-19 and produces more side effects than standard care [259,260]. Similarly, an early observational study of more than 1400 patients showed that hydroxychloroquine did not improve mortality rates or risk of intubation [261].

Preliminary results from a study published in July 2020 by New England Journal of Medicine (NEJM) supports the findings from the previously mentioned studies. The NEJM study demonstrated that compared to standard care hydroxychloroquine alone, or in combination with azithromycin did not improve the clinical status among patients hospitalized with mild to moderate COVID-19. In addition, their results reveal safety concerns as prolongation of QT interval and elevated liver enzymes were more frequent in patients who received hydroxychloroquine [262].

Due to safety and efficacy concerns, some clinical trials using hydroxychloroquine were discontinued and regulatory agencies have released specific guidelines. A small study in Brazil was stopped after COVID-19 patients taking a higher dose of chloroquine developed potentially fatal irregular heartbeats [263,264]. On May 25, 2020, the World Health Organization (WHO) announced that it had temporarily suspended clinical trials of hydroxychloroquine as a precautionary measure [265]. This announcement came after the release of an observational study in The Lancet that indicated the drug did not demonstrate clinical benefits and could increase the risk of death and frequency of potentially fatal arrhythmias [266]. In May 2020 the National Institutes of Health (NIH) released guidelines recommending against the use of hydroxychloroquine plus azithromycin for COVID-19 [267]. In June 2020, the FDA revoked the prior emergency use authorization (EUA) to use hydroxychloroquine and chloroquine to treat hospitalized COVID-19 patients [268]. In July 2020, the WHO discontinued the hydroxychloroquine arm of the Solidarity Trial due lack of efficacy. This trial was established by the WHO to identify an effective treatment for hospitalized COVID-19 patients [269].

As of October 9, 2020, the National Institutes of Health (NIH) recommends against the use of chloroquine or hydroxychloroquine with or without azithromycin to treat hospitalized patients with COVID-19. They also recommend against the use of these medications in non-hospitalized patients as well [270].

On October 15, 2020, the WHO published the results of its SOLIDARITY trial which investigated the effects of four repurposed antiviral drugs (remdesivir, hydroxychloroquine, lopinavir/ritonavir and interferon-beta1a) on in-hospital mortality. The trial was conducted in 405 hospitals, in 30 countries and involved 11,266 adult patients. Of the total number of participants 4088 patients acted as the control group which involved taking no study drug. The results revealed that none of the drugs studied definitely reduced mortality, ventilation or length of hospitalization [271]. For example, there were 104 deaths in the group who received hydroxychloroquine compared to 84 deaths in the control group.

The researchers conclude that these drugs "appeared to have little or no effect on hospitalized COVID-19, as indicated by overall mortality, initiation of ventilation and duration of hospital stay". This comes from a pre-print study that had not been peer reviewed [271].

Remdesivir

Researchers all over the world are currently exploring antiviral drug candidates to fight COVID-19. One of the top candidates is the broad-spectrum antiviral drug remdesivir. This drug was originally developed by Gilead Sciences Inc., to treat severe viral diseases including Ebola and works by inhibiting viral replication [272,273].

Remdesivir has been shown to protect cells against infection by the SARS-CoV-2 virus and has demonstrated antiviral effects against SARS and MERS [272]. It has also been shown to prevent disease progression of COVID-19 in an animal study [274].

Remdesivir was one of the first antiviral drugs used in the treatment of the very first US reported COVID-19 case in January 2020 [275]. Soon after, the first report of remdesivir in a compassionate use program was published and showed clinical improvement in 68% of patients with severe COVID-19 [276].

Since then, multiple clinical trials launched to investigate remdesivir as a treatment for COVID-19. In April 2020, preliminary results from the Adaptive COVID-19 Treatment Trial (ACTT-1) which first began in February 2020 indicated that COVID-19 patients who were treated with remdesivir recovered faster and had a reduced rate of mortality compared to placebo [277]. This randomized, double blind, placebo-controlled trial involved 1,062 hospitalized patients with mild, moderate and severe COVID-19 and was conducted by the National Institute of Allergy and Infectious Disease (NIAID). The final report of the ACTT-1 was published in early October 2020 in the NEJM and confirmed their initial findings. They concluded their "data show that remdesivir was superior to placebo in shortening the time to recovery in adults who were hospitalized with Covid-19 and had evidence of lower respiratory tract infection" [278].

A randomized, open label phase 3 trial published in the NEJM in late May 2020 showed no difference between a 5-day and 10-day course of remdesivir. The study included 397 patients with confirmed SARS-COV2 infection, oxygen saturation 94% or below and radiographic signs of pneumonia. They were randomized to receive either 5 or 10 days of treatment. At day 14, patients in both groups had similar clinical statuses. 65% of patients treated for 5 days showed clinical improvement compared to 54% of patients treated for 10 days. Similar results were found for patients experiencing adverse events. 70% of patients reported adverse events in the 5-day group compared to 74% in the 10-day group. The researchers concluded that for severe COVID-19 patients not requiring ventilation, "our trial did not show a significant difference between a 5-day course and 10-day course of remdesivir" [246].

In August 2020, a randomized controlled clinical trial involving nearly 600 patients with moderate COVID-19 was published that evaluated the effect of a 10-day course and a 5-day course of remdesivir vs standard care. They found that hospitalized patients with moderate COVID-19 treated with a 5-day course of remdesivir had a statistically significant difference in clinical status compared with standard of care. However, the difference was uncertain regarding clinical importance [279].

On October 15, 2020, the WHO published results of its SOLIDARITY trial which investigated the effects of four repurposed antiviral drugs (remdesivir, hydroxychloroquine, lopinavir/ritonavir and

interferon-beta1a) on in-hospital mortality. The trial was conducted in 405 hospitals, in 30 countries and involved 11,266 adult patients. Of the total number of participants 4088 patients acted as the control group which involved no study drug. The results show that none of the drugs studied definitely reduced mortality, ventilation or length of hospitalization [271]. For example, there were 301 deaths in the group who received remdesivir compared to 303 deaths in the control group. The researchers conclude that these drugs "appeared to have little or no effect on hospitalized COVID-19, as indicated by overall mortality, initiation of ventilation and duration of hospital stay". This information was gleamed from a pre-print study that had not been peer reviewed at the time [271].

On October 22, 2020 the FDA approved remdesivir for the treatment of COVID-19 in hospitalized adult and pediatric patients. Although the antiviral drug had been in use under an Emergency Use Authorization (EUA) since May 2020, this is the first drug to receive FDA approval [280]. The approval of remdesivir was specifically supported by the FDA's analysis of the aforementioned randomized, controlled trials [278,279,281] except the SOLIDARITY trial.

Favipiravir

Favipiravir, also known as Avigan is an antiviral drug that has emerged as a treatment option for COVID-19. Early human clinical trials show that Favipiravir may benefit COVID-19 patients in a number of ways and is safer than other antiviral medications.

A prospective, randomized controlled trial conducted in China involving 240 COVID-19 patients demonstrated that patients treated with Favipiravir had quicker recovery from fever and cough. Despite this positive finding there was no significant difference in the clinical recovery rate or requirement for respiratory therapy between patients who received Favipiravir and Umifenovir [282]. This study is a pre-print and has not been peer reviewed yet.

An open, label, non-randomized trial comparing the effects of favipiravir and Lopinavir/ritonavir in 80 patients with COVID-19 showed that patients treated with favipiravir had a faster viral clearance time, a significant improvement in CT imaging scores and experienced fewer adverse reactions. The authors concluded that favipiravir "showed significantly better treatment effects on COVID-19 in terms of disease progression and viral clearance" [283].

A small clinical trial evaluating the effect of cocktail therapy including favipiravir, methylprednisolone and heparin in thirteen patients with COVID-19 who required mechanical ventilation showed minimally promising results. The results indicated that the cocktail treatment could partially control the inflammatory mediators involved in COVID-19, but could not improve respiratory status. Overall, the results suggest that favipiravir was of some benefit in reducing inflammation and the findings help inform a treatment strategy for COVID-19 [284]. This is a preliminary report that had not undergone peer review yet at the time it was reviewed for this white paper.

The largest study conducted to evaluate favipiravir in patients with COVID-19 is the Favipiravir Observational Study in Japan which involved over 2,000 patients [285]. The Favipiravir Observational Study was a compassionate use study to assess the effects of favipiravir in

hospitalized patients with COVID-19. Patients had mild, moderate and severe disease defined by not requiring oxygen, requiring oxygen and requiring mechanical ventilation.

The results from the preliminary report indicate that clinical improvements were seen in patients of all severity of illness at day 7 (73.8%, 66.6% and 40.1% for mild, moderate and severe disease, respectively) and day 14 (87.8%, 84.5% and 60.3%, respectively.)

In general, favipiravir was shown to be safe with a total of 626 adverse events reported for 532 patients. The most common adverse event included hyperuricemia (15.52%), liver injury or abnormal liver function tests (7.37%).

As clinical trials for favipiravir are ongoing [286,287], favipiravir is currently being administered to COVID-19 patients as an off-label, compassionate use measure in Japan [285].

Ivermectin

The FDA approved, anti-parasitic drug, Ivermectin commonly used to treat intestinal worms and other parasites is currently being investigated for its role in the treatment of COVID-19 and early data is promising [288].

In addition to its anti-parasitic properties Ivermectin has been shown to have potent anti-inflammatory and anti-viral properties [289–293], all of which could be useful in COVID-19. In June 2020, an in vitro study demonstrated that Ivermectin inhibits SARS CoV-2 and that a single treatment had a 5000 fold reduction in the virus [293].

In humans, a 5-day course of Ivermectin resulted in an earlier viral clearance compared to placebo indicating that early intervention could limit viral replication within the host and reduce contagion. Patients treated with Ivermectin also had a significant drop in the inflammatory markers, CRP and LDH. Although the study only included 72 patients, the authors conclude that their results provide evidence of the potential benefit of early intervention with Ivermectin [294].

The ICON study showed Ivermectin significantly reduced mortality rates among 280 hospitalized patients with confirmed SARS-CoV-2 compared to usual care. The mortality rate was also lower among patients with severe pulmonary disease [295].

Although Ivermectin is not an FDA approved drug for the treatment of COVID-19 and as of their latest updates the National Institutes of Health (NIH) recommends against the use of ivermectin [296], trials are ongoing [297].In addition, it is also part of the "EVMS Critical Care COVID-19 Management Protocol" [217].

Other Anti-viral medications

In addition to remdesivir and favipiravir, other antiviral drugs are being investigated for COVID-19 including nitazoxanide [298–304], and lopinavir/ritonavir [305,306].

In July 2020, a single-center, randomized prospective trial involving 101 patients with mild to moderate COVID-19 compared the effectiveness of three different antiviral regimens; 1) ribavirin plus interferon-α, 2) lopinavir/ritonavir plus interferon-α and 3) ribavirin plus lopinavir/ritonavir

plus interferon-α [307]. The results indicate that there was no significant difference among three different regimens in terms of antiviral effectiveness.

As of their latest updates the National Institutes of Health (NIH) recommends against the use of ivermectin [296] and lopinavir/ritonavir and other HIV protease inhibitors [308] for the treatment of COVID-19, except in a clinical trial.

Other Medications

Aspirin

Aspirin, the common over the counter medication, also known as acetylsalicylic acid (ASA) is gaining recognition as a potential tool in the treatment of COVID-19. ASA has a number of therapeutic properties relevant to COVID-19 including being an analgesic, anti-inflammatory, and anti-coagulant. ASA has also been shown to have anti-viral properties in humans [309].

In a recent study published in the medical journal, Anesthesia & Analgesia, aspirin was shown to be highly useful in treating patients with COVID-19. This observational, cohort study involved just over 400 hospitalized COVID-19 patients who did or did not receive aspirin during admission. Their data indicates that aspirin use was associated with a significant decreased risk of mechanical ventilation, ICU admission and in-hospital mortality. The authors of this study concluded that "Aspirin use may be associated with improved outcomes in hospitalized COVID-19 patients" [310].

ASA is also part of the "EVMS Critical Care COVID-19 Management Protocol" [217] due to its various therapeutic properties relevant to COVID-19.

Statins

In addition to their cholesterol lowering ability, statins may be useful in COVID-19 due to their anti-inflammatory, anti-oxidative, cardioprotective and immunomodulatory effects [311].

Statins have also been shown to be useful in viral infections as a number of observational studies have reported the effectiveness of statins in reducing influenza related hospitalizations and deaths [312]. A 2018 trial demonstrated significant improvement of symptoms in patients hospitalized for seasonal influenza after receiving atorvastatin, a common statin medication [313]. Statin medication has also been shown to reduce mortality in those with ventilator associated pneumonia [314].

Statins may also be useful in COVID-19 as they interfere with ACE2, the enzyme that the SARS-CoV-2 virus uses to enter cells. As discussed in previous sections, SARS-CoV-2 virus enters cells via ACE2 and once inside reduces the expression of ACE2. This results in a significant imbalance between ACE and ACE2 and causes subsequent deleterious effects [315]. Statin medications are known to experimentally increase ACE2 and therefore may be beneficial for COVID-19 patients in this regard [315,316] In fact, a number of clinical trials investigating statin medications in COVID-19 are underway [317] and initial results from one recent trial is very promising.

A Belgian study of COVID-19 patients showed that those who took a statin medication were almost three times more likely to not have symptoms during their infection regardless of age, sex, functional status, or having diabetes, and or hypertension. Although the effects of statins on hospitalization and death were overall beneficial, they did not reach statistical significance. The authors conclude that "Our data indicate that statin intake in old, frail people could be associated with a considerable beneficial effect on COVID-19 related clinical symptoms" [318].

The cardioprotective effects of statin therapy should also be considered in regards to COVID-19 as studies have found that elderly people with underlying cardiovascular conditions are more likely to be infected by the SARS-CoV-2 virus and develop severe symptoms [315]. Statins can also be useful in treating the high serum cholesterol associated with antiviral and immunosuppressive medications for COVID-19 [311]. Since some surviving SARS patients have been shown to have long term abnormal cholesterol profiles, statins could mitigate such changes in COVID-19 patients [67].

As of their latest updates the National Institutes of Health (NIH) recommends that people prescribed statin therapy should continue therapy. However, they do not recommend the use of statins for the treatment of COVID-19, except in a clinical trial [319] .

Although not initially thought of as a treatment option for COVID-19, statins may be beneficial and improve the clinical progression of patients with COVID-19 via their various therapeutic effects including their effect on ACE2.

Steroids

Research indicates that an inexpensive, widely available steroid medication may benefit severe COVID-19 patients. A recent study published in the prestigious New England Journal of Medicine (NEJM) demonstrated that the use of Dexamethasone resulted in lower 28-day mortality among COVID-19 patients who received respiratory support (either mechanical ventilation or oxygen alone). This study entitled, The RECOVERY Trial provides evidence that the use of 6mg of Dexamethasone once daily for up to 10 days reduces 28-day mortality in patients with COVID-19 who receive respiratory support [320].

A different steroid medication, methylprednisolone has also been shown to be beneficial in treating cytokine storms associated with COVID-19. The COVID-19 High Intensity Immunosuppression in Cytokine Storm Syndrome (CHIC) study demonstrated that a course of high dose methylprednisolone with or without tocilizumab, an IL-6 inhibitor may improve respiratory recovery. Compared to a control group, treated patients were 79% more likely to achieve improvements in respiratory status. In addition, the results of this study suggest that steroid medication may also lower hospital mortality and reduce likelihood of invasive mechanical ventilation in patients in the grips of a COVID-19 cytokine storm [321].

In response to the newly published data, groups such as the National Institutes of Health (NIH) and the Infectious Diseases Society of America (IDSA) issued guidelines recommending the use of steroids to treat patients with severe COVID-19 [322,323].

The World Health Organization (WHO) has also updated their guidelines regarding steroid therapy [324]. On September 2, 2020 the WHO's Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group published a new meta-analysis that demonstrated that corticosteroids were again associated with a lower 28-day mortality and had a 34% reduction in risk of death [325,326]. With this new evidence the WHO updated their guidelines and now recommends that steroids become part of the standard of care for patients with advanced COVID-19 [326].

Biological Drugs

REGN-COV2

On September 29, 2020 Regeneron Pharmaceuticals announced preliminary data from a multi-phase trial of its investigational drug, REGN-COV2 for patients with COVID-19. REGN-COV2 is a biological drug "cocktail" of two monoclonal antibodies and is designed to specifically block infectivity of SARS-CoV-2 [327].

Regeneron's most recent study involved 275 participants and was designed to evaluate the anti-viral activity of REGN-COV2 and identify patients most likely to benefit from treatment [327]. In this randomized study two single infusion doses were tested against a placebo: a low dose (2.4 grams) and high dose (8 grams). This study is ongoing and preliminary results have not been peer-reviewed yet.

The preliminary data does indicate that REGN-COV2 is safe and well tolerated with minimal serious adverse events. REGN-COV2 was shown to reduce viral loads and reduce time to alleviate symptoms in non-hospitalized patients with COVID-19 [327].

On October 28, Regeneron released results from their ongoing phase 2/3 trial which included an additional 524 non-hospitalized patients with COVID-19. The results that REGN-COV2 can significantly reduce viral load and decrease the need for further medical attention in outpatients with COVID-19. By day 5 of treatment there was on average, a greater than 10-fold reduction in viral load compared to placebo. They also showed no significant difference between the low and high dose of the drug. In the combined population of the phase 1 and phase 2/3 trial, REGN-COV2 reduced COVID-19 related medical visits by 57%. In those with one or more risk factors such as cardiovascular or lung disease, the drug reduced medical visits by 72%. In addition, REGN-COV was deemed safe and well tolerated with serious adverse events occurring more frequently in the placebo group [328].

As the phase 3 portion of this trial continues, Regeneron has requested emergency use authorization (EUA) for REGN-COV from the FDA and is awaiting approval.

REGN-COV2 is currently being studied in a Phase 2/3 clinical trial for hospitalized patients with COVID-19, the Phase 3 RECOVERY Trial of hospitalized patients in the UK and a Phase 3 trial for the prevention of COVID-19 [327].

Bamlanivimab

On November 9, 2020 the FDA approved an emergency use authorization (EUA) for the biological drug bamlanivimab for the treatment of mild to moderate COVID-19 in both adult and pediatric patients over 12 years of age who are at risk for developing severe COVID-19. The investigational drug created by Eli Lily is a monoclonal antibody similar to Regeneron's dual monoclonal antibody drug, REGN-COV2 and was designed to specifically block viral attachment to and entry into human cells [329].

The results from an interim analysis of a phase 2 placebo controlled trial titled BLAZE-1 (NCT04427501) show that bamlanivimab may be effective in the treatment of COVID-19 [330]. The trial involved 645 non-hospitalized patients with mild to moderate COVID-19 who were at risk for developing severe COVID-19 and revealed that in all treatment groups most patients cleared the virus within 11 days. More importantly, the results also demonstrated that in patients who were treated with bamlanivimab, hospitalizations and emergency room (ER) visits only occurred in 3% compared to 10% in the placebo group. The effects of bamlanivimab on viral load, reduction in hospitalization and ER visits were found to be similar among patients who received any dose [329].

Bamlanivimab is given as a single dose intravenous infusion administered over 60 minutes. Reported adverse effects include nausea, dizziness, headache, itchiness, diarrhea and vomiting. Immediate nonserious hypersensitivity reactions have also been reported and include fever, chills, cough, low blood pressure and anaphylactic symptoms such as throat irritation, lip and tongue swelling, rash, etc. [331]

Tocilizumab

Tocilizumab also known as Actemra, is a drug that is used to reduce inflammation in multiple inflammatory diseases including rheumatoid arthritis. It is considered a 'biologic drug' and works by blocking the pro-inflammatory cytokine IL-6 [332,333].

Tocilizumab and other IL-6 blockers are being investigated for COVID-19 because not only can they reduce inflammation that is associated with lung injury and ARDS but they have the ability to prevent cytokine storms [35,334]. A cytokine storm is a severe overreaction of the immune system and is considered to be a main cause of organ failure and death in critically-ill COVID-19 patients [40].

As dozens of trials are underway to evaluate tocilizumab for COVID-19 [335], China has already approved its use for COVID-19 [334] and initial results from a small study and case report suggest that it is an effective treatment forCOVID-19 patients experiencing cytokine storms [336,337].

As of August 27, 2020 the National Institutes of Health (NIH) recommends against the use of tocilizumab and other IL-6 blockers to treat patients with COVID-19, except in a clinical trial [338].

Anakinra

Another biologic drug being investigated for use in COVID-19 patients is anakinra, also known as Kineret. Similar to tocilizumab, anakinra is a biological drug used to reduce inflammation and prevent cytokine storm by blocking the proinflammatory cytokine IL-1 [35,339]. Previous clinical

data has shown it to significantly improve the survival of patients experiencing a cytokine storm without increasing adverse effects [340].

Although limited clinical data has been published, there are numerous trials underway investigating the effect of anakinra in COVID-19 [341]. As of July 17, 2020 the National Institutes of Health (NIH) states that there are insufficient data to recommend either for or against the use of anakinra and other IL-1 blockers to treat patients with COVID-19 [338].

Ruxolitinib

Ruxolitinib is another biologic drug that has gained attention in the midst of the COVID-19 pandemic. Also known as Jakafi, ruxolitinib is used in the treatment of a number of conditions including myelofibrosis and polycythemia vera [342].This drug works by inhibiting Janus Associated Kinases (JAK1/JAK2) which control the signaling of various cytokines that are important for the immune system and are involved in the development of cytokine storms [343]. Because many patients with severe COVID-19 have clinical features consistent with a cytokine storm and increased activation of JAK, researchers hypothesize that ruxolitinib may be useful in treating such patients [344]. Ruxolitinib and other JAK inhibiting drugs may also be useful in COVID-19 as they may affect the ability of the coronavirus from entering cells thus reducing infection [345].

Currently, there are a number of clinical trials underway to investigate its safety and effectiveness in COVID-19 patients [346]. As of July 17, 2020 the National Institutes of Health (NIH) recommends against the use of ruxolitinib and other JAK inhibitors, except in a clinical trial [338].

Interferon Beta

The preliminary results from a clinical trial involving nine UK hospitals suggest that inhaled Interferon Beta, a biological drug commonly used in multiple sclerosis, may reduce the number of COVID-19 patients needing intensive care and confer other benefits.

The small study found that interferon beta reduced the chance of hospitalized COVID-19 patient developing severe disease and requiring mechanical ventilation by 79%. In addition, their results suggest that treated patients were 2-3 times more likely to recover to the point where everyday activities were not compromised and that the average hospital stay was reduced by a third [347].

Although the trial is small with just over 100 participants and final results are not yet published, the results are promising and warrant further investigation. Larger clinical trials will be required to confirm safety and efficacy of this drug in the treatment of COVID-19.

As of August 27, 2020, the National Institutes of Health (NIH) states there is insufficient data to recommend for or against the use of interferon beta to treat mild or moderate COVID-19. They also recommend against the use of interferons for the treatment of severely or critically ill patients with COVID-19, except in a clinical trial [338].

On October 15, 2020, the WHO published the results of its SOLIDARITY trial which investigated the effects of four repurposed antiviral drugs (remdesivir, hydroxychloroquine, lopinavir/ritonavir and interferon-beta1a) on in-hospital mortality. The trial was conducted in 405 hospitals, in 30 countries and involved 11,266 adult patients. Of the total number of participants 4088 patients acted as the control group which involved no study drug. The results show that none of the drugs studied definitely reduced mortality, ventilation or length of hospitalization [271]. For example, there were 243 deaths in the group who received interferon-beta1a compared to 216 deaths in the control group.

The researchers concluded that these drugs "appeared to have little or no effect on hospitalized COVID-19, as indicated by overall mortality, initiation of ventilation and duration of hospital stay". This is a pre-print study and has not been peer reviewed yet [271].

Natural Substances

Vitamin C

Vitamin C, as known as ascorbic acid, has an impressive record in the treatment of lung conditions and has been recognized as a potential treatment tool for COVID-19. While clinical trials are underway to demonstrate its safety and effectiveness, intravenous (IV) vitamin C is currently being used in the US and abroad.

IV vitamin C has been extensively studied in viral illnesses, pneumonia, acute respiratory distress syndrome (ARDS) and SARS coronavirus [348]. It been shown to be safe in patients with severe sepsis, reduce mortality in patients with sepsis and ARDS and have significant benefit in patients with pneumonia [349–353]. IV vitamin C has also been shown to shorten the length of ICU stays and reduce the length of time on mechanical ventilation [354,355]. The findings from these studies are clearly relevant to the current pandemic and are being confirmed in on-going clinical trials of COVID-19.

Trials to investigate the safety and effectiveness of IV vitamin C in COVID-19 began early in China [356]. Now a number of clinical trials have begun all over the world [215,357–362]. While these are underway, hospitals in China and the US have already begun using IV vitamin C and initial reports have been promising.

The Expert Group on Clinical Treatment of New Coronavirus Disease in Shanghai released clinical data showing that patients who received IV vitamin C all improved and on average had shorter hospital stays and lower mortality rates [363]. After reporting promising results in 50 consecutive COVID-19 treated with IV vitamin C, the Shanghai panel now recommends the use of this therapy and other supportive therapies including Vitamin D and Zinc for the treatment of ARDS [364].

Reports confirm that hospitals in New York are using IV vitamin C to treat COVID-19 patients and although no data has been published yet, the results are said to be positive [365,366]. Furthermore, case studies from around the world have also demonstrated positive effects using

IV and oral vitamin C [364,367,368]. As previously mentioned, IV vitamin C is also part of the "EVMS Critical Care COVID-19 Management Protocol" to treat ICU patients [217].

In addition to IV vitamin C, oral vitamin C supplementation is being currently being studied in COVID-19 and experts already recommend it for prevention [215,358,361,362,369]. Oral vitamin C is also part of the "EVMS Critical Care COVID-19 Management Protocol" for prophylaxis, symptomatic patients at home, and mildly symptomatic patients in hospital [217].

Vitamin D

Vitamin D, commonly used to support bone health may be beneficial in the treatment of COVID-19. As it pertains to the current pandemic, Vitamin D has been shown to reduce the risk of respiratory infection [370–372] and enhance the immune system [373–376]. It has also been shown to reduce overall mortality in older adults and reduce inflammation associated with cytokine storms [377,378]. As mentioned previously, a cytokine storm is a severe overreaction of the immune system that can be life threatening [379,380]. In fact, many severe cases of COVID-19 and related deaths are thought to be due to cytokine storms [35].

Taking Vitamin D may be especially important for the aging population and those who have low serum levels of it. Vitamin D deficiency is very common in older adults, who are most at risk for severe symptoms and death due to COVID-19 [381].

Low Vitamin D has been associated with the increased risk of pneumonia in adults, increased risk of viral pneumonia in children, and increased risk of mortality in patients with pneumonia [382–384]. It has also been suggested that people lacking Vitamin D have a weaker innate immune defense against SARS-CoV-2 [13].

In addition, mounting evidence suggests that Vitamin D deficiency may be linked with cardiovascular conditions such as high blood pressure, diabetes and heart disease, all of which have been shown to increase the risk of severe cases of COVID-19 [385].

There is now some clinical evidence that suggests that Vitamin D deficiency is associated with increased risk of infection, severe COVID-19 cases and that supplementation could improve clinical outcomes. A study from three hospitals showed that COVID-19 patients with deficient levels of Vitamin D had an eightfold higher risk of having severe illness. The authors concluded that Vitamin D supplementation could possibly improve clinical outcomes of COVID-19 patients [140]. Findings from a recent study confirm the link between Vitamin D status and the severity of COVID-19, showing that patients with a severe vitamin D deficiency had a 17.3% risk of developing severe COVID-19. Furthermore, their results suggest that vitamin D may suppress cytokine storms and reduce associated mortality [386]. Similarly, an analysis of published data from 792 patients with COVID-19 suggests that adequate Vitamin D supplementation may reduce the number of severe COVID-19 cases by up to 15% by lowering the risk of cytokine storms [138].

Published in late August 2020, a double blind, randomized control trial involving 76 patients hospitalized for COVID-19 who were either treated with standard of care alone or standard of care plus Vitamin D also demonstrated the promise of this vitamin. The results from this study

indicate that supplementation with Vitamin D, significantly reduced the need for ICU admission and reduced the severity of the disease [387].

More recently, a cohort study published in September 2020, showed that deficient vitamin D status was associated with an increased risk of COVID-19. They show that the relative risk for testing positive for COVID-19 was 1.77 times greater for patients with a deficient vitamin D status compared to those with a sufficient status [388].

Although clinical evidence is limited to a handful of studies at this time, the initial data is most promising. In addition, the various therapeutic properties of Vitamin D and its proven record of therapeutic importance specifically regarding inflammation, the immune system, and lung health are compelling. .

Vitamin D is also part of the "EVMS Critical Care COVID-19 Management Protocol" for all levels of severity [217].

Glutathione and NAC

Glutathione and its precursor N-acetyl cysteine (NAC) may be useful in COVID-19 due to their numerous therapeutic properties.

Glutathione plays a vital role in lung health and is the most abundant antioxidant in the lung [389]. It has been shown to neutralize oxidants that cause lung injury and reduce inflammation that is associated with ARDS [390–392] .

Glutathione also plays an essential role in the immune system and has been shown to inhibit the replication of the influenza virus in laboratory studies [393–396] .

Adequate levels of glutathione are important as deficiency has been reported in numerous lung diseases including ARDS and pneumonia [389,390,394]. Some believe that glutathione deficiency is most likely the cause of severe cases and deaths from COVID-19 [397].

Similar to glutathione, NAC also plays a vital role in lung health and is a precursor to glutathione. NAC, a nutritional supplement and FDA approved drug has been widely used in chronic respiratory diseases and for the treatment of lung injury and ARDS [398–401]. NAC has been shown to increase oxygen delivery, improve lung compliance and resolve pulmonary edema in patients with ARDS [400]. NAC when nebulized with heparin has been shown to improve lung function and reduce the need for mechanical ventilation [401].

NAC also acts as an antioxidant and is a precursor for the synthesis of glutathione [402]. Like glutathione, NAC has been reported to regulate the activity of NFKB which is associated with the lung inflammation seen in COVID-19 [403].

NAC has been shown to reduce inflammatory markers in patients with community acquired pneumonia and has demonstrated similar chest CT scores as a conventional treatment [399]. In addition to anti-oxidant and anti-inflammatory properties experimental studies have shown NAC to exert anti-viral properties [404,405].

Although the findings of these studies are promising clinical data on the effect of glutathione and NAC on COVID-19 is currently limited. There is only one trial of NAC listed on ClinicalTrials.gov although a small study using glutathione has already showed positive results [406,407]. The authors of the study concluded that glutathione and glutathione precursors "may represent a novel treatment approach for blocking NFKB and addressing the 'cytokine storm syndrome' and respiratory distress in patients with COVID-19 pneumonia " [407].

While we wait for the results there is sufficient data indicating the numerous therapeutic effects of glutathione and NAC in COVID-19.

Magnesium

Magnesium may be useful in COVID-19 due its ability to reduce inflammation and inhibit the activity of the NLRP3 inflammasome. As previously discussed in the science section of this paper, the NLRP3 inflammasome is a major cause of inflammation and has been linked to acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) [29,31,32]. Magnesium may be able to prevent the inflammatory cascade that causes the activation of the inflammasome and therefore reduce inflammation and risk of developing ALI and ARDS [408–410].

In addition, magnesium has been shown to reduce C-reactive protein (CRP), a common marker of inflammation that is associated with COVID-19 [143,411–415].

Aside from inflammation, magnesium is also important for common underlying conditions of severe COVID-19 such as diabetes, high blood pressure and cardiovascular disease [416,417]. Not only is low magnesium linked to these conditions, the NLRP3 inflammasome is believed to cause the inflammation seen in these conditions [418–420]. Low levels of magnesium have also been shown to be associated with a greater risk of death, sepsis, need for mechanical ventilation and increased length of ICU stays [421]. Supplementation with magnesium can also increase melatonin which may be important in COVID-19 [422] .

Although there is limited published clinical data on the effect of magnesium in COVID-19 patients, evidence from relevant experimental studies and clinical trials is promising.

Melatonin

The commonly used sleep (hormone) supplement, melatonin has anti-inflammatory, anti-oxidant and immune enhancing properties and is protective against ALI/ARDS caused by viral infections [423].

Similar to magnesium, melatonin also inhibits the NLRP3 inflammasome [424–426] and has been found to significantly reduce lung inflammation and lung tissue injury as well as reduce progression of ARDS by inhibiting NLRP3 inflammasomes [424,427].

Although melatonin is not antiviral it has indirect antiviral actions [428–430] and has been shown to significantly increase survival rates of mice infected with the H1N1 influenza A virus [431].

For those who require mechanical ventilation, melatonin may be useful as it has been shown to prevent ventilator induced lung damage in experimental studies [432]. Melatonin has also shown to

be beneficial in critical care patients by reducing anxiety, sedation use and improving sleep quality which might be beneficial for better clinical outcomes in COVID-19 [423].

Melatonin may be the reason why children under the age of 9 rarely show severe symptoms of COVID-19 and why older patients have higher death rates. Compared to healthy seniors, young children can easily have up to ten times their melatonin levels [433]. Melatonin concentration is highest in young children then declines with age. This decline becomes very steep after age 50 with production of melatonin becoming negligible [434].

Melatonin may also be the reason why none of the pregnant mothers who were admitted to Zhongnan Hospital for COVID-19 developed severe pneumonia as melatonin secretion in the third trimester of pregnancy is more than double compared to the first [435,436].

As of yet, there is limited published clinical data on melatonin and COVID-19, however, ClinicalTrials.gov lists one trial investigating the efficacy of melatonin to prevent COVID-19 among healthcare workers [437].

While we wait for the results of the aforementioned study there is significant data showing numerous therapeutic effects of melatonin relevant in COVID-19. Melatonin is also part of the "EVMS Critical Care COVID-19 Management Protocol" for all levels of severity [217].

Quercetin

Quercetin, a carbohydrate-free flavonoid found in many fruits and vegetables has antiviral properties and has previously been shown to be effective against multiple viruses including parainfluenza virus, respiratory syncytial virus (RSV), Ebola and Zika viruses [438–440]. Multiple laboratory studies have also shown it to be effective against SARS coronavirus [441–444]. In addition, quercetin may reduce coronavirus infection by inhibiting mTOR which is present in all cells and is used by the virus to replicate [445].

More recently, quercetin was identified by the most powerful IBM supercomputer as a top treatment candidate that might interfere with the current coronavirus binding to cells [446]. Another study using computer models demonstrated similar results [447].

Eastern Virginia Medical School (EVMS) recently published their Critical Care COVID-19 Management Protocol that includes the use of quercetin for prevention of COVID-19 and treatment of mildly symptomatic patients [217].

Although there is limited published data on quercetin in COVID-19, researchers from the Clinical Research Institute of Montreal are conducting a small clinical trial to investigate the effectiveness of quercetin in COVID-19 patients [448].

Silver

Prior to the advent of antibiotics, silver was known for its therapeutic properties and commonly used to treat infections. While there is no clinical evidence showing that silver is effective against viruses in humans the antimicrobial properties of silver have been confirmed [449].

Experimental studies have shown silver to be effective against several types of bacteria, and viruses including corona virus. A 2009 study revealed that silver reduced viral activity of a coronavirus strain commonly used as a model for the 2003 SARS virus by 90% within 60 minutes of exposure and by 99.99% after 24 hours of exposure [437,450].

Silver has also been shown to be active against other viruses including human immunodeficiency virus (HIV), hepatitis B virus, herpes simplex virus (HSV), and respiratory syncytial virus (RSV) [449,451].

Despite the lack of human evidence regarding the anti-viral effects of ingesting silver we use colloidal silver extensively in our practice without any safety issues. Proper formulations of very low parts-per-million (PPM) nanoparticles (1 to 100 nm), silver colloid such as Sovereign Silver, will not accumulate in body tissue and is extremely safe. Gargling and use of nasal spray preparations MAY reduce viral loads, if used several times a day.

Sulforaphane

Sulforaphane, a Sulphur-rich compound found in cruciferous vegetables such as broccoli and kale may be protective against COVID-19.

Experimental studies have shown that sulforaphane can reduce inflammation leading to lung damage seen in acute respiratory distress syndrome (ARDS) and help balance the anti-oxidant system and impair viral replication [452–455].

Studies have shown that sulforaphane can reduce viral loads in the nasal passages and increase the production of natural killer cells responsible for directly killing viruses [456,457]. It has also been shown to have antiviral activity against the H1N1 Influenza virus, Hepatitis C virus and HIV in experimental studies [458,459]. In addition, consumption of sulforaphane has been found to stimulate the production of heat shock proteins (HSPs) which are known to exert anti-viral properties [460,461].

Although there are no clinical trials investigating the effects of sulforaphane in COVID-19, evidence from research studies is compelling. While we wait for more evidence, this safe and commercially available compound may prove be an important low-cost tool for the prevention and treatment of COVID-19.

Zinc

Zinc may also be beneficial in the treatment of COVID-19 as it has been shown to have antiviral properties and [462–465] and inhibit SARS coronavirus [466].

Although the exact mechanism of zinc's antiviral activity is unclear, it is similar to that of the anti-viral drug Remdesivir which is being investigated for COVID-19 [465,466]. Zinc has also been shown to reduce inflammation by reducing inflammatory cytokines and significantly improve total antioxidant capacity [412]. In addition, Zinc has been shown to be effective at reducing the duration and severity of common colds [465]. The effects of zinc may be enhanced by chloroquine as it seems to help zinc get into cells and reach high intracellular levels [467].

Zinc is currently being investigated for COVID-19 in a number of other clinical trials [215,359,361,468] . The rationale for use of zinc in COVID-19 has also been thoroughly reported [469–471].

An anecdotal study assessing the effect of adding zinc sulfate to hydroxychloroquine and azithromycin demonstrated that zinc did not impact length of hospitalization, duration of ventilation or ICU duration. However, upon further analysis, they found that zinc supplementation increased the frequency of patients being discharged from the hospital, decreased the need for ventilation, decreased admission rates to the ICU and decreased mortality in patients who were not admitted to the ICU. This is a pre-print study and has not been peer reviewed yet [472].

Despite the limited available clinical data on zinc and COVID-19, there is significant data showing the relevant therapeutic effects of zinc which may be beneficial in COVID-19 patients. Zinc is also part of the "EVMS Critical Care COVID-19 Management Protocol" for most levels of severity [217].

EVMS Critical Care COVID-19 Management Protocol

Eastern Virginia Medical School (EVMS) has published a series of protocols for the management of COVID-19 in a document titled "EVMS Critical Care COVID-19 Management Protocol" [217]. The EVMS has established protocols for four different groups based on severity. These groups include 1) prophylaxis, 2) symptomatic patient at home, 3) mildly symptomatic patients in the hospital, and 4) patients with progressive respiratory symptoms in the ICU. The rationale for the EVMS protocol for COVID-19 has been thoroughly discussed and has been scientifically reviewed [473].

The foundational treatment components of groups 1-3 include oral natural substances such as vitamin C, vitamin D, melatonin, quercetin, and zinc. Other the counter medications such as famotidine and aspirin are also included.

For patients with more severe illness (groups 3 and 4) coagulation therapy using enoxaparin and steroid therapy using methylprednisolone is added to the protocol. There is now overwhelming evidence that steroid therapy reduces the risk of death in patients with severe COVID-19 [217].

The "MATH+" protocol is for severely ill patients in the ICU with progressive respiratory symptoms. This protocol includes methylprednisolone, intravenous ascorbic acid (vitamin C), thiamine (vitamin B1) heparin, an anti-coagulant and others such as vitamin D and melatonin.

Advanced Therapies for COVID-19: Convalescent Plasma, Ozone Therapy, Stem cell Therapy and Exosome Therapy

Convalescent Plasma

Convalescent plasma (CP), an antibody rich blood product collected from donors who have recovered from COVID-19 is being investigated for the treatment of COVID-19.

The majority of people who recover from COVID-19 develop antibodies against the SARS-CoV 2 virus. These antibodies are found in the plasma portion of blood. Through a process called apheresis, the blood from an eligible donor is collected and separated into different components. The plasma component is removed and the rest of the blood is returned to the donor. The concept behind CP is that donor plasma rich in SARS CoV-2 antibodies will be beneficial in those without SARS-CoV 2 antibodies or with low levels of these antibodies [474].

Although an early clinical trial from China involving 103 participants did not demonstrate significant improvement or reduction in mortality when added to standard therapy, other studies have shown CP to be effective [475].

In March 2020, a case series study of 5 critically ill patients with COVID-19 demonstrated that numerous clinical biomarkers including body temperature, oxygenation, viral loads and antibody levels improved following CP therapy. In addition, ARDS resolved in 4 patients 12 days after treatment and 3 patients were weaned from mechanical ventilation within 2 weeks of treatment [476].

In April 2020, a similar study was done with 10 patients with COVID-19 which concluded that CP therapy was well tolerated and could improve clinical outcomes in patients with severe COVID-19 [477]. Quickly following, a matched control study of 39 hospitalized COVID-19 patients demonstrated that patients who received CP therapy maintained or improved oxygen requirements and improved survival of non-intubated patients compared to the control group. This study is a pre-print study and has not yet been peer reviewed [478].

The first systematic review on CP therapy in COVID-19 was published in May 2020 and includes five studies. This review found that CP may reduce mortality in critically ill patients, increase neutralizing antibody titers with subsequent disappearance of SARS-CoV-2 RNA and have a beneficial effect on clinical symptoms. The authors conclude that although larger, multi-center trial studies should be conducted, CP therapy appears safe, clinically effective and reduces mortality in COVID-19 patients [479].

In contrast, a systematic review performed by the Cochrane Review involving 20 completed studies with 5443 participants found that the evidence was very limited with only one randomized study and most of the studies having failed to use reliable methods to gage clinical results. As such they concluded that it is very uncertain whether CP therapy is a safe and effective treatment for hospitalized COVID-19 patients [480].

Most recently, a large study run by the Mayo Clinic and sponsored by the National Institutes of Health demonstrated that high antibody convalescent plasma significantly reduced seven day and 30-day mortality of hospitalized COVID-19 patients. They also demonstrated that patients who received the transfusion within 3 days of diagnosis experienced a lower seven-day mortality rate. Although the results are promising, this study did not include a placebo group which has many experts struggling to interpret the data. Furthermore, this study is a pre-print study and has not yet been peer reviewed [481].

In response to the amounting evidence, the FDA issued an Emergency Use Authorization (EUA) for CP therapy to treat hospitalized patients with COVID-19 in August 2020. After reviewing available published and unpublished data on convalescent plasma, the COVID-19 Treatment Guidelines Panel supported the FDA's decision. However, outside of the EUA, the panel does not support the use of convalescent plasma therapy and does not recommend that it should be considered standard of care as there is insufficient data [482].

Ozone Therapy

Recent reports from multiple countries including China, Italy and Spain suggest that ozone therapy is effective in the treatment of COVID-19.

The first reported case from China of a critically ill COVID-19 patient treated with intravenous ozone therapy demonstrated positive results.

Just hours after the first treatment the 56-year-old male patient's lung function and oxygenation level dramatically improved and continued to improve over the next few days of treatment. After his final ozone therapy treatment, his overall status had stabilized and he was transferred from the ICU to the general COVID-19 ward of the hospital.

Approximately three days later his test results (throat and sputum) were negative for SARS-CoV-2. Within 10 days, his stool samples were negative for the virus, his chest CT showed almost complete lung recovery and he was discharged from the hospital [483]. In addition to this report, there are currently at least three clinical trials underway in China investigating ozone therapy for COVID-19 [484–486].

Reports from multiple Italian hospitals demonstrate the positive effects of ozone therapy in COVID-19 patients. Italy, another country majorly affect by the pandemic is also using ozone therapy to treat COVID-19. The first report from the Scientific Society of Oxygen Ozone Therapy (SIOOT) on hospitals in Italy where ozone therapy is being used for COVID-19 patients indicates promising results. Of the 11 patients in serious or severe condition, 10 showed rapid improvement after receiving intravenous ozone therapy treatment. Of the patients initially using a ventilator, all are significantly improving and one was able to wean off it [487].

The second report was released in early April 2020 and compiled data for 46 COVID-19 patients from 6 Italian hospitals treated with ozone therapy. Of the 46 patients, four died due to organ failure before therapy was completed. Of the remaining 42 patients, 39 showed significant improvement after ozone therapy and at the time of the report five tested negative for the virus [488].

The third report was just released and reflects the benefits of ozone therapy in patients with COVID-19 [489]. At a hospital in Udine, Italy 36 COVID-19 patients who developed pneumonia and severe breathing difficulty were treated with intravenous ozone therapy. 35 of the 36 patients showed significant and rapid recovery and did not enter the ICU or require ventilation. Based on the initial results the University of Friuli hopes to begin a trial of 200 patients to investigate the effectiveness of ozone therapy in COVID-19 [490].

Initial results from a hospital in Spain also corroborate the results of the previously mentioned reports. The Nuestra Señora del Rosario Polyclinica in Ibiza, Spain has just begun administering ozone therapy for COVID-19 patients. Their first report of a COVID-19 patient treated with intravenous ozone therapy was a 49-year-old male in the ICU whose status was deteriorating rapidly. Intubation and mechanical ventilation were planned, but after the first ozone treatment the patient improved significantly and his need for supportive oxygen was reduced [491]. The hospital has registered a clinical trial and urges hospitals around the world to begin using ozone therapy in COVID-19 patients immediately.

According to Dr. Jose Baeza, President of the Spanish Society of Ozone and Vice President of the World Federation of Ozone Therapy, ozone therapy is ideal because it can dramatically reduce the hospital stay of COVID-19 patients from the typical three weeks to less than a week, it doesn't have side effects and is very economical [492].

The initial results from these reports are promising and we wait for more evidence from additional clinical trials. In the meantime, given the paucity of effective treatment options for COVID-19, experts in the field recommend that all hospitals begin using intravenous ozone therapy in treating their COVID-19 patients [492].

Stem Cell Therapy

Due to their various therapeutic properties stem cells and exosomes may be useful in COVID-19. Stem cells have long been used in studies as an emerging therapy for lung disease such as chronic obstructive pulmonary disease, ARDS and pneumonia [493–496]. They also have anti-viral properties, and have been shown to reduce viral mediated inflammation, support the immune system, and reduce an overactive immune response [497–501]. In addition, stem cell therapy has proven to be beneficial for many of the underlying health conditions common to more serious cases of COVID-19 such as heart, lung and kidney disease [493–495,502,503].

Recently, stem cells have been identified as a potentially effective treatment option for COVID-19 due to various therapeutic properties. In fact, two clinical trials from China have already demonstrated promising results of intravenous stem cells in moderate and severe COVID-19 cases [504,505].

In addition, Pluristem Therapeutics, a leading regenerative medicine company released preliminary results of their compassionate use program which demonstrated promising responses in COVID-19 patients who received stem cell therapy [506]. Similarly, Mesoblast, a world leader in regenerative medicine released initial results in May 2020 of a study which used their mesenchymal adult stem cell product, Remestemcel-L under the approval of the FDA's "expanded access for compassion use" program. The small study demonstrated positive effects in ventilator-dependent COVID-19 patients with ARDS [507,508] . Based on the promising results, they have started a phase 2/3 trial involving 300 COVID-19 patients [509].

At the encouragement of the White House Coronavirus Task Force, Personalized Stem Cells (PSC) Inc., applied for accelerated FDA approval for their stem cell product, CoronaStem 1.

In May 2020, Organicell Regenerative Medicine Inc, a biopharmaceutical company, received FDA approval for their Investigational New Drug (IND), Organicell Flow (Folfin™) for patients with moderate to severe COVID-19. Organicell Flow is an acellular product derived from amniotic fluid that contains exosomes, hyaluronic acid and other constituents. Organicell's clinical trial will be the first to investigate the safety and efficacy of an amniotic derived therapy for COVID-19 [512] .

Organicell Regenerative Medicine and Its Investigational Therapeutic Zofin™ Featured in Two National Publications Examining Potential Therapies for COVID-19 Long-Haulers.

ReStem, a leading cell-based therapeutics company received FDA approval in mid-May 2020 for a phase I/IIa clinical trial using their umbilical cord mesenchymal stem cell product to treat COVID-19. The clinical trial, officially known as the "Systemic Umbilical Cord Cells to Ease Severe Syndrome with COVID-19 (SUCCESS)" is designed to investigate the safety and efficacy of their stem cell product in hospitalized patients with severe COVID-19 [513]. This comes after ReStem showed promising results in treating hospitalized COVID-19 patients with ARDS under an emergency approval from the FDA [514].

In late August 2020, a small trial investigating umbilical cord derived mesenchymal stem cells (UCMSCs) in patients with COVID-19 was published in the journal Nature. This non-randomized phase I clinical study involved 18 hospitalized patients with moderate and severe COVID-19. The results of this study demonstrate that UCMSC therapy was safe and well tolerated among participants. No serious treatment related adverse events were reported [515].

Currently, there are a number of clinical trials underway investigating the effects of stem cells on COVID-19 patients [516,517]. While we wait for the results, data from early phase trials is very promising.

Exosome Therapy

Exosomes, which share many of the therapeutic properties of stem cells, may also be beneficial in COVID-19. Experimental studies have shown exosomes to inhibit viral replication of the influenza virus, significantly reduce viral shedding and reduce lung damage [518]. Exosomes have also been extensively investigated for ARDS and other inflammatory lung diseases and have demonstrated positive results [519,520].

Although there are no clinical trials showing its efficacy in COVID-19, a trial for inhaled exosomes is underway in China and a New Jersey doctor has reported significant improvement in a COVID-19 patient with ARDS after being treated with exosomes [521,522].

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