

COVID-19 Condition Monograph
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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

¹ Yanuck, S. F., Pizzorno, J., Messier, H., & Fitzgerald, K. N. (2020). Evidence Supporting a Phased Immuno-physiological Approach to COVID-19 From Prevention Through Recovery. *Integrative medicine* (Encinitas, Calif.), 19(Suppl 1), 8–35.

² Copaescu, A., Smibert, O., Gibson, A., Phillips, E. J., & Trubiano, J. A. (2020). The role of IL-6 and other mediators in the cytokine storm associated with SARS-CoV-2 infection. *The Journal of allergy and clinical immunology*, 146(3), 518–534.e1. <https://doi.org/10.1016/j.jaci.2020.07.001>

³ Laguna-Goya, R., Utrero-Rico, A., Talayero, P., Lasa-Lazaro, M., Ramirez-Fernandez, A., Naranjo, L., Segura-Tudela, A., Cabrera-Marante, O., Rodriguez de Frias, E., Garcia-Garcia, R., Fernández-Ruiz, M., Aguado, J. M., Martinez-Lopez, J., Lopez, E. A., Catalan, M., Serrano, A., & Paz-Artal, E. (2020). IL-6-based mortality risk model for hospitalized patients with COVID-19. *The Journal of allergy and clinical immunology*, 146(4), 799–807.e9. <https://doi.org/10.1016/j.jaci.2020.07.009>

⁴ Long, Q. X., Tang, X. J., Shi, Q. L., Li, Q., Deng, H. J., Yuan, J., Hu, J. L., Xu, W., Zhang, Y., Lv, F. J., Su, K., Zhang, F., Gong, J., Wu, B., Liu, X. M., Li, J. J., Qiu, J. F., Chen, J., & Huang, A. L. (2020). Clinical and immunological assessment of asymptomatic SARS-CoV-2 infections. *Nature medicine*, 10.1038/s41591-020-0965-6. Advance online publication. <https://doi.org/10.1038/s41591-020-0965-6>

⁵ Restivo, D. A., Centonze, D., Alesina, A., & Marchese-Ragona, R. (2020). Myasthenia Gravis Associated With SARS-CoV-2 Infection. *Annals of internal medicine*, L20-0845. Advance online publication. <https://doi.org/10.7326/L20-0845>

⁶ Koralnik, I. J., & Tyler, K. L. (2020). COVID-19: a global threat to the nervous system. *Annals of neurology*, 10.1002/ana.25807. Advance online publication. <https://doi.org/10.1002/ana.25807>

⁷ WebMD:

<https://www.webmd.com/lung/news/20200423/the-great-invader-how-covid-attacks-every-organ>

⁸ Gupta, A., Madhavan, M. V., Sehgal, K., Nair, N., Mahajan, S., Sehrawat, T. S., Bikdeli, B., Ahluwalia, N., Ausiello, J. C., Wan, E. Y., Freedberg, D. E., Kirtane, A. J., Parikh, S. A., Maurer, M. S., Nordvig, A. S., Accilli, D., Bathon, J. M., Mohan, S., Bauer, K. A., Leon, M. B., ... Landry, D. W. (2020). Extrapulmonary manifestations of COVID-19. *Nature medicine*, 26(7), 1017–1032. <https://doi.org/10.1038/s41591-020-0968-3>

⁹ Rubino, F., Amiel, S. A., Zimmet, P., Alberti, G., Bornstein, S., Eckel, R. H., Mingrone, G., Boehm, B., Cooper, M. E., Chai, Z., Del Prato, S., Ji, L., Hopkins, D., Herman, W. H., Khunti, K., Mbanya, J. C., & Renard, E. (2020). New-Onset Diabetes in Covid-19. *The New England journal of medicine*, 10.1056/NEJMc2018688. Advance online publication. <https://doi.org/10.1056/NEJMc2018688>

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.^{10 11 12 13 14}

Pathophysiology

Exposure to SARS-CoV-2 occurs most frequently through the air, in respiratory droplets or aerosolized particles.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.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.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

¹⁰ Carfi, A., Bernabei, R., Landi, F., & Gemelli Against COVID-19 Post-Acute Care Study Group (2020). Persistent Symptoms in Patients After Acute COVID-19. *JAMA*, 10.1001/jama.2020.12603. Advance online publication. <https://doi.org/10.1001/jama.2020.12603>

¹¹ Tenforde, M. W., Kim, S. S., Lindsell, C. J., Billig Rose, E., Shapiro, N. I., Files, D. C., Gibbs, K. W., Erickson, H. L., Steingrub, J. S., Smithline, H. A., Gong, M. N., Aboodi, M. S., Exline, M. C., Henning, D. J., Wilson, J. G., Khan, A., Qadir, N., Brown, S. M., Peltan, I. D., Rice, T. W., ... IVY Network Investigators (2020). Symptom Duration and Risk Factors for Delayed Return to Usual Health Among Outpatients with COVID-19 in a Multistate Health Care Systems Network - United States, March-June 2020. *MMWR. Morbidity and mortality weekly report*, 69(30), 993–998. <https://doi.org/10.15585/mmwr.mm6930e1>

¹² Townsend, L., Dyer, A. H., Jones, K., Dunne, J., Mooney, A., Gaffney, F., O'Connor, L., Leavy, D., O'Brien, K., Dowds, J., Sugrue, J. A., Hopkins, D., Martin-Loeches, I., Ni Cheallaigh, C., Nadarajan, P., McLaughlin, A. M., Bourke, N. M., Bergin, C., O'Farrelly, C., Bannan, C., ... Conlon, N. (2020). Persistent fatigue following SARS-CoV-2 infection is common and independent of severity of initial infection. *PLoS one*, 15(11), e0240784. <https://doi.org/10.1371/journal.pone.0240784>

¹³ Medrxiv. Retrieved from: <https://www.medrxiv.org/content/10.1101/2020.10.19.20214494v1.full.pdf>

¹⁴ Medrxiv. Retrieved from: <https://www.medrxiv.org/content/10.1101/2020.10.14.20212555v1>

¹⁵ CDC.gov. Retrieved from:

<https://www.cdc.gov/coronavirus/2019-ncov/prevent-getting-sick/how-covid-spreads.html>

¹⁶ Transmission of SARS-CoV-2: Implications for infection prevention precautions. (n.d.). Retrieved July 28, 2020, from

<https://www.who.int/news-room/commentaries/detail/transmission-of-sars-cov-2-implications-for-infection-prevention-precautions>

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.^{18 19}

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.^{20 21}

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."^{22 23} 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.²⁴

¹⁸ Gupta, A., Madhavan, M. V., Sehgal, K., Nair, N., Mahajan, S., Sehrawat, T. S., Bikdeli, B., Ahluwalia, N., Ausiello, J. C., Wan, E. Y., Freedberg, D. E., Kirtane, A. J., Parikh, S. A., Maurer, M. S., Nordvig, A. S., Accilli, D., Bathon, J. M., Mohan, S., Bauer, K. A., Leon, M. B., ... Landry, D. W. (2020).

Extrapulmonary manifestations of COVID-19. *Nature medicine*, 26(7), 1017–1032.

<https://doi.org/10.1038/s41591-020-0968-3>

¹⁹ Libby, P., & Lüscher, T. (2020). COVID-19 is, in the end, an endothelial disease. *European heart journal*, 41(32), 3038–3044. <https://doi.org/10.1093/eurheartj/ehaa623>

²⁰ Remy, K. E., Mazer, M., Striker, D. A., Ellebedy, A. H., Walton, A. H., Unsinger, J., Blood, T. M., Mudd, P. A., Yi, D. J., Mannion, D. A., Osborne, D. F., Martin, R. S., Anand, N. J., Bosanquet, J. P., Blood, J., Drewry, A. M., Caldwell, C. C., Turnbull, I. R., Brakenridge, S. C., Moldwauer, L. L., ... Hotchkiss, R. S. (2020). Severe immunosuppression and not a cytokine storm characterizes COVID-19 infections. *JCI insight*, 5(17), 140329. <https://doi.org/10.1172/jci.insight.140329>

²¹ Laterre, P. F., François, B., Collienne, C., Hantson, P., Jeannet, R., Remy, K. E., & Hotchkiss, R. S. (2020). Association of Interleukin 7 Immunotherapy With Lymphocyte Counts Among Patients With Severe Coronavirus Disease 2019 (COVID-19). *JAMA network open*, 3(7), e2016485.

<https://doi.org/10.1001/jamanetworkopen.2020.16485>

²² Medrxiv. Retrieved from: <https://www.medrxiv.org/content/10.1101/2020.10.21.20216192v2>

²³ Woodruff, M. C., Ramonell, R. P., Nguyen, D. C., Cashman, K. S., Saini, A. S., Haddad, N. S., Ley, A. M., Kyu, S., Howell, J. C., Ozturk, T., Lee, S., Suryadevara, N., Case, J. B., Bugrovsky, R., Chen, W., Estrada, J., Morrison-Porter, A., Derrico, A., Anam, F. A., Sharma, M., ... Sanz, I. (2020). Extrafollicular B cell responses correlate with neutralizing antibodies and morbidity in COVID-19. *Nature immunology*, 10.1038/s41590-020-00814-z. Advance online publication. <https://doi.org/10.1038/s41590-020-00814-z>

²⁴ Garvin, M. R., Alvarez, C., Miller, J. I., Prates, E. T., Walker, A. M., Amos, B. K., Mast, A. E., Justice, A., Aronow, B., & Jacobson, D. (2020). A mechanistic model and therapeutic interventions for COVID-19 involving a RAS-mediated bradykinin storm. *eLife*, 9, e59177. <https://doi.org/10.7554/eLife.59177>

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 obesity²⁵ (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.²⁶ Being overweight (body mass index [BMI] between 25 and 30) has also been found to increase risk.²⁷ Cigarette smoking and electronic cigarette use, especially in young persons, greatly increases risk.^{28 29}

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 risk³⁰), 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.³¹

According to the CDC, the older you get, the greater the risk.³² 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

²⁵ Morbidity and Mortality Weekly Report:

https://www.cdc.gov/mmwr/volumes/69/wr/mm6915e3.htm?s_cid=mm6915e3_w

²⁶ Rebello, C. J., Kirwan, J. P., & Greenway, F. L. (2020). Obesity, the most common comorbidity in SARS-CoV-2: is leptin the link?. *International journal of obesity* (2005), 1–8. Advance online publication. <https://doi.org/10.1038/s41366-020-0640-5>

²⁷ Centers for Disease Control. Retrieved from:

<https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html>

²⁸ Medrxiv. Retrieved from: <https://www.medrxiv.org/content/10.1101/2020.09.22.20199802v1>

²⁹ Gaiha, S. M., Cheng, J., & Halpern-Felsher, B. (2020). Association Between Youth Smoking, Electronic Cigarette Use, and Coronavirus Disease 2019. *The Journal of adolescent health : official publication of the Society for Adolescent Medicine*, 67(4), 519–523. Advance online publication. <https://doi.org/10.1016/j.jadohealth.2020.07.002>

³⁰ Baral, R., White, M., & Vassiliou, V. S. (2020). Effect of Renin-Angiotensin-Aldosterone System Inhibitors in Patients with COVID-19: a Systematic Review and Meta-analysis of 28,872 Patients. *Current atherosclerosis reports*, 22(10), 61. <https://doi.org/10.1007/s11883-020-00880-6>

³¹ Centers for Disease Control. Retrieved from:

https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fcoronavirus%2F2019-ncov%2Fneed-extra-precautions%2Fgroups-at-higher-risk.html

³² Centers for Disease Control: Retrieved from:

<https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/older-adults.html>

purpose of inducing death in cells that have been hijacked by SARS-CoV-2.³³ In addition, the absence of a vigorous CD8⁺ T cell immune response in the elderly is indicated.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.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.³⁶ Non-whites were at higher risk of dying than white patients.³⁷

Other risk factors include ApoE4 gene variant³⁸, ACE2 gene variant³⁹, blood type ‘A’^{40 41 42 43}, exposure to higher SARS-CoV-2 viral load⁴⁴, impaired glutathione function (GSTP1 variant)⁴⁵,

³³ Cunningham, L., Simmonds, P., Kimber, I., Basketter, D. A., & McFadden, J. P. (2020). Perforin and resistance to SARS coronavirus 2. *The Journal of allergy and clinical immunology*, 146(1), 52–53. <https://doi.org/10.1016/j.jaci.2020.05.007>

³⁴ Biorxiv. Retrieved from: <https://www.biorxiv.org/content/10.1101/2020.08.21.262329v1>

³⁵ Medrxiv. Retrieved from: <https://www.medrxiv.org/content/10.1101/2020.07.30.20164921v2>

³⁶ Gadi, N., Wu, S. C., Spihlman, A. P., & Moulton, V. R. (2020). What's Sex Got to Do With COVID-19? Gender-Based Differences in the Host Immune Response to Coronaviruses. *Frontiers in immunology*, 11, 2147. <https://doi.org/10.3389/fimmu.2020.02147>

³⁷ Williamson, E. J., Walker, A. J., Bhaskaran, K., Bacon, S., Bates, C., Morton, C. E., Curtis, H. J., Mehrkar, A., Evans, D., Inglesby, P., Cockburn, J., McDonald, H. I., MacKenna, B., Tomlinson, L., Douglas, I. J., Rentsch, C. T., Mathur, R., Wong, A., Grieve, R., Harrison, D., ... Goldacre, B. (2020). OpenSAFELY: factors associated with COVID-19 death in 17 million patients. *Nature*, 10.1038/s41586-020-2521-4. Advance online publication. <https://doi.org/10.1038/s41586-020-2521-4>

³⁸ Kuo, C. L., Pilling, L. C., Atkins, J. L., Masoli, J., Delgado, J., Kuchel, G. A., & Melzer, D. (2020). APOE e4 genotype predicts severe COVID-19 in the UK Biobank community cohort. *The journals of gerontology. Series A, Biological sciences and medical sciences*, glaa131. Advance online publication. <https://doi.org/10.1093/gerona/glaa131>

³⁹ Nicin, L., Abplanalp, W. T., Mellentin, H., Kattih, B., Tombor, L., John, D., Schmitto, J. D., Heineke, J., Emrich, F., Arsalan, M., Holubec, T., Walther, T., Zeiher, A. M., & Dimmeler, S. (2020). Cell type-specific expression of the putative SARS-CoV-2 receptor ACE2 in human hearts. *European heart journal*, 41(19), 1804–1806. <https://doi.org/10.1093/eurheartj/ehaa311>

⁴⁰ Ellinghaus, D., Degenhardt, F., Bujanda, L., Buti, M., Albillos, A., Invernizzi, P., Fernández, J., Prati, D., Baselli, G., Asselta, R., Grimsrud, M. M., Milani, C., Aziz, F., Kässens, J., May, S., Wendorff, M., Wienbrandt, L., Uellendahl-Werth, F., Zheng, T., Yi, X., ... Severe Covid-19 GWAS Group (2020). Genomewide Association Study of Severe Covid-19 with Respiratory Failure. *The New England journal of medicine*, 10.1056/NEJMoa2020283. Advance online publication. <https://doi.org/10.1056/NEJMoa2020283>

⁴¹ Medrxiv. Retrieved from: <https://www.medrxiv.org/content/10.1101/2020.07.12.20152074v1>

⁴² Medrxiv. Retrieved from: <https://www.medrxiv.org/content/10.1101/2020.11.05.20226100v1>

⁴³ Hoiland, R. L., Fergusson, N. A., Mitra, A. R., Griesdale, D., Devine, D. V., Stukas, S., Cooper, J., Thiara, S., Foster, D., Chen, L., Lee, A., Conway, E. M., Wellington, C. L., & Sekhon, M. S. (2020). The association of ABO blood group with indices of disease severity and multiorgan dysfunction in COVID-19. *Blood advances*, 4(20), 4981–4989. <https://doi.org/10.1182/bloodadvances.2020002623>

⁴⁴ Medrxiv. Retrieved from: <https://www.medrxiv.org/content/10.1101/2020.10.03.20206110v4>

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>

and stress.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.^{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.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.⁵⁰

The clearest indicator that one has COVID-19 is loss of taste and/or smell.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.⁵²

⁴⁶ Shields, G. S., Spahr, C. M., & Slavich, G. M. (2020). Psychosocial Interventions and Immune System Function: A Systematic Review and Meta-analysis of Randomized Clinical Trials. *JAMA psychiatry*, 10.1001/jamapsychiatry.2020.0431. Advance online publication.

<https://doi.org/10.1001/jamapsychiatry.2020.0431>

⁴⁷ Almario, C., Chey, W. & Spiegel, B. (2020). Increased Risk of COVID-19 Among Users of Proton Pump Inhibitors. Retrieved from:

[https://journals.lww.com/ajg/Documents/AJG-20-1811_R1\(PUBLISH%20AS%20WEBPART\).pdf](https://journals.lww.com/ajg/Documents/AJG-20-1811_R1(PUBLISH%20AS%20WEBPART).pdf)

⁴⁸ Kow, C. S., & Hasan, S. S. (2020). Use of proton pump inhibitors and risk of adverse clinical outcomes from COVID-19: a meta-analysis. *Journal of internal medicine*, 10.1111/joim.13183. Advance online publication. <https://doi.org/10.1111/joim.13183>

⁴⁹ Centers for Disease Control:

<https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html>

⁵⁰ Scully, E.P., Haverfield, J., Ursin, R.L. et al. (2020). Considering how biological sex impacts immune responses and COVID-19 outcomes. *Nature Reviews Immunology*, <https://doi.org/10.1038/s41577-020-0348-8>

⁵¹ Medrxiv. Retrieved from: <https://www.medrxiv.org/content/10.1101/2020.07.22.20157263v1>

⁵² Menni, C., Valdes, A. M., Freidin, M. B., Sudre, C. H., Nguyen, L. H., Drew, D. A., Ganesh, S., Varsavsky, T., Cardoso, M. J., El-Sayed Moustafa, J. S., Visconti, A., Hysi, P., Bowyer, R., Mangino, M., Falchi, M., Wolf, J., Ourselin, S., Chan, A. T., Steves, C. J., & Spector, T. D. (2020). Real-time tracking of self-reported symptoms to predict potential COVID-19. *Nature medicine*, 10.1038/s41591-020-0916-2. Advance online publication. <https://doi.org/10.1038/s41591-020-0916-2>

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>

⁵⁴ Mueller, A. L., McNamara, M. S., & Sinclair, D. A. (2020). Why does COVID-19 disproportionately affect older people?. *Aging*, 12(10), 9959–9981. <https://doi.org/10.18632/aging.103344>

⁵⁵ Davies, N. G., Klepac, P., Liu, Y., Prem, K., Jit, M., CMMID COVID-19 working group, & Eggo, R. M. (2020). Age-dependent effects in the transmission and control of COVID-19 epidemics. *Nature medicine*, 10.1038/s41591-020-0962-9. Advance online publication. <https://doi.org/10.1038/s41591-020-0962-9>

⁵⁶ Medrxiv. Retrieved from: <https://www.medrxiv.org/content/10.1101/2020.08.17.20161760v1>

⁵⁷ Afshar, Y., Gaw, S. L., Flaherman, V. J., Chambers, B. D., Krakow, D., Berghella, V., Shamshirsaz, A. A., Boatman, A. A., Aldrovandi, G., Greiner, A., Riley, L., Boscardin, W. J., Jamieson, D. J., & Jacoby, V. L. (2020). Clinical Presentation of Coronavirus Disease 2019 (COVID-19) in Pregnant and Recently Pregnant People. *Obstetrics and gynecology*, 10.1097/AOG.0000000000004178. Advance online publication. <https://doi.org/10.1097/AOG.0000000000004178>

⁵⁸ <https://www.medrxiv.org/content/10.1101/2020.08.20.20178657v1>

⁵⁹ Dumitriu, D., Emeruwa, U. N., Hanft, E., Liao, G. V., Ludwig, E., Walzer, L., Arditi, B., Saslaw, M., Andrikopoulou, M., Scripps, T., Baptiste, C., Khan, A., Breslin, N., Rubenstein, D., Simpson, L. L., Kyle, M. H., Friedman, A. M., Hirsch, D. S., Miller, R. S., Fernández, C. R., ... Gyamfi-Bannerman, C. (2020). Outcomes of Neonates Born to Mothers With Severe Acute Respiratory Syndrome Coronavirus 2

protective properties in placental tissue.⁶⁰ The Centers for Disease Control suggests there is increased risk for severe illness.⁶¹ In nursing women, SARS-CoV-2 has not shown to be transmitted to infants.⁶² ⁶³ Alternatively, one study has shown protected antibodies were transmitted from an infected mother to her infant.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.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-19.⁶⁹ Guangzhou Institute of Respiratory Health created a calculation tool for predicting critically ill COVID-19 at admission.
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

Infection at a Large Medical Center in New York City. *JAMA pediatrics*, e204298. Advance online publication. <https://doi.org/10.1001/jamapediatrics.2020.4298>

⁶⁰ Taglauer, E., Benarroch, Y., Rop, K., Barnett, E., Sabharwal, V., Yarrington, C., & Wachman, E. M. (2020). Consistent localization of SARS-CoV-2 spike glycoprotein and ACE2 over TMPRSS2 predominance in placental villi of 15 COVID-19 positive maternal-fetal dyads. *Placenta*, 100, 69–74. Advance online publication. <https://doi.org/10.1016/j.placenta.2020.08.015>

⁶¹ The Centers for Disease Control. Retrieved from:

https://www.cdc.gov/mmwr/volumes/69/wr/mm6944e3.htm?s_cid=mm6944e3_w

⁶² Chambers, C., Krogstad, P., Bertrand, K., Contreras, D., Tobin, N. H., Bode, L., & Aldrovandi, G. (2020). Evaluation for SARS-CoV-2 in Breast Milk From 18 Infected Women. *JAMA*, e2015580. Advance online publication. <https://doi.org/10.1001/jama.2020.15580>

⁶³ Flaherman, V. J., Afshar, Y., Boscardin, J., Keller, R. L., Mardy, A., Prah, M. K., Phillips, C., Asiodu, I. V., Berghella, W. V., Chambers, B. D., Crear-Perry, J., Jamieson, D. J., Jacoby, V. L., & Gaw, S. L. (2020). Infant Outcomes Following Maternal Infection with SARS-CoV-2: First Report from the PRIORITY Study. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*, ciaa1411. Advance online publication. <https://doi.org/10.1093/cid/ciaa1411>

⁶⁴ Medrxiv. Retrieved from: <https://www.medrxiv.org/content/10.1101/2020.08.18.20176743v1>

⁶⁵ Fox, A., Marino, J., Amanat, F., Krammer, F., Hahn-Holbrook, J., Zolla-Pazner, S., & Powell, R. L. (2020). Robust and Specific Secretory IgA Against SARS-CoV-2 Detected in Human Milk. *iScience*, 23(11), 101735. <https://doi.org/10.1016/j.isci.2020.101735>

⁶⁶ Medrxiv. Retrieved from: <https://www.medrxiv.org/content/10.1101/2020.07.09.20149534v1>

⁶⁷ Medrxiv. Retrieved from: <https://www.medrxiv.org/content/10.1101/2020.04.16.20067835v1>

⁶⁸ FDA.gov. Retrieved from:

<https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-issues-emergency-use-authorization-yale-school-public-health>

⁶⁹ Centers for Disease Control: <https://www.cdc.gov/coronavirus/2019-nCoV/hcp/clinical-criteria.html>

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%.⁷¹

Aside from a positive test for active infection, a full blood workup including CBC (looking for elevated neutrophil count⁷² and lymphocyte count below 1000⁷³), Chem Screen, C-reactive protein (elevated level is an indicator)⁷⁴, D-Dimer (elevated level is an indicator)⁷⁵, and 25(OH)D especially below 30 ng/mL⁷⁶ 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 TNF α can also be helpful for diagnosing who may be more susceptible to the cytokine storm.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.^{78 79}

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

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>

⁷² Medrxiv. Retrieved from: <https://www.medrxiv.org/content/10.1101/2020.07.08.20141218v1>

⁷³ Wagner, J., DuPont, A., Larson, S., Cash, B., & Farooq, A. (2020). Absolute lymphocyte count is a prognostic marker in Covid-19: A retrospective cohort review. *International Journal of Laboratory Hematology*, 1–5. <https://doi.org/10.1111/ijlh.13288>

⁷⁴ Medrxiv. Retrieved from: <https://www.medrxiv.org/content/10.1101/2020.10.26.20219360v1>

⁷⁵ Medrxiv. Retrieved from: <https://www.medrxiv.org/content/10.1101/2020.06.24.20139600v1>

⁷⁶ Rhodes, J. M., Subramanian, S., Laird, E., & Kenny, R. A. (2020). Editorial: low population mortality from COVID-19 in countries south of latitude 35 degrees North supports vitamin D as a factor determining severity. *Alimentary pharmacology & therapeutics*, 51(12), 1434–1437. <https://doi.org/10.1111/apt.15777>

⁷⁷ Medrxiv. Retrieved from: <https://www.medrxiv.org/content/10.1101/2020.07.17.20155242v1>

⁷⁸ Bernheim, A., Mei, X., Huang, M., Yang, Y., Fayad, Z. A., Zhang, N., Diao, K., Lin, B., Zhu, X., Li, K., Li, S., Shan, H., Jacobi, A., & Chung, M. (2020). Chest CT Findings in Coronavirus Disease-19 (COVID-19): Relationship to Duration of Infection. *Radiology*, 295(3), 200463. <https://doi.org/10.1148/radiol.2020200463>

⁷⁹ Czawlytko, C., Hossain, R., White, C.S. (2020). COVID-19 Diagnostic Imaging Recommendations. *Applied Radiology*, 49(3):10-15.

⁸⁰ Medscape: <https://www.medscape.com/viewarticle/930223>

⁸¹ Feldstein, L. R., Rose, E. B., Horwitz, S. M., Collins, J. P., Newhams, M. M., Son, M., Newburger, J. W., Kleinman, L. C., Heidemann, S. M., Martin, A. A., Singh, A. R., Li, S., Tarquinio, K. M., Jaggi, P., Oster, M. E., Zackai, S. P., Gillen, J., Ratner, A. J., Walsh, R. F., Fitzgerald, J. C., ... Randolph, A. G. (2020). 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.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.⁸³ However, antibodies were not detectable in everyone exposed to the virus.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.⁸⁵

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.⁸⁶

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

⁸² Varatharaj, A., Thomas, N., Ellul, M. A., Davies, N., Pollak, T. A., Tenorio, E. L., Sultan, M., Easton, A., Breen, G., Zandi, M., Coles, J. P., Manji, H., Al-Shahi Salman, R., Menon, D. K., Nicholson, T. R., Benjamin, L. A., Carson, A., Smith, C., Turner, M. R., Solomon, T., ... CoroNerve Study Group (2020). Neurological and neuropsychiatric complications of COVID-19 in 153 patients: a UK-wide surveillance study. *The Lancet. Psychiatry*, S2215-0366(20)30287-X. Advance online publication. [https://doi.org/10.1016/S2215-0366\(20\)30287-X](https://doi.org/10.1016/S2215-0366(20)30287-X)

⁸³ Biorxiv. Retrieved from: <https://www.biorxiv.org/content/10.1101/2020.11.01.362319v1>

⁸⁴ Medrxiv. Retrieved from: <https://www.medrxiv.org/content/10.1101/2020.06.07.20124636v2>

⁸⁵ Long, Q. X., Tang, X. J., Shi, Q. L., Li, Q., Deng, H. J., Yuan, J., Hu, J. L., Xu, W., Zhang, Y., Lv, F. J., Su, K., Zhang, F., Gong, J., Wu, B., Liu, X. M., Li, J. J., Qiu, J. F., Chen, J., & Huang, A. L. (2020). Clinical and immunological assessment of asymptomatic SARS-CoV-2 infections. *Nature medicine*, 10.1038/s41591-020-0965-6. Advance online publication. <https://doi.org/10.1038/s41591-020-0965-6>

⁸⁶ Scientific American. Retrieved from:

<https://www.scientificamerican.com/article/for-covid-drugs-months-of-frantic-development-lead-to-few-outright-successes/>

⁸⁷ Yanuck, S. F., Pizzorno, J., Messier, H., & Fitzgerald, K. N. (2020). Evidence Supporting a Phased Immuno-physiological Approach to COVID-19 From Prevention Through Recovery. *Integrative medicine (Encinitas, Calif.)*, 19(Suppl 1), 8–35.

For example, in addition to the World Health Organization protocol⁸⁸, 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.^{89 90 91} China uses a combination of conventional medicine and Chinese medicine. Greece has found the older anti-inflammatory drug colchicine helpful.⁹² Pakistan found tocilizumab to be effective and economical, yet several studies in the United States has not found it to be effective.⁹³ 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.⁹⁴

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.⁹⁵ 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-19.⁹⁶ 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.^{97 98 99 100} Other hospitals used the

⁸⁸ Lamontagne, F., Agoritsas, T., Macdonald, H., Leo, Y. S., Diaz, J., Agarwal, A., Appiah, J. A., Arabi, Y., Blumberg, L., Calfee, C. S., Cao, B., Cecconi, M., Cooke, G., Dunning, J., Geduld, H., Gee, P., Manai, H., Hui, D. S., Kanda, S., Kawano-Dourado, L., ... Vandvik, P. O. (2020). A living WHO guideline on drugs for covid-19. *BMJ (Clinical research ed.)*, 370, m3379. <https://doi.org/10.1136/bmj.m3379>

⁸⁹ Medrxiv. Retrieved from: <https://www.medrxiv.org/content/10.1101/2020.06.22.20133413v1>

⁹⁰ Medrxiv. Retrieved from: <https://www.medrxiv.org/content/10.1101/2020.07.20.20157503v1>

⁹¹ Thibault, R., Coëffier, M., Joly, F., Bohé, J., Schneider, S. M., & Déchelotte, P. (2020). How the Covid-19 epidemic is challenging our practice in clinical nutrition-feedback from the field. *European journal of clinical nutrition*, 1–10. Advance online publication. <https://doi.org/10.1038/s41430-020-00757-6>

⁹² Deftereos, S. G., Giannopoulos, G., Vrachatis, D. A., Siasos, G. D., Giotaki, S. G., Gargalianos, P., Metallidis, S., Sianos, G., Baltagiannis, S., Panagopoulos, P., Dolianitis, K., Randou, E., Syrigos, K., Kotanidou, A., Koulouris, N. G., Milionis, H., Sipsas, N., Gogos, C., Tsoukalas, G., Olympios, C. D., ... GRECCO-19 investigators (2020). Effect of Colchicine vs Standard Care on Cardiac and Inflammatory Biomarkers and Clinical Outcomes in Patients Hospitalized With Coronavirus Disease 2019: The GRECCO-19 Randomized Clinical Trial. *JAMA network open*, 3(6), e2013136. <https://doi.org/10.1001/jamanetworkopen.2020.13136>

<https://doi.org/10.1001/jamanetworkopen.2020.13136>

⁹³ Medrxiv. Retrieved from: <https://www.medrxiv.org/content/10.1101/2020.06.23.20134072v1>

⁹⁴ Clinicaltrials.gov. Retrieved from: <https://www.clinicaltrials.gov/ct2/show/NCT04311697>

⁹⁵ Medrxiv. Retrieved from: <https://www.medrxiv.org/content/10.1101/2020.06.29.20141283v1>

⁹⁶ Medrxiv. Retrieved from: <https://www.medrxiv.org/content/10.1101/2020.11.19.20234153v1>

⁹⁷ National Institutes of Health: <https://www.covid19treatmentguidelines.nih.gov/whats-new/>

⁹⁸ Spinner, C. D., Gottlieb, R. L., Criner, G. J., Arribas López, J. R., Cattelan, A. M., Soriano Viladomiu, A., Ogbuagu, O., Malhotra, P., Mullane, K. M., Castagna, A., Chai, L., Roestenberg, M., Tsang, O., Bernasconi, E., Le Turnier, P., Chang, S. C., SenGupta, D., Hyland, R. H., Osinusi, A. O., Cao, H., ... GS-US-540-5774 Investigators (2020). Effect of Remdesivir vs Standard Care on Clinical Status at 11 Days in Patients With Moderate COVID-19: A Randomized Clinical Trial. *JAMA*, 324(11), 1048–1057. <https://doi.org/10.1001/jama.2020.16349>

⁹⁹ Medrxiv. Retrieved from: <https://www.medrxiv.org/content/10.1101/2020.11.05.20226373v1>

¹⁰⁰ Medrxiv. Retrieved from: <https://www.medrxiv.org/content/10.1101/2020.10.15.20209817v1.full.pdf>

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.^{101 102 103 104 105} Anti-inflammatories, especially steroids, have been confirmed as successful treatments in most cases, especially if the patient shows elevated C-reactive protein level.^{106 107} 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.¹⁰⁸ Recent data suggests an antiparasitic called ivermectin has been shown to inhibit replication of SARS-CoV-2.^{109 110} 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.¹¹¹ Researchers purport that the commonly used medication Heparin could be used as an intervention for excessive clotting.¹¹² 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

¹⁰¹ Medrxiv. Retrieved from: <https://www.medrxiv.org/content/10.1101/2020.08.16.20175752v1>

¹⁰² Medrxiv. Retrieved from: <https://www.medrxiv.org/content/10.1101/2020.09.09.20184143v1>

¹⁰³ COVID-19 RISK and Treatments (CORIST) Collaboration members: (2020). Use of hydroxychloroquine in hospitalised COVID-19 patients is associated with reduced mortality: Findings from the observational multicentre Italian CORIST study. *European journal of internal medicine*, S0953-6205(20)30335-6. Advance online publication. <https://doi.org/10.1016/j.ejim.2020.08.019>

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>

¹⁰⁶ Keller, M. J., Kitsis, E. A., Arora, S., Chen, J., Agarwal, S., Ross, M. J., . . . Southern, W. (2020). Effect of Systemic Glucocorticoids on Mortality or Mechanical Ventilation in Patients With COVID-19. *Journal of Hospital Medicine*, (2020-07-22 ONLINE FIRST). doi:10.12788/jhm.3497

¹⁰⁷ WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group, Sterne, J., Murthy, S., Diaz, J. V., Slutsky, A. S., Villar, J., Angus, D. C., Annane, D., Azevedo, L., Berwanger, O., Cavalcanti, A. B., Dequin, P. F., Du, B., Emberson, J., Fisher, D., Giraudeau, B., Gordon, A. C., Granholm, A., Green, C., Haynes, R., . . . Marshall, J. C. (2020). Association Between Administration of Systemic Corticosteroids and Mortality Among Critically Ill Patients With COVID-19: A Meta-analysis. *JAMA*, 10.1001/jama.2020.17023. Advance online publication. <https://doi.org/10.1001/jama.2020.17023>

¹⁰⁸ University of Oxford. Retrieved from:

<https://www.recoverytrial.net/news/low-cost-dexamethasone-reduces-death-by-up-to-one-third-in-hospitalised-patients-with-severe-respiratory-complications-of-covid-19>

¹⁰⁹ Bray, M., Rayner, C., Noël, F., Jans, D., & Wagstaff, K. (2020). Ivermectin and COVID-19: A report in *Antiviral Research*, widespread interest, an FDA warning, two letters to the editor and the authors' responses. *Antiviral research*, 178, 104805. Advance online publication. <https://doi.org/10.1016/j.antiviral.2020.104805>

¹¹⁰ Medrxiv. Retrieved from: <https://www.medrxiv.org/content/10.1101/2020.10.29.20222661v1>

¹¹¹ Gao, C., Cai, Y., Zhang, K., Zhou, L., Zhang, Y., Zhang, X., Li, Q., Li, W., Yang, S., Zhao, X., Zhao, Y., Wang, H., Liu, Y., Yin, Z., Zhang, R., Wang, R., Yang, M., Hui, C., Wijns, W., McEvoy, J. W., . . . Li, F. (2020). Association of hypertension and antihypertensive treatment with COVID-19 mortality: a retrospective observational study. *European heart journal*, 41(22), 2058–2066. <https://doi.org/10.1093/eurheartj/ehaa433>

¹¹² Kim, S. Y., Jin, W., Sood, A., Montgomery, D. W., Grant, O. C., Fuster, M. M., Fu, L., Dordick, J. S., Woods, R. J., Zhang, F., & Linhardt, R. J. (2020). Characterization of heparin and severe acute respiratory syndrome-related coronavirus 2 (SARS-CoV-2) spike glycoprotein binding interactions. *Antiviral research*, 181, 104873. Advance online publication. <https://doi.org/10.1016/j.antiviral.2020.104873>

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-1 β 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

¹¹³ Food and Drug Administration. Retrieved from:

https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-monoclonal-antibody-treatment-covid-19?utm_medium=email&utm_source=govdelivery

¹¹⁴ Tomazini, B. M., Maia, I. S., Cavalcanti, A. B., Berwanger, O., Rosa, R. G., Veiga, V. C., Avezum, A., Lopes, R. D., Bueno, F. R., Silva, M., Baldassare, F. P., Costa, E., Moura, R., Honorato, M. O., Costa, A. N., Damiani, L. P., Lisboa, T., Kawano-Dourado, L., Zampieri, F. G., Olivato, G. B., ... COALITION COVID-19 Brazil III Investigators (2020). Effect of Dexamethasone on Days Alive and Ventilator-Free in Patients With Moderate or Severe Acute Respiratory Distress Syndrome and COVID-19: The CoDEX Randomized Clinical Trial. *JAMA*, 324(13), 1307–1316. <https://doi.org/10.1001/jama.2020.17021>

¹¹⁵ Elharrar, X., Trigui, Y., Dols, A. M., Touchon, F., Martinez, S., Prud'homme, E., & Papazian, L. (2020). Use of Prone Positioning in Nonintubated Patients With COVID-19 and Hypoxemic Acute Respiratory Failure. *JAMA*, 323(22), 2336–2338. Advance online publication. <https://doi.org/10.1001/jama.2020.8255>

¹¹⁶ Medrxiv. Retrieved from: <https://www.medrxiv.org/content/10.1101/2020.05.08.20095471v1>

¹¹⁷ Medrxiv. Retrieved from: <https://www.medrxiv.org/content/10.1101/2020.07.23.20160796v1>

¹¹⁸ Medrxiv. Retrieved from: <https://www.medrxiv.org/content/10.1101/2020.09.21.20199109v2>

¹¹⁹ Schett, G., Manger, B., Simon, D., & Caporali, R. (2020). COVID-19 revisiting inflammatory pathways of arthritis. *Nature reviews rheumatology* (2020). <https://doi.org/10.1038/s41584-020-0451-z>

¹²⁰ van de Veerdonk, F. L., & Netea, M. G. (2020). Blocking IL-1 to prevent respiratory failure in COVID-19. *Critical care (London, England)*, 24(1), 445. <https://doi.org/10.1186/s13054-020-03166-0>

¹²¹ Del Valle, D. M., Kim-Schulze, S., Hsin-Hui, H., Beckmann, N. D., Nirenberg, S., Wang, B., Lavin, Y., Swartz, T., Madduri, D., Stock, A., Marron, T., Xie, H., Patel, M. K., van Oekelen, O., Rahman, A., Kovatch, P., Aberg, J., Schadt, E., Jagannath, S., Mazumdar, M., ... Gnjatic, S. (2020). An inflammatory cytokine signature helps predict COVID-19 severity and death. *medRxiv : the preprint server for health sciences*, 2020.05.28.20115758. <https://doi.org/10.1101/2020.05.28.20115758>

ameliorate the cytokine storm.^{122 123} 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.^{124 125}

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.¹²⁶ Richard Bartlett, MD has found success using the nebulized corticosteroid budesonide (pulmicort), macrolide antibiotic, low dose aspirin, and zinc.¹²⁷

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.¹²⁸ The Centers for Disease Control has also stated that hospital readmission for lingering COVID-19 symptoms is more common than desired.¹²⁹

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

¹²² Biorxiv. Retrieved from: <https://www.biorxiv.org/content/10.1101/2020.07.18.210161v1>

¹²³ Annweiler, G., Corvaisier, M., Gautier, J., Dubée, V., Legrand, E., Sacco, G., & Annweiler, C. (2020). Vitamin D Supplementation Associated to Better Survival in Hospitalized Frail Elderly COVID-19 Patients: The GERIA-COVID Quasi-Experimental Study. *Nutrients*, 12(11), E3377. <https://doi.org/10.3390/nu12113377>

¹²⁴ Hernández, J. L., Nan, D., Fernandez-Ayala, M., García-Unzueta, M., Hernández-Hernández, M. A., López-Hoyos, M., Muñoz-Cacho, P., Olmos, J. M., Gutiérrez-Cuadra, M., Ruiz-Cubillán, J. J., Crespo, J., & Martínez-Taboada, V. M. (2020). Vitamin D Status in Hospitalized Patients with SARS-CoV-2 Infection. *The Journal of clinical endocrinology and metabolism*, dgaa733. Advance online publication. <https://doi.org/10.1210/clinem/dgaa733>

¹²⁵ Medrxiv. Retrieved from: <https://www.medrxiv.org/content/10.1101/2020.06.05.20123554v3?%253fcollection=>

¹²⁶ Critical Care COVID-19 Protocol. Retrieved from: https://www.evms.edu/media/evms_public/departments/internal_medicine/Marik-Covid-Protocol-Summary.pdf

¹²⁷ SARS-CoV-2 and The Case for Empirical Treatment. Retrieved: <https://americacanwetalk.org/wp-content/uploads/2020/07/ColumnByDrBartlettReCOVID-5.pdf>

¹²⁸ Symptom Duration and Risk Factors for Delayed Return to Usual Health Among Outpatients with COVID-19 in a Multistate Health Care Systems Network - United States, March–June 2020. (2020, July 24). Retrieved July 28, 2020, from <https://www.cdc.gov/mmwr/volumes/69/wr/mm6930e1.htm>

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.^{130 131 132 133 134 135 136 137}

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.¹³⁸

Integrative Perspective of Causes

¹³⁰ Patel, M. M., Thornburg, N. J., Stubblefield, W. B., Talbot, H. K., Coughlin, M. M., Feldstein, L. R., & Self, W. H. (2020). Change in Antibodies to SARS-CoV-2 Over 60 Days Among Health Care Personnel in Nashville, Tennessee. *JAMA*, 10.1001/jama.2020.18796. Advance online publication. <https://doi.org/10.1001/jama.2020.18796>

¹³¹ Gudbjartsson, D. F., Norddahl, G. L., Melsted, P., Gunnarsdottir, K., Holm, H., Eythorsson, E., Arnthorsson, A. O., Helgason, D., Bjarnadottir, K., Ingvansson, R. F., Thorsteinsdottir, B., Kristjansdottir, S., Birgisdottir, K., Kristinsdottir, A. M., Sigurdsson, M. I., Arnadottir, G. A., Ivarsdottir, E. V., Andresdottir, M., Jonsson, F., Agustsdottir, A. B., ... Stefansson, K. (2020). Humoral Immune Response to SARS-CoV-2 in Iceland. *The New England journal of medicine*, 10.1056/NEJMoa2026116. Advance online publication. <https://doi.org/10.1056/NEJMoa2026116>

¹³² Wu, F., Liu, M., Wang, A., Lu, L., Wang, Q., Gu, C., Chen, J., Wu, Y., Xia, S., Ling, Y., Zhang, Y., Xun, J., Zhang, R., Xie, Y., Jiang, S., Zhu, T., Lu, H., Wen, Y., & Huang, J. (2020). Evaluating the Association of Clinical Characteristics With Neutralizing Antibody Levels in Patients Who Have Recovered From Mild COVID-19 in Shanghai, China. *JAMA internal medicine*, 10.1001/jamainternmed.2020.4616. Advance online publication. <https://doi.org/10.1001/jamainternmed.2020.4616>

¹³³ Medrxiv. Retrieved from: <https://www.medrxiv.org/content/10.1101/2020.08.11.20171843v2>

¹³⁴ Ripperger, T. J., Uhrlaub, J. L., Watanabe, M., Wong, R., Castaneda, Y., Pizzato, H. A., Thompson, M. R., Bradshaw, C., Weinkauff, C. C., Bime, C., Erickson, H. L., Knox, K., Bixby, B., Parthasarathy, S., Chaudhary, S., Natt, B., Cristan, E., El Aini, T., Rischard, F., Campion, J., ... Bhattacharya, D. (2020). Orthogonal SARS-CoV-2 Serological Assays Enable Surveillance of Low-Prevalence Communities and Reveal Durable Humoral Immunity. *Immunity*, S1074-7613(20)30445-3. Advance online publication. <https://doi.org/10.1016/j.immuni.2020.10.004>

¹³⁵ Isho, B., Abe, K. T., Zuo, M., Jamal, A. J., Rathod, B., Wang, J. H., Li, Z., Chao, G., Rojas, O. L., Bang, Y. M., Pu, A., Christie-Holmes, N., Gervais, C., Ceccarelli, D., Samavarchi-Tehrani, P., Guvenc, F., Budyłowski, P., Li, A., Paterson, A., Yue, F. Y., ... Gingras, A. C. (2020). Persistence of serum and saliva antibody responses to SARS-CoV-2 spike antigens in COVID-19 patients. *Science immunology*, 5(52), eabe5511. <https://doi.org/10.1126/sciimmunol.abe5511>

¹³⁶ Tillett, R. L., Sevinsky, J. R., Hartley, P. D., Kerwin, H., Crawford, N., Gorzalski, A., Laverdure, C., Verma, S. C., Rossetto, C. C., Jackson, D., Farrell, M. J., Van Hooser, S., & Pandori, M. (2020). Genomic evidence for reinfection with SARS-CoV-2: a case study. *The Lancet. Infectious diseases*, S1473-3099(20)30764-7. Advance online publication. [https://doi.org/10.1016/S1473-3099\(20\)30764-7](https://doi.org/10.1016/S1473-3099(20)30764-7)

¹³⁷ Biorxiv. Retrieved from: <https://www.biorxiv.org/content/10.1101/2020.11.15.383323v1>

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.¹³⁹ 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.¹⁴⁰ This would render indoor areas with poor ventilation as major areas of transmission, such as cruise ships and old buildings.¹⁴¹

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.¹⁴² SARS-CoV-2 can survive on human skin for nine hours if not disinfected with ethanol treatment.¹⁴³

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.¹⁴⁴

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

¹³⁹ Centers for Disease Control:

<https://www.cdc.gov/coronavirus/2019-ncov/daily-life-coping/activities.html>

¹⁴⁰ New WHO guidance calls for more evidence on airborne transmission. Retrieved from:

<https://www.reuters.com/article/us-health-coronavirus-who-airborne/new-who-guidance-calls-for-more-evidence-on-airborne-transmission-idUSKBN24A2E5>

¹⁴¹ Medrxiv. Retrieved from: <https://www.medrxiv.org/content/10.1101/2020.07.08.20148775v1>

¹⁴² Kampf, G., Todt, D., Pfaender, S., & Steinmann, E. (2020). Persistence of coronaviruses on inanimate surfaces and their inactivation with biocidal agents. *The Journal of hospital infection*, 104(3), 246–251. <https://doi.org/10.1016/j.jhin.2020.01.022>

¹⁴³ Hirose, R., Ikegaya, H., Naito, Y., Watanabe, N., Yoshida, T., Bandou, R., Daidoji, T., Itoh, Y., & Nakaya, T. (2020). Survival of SARS-CoV-2 and influenza virus on the human skin: Importance of hand hygiene in COVID-19. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*, ciaa1517. Advance online publication. <https://doi.org/10.1093/cid/ciaa1517>

¹⁴⁴ Wu, P., Duan, F., Luo, C., Liu, Q., Qu, X., Liang, L., & Wu, K. (2020). Characteristics of Ocular Findings of Patients With Coronavirus Disease 2019 (COVID-19) in Hubei Province, China. *JAMA ophthalmology*, 138(5), 575–578. Advance online publication. <https://doi.org/10.1001/jamaophthalmol.2020.1291>

produce enough nitric oxide.¹⁴⁵ Implementing breathing exercises for prevention or if symptomatic have been touted as helpful.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.¹⁴⁷

Inferior nutritional status is often missing in public health discussions regarding an optimally functioning immune system for preventing COVID-19.¹⁴⁸ 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.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

¹⁴⁵ Ignarro, Louise. Retrieved from:

<https://www.oregonlive.com/coronavirus/2020/06/the-science-behind-why-this-is-the-safest-way-to-breathe-to-avoid-coronavirus.html>

¹⁴⁶ Hamzelou J. (2020). Can breathing exercises help protect you from covid-19?. *New scientist* (1971), 246(3279), 10–11. [https://doi.org/10.1016/S0262-4079\(20\)30789-2](https://doi.org/10.1016/S0262-4079(20)30789-2)

¹⁴⁷ American Nutrition Association: <https://theana.org/COVID-19>

¹⁴⁸ Calder, P. C., Carr, A. C., Gombart, A. F., & Eggersdorfer, M. (2020). Optimal Nutritional Status for a Well-Functioning Immune System Is an Important Factor to Protect against Viral Infections. *Nutrients*, 12(4), 1181. <https://doi.org/10.3390/nu12041181>

¹⁴⁹ Gasmi, A., Tippairote, T., Mujawdiya, P. K., Peana, M., Menzel, A., Dadar, M., Benahmed, A. G., & Bjørklund, G. (2020). Micronutrients as immunomodulatory tools for COVID-19 management. *Clinical immunology (Orlando, Fla.)*, 108545. Advance online publication. <https://doi.org/10.1016/j.clim.2020.108545>

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.¹⁶² 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.¹⁶³ 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.

¹⁵⁰ Medrxiv. Retrieved from: <https://www.medrxiv.org/content/10.1101/2020.06.24.20138644v1>

¹⁵¹ Medrxiv. Retrieved from: <https://www.medrxiv.org/content/10.1101/2020.07.01.20144329v1>

¹⁵² ASBMR. Joint Guidance On Vitamin D in the Era of COVID-19 From the ASBMR, AACE, ENDOCRINE SOCIETY, ECTS, NOF, AND IOF. Retrieved from:

<https://www.asbmr.org/ASBMRStatementsDetail/joint-guidance-on-vitamin-d-in-era-of-covid-19-fro>

¹⁵³ Meltzer, D. O., Best, T. J., Zhang, H., Vokes, T., Arora, V., & Solway, J. (2020). Association of Vitamin D Status and Other Clinical Characteristics With COVID-19 Test Results. *JAMA network open*, 3(9), e2019722. <https://doi.org/10.1001/jamanetworkopen.2020.19722>

¹⁵⁴ Medrxiv. Retrieved from: <https://www.medrxiv.org/content/10.1101/2020.09.04.20188268v1>

¹⁵⁵ Verdoia, M., & De Luca, G. (2020). Potential role of hypovitaminosis D and Vitamin D supplementation during COVID-19 pandemic. *QJM : monthly journal of the Association of Physicians*, hcaa234. Advance online publication. <https://doi.org/10.1093/qjmed/hcaa234>

¹⁵⁶ Medscape. Retrieved from: <https://www.medscape.com/viewarticle/937567>

¹⁵⁷ Brenner, H., Holleczeck, B., & Schöttker, B. (2020). Vitamin D Insufficiency and Deficiency and Mortality from Respiratory Diseases in a Cohort of Older Adults: Potential for Limiting the Death Toll during and beyond the COVID-19 Pandemic?. *Nutrients*, 12(8), 2488. <https://doi.org/10.3390/nu12082488>

¹⁵⁸ Somasundaram, N. P., Ranathunga, I., Ratnasamy, V., Wijewickrama, P., Dissanayake, H. A., Yogendranathan, N., Gamage, K., de Silva, N. L., Sumanatilleke, M., Katulanda, P., & Grossman, A. B. (2020). The Impact of SARS-Cov-2 Virus Infection on the Endocrine System. *Journal of the Endocrine Society*, 4(8), bvaa082. <https://doi.org/10.1210/jendso/bvaa082>

¹⁵⁹ 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>

¹⁶⁰ Vyas, N., Kurian, S. J., Bagchi, D., Manu, M. K., Saravu, K., Unnikrishnan, M. K., Mukhopadhyay, C., Rao, M., & Miraj, S. S. (2020). Vitamin D in Prevention and Treatment of COVID-19: Current Perspective and Future Prospects. *Journal of the American College of Nutrition*, 1–14. Advance online publication. <https://doi.org/10.1080/07315724.2020.1806758>

¹⁶¹ Luo, X., Liao, Q., Shen, Y., Li, H., & Cheng, L. (2020). Vitamin D Deficiency Is Inversely Associated with COVID-19 Incidence and Disease Severity in Chinese People. *The Journal of nutrition*, nxaa332. Advance online publication. <https://doi.org/10.1093/jn/nxaa332>

¹⁶² Muscogiuri, G., Barrea, L., Savastano, S., & Colao, A. (2020). Nutritional recommendations for CoVID-19 quarantine. *European journal of clinical nutrition*, 74(6), 850–851. <https://doi.org/10.1038/s41430-020-0635-2>

¹⁶³ Medscape: https://www.medscape.com/viewarticle/928287#vp_1

Lack of humidity indoors during the winter months or in very dry climates allows greater transmission of SARS-CoV-2.^{164 165 166 167 168} 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.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.^{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.¹⁷²

¹⁶⁴ Sajadi, M. M., Habibzadeh, P., Vintzileos, A., Shokouhi, S., Miralles-Wilhelm, F., & Amoroso, A. (2020). Temperature, Humidity, and Latitude Analysis to Estimate Potential Spread and Seasonality of Coronavirus Disease 2019 (COVID-19). *JAMA network open*, 3(6), e2011834.

<https://doi.org/10.1001/jamanetworkopen.2020.11834>

¹⁶⁵ Paez, A., Lopez, F. A., Menezes, T., Cavalcanti, R., & Pitta, M. (2020). A Spatio-Temporal Analysis of the Environmental Correlates of COVID-19 Incidence in Spain. *Geographical analysis*, 10.1111/gean.12241. Advance online publication. <https://doi.org/10.1111/gean.12241>

¹⁶⁶ Ward, M. P., Xiao, S., & Zhang, Z. (2020). Humidity is a consistent climatic factor contributing to SARS-CoV-2 transmission. *Transboundary and emerging diseases*, 10.1111/tbed.13766. Advance online publication. <https://doi.org/10.1111/tbed.13766>

¹⁶⁷ Medrxiv. Retrieved from: <https://www.medrxiv.org/content/10.1101/2020.11.13.20231472v1>

¹⁶⁸ Medrxiv. Retrieved from: <https://www.medrxiv.org/content/10.1101/2020.11.12.20230888v1>

¹⁶⁹ Biorxiv. Retrieved: <https://www.biorxiv.org/content/10.1101/2020.08.30.274241v1>

¹⁷⁰ Nikolich-Zugich, J., Knox, K. S., Rios, C. T., Natt, B., Bhattacharya, D., & Fain, M. J. (2020). SARS-CoV-2 and COVID-19 in older adults: what we may expect regarding pathogenesis, immune responses, and outcomes. *GeroScience*, 42(2), 505–514. <https://doi.org/10.1007/s11357-020-00186-0>

¹⁷¹ Weisberg, S. P., Connors, T. J., Zhu, Y., Baldwin, M. R., Lin, W. H., Wontakal, S., Szabo, P. A., Wells, S. B., Dogra, P., Gray, J., Idzikowski, E., Stelitano, D., Bovier, F. T., Davis-Porada, J., Matsumoto, R., Poon, M., Chait, M., Mathieu, C., Horvat, B., Decimo, D., ... Farber, D. L. (2020). Distinct antibody responses to SARS-CoV-2 in children and adults across the COVID-19 clinical spectrum. *Nature immunology*, 10.1038/s41590-020-00826-9. Advance online publication. <https://doi.org/10.1038/s41590-020-00826-9>

¹⁷² Fusco, R., Siracusa, R., Genovese, T., Cuzzocrea, S., & Di Paola, R. (2020) Focus on the Role of NLRP3 Inflammasome in Diseases. *International Journal of Molecular Sciences*, (21) 4223. <https://doi.org/10.3390/ijms21124223>

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.¹⁷³ 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-2.¹⁷⁴

Nutritional and lifestyle intervention is critical to enhance immunity in viral infections such as COVID-19.¹⁷⁵ ¹⁷⁶ ¹⁷⁷ Whey protein is one foodstuff shown to have an antiviral effect against SARS-CoV-2.¹⁷⁸

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.¹⁷⁹ ¹⁸⁰

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.¹⁸¹

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.

¹⁷³ Biorxiv. Retrieved from: <https://www.biorxiv.org/content/10.1101/2020.08.26.268854v1>

¹⁷⁴ SSRN. Retrieved from: https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3612934

¹⁷⁵ Jayawardena, R., Sooriyaarachchi, P., Chourdakis, M., Jeewandara, C., & Ranasinghe, P. (2020). Enhancing immunity in viral infections, with special emphasis on COVID-19: A review. *Diabetes & metabolic syndrome*, 14(4), 367–382. Advance online publication. <https://doi.org/10.1016/j.dsx.2020.04.015>

¹⁷⁶ Frates, E. P., & Rifai, T. (2020). Making the Case for "COVID-19 Prophylaxis" With Lifestyle Medicine. *American journal of health promotion : AJHP*, 34(6), 689–691. <https://doi.org/10.1177/0890117120930536c>

¹⁷⁷ Medrxiv. Retrieved from: <https://www.medrxiv.org/content/10.1101/2020.10.19.20215525v1>

¹⁷⁸ Biorxiv. Retrieved from: <https://www.biorxiv.org/content/10.1101/2020.08.17.254979v1>

¹⁷⁹ Liu, Y., Yan, L. M., Wan, L., Xiang, T. X., Le, A., Liu, J. M., Peiris, M., Poon, L., & Zhang, W. (2020). Viral dynamics in mild and severe cases of COVID-19. *The Lancet. Infectious diseases*, 20(6), 656–657. [https://doi.org/10.1016/S1473-3099\(20\)30232-2](https://doi.org/10.1016/S1473-3099(20)30232-2)

¹⁸⁰ Medrxiv. Retrieved from: <https://www.medrxiv.org/content/10.1101/2020.11.13.20229666v1>

¹⁸¹ Yanuck, S. F., Pizzorno, J., Messier, H., & Fitzgerald, K. N. (2020). Evidence Supporting a Phased Immuno-physiological Approach to COVID-19 From Prevention Through Recovery. *Integrative medicine (Encinitas, Calif.)*, 19(Suppl 1), 8–35.

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+. ¹⁸² 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. ¹⁸³

¹⁸² U.S. Senate Committee on Homeland Security and Governmental Affairs. Retrieved from: <https://www.hsgac.senate.gov/imo/media/doc/Testimony-Kory-2020-05-06-REVISED.pdf>

¹⁸³ Dietz, L., Horve, P. F., Coil, D. A., Fretz, M., Eisen, J. A., & Van Den Wymelenberg, K. (2020). 2019 Novel Coronavirus (COVID-19) Pandemic: Built Environment Considerations To Reduce Transmission. *mSystems*, 5(2), e00245-20. <https://doi.org/10.1128/mSystems.00245-20>

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.

¹⁸⁴ Bousquet, J., Anto, J. M., Iaccarino, G., Czarlewski, W., Haahtela, T., Anto, A., Akdis, C. A., Blain, H., Canonica, G. W., Cardona, V., Cruz, A. A., Illario, M., Ivancevich, J. C., Jutel, M., Klimek, L., Kuna, P., Laune, D., Larenas-Linnemann, D., Mullol, J., Papadopoulos, N. G., ... ARIA group (2020). Is diet partly responsible for differences in COVID-19 death rates between and within countries?. *Clinical and translational allergy*, 10, 16. <https://doi.org/10.1186/s13601-020-00323-0>

¹⁸⁵ Medrxiv. Retrieved from: <https://www.medrxiv.org/content/10.1101/2020.10.19.20214395v2>

¹⁸⁶ Korytkowski, M., Antinori-Lent, K., Drincic, A., Hirsch, I. B., McDonnell, M. E., Rushakoff, R., & Muniyappa, R. (2020). A Pragmatic Approach to Inpatient Diabetes Management during the COVID-19 Pandemic. *The Journal of clinical endocrinology and metabolism*, dgaa342. Advance online publication. <https://doi.org/10.1210/clinem/dgaa342>

¹⁸⁷ Demasi M. (2020). COVID-19 and metabolic syndrome: could diet be the key?. *BMJ evidence-based medicine*, bmjebm-2020-111451. Advance online publication. <https://doi.org/10.1136/bmjebm-2020-111451>

¹⁸⁸ Wang, Q., Fang, P., He, R., Li, M., Yu, H., Zhou, L., Yi, Y., Wang, F., Rong, Y., Zhang, Y., Chen, A., Peng, N., Lin, Y., Lu, M., Zhu, Y., Peng, G., Rao, L., & Liu, S. (2020). O-GlcNAc transferase promotes influenza A virus-induced cytokine storm by targeting interferon regulatory factor-5. *Science advances*, 6(16), eaaz7086. <https://doi.org/10.1126/sciadv.aaz7086>

¹⁸⁹ World Health Organization:

<https://www.euro.who.int/en/health-topics/disease-prevention/alcohol-use/news/news/2020/04/alcohol-does-not-protect-against-covid-19-access-should-be-restricted-during-lockdown>

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

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-s4SA3170UnwoKuZIO9gKKup8iFNU7XKMtEmCohMWI5SCwpZ3uDQ>

¹⁹¹ Dofferhoff, A., Piscaer, I., Schurgers, L., Walk, J., van den Ouweland, J., Hackeng, T., Lux, P., Maassen, C., Karssemeijer, E., Wouters, E., & Janssen, R. (2020). Reduced Vitamin K Status as a Potentially Modifiable Prognostic Risk Factor in COVID-19. Preprints, 2020040457; doi: 10.20944/preprints202004.0457.v1.

¹⁹² Lippi, G., South, A. M., & Henry, B. M. (2020). Electrolyte imbalances in patients with severe coronavirus disease 2019 (COVID-19). *Annals of clinical biochemistry*, 57(3), 262–265. <https://doi.org/10.1177/0004563220922255>

¹⁹³ Vallat, R., Shah, V. D., Redline, S., Attia, P., & Walker, M. P. (2020). Broken sleep predicts hardened blood vessels. *PLoS biology*, 18(6), e3000726. <https://doi.org/10.1371/journal.pbio.3000726>

¹⁹⁴ Shields, G. S., Spahr, C. M., & Slavich, G. M. (2020). Psychosocial Interventions and Immune System Function: A Systematic Review and Meta-analysis of Randomized Clinical Trials. *JAMA psychiatry*, e200431. Advance online publication. <https://doi.org/10.1001/jamapsychiatry.2020.0431>

¹⁹⁵ Alkhatib A. (2020). Antiviral Functional Foods and Exercise Lifestyle Prevention of Coronavirus. *Nutrients*, 12(9), E2633. <https://doi.org/10.3390/nu12092633>

¹⁹⁶ Medrxiv. Retrieved from: <https://www.medrxiv.org/content/10.1101/2020.08.21.20179499v1>

¹⁹⁷ Medrxiv. Retrieved from: <https://www.medrxiv.org/content/10.1101/2020.10.14.20212704v1>

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-2¹⁹⁸, 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.¹⁹⁹ Probiotic strains of lactobacilli and bifidobacteria exhibited an ameliorating impact on the clinical conditions of hospitalized patients positive for SARS-CoV-2 infection.²⁰⁰

If where one resides does not offer the ability to breathe pristinely clean air, such as big cities or areas with power plants,²⁰¹ one can assure their domicile has clean air by installing a HEPA filter.^{202 203} In areas with high concentrations of fine particulate matter, the increased risk of death was 15% higher.²⁰⁴ This is especially important during hot weather months where one must be indoors with air conditioning.²⁰⁵ In addition, a humidifier in the winter is essential, as viruses are not as virulent when there is more moisture in the air.^{206 207} 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.²⁰⁸

¹⁹⁸ Medrxiv. Retrieved from: <https://www.medrxiv.org/content/10.1101/2020.04.04.20053058v1>

¹⁹⁹ Dhar, D., & Mohanty, A. (2020). Gut microbiota and Covid-19- possible link and implications. *Virus research*, 285, 198018. <https://doi.org/10.1016/j.virusres.2020.198018>

²⁰⁰ D'ettore, G., Ceccarelli, G., Marazzato, M., Campagna, G., Pinacchio, C., Alessandri, F., . . . Mastroianni, C. M. (2020). Challenges in the Management of SARS-CoV2 Infection: The Role of Oral Bacteriotherapy as Complementary Therapeutic Strategy to Avoid the Progression of COVID-19. *Frontiers in Medicine*, 7. doi:10.3389/fmed.2020.00389

²⁰¹ Medrxiv. Retrieved from: <https://doi.org/10.1101/2020.04.05.20054502>

²⁰² Institute of Labor Economics. Retrieved from: <http://ftp.iza.org/dp13367.pdf>

²⁰³ Medrxiv. Retrieved from: <https://www.medrxiv.org/content/10.1101/2020.10.02.20205633v2>

²⁰⁴ Hornyak, T. (2020). Air Pollution Can Worsen the Death Rate from COVID-19. *Eos*, 101. doi:10.1029/2020eo142660

²⁰⁵ ASHRAE Epidemic Task Force. Retrieved from: <https://www.ashrae.org/file%20library/technical%20resources/covid-19/ashrae-building-readiness.pdf>

²⁰⁶ American Lung Association: <https://www.lung.org/media/press-releases/state-of-the-air-2020>

²⁰⁷ Medrxiv. Retrieved from: <https://www.medrxiv.org/content/10.1101/2020.08.18.20177444v3>

²⁰⁸ Medrxiv. Retrieved from: <https://www.medrxiv.org/content/10.1101/2020.07.29.20164152v1>

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.²⁰⁹ 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.²¹⁰ 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.²¹¹

Just eating a healthy diet will not suffice. You need supplemental support.^{212 213 214 215}

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

VITAMIN C (Ascorbic Acid)

Critical for almost every cellular function.²¹⁶ 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.²¹⁷

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

²⁰⁹ Waqas Khan, H. M., Parikh, N., Megala, S. M., & Predeteanu, G. S. (2020). Unusual Early Recovery of a Critical COVID-19 Patient After Administration of Intravenous Vitamin C. *The American journal of case reports*, 21, e925521. <https://doi.org/10.12659/AJCR.925521>

²¹⁰ Clinicaltrials.gov: <https://clinicaltrials.gov/ct2/show/NCT04264533>

²¹¹ Horowitz, R. I., Freeman, P. R., & Bruzzese, J. (2020). Efficacy of glutathione therapy in relieving dyspnea associated with COVID-19 pneumonia: A report of 2 cases. *Respiratory medicine case reports*, 30, 101063. Advance online publication. <https://doi.org/10.1016/j.rmcr.2020.101063>

²¹² McAuliffe, S., Ray, S., Fallon, E., Bradfield, J., Eden, T., & Kohlmeier, M. (2020, June 18). Dietary micronutrients in the wake of COVID-19: An appraisal of evidence with a focus on high-risk groups and preventative healthcare. Retrieved June 27, 2020, from <https://nutrition.bmj.com/content/early/2020/06/17/bmjnph-2020-000100>

²¹³ BourBour, F., Mirzaei Dahka, S., Gholamalizadeh, M., Akbari, M. E., Shadnough, M., Haghighi, M., Taghvaye-Masoumi, H., Ashoori, N., & Doaei, S. (2020). Nutrients in prevention, treatment, and management of viral infections; special focus on Coronavirus. *Archives of physiology and biochemistry*, 1–10. Advance online publication. <https://doi.org/10.1080/13813455.2020.1791188>

²¹⁴ Jovic, T. H., Ali, S. R., Ibrahim, N., Jessop, Z. M., Tarassoli, S. P., Dobbs, T. D., Holford, P., Thornton, C. A., & Whitaker, I. S. (2020). Could Vitamins Help in the Fight Against COVID-19?. *Nutrients*, 12(9), E2550. <https://doi.org/10.3390/nu12092550>

²¹⁵ Shakoor, H., Feehan, J., Dhaheri, A. S., Ali, H. I., Platat, C., Ismail, L. C., . . . Stojanovska, L. (2021). Immune-boosting role of vitamins D, C, E, zinc, selenium and omega-3 fatty acids: Could they help against COVID-19? *Maturitas*, 143, 1-9. doi:10.1016/j.maturitas.2020.08.003

²¹⁶ American Nutrition Association: <https://theana.org/COVID-19>

²¹⁷ Patterson, G., Isales, C., Fulzele, S. (2020). Low level of Vitamin C and dysregulation of Vitamin C transporter might be involved in the severity of COVID-19 Infection. *Aging and Disease*, 10.14336/AD.2020.0918.

****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)

²¹⁸ Singh, S. (2020). Covariation of Zinc Deficiency with COVID19 Infections and Mortality in European Countries: Is Zinc Deficiency a Risk Factor for COVID-19? *Journal of Scientific Research*, 64(02), 153-157. doi:10.37398/jsr.2020.640222

²¹⁹ Medrxiv. Retrieved from:

<https://www.medrxiv.org/content/10.1101/2020.10.07.20208645v1?%253fcollection=>

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-s4SA3I70UnwoKuZIO9gKKup8iFNU7XKMtEmCohMWI5SCwpZ3uDQ>

²²¹ Mossink, J. P. (2020). Zinc as nutritional intervention and prevention measure for COVID-19 disease. *BMJ Nutrition, Prevention & Health*. doi:10.1136/bmjnph-2020-000095

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.²²² 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.²²³

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%.^{224 225 226 227}

²²² Schlievert, P. M., Kilgore, S. H., Kaus, G. M., Ho, T. D., & Ellermeier, C. D. (2018). Glycerol Monolaurate (GML) and a Nonaqueous Five-Percent GML Gel Kill Bacillus and Clostridium Spores. *mSphere*, 3(6), e00597-18. <https://doi.org/10.1128/mSphereDirect.00597-18>

²²³ Zhang, M. S., Tran, P. M., Wolff, A. J., Tremblay, M. M., Fosdick, M. G., & Houtman, J. (2018). Glycerol monolaurate induces filopodia formation by disrupting the association between LAT and SLP-76 microclusters. *Science signaling*, 11(528), eaam9095. <https://doi.org/10.1126/scisignal.aam9095>

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

²²⁵ Kaufman, H. W., Niles, J. K., Kroll, M. H., Bi, C., & Holick, M. F. (2020). SARS-CoV-2 positivity rates associated with circulating 25-hydroxyvitamin D levels. *PloS one*, 15(9), e0239252. <https://doi.org/10.1371/journal.pone.0239252>

²²⁶ Entrenas Castillo, M., Entrenas Costa, L. M., Vaquero Barrios, J. M., Alcalá Díaz, J. F., López Miranda, J., Bouillon, R., & Quesada Gomez, J. M. (2020). "Effect of calcifediol treatment and best available therapy versus best available therapy on intensive care unit admission and mortality among patients hospitalized for COVID-19: A pilot randomized clinical study". *The Journal of steroid biochemistry and molecular biology*, 203, 105751. Advance online publication. <https://doi.org/10.1016/j.jsbmb.2020.105751>

²²⁷ Medrxiv. Retrieved from: <https://www.medrxiv.org/content/10.1101/2020.10.24.20218974v1>

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.

²²⁸ Medrxiv. Retrieved from: <https://www.medrxiv.org/content/10.1101/2020.07.14.20152728v1>

²²⁹ Iddir, M., Brito, A., Dingo, G., Fernandez Del Campo, S. S., Samouda, H., La Frano, M. R., & Bohn, T. (2020). Strengthening the Immune System and Reducing Inflammation and Oxidative Stress through Diet and Nutrition: Considerations during the COVID-19 Crisis. *Nutrients*, 12(6), E1562. <https://doi.org/10.3390/nu12061562>

²³⁰ Cleveland Clinic: <https://riskcalc.org/COVID19/>

²³¹ Zhou, Y., Hou, Y., Shen, J., Kallianpur, A., Zein, J., Culver, D. A., Farha, S., Comhair, S., Fiocchi, C., Gack, M. U., Mehra, R., Stappenbeck, T., Chan, T., Eng, C., Jung, J. U., Jehi, L., Erzurum, S., & Cheng, F. (2020). A Network Medicine Approach to Investigation and Population-based Validation of Disease Manifestations and Drug Repurposing for COVID-19. *ChemRxiv : the preprint server for chemistry*, 10.26434/chemrxiv.12579137.v1. <https://doi.org/10.26434/chemrxiv.12579137>

²³² Kleszczyński, K., Slominski, A. T., Steinbrink, K., & Reiter, R. J. (2020). Clinical Trials for Use of Melatonin to Fight against COVID-19 Are Urgently Needed. *Nutrients*, 12(9), E2561. <https://doi.org/10.3390/nu12092561>

QUERCETIN

Flavonoids have antiviral properties.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.^{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.

²³³ Ninfali, P., Antonelli, A., Magnani, M., & Scarpa, E. S. (2020). Antiviral Properties of Flavonoids and Delivery Strategies. *Nutrients*, 12(9), E2534. <https://doi.org/10.3390/nu12092534>

²³⁴ McKee, D. L., Sternberg, A., Stange, U., Laufer, S., & Naujokat, C. (2020). Candidate drugs against SARS-CoV-2 and COVID-19. *Pharmacological research*, 157, 104859. <https://doi.org/10.1016/j.phrs.2020.104859>

²³⁵ Colunga Biancatelli, R., Berrill, M., Catravas, J. D., & Marik, P. E. (2020). Quercetin and Vitamin C: An Experimental, Synergistic Therapy for the Prevention and Treatment of SARS-CoV-2 Related Disease (COVID-19). *Frontiers in immunology*, 11, 1451. <https://doi.org/10.3389/fimmu.2020.01451>

****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.**

²³⁶ Wallace T. C. (2020). Combating COVID-19 and Building Immune Resilience: A Potential Role for Magnesium Nutrition?. *Journal of the American College of Nutrition*, 1–9. Advance online publication. <https://doi.org/10.1080/07315724.2020.1785971>

²³⁷ Fantacone, M. L., Lowry, M. B., Uesugi, S. L., Michels, A. J., Choi, J., Leonard, S. W., Gombart, S. K., Gombart, J. S., Bobe, G., & Gombart, A. F. (2020). The Effect of a Multivitamin and Mineral Supplement on Immune Function in Healthy Older Adults: A Double-Blind, Randomized, Controlled Trial. *Nutrients*, 12(8), 2447. <https://doi.org/10.3390/nu12082447>

²³⁸ Yanuck, S. F., Pizzorno, J., Messier, H., & Fitzgerald, K. N. (2020). Evidence Supporting a Phased Immuno-physiological Approach to COVID-19 From Prevention Through Recovery. *Integrative medicine (Encinitas, Calif.)*, 19(Suppl 1), 8–35.

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.²³⁹

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

²³⁹ Panigrahy, D., Gilligan, M. M., Huang, S., Gartung, A., Cortés-Puch, I., Sime, P. J., Phipps, R. P., Serhan, C. N., & Hammock, B. D. (2020). Inflammation resolution: a dual-pronged approach to averting cytokine storms in COVID-19?. *Cancer metastasis reviews*, 1–4. Advance online publication. <https://doi.org/10.1007/s10555-020-09889-4>

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.

²⁴⁰ Health Times. Retrieved from:

<https://healthtimes.com.au/hub/diseases/24/news/aap/researchers-in-australia-are-testing-a-treatment-for-covid19/5238/>

²⁴¹ Medrxiv. Retrieved from: <https://www.biorxiv.org/content/10.1101/2020.09.16.297366v1>

²⁴² Adusumilli, N. C., Zhang, D., Friedman, J. M., & Friedman, A. J. (2020). Harnessing nitric oxide for preventing, limiting and treating the severe pulmonary consequences of COVID-19. Nitric oxide : biology and chemistry, 103, 4–8. Advance online publication. <https://doi.org/10.1016/j.niox.2020.07.003>

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 Medicine²⁴⁵ 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

²⁴³ Laukkanen, J. A., Laukkanen, T., & Kunutsor, S. K. (2018). Cardiovascular and Other Health Benefits of Sauna Bathing: A Review of the Evidence. *Mayo Clinic proceedings*, 93(8), 1111–1121.

<https://doi.org/10.1016/j.mayocp.2018.04.008>

²⁴⁴ Thibodeaux, K., Speyrer, M., Raza, A., Yaakov, R., & Serena, T. E. (2020). Hyperbaric oxygen therapy in preventing mechanical ventilation in COVID-19 patients: a retrospective case series. *Journal of wound care*, 29(Sup5a), S4–S8. <https://doi.org/10.12968/jowc.2020.29.Sup5a.S4>

²⁴⁵ Shahzad, F., Anderson, D., & Najafzadeh, M. (2020). The Antiviral, Anti-Inflammatory Effects of Natural Medicinal Herbs and Mushrooms and SARS-CoV-2 Infection. *Nutrients*, 12(9), E2573.

<https://doi.org/10.3390/nu12092573>

²⁴⁶ Liu, W. H., Guo, S. N., Wang, F., & Hao, Y. (2020). Understanding of guidance for acupuncture and moxibustion interventions on COVID-19 (Second edition) issued by CAAM. *World journal of acupuncture-moxibustion*, 30(1), 1–4. Advance online publication.

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Mouthwash may have an inhibitory effect on SARS-CoV-2.^{252 253}

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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