I-RECOVER℠

LONG COVID TREATMENT

An approach to treating long COVID

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DISCLAIMER

The information in this document is our recommended approach to long COVID and spike protein-related disease. It based on the best (and most recent) literature and aims to provide guidance to healthcare providers worldwide. Our guidance should only be used by medical professionals in formulating their approach to patients with long COVID and spike protein-related disease. Patients should always consult with a provider before starting any medical treatment.

As this is a highly dynamic topic, we will update these guidelines as new information emerges. Please check to ensure you are using the latest version of this document. Furthermore, due to the marked overlap between long COVID and post-vaccine syndrome, please refer also to the *I-RECOVER Post Vaccine Treatment* strategy. This document highlights the differences between these two syndromes.

ABOUT LONG COVID

Many patients experience prolonged illness after COVID-19. This is commonly known as 'long COVID', 'Long Haul COVID Syndrome (LHCS)' and, more recently, by the terminology 'Post-acute sequelae of COVID-19 (PASC)'.

Long COVID may persist for months after the acute infection and almost half of patients report reduced quality of life. (1, 2) At least 65 million individuals worldwide are estimated to have long COVID. (3)

A puzzling feature of long COVID is that initial disease severity is not an accurate predictor; long COVID frequently occurs in people who had mild-to-moderate COVID cases as well as in younger adults who did not require respiratory support or intensive care. (4)

Many of the symptoms of long COVID are common to COVID-19 vaccine injury (also known as long vax); indeed, both disorders are considered manifestations of "spike protein-related disease" with a significant overlap in symptoms, pathogenesis, and treatment.

The major difference between long COVID and long vax is unresolved organizing pneumonia with persistent respiratory symptoms in patients with long COVID. Clinicians have also noted that long vax patients tend to have more severe illness due to a higher incidence and severity of neuropathic symptoms and dysautonomia.

Long COVID is a heterogenous syndrome, meaning its symptoms and clinical features vary widely in presentation, severity, and underlying causes or contributing factors. It is characterized by prolonged malaise, headaches, generalized fatigue, sleep difficulties, hair loss, smell disorder, decreased appetite, painful joints, dyspnea, chest pain, and cognitive dysfunction. (1, 4-15) Patients may suffer prolonged neuropsychological symptoms, including multiple domains of cognition. (1, 2)

The symptom set of long COVID is, in the majority of cases, very similar to chronic inflammatory response syndrome (CIRS)/myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). (4) An important differentiating factor from CIRS is the observation that long COVID continues to improve on its own, albeit slowly in most cases. Another important observation is that long COVID includes more young people compared to severe COVID, which affects older people or persons with comorbidities.

Furthermore, the similarity between mast cell activation syndrome (MCAS) and long COVID has been observed, and many consider long COVID to be a variant of MCAS.

Theories For Why Long COVID Occurs

Long COVID likely results from a variety of pathogenetic mechanisms. Furthermore, delayed treatment in the early symptomatic phase, which results in a high viral load (high spike protein load), may increase the risk and severity of long COVID. This underlines the importance of early identification and treatment of COVID infection. See *I-CARE Early COVID Treatment* for more information.

Several theories have been postulated to explain long COVID, including: (4)

1. Ongoing respiratory symptoms (shortness of breath, cough, reduced effort tolerance) may be related to unresolved organizing pneumonia (activated pulmonary macrophages).
2. Monocyte and microglia activation. Persistence of spike protein in monocytes, macrophages, pericytes and microglia results in an ongoing inflammatory response in an attempt by the immune system to clear the offending protein(s) and viral RNA fragments. (16)
3. The neurological symptoms may be related to micro- and/or macrovascular thrombotic disease, which appears to be common in severe COVID-19 disease. (17) The brain microvasculature expresses ACE-2 receptors and SARS-CoV-2 “pseudovirions” may bind to the microvascular endothelium causing cerebral microvascular inflammation and clotting. (18) Brain MRIs three months post-infection demonstrated micro-structural changes in 55% of patients. (19)
4. Due to molecular mimicry, the spike protein results in a vast spectrum of autoantibodies, many of which are associated with neurological complications. In particular, features of encephalopathy may be related to encephalitis and auto-reactive brain antibodies. (20) Small fiber neuropathy and autonomic neuropathy (POTS) are directly associated with the presence of autoantibodies. Antibodies against the ACE2 receptor and G-coupled membrane receptors are commonly found in long COVID patients.
5. An unmasking or triggering of MCAS. Mast cells are present in the brain, especially in the median eminence of the hypothalamus, where they are located perivascularly close to nerve endings positive for corticotropin releasing hormone. (21) Following stimulation, mast cells release proinflammatory mediators such as histamine, tryptase, chemokines, and cytokines, which may result in neurovascular inflammation. (21) The “brain fog,” cognitive impairment and general fatigue reported in long COVID may be due to mast cell related neurovascular inflammation.
6. Immune suppression with reactivation of dormant viruses and/or reactivation of chronic bacterial infections (i.e., Lyme disease, etc.).

Groups of Symptoms

Further, the clinical signs and symptoms can be grouped in the following clusters. The reason for this grouping is to allow organ-specific targeted therapy or individualized therapy:

1. **Respiratory**: shortness of breath, congestion, persistent cough, etc.
2. **Neurological/psychiatric**: brain fog, malaise, tiredness, headaches, migraines, depression, inability to focus or concentrate, altered cognition, insomnia, vertigo, panic attacks, tinnitus, anosmia, phantom smells, etc.
3. **Musculoskeletal**: myalgias, fatigue, weakness, joint pains, inability to exercise, post-exertional malaise, inability to perform normal activities of daily life

4. **Cardiovascular**: Palpitations, arrhythmias, Raynaud-like syndrome, hypotension, and tachycardia on exertion
5. **Autonomic**: Postural tachycardia syndrome (POTs), abnormal sweating
6. **Gastrointestinal disturbance**: anorexia, diarrhea, bloating, vomiting, nausea, etc.
7. **Dermatologic**: itching, rashes, dermatographia
8. **Mucus membranes**: running nose, sneezing, burning and itchy eyes

TREATMENT STRATEGY FOR LONG COVID

Initial Screening Tests

Many patients undergo a vast array of diagnostic tests including cytokines and chemokines, autoantibodies, and toxicological studies. These tests are expensive, have very little clinical relevance and only complicate the management of these patients.

The following basic tests are recommended:

- CBC with lymphocyte count and CD8+ count
- Chemistry with liver function tests
- CRP (inflammation)
- Ferritin (macrophage activation)
- D-dimer
- Early morning cortisol
- Thyroid function tests
- HbA1C—long COVID patients are at an increased risk of developing diabetes
- Autoantibodies: antiphospholipid antibody and ANA
- In patients with allergic features or those who experienced an acute reaction to the vaccine, the following tests may be helpful: eosinophil count; IgE levels, RAST testing and/or skin testing. Serum tryptase, serum histamine and/or 24-h urine N-methylhistamine should be considered in MCAS. (22)
- Reactivated viruses: Antibodies/PCR against EBV Herpes I/II and CMV
- Vitamin D level

Specific Phenotypic tests

- CXR / chest CT with contrast
- Brain MRI
- ECHO

General Approach to Treatment

Although numerous reports describe the epidemiology and clinical features of long COVID, (1, 5-14) studies evaluating treatment options are glaringly sparse. (23) Indeed, the NICE guideline for managing the long-term effects of COVID-19 provide no specific pharmacologic treatment recommendations. (24) Patients with long COVID should be managed by clinicians who have experience treating this troublesome disorder.

The treatment approach should be individualized according to the grouping of clinical signs and symptoms. However, in general, it is likely that patients who did not receive adequate antiviral treatment (e.g**.,** ivermectin, etc.) and adequate anti-inflammatory/macrophage repolarization treatment during the acute symptomatic phase of COVID-19 are more likely to develop long COVID.

The core problem in long COVID is chronic "immune dysregulation." The primary treatment goal is to help the body to restore and normalize the immune system — in other words, to let the body heal itself. We recommend the use of immune-modulating agents and interventions to dampen and normalize the immune system rather than the use of immunosuppressant drugs, which may make the condition worse. However, the concomitant use of a controlled course of an immunosuppressant drug may be appropriate in patients with specific autoimmune conditions.

In addition to treating organizing pneumonia, as noted below, our suggested treatment strategy involves two major approaches i) promote autophagy to help rid the cell of the spike protein and ii) interventions that limit the toxicity/pathogenicity of the spike protein.

Treatment must be individualized according to each patient's presenting symptoms and disease syndromes. Not all patients respond equally to the same intervention; this suggests that the treatment must be individualized according to each patient's specific response. Patients should serve as their own controls and the response to treatment should dictate the modification of the treatment plan. One (or at most two) new interventions should be added at a time to evaluate what helps the patient and those interventions that are not helpful.

Early treatment is essential; the response to treatment will likely be attenuated when treatment is delayed.

Patients should be started on the primary treatment strategy; this should, however, be individualized according to the patient's particular clinical features. The response to the primary treatments should dictate the addition or subtraction of additional therapeutic interventions. Second-line therapies should be started in those who have responded poorly to the core therapies and in patients with severe incapacitating disease.

Patients with long COVID must not receive further COVID-19 vaccines of any type.

Treating Organizing Pneumonia

As noted previously, the major difference between long COVID and long vax is unresolved organizing pneumonia with persistent respiratory symptoms. Therefore, in patients with ongoing respiratory symptoms, chest imaging is suggested (preferably a chest CT scan).

Those with unresolved pulmonary inflammation (organizing pneumonia with ground glass opacification) should be treated with a course of corticosteroids. Low-dose prednisolone/methylprednisolone (10 mg/day) for six weeks is suggested. (25) However, the patients' symptoms and CRP should be followed closely, as a dose escalation may be required in those who respond poorly.

An unknown number of patients who have recovered from COVID-19 organizing pneumonia will develop pulmonary fibrosis with associated limitation of activity. Pulmonary function testing demonstrates a restrictive type pattern with decreased residual volume and DLCO. (11) These patients should be referred to a pulmonologist with expertise in pulmonary fibrosis. Anti-fibrotic therapy may have a role in these patients, (26-29) however additional data is required before this therapy can be more generally recommended. The serotonin receptor blocker cyproheptadine may reduce the risk of pulmonary fibrosis. (30)

FIRST-LINE THERAPIES

(Not symptom specific; listed in order of importance)

Intermittent daily fasting or periodic daily fasts

Fasting has a profound effect on promoting immune system homeostasis, improving mitochondrial health, and increasing stem cell production. Fasting stimulates the clearing of damaged mitochondria (mitophagy), misfolded and foreign proteins, and damaged cells (autophagy). Autophagy likely removes spike protein and misfolded proteins induced by the spike protein. Autophagy may therefore play a critical role in reversing the "spikopathy" induced by COVID infection. Indeed, activation of autophagy may be the only mechanism to remove intracellular spike protein.

The reader is referred to the *FLCCC Guide to Intermittent Fasting and Healthy Eating* for more detailed information.

Ivermectin (IVM)

It is likely that ivermectin and intermittent fasting act synergistically to rid the body of the spike protein. Ivermectin binds to the spike protein, aiding in the elimination by the host. (31-33) A trial of ivermectin should be included in the first-line treatment approach. Ivermectin has potent anti-inflammatory properties. (34-36)

Dosing and administration

Ivermectin is best taken with or just following a meal for greater absorption.

Based on the most updated clinical experiences in our collaborative network, we propose the following treatment approach:

- Initiate therapy with 0.3 mg/kg daily. Reassess for improvements in 2-3 weeks.
    - If no improvement is noted, a trial of discontinuation should be initiated. Be aware that in a minority of cases, patients who did not initially sense a benefit with use will report worsening of symptoms when IVM is discontinued. These patients should be restarted on daily ivermectin.
    - If improvements or a reduction in symptoms are noted, a 10-day trial of a higher dose should be initiated, typically by doubling the dose (0.6mg/kg day), given that a

significant proportion of ivermectin-responsive patients report even greater benefits at higher doses.

- If the patient reports additional benefit with doubling the initial dose, continue patient on 0.6mg/kg daily.

- If the patient does not report additional benefit at the higher dose, reduce ivermectin to the initial dose of 0.3mg/kg daily.

- For ivermectin responders, prolonged and chronic daily treatment is often necessary to support their recovery. In many, if the daily ivermectin is discontinued worsening symptoms often recur within days.

- Weaning/discontinuation – once patients have clinically improved to a desirable extent on a treatment regimen that includes daily ivermectin, we maintain the treatment regimen for at least 2 months before trying to decrease dose and/or reduce the frequency of ivermectin. Weaning and/or discontinuing is not possible in many patients due to recurrence of symptoms.

Table 1. How to Calculate Ivermectin Dose

Use the table below to help determine how much ivermectin you should take, based on your body weight and the specific recommendation in the strategy or guide you are following. Based on the dosage, you can then determine how many pills or capsules you need to take, bearing in mind that ivermectin is available in different strengths (e.g., 3, 6, or 12 mg) and administration forms (tablets, capsules, drops, etc.). Remember that tablets can be halved for more accurate dosing, while capsules cannot.

For example: A 160 lb. person needs to take a daily dose of 0.3 mg/kg. Her doctor has provided her with 3 mg tablets. Based on this table, her daily dose should be 21-23 mg, so she should take 7 tablets.

How much do I weigh?		The strategy says…			
In pounds	In kilos	"0.2 mg/kg"	"0.3 mg/kg"	"0.4 mg/kg"	"0.6 mg/kg"
		So my dose is…			
70–90	32–41	6-8 mg	10-12 mg	13-16 mg	19-25 mg
91–110	41–50	8-10 mg	12-15 mg	17-20 mg	25-30 mg
111–130	50–59	10-12 mg	15-18 mg	20-24 mg	30-35 mg
131–150	60–68	12-14 mg	18-20 mg	24-27 mg	36-41 mg
151–170	69–77	14-15 mg	21-23 mg	27-31 mg	41-46 mg
171–190	78–86	16-17 mg	23-26 mg	31-35 mg	47-52 mg
191–210	87–95	17-19 mg	26-29 mg	35-38 mg	52-57 mg
211–230	96–105	19-21 mg	29-31 mg	38-42 mg	58-63 mg
231–250	105–114	21-23 mg	32-34 mg	42-45 mg	63-68 mg
251–270	114–123	23-25 mg	34-37 mg	46-49 mg	68-74 mg
271–290	123–132	25-26 mg	37-40 mg	49-53 mg	74-79 mg
291–310	132–141	26-28 mg	40-42 mg	53-56 mg	79-85 mg

Cautions and contraindications

Due to the possible drug interaction between quercetin and ivermectin, these drugs should not be taken simultaneously (i.e., should be staggered morning and night). The safety of ivermectin in pregnancy is uncertain and this drug should therefore be avoided in the first trimester of pregnancy. (37)

Moderating physical activity

Patients with long COVID frequently suffer from severe post-exertional fatigue and/or worsening of symptoms with exercise. (38, 39) Aerobic exercise is reported to be one of the worst therapeutic interventions for these patients.

Dosing and administration

We recommend moderating activity to tolerable levels that do not worsen symptoms, keeping the patient's heart rate under 110 BPM. Furthermore, patients need to identify the activity level beyond which their symptoms worsen, and then aim to stay below that level of activity. Stretching and low-level resistance exercises are preferred over aerobic exercises.

Mechanisms

Similar to patients with chronic fatigue syndrome, post-exertional fatigue may be related to mitochondrial dysfunction and the inability to augment production of ATP. (38, 40, 41) Magnetic resonance–augmented cardiopulmonary exercise testing suggests failure to augment stroke volume as a potential mechanism of exercise intolerance in patients with long COVID. (42)

Low-dose naltrexone (LDN)

LDN has been demonstrated to have anti-inflammatory, analgesic, and neuromodulating properties. (43, 44)

Dosing and administration

1-4.5 mg daily. Begin with 1 mg/day and increase to 4.5 mg/day, as required. May take 2 to 3 months to see the full effect.

Cautions and contraindications

Clinicians should exercise caution when using LDN in patients who are also taking opioids for chronic pain, as they may exhibit withdrawal symptoms if these medications are taken simultaneously.

Nattokinase

Dosing and administration

100-200 mg (2000-4000 FU) twice daily. Aspirin/ASA 81 mg daily can be added in low-risk patients.

Mechanisms

Nattokinase is a highly effective fibrinolytic and antiplatelet agent which targets the abnormal clotting in the long COVID and spike-injured patient. In addition, nattokinase has been demonstrated to lyse extracellular spike protein; this may further enhance the anti-clotting action of nattokinase**.**

Melatonin

Melatonin has anti-inflammatory and antioxidant properties and is a powerful regulator of mitochondrial function. (45-49)

Dosing and administration
2-6 mg *slow release/extended release* prior to bedtime. The dose should be started at 750 mcg (µg) to 1 mg at night and increased as tolerated.

Cautions and contraindications
Patients who are slow metabolizers may have very unpleasant and vivid dreams with higher doses.

Magnesium

Dosing and administration
A starting dose of 100 to 200 mg daily is suggested, increasing the dose as tolerated up to 300 mg (females) to 400 mg daily. Endpoints of treatment include an RBC-Mag at the higher end of the normal range (between 4.2 and 6.8 mg/dL to be about 6.0 ng/dL).

Mechanisms
There are at least 11 different types of magnesium that can be taken in supplement form with varying bioavailability. Generally, organic salts of Mg have a higher solubility than inorganic salts and have greater bioavailability. (50) Magnesium citrate is a widely used type of magnesium in salt form and is often recommended to treat constipation; high doses may cause diarrhea and prolonged use should be avoided. Magnesium oxide and magnesium citrate compounds, commonly prescribed by physicians, have poor bioavailability. (51) Magnesium Malate, Taurate, Glycinate, and L-threonate have good bioavailability and will readily increase RBC magnesium levels. Magnesium taurate and magnesium L-threonate significantly increase magnesium levels in brain cells; hence they are used in the treatment of depression and Alzheimer's disease. (51, 52)

Cautions and contraindications
High intakes of magnesium from dietary supplements and medications can cause diarrhea, nausea, and abdominal cramping.

Methylene blue

Low Dose Methylene Blue (LDMB) is a therapeutic option in patients with brain fog and other neurological symptoms; this can be combined with transcranial photobiomodulation.

Dosing and administration
10-30 mg daily. The optimal dose is highly individualized and each patient needs to find the right dose for them.

It is important that patients and/or their healthcare providers purchase high-quality, impurity-free, pharmaceutical-grade methylene blue. Patients may purchase a 1% methylene blue solution (e.g. https://www.bphchem.com/product/methylene-blue-1-usp-grade-50-ml-1-drop-contains-0-5-mg-of-methylene-blue), MB in a powder form requiring reconstitution into a 1% solution (e.g. from CZTL at https://cztl.bz/?ref=Lwr85) or MB Buccal Trouches (https://troscriptions.com/products/) (will cause blue staining of mouth and teeth; trouches can be swallowed to avoid this effect).

A 1% methylene blue solution contains 10 mg MB in 1 ml solution (and 0.5 mg/drop). A 1% MB solution is formulated by mixing 1 gram of methylene blue with 100 ml of water. Use a dropper bottle to administer — 1 drop of 1% solution is approximately 0.5 mg of methylene blue).

Dosing of LDMB:

- Start with 5 mg (.5 ml) twice daily for the first week.
- Gradually increase the dosage every 2-3 days (guided by symptoms - i.e., improvement in fatigue and/or cognitive improvement) until you reach a maximum of 30 mg (3 ml) per day.
- Take the 7th day off every week to allow the body to "reset".

Mechanisms

Methylene blue (MB) has a number of biological properties that may be potentially beneficial in long COVID patients. MB induces mitophagy (mitochondrial autophagy) and has anti-inflammatory, antioxidant, neuroprotective, and antiviral properties. (53, 54) A study in 2013 found that methylene blue-induced neuroprotection is mediated, at least in part, by macroautophagy through activation of AMPK signaling. (55)

MB easily crosses the BBB and preferentially enters neuronal mitochondria. MB has high bioavailability to the brain with brain tissue levels tenfold higher than serum levels. (56, 57) Low-dose methylene blue (LDMB) stimulates mitochondrial respiration by donating electrons to the electron transport chain. MB can reroute electrons directly from complex I to complex III, avoiding electron leakage and subsequent ROS production.

MB and photobiomodulation (PBM) have similar beneficial effects on mitochondrial function, oxidative damage, and inflammation. Treatment with MB is therefore often combined with PBM therapy. (58, 59). However, because PBM and MB exert beneficial effects through distinct mechanisms, combining the use of these two therapies is expected to improve therapeutic outcomes synergistically. Numerous studies indicate an improvement in brain mitochondrial function and neurological function following treatment with MB and PBM for a spectrum of neurological diseases. (57, 58, 60)

Cautions and contraindications

LDMB will cause your urine to be blue or blue-green. Some patients may experience a Herx reaction. A Herx reaction may cause fatigue, nausea, headache, or muscle pain. If you experience a Herx reaction, stop the treatment for 48 hours and then resume again slowly.

DO NOT take MB if you are pregnant or breastfeeding.

MB is a potent monoamine oxidase inhibitor (MAOI) that, in conjunction with an SSRI, can potentiate serotonin syndrome, a life-threatening medical emergency. This combination of medications is to be strongly avoided. **Do not take FLUVOXAMINE, FLUOEXETINE or BUPROPION or any other SSRI -NDRI (norepinepine-Dopamine Reutake Inhibitor) with MB.**

MB increases toxicity of hydrocodone bitartrate by increasing serotonin levels in the blood. This combination should be avoided.

Individuals with glucose-6-phosphate dehydrogense deficiency (G6PD) should not be treated with MB as it can cause hemolytic anemia.

Sunlight and Photobiomodulation (PBM)

Sunlight has great therapeutic powers. Our forefathers roamed the earth and were exposed to sunlight on a daily basis, likely with profoundly important health benefits. (61)

Dosing and administration

We suggest that patients expose themselves to about 30 mins of midday sunshine whenever possible (at least 3 times a week). A brisk midday walk is a viable alternative. When neither of these interventions is feasible or practical, and in those who wish to avoid ultraviolet radiation exposure, patients can expose themselves to red and NIR radiation emitted from LED panels.

Those interested in this therapy are recommended to read the book by Ari Whitten entitled "The Ultimate Guide to Red Light Therapy." (62)

A number of LED panels with multiple red and IR lights are commercially available (e.g. https://mitoredlight.com/, https://hoogahealth.com/, https://platinumtherapylights.com/. The disadvantage of LED panels is they do not mimic that of solar radiation as they deliver 1-10 nm wide spiked emissions of red light at 660 nm and NIR-A at 830 nm. In contrast, ThermaLight® bulbs (SaunaSpace® Saunas™) have a radiation spectrum closely resembling that of solar radiation, but without UV radiation. About 39% of the emitted spectrum of the ThermaLight® bulb is NIR-A (the solar spectrum has 41% IR-A) and about 41% of the radiation is in the IR-B range; part of IR-A and IR-B (1000-3000 nm) contributes to the thermal effects of emitted radiation, which promotes induced hyperthermia (sauna therapy).

Mechanisms

PBM is referred to in the literature as low-level light therapy, red light therapy, and near-infrared light therapy. The spectral radiance of solar radiation extends from 10 nm to about 3000 nm i.e., the spectrum from ultraviolet (10-400 nm), visible (400-700 nm with red light 600-700 nm), near-infrared radiation (750-1500 nm (NIR-A)) and mid-infrared radiation (1500- 3000 nm (NIR-B)).

Of all the wavelengths of sunlight, NIR-A radiation has the deepest penetration into tissues, being up to 23cm. NIR-A in the range of 1000 to 1500 nm is optimal for heating tissues. Indeed, during the 1918 influenza pandemic, "open-air treatment of influenzae" appeared to be the most effective treatment for seriously ill patients. (63) The Surgeon-General of Massachusetts reported that "*plenty of air and sunshine*" was highly effective for the treatment of influenzae pneumonia. He reported that *"very little medicine was given after the value of plenty of air and sunshine had been demonstrated*." Further, he comments "*from being discouraged, the medical staff became enthusiastic, and the patients were treated with the confidence that at last something had been found which would give good results*."

A more recent large prospective study demonstrated that avoiding sun exposure is a risk factor for all-cause mortality. (64) In this study, the mortality rate amongst avoiders of sun exposure was approximately twofold higher compared with the highest sun exposure group. Apart from UV radiation stimulating vitamin D synthesis, red and near-infrared (NIR) radiation have a profound effect on human physiology, notably acting as a mitochondrial stimulant and increasing ATP production. (65)

The most well-studied mechanism of action of PBM centers around enhancing the activity of cytochrome c oxidase, which is unit four of the mitochondrial respiratory chain, responsible for the final reduction of oxygen to water. In addition, one of the most reproducible effects of PBM is an overall reduction in inflammation. PBM has been shown to reduce markers of M1 phenotype in activated macrophages. (65) Many reports have shown reductions in reactive nitrogen species and prostaglandins in various animal models. In addition, PBM activates a wide range of transcription factors leading to improved cell survival. It has also been suggested that NIR light increases the production of melatonin in mitochondria. (66)

In an outstanding *in vitro* study, Aguida et al demonstrated that infrared light caused a marked reduction in the TLR-4-dependent inflammatory response pathway in a human cell culture line. (67) In this study, infrared light exposure resulted in a significant decline in NFkB and AP1 activity as well as a marked decrease in the expression of proinflammatory genes. The increased body temperature induced by NIR-A and NIR-B activates the production of heat shock proteins (which increase autophagy) as well as essential cell stress survival pathways.

Emerging data suggest that transcranial PBM has beneficial effects in a range of neuro-psychiatric diseases including stroke, traumatic brain injury, Alzheimer's disease, Parkinson's disease, and depression. (68-71) PBM has been suggested to have a role in the prevention and treatment of COVID-19. (72) A recent double-blind, sham-controlled study using an LED device demonstrated a marked improvement in the condition of hospitalized patients with acute COVID-19 infection. (73)

Vitamin D and Vitamin K2

Vitamin D (4000-5000 units/day) and Vitamin K2 (100 mcg/day); The dose of Vitamin D should be adjusted according to the baseline Vitamin D level. However, a dose of 4000-5000 units/day of Vitamin D, together with Vitamin K2 100 mcg/day is a reasonable starting dose.

Resveratrol or a combination flavonoid

Resveratrol is a plant phytochemical (flavonoid) that has remarkable biological properties. (74-76) Most importantly it activates autophagy. (77, 78)

Dosing and administration

400-500 mg daily. Resveratrol may potentiate the effect of time restricted feeding (intermittent fasting) in activating autophagy. Resveratrol should therefore be taken during fasting and not with a meal. For acutely symptomatic patients, resveratrol in a dose of 500 mg twice daily is suggested. In recovered patients and those on preventative/maintenance therapy, a dose of 400-500 mg/day should suffice.

Mechanisms

Resveratrol has anti-inflammatory, antiviral, antioxidant, and anticoagulant properties and has beneficial effects on the microbiome. Resveratrol also binds to spike protein helping to promote autophagy.

Quercetin, a plant flavonoid with many of the biological properties of resveratrol, acts synergistically with resveratrol and increases the bioavailability of resveratrol. (79-81) Pterostilbene, is another plant flavonoid similar to resveratrol in structure with similar biological properties. (82-84) However, pterostilbene's unique structure makes it more oil-soluble than resveratrol, which increases its absorption and cellular uptake while reducing the rate of elimination from the body. Research has shown that pterostilbene has seven times the half-life of resveratrol and has greater bioactivity in reducing the effects of oxidative stress. We, therefore, suggest a "high quality" combination supplement with resveratrol and quercetin and ideally also containing pterostilbene.

Cautions and contraindications

Generally, the oral bioavailability of resveratrol is poor. (85) However, a bio-enhanced formulation containing trans-resveratrol from Japanese Knotweed Root appears to have improved bioavailability.

The safety of these phytochemicals has not been determined in pregnancy and they should therefore be avoided.

Due to the possible drug interaction between quercetin and ivermectin these drugs should not be taken simultaneously (i.e., should be staggered morning and night).

The use of quercetin has rarely been associated with hypothyroidism. (86) The clinical impact of this association may be limited to those individuals with pre-existent thyroid disease or those with subclinical thyroidism. Quercetin should be used with caution in patients with hypothyroidism and TSH levels should be monitored.

Probiotics/prebiotics

Patients with long COVID classically have a severe dysbiosis with loss of Bifidobacterium. (87-89)

Dosing and administration

A no-sugar-added, Greek yogurt with both pre- and probiotics is recommended. Suggested probiotics include Megasporebiotic (Microbiome labs), TrueBifidoPro (US Enzymes), and yourgutplus+. (90) In addition, the use of Glucomannan (from Konjac root) and/or Chia seeds provide soluble and insoluble fiber (prebiotic) required for the normalization of the microbiome.

Cautions and contraindications

If patients have moderate to severe dysbiosis and/or small bowel bacterial overgrowth (SBIO) then prebiotics may have the unwanted effect of ''feeding the bad bacteria" and contributing to worsening of the dysbiosis. Probiotics alone and/or fermented foods are less likely to harbor and nourish commensal and abnormal gut microbes. Depending on the brand, some pro/prebiotic products can be very high in sugar, which promotes inflammation. Look for brands without added sugar and try to choose products that are also gluten-free, casein-free, and soy free.

ADJUNCTIVE/SECOND-LINE THERAPIES

(Listed in order of importance)

Omega-3 fatty acids We suggest a combination of EPA/DHA with an initial dose of 1 g/day (combined EPA and DHA) and increasing up to 4 g/day (of the active omega-3 fatty acids). The omega-3 fatty acids have anti-inflammatory and cardioprotective effects and play an important role in the resolution of inflammation by inducing resolvin production. (91, 92) Furthermore, omega-3 fatty acids are believed to afford potent vasculoprotective effects, by improving endothelial function, limiting vascular inflammation, reducing thrombosis, and limiting reactive oxygen species production. (93) Fish, particularly wild Atlantic (or Alaskan) salmon, are a good source of omega-3 fatty acids. Omega-3 supplements include Vascepa™ (icosapent ethyl; an ethyl ester of eicosapentaenoic acid [EPA]), Lovaza™ (a combination of ethyl esters of EPA and docosahexaenoic acid [DHA]) as well as “regular fish oil supplements” containing a combination of EPA/DHA. It is unclear if the reported cardiovascular and anti-inflammatory benefits of omega-3 fatty acids are predominantly due to EPA (i.e., Pharma marketing) or the combination of EPA and DHA. (94-101) However, it is now widely appreciated that ”*EPA and DHA are metabolized to different mediators and are equally important with respect to cardiovascular protection (and inflammation)*.” (98) Based on this data we suggest a combination of EPA/DHA with an initial dose of 1 g/day (combined EPA and DHA) and increasing up to 4 g/day (of the active omega-3 fatty acids).

N-acetyl cysteine (NAC) 600-1500 mg/day (102-104) NAC is the precursor of reduced glutathione. NAC penetrates cells where it is deacetylated to yield L-cysteine thereby promoting GSH synthesis. (104) Based on a broad range of antioxidant, anti-inflammatory, and immune-modulating mechanisms, the oral administration of NAC likely plays an adjuvant role in the treatment of spike

protein-related disease. Several studies showed that NAC is well absorbed by the intestine and that a supplementation with NAC is effective for increasing GSH levels.

Oral glutathione is poorly absorbed and is generally not recommended. (105, 106) However, acetyl glutathione is more lipophilic than glutathione, sufficiently so to be taken up intact by cells, and has been shown to rapidly raise intracellular GSH levels. A combination supplement that contains acetyl glutathione, NAC and Vitamin C may enhance the bioavailability of glutathione. In addition, liposomal glutathione has been demonstrated to increase tissue levels, antioxidant capacity and immune function. (107)

Cardio Miracle™ and L-arginine/L-citrulline supplements Cardio Miracle is a supplement with over 50 ingredients formulated to increase nitric oxide (NO) production. The supplement contains L-arginine, L-citrulline, Beetroot (high in dietary nitrates), L-Ornithine, CoQ10, as well as a blend of fruit and vegetable phytonutrients. L-Arginine is the substrate used for NO production by nitric oxide synthetase (NOS). Patients with acute COVID-19 infection have been demonstrated to have low plasma L-arginine levels. In addition, COVID-19 syndromes are characterized by suppressed endothelial nitric oxide synthase (eNOS) activity compounding the deficiency of NO. The spike protein itself may play a major role in inhibiting eNOS activity. The NO deficiency is a major factor causing endothelial dysfunction and thrombotic events. Furthermore, activation of the NO-cyclic GMP pathway has anti-inflammatory effects modulating activated T cells, reducing cytokine release, and stimulating vascular repair. In addition, L-arginine itself is important for normal T cell function and macrophage M1-to-M2 switch. It is likely that an L-arginine/L-citrulline supplement will have additive or synergistic effects when combined with a phosphodiesterase-5 inhibitor. (see below). L-arginine should likely be avoided in patients with active malignancies. (108, 109)

Nigella sativa 200-500 mg encapsulated oil twice daily. *Nigella sativa* is a small shrub native to Southern Europe, North Africa, and Southeast Asia. The seeds and oil of *Nigella sativa* have been used as a medical agent for thousands of years. The most important active component is thymohydroquinone. *Nigella sativa* has antibacterial, antifungal, antiviral (SARS-CoV-2), anti-inflammatory, antioxidant, and immunomodulatory properties. (110, 111) A dose of 200-500 mg twice daily of the encapsulated oil is suggested. (110-113) It should be noted that thymohydroquinone decreases the absorption of cyclosporine and phenytoin. Patients taking these drugs should, therefore, avoid taking *Nigella sativa*. (114) Furthermore, two cases of serotonin syndrome have been reported in patients taking *Nigella sativa* who underwent general anesthesia (probable interaction with opiates). (115)

Sildenafil with or without L-arginine-L-Citrulline (116-121) Sildenafil doses titrated up from 25 to 100 mg 2-3 times daily with L-arginine/L-citrulline powder twice daily. May be helpful for brain fog as well as microvascular disease with clotting and poor perfusion. It is noteworthy that curcumin, resveratrol, EGGG, and valproic acid all potentiate phosphodiesterase 5 (PDE5) inhibitors.

Bromelain (500 mg twice daily) *In Vitro* studies have demonstrated that bromelain cleaves the spike protein. (122, 123) This effect appears to be enhanced by the addition of NAC (see below). (124)

Vitamin C 1000 mg orally two to three times a day. Vitamin C has important anti-inflammatory, antioxidant, and immune-enhancing properties, including increased synthesis of type I interferons. (125-129) Avoid in patients with a history of kidney stones. Oral Vitamin C helps promote the growth of protective bacterial populations in the microbiome.

Spermidine 1000-2000 mg (wheat germ extract) daily. Spermidine is a naturally occurring polyamine that, like resveratrol, has anti-inflammatory and antioxidant properties. It preserves mitochondrial function and has been shown to reduce cardiovascular disease and all-cause mortality and prolong lifespan. (130, 131) Furthermore, like resveratrol, spermidine promotes autophagy. However, resveratrol and spermidine activate autophagy via different metabolic pathways and are therefore likely to have additive or synergistic effects. (132) Wheatgerm, mushrooms, grapefruit, apples, and mango are high natural sources of spermidine. (133) Wheatgerm supplements contain high amounts of spermidine with good bioavailability. A dose of 1000-2000 mg wheat germ extract daily is suggested. Cancer cells are reported to have dysregulated polyamine metabolism and spermidine is therefore best avoided in patients with a known malignancy. (134) In addition, spermidine should be avoided in men over the age of 60 who are at high risk of an ischemic stroke. (135)

Non-invasive brain stimulation (NIBS) Using transcranial direct current stimulation or transcranial magnetic stimulation, NIBS has been demonstrated to improve cognitive function in patients with long COVID as well as other neurological diseases. (136-143) NIBS is painless, extremely safe, and easy to administer. NIBS is a recognized therapy offered by many Physical Medicine and Rehabilitation Centers (e.g., see https://www.hopkinsmedicine.org/physical_medicine_rehabilitation/services/programs/brain-stimulation/treatment.html). Patients may also purchase an FDA-approved device for home use (e.g., https://www.fisherwallace.com)

Intravenous Vitamin C 25 g weekly, together with oral Vitamin C 1000 mg (1 gram) 2-3 times per day. High-dose IV vitamin C is “caustic” to the veins and should be given slowly over 2-4 hours. Furthermore, to assess patient tolerability the initial dose should be between 7.5-15 g. Total daily doses of 8-12 g have been well-tolerated, however, chronic high doses have been associated with the development of kidney stones, so the duration of therapy should be limited. Wean IV Vitamin C as tolerated.

Behavioral modification, relaxation therapy, mindfulness therapy (144), and psychological support may help improve patients’ overall well-being and mental health. (4) Support groups and consultation with mental health professionals are important. Tai Chi, a health-promoting form of traditional Chinese martial art, has been shown to be beneficial for preventing and treating diseases including long COVID. (145, 146) Yoga has immunomodulating properties that may be beneficial in long COVID patients. (147)

THIRD LINE THERAPIES

Hyperbaric oxygen therapy (148-156); HBOT has potent anti-inflammatory properties, decreasing pro-inflammatory cytokines while increasing IL-10. Furthermore, HBOT polarizes macrophages toward the M2 phenotype and improves mitochondrial function. Surprisingly, it is the increased pressure, rather than the increase in the concentration of dissolved oxygen, that appears to mediate these effects. HBOT is delivered at varying pressures, both with and without oxygen. The addition of oxygen increases the clinical response. Maximal clinical response is achieved via the use of high-pressure chambers (typically reaching 2.4 ATM) with 100% oxygen for 60-90 minutes. If HBOT is delivered using lower pressure chambers (less than 1.5 ATM) without supplemental oxygen, the clinical response, although present, is significantly less such that a higher number of sessions will be needed to reach a clinical plateau.

Zilberman-Itskovich et al performed a randomized, sham-controlled, double-blind trial that evaluated the effect of HBOT in 73 patients with long COVID. (23) Both HBOT and sham patients received 40 daily sessions (five times a week) in a multi-place chamber. The HBOT protocol included breathing 100% oxygen by mask at 2 ATM for 90 minutes. In the HBOT group, there was a significant improvement in global cognitive function, attention, and executive function as well as an improvement in the energy domain, psychiatric symptoms, and pain level. Clinical outcomes were associated with significant improvement in brain MRI perfusion and microstructural changes. In general, the duration of treatment of HBOT should be based on clinical response and continued for at least 40 sessions and until the benefit has plateaued. If no benefit is evident clinically after 10 sessions, then HBOT should be considered a therapeutic failure. This therapy is limited by logistical issues and cost. A number of companies offer to rent portable, low-pressure chambers with the option to purchase (https://www.oxyhealth.com/vitaeris-320.html, https://summit-to-sea.com/, https://www.aha-hyperbarics.com/)

Low Magnitude Mechanical Stimulation (LMMS or Whole-Body Vibration). Low-magnitude (0.3-0.4G), high-frequency (32-40 Hz) mechanical stimulation has been demonstrated to increase bone density as well as indices of general well-being in patients with a variety of medical disorders. (157) It is postulated that this intervention recruits bone marrow stem cells in addition to having metabolic and immunologic effects. In humans, low-magnitude acceleration is applied through the feet by standing on a platform oscillating at relatively high resonant frequency. These parameters are very safe, painless, and easy to administer. This therapy is offered by Physical Medicine and Rehabilitation Centers, or a device may be purchased for home use https://www.juvent.com/health/) similarly with noninvasive brain stimulation (NIBS).

"Mitochondrial energy optimizer" with pyrroloquinoline quinone, glycophospholipids, CoQ10, NADH, and other nutrients (e.g., Life Extension Energy Optimizer, Restorative Solutions Mitochondrial Nutrition PQQ, Researched Nutritionals ATP 360® and ATP Fuel® and Pure Encapsulations Mitochondria-ATP) (158-164)

Hydroxychloroquine (HCQ) 200 mg twice daily for 1-2 weeks, then reduce as tolerated to 200 mg/day. HCQ is a potent immunomodulating agent and is considered the drug of choice for systemic lupus erythematosus (SLE), where it has been demonstrated to reduce mortality from this disease. Thus, in patients with positive autoantibodies or where autoimmunity is suspected to be a prominent underlying mechanism, HCQ should be considered earlier. Further, it should be noted that SLE and long COVID have many features in common. HCQ is safe in pregnancy; indeed, this drug has been used to treat preeclampsia. (165-169) With long-term usage, the dose should be reduced (100 or 150mg/day) in patients weighing less than 61 kg (135 lbs.). It should be noted that HCQ will limit the effectiveness of intermittent fasting.

Low dose corticosteroid 10-15 mg/day prednisone for 3 weeks. Taper to 10 mg/day and then 5 mg/day, as tolerated.

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