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UNDERSTANDING & TREATING
SPIKE PROTEIN-INDUCED DISEASES

October 14-16, 2022 • Orlando, Florida

Low Dose Naltrexone and Spike Protein Induced Disease

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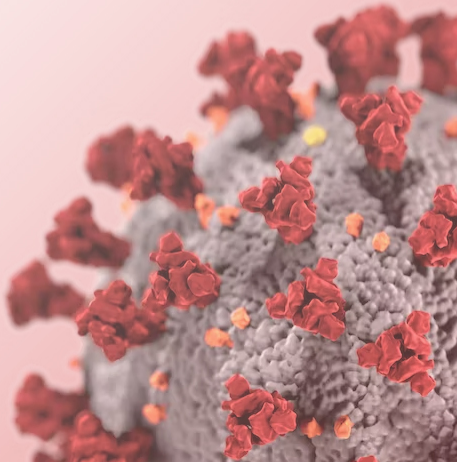
October 15, 2022



Foundation

- Definition: “The underlying basis or principle for something”
  - Current medical thinking is to be reactive and treat symptoms and thus treat from “top –down.”
  - A better holistic approach is to treat from “bottom-up” and thereby build a strong base from which the body will work from.

Long Haul Syndrome: Post COVID 19 infection

- Studies have shown that as many 50 to 80% of individuals still have symptoms after recovering from COVID 19 infection.

- According to the U.S. General Accountability Office estimates that between 7.7 to 23 million Americans have Long Haul COVID
  - Symptoms include prolonged malaise, “brain fog,” headaches, generalized fatigue, insomnia, hair loss, impaired smell, tinnitus, joint and muscle pain, loss of appetite, lightheadedness and post-exercise fatigue and tachycardia.

Website: Science & Tech Spotlight: Long COVID | U.S. GAO

Long Haul Syndrome

The Northwestern Medicine Neuro COVID 19 Clinic in a recent study published in the “Annals of Clinical and Translational Medicine” identified individuals with neurologic symptoms after having a mild case of COVID-19 infection.

- These individuals dubbed “COVID-19” long haulers continued to experience symptoms for on average 15-months after disease onset.
- The symptoms included brain fog, numbness/tingling, headache, dizziness, blurred vision, tinnitus and fatigue.

Sareen, T. Ali, Anthony K. Kang, et al., Evolution of Neurologic Symptoms in Non-hospitalized COVID-19 “Long Haulers, Annals of Clinical and Translational Medicine, May 24, 2022.

Long Haul Syndrome

UCLA researchers in a study published in *the "Journal of General Internal Medicine"* found that 30% of patients with COVID-19 infection developed Long COVID.

- 309 out of 1,038 people developed symptoms consistent with Post Acute Sequelae of COVID-19 (PASC) also known as long haul syndrome.
- The most common symptoms included fatigue, shortness of breath and lose of smell.
- Common risk factors included hospitalization from COVID-19, diabetes mellitus and higher body mass index.

Yoo, M. Sun, MD, MPH, Teresa C. Liu, MD, PPH, et al., Factors Associated with Post-Acute Sequelae of SARS-CoV-2 (PASC) After Diagnosis of Symptomatic COVID-19 in the Inpatient and Outpatient Setting in a Diverse Cohort, Journal of Internal Medicine, April 7, 2022.

Mechanisms of Spike Protein Induced Disease

- Post - Inflammatory
- Post – Viral
- Hypercoagulable state
- Histamine Intolerance/Mast Cell Activation Syndrome
- Auto-immune

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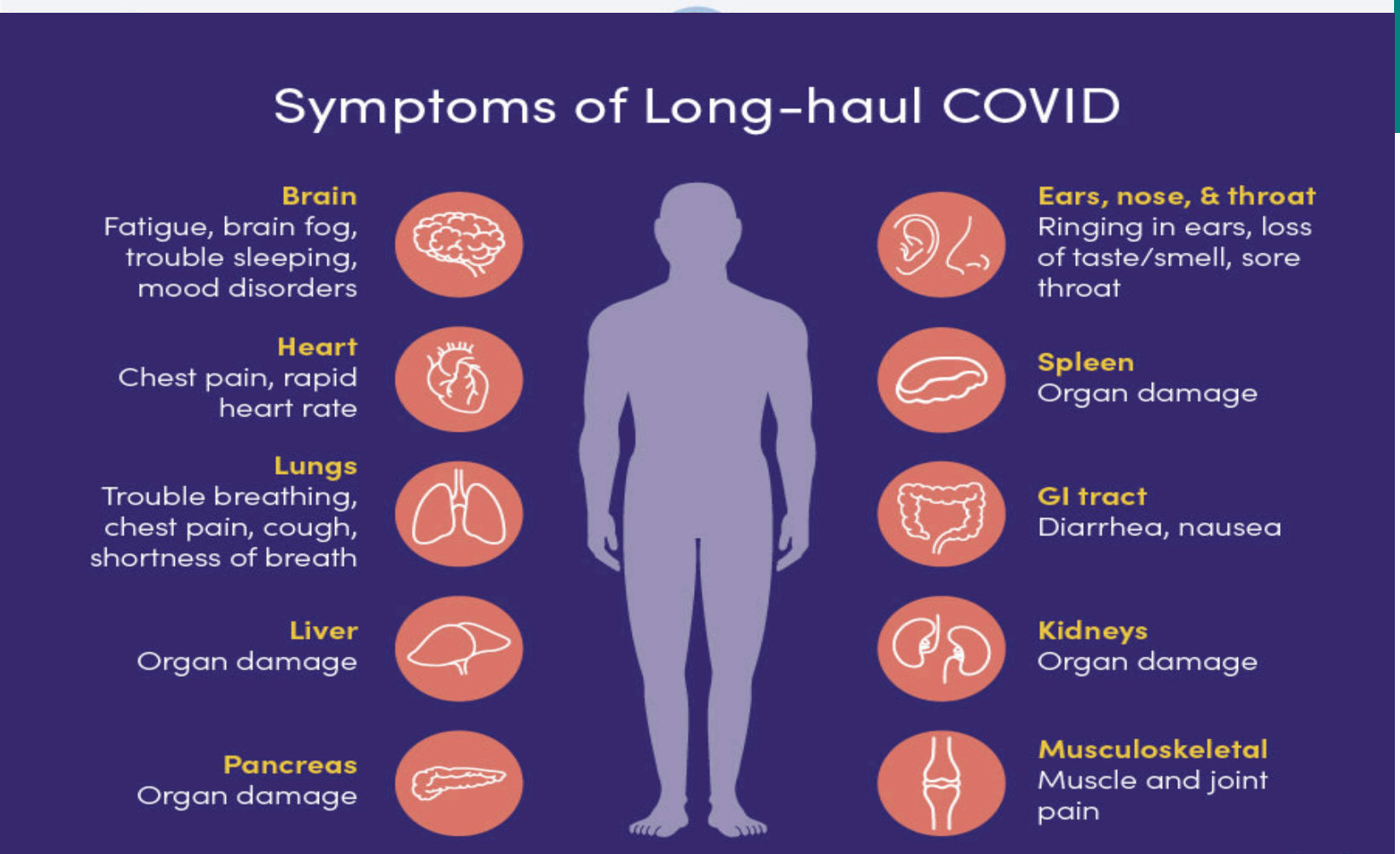
Symptoms of Long-haul COVID



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Post-viral

Possible mechanism is persistence of “viral debris” and/or reactivation of Epstein Barr Virus

- Viral Debris: Spike protein inserts itself into monocytes and microglia causing a persistent inflammatory response.
  - Here the immune system is unable to clear remaining viral RNA fragments which continue to cause damage. (COVID 19 is an RNA virus)
- Epstein Barr Virus (EBV): EBV is a member of the herpes virus family (Human Herpesvirsus 4).
  - It is one of the most common human viruses. Most people are infected with EBV (infective mononucleosis) at some point in their lives typically in their teens and/or twenties.
  - EBV spreads most commonly through bodily fluids, primarily saliva.

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Epstein Barr Virus

Toll-like receptors (TLR) play an important role in recognition of viral particles and activation of the innate immune system.

- Toll-like receptor agonists synergistically increase proliferation and activation of B cells by Epstein-Barr virus (EBV)
- Activation of TLR pathways leads to secretion of pro-inflammatory cytokines, such as interleukin-1 (IL-1), IL-6, and tumor necrosis factor-α, as well as type 1 interferon.
- Different TLRs, like TLR2, TLR3, TLR4, TLR6, TLR7, TLR8, and TLR9 are potentially important in COVID-19 infection.
  - TLRs could be a potential target in controlling the infection in the early stages of disease and production of vaccine against SARS-CoV-2.

Khanmohamnadi, Shaghayeh., Role of Toll-Like Receptors in the Pathogenesis of COVID-19, *Journal of Medical Virology*. 2021 May; 93 (5): 2735-2736

Hypercoagulable State

- There is possible mechanism with micro and/or macrovascular thrombotic disease and its potential impact on metabolic health.
- The brain microvasculature expresses ACE-2 receptors and SARS 2 “pseudovirons” may bind to the microvascular endothelium causing cerebral microvascular inflammation and clotting.

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Histamines

- Histamine is not only the major mediator of the acute inflammatory and immediate hypersensitivity responses but has also been demonstrated to affect chronic inflammation and regulate several essential events in the immune response.

- It can influence numerous functions of the cells involved in the regulation of immune response and hematopoiesis including macrophages, dendritic cells, T lymphocytes, B lymphocytes and endothelial cells.
  - Elevated histamine levels which can trigger a mast cell activation syndrome.
  - Mast cells can impact the skin, liver, spleen, brain, bone marrow and/or intestines.
  - Excessive production of mast cells can trigger allergic-like symptoms.

Histamines

Impact on the brain

- Mast cells in the brain may lead to the release of proinflammatory mediators including histamine, tryptase, chemokines and cytokines which in turn can trigger neurovascular inflammation.
- Individuals can develop “brain fog,” cognitive impairment and generalized fatigue.

Treatment Options

Low Dose Naltrexone

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History of Low Dose Naltrexone

- Low Dose Naltrexone was discovered by Dr. Ian Zagon and Dr. Patricia J. McLaughlin and their team at Penn State University's Hershey Medical Center
  - Dr. Patricia J. McLaughlin publishes a paper in Science in 1983 describing the potential benefits of LDN
  - Naltrexone was licensed in 1984 by the FDA in a 50 mg dose as a treatment for heroin addiction.
    - LDN is an opiate antagonist that inhibits the opioid receptors that heroin acts on in the brain.
  - The scientists described that the anti-opiate addiction drug naltrexone revealed completely different purposes including treating chronic and autoimmune disease when used in small doses.

History of Low Dose Naltrexone

Dr. Bernard Bihari (1931 – 2010), a New York City physician started using the LDN in clinical practice both on individuals with HIV/AIDS and multiple sclerosis

- In 1986, his clinical trial at Downstate Medical Center showed that LDN helped protect the challenged immune systems of his HIV/AIDS patients
  - In the control group of the patients that received a placebo approximately 31% of the patients had developed an opportunistic infection during the trial.
  - In contrast, the experimental group the patients who received Low Dose Naltrexone, none of the 22 patients had developed any opportunistic infections.

History of Low Dose Naltrexone

As of 2004, Dr. Bihari had treated almost four hundred patients with Multiple Sclerosis. Only two of these patients had new disease flare after staring treatment with LDN.

- One was a 41-year-old woman who, after 18 months on LDN, had an episode of optic neuritis which cleared in 4 weeks.
- The other was a patient who, after 8 months on LDN, had an episode of numbness in the left leg that had not been experienced previously and which cleared after 3 weeks.

Conversations ., Bernard Bihari, M.D.: Low-Dose Naltrexone for Normalizing Immune System Function, Alternative Therapies, March/April 2013; 56-65.

Pharmacology of LDN

Every drug has two forms called isomers, which are mirror images (Levo & Dextro) of each other, but normally only one isomer offers a therapeutic effect. Naltrexone's is unique in that both isomers contribute different therapeutic effects. Doses range from 0.5 mg to 4.5 mg.

- **DEXTRO-Naltrexone**
  - Blocks certain Toll-like receptors
  - Reduces production of pro-inflammatory cytokines
  - Suppresses inflammation cascade
  - Central and system effects as Toll-like receptors are present on microglial cells, mast cells, and macrophages
- **LEVO-Naltrexone**
  - Blocks opiate receptors for a brief period
  - Increases the natural production of anti-inflammatory endorphins
  - Upregulates the opiate receptors
  - Has a direct effect on some cell proliferation rates

https://ldnresearchtrust.org/how-low-dose-naltrexone-works

Advantages of LDN

- Low cost
  - Unfortunately needs to be compounded
  - Can be made as a liquid, tablet and/or capsule
- Few drug/supplement interactions
- Mild side effects
  - “Vivid dreams”
  - Headaches
  - Possible others include:
    - Anxiety
    - Tachycardia

Mechanisms of Action

- Action on opioid receptors to increase release of β-endorphins
- Ability to reduce pro-inflammatory cytokines and increase anti-inflammatory cytokines
  - Blocks toll-like receptor signaling which decreases glial cell activation, decreases cytokines, decreases neuroinflammation
- Regulation of the opioid growth factor (OGF)/opioid growth factor receptors (OGFr) axis.
- Modulates T and B lymphocyte production

Toljan, Karlo, and Vrooman, Bruce., Low-dose Naltrexone, Review of Therapeutic Utilization, Med. Sci (Basel). Dec 6(4): 82, 2018.

Impact of B-endorphins

Low-dose naltrexone is still considered an opioid receptor antagonist, but only for a short duration (6 hours a day). This leads to an analgesic effect.

- Research has shown that LDN increases levels of endogenous opioids
- LDN stimulates the body's own production of endorphins, even after the LDN is no longer in the system.
- In a 2008 study, researchers found elevations in endorphins even 1 month after discontinuation of LDN doses of less than 5.0 mg.

Li, Zijian, et.al. Low-dose naltrexone (LDN): A promising treatment in immune-related diseases and cancer therapy. *International Immunopharmacology. August 2018, Pages 178-184*

Reduction in Inflammatory Cytokines

LDN reduces inflammation by reducing multiple pro-inflammatory cytokines.

- Cytokines are chemical messengers, often made by immune cells, whose net effect can be to either increase or decrease immune function.
- The coordination of the immune system rests on the body's ability to keep a balance between cytokines that promote inflammation and those that reduce it.
  - In an 8-week single-blinded pilot study using 4.5 mg of LDN each night, serum levels of numerous proinflammatory cytokines including interleukin (IL)-1, IL-2, IL-12, IL-18, interferon gamma (IFN-γ), granulocyte-macrophage colony-stimulating factor (GM-CSF), and TNF-α were significantly reduced when compared to baseline in patients suffering from fibromyalgia

Younger, Jared and Mackey, Sean ., Fibromyalgia Symptoms Are Reduced by Low-Dose Naltrexone: A Pilot Study. Pain Med, May-Jun 2009, 663-672.

Impact on Immune Response

Works to balance the TH1 and TH2 immune response

- Th1-type cytokines tend to produce the proinflammatory responses responsible for killing intracellular parasites and for perpetuating autoimmune responses.
  - Interferon gamma is the main Th1 cytokine.
  - Excessive proinflammatory responses can lead to uncontrolled tissue damage, so there needs to be a mechanism to counteract this.
- The Th2-type cytokines include:
  - Interleukins 4, 5, and 13, which are associated with the promotion of IgE and eosinophilic responses in atopy
  - Interleukin-10, which has more of an anti-inflammatory response.
  - In excess, Th2 responses will counteract the Th1 mediated microbicidal action.

Berger, Abi., Th1 and Th2 responses: what are they? BMJ. 2000 Aug 12; 321(7258): 424.

Upregulation of Opioid Growth Factor

Low-dose naltrexone has been shown to upregulate the OGF/OGFr axis.

- Opioid growth factor (OGF) is an opioid peptide ([Met]-enkephalin).
- There is evidence that the OGF/OGFr axis pathway is involved in the regulation of tumor growth.
- The use of LDN to regulate this pathway is of interest in cancer research and in the treatment of neurodegenerative diseases such as multiple sclerosis.
  - In addition, research has shown that cell proliferation is altered when OGF binds to the OGF receptors.
  - When the OGF/OGFr axis pathway is upregulated, tumor growth may be decreased.

Donahue, Renee and McLaughlin, Patricia., The opioid growth factor (OGF) and low dose naltrexone (LDN) suppress human ovarian cancer progression in mice. Gynecology Oncology, August 2011; 382-8.

Clinical Use of Low Dose Naltrexone

- The first LDN clinical trial was initiated at Hershey Medical Center in 2002 by Moshe Rogosnitzky, who went on to found the MedInsight Research Institute that later launched LDNscience
- The first application of LDN in gastrointestinal-related issues was in 2006, when an Israeli research group presented a pilot study involving 42 patients suffering from irritable bowel syndrome (IBS)
  - It was an open-label study where 0.5 mg LDN was given daily for 4 weeks. The drug was well tolerated and more than 75% of patients were considered responders per a subjective scale measuring pain-free days and symptom relief.

Toljan, Karlo, and Vrooman, Bruce., Low-dose Naltrexone, Review of Therapeutic Utilization, Med. Sci (Basel). Dec 6(4): 82, 2018.

Impact of LDN on Spike Protein Induced Disease

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Impact on Inflammation/Neuroinflammation

Impact on Inflammation (cross blood brain barrier)

- The neuroprotective action appears to result when microglia activation in the brain and spinal cord is inhibited
- By suppressing microglia activation, naltrexone reduces the production of reactive oxygen species and other potentially neuroexcitatory and neurotoxic chemicals
- The anti-inflammatory effect of opioid antagonists may also extend to the periphery, as evidenced by suppressed TNF-alpha, IL-6, MCP-1, and other inflammatory agents in peripheral macrophages

Impact on Post-viral Syndrome

The British Medical Journal as recent as Jan 2020 published three case reports on the positive effects on the use of LDN in chronic fatigue (fibromyalgia) associated with Epstein Barr Virus (EBV)

- Fibromyalgia may represent a state of increased microglial activity and inflammation in the central nervous system
  - Microglia are the resident macrophages of the central nervous system, and the primary form of immune defense in the brain and spinal cord.
  - Once activated they produce proinflammatory factors including cytokines, excitatory amino acids, and nitric multiple channels
  - This causes the symptoms such as hyperalgesia and fatigue
- Low dose naltrexone by acting on Toll-like receptor 4 and therefore antagonizing microioglial activity can suppress the release of proinflammatory factors and thereby reduce pain and other symptoms of fibromyalgia.

Bolton, Monica and et. al. Low-dose naltrexone as a treatment for chronic fatigue syndrome. BMJ Case Report Jan 6, 2020: 13.

Impact on Thrombosis/Micro-clotting

- Coronavirus disease 2019 (COVID-19) is characterized by striking dysregulation of the immune system, with evidence of hyperinflammation, an impaired induction of interferons, and delayed adaptive immune responses.
  - Professor Pretorius's group "…found high levels of various inflammatory molecules trapped in micro clots present in the blood of individuals with Long COVID. Some of the trapped molecules contain clotting proteins such as fibrinogen, as well as alpha(2)-antiplasmin."
- Mechanistically, LDN can blunt innate immune responses and Toll-like receptor signaling, reducing interleukin-1 (IL-1), tumor necrosis factor-alpha (TNF-α), and interferon (IFN) levels.

Pretorius, Etheresia and et.al., Persistent clotting protein pathology in Long COVID/Post-Acute Sequelae of COVID-19 (PASC) is accompanied by increased levels of antiplasmin. Cardiovascular Diabetology, August 23, 2021; 172.

Patient Case: BMJ Medical Journal

A patient with severe postural orthostatic tachycardia syndrome (POTS) and mast cell activation syndrome (MCAS) received immunotherapy with low-dose naltrexone (LDN) and intravenous immunoglobulin (IVIg) and antibiotic therapy for small intestinal bacterial overgrowth (SIBO).

- A dramatic and sustained response was documented.
- The utility of IVIg in autoimmune neuromuscular diseases has been published, but clinical experience with POTS is relatively unknown and has not been reported in MCAS.
- As a short-acting mu-opioid antagonist, LDN paradoxically increases endorphins which then bind to regulatory T cells which regulate T-lymphocyte and B-lymphocyte production and this reduces cytokine and antibody production.
- Diagnosis and treatment of SIBO in POTS is a new concept and appears to play an important role.

Leonard B. Weinstock et al., Successful Treatment of Postural Orthostatic Tachycardia and Mast Cell Activation Syndromes Using Naltrexone, Immunoglobulin and Antibiotic Treatment. British Medical Journal Case Reports, Jan 11, 2018.

Impact on Mast Cells

Mast cells react to potential threats to the body such as infection and mediate inflammatory responses such as hypersensitivity and allergic reactions.

- When activated, mast cells release their contents, called mediators, which both promote and regulate activity in other cells related to immunological as well as non-immunological processes.
  - LDN stops the immune cascade at the Toll-like receptors and by releasing endorphins.
  - LDN also reduces B-cell activity and hence could reduce antibody stimulated mast cell activity.

Treatment: A Clinician's Perspective

- "Start low and go slow" – begin at a dose of 0.5 to 1.5 mg a day and increase (0.5 to 1.5 mg) every 2 weeks to a maximum dose of 4.5 mg.
  - Not everyone needs to be increased to dose of 4.5 mg to benefit.
- Have patience – some patients may not see benefit for 3 to 6 months.
- Some individuals do not tolerate medication because of insomnia – in these individuals change dosing from evening to morning
- Length of treatment can be 3 -12 months
  - Individuals with autoimmune disease may need to stay on medication for a longer duration.

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Usage of LDN

- By September 2016, over 60 publications existed concerning the clinical use of low dose naltrexone.
- As of September 2016, over 300,000 patients worldwide enjoy the benefits of LDN.

LDNscience. Medsight.

Summary of Benefits of LDN

- Increases the amount of OGF thereby increasing immune-healing repair and decreasing the severity of pain.
- Acts as an immuno-modulator by not boosting the immune system by instead selectively improving its function
- Decreases inflammation/neuroinflammation
  - Reduces the activity of microglia
  - Temporarily blocks Toll-like receptors on sensory nerves (reducing pain) and on mast cells (decreasing autoimmune processes)

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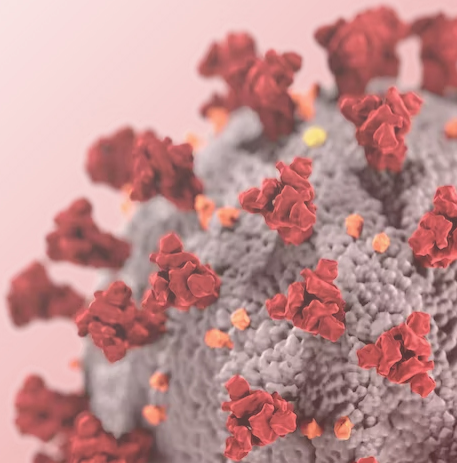

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