I-RECOVER℠

POST-VACCINE TREATMENT

An approach to managing post-vaccine syndrome

March 2024

Information sent by Bazook894

Updates: order of suggested therapies changed; added treatment of mast cell activation; vagus nerve stimulation; ARC microcurrent device.

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Summary of Suggested Therapies

First-Line Therapies	Adjunctive/Second-Line Therapies	Third Line Therapies
Intermittent daily fasting or periodic daily fasts	Hyperbaric oxygen therapy	Low Magnitude Mechanical Stimulation (LMMS or Whole-Body Vibration)
Ivermectin (0.2-0.3 mg/kg daily)	Triple anticoagulation	"Mitochondrial energy optimizer"
Moderating physical activity	Vitamin D (4000-5000 units daily) and Vitamin K2 (100 mcg daily)	Low dose corticosteroid; 10-15 mg daily prednisone for 3 weeks. Taper to 10 mg daily and then 5 mg daily, as tolerated
L-Arginine (1.5 -2g twice daily) and Vitamin C (1000 mg orally two to three times daily)	Magnesium (100-200 mg daily)	
Low-dose naltrexone (1-4.5 mg daily)	Omega-3 fatty acids; we suggest a combination of EPA/DHA with an initial dose of 1 g daily (combined EPA and DHA) and increasing up to 4 g daily (of the active omega-3 fatty acids)	
Nattokinase (100-200 mg / 2000-4000 Fibrinolytic Units twice daily). Low dose aspirin (81 mg daily) can be added in low-risk patients.	N-acetyl cysteine (NAC) (600-1500 mg daily)	
Treatment of Mast Cell Activation with histamine blockers and mast cell stabilizers	Sildenafil with or without L-arginine-L-Citrulline	
Sunlight and Photobiomodulation (PBM)	Spermidine; 1000-2000 mg (wheat germ extract) daily	
Melatonin (2-6 mg *slow release/extended release* prior to bedtime)	ARC microcurrent device	
Bromelain (500 mg twice daily) +/- N-acetyl cysteine (NAC) (600 mg twice daily)	Methylene blue (10-30 mg daily)	
Nigella sativa (200-500 mg encapsulated oil twice daily)	Non-invasive brain stimulation (NIBS)	
Resveratrol or a combination flavonoid (400-500 mg daily)	Intravenous Vitamin C; 25 g weekly, together with oral Vitamin C 1000 mg (1 gram) 2-3 times per day	
Probiotics/prebiotics	Behavioral modification, relaxation therapy, mindfulness therapy, and psychological support	
Vagus Nerve Stimulation and nicotinic agonists		

Disclaimer

This document is primarily intended to assist healthcare professionals in providing appropriate medical care for vaccine-injured patients. Patients should always consult a trusted healthcare provider before embarking on any new treatment.

Definition

Although no official definition exists for 'post-COVID-vaccine syndrome,' a temporal correlation between receiving a COVID-19 vaccine and the beginning or worsening of a patient's clinical manifestations is sufficient to diagnose as a COVID-19 vaccine-induced injury when the symptoms are unexplained by other concurrent causes.

Contributors

This protocol was a collaborative effort drawing on the expertise of a dozen world-renowned physicians. Dr. Pierre Kory and Dr. Paul Marik are thankful for the contributions of: Dr. Flavio Cadegiani; Dr. Suzanne Gazda; Scott Marsland, FNP; Dr. Meryl Nass; Dr. Tina Peers; Dr. Yusuf (JP) Saleeby; Dr. Eugene Shippen; Dr. Mobeen Syed; and Dr. Fred Wagshul.

We are also extremely grateful to the many vaccine-injured people who shared their feedback and experiences with us.

Note that there are significant overlaps between the symptoms and features of long COVID/long-hauler syndrome and post-vaccine syndrome. However, a number of clinical features appear to be characteristic of post-vaccine syndrome; most notably, severe neurological symptoms appear to be more common following vaccination. To complicate matters further, patients with long COVID are often also vaccinated, making the issue of definition more difficult.

Epidemiology

The Centers for Disease Control (CDC), National Institutes for Health (NIH), Food and Drug Administration (FDA), and World Health Organization (WHO) do not recognize post-COVID-19 vaccine injuries as a specific medical condition, (1) even though there is a specific ICD-10 code. Curiously, the code U12.9 is recognized in Europe but not in the United States. There have been no prospective studies that have *accurately classified and logged* the incidence of this complication; therefore, the true magnitude of post-vaccine syndrome is unknown.

The true incidence of adverse events following COVID-19 injections, including deaths and serious vaccine injuries, is unknown; this is complicated by the deliberate and willful manipulation of data (underreporting) by governmental agencies in the United States, United Kingdom, Israel, and many other countries. (2, 3).

However, available data consistently and reproducibly demonstrates a rate of serious adverse events (SAE) of about 8%. (2, 3) Most importantly, the V-SAFE database administered by the CDC demonstrates an 8% rate of SAE (https://www.cdc.gov/coronavirus/2019-ncov/vaccines/safety/vsafe.html, https://icandecide.org/v-safe-data/. Translated to the U.S. vaccinated population, this would mean approximately 18 million vaccine injuries. A Pollfish survey released on July 4, 2022 reported that 8.64% of adult respondents who had received a COVID-19 vaccine in the U.S. developed a vaccine injury. A Rasmussen report published in December 2022 reported a 7% rate of SAE those jabbed. In a nationwide cohort of U.S. veterans, an adverse reaction was reported in 8.5% of recipients of the Pfizer vaccine and 7.9% of those receiving the Moderna vaccine. (4)

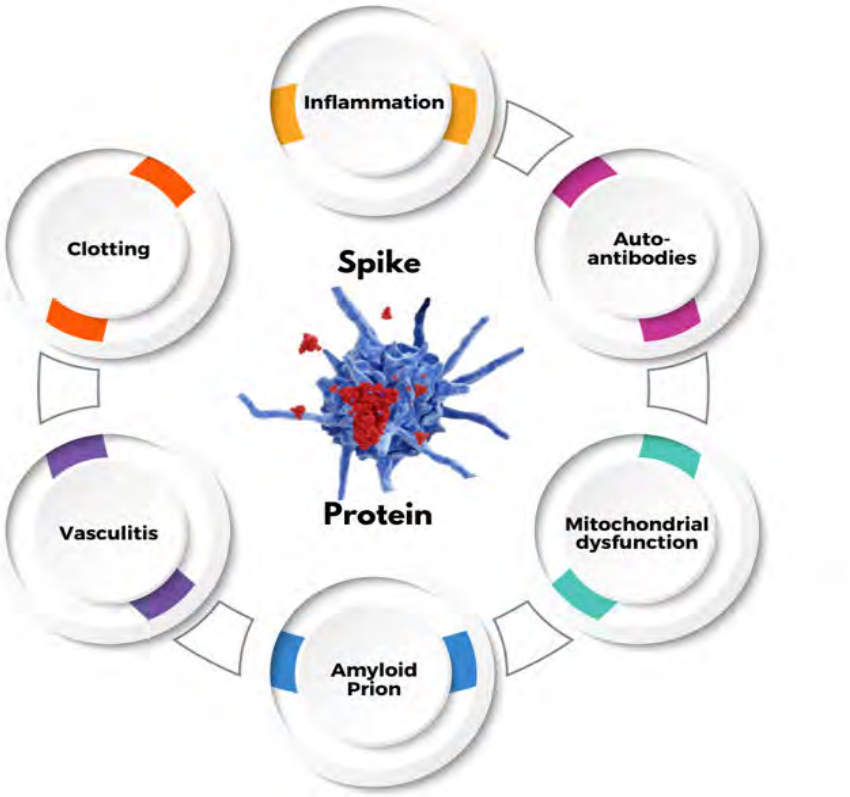
As the mainstream medical community does not recognize this serious humanitarian disaster, these patients have been shunned and denied access to the care they need and deserve. Furthermore, there is limited clinical, molecular, and pathological data on these patients to inform an approach to treating the condition. Consequently, our approach to the management of vaccine-injured patients is based on the presumed pathogenetic mechanism, pharmacologic principles, as well as the clinical observations of physicians and patients themselves.

Pathogenesis

The spike protein, notably the S1 segment, is likely the major pathogenetic factor leading to post-vaccine syndrome (see figure 1). (4-6) The S1 protein is profoundly toxic. Multiple intersecting and overlapping pathophysiologic processes likely contribute to the vast spectrum of vaccine injuries: (1, 7)

- The acute, immediate reaction (within minutes to hours) is likely the result of an acute type I IgE-mediated hypersensitivity reaction. The type I response may be due to preformed antibodies against mRNA, polyethylene glycol (PEG) (8, 9), or other components of the nano-lipid particle. In addition, PEG activates multiple 'complement components,' the activation of which may be responsible for both anaphylaxis and cardiovascular collapse. (9-11) A prospective study on 64,900 medical employees, in which reactions to their first mRNA vaccination were carefully monitored, found that 2.1% of subjects reported acute allergic reactions. (12)
- The acute myocarditis/sudden cardiac death syndrome that occurs post-vaccination (within hours to 48 hours), noted particularly in young athletes, may be caused by a "stress cardiomyopathy" due to excessive catecholamines produced by the adrenal medulla in response to spike protein-induced metabolic aberrations. (13)
- The subacute and chronic myocarditis is likely the result of a spike protein-induced inflammatory response mediated by pericytes and macrophages. (14, 15)
- The subacute (days) and chronic (weeks to years) vaccine-related injuries likely result from the overlapping effects of an S1-induced inflammatory response, the production of autoantibodies, activation of the clotting cascade, and secondary viral reactivation.
- The inflammatory response is mediated by spike protein-induced mononuclear cell activation in almost every organ in the body but most notably involving the brain, heart, and endocrine organs.
- Patients with long COVID and those post-vaccination may have spike protein circulating in the blood for as long as 15 months. (16-18) Spike protein inhibits natural killer (NK) cell activity, (19-22) cytotoxic T-cells, and inhibits autophagy (23); this may account for the persistence of the spike protein.
- The lipid nanoparticles (LNP) themselves are highly pro-inflammatory, as evidenced by excessive neutrophil infiltration, activation of diverse inflammatory pathways, and production of various inflammatory cytokines and chemokines. (24-26)
- Neuro-COVID, the neurological manifestations related to the spike protein, are related to the complex interplay of neuroinflammation, (27) production of amyloid and prion protein, autoantibodies, microvascular thrombosis, and mitochondrial dysfunction.

Figure 1. Complex pathophysiology of spike-related vaccine-induced disease



The spike protein of SARS-CoV-2 has extensive sequence homology with multiple endogenous human proteins and could prime the immune system toward development of both auto-inflammatory and autoimmune disease. (11) As a consequence of molecular mimicry with the spike protein, a diverse spectrum of autoantibodies has been reported. These autoantibodies are the likely cause of Guillain-Barré Syndrome (GBS), transverse myelitis, immune thrombocytopenia, and Small Fiber Neuropathy (SFN)/Autonomic neuropathy. (28-35)

Many of these antibodies are directed against G-protein-coupled cell membrane receptors. Anti-neuronal antibodies likely contribute to the myriad of neurological findings. SFN/autonomic neuropathy appears to be a characteristic disorder following vaccination and is strongly associated with a vast array of autoantibodies. Further, autoantibodies may result in a number of specific syndromes, including anti-phospholipid syndrome, systemic lupus erythematosus (SLE), rheumatoid arthritis, etc.

The spike protein is highly thrombogenic, directly activating the clotting cascade; in addition, the clotting pathway is initiated via inflammatory mediators produced by mononuclear cells and platelets. (6) Activation of the clotting cascade leads to both large clots (causing strokes and pulmonary emboli) as well as micro clots (causing microinfarcts in many organs, but most notably the brain). Emerging data suggest that the vaccines can induce an allergic diathesis (eczema, skin rashes, asthma, skin and eye itching, food allergies, etc.) This appears to be due to a unique immune dysregulation with antibody

class switching (by B cells) and the production of IgE antibodies. There is an overlap with Mast Cell Activation Syndrome (MCAS) and the distinction between the two disorders is not clear. (36, 37) However, by definition MCAS has no identifiable causes, is not caused by allergen-specific IgE, and has no detectable clonal expansion of mast cells. (36)

And finally, due to altered immune function, the activation of dormant viruses and bacterial pathogens may occur, resulting in reactivated Herpes Simplex, Herpes Zoster, Epstein Barr Virus (EBV), and cytomegalovirus (CMV) infection, as well as reactivation of Lyme disease and mycoplasma. (38-41)

The common factor underlying the pathogenic mechanism in the vaccine-injured patient is "immune dysregulation." The development of immune dysfunction and the severity of dysfunction likely result from several intersecting factors, including:

- **Genetics**: First-degree relatives of patients who have suffered a vaccine injury appear to be at a very high risk of vaccine injury. Those patients with a methylenetetrahydrofolate reductase (MTHFR) gene mutation (42) and those with Ehlers-Danlos type syndromes may be at an increased risk of injury. MTHFR C677T polymorphism is the most common MTHFR single nucleotide polymorphism (SNP) and the most common genetic cause of hyper-homocysteinemia. (43) Increased homocysteine levels have been linked to worse outcomes in patients with COVID-19. (44, 45) Increased homocysteine levels may potentiate the microvascular injury and thrombotic complications associated with the "spikopathy". (43, 46)
- **mRNA load and quantity of spike protein produced**: This may be linked to specific vaccine lots that contain a higher concentration of mRNA. (1) The Moderna vaccine is reported to contain 100 ug of mRNA as compared to 30 ug mRNA for the Pfizer vaccine (10 ug in children 5-11 years of age), however, it is likely that the true concentration varies widely.
- **Sex**: It appears that about 80% of vaccine-injured patients are female. Furthermore, treatment with estrogens has been reported to worsen or precipitate an event/relapse. Women are known to be at a much higher risk of autoimmune diseases (especially SLE) and this likely explains this finding. Estrogens interfere with glucocorticoid receptor signaling. (47) In addition, estrogens modulate B and T cell function.
- **Underlying nutritional status and comorbidities**: Certain preexisting conditions may likely have primed the immune system to be more reactive after vaccination. This includes those with preexisting autoimmune disorders and chronic inflammatory diseases such as Lyme disease. Those patients with a poor nutritional status including those with deficiencies of nutrients such as Vitamin D, Vitamin B12, folate, and magnesium may be at an increased risk of injury.

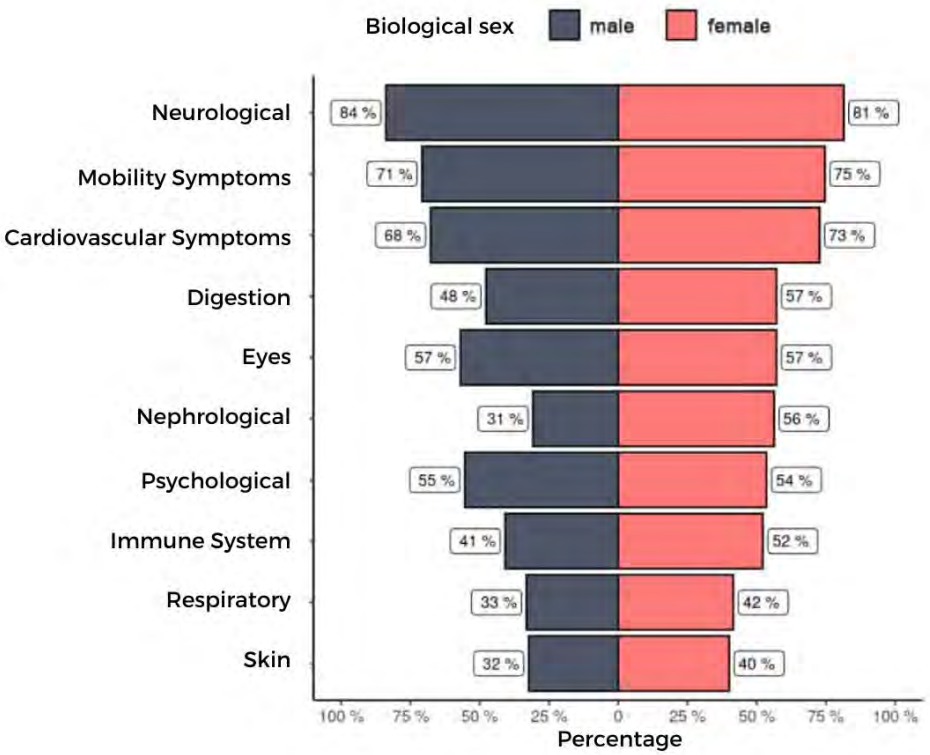
Complications/ injuries caused by COVID injections

Over 3,000 peer-reviewed articles have been published on COVID vaccine injuries. Find links to these studies at COVID Vaccine Injuries, REACT19, and on Substack. A selection of symptoms is listed below:

- Myocarditis, pericarditis, stress cardiomyopathy (contraction band necrosis)
- Takotsubo cardiomyopathy
- Acute coronary syndrome
- Hypertension
- MIS-V, Multisystem Inflammatory Syndrome
- Thrombosis, including pulmonary emboli and stroke (prothrombotic state)
- Cerebral venous thrombosis
- Thrombocytopenia
- Thrombotic thrombocytopenic purpura
- Idiopathic thrombocytopenic purpura
- Henoch Schönlein Purpura
- Immune-mediated hemolysis
- Reactivation and exacerbation of chronic underlying diseases/disorders
- Immune dysregulation
- Metabolic dysregulation (diabetes)
- Menstrual irregularities
- Menorrhagia
- Amenorrhea
- Spontaneous abortion
- Vulval and vaginal ulcers
- Vasculitis, including Leukocytoclastic vasculitis, Granulomatous vasculitis, microscopic polyangiitis.
- Guillain-Barre Syndrome
- Acute Myelitis
- Systemic lupus erythematosus
- Bell's Palsy
- Stills disease.
- Sweets syndrome
- Facial nerve palsy
- Multiple sclerosis
- Polyarthralgia/polyarthritis
- Cryoglobulinemia
- Lymphadenopathy, local and generalized.
- Anaphylaxis
- Allergic reactions
- Intracerebral hemorrhage
- Strokes (thrombotic strokes)
- Generalized neurological symptoms including "brain fog", cognitive decline, memory loss.
- Alzheimer's Disease like syndrome
- Acute hyperactive encephalopathy
- Acute disseminated encephalomyelitis
- Neuromyelitis Optica
- Ageusia and anosmia
- Aphasia
- Depression
- New onset panic disorders
- New onset psychosis and delirium
- Small fiber neuropathy
- Autonomic neuropathy
- POTS syndrome (postural Orthostatic Tachycardia syndrome)
- Mononeuritis multiplex, polyneuropathy
- Acute inflammatory neuropathies
- Tinnitus (severe and persistent)
- Sensorineural hearing loss
- Vestibulitis
- Severe headaches and migraines
- Seizures and status epilepticus
- Prion disease i.e., Mad Cow Disease
- Acute macular retinopathy
- Uveitis
- Acute Optic Neuropathy
- Rhabdomyolysis
- Keratolysis
- Herpes Keratitis
- Inflammatory myositis
- Immune mediate hepatitis
- Pancreatitis
- Acute kidney injury
- Nephrotic syndrome
- ANCA glomerulonephritis

- Skin reactions including rashes, urticaria, Pityriasis rosea
- Pemphigus vulgaris
- Hemorrhagic bullous pyoderma gangrenosum
- Eosinophilic dermatosis
- Alopecia, including alopecia areata
- Psoriasis
- Toxic epidermal necrolysis
- Erythema multiforme
- Hemophagocytic histiocytosis
- Varicella Zoster infection
- Epstein-Barr viral reactivation
- CMV reactivation
- Herpes Simplex reactivation
- Zoster meningitis
- Ramsay Hunt syndrome
- Thyroiditis
- Tolosa-Hunt syndrome
- Acute eosinophilic pneumonia
- Cancer recurrences
- New and unusual malignancies, including Angioimmunoblastic T Cell Lymphoma

Figure 2. Vaccine injury is a multi-symptomatic disease*



The most common symptoms recorded in post-vaccine syndrome are presented in Figure 2. On average, patients reported 23 distinct symptoms. (Results from PVS Germany Survey; Reproduced with permission from React19/PVS Germany https://react19.org/post-vaccine-syndrome-survey-results/

Treatment Approach

A number of principles are essential for the optimal management of post-vaccine syndrome:

It is important to emphasize that there are no published reports detailing the management of vaccine-injured patients. Our treatment approach is, therefore, based on the postulated pathogenetic mechanism, pharmacologic principles, clinical observation, and feedback from vaccine-injured patients.

The core problem in post-vaccine syndrome 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.

A note about anesthesia and surgery:

Patients should notify their anesthesia team if using the following medications and/or nutraceuticals, as they can increase the risk of Serotonin syndrome (SS) with opioid administration:

- Methylene blue
- Curcumin
- Nigella Sativa
- Selective Serotonin Reuptake Inhibitors (SSRIs)

The 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. A peculiar finding is that a particular intervention (e.g., Hyperbaric oxygen therapy) may be lifesaving for one patient and totally ineffective for another.

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 in order 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.

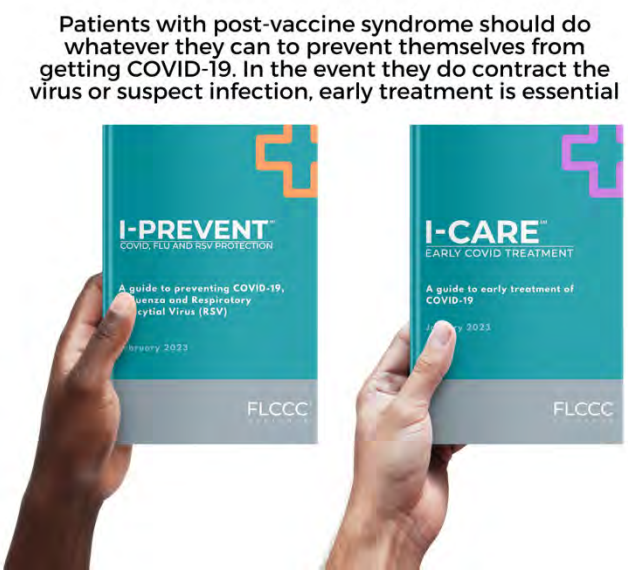
Patients should be started on the primary treatment protocol; this should, however, be individualized according to the patient's particular clinical features. The response to the primary treatment protocol should dictate the addition or subtraction of additional therapeutic interventions. Second-line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

Patients with post-vaccine syndrome must not receive further COVID-19 vaccines of any type. Likewise, patients with long COVID should avoid all COVID vaccinations.

Patients with post-vaccine syndrome should do whatever they can to prevent themselves from getting COVID-19. This may include a preventative protocol (see FLCCC protocols).

In the event they do contract the virus or suspect infection, early treatment is essential (see FLCCC protocols). COVID-19 will likely exacerbate the symptoms of vaccine injury.

Vaccine-injured patients are frequently desperate to try any medication or intervention they believe may help them. Unfortunately, unscrupulous providers will take advantage of these very vulnerable patients and sell them expensive and unproven remedies.



Patients should avoid unscientific and poorly validated “Spike Protein Detox” programs.

Hyperbaric oxygen therapy (HBOT) should be considered in cases of severe neurological injury and in patients showing a rapid downhill course (see below).

Once a patient has shown a clinical improvement the various interventions should be reduced or stopped one at a time. A less intensive maintenance approach is then suggested.

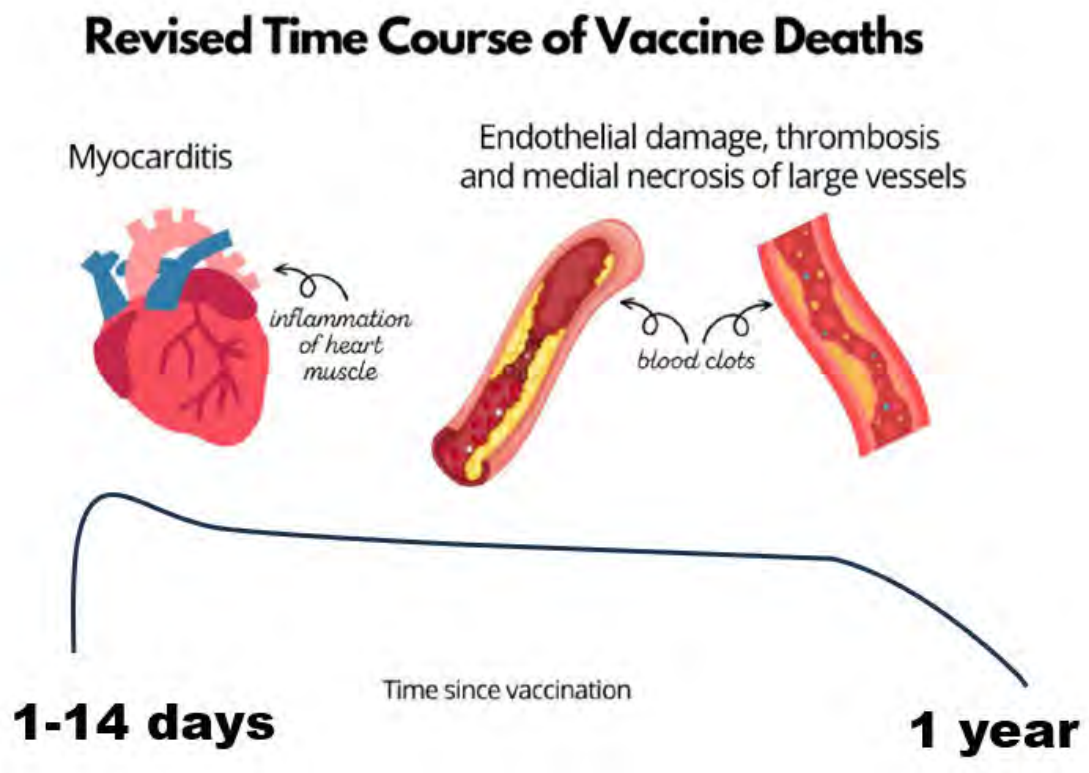
Baseline Testing

Post-vaccine patients are often subjected to an extensive battery of diagnostic tests. These tests are rarely helpful, usually confusing the situation and leading to inappropriate therapeutic interventions. Patients frequently undergo diagnostic tests that are “experimental,” unvalidated, and clinically meaningless; patients should avoid getting such tests. **Remember the dictum: Only do a test if the result will change your treatment plan.** We recommend a number of simple, basic screening tests that should be repeated, as clinically indicated, every 4 to 6 months.

- CBC with differential and platelet count
- Standard blood chemistries, including liver function tests
- D-Dimer—as a marker of clotting activation. Those with a markedly elevated D-dimer should probably undergo screening for an inherited thrombophilia.
- CRP—as a marker of ongoing inflammation (A comprehensive extensive cytokine/chemokine panel is unnecessary and very costly, and the results will not change the treatment approach.)
- Early morning cortisol—some patients develop autoimmune adrenal failure)
- TSH—to exclude thyroid disease
- Homocysteine level (normal 5-15 µmol/l)
- HbA1C—Vaccine-injured patients are at an increased risk of developing diabetes
- Troponin and pro-BNP to exclude cardiac disease.

- CMV, EBV (early antigen-D IgG or nuclear antigen IgG), Herpes simplex, HHV6 and mycoplasma serology/PCR—to exclude viral/bacterial reactivation (In patients who respond poorly to therapy, it may be helpful to check for Lyme (Bb), Bartonella and Babesia tick-borne diseases—e.g., https://igenex.com/ and https://www.mdlab.com/). (41)
- Vitamin D level (25OH Vitamin D)
- In patients with allergic features and 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. (36)
- In patients who present with deep venous thrombosis (DVT) and/or pulmonary embolism soon after vaccination screening for an inherited thrombophilia is suggested. (48)
- Limited screening autoantibodies. Lupus anticoagulant (if positive B2 microglobulin etc.) and ANA. Vaccine-injured patients, particularly those with autonomic dysfunction/SFN frequently have an extensive array of autoantibodies directed against G-protein coupled cell surface receptors, ACE-2, (49) neurons, myelin, and other self-epitopes. The presence or absence of these antibodies has little impact on the management of these patients.

Figure 3. Time course of sudden cardiac deaths following COVID-19 vaccination



Anticoagulation post-vaccination and the three clinical phenotypes of the vaccine injured

The need for anticoagulation in post-vaccination patients is a complex and controversial issue. Three distinct clinical phenotypes with differing pathophysiological and clinical presentations exist (see Figure 3).

- The first is the "typical" post-vaccine, muti-symptomatic syndrome characterized typically by fatigue, post-exertional malaise (PEM), brain fog, and other multiple complex symptoms (see figure 2). This syndrome is characterized by microvascular inflammation and microvascular thrombosis as part of the complex pathophysiology of post-vaccine spike related disease (see Figure 1).
- The second is that of sudden cardiac death within the first 2 weeks (usually first 7 days) following the last dose of vaccination. The early sudden deaths are likely arrhythmogenic deaths related to catecholamine-induced contraction band necrosis and spike-induced inflammatory myocarditis (often focal myocarditis).
- The third phenotype includes those otherwise healthy patients who "die suddenly" up to a year after the last dose of the COVID vaccine. Patients with this phenotype typically lack the typical symptoms characteristic of post-vaccine syndrome. While the pathology of this syndrome has not been studied (as it has been dismissed by governmental agencies), it is likely the result of a progressive spike-induced endothelialitis complicated by thrombosis.

Dr. Gundry, a cardiac surgeon, performed a biomarker-based cardiac risk assessment score (the PULS Cardiac Test now available as the SMART*Vascular* Dx provided by SmartHealth Dx https://www.smarthealthdx.com) in 566 patients 2 to 10 weeks following the 2nd mRNA COVID shot and compared this score to the PULS score drawn 3 to 5 months prior to the jab. (50) The PULS score is a marker of endothelial inflammation. In this study, the 5-year Acute Coronary Risk Score (ACS) increased from a baseline of 11% to 25% after the jab. This study clearly demonstrates that the mRNA 'jabs" lead to progressive endothelial inflammation.

To complicate matters further, the clots (micro-clots and macro-clots) that develop in patients with spike-related disease are distinctly different from "usual clots" and have a number of unique characteristics. These clots are rich in fibrin with amyloid-like fibrils and are more resistant to fibrinolysis. Immunohistochemical staining demonstrates a high concentration of spike protein within the clots; this is important as spike protein via multiple mechanisms activates clotting as well as altering the structure of fibrin resulting in amyloid-like fibrils.

Based on this information, it would seem intuitive that the use of anti-coagulants and the approach to treatment would be different for these three phenotypes; however, the ideal approach has yet to be determined. A provisional approach to anticoagulation is provided below. A review of the pharmacological properties of the various anticoagulants available to the healthcare provider is provided. The general approach to the management of the multi-symptom vaccine syndrome is then reviewed.

The greatest risk with the use of anticoagulant drugs is clinically significant bleeding. A number of factors increase the risk of bleeding; (51-53) these include age > 65 years (advanced age is a major risk

factor for bleeding), hypertension, renal impairment, diabetes, previous stroke, a previous bleed, and male sex. Furthermore, the risk of bleeding increases as the number of anticoagulant/anti-platelet drugs is increased. (52, 54)

Antiplatelet drugs:

Aspirin (ASA): ASA produces a clinically relevant antiplatelet effect by irreversibly acetylating the active site of cyclooxygenase-1 (COX-1), which is required for the production of thromboxane A2, a powerful promoter of platelet aggregation. These effects are achieved by daily doses of 75 mg (and higher). The major adverse effect is bleeding. Bleeding most commonly occurs in the gastrointestinal tract and is rarely fatal. Bleeding also occurs at other sites, with intracranial bleeding being the rarest (approximately 4 per 10,000) but the most serious (with a 50% case fatality rate).

Clopidogrel (Plavix): Clopidogrel requires *in vivo* biotransformation to an active thiol metabolite. The active metabolite irreversibly blocks the ADP receptors on the platelet surface, which prevents activation of the GPIIb/IIIa receptor complex, thereby reducing platelet aggregation. Similar to ASA, platelets blocked by clopidogrel are affected for the remainder of their lifespan (~7 to 10 days). The usual dose is 75mg daily.

Direct oral anticoagulants (DOAC):

Apixaban (Eliquis): Inhibits platelet activation and fibrin clot formation via direct, selective, and reversible inhibition of free and clot-bound factor Xa (FXa). FXa, as part of the prothrombinase complex consisting also of factor Va, calcium ions, and phospholipid, catalyzes the conversion of prothrombin to thrombin. Thrombin both activates platelets and catalyzes the conversion of fibrinogen to fibrin. Typical dose is 2.5 to 5mg twice daily.

Rivaroxaban (Xarelto): Mechanism of action similar to apixaban. Typical dosage is 10–20 mg once daily with the evening meal.

Oral Fibrinolytic agents:

Nattokinase: Nattokinase (NK) is a serine protease purified and extracted from natto, a traditional Japanese (cheese like) food produced from the fermentation of soybeans with the bacterium, Bacillus subtilis. (55-57) Recent studies demonstrated that a high natto intake was associated with decreased risk of total cardiovascular disease mortality and, in particular, a decreased risk of mortality from ischemic heart diseases. (58)

Nattokinase has potent fibrinolytic, antithrombotic, and antiplatelet activity. (55, 56, 59-62) NK degrades fibrin directly and also increases the release of tPA with a subsequent increase in the formation of plasmin. (63) Furthermore, NK enhances fibrinolysis through cleavage and inactivation of PAI-1. (57, 62) In a study comparing the antiplatelet effects of NK and aspirin, NK was shown to display excellent antiplatelet aggregation and antithrombotic activities in vitro and in vivo, inhibiting thromboxane B2 formation from collagen-activated platelets. (64) In addition, in both animal and human studies, NK also has antihypertensive, anti-atherosclerotic, lipid-lowering, and neuroprotective actions. (56, 62, 65) Of particular relevance to patients with spike-related clotting, nattokinase causes the proteolytic cleavage of both spike protein and amyloid proteins. (66) In a randomized study, NK proved to be more effect than statins (simvastatin) in reducing carotid artery atherosclerosis. (67)

Chen et al demonstrated that high dose NK (10 800 Fibrinolytic Units [FU]/day; ~ 500 mg/day) reduced the thickness of the carotid artery intima-media and the size of the carotid plaque. (68) The authors reported a synergistic effect between NK and ASA.

Studies indicate that an oral administration of NK can be absorbed by the intestinal tract. (65, 69) NK, unlike most proteins, is more resistant to the highly acidic gastric fluids in the stomach and can be absorbed in the later sections of the digestive tract.

The optimal dose of nattokinase is unclear, however, a dose of 100-200 mg (2000- 4000 FU/day) twice daily has been suggested.

While NK appears to have an excellent safety profile, (68, 70) bleeding has rarely been reported in patients with risk factors for bleeding (advanced age, renal failure, hypertension, concomitant ASA, etc). (71, 72) High concentrations of vitamin K_2 in natto can reduce the INR when coadministered with warfarin; this may also occur with nattokinase supplements if vitamin K_2 is not removed during the production process. Information regarding safety and efficacy in pregnancy and lactation is lacking.

Lumbrokinase: Lumbrokinase derives from a group of enzymes extracted from earthworms. The enzymes are sourced mostly from the earthworm *Lumbricus rubellus*. Lumbrokinase has very similar pharmacodynamic properties to Nattokinase, i.e., it directly breaks down fibrin clots, inhibits PAI-1 activity, enhances t-PA activity, has antiplatelet activity, and proteolytically cleaves amyloid. (73-75) The recommended dose is 300,000 to 600,000 IU/day (20-40 mg). Lumbrokinase has been widely used for patients with acute ischemic stroke in China; however, because rigorously designed studies are lacking, the safety and efficacy of lumbrokinase remains largely unknown. (76) As the pharmacology, clinical effectiveness, and safety of nattokinase has been assessed in a number of experimental and clinical studies, this agent is preferred over lumbrokinase.

Provisional approach to anticoagulation in the post-vaccine phenotypes

For more information see I-PREVENT: Vaccine Injury

- "Typical" post-vaccine syndrome. Nattokinase 100-200mg (2000 – 4000FU) twice daily is recommended. Low-dose aspirin (ASA) (81mg daily) can be added in patients at a low risk of bleeding complications (see risk factors). Pretorius et al reported on the use of "triple therapy" in 24 patients with long COVID and the presence of fibrin amyloid microclots on live blood analysis. (77) Patients were treated with one month of dual antiplatelet therapy (Clopidogrel 75mg/Aspirin 75mg) once a day, as well as Apixaban 5 mg twice a day. This was followed by ASA and nattokinase alone. These authors reported that "each of the 24 treated cases reported that their main symptoms were resolved, and this was also reflected in a decrease of both the fibrin amyloid microclots and platelet pathology scores." Triple therapy can be considered in patients at low risk of bleeding (see risk factors) who have responded poorly to the combination of ASA and nattokinase alone; however, triple therapy should only be instituted under the direct supervision and monitoring of a clinician with expertise in the management of anti-coagulation.
- Early sudden death. Early post-vaccination sudden cardiac death is a condition of young patients, especially men. This is the most problematic phenotype with no clear guidance on the prevention of this fatal condition (except to stop vaccination in this high-risk group). Many of the deaths occur during physical activity (sudden death in athletes) and may be mediated by catecholamine surges;(13) consequently, vigorous physical activity should be avoided for at least

3 weeks following vaccination. Magnesium supplementation (see section on magnesium) may reduce the risk of arrhythmic deaths. The role of anti-inflammatory agents (e.g., curcumin, resveratrol, Nigella sativa, Omega-3 fatty acids) is unclear.

- Late cardiac deaths (up to 1 year after "jab"). Ideally, these asymptomatic patients should be risk stratified with the initiation of prophylactic measures in the moderate to high-risk groups. Unfortunately, as this catastrophic disorder is not generally recognized and has therefore not been studied, there is no data to allow for risk stratification. Serial cardiac risk biomarker analysis may be helpful; (50) however, this test is expensive and not widely available. In the absence of a risk-stratified approach, the following interventions may reduce the risk of acute myocardial infarction and sudden death: (78)

    - Nattokinase 100-200 mg twice daily
    - ASA 81 mg daily (in those with low risk of bleeding)
    - Omega-3 fatty acids 2-4 g daily
    - Resveratrol or flavonoid combination supplement
    - Melatonin 3-10 mg at night (slow release/extended release).
    - Bromelain 500 mg twice daily +/- N-acetyl cysteine (NAC) 600 mg twice daily.
    - Berberine 500-600 mg twice daily.
    - "Green based diet"- Low carbohydrate, high fat diet (low in omega-6 vegetable oils)

Given the numerous and complex pathophysiologies underlying post-vaccine injury syndrome, as well as the current and challenging lack of biomarkers or tests that can provide an indication for a specific therapy, we suggest a treatment approach whereby patients receive a sequence of therapeutic trials to determine what works and what doesn't.

Although the therapies proposed below are ordered as 1st, 2nd, and 3rd line, in our clinical experience, this does not necessarily correlate with clinical response. Significantly more clinical research is needed to provide definitive guidance on this issue. In the interim, we have ordered the therapeutic trials based on a combination of supporting clinical data along with an assessment of safety, accessibility, cost, and mechanistic support.

Individual practitioners may vary the sequence in which therapies are offered as per their experience and/or their estimation of importance in terms of efficacy and safety.

We propose that sequential trials of therapy be offered to patients separated by time so that each patient serves as their own "control." When a therapeutic trial is found to have no clinical response, it should be discontinued. However, some therapies that do not bring about a temporally associated discernable response may still be necessary to support the efficacy of other therapies (i.e., magnesium, nattokinase, melatonin, hydroxychloroquine etc.).

First-Line Therapies

(Not symptom specific; listed in order of importance)

Intermittent daily fasting or periodic daily fasts

> *"A little starvation can really do more for the average sick man than can the best medicines and the best doctors."*
> *—Mark Twain*
> *(1835-1910)*

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 injections. Indeed, activation of autophagy may be the only mechanism to remove intracellular spike protein. A large body of theoretical information supports the concept that activation of autophagy is an effective strategy to remove spike protein. (79) In addition, intermittent fasting is likely to induce a state of ketosis. Ketosis has been demonstrated to have enormous beneficial effects in patients with inflammatory and neurological diseases. (80-82)

The reader is referred to the FLCCC Guide on intermittent Fasting and Healthy Eating Habits for more detailed information.
https://covid19criticalcare.com/tools-and-guides/guide-to-intermittent-fasting/

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, (83-88) aiding in the elimination by the host. Ivermectin reverses spike protein induced hemagglutination. (89, 90) In addition, Ivermectin has potent anti-inflammatory properties. (91-93) A trial of ivermectin should be included in the first-line treatment approach.

Dosing and administration

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

It appears that vaccine-injured patients can be grouped into two categories: i) ivermectin responders and ii) ivermectin non-responders. This distinction is important, as the latter group is more difficult to treat and requires more aggressive therapy.

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 patients, 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.

Cautions and contraindications.

Ivermectin is contraindicated in patients taking the immunosuppressive agent tacrolimus. 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. (94)

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 protocol 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 protocol 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

Moderating physical activity

Patients with long COVID and post-vaccine symptoms frequently suffer from severe post-exertional fatigue and/or worsening of symptoms with exercise. (95, 96) 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. Measures which improve mitochondrial function may also be of benefit, i.e. melatonin and photobiomodulation.

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. (95, 97, 98) Recent studies in patients with long COVID and post-exertional fatigue demonstrated marked abnormalities in skeletal muscle with normal cardiac function and oxygen delivery. (99, 100) These studies demonstrate a muscle

fiber switch to a less aerobic phenotype with a decrease oxidative phosphorylation and mitochondrial dysfunction with amyloid deposition in extracellular matrix between muscle fibers.

L-Arginine and Vitamin C

Dosing and administration
We suggest a dose of L-arginine of 1.5 -2g twice daily, plus Vitamin C 1000 mg orally two to three times a day.

Mechanisms
In a single-blind randomized, placebo-controlled trial, participants were randomized 1:1 to receive twice-daily orally either a combination of 1.66 g L-arginine plus 500 mg vitamin C or a placebo for 28 days. The primary outcome was the distance walked on the 6-minute walk test. (101)

At 28 days, L-arginine plus vitamin C increased the 6-minute walk distance (+30 (40.5) m; placebo: +0 (75) m, p = 0.001) and induced a greater improvement in handgrip strength (+3.4 (7.5) kg) compared with the placebo (+1 (6.6) kg, p = 0.03). At 28 days, fatigue was reported by two participants in the active group (8.7%) and 21 in the placebo group (80.1%; p < 0.0001). The results of this study are supported by a survey study investigating the role of combined L-arginine and vitamin C. (102)

L-Arginine is the substrate used for nitric oxide (NO) production by nitric oxide synthetase (NOS). (103-105) Patients with acute COVID-19 infection have been demonstrated to have low plasma L-arginine levels. (106, 107) In addition, COVID-19 syndromes are characterized by suppressed endothelial nitric oxide synthase (eNOS) activity compounding the deficiency of NO. (104) The spike protein itself may play a major role in inhibiting eNOS activity.(108) 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. (109) In addition, L-arginine itself is important for normal T cell function and macrophage M1-to-M2 switch. (103-105) 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).

Vitamin C has important anti-inflammatory, antioxidant, and immune-enhancing properties, including increased synthesis of type I interferons. (110-114) Oral vitamin C helps promote the growth of protective bacterial populations in the microbiome.

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.

Cautions and contraindications
Avoid vitamin C in patients with a history of kidney stones.

Low-dose naltrexone (LDN)
LDN has been demonstrated to have anti-inflammatory, analgesic, and neuromodulating properties. (115, 116) In a before-after study in patients with long COVID, O'Kelley demonstrated that LDN (1-3 mg) was safe and significantly improved fatigue, well-being and reduce symptomatology, including chest and joint pain. (117) Similarly, Bonilla et al demonstrated that the use of LDN was associated with a fewer

number of symptoms, improved clinical symptoms (fatigue, post-exertional malaise, unrefreshing sleep, and abnormal sleep pattern), and a better functional status. (118)

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 abnormal clotting in the spike injured patient. In addition, nattokinase has been demonstrated to lyse extracellular spike protein; this may further enhance the anti-clotting action of nattokinase**.** (59, 64, 66)

Treatment of Mast Cell Activation

An empiric trial of treatment of Mast Cell Activation Syndrome (MCAS) is supported by both peer-reviewed literature and extensive clinical experience. (119-121) A combination regimen of both H1 and H2 receptor blockers along with a mast-cell stabilizer is favored. A low histamine diet should also be trialed (https://www.healthline.com/health/low-histamine-diet and) (122) and (https://covid19criticalcare.com/tools-and-guides/histamines-and-gut-health).

Histamine Blockers:
- H1 receptor blockers. Loratadine 10 mg/day, Cetirizine 5-10 mg/day, Fexofenadine 180 mg/day. (123)
- H2 receptor blockers. Famotidine 20 mg twice daily as tolerated.

Mast Cell Stabilizers:
- Ketotifen. 1 mg in 5 ml. Start with 0.5 ml at night. Once patients get used to it, as it has a strong hypnotic effect, increase by 0.5 ml increments up to 5 ml. Some patients can increase up to 10 ml daily (1 mg twice daily). Ketotifen has antihistamine effects and is a mast cell stabilizer. Ketotifen may be particularly useful in patients with GI hypersensitivity. (124, 125)
- Cromolyn, a mast cell stabilizer, 200 mg three times daily. (123)
- The novel flavonoid, luteolin, is reported to be a potent mast cell inhibitor. (126-129) Luteolin 20-100 mg/day is suggested.
- Vitamin C; 1000 mg twice daily. Vitamin C is strongly recommended for allergic conditions and MCAS. Vitamin C modulates immune cell function and is a potent histamine inhibitor. (130-132)
- Turmeric (curcumin); 500 mg/day. Curcumin has been reported to block H1 and H2 receptors and to limit mast cell degranulation. (133, 134) Curcumin has low solubility in water and is poorly absorbed by the body; (135) consequently, it is traditionally taken with full-fat milk and black pepper, which

enhance its absorption. Nano-curcumin preparations or formulations designed to enhance absorption are encouraged. (136-139)

- Montelukast 10 mg/day. Caution as this drug may cause depression in some patients. The efficacy of montelukast as a "mast cell stabilizer' has been questioned. (36)

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. (140) Recently Bowen and Arany demonstrated that either transcranial (helmet) or whole-body photobiomodulation treatments improved COVID-19 brain fog. (141)

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 midday walk (below fatiguability level) 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." (142)

A number of LED panels with multiple red and IR lights are commercially available (e.g. https://sunpowerled.com, /https://mitoredlight.com/, https://hoogahealth.com/, https://platinumtherapylights.com/. We have received positive feedback from patients with the use of the $40 Hooga HG24 hand-held device. We have found patients need between 2 to 10 minutes (typically around 5), and usually, it's given on alternating days 3-4 times a week. Sometimes individuals with a greater need (e.g., a fragile system) need it daily and, in rarer instances, twice daily.

The theoretical 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/1070nm. In contrast, ThermaLight® bulbs (SaunaSpace® Saunas™ https://sauna.space/ and Therabulb (https://www.therabulb.com/) have a radiation spectrum closely resembling that of solar radiation, but without UV radiation. It should be noted that in the study by Bowen and Arany a narrow spectrum of red/IR light was used; helmet (1070 nm) and a light bed (660 and 850 nm).

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. (143) 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. (144) 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. (145)

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. (145) 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. (146) 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. (147) 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.

Melatonin

Melatonin has anti-inflammatory and antioxidant properties and is a powerful regulator of mitochondrial function. (148-152)

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.

Bromelain

Dosing and administration

Bromelain 500 mg twice daily +/- N-acetyl cysteine (NAC) 600 mg twice daily.

Mechanisms

In vitro studies have demonstrated that bromelain cleaves spike protein. (153-155) This effect appears to be enhanced by the addition of NAC. (156) In addition, Bromelain was demonstrated to induce a dose- and time-dependent reduction of ACE-2 and TMPRSS2 expression in Vero E6 cells. (153) Experimental studies have demonstrated that bromelain presents unique immunomodulatory actions by downregulation of the proinflammatory prostaglandin PGE-2 through inhibition of NF-kB and cyclooxygenase 2 (COX-2) and upregulation of the antiinflammatory PGE-1.(157)

Bromelain has dose-dependent anticoagulant effects by downregulation of PGE-2 and thromboxane A2 and promotion of fibrinolysis by stimulating the conversion of plasminogen to plasmin and prevention of platelet aggregation. (157) Dr Peter McCullough has proposed a regimen for the treatment of the vaccine injured. which includes bromelain and nattokinase. (157, 158)

Nigella Sativa

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.

Dosing and administration

Nigella Sativa 200-500 mg encapsulated oil twice daily.

Mechanisms

The most important active component is thymohydroquinone. *Nigella sativa* has antibacterial, antifungal, antiviral (SARS-CoV-2), anti-inflammatory, antioxidant, and immunomodulatory properties. (159, 160)

Cautions and contraindications

It should be noted that thymohydroquinone decreases the absorption of cyclosporine and phenytoin. Patients taking these drugs should, therefore, avoid taking *Nigella sativa*. (163) Furthermore, two cases of serotonin syndrome have been reported in patients taking *Nigella sativa* who underwent general anesthesia (probable interaction with opiates). (164)

Resveratrol or a combination flavonoid

Resveratrol is a plant phytochemical (flavonoid) that has remarkable biological properties. (165-167) Most importantly it activates autophagy. (168, 169)

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 (SARS-CoV-2), 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. (170-172) Pterostilbene, is another plant flavonoid similar to resveratrol in structure with similar biological properties. (173-175) 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. (176) 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. (177) 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 post-vaccine syndrome classically have a severe dysbiosis with loss of Bifidobacterium. (178-180)

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+. (181) 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.(182, 183)

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.

Vagus Nerve Stimulation and nicotinic agonists

The spike protein has been shown to also contain a ‘toxin-like’ domain in the RBD on S1, with sequence homology to neurotoxin NL-1, which binds to the α7 Nicotinic Acid Acetylcholine Receptors (α7 nAChR) of the cholinergic system. (184-186) Neurotoxin NL-1 is a neurotoxin, similar to the archetypal bungarotoxin, a known inhibitor of the α7 nAChR, with high binding affinity. The nicotinic receptor is the principal structure of cholinergic neuromodulation. The nACHR is an essential part of the interneuronal communication within the CNS and the autonomic nervous system (vagus nerve).

Vagus nerve dysfunction may be a common feature in patients with spike related injuries, particularly those with dysautonomia; this may be related to the anti-cholinergic effects of spike protein as well as inflammation of the vagus nerve. Woo et al performed a histopathological characterization of postmortem vagus nerves from COVID-19 patients and detected SARS-CoV-2 RNA together with an inflammatory cell infiltration composed primarily of monocytes. (187) These authors concluded that SARS-CoV-2 induces vagus nerve inflammation followed by autonomic dysfunction, which might contribute to the dysautonomia observed in long COVID.

Stimulation of the vagus nerve has anti-inflammatory, analgesic, and antidepressant effects. These effects are driven via the vagus nerve acting both via central and peripheral mechanisms. Non-invasive

vagus nerve stimulation may be administered with a variety of different technologies. (188) Transcutaneous auricular vagus nerve stimulation (taVNS) involves stimulation of the auricular branch of the vagus nerve that bilaterally innervates the human ear. In a small double-blind, telemedicine-controlled study, taVNS was associated with a moderate improvement in symptoms of long COVID.(189) Similarly, in a small pilot study by Natelson et al, 8 of 14 patients with long-COVID reported an improvement in symptoms with taVNS. (190)

The agonist ligand nicotine shows up to a 30-fold higher affinity for the nACHR than acetylcholine. (191) It has therefore been suggested that nicotine could displace the spike protein from nAChR attachment, resulting in unimpaired cholinergic signal transmission. (192) This observation may explain the finding that smoking tends to reduce the severity of COVID-19. (193) Treating patients with post-COVID-19 syndrome with a nicotine patch has been reported to produce a substantial improvement in symptoms. (192) 1-Methylnicotinamide (1-MNA) is an endogenic substance that is produced in the liver when nicotinic acid is metabolized. 1-MNA demonstrates anti-inflammatory and antithrombotic properties. (194) In a randomized study conducted in patients with long COVID, patients who received 1-MNA demonstrated a significant improvement in the 6-minute walk test with a significant reduction in fatigue. (194)

Adjunctive/Second-Line Therapies

(Listed in order of importance)

Hyperbaric oxygen therapy (HBOT) (195-203); 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. (204) 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/)

Triple anticoagulation. Long-COVID is characterized by thrombotic events involving the venous and arterial circulation as well as the microcirculation. The mechanisms accounting for thrombosis in long COVID has not been fully clarified. (205) However, viral spike proteins and RNA can be detected months after patients have recovered from acute COVID, findings that may be responsible for persistent thromboinflammation and the development of microclots. (206) Ongoing vascular endothelial damage promotes platelet adhesion and coagulation, resulting in the impairment of organ functions. Furthermore, thrombosis will further aggravate vasculitis contributing to further deterioration. Pretorius et al demonstrated that the plasma from long covid patients contains large anomalous amyloid microclots. (207-210) Furthermore, in these studies various inflammatory molecules were significantly increased in both the supernatant and trapped in the solubilized clots from these patients.
The role of anticoagulants in the prevention or treatment of long-covid is controversial. (205, 206, 211, 212) However, anticoagulation can prevent the release of or remove procoagulant substances, thereby protecting the vascular endothelium from damage, reducing thrombotic sequelae, and provide symptomatic improvement in long-COVID patients. (212) There is however limited clinical data to support this strategy. Pretorius et al reported on the use of "triple therapy" in 24 patients with long COVID and the presence of fibrin amyloid microclots on live blood analysis. (77) Patients were treated with one month of dual antiplatelet therapy (Clopidogrel 75mg/Aspirin 75mg) once a day, as well as Apixaban 5 mg twice a day. This was followed by ASA and nattokinase alone. These authors reported that "each of the 24 treated cases reported that their main symptoms were resolved, and this was also reflected in a decrease of both the fibrin amyloid microclots and platelet pathology scores." Triple therapy can be considered in patients at low risk of bleeding who have responded poorly to the combination of ASA and nattokinase alone; however, triple therapy should only be instituted under the direct supervision and monitoring of a clinician with expertise in the management of anti-coagulation.

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.

Magnesium. 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). 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. (213) 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. (214) 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. (214, 215) High intakes of magnesium from dietary supplements and medications can cause diarrhea, nausea, and abdominal cramping.

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. (216, 217) 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. (218) 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. (219-226) 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)*." (223) 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 (227-229) NAC is the precursor of reduced glutathione. NAC penetrates cells where it is deacetylated to yield L-cysteine thereby promoting GSH synthesis. (229) 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 the vaccine injured. 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. (230, 231) 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. (232)

Sildenafil with or without L-arginine-L-Citrulline (233-238); 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.

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. (239, 240) 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. (241) Wheatgerm, mushrooms, grapefruit, apples, and mango are high natural sources of spermidine. (242) 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. (243) In addition, spermidine should be avoided in men over the age of 60 who are at high risk of an ischemic stroke. (244)

ARC microcurrent device. Microcurrent is a non-invasive and safe electrotherapy applied through a series of sub-sensory electrical currents (less than 1 mA), which are of a similar magnitude to the currents generated endogenously by the human body. Sub-sensory bio-currents influence growth, adaptation, and tissue repair, by optimizing physiological functions, including nervous system signalling, muscle growth, and remodelling. (245) The ARC microcurrent device is worn on the lower legs of subjects and goes through a 3-hour alternating cycle. Anecdotal reports from vaccine injured patients

suggest that this device provides significant symptomatic improvement. The physiological mechanism by which the devise has systemic effects is somewhat unclear.

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 vaccine-injured patients. MB induces mitophagy (mitochondrial autophagy) and has anti-inflammatory, antioxidant, neuroprotective, and antiviral properties. (246, 247) A study in 2013 found that methylene blue-induced neuroprotection is mediated, at least in part, by macroautophagy through activation of AMPK signaling. (248)

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. (249, 250) 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. (251, 252). 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. (250, 251, 253)

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 protocol 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.

Non-invasive brain stimulation (NIBS), using transcranial direct current stimulation or transcranial magnetic stimulation, has been demonstrated to improve cognitive function in patients with long COVID as well as other neurological diseases. (254-261) 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 (262), **and psychological support** may help improve patients’ overall well-being and mental health. (263) Suicide is a real problem in the vaccine-injured patient. 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. (264, 265) Yoga has immunomodulating properties that may be beneficial in vaccine-injured patients. (266)

Third Line Therapies

- **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. (267) 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, 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) (268-274). CoQ10 is not recommended; in a double-blind randomized controlled trial high dose CoQ10 did not reduce the number or severity of long Covid related symptoms when compared to placebo. (275)

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

Other Potential Treatments

(Require further evaluation)

- **Plasmapheresis**. Plasmapheresis improves systemic cytokine levels, coagulopathy, and immune responsiveness in patients with severe COVID with a potential mortality benefit. (276-283) Kiprov, et. al. have published a case report of a dramatic clinical improvement in a patient with long COVID. (284) In this report, the patient's markers of inflammatory macrophages diminished, and markers of lymphocytes, including natural killer cells and cytotoxic CD8 T-cells, increased; in addition, circulating inflammatory proteins diminished. Furthermore, it is likely that plasmapheresis removes autoantibodies and improves the coagulopathy of these patients. We are aware of anecdotal reports of marked improvement in neurological symptoms, especially SFN and brain fog in vaccine-injured patients treated with this therapeutic modality. However, this is a limited and expensive resource that, in itself, is not without complications. Furthermore, the durability of the clinical response needs to be determined. While plasmapheresis/plasma exchange is a therapeutic option for the severely neurologically impaired patient following vaccination, additional data is required before this modality can be widely recommended.

- **Intravenous immunoglobulin (IVIG) treatment;** The role of IVIG in the treatment of the vaccine injured is unclear. The response to IVIG in the general population of vaccine-injured patients is mixed, with very few showing long-term improvement. Many patients who report an

initial improvement will relapse in 2 to 3 weeks. Other patients report no benefit, while some appear worsened. Due to the presence of non-neutralizing anti-SARS-CoV-2 antibodies and anti-ACE-2 antibodies, etc., the real possibility exists that IVIG will cause antibody-dependent immune enhancement (ADE) with a severe exacerbation of symptoms.

IVIG is, however, recommended in specific autoimmune syndromes, which include Guillain Barré Syndrome, transverse myelitis, and immune thrombocytopenia. These patients should concomitantly be treated with the core immune-modulating therapies. IVIG proved to be ineffective in an RCT that enrolled patients with small fiber neuropathy. (285) The fact that many patients report an initial response to IVIG supports the notion that many aspects of this disease are due to autoantibodies. IVIG will remove preformed antibodies, but they do not prevent the B cells from ongoing antibody production; hence the response is likely to be short-lived, and interventions that limit the production of autoantibodies are therefore required (core immune-modulating therapies).

- **Valproic acid** (286, 287); Depakote, 250mg 2-3 times daily. Valproic acid has anti-inflammatory effects and polarizes macrophages towards an M2 phenotype. (288) Histone deacetylase (HDAC) inhibitors are being studied for neural regeneration. In addition, valproic acid has important anticoagulant and anti-platelet effects (289) and is an inducer of heat shock proteins. (290) Valproic acid may be helpful for neurological symptoms. Treatment should be limited to less than 6 to 9 months due to the concern for the loss of brain volume particularly in those patients with cognitive dysfunction. (291) In a cerebral ischemia/hypoxia model resveratrol markedly enhanced the neuroprotective effects of valproic acid. (292) Furthermore, resveratrol has been reported to reverse the toxicity of valproic acid, (293, 294). These data suggest that resveratrol (in a dose of 500 mg – 1000 mg twice daily) should be recommended in patients prescribed valproic acid.

- **Induced hyperthermia and Cold Hydrotherapy.** The role of sauna bathing and cold therapy (cold showers, cold baths) in patients with long COVID and the vaccine-injured is unknown. (295, 296) Regular sauna bathing has been proven to reduce all-cause and cardiovascular mortality, prolong the lifespan, improve exercise performance, and improve the outcome of patients with neuropsychiatric disease. (297-301) Induced hyperthermia increases the expression of heat shock proteins, which activates autophagy. In addition, heat therapy increases the expression of cell stress pathways, has antioxidant and anti-inflammatory effects, and improves mitochondrial function. (295) Sauna bathing has very similar physiologic effects to that of aerobic exercise (increase heart rate, stroke volume, and cardiac output). (302, 303) As patients with long COVID and the vaccine-injured are exercise intolerant (they cannot increase cardiac output) (304) sauna bathing may be poorly tolerated. However, sauna bathing and induced hyperthermia have been shown to improve endothelial and cardiac function in patients with chronic heart failure. (305) Furthermore a recent meta-analysis reported that sauna bathing improved cardiac function in patients with chronic heart failure. (306) Waon therapy (infrared dry sauna) has shown promising results in patients with chronic fatigue syndrome. (307, 308) Patients interested in sauna bathing should determine their tolerance to short sessions (5-10 mins) and increase the duration as tolerated (up to 20 minutes) three to four times a week. Similarly, the role of cold therapy in the vaccine-injured is unknown; patients should similarly determine their tolerance to this treatment approach. (309, 310)

- **Pentoxifylline (PTX)**; PTX ER, 400 mg three times daily, should be considered in those patients with severe microcirculatory disturbances. PTX is a non-selective phosphodiesterase drug that has anti-inflammatory and antioxidant effects. In addition, PTX improves red blood cell deformability and reduces blood viscosity, so can mitigate the hyper-viscosity and RBCs hyper-aggregation, which is linked with the development of coagulopathy in the vaccine injured.

- **Maraviroc;** 300 mg orally twice daily. If 6 to 8 weeks have elapsed and significant symptoms persist despite the above therapies, this drug can be considered. Note Maraviroc can be expensive and has a risk of significant side effects and drug interactions. Maraviroc is a C-C chemokine receptor type 5 (CCR5) antagonist. While many long COVID and post-vaccine patients have been treated with Maraviroc, the role of this drug requires further evaluation. (311)

- **Sulforaphane (broccoli sprout powder)** 500 mcg – 1g twice a day. While sulforaphane has many potential benefits in patients with COVID, (312-314) long COVID, and post-vaccine syndrome, there is limited clinical data to support this intervention. Sulforaphane has immunomodulatory effects by targeting monocytes/macrophages, suggesting a benefit in chronic inflammatory conditions. (312-314) Sulforaphane is a beneficial supplement that may be useful for reducing microglial-mediated neuroinflammation and oxidative stress. In addition, as has been well-popularized, sulforaphane has an important role in cancer prophylaxis. The pharmacology and optimal dosing of sulforaphane are complex. Sulforaphane itself is unstable. The supplement should contain the two precursors, *glucoraphanin* and *myrosinase*, which react when the supplement is consumed. Broccoli "extracts" are produced in a way that completely destroys the activity of the myrosinase enzyme. As such, these extracts are incapable of producing sulforaphane when consumed in a supplement or food. (315, 316) We recommend a 100% whole broccoli sprout powder, which maximally retains both glucoraphanin and myrosinase whilst, at the same time, deactivating the inhibitors.

- **Dandelion** (*Taraxacum officinale*). The root, flower, and leaves of dandelion contain an array of phytochemicals that have anti-inflammatory, antioxidant, hypolipidemic, antimicrobial, and anticoagulant properties**.** (317, 318) It is widely reported that dandelion is effective for 'detoxifying' spike protein. An *in vitro* study demonstrated that a dandelion leaf extract altered the binding of SARS-CoV-2 spike protein to the ACE receptor**.** (319) It would appear that this effect was due to alterations (binding) of the ACE-2 receptor rather than binding to the spike protein. It, therefore, remains unclear whether dandelion extract actually binds to the spike protein and would potentiate clearance of this protein. The European Scientific Cooperative on Phytotherapy recommends a dose of 4-10 g TID (20-30mg/ml in hot water). (320) It should be noted that Dandelion extract is considered contraindicated in those with liver and biliary disease, bile duct obstruction, gallstones, cholangitis, and active peptic ulcer. (320) Furthermore dandelion is rich in potassium and should be used cautiously in patients with kidney failure.

- **Immunosuppressive therapies**; As a rule, immunosuppressive therapy should be avoided, as these drugs may exacerbate the immune dysfunction in vaccine-injured patients and prevent the restoration of immune homeostasis. A trial of immunosuppressive therapy may be indicated in patients with an established autoimmune syndrome who have failed other therapeutic interventions.

Patients with elevated homocysteine levels

Patients with elevated homocysteine levels may benefit from treatment with 800 ug of 5-methyl tetrahydrofolate (5-MTHF), the most biologically active form of folic acid. (321) Supplementation with folic acid alone will paradoxically increase homocysteine levels, particularly in patients with MTHFR polymorphism. (321) In addition, B complex vitamins containing B2 (riboflavin) and Vitamin B6, magnesium, and Vitamin D should be added. (43)

Disease-Specific Therapeutic Adjuncts

Small fiber neuropathy (SFN)/autonomic neuropathy

SFN is one of the commonest, most enduring, and most disabling complications in the vaccine injured. As symptoms appear once the nerve is already injured and inflamed it may be difficult to treat and reverse. It is likely that there is no single magic bullet to treat this disease and that a combination of therapies should be sequentially attempted in order to find a personalized therapy that has some benefit.

- Low-dose naltrexone (LDN) appears to play a pivotal role in the treatment of SFN.
- Tricyclic antidepressants (start at a low dose and increase as tolerated)
- Gabapentin: 300 mg twice daily and increase as tolerated
- Alpha lipoic acid; 600 mg/day (alpha-lipoic acid is an inducer of heat shock proteins). (322, 323)
- Zinc; 25 mg daily (elemental zinc) together with the zinc ionophore quercetin. SFN is an autoimmune disease; zinc deficiency has been associated with the development of autoimmune diseases. (324)
- Magnesium; 100-400 mg daily. Magnesium is an important nerve stabilizer.
- Resveratrol 500 mg twice a day. Resveratrol has important anti-inflammatory and immunomodulating properties. In addition, resveratrol activates autophagy.
- Cardio Miracle™ and L-arginine/L-citrulline supplements**.** Cardio Miracle is a supplement with over 50 ingredients formulated to increase nitric oxide (NO) production. Nitric oxide releasing lozenges or tablets are an alternative. NO likely improves microvascular flow and nerve repair. Sildenafil with or without L-arginine-L-Citrulline (233-238); Sildenafil doses titrated up from 25 to 100 mg 2-3 times daily with L-arginine/L-citrulline powder twice daily.
- Omega-3 fatty acids 2-4g/day. Omega-3 fatty acids have important anti-inflammatory and immunomodulating properties.
- Near infra-red photobiomodulation. PBM likely improves neuropathy via NO pathways and improving axonal and Schwann cell mitochondrial function. (325, 326)
- Whole-body vibration therapy has been shown to improve symptoms of small fiber neuropathy. (327, 328)
- POTS – ensure sufficient hydration and consider the use of compression stockings or abdominal binders.
- POTS – Clonidine; 0.1 mg twice daily as tolerated.
- POTS – Fludrocortisone; 0.1 to 0.2 mg/day or licorice root (has glycyrrhizinic acid, an aldosterone-like compound).
- POTS – midodrine; 5-10 mg three times daily
- A trial of hyperbaric oxygen therapy (HBOT)
- It should be noted that the diagnosis of small fiber neuropathy/autonomic neuropathy is a clinical diagnosis. (28-35) Complex and expensive tests are NOT required to make this diagnosis.

It should be noted that SFN is closely associated with multiple autoantibodies. Testing for these autoantibodies serves no useful clinical purpose as it does not change the treatment plan.

Generalized neurologic symptoms/"brain fog"/fatigue/visual symptoms

- LDN appears to play a pivotal role in the treatment of many neurological symptoms.
- Methylene blue (as indicated above) and photobiomodulation.
- Nigella Sativa; 200-500 mg twice daily.
- Non-invasive brain stimulation (NIBS) should be considered in patients with "brain fog," memory disturbances, and as well as other cognitive issues.
- Bupropion, a norepinephrine-dopamine reuptake inhibitor has been demonstrated to improve fatigue and "brain fog" in patients with both cancer and non-cancer related fatigue. The suggested dose is 150 mg extended-release tablet daily. After a month the dose can be cautiously increased to 300 mg daily. **Bupropion is CONTRAINDICATED in combination with methylene blue.**
- Intranasal oxytocin. Oxytocin is a nonapeptide produced in the hypothalamus, acting as a neuropeptide in different brain areas (most notably the amygdala and hippocampus) and as a hormone and paracrine substance in peripheral organs. (329-331) Oxytocin has colloquially been referred to as the "love hormone'', given its role in social interaction and bonding. (332) Oxytocin has powerful anti-inflammatory and immunomodulating properties and may play an important role in minimizing neuro-inflammation. In addition, oxytocin has been demonstrated to stimulate neuronal growth (330) Oxytocin plays an important role in modulating the stress response. (333) Oxytocin has also been reported to have a role in the prevention and treatment of migraine. (334, 335) The nasal route appears to be the preferred mode of administration. Martins et al performed a dose-finding study in healthy human volunteers. These authors measured changes in amygdala blood flow and demonstrated an inverse dose-response curve, with lower doses resulting in a greater increase in blood flow. They report the optimal dose as being between 9-18 IU. This suggests that one to two puffs to each nostril (4 IU per puff) two times a day may be optimal (total dosage of 16-32 IU per day). Oxytocin must be avoided in pregnancy. Oxytocin nasal spray should be compounded at 12 to 15 units/0.1ml (spray) and administered at onset aggressively to upregulate receptors at 2 sprays each nostril BID (8-sprays per day) for the first week and then maintenance at 2 sprays ea. nostril (4/d) once daily. (336) Oxytocin can also be delivered via SL liquid or via lozenge.
- Spermidine and Resveratrol**.** Experimental studies have demonstrated that spermidine reduces neuroinflammation, reduces accumulation of amyloid protein, and improves cognitive function. (337, 338) Similarly, resveratrol has been shown to be useful in the prevention and treatment of Alzheimer's disease. (169)
- Valproic acid and pentoxifylline may be of value in these patients.
- Fluvoxamine: Start on a low dose of 12.5 mg/day and increase slowly as tolerated. Some patients report a significant improvement with fluvoxamine while other patients appear to tolerate this drug poorly. Fluoxetine 20 mg/day is an alternative, as are tricyclic anti-depressants (see section on Depression below).
- These symptoms may be mediated by Mast Cell Activation Syndrome (MCAS); see specific treatment below.

Depression

- See the forthcoming FLCCC monograph on the management of depression.

- Depression is a serious problem in long COVID and post-vaccine patients and, unfortunately, suicide is not uncommon. (339-341) Patients with a history of depression and/or those taking SSRI medications appear to be at particular risk of severe depression.
- Long-term SSRI medications are generally not recommended due to the long-term effects of these drugs on serotonin receptors, intracellular messenger pathways as well as genetic and epigenetic effects. (342, 343) It should be noted that most SSRI/SNRI agents, but notably sertraline, fluvoxamine, paroxetine, venlafaxine, and duloxetine are associated with severe anxiety which may progress to mania, self-inflicted harm, suicide, anger outbursts, physical violence, homicidal thoughts, and homicide. (344-347) Patients who are treated with antidepressant agents, therefore, require close monitoring for the development of these serious adverse reactions.
- There appears to be an interaction between vaccination, COVID-19, zinc levels, and depression. (348-351) COVID-19 infection and COVID vaccines may lead to low zinc levels. Zinc deficiency is associated with an increased risk of depression. Treatment with zinc has been shown to have antidepressant effects and to act synergistically with SSRI medication. (352) 25 mg zinc daily (elemental), together with the zinc ionophore quercetin is therefore suggested. (351)
- Non-invasive brain stimulation (NIBS) using transcranial direct current stimulation or transcranial magnetic stimulation has been demonstrated to be highly effective in the treatment of depression. (353-357) Indeed, The Fisher Wallace Stimulator® is FDA approved for the treatment of depression, anxiety, and insomnia. NIBS is painless, extremely safe, and easy to administer. NIBS is a recognized therapy offered by many Physical Medicine and Rehabilitation Centers. Patients may also purchase an FDA-approved device for home use (https://www.fisherwallace.com/).
- Methylene blue (dose as indicated above) has been proven to be beneficial in patients with depression. (358, 359) **Do NOT TAKE FLUVOXAMINE, FLUOXETINE, BUPROPION or any other SSRI-NDRI with MB.**
- Photobiomodulation and sauna bathing have been shown to be highly effective for the treatment of depression. (300, 360-362)
- In experimental models, *Nigella sativa* has been shown to have a role in the treatment of depression. (363)
- Altered gut flora/dysbiosis has been linked to anxiety and depression and the use of probiotics has been associated with an improvement in mood. (364-368) Since infection with SARS-CoV-2 and those who have been vaccinated have dysbiosis the use of pre- and probiotics are suggested. (179, 180, 369, 370) Unsweetened Greek yogurt with pre and probiotics is recommended. Suggested probiotics include Megasporebiotic (Microbiome labs) and TrueBifidoPro (US Enzymes) and yourgutplus+. (181) In addition, the use of Glucomannan (from Konjac root) and/or Chia seeds provide soluble and insoluble fiber required for the normalization of the microbiome. (182, 183, 371) 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.

Patients with elevated DIC and those with evidence of thrombosis

- See section on anticoagulation. The patient's risk of bleeding needs to be assessed as this will determine the aggressiveness of anticoagulation.
- These patients should be treated with a DOAC or coumadin for at least three months and then reevaluated for ongoing anticoagulation.
- Patients should continue ASA 81 mg/day unless at high risk of bleeding.
- Nattokinase 100-200mg twice daily is suggested unless at high risk of bleeding.

- Triple anticoagulation should be considered in select patients. (77) Treat no longer than one month. Triple anticoagulation increases the risk of serious bleeding; patients should be counseled regarding this complication.
- In those patients with marked microvascular disease/thrombosis, the combination of pentoxifylline and sildenafil should be given a therapeutic trial. (372, 373)

Vaccine-induced myocarditis/pericarditis

- ACE inhibitor/ARB, together with carvedilol as tolerated to prevent/limit progressive decline in cardiac function.
- Colchicine in patients with pericarditis – 0.6 mg/day orally; increase to 0.6 mg twice daily if required. Reduce dose if patients develop diarrhea. Monitor white blood cell count. Decrease dose with renal impairment.
- Magnesium to reduce the risk of serious arrhythmias (see dosing above).
- Coenzyme Q (CoQ) 200-400mg/day. (374-377)
- Omega-3 fatty acids – EPA/DHA 2-4 g/day (378-380) Increase dose slowly as tolerated.
- Resveratrol/flavanoid combination for its anti-inflammatory and antioxidant properties.
- Referral to a cardiologist or ER in case of persistent chest pain or other signs and symptoms of cardiac events are observed.

Herpes virus reactivation syndrome

- Valtrex; 500-1000 mg twice daily for 7-10 days (acyclovir is an alternative). (381)
- Spironolactone 50-100 mg daily (382). Spironolactone has antiviral properties against Epstein Barr Virus by inhibiting viral capsid antigen synthesis and capsid formation. Spironolactone likely has antiviral effects against other Herpes viruses.
- L-Lysine; 1000 mg twice daily (383, 384)
- Valproic acid; Depakote, 250 mg 2-3 times daily. Valproic acid has activity against HSV-1, HSV-2, HZV, CMV, and EBV. (385-387)
- Zinc 40 mg daily (388, 389)
- Quercetin “Phytosome” 500 mg twice daily (antiviral properties and a Zinc ionophore) (390)

Tinnitus

- This a frequent and disabling complication reported in post-vaccine syndrome.
- Tinnitus refers to the sensation of sound in the absence of a corresponding external acoustic stimulus and can, therefore, be classified as a phantom phenomenon. Tinnitus sensations are usually of an unformed acoustic nature such as buzzing, hissing, or ringing. Tinnitus can be localized unilaterally or bilaterally, but it can also be described to emerge within the head. (391)
- Ideally, patients should be evaluated by an ENT specialist or audiologist to exclude underlying disorders.

- A number of treatment approaches exist to manage this disabling disease including: (391-393)
    - Cognitive behavioral therapy (394)
    - Specialized therapy including tinnitus retraining therapy, hearing aids, sound therapy, auditory perceptual training, and repetitive transcranial magnetic stimulation. (391)
    - A number of pharmacologic agents have been used to treat tinnitus. Anticonvulsants including carbamazepine have generally been disappointing. The following drugs have shown some clinical benefit.

        - Tricyclic antidepressant agents particularly nortriptyline and amitriptyline. (395, 396) In addition, the SSRI sertraline has shown some efficacy. (397)
        - Clonazepam and or other benzodiazepines. These drugs may provide temporary relief, however, due to issues of dependence, long-term use is not recommended. (398)
        - Melatonin slow release 2-6 mg at bedtime. (399)
- Oxytocin nasal spray. Oxytocin acts as a neurotransmitter affecting several neural circuits, particularly in the hypothalamus and amygdala. (331) Oxytocin nasal spray has shown promising results for the treatment of tinnitus (one puff to each puff nostril two times a day; a total dosage of 16 IU per day). (400) Oxytocin must be avoided in pregnancy. Oxytocin nasal spray should be compounded at 12 to 15 units/0.1ml (spray) and administered at onset aggressively to upregulate receptors at 2 sprays each nostril BID (8-sprays per day) for the first week and then maintenance at 2 sprays ea. nostril (4/d) once daily. (336) Oxytocin can also be delivered via SL liquid or via lozenge.
- Non-invasive brain stimulation (NIBS) has proven to be effective in controlling treatment-resistant tinnitus. (260, 261)

Ageusia and anosmia (Loss of taste and smell)

- Loss of smell and taste is a troubling symptom in post-COVID patients and in the vaccine injured. The loss of taste usually follows the loss of smell. Multiple mechanisms may explain the loss of smell including direct injury to the olfactory bulb. (401) Anosmia is a particularly difficult condition to treat. (402)
- Oxytocin nasal spray. Oxytocin receptors are highly expressed on olfactory neurons as well as limbic structures. Oxytocin nasal spray has been demonstrated to improve the sense of smell in patients with schizophrenia. A dose of one puff in each nostril two times a day for a total dosage of 16 IU per day is suggested. (403) Oxytocin must be avoided in pregnancy.
- Olfactory training appears to be a promising therapy for patients with post viral olfactory loss to partly regain their sense of smell. (404)
- Nasal corticosteroids appear ineffective and are not recommended for the use of anosmia. (405)

Bell's palsy/facial paresthesia/visual issues

- Low-dose naltrexone. Begin with 1 mg/day and increase to 4.5 mg/day as required. May take 2-3 months for full effect.
- Low dose corticosteroid: 10-15 mg/day prednisone for 3 weeks. Taper to 10 mg/day and then 5 mg/day as tolerated.
- Reduced workload, stress, and light exercises for a couple of months.

Alopecia (hair loss)

Three types of alopecia have been described in connection with COVID-19 infection, long COVID, and post-vaccine syndrome. (406)

- Androgenetic alopecia (worsening of male pattern baldness)
- Alopecia areata, an autoimmune disorder that usually results in unpredictable, patchy hair loss. In most cases, hair falls out in small patches around the size of a quarter. There is currently no cure for alopecia areata; referral to a dermatologist is suggested. Preliminary research in animals has found that quercetin can protect against the progression of alopecia areata and may promote hair regrowth. (407, 408)

- Telogen effluvium, which results in temporary thinning of the hair, particularly on the scalp. Telogen effluvium is a reversible condition in which hair falls out after a stressful experience. The stress pushes large numbers of hair follicles into a resting phase. Within a few months, those hairs can fall out. This condition occurs predominantly in females and may be related to increased expression of pro-inflammatory mediators. No specific treatment is required, as the hair will usually grow back.
- Photobiomodulation treatments appear to be very effective in inducing hair regrowth. (409, 410)
- Nutritional supplements containing omega-3 fatty acids (Vascepa), vitamin D, vitamin C, and zinc are useful adjuncts to promote hair regrowth. (411-413)
- Topical minoxidil may promote hair regrowth. (414) Finasteride 2.5 mg daily is an option in both men and women; (415) consult with a dermatologist and treatment for less than 1 year is generally recommended.
- Topical valproic acid has been shown to stimulate hair regrowth. (416, 417)

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