COVID-19

**Definition of Condition**

COVID-19, an unusually severe disease derived from SARS-CoV-2 infection, is predominantly characterized by excessive immune reaction that affects myriad organ systems, highlighted by a “cytokine storm” that creates devastating, and sometimes deadly inflammation.¹ ² ³

It must be noted that up to 45% of all SARS-CoV-2 infections could be asymptomatic, and up to 70% in young persons, yet the potential still exists for body systems to be affected adversely, such as ground glass opacities in the lungs, without these individuals even knowing they have these pathologies.⁴

**Body Systems Affected**

Lungs, heart, brain⁵, gastrointestinal system, nervous system⁶, blood vessels, eyes, nasopharynx, epidermis, among others are affected.⁷ ⁸ COVID-19 has also been purported to be a factor in new-onset diabetes.⁹ A large majority of recovered COVID-19 patients report having at least one

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persistent symptom for weeks or months after the height of infection. Complaints echo myalgic encephalomyelitis, which is known as chronic fatigue syndrome. Common symptoms include brain fog, fatigue, pain, immune issues, and malaise after exercise.\textsuperscript{10} 11 12 13 14

**Pathophysiology**

Exposure to SARS-CoV-2 occurs most frequently through the air, in respiratory droplets or aerosolized particles.\textsuperscript{15} It takes exposure to approximately one million respiratory droplets for 15 minutes to become infected. Aerosolized particles may last in the air for several hours and can travel up to 27 feet.\textsuperscript{16}

SARS-CoV-2 usually infects cells in the nose before moving into the lungs, using angiotensin-converting enzyme 2 (ACE2) protein for entry, eventually entering blood vessels.\textsuperscript{17}

If allowed to replicate rapidly, succumbing to COVID-19 disease becomes a multisystem event. The problem is, especially for those who have one or more comorbidities, almost every aspect of the immune arsenal attempts to neutralize SARS-CoV-2. This overactivity, along with the pernicious and impervious nature of SARS-CoV-2, creates the “cytokine storm,” in which the immune system becomes hyper-inflamed, thus destroying healthy tissue. When the lungs become hyper-inflamed, especially, hypoxia ensues and affects oxygen-dependent organs like the heart and brain, leading to a downward spiral in overall organ function. Moreover, when SARS-CoV-2

\textsuperscript{14} Medrxiv. Retrieved from: https://www.medrxiv.org/content/10.1101/2020.10.14.20212555v1
\textsuperscript{17} Medrxiv. Retrieved from: https://www.medrxiv.org/content/10.1101/2020.07.02.20144717v2
spreads to blood vessels, the ensuing hyper-inflammation affects almost every organ of the body adversely, thus transforming into an endothelial disease.  

There is a developing theory that in some severe COVID-19 patients, a weakened immune system impairs the ability to fight off SARS-CoV-2, thus clinicians must pay strict attention to a patient’s medical history, symptoms, and bloodwork (especially interleukin 7 levels) to discern what treatments will be needed for this demographic.

Conversely, there is an emerging theory that the hyper-inflammation leading to the sickest patients comes from the inability to turn off antibody production, thus the creation of “autoantibodies.” As cited later, this confirms why steroids have been one of the few effective treatments used around the world.

Scientists at Oak Ridge National Laboratory suggest the bradykinin hypothesis for many of COVID-19-related symptoms. In a novel study, researchers used artificial intelligence (AI) to analyze gene expression data from cells in lung fluid from COVID-19 patients, which indicated elevated bradykinin levels as the driving force. The AI program then screened thousands of substances and found vitamin D to be one of the most effective at attenuating bradykinin levels.

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Risk factors for severe illness at any age include: Chronic kidney disease, COPD (chronic obstructive pulmonary disease), immunocompromised state (weakened immune system) from solid organ transplant, serious heart conditions such as heart failure, coronary artery disease, or cardiomyopathies, sickle cell disease, and type 2 diabetes mellitus. The consensus is that obesity (body mass index [BMI] of 30 or higher) is the most common risk factor for severe illness at any age, with research suggesting that high circulating leptin levels are to blame for the connection. Being overweight (body mass index [BMI] between 25 and 30) has also been found to increase risk. Cigarette smoking and electronic cigarette use, especially in young persons, greatly increases risk.

Risk factors that may increase risk at any age include: Asthma (moderate-to-severe), cerebrovascular disease (affects blood vessels and blood supply to the brain), cystic fibrosis, hypertension or high blood pressure (which is why those taking blood pressure medication seem to be less at risk), immunocompromised state (weakened immune system) from blood or bone marrow transplant, immune deficiencies, HIV, use of corticosteroids, or use of other immune weakening medicines, neurologic conditions such as dementia, liver disease, pregnancy, pulmonary fibrosis (having damaged or scarred lung tissues), smoking, thalassemia (a type of blood disorder), type 1 diabetes mellitus.

According to the CDC, the older you get, the greater the risk. Patients older than 80 were at least 20 times more likely to die from COVID-19 than those in their 50s, and hundreds of times more likely to die than those below the age of 40. One reason for this disparity could be the weakened expression of perforin, a protein that allows cytotoxic proteases to enter cells with the
purpose of inducing death in cells that have been hijacked by SARS-CoV-2.\textsuperscript{33} In addition, the absence of a vigorous CD8+ T cell immune response in the elderly is indicated.\textsuperscript{34} Men with the virus had a higher likelihood of dying than women of the same age, as it is believed that estrogen has a protective effect from severe symptoms, as well as contractility.\textsuperscript{35} In addition, females tend to mount stronger immune responses to infections than males, a trait that may be linked to increased susceptibility to inflammatory and autoimmune diseases in females.\textsuperscript{36} Non-whites were at higher risk of dying than white patients.\textsuperscript{37}

Other risk factors include ApoE4 gene variant\textsuperscript{38}, ACE2 gene variant\textsuperscript{39}, blood type ‘A’\textsuperscript{40} 41 42 43, exposure to higher SARS-CoV-2 viral load\textsuperscript{44}, impaired glutathione function (GSTP1 variant)\textsuperscript{45},

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\item\textsuperscript{34} Biorxiv. Retrieved from: https://www.biorxiv.org/content/10.1101/2020.08.21.262329v1
\item\textsuperscript{35} Medrxiv. Retrieved from: https://www.medrxiv.org/content/10.1101/2020.07.30.20164921v2
\item\textsuperscript{41} Medrxiv. Retrieved from: https://www.medrxiv.org/content/10.1101/2020.07.12.20152074v1
\item\textsuperscript{42} Medrxiv. Retrieved from: https://www.medrxiv.org/content/10.1101/2020.11.05.20226100v1
\item\textsuperscript{44} Medrxiv. Retrieved from: https://www.medrxiv.org/content/10.1101/2020.10.03.20206110v4
\item\textsuperscript{45} Polonikov A. (2020). Endogenous Deficiency of Glutathione as the Most Likely Cause of Serious Manifestations and Death in COVID-19 Patients. ACS infectious diseases, acsinfecdis.0c00288. Advance online publication. https://doi.org/10.1021/acsinfecdis.0c00288
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and stress.\textsuperscript{46} Those taking proton pump inhibitors (PPIs) once daily have exhibited double the risk for COVID-19, while taking PPIs twice daily triples the risk for COVID-19.\textsuperscript{47, 48}

**Allopathic Diagnosis & Treatment**  
**Symptoms**
Symptoms are vast and still being discovered. However, the most common symptoms are high fever, stuffy nose, sore throat, dry cough, dyspnea (shortness of breath) or difficulty breathing, prolonged fatigue and malaise, hypoxia, nausea, vomiting, gastrointestinal upset including diarrhea, lost sense of smell or taste, and conjunctivitis.\textsuperscript{49}

While many infected persons are asymptomatic, for those who do exhibit symptoms, the CDC recommends that certain symptoms warrant speaking with your physician or visiting an emergency room. These symptoms are: high fever that either does not abate or fluctuates for several days, shortness of breath or heaviness on the chest, forgetfulness, extreme fatigue or malaise.\textsuperscript{50}

The clearest indicator that one has COVID-19 is loss of taste and/or smell.\textsuperscript{51} While a combination of loss of taste and smell, extreme fatigue, cough and loss of appetite was the best predictor of having a positive result from the PCR test, loss of taste and/or smell seems to be by far the most abundant single symptom reported.\textsuperscript{52}

\textsuperscript{49} Centers for Disease Control: https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html  
\textsuperscript{51} Medrxiv. Retrieved from: https://www.medrxiv.org/content/10.1101/2020.07.22.20157263v1  
King’s College London used machine learning from cases in the United Kingdom, United States, and Sweden to determine six distinct symptom clusters that indicate the progression of severe COVID-19 disease.\(^53\)

1. (‘flu-like’ with no fever): Headache, loss of smell, muscle pains, cough, sore throat, chest pain, no fever.
2. (‘flu-like’ with fever): Headache, loss of smell, cough, sore throat, hoarseness, fever, loss of appetite.
3. (gastrointestinal): Headache, loss of smell, loss of appetite, diarrhea, sore throat, chest pain, no cough.
4. (severe level one, fatigue): Headache, loss of smell, cough, fever, hoarseness, chest pain, fatigue.
5. (severe level two, confusion): Headache, loss of smell, loss of appetite, cough, fever, hoarseness, sore throat, chest pain, fatigue, confusion, muscle pain.
6. (severe level three, abdominal and respiratory): Headache, loss of smell, loss of appetite, cough, fever, hoarseness, sore throat, chest pain, fatigue, confusion, muscle pain, shortness of breath, diarrhea, abdominal pain.

Any of the aforementioned needs to be taken even more seriously in persons 65 years of age or older, who represent 80\% of hospitalizations and have a 23-fold greater risk of death than those under 65.\(^54\) Those under 20 are half as susceptible to getting COVID-19.\(^55\)

Pregnancy, while considered a COVID-19 risk factor, has mixed results with regard to greater severity compared with non-pregnant patients.\(^56\)\(^57\) While there have been several cases purported regarding transmission of SARS-CoV-2 from pregnant mothers to their fetuses, so far these are rare. Several studies have shown no evidence of transmission.\(^58\)\(^59\) Another study has shown

\(^{53}\)Medrxiv. Retrieved from: https://www.medrxiv.org/content/10.1101/2020.06.12.20129056v1


\(^{56}\)Medrxiv. Retrieved from: https://www.medrxiv.org/content/10.1101/2020.08.17.20161760v1


\(^{58}\)https://www.medrxiv.org/content/10.1101/2020.08.20.20178657v1

protective properties in placental tissue.\textsuperscript{60} The Centers for Disease Control suggests there is increased risk for severe illness.\textsuperscript{61} In nursing women, SARS-CoV-2 has not shown to be transmitted to infants.\textsuperscript{62, 63} Alternatively, one study has shown protected antibodies were transmitted from an infected mother to her infant.\textsuperscript{64, 65}

**Diagnosis**

If presenting with what the CDC considers high priority or priority, a COVID-19 viral test to screen for active infection is suggested. Nasal swab or saliva are accepted methods to extract samples.\textsuperscript{66, 67, 68} High priority is considered hospitalization with older person symptoms, healthcare workers or first responders, and residents of long-term care facilities. Priority is considered anyone with classic symptoms of COVID-19, or those who are suspected through contact tracing have been exposed to someone else with COVID-19.\textsuperscript{69} Guangzhou Institute of Respiratory Health created a calculation tool for predicting critically ill COVID-19 at admission.\textsuperscript{70}

Testing too early may bring a higher number of false negatives. Patients tested with SARS-CoV-2 in the four days after infection were 67\% more likely to test negative, even if they had the virus. When the average patient began displaying symptoms of the virus, the

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\textsuperscript{61} The Centers for Disease Control. Retrieved from: https://www.cdc.gov/mmwr/volumes/69/wr/mm6944e3.htm?s_cid=mm6944e3_w


\textsuperscript{64} Medrxiv. Retrieved from: https://www.medrxiv.org/content/10.1101/2020.08.18.20176743v1


\textsuperscript{66} Medrxiv. Retrieved from: https://www.medrxiv.org/content/10.1101/2020.07.09.20149534v1

\textsuperscript{67} Medrxiv. Retrieved from: https://www.medrxiv.org/content/10.1101/2020.04.16.20067835v1


\textsuperscript{69} Centers for Disease Control: https://www.cdc.gov/coronavirus/2019-nCoV/hcp/clinical-criteria.html

\textsuperscript{70} Guangzhou Institute of Respiratory Health. Retrieved from: http://118.126.104.170/
false-negative rate was 38%. The test performed best eight days after infection (on average, three
days after symptom onset), but even then had a false negative rate of 20%.\textsuperscript{71}

Aside from a positive test for active infection, a full blood workup including CBC (looking for
elevated neutrophil count\textsuperscript{72} and lymphocyte count below 1000\textsuperscript{73}), Chem Screen, C-reactive
protein (elevated level is an indicator)\textsuperscript{74}, D-Dimer (elevated level is an indicator)\textsuperscript{75}, and 25(OH)D
especially below 30 ng/mL\textsuperscript{76} may help ascertain the severity of the infection and how it is
affecting the body. Knowing the patient’s genetic predisposition to inflammatory genes’ IL-6,
CRP, and TNFα can also be helpful for diagnosing who may be more susceptible to the cytokine
storm.\textsuperscript{77}

If the patient is complaining of shortness of breath or heaviness on the chest, a lung ultrasound,
CT scan, or chest radiography may be performed for detection of COVID-19 abnormalities,
including myocarditis, which can still occur in those who are asymptomatic.\textsuperscript{78}\textsuperscript{79}

Children involving symptoms seen with atypical Kawasaki disease and toxic shock syndrome
may be linked to COVID-19 infection.\textsuperscript{80}\textsuperscript{81}

\textsuperscript{71} Kucirka, L. M., Lauer, S. A., Laeyendecker, O., Boon, D., & Lessler, J. (2020). Variation in
False-Negative Rate of Reverse Transcriptase Polymerase Chain Reaction-Based SARS-CoV-2 Tests by
Time Since Exposure. Annals of internal medicine, M20-1495. Advance online publication.
https://doi.org/10.7326/M20-1495
\textsuperscript{72} Medrxiv. Retrieved from: https://www.medrxiv.org/content/10.1101/2020.07.08.20141218v1
\textsuperscript{73} Wagner, J., DuPont, A., Larson, S., Cash, B., & Farooq, A. (2020). Absolute lymphocyte count is a
Hematology, 1–5. https://doi.org/10.1111/ijlh.13288
\textsuperscript{74} Medrxiv. Retrieved from: https://www.medrxiv.org/content/10.1101/2020.10.26.20219360v1
\textsuperscript{75} Medrxiv. Retrieved from: https://www.medrxiv.org/content/10.1101/2020.06.24.20139600v1
from COVID-19 in countries south of latitude 35 degrees North supports vitamin D as a factor determining
\textsuperscript{77} Medrxiv. Retrieved from: https://www.medrxiv.org/content/10.1101/2020.07.17.20155242v1
\textsuperscript{78} Bernheim, A., Mei, X., Huang, M., Yang, Y., Fayad, Z. A., Zhang, N., Diao, K., Lin, B., Zhu, X., Li, K., Li,
Relationship to Duration of Infection. Radiology, 295(3), 200463.
https://doi.org/10.1148/radiol.2020200463
\textsuperscript{80} Medscape: https://www.medscape.com/viewarticle/930223
\textsuperscript{81} Feldstein, L. R., Rose, E. B., Horwitz, S. M., Collins, J. P., Newhams, M. M., Son, M., Newburger, J. W.,
Multisystem Inflammatory Syndrome in U.S. Children and Adolescents. The New England journal of
medicine, NEJMoa2021680. Advance online publication. https://doi.org/10.1056/NEJMoa2021680
Neurological and neuropsychiatric complications such as intracerebral hemorrhage, central nervous system vasculitis, altered mental status, myasthenia gravis, encephalopathy, encephalitis, new-onset psychosis, dementia-like syndromes, and affective disorder have been found in COVID-19 patients of all ages.\textsuperscript{82}

A serum antibody test for IgA, IgG, and IgM can be performed to learn of past infection. This can help gauge potential severity of symptoms. Initial results suggest that COVID-19 antibodies only remain stable in the blood of the majority of infected individuals between two to six months after diagnosis and possibly longer.\textsuperscript{83} However, antibodies were not detectable in everyone exposed to the virus.\textsuperscript{84}

For asymptomatic individuals who test positive for COVID-19, a complete blood count, blood biochemistry, coagulation function, liver and renal function, infection biomarkers, and chest computed tomography may be measured.\textsuperscript{85}

\textbf{Treatment}

Treatment is trial and error because COVID-19 comes from a novel coronavirus strain and there is still so much we do not know. Thus, the current treatments have been a mixed bag.\textsuperscript{86}

The most difficult aspect of treating COVID-19 patients has been breaking the “cytokine storm” or inflammatory cascade.\textsuperscript{87} Treatment varies widely depending upon the country.


\textsuperscript{83} Biorxiv. Retrieved from: https://www.biorxiv.org/content/10.1101/2020.11.01.362319v1

\textsuperscript{84} Medrxiv. Retrieved from: https://www.medrxiv.org/content/10.1101/2020.06.07.20124636v2


For example, in addition to the World Health Organization protocol, European countries like Italy, France, and Spain include a nutritional element from a nourishing diet, as well as the IL-6 inhibitor tocilizumab, and the steroid methylprednisolone. China uses a combination of conventional medicine and Chinese medicine. Greece has found the older anti-inflammatory drug colchicine helpful. Pakistan found tocilizumab to be effective and economical, yet several studies in the United States has not found it to be effective. Israel is using aviptadil, a synthetic form of a natural peptide that the US Food and Drug Administration has fast-tracked to enhance recovery from critical respiratory failure.

Treatment in the United States varies depending upon the hospital. Some hospitals will use ventilators, but only as a last resort. Helmet non-invasive ventilation is a form of continuous positive applied pressure that has emerged for COVID-19 patients who require respiratory support but may not require invasive ventilation. Others will use supplementary oxygen. Some hospitals use antiviral combinations, including Remdesivir, which is approved by the US Food and Drug Administration to shorten the duration of COVID-19. Although, some research has shown it to be ineffective, as well as causing cases of liver toxicity, so the World Health Organization is recommending that doctors not use Remdesivir. Other hospitals used the

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89 Medrxiv. Retrieved from: https://www.medrxiv.org/content/10.1101/2020.06.22.20133413v1
93 Medrxiv. Retrieved from: https://www.medrxiv.org/content/10.1101/2020.06.23.20134072v1
95 Medrxiv. Retrieved from: https://www.medrxiv.org/content/10.1101/2020.06.29.20141283v1
97 National Institutes of Health: https://www.covid19treatmentguidelines.nih.gov/whats-new/
99 Medrxiv. Retrieved from: https://www.medrxiv.org/content/10.1101/2020.11.05.20226373v1
antimalarial chloroquine or hydroxychloroquine, but the FDA revoked its emergency use status and has been banned from use, even though numerous studies outside of the United States purports a benefit, especially when combined with zinc. Anti-inflammatories, especially steroids, have been confirmed as successful treatments in most cases, especially if the patient shows elevated C-reactive protein level. The steroid dexamethasone is the first drug to reduce COVID deaths, one in eight patients on ventilators, and one in 25 of patients on oxygen. Recent data suggests an antiparasitic called ivermectin has been shown to inhibit replication of SARS-CoV-2. Medication to prevent blood clots traveling from the legs to the lungs to patients at heightened risk seems to have helped reduce the risk for catastrophic COVID-related death. Researchers purport that the commonly used medication Heparin could be used as an intervention for excessive clotting. The US Food and Drug Administration has approved the emergency use authorization of monoclonal antibody therapy bamlanivimab for lowering COVID-19-related hospitalization or emergency room visits in patients at high risk for COVID-19-related hospitalization or emergency room visits in patients at high risk for 

101 Medrxiv. Retrieved from: https://www.medrxiv.org/content/10.1101/2020.08.16.20175752v1
104 Medrxiv. Retrieved from: https://www.medrxiv.org/content/10.1101/2020.08.19.20178376v1
105 Medrxiv. Retrieved from: https://www.medrxiv.org/content/10.1101/2020.08.20.20178772v1
disease progression within 28 days after treatment when compared to placebo in mild-to-moderate cases. 113

The first comprehensive review, while still based upon limited evidence, suggests glucocorticoids being the most effective at reducing mortality. 114

Many hospitals have found that simple techniques such as putting severe hypoxic patients in the prone position for improved oxygenation to be extremely helpful in lieu of ventilators, which have an extremely high death rate. 115

Transfusions of plasma from recovered COVID-19 patients into critically ill patients has shown promise in several patient trials with no adverse side effects and is considered a safe treatment option for patients with severe COVID-19 disease. 116 117 118

Research suggests the same inflammatory pathways that lead to Rheumatoid arthritis may affect alveolar structures in COVID-19. Preventing the cytokine storm may be ameliorated, and increase survival, by using treatments to inhibit IL-6, IL-1β or TNF or targeting cytokine signalling via Janus kinase inhibition. 119 120 121

A multi-country study found that adding vitamin D to immunomodulatory drugs, especially steroids, can down-regulate hyper-inflammation in severe COVID-19 patients, which helps

116 Medrxiv. Retrieved from: https://www.medrxiv.org/content/10.1101/2020.05.08.20095471v1
ameliorate the cytokine storm. Vitamin D levels should be assessed in COVID patients as one Spanish hospital found 80% to be deficient, while a meta-analysis found all admitted COVID-19 patients to be low in 25-hydroxy D.

In rare cases, some physicians and hospitals find that a mix of allopathic and integrative therapies work best. Paul Marik, MD, from Eastern Virginia Medical School, created a COVID-19 protocol that spans from mild to severe symptoms that include targeted medications and nutrients together. Richard Bartlett, MD has found success using the nebulized corticosteroid budesonide (pulmicort), macrolide antibiotic, low dose aspirin, and zinc.

Patients should understand and continue with targeted COVID-19 disease treatment as lingering symptoms can last for weeks, if not months after twice testing negative. The Centers for Disease Control has also stated that hospital readmission for lingering COVID-19 symptoms is more common than desired.

One major question scientists have been trying to answer is immunity, to what degree, and can one catch COVID-19 more than once. These answers to these questions are still coming to fruition. From what the research tells us so far, antibody immunity wanes in many COVID patients after three to nine months, and one can catch COVID-19 more than once, albeit in

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125 Medrxiv. Retrieved from: https://www.medrxiv.org/content/10.1101/2020.06.05.20123554v3?%253fcollection=
129 Centers for Disease Control. Retrieved from: https://www.cdc.gov/mmwr/volumes/69/wr/mm6945e2.htm?s_cid=mm6945e2_w
almost every case the symptoms are milder and at least six months or longer after first infection, thus indicating an adaptive immunity via memory B and T cells.\textsuperscript{130 131 132 133 134 135 136 137}

\textbf{When to Refer}

Any patient who has one or more comorbidities, or anyone older than 60 years of age, should seek out their physician if they even feel the slightest symptoms or have been exposed to a person with a positive result for SARS-CoV-2 infection. In a person without any of the aforementioned, if they exhibit one or a combination of the following, should seek out their physician: shortness of breath, heaviness of the chest, diarrhea, high fever that does not abate and fluctuates wildly, forgetfulness, and severe fatigue or malaise.\textsuperscript{138}

\textbf{Integrative Perspective of Causes}


\textsuperscript{133} Medrxiv. Retrieved from: https://www.medrxiv.org/content/10.1101/2020.08.11.20171843v2


\textsuperscript{137} Biorxiv. Retrieved from: https://www.biorxiv.org/content/10.1101/2020.11.15.383323v1

\textsuperscript{138} Centers for Disease Control: https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html
Close contact with a person who is infected is the main cause of transmission. Cough or sneeze is more strongly associated with contraction of SARS-CoV-2, but a person speaking loudly and forcefully can transmit saliva droplets. As recently as July 9th, the World Health Organization is considering changing the main aspect of transmission SARS-CoV-2 as aerosol, which means the virus could stay on droplets in the air for a number of hours. This would render indoor areas with poor ventilation as major areas of transmission, such as cruise ships and old buildings.

An infected person who has the virus can also leave remnants on surfaces, although transmission is more difficult. The surfaces most likely to transmit are door handles, phone or computer interfaces, and more. Some public health experts urge anyone with a mobile phone to decontaminate their devices daily with either 70 percent isopropyl alcohol or by sanitizing with (ultraviolet) devices. SARS-CoV-2 can survive on human skin for nine hours if not disinfected with ethanol treatment.

SARS-CoV2 can enter the body through the eyes (because the eyes contain the ACE2 protein receptors), mouth, nose, and ears, mostly through touch by infected hands or inundation from a SARS-CoV-2 cloud.

Breathing through the nose and exhaling through your mouth is a preferred way to breathe for extra viral infection protection. Nitric oxide, which helps oxygenate the blood and thus reduces the ability of viruses to replicate, is produced only in the nasal cavity, so mouth breathers do not

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141 Medrxiv. Retrieved from: https://www.medrxiv.org/content/10.1101/2020.07.08.20148775v1
produce enough nitric oxide.\textsuperscript{145} Implementing breathing exercises for prevention or if symptomatic have been touted as helpful.\textsuperscript{146}

Dietary sugar, including added sugar, sweets, sugary beverages, or any other sugary product that is not naturally occurring (i.e. fruit) weakens the immune system more than any foodstuff.\textsuperscript{147}

Inferior nutritional status is often missing in public health discussions regarding an optimally functioning immune system for preventing COVID-19.\textsuperscript{148} Numerous vitamins, including vitamins A, B6, B12, C, D, E, and folate; and trace elements, including zinc, iron, selenium, magnesium, and copper, among others, play important and complementary roles as immunomodulatory agents in supporting both the innate and adaptive immune systems.\textsuperscript{149} Deficiencies or suboptimal status in micronutrients negatively affect immune function and can decrease resistance to infections. Vitamin D deficiency has been the focus of copious COVID-19 research to the degree that public health experts are calling for universal screening, and medical associations are asking for mandatory supplementation during the pandemic. In November, the

\textsuperscript{147} American Nutrition Association: https://theana.org/COVID-19
Stress can impair immune function in more ways than one. Along with the direct effect, stress can lead to overeating or a migration to comfort food.\footnote{Stohs, S. J., & Aruoma, O. I. (2020). Vitamin D and Wellbeing beyond Infections: COVID-19 and Future Pandemics. Journal of the American College of Nutrition, 1–2. Advance online publication. https://doi.org/10.1080/07315724.2020.1786302} Hence, stress weakens the body’s initial defenses when they are most needed to fight off initial SARS-CoV-2 exposure. Increases in levels of the inflammatory cytokine interleukin-6 (IL-6) correspond to increased levels of worrying.\footnote{Medscape: https://www.medscape.com/viewarticle/928287#vp_1} This can be specifically detrimental for many that have one or more mutations of the IL-6 gene. After subjects did a 10-minute relaxation induction task that focused on deep breathing, there were significant reductions in levels of IL-6. This is further evidence of the important mind-body connection and its influence from stress.

Lack of humidity indoors during the winter months or in very dry climates allows greater transmission of SARS-CoV-2.\textsuperscript{164} SARS-CoV-2 virus lasts longer on various surfaces during cold weather months, so extra vigilance should be taken for cleaning during fall and winter.\textsuperscript{169}

**Specialized Integrative Analysis**

The primary interface between ourselves and SARS-CoV-2 is our immune system. SARS-CoV-2’s initial entry is in the throat and nasopharynx area via the nose, mouth, or eyes. If SARS-CoV-2 gets to the lungs and blood vessels, the potential for devastation grows.

SARS-CoV-2 draws the innate immune response of T-antibodies, IgM, other IgGs, and neutrophils more than lymphocytes. It seems particularly deadly in adults because it may be able to evade these initial innate immune responses, whereas children rely more on their adaptive immune response.\textsuperscript{170, 171}

Pyroptosis, a novel form of inflammatory cell death, may be a cause of the increased virulence of COVID-19. Pyroptosis initiates the upregulation of inflammasome NLRP3. Chronic activation of pyroptosis can occur with proinflammatory, high-sugar and -processed food diets, gut dysbiosis, stress, toxins, drugs, etc. Chronic activation has been noted in inflammatory diseases such as type 2 diabetes, obesity, autoimmune disease, cardiovascular disease, and cancer.\textsuperscript{172}


\textsuperscript{167} Medrxiv. Retrieved from: https://www.medrxiv.org/content/10.1101/2020.11.13.20231472v1

\textsuperscript{168} Medrxiv. Retrieved from: https://www.medrxiv.org/content/10.1101/2020.11.12.20230888v1

\textsuperscript{169} Biorxiv. Retrieved: https://www.biorxiv.org/content/10.1101/2020.08.30.274241v1


Discerning between COVID-19, cold, allergy, strep or flu can be difficult initially because many of the symptoms are similar, including fatigue, fever, headache, aches and pains, diarrhea and gastrointestinal upset.

SARS-CoV-2 is the only coronavirus with a furin cleavage site, which is why scientists believe neutralizing this is the key to stopping it. Not even distant relatives of SARS-CoV-2 have it, and the coronaviruses that do have it share only 40% of SARS-CoV-2’s genome. Lifestyle intervention is critical for attenuating this cleavage site from SARS-CoV-2.

Nutritional and lifestyle intervention is critical to enhance immunity in viral infections such as COVID-19. Whey protein is one foodstuff shown to have an antiviral effect against SARS-CoV-2.

The amount of SARS-CoV-2 exposure, or viral load, often warrants how serious the COVID-19 infection may be. Ascertaining this from the patient can assist in treatment decisions.

There are four phases in the timeline of COVID-19. Knowing the phases and what self-treatment they require is important as SARS-CoV-2 puts our immune system at odds. We need early activation but not continued overactivity.

Phase One - Prevention
Prevention means you are prepping your immune system for peak surveillance to detect SARS-COV-2, as well as reducing daily levels of inflammation, to improve outcomes if you become infected.

178 Biorxiv. Retrieved from: https://www.biorxiv.org/content/10.1101/2020.08.17.254979v1
Phase Two - Infection
If you happen to be infected with SARS-CoV-2, support for infection emphasizes specialized immune activity against infection.

Phase Three - Escalating Inflammation
If SARS-CoV-2 over-stimulates the immune response to the point that you are symptomatic, support is focused on anti-inflammatory measures.

Phase Four - Recovery
Once you are not symptomatic, support should still be focused on resolving inflammation, inhibiting tissue damage, curtailing losses of function, and restoring and reoptimizing function.

Because patients have been observed to relapse into the Escalating Inflammation Phase, it is essential to communicate with your health professional to continue following the protocol well into what may appear to be the Recovery Phase.

In-depth strategies to support the four phases are below. Public health measures such as wearing a mask, social distancing, not touching your face, washing your hands, and the like were not included in this monograph, as most are aware of these measures.

Integrative Support Protocols
Before explaining how important diet and lifestyle choices are, five critical care physicians developed and are using an integrative protocol for hospitalized COVID-19 patients called MATH+. The protocol calls for the use of intravenous methylprednisolone, vitamin C and subcutaneous heparin within six hours of admission into the hospital, along with high-flow nasal oxygen. Optional additions include thiamine, zinc and vitamin D. They have successfully used this protocol to prevent severe COVID-19 symptoms of hyperinflammation, hypercoagulation and hypoxia.

Two economical things every home and office can do to lower the transmission of COVID-19 are opening up windows to improve air flow and letting more natural light into a room, creating a healthier environment.

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Diet and Lifestyle Choices

Nutrient support via an anti-inflammatory diet and targeted vitamins, minerals, and antioxidants are important to stave off infection, but critical if one presents with severe COVID-19 to stave off death. 184

Public health experts are imploring populations all over the world to keep good glucose control to avoid infection. 185 Being extra vigilant regarding sugars and sugar control to avoid peaks and valleys is crucial, especially for those with blood sugar disorders, and those who are hospitalized with COVID-19. 186 187 Higher glucose levels lead to higher inflammatory cytokine activity, which if not mitigated, may lead to severe COVID-19. 188

Alcohol may put people at increased risk for the coronavirus, weakening the body's immune system and leaving drinkers at risk for other risky behaviors that could increase the likelihood of contracting coronavirus. While alcohol does work as a disinfectant on surfaces, excessive alcohol consumption can actually make the body less capable of handling SARS-CoV-2. Crucially, alcohol, especially in strong concentrations and large amounts, can be a vasoconstrictor, leaving one more susceptible to serious COVID-19 symptoms. 189

Eat copious amounts of fruit and vegetables. Not only do they provide fluid and electrolytes, their phytochemicals protect the throat and lungs, and most importantly help maintain your acid/alkaline balance. It is much tougher for viruses to take hold when the body's pH level is between 6.8 and 7.2, which is slightly alkaline. Being too acidic or too alkaline is also not ideal.

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Cruciferous vegetables from the Brassica family also help boost our Th1 immune antibodies.\(^{190}\) Leafy greens rich in vitamin K can help promote optimal coagulation as those with accelerated COVID-19 severity seem to have low vitamin K levels.\(^{191}\)

Drink a lot of fluid (warm or hot) to avoid dehydration. Electrolytes, especially potassium, are crucial. One of the things that happens with infection in severe cases is hypokalemia.\(^{192}\) Sodas, juices, and sweetened coffee or tea drinks are not recommended. A sip of warm water every 20 minutes may wash any existing viruses down the throat down into the gastric juices of the stomach where they have trouble surviving the ultra-acidic environment.

Healthy sleep supports antiviral immune response. Disordered sleep promotes inflammation. Data shows that patients hospitalized with COVID-19 are often those who slept the least.\(^{193}\) Six to eight hours of sleep is ideal.

Psychosocial interventions such as cognitive behavioral therapy (CBT) are associated with positive changes in immune system function, and decreases in harmful immune function that persisted for at least 6 months following treatment for participants randomly assigned to CBT psychosocial intervention versus a control group.\(^{194}\)

Exercise and movement is essential for prevention of COVID-19 and has been shown to reduce symptomatic days if you do get COVID-19, as well as prevent hospitalizations.\(^{195}\)\(^{196}\)\(^{197}\) The key is not to do too much or too little. Move around, even if you just get up every 20 minutes or so. To decrease inflammation, the right exercise intensity is critical with moderate levels effective at

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\(^{190}\) The Institute for Functional Medicine: https://www.ifm.org/news-insights/the-functional-medicine-approach-to-covid-19-virus-specific-nutraceutical-and-botanical-agents/?fbclid=IwAR24Kg3-s4SA3i70UNwoKuZlO9gKKup8iFNU77KMtEmCohMWl5SCwpZ3uDQ


\(^{196}\) Medrxiv. Retrieved from: https://www.medrxiv.org/content/10.1101/2020.08.21.20179499v1

lowering inflammatory markers, while overtly intense exercise does not. Caution should be used when considering the form and duration of exercise during the pandemic.

Spending time outdoors not only lowers transmission of SARS-CoV-2\textsuperscript{198}, but being outdoors, especially in nature, has multimodal beneficial effects.

The state of the gut microbiome has been shown to contribute either positively or negatively to SARS-CoV-2 infection. Both the lung and the GI tract have a microbiome. The complex relationship between them and the immune system is emerging. Disrupted balance of GI microbiome bacteria has been shown to be a source of systemic inflammation. Consuming ample dietary fiber helps the gut and perpetuates beneficial lung health. Optimal diet, but also pre- and probiotic supplementation may be warranted for this.\textsuperscript{199} Probiotic strains of lactobacilli and bifidobacteria exhibited an ameliorating impact on the clinical conditions of hospitalized patients positive for SARS-CoV-2 infection.\textsuperscript{200}

If where one resides does not offer the ability to breathe pristinely clean air, such as big cities or areas with power plants,\textsuperscript{201} one can assure their domicile has clean air by installing a HEPA filter. In areas with high concentrations of fine particulate matter, the increased risk of death was 15% higher.\textsuperscript{204} This is especially important during hot weather months where one must be indoors with air conditioning.\textsuperscript{205} In addition, a humidifier in the winter is essential, as viruses are not as virulent when there is more moisture in the air.\textsuperscript{206} Keeping your humidifier set to 25-40% is ideal. Research suggests that every degree Celsius increase in daily average temperature results in a 2.88% decrease in new daily COVID-19 cases.\textsuperscript{208}
In those that need to be hospitalized, many hospitals around the world are using intravenous nutrients, such as vitamin C and glutathione, with positive case reports. A clinical trial that started in February will be completed this fall regarding the effectiveness of IV vitamin C therapy in COVID-19-related pneumonia. A case report found IV glutathione, glutathione precursors (N-acetyl-cysteine), and alpha lipoic acid may represent a novel treatment approach for addressing "cytokine storm syndrome" and respiratory distress in patients with COVID-19 pneumonia.

Just eating a healthy diet will not suffice. You need supplemental support.

Supplements for All Four COVID-19 Timeline Phases - Prevention, Infection, Escalating Inflammation, Recovery

VITAMIN C (Ascorbic Acid)
Critical for almost every cellular function. If you have one or both mutations of the Vitamin C gene SLC23A1 (rs33972313), you may need extra vitamin C as you do not transport it into the cell as well as those without a mutation.

Dosage: 500mg - 700 mg twice daily for adults; 250mg - 350 mg twice daily for children.

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210 Clinicaltrials.gov: https://clinicaltrials.gov/ct2/show/NCT04264533
216 American Nutrition Association: https://theana.org/COVID-19
**During Inflammation Phase, increase to 2,000mg - 4,000mg if tolerated digestively.**

ZINC
Zinc deficiency is believed to be a risk factor for COVID-19.\(^218\)\(^219\) Oral tablets/capsules along with zinc lozenges/zinc sulfate solution have been proven to be effective in blocking coronavirus (and most other viruses) from multiplying in your throat and nasopharynx.\(^220\)\(^221\)

Loss of smell (anosmia) and distorted sense of taste (dysgeusia), the most frequent complaint in those with COVID-19, are classic symptoms of zinc deficiency.

It is especially important that you take zinc if you have the SLC30A genetic mutation that impedes absorption. Mutation(s) of the gene increases risk for the viral infections varicella (chicken pox), zoster (shingles), herpes, coronavirus (common cold), influenza, hepatitis, viral warts, stomach flu, HPV, and now COVID-19.

Dosage: 20mg - 30mg capsules/tablets with a 60mg maximum daily for adults (so if you take a multi with extra zinc you should be good). 15mg - 30mg for children. Always take oral zinc with a protein meal.

For lozenges, let them dissolve in the back of your throat and nasopharynx.

For children who cannot swallow a pill, a 15 mg. zinc sulfate solution can be added to water.

There is also a 2 mg zinc sulfate solution that can be gargled and swallowed twice daily by anyone as a preventive or for sore throats.

**During Infection and Inflammation Phase, take at least 60mg supplemental zinc until Recovery Phase.**

MONOLAURIN (glycerol monostearate)

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\(^{220}\) The Institute for Functional Medicine: https://www.ifm.org/news-insights/the-functional-medicine-approach-to-covid-19-virus-specific-nutraceutical-and-botanical-agents/?fbclid=IwAR24Kg3-s4SA3l70UnwoKuZIO9gKKup8iFNu7XKMtEmCohMWI5SCwp23uDQ

Similar to how washing our hands with soap kills viruses, monolaurin does a similar thing in our bodies at the cellular level. A natural antiviral derived from coconut, glycerol monostearate mirrors the immune property monolaurin, found in human breast milk. Monolaurin kills viruses by breaking down their phospholipid layer, leading to apoptosis (cell death). As a natural emulsifier, it takes the fight to viruses on the cellular level because of its natural foaming properties.

Monolaurin also inactivates lipid-coated viruses by binding to the lipid-protein envelope of the virus, thereby preventing it from attaching and entering host cells, making infection and replication impossible. Monolaurin can also disintegrate the protective viral envelope, killing the virus (SARS-CoV-2 has this viral envelope). Monolaurin can balance out T-cell antibody and cytokine overactivity.

Dosage: 600mg daily for adults and teens; 300mg for young children.

**During Infection and Inflammation Phase, increase to 2400mg daily for adults and teens, 1200mg daily for children.

**Contraindicated in those with coconut intolerance.

VITAMIN D3

Having optimal vitamin D levels can reduce severity of COVID-19 symptoms and mortality by 50%.

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224 Medrxiv: https://www.medrxiv.org/content/10.1101/2020.04.08.20058578v4


It is especially important to have enough vitamin D3 if you had a low level previously or you have genetic mutations of specific vitamin D genes that impede absorption. An optimal D3 level is between 50-75 ng/ML. ²²⁸

Dosage: 5000IU (125 mcg) - 10,000IU (250 mcg) daily for adults until herd immunity is reached; 1000IU (25 mcg) - 5000IU (125 mcg) for children.

VITAMIN A (not beta carotene)
Vitamin A is critical not only because it helps vitamin D absorption, and vice versa, but it is a crucial immune nutrient for numerous viruses. ²²⁹ It is even more critical to take supplemental vitamin A if you have a genetic mutation that blocks your ability to turn beta carotene into vitamin A (BCMO1).

Dosage: 3000IU (900mcg) - 5000IU (1500mcg) daily for adults; 500IU (150mcg) - 1500IU (600mcg) daily for children. Note micrograms, not milligrams.

**During Infection and Inflammation Phase, double the dose.

MELATONIN
Aside from exhibiting preventive characteristics against SARS-CoV-2, melatonin helps restorative sleep, which is important for recharging your immune system. Cleveland Clinic recently launched a COVID-19 Risk Calculator, in which one major risk factor was low melatonin levels.²³⁰ Their study found subjects were with a 30% reduced likelihood of testing positive for COVID-19. ²³¹ Scientists around the world are calling for more clinical trials regarding melatonin as treatment for COVID-19.²³²

Dosage: 3mg - 10mg daily for adults 20 minutes before bed; 0.5mg - 3mg for children.

²³⁰ Cleveland Clinic: https://riskcalc.org/COVID19/
QUERCETIN
Flavonoids have antiviral properties.\textsuperscript{233} Quercetin helps transport zinc into the cell. In a new study looking for agents that could bind to SARS-CoV-2 viral spike protein and inhibit its activity, researchers found quercetin was the fifth most effective of 77 agents.\textsuperscript{234, 235}

Dosage: 500mg daily (250mg with breakfast and dinner) for adults; 125mg - 250mg for children.

EPA/DHA FISH OIL
Fish or cod liver oil are natural anti-inflammatory agents which are necessary to extinguish initial immune overactivity when presented with an infectious agent.

Dosage: 1200mg - 2400 mg. daily total for adults; 600mg - 1200mg for children.

**During Inflammation and Recovery Phase, double your daily dose or take SPMs (see below).**

**If you are on blood thinners, please speak with your physician.

REDUCED GLUTATHIONE OR N-ACETYL CYSTEINE (NAC)
The glutathione pathway is critical for assuring proper oxygen efficiency without extra inflammation. Much of the human population have genetic mutations that warrant supplemental use. However, some do not have the glutathione genetic mutation (GSTP1), in which supplementation can then be harmful.

In this case especially, knowing your genetics is very important. NAC is the precursor to glutathione. Some health professionals prefer NAC to glutathione. We have always preferred glutathione in reduced form.

Dosage for NAC: 900mg through all phases for adults; speak with a pediatrician for children.

Dosage for Reduced Glutathione: 100mg - 200mg for adults; speak with a pediatrician for children.

**During Inflammation and Recovery Phases, increase glutathione to 500mg or NAC to 1800mg.

MAGNESIUM GLYCINATE
Magnesium is critical for over 300 bodily functions, but during the pandemic is most helpful for stress, anxiety, and restful sleep. Hypomagnesia, which can lead to hypokalemia, one of the pathologies of severe COVID-19, may be avoided with optimal magnesium supplementation.²³⁶

Dosage: 350mg daily for adult women; 400mg daily for adult men; 100mg - 200mg for children. Best taken upon waking and before bed.

MULTIVITAMIN/MINERAL
Foundational support to fill in other nutrient cracks as well as provide immune support.²³⁷ Some multis may contain sufficient amounts of the aforementioned nutrients.

Dosage: brand and amount is too broad to recommend here.

Supplements for Infection Phase
(at first sign of symptoms)

ANDROGRAPHIS
Andrographis is a herb with a long history of use in both Ayurveda and Traditional Chinese Medicine for treating viral infections, particularly of the upper respiratory tract, and relieving cold and flu symptoms. The bitter herb is a powerful immune modulator, down to the andrographolides in the plant which are thought to enhance the production of white blood cells, to support the release of interferon, and to promote the healthy activity of the lymphatic system.²³⁸

Dosage: 1800mg (divided equally at three meals) for adults; halve for children.

**During Prevention Phase, 200 mg is optional.

GRAPEFRUIT SEED EXTRACT
GSE oral tablet/capsule and via liquid or throat spray if symptoms begin.

Dosage: 250mg - 500 mg for adults; 125mg - 250 mg for children

**During Prevention Phase, 125mg - 250mg is optional.

**Do not take with certain heart medications, especially statins.

POTASSIUM
COVID-19 depletes potassium at an alarming rate. During infection phase, high potassium foods may not be enough. We suggest speaking with your physician before taking supplemental potassium, especially if you are on meds for hypertension or other heart-related issues.

Dosage: 99mg - 200 mg; not advised for children unless authorized by a pediatrician.

**Supplements for Escalating Inflammation and Recovery Phases**
The goal for these two phases is to stop your immune system from harming your own tissue, as well as heal enough to achieve homeostasis.

**SPECIALIZED PRO-RESOLVING MEDIATORS (SPMs)**
This anti inflammatory agent is naturally occurring in fish oil in small amounts, but you'd have to take a ton of fish oil to get what is provided in a therapeutic dose of SPM supplement. Resolvins and other SPMs stimulate clearance of debris and counter pro-inflammatory cytokine production, a process called inflammation resolution. SPMs exhibit antiviral activity at nano doses in the setting of influenza without being immunosuppressive. SPMs also promote antiviral antibodies and lymphocyte activity, highlighting their potential use in the treatment of COVID-19.

Resolvins also prevent pathological thrombosis and promote clot removal, which is emerging as a key pathology of COVID-19 infection. Thus, SPMs may promote the resolution of inflammation in COVID-19, thereby reducing acute respiratory distress syndrome (ARDS) and other life-threatening complications associated with robust viral-induced inflammation.

Dosage: 2g - 4g for adults; 1g - 2g for children (note this is grams, not milligrams).

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CURCUMIN
Not recommended for anyone who has GERD, salicylate intolerance, or is overly acidic.

Dosage: 1000mg for adults; 250mg for children.

BROMELAIN
Australian researchers are currently testing bromelain as an antiviral agent, and have found bromelain render SARS-CoV-2 spike protein inactive.\(^{240}\) Bromelain also showed to reduce SARS-CoV-2 activity in vivo.\(^{241}\) Do not use it if you have a pineapple intolerance.

Dosage: 600mg - 2400 mg for adults; 200mg - 800mg for children.

ASTAXANTHIN
Finding ways to enhance nitric oxide production may be helpful tampering inflammation by supporting ACE2 homeostasis. In lieu of intravenous nitric oxide, astaxanthin is a safe supplement.\(^{242}\)

Dosage: 8mg for adults; 4mg for children

Supplements for Sleep and Adrenal Support

RHODIOLA ROSEA
For adrenal and mood support.

Dosage: 100mg - 200 mg for adults and teens; not recommended for children.

VALERIAN ROOT, L-THEANINE, LAVELA OIL, HEMP OIL
For extra sleep assistance if melatonin is not enough. Hemp Oil should only be used if none of the other sleep supplements are effective. None of these should be used if taking sleep medication.

Dosage varies widely depending upon brand and source.


Other Integrative Therapies for COVID-19

Far Infrared Sauna Therapy (if you have at home) or sauna bathing can lower blood pressure.\(^{243}\)

Hyperbaric Oxygen Therapy is already being used in some hospitals in patients with hypoxia (lacking oxygen) and also to prevent using ventilators.\(^{244}\)

Acupuncture and Traditional Chinese Medicine\(^ {245}\) have shown success in treating symptoms of COVID-19 in or out of the hospital setting.\(^ {246}\)\(^ {247}\)

Chiropractic has been found to be particularly useful during lockdown as lack of movement has caused many more cases of back trouble.\(^ {248}\)

Ceiling fixtures emitting a safe form of ultraviolet light called far-UVC seem to be efficient at killing airborne coronaviruses.\(^ {249}\)\(^ {250}\)

Chewing gum sweetened with xylitol may have an inhibitory effect on SARS-CoV-2 as shown in cell cultures.\(^ {251}\)

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\(^ {251}\) Biorxiv. Retrieved from: https://www.biorxiv.org/content/10.1101/2020.08.19.225854v1
Mouthwash may have an inhibitory effect on SARS-CoV-2.  

Concluding Thought
One of the most honest accounts of the coronavirus saga was uttered recently by WHO official Mike Ryan: "This virus may become just another endemic virus in our communities, and this virus may never go away." SARS-CoV-2 could become a long-term fact of life that must be managed, not an enemy that can be permanently eradicated. The sooner we come to this realization, and not pine away for a "moon shot vaccine," as Mr. Ryan put it, we will be able to function as a society.

We can successfully live with SARS-CoV-2, as we have with myriad viruses, including other coronaviruses, over millennia. The best way to do that is to take better care of ourselves.

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