An Approach to the Management of Post-Vaccine Syndrome

I-RECOVER℠
POST-VACCINE TREATMENT

Disclosure

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

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. Keith Berkowitz; Dr. Flavio Cadegiani; Dr. Suzanne Gazda; Dr. Meryl Nass; Dr. Tina Peers; Dr. Robin Rose; Dr. Yusuf (JP) Saleeby; Dr. Eugene Shippen; Dr. Mobeen Syed; and Dr. Fred Wagshul.

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

Definition

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

Since Phase 3 and Phase 4 clinical trials are still ongoing, the full safety and toxicity profile for COVID-19 vaccines cannot be fully determined. From a bioethical perspective, cases of any new onset or worsened signs, symptoms or abnormalities following any dose of COVID-19 vaccine must be considered as an injury caused by the vaccine, until proven otherwise.

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-vaccine injuries and there is no specific ICD classification code for this disease. Thus, the accurate prevalence of post-vaccine syndrome is unknown. [1]

However, as of May 16, 2022, 815,385 adverse events have been reported in the United States alone following COVID-19 vaccination. In addition, over 5,309 cases of myocarditis, 151,796 serious adverse events, and 14,613 deaths have been recorded in the U.S. Vaccine Adverse Event Reporting System (VAERS) following COVID-19 vaccination. Note that the VAERS database is limited by underreporting, by a factor of at least 30-fold. [2]

Furthermore, published trials data suggest that at least 1 to 1.5 percent of vaccinated patients develop serious adverse events following vaccination. [2,3] Since 572 million doses of a COVID-19 vaccine have been administered in the U.S.—and 11 billion worldwide—it is likely there are millions of vaccine-injured patients worldwide, and at least 2 million cases in the U.S.

As the medical community does not recognize this serious humanitarian disaster, these patients have unfortunately been shunned and denied access to the medical 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, 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. [4,5] The S1 protein is profoundly toxic. Multiple intersecting and overlapping pathophysiologic processes likely contribute to the vast spectrum of vaccine injuries: [1,6]

- The acute, immediate reaction (within minutes to hours) is likely the results of an acute type I IgE mediated hypersensitivity reaction. The type I response may be due to preformed antibodies against mRNA, polyethylene glycol [7] or other components of the nano-lipid particle.
- 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. [8]
- The subacute and chronic myocarditis is likely the result of a spike protein-induced inflammatory response mediated by pericytes and macrophages. [9,10]
- 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.

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Due to molecular mimicry with the spike protein, a diverse spectrum of autoantibodies is produced. [11-20] These autoantibodies are the likely cause of Guillain-Barré Syndrome (GBS), transverse myelitis, immune thrombocytopenia, and Small Fiber Neuropathy (SFN)/Autonomic neuropathy. [21-28]

Many of these antibodies are directed against G-protein coupled cell membrane receptors. [17,19] 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. [5] 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 suggests 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. [29,30] However, by definition MCAS has no identifiable causes, is not caused by allergen specific IgE and has no detectable clonal expansion of mast cells. [29]

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. [31-33]

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 a number of 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.
- **mRNA load and quantity of spike protein produced**: This may be linked to specific vaccine lots that contain a higher concentration of mRNA. [1]
- **Sex**: It appears that about 80 percent 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. [34] In addition, estrogens modulate B and T cell function.
- **Underlying nutritional status and comorbidities**: It is likely that certain preexisting conditions may 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 with methylenetetrahydrofolate reductase (MTHFR) gene mutations and Ehlers-Danlos type syndromes may be at an increased risk, as well as those with deficiencies of nutrients such as Vitamin B12, Vitamin D and magnesium.

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, clinical observation, and patient anecdotes.
- 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.
- Treatment must be individualized according to each patient's presenting symptoms and disease syndromes. It is likely that not all patients will 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 life-saving 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.
- Early treatment is essential; it is likely that the response to treatment will 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). It is likely that COVID-19 will 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.
- Similarly, 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. We recommend a number of simple, basic screening tests that should be repeated, as clinically indicated, every 4 to 6 months. Remember the dictum: Only do a test if the result will change your treatment plan.
- Hyperbaric oxygen therapy (HBOT) should be considered in cases of severe neurological injury and in patients showing a rapid downhill course (see below).
- Patients should avoid unscientific and poorly validated "Spike Protein Detox" programs.

Baseline Testing

- CBC with differential and platelet count
- Standard blood chemistries, including liver function tests
- D-Dimer—as a marker of clotting activation)
- 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
- HbA1C—Vaccine-injured patients are at an increased risk of developing diabetes.
- Troponin, pro-BNP, Galectin-3, and ST2—to exclude cardiac disease.
- CMV, EBV, 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/)
- 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. [29]
- 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, [17,19] ACE-2, [35] neurons, myelin, and other self-epitopes. The presence or absence of these antibodies has little impact on the management of these patients.

First Line Therapies (not symptom specific; listed in order of importance)

- **Intermittent daily fasting** or periodic daily fasts; Fasting has a profound effect on promoting immune system homeostasis, partly by stimulating autophagy and clearing misfolded and foreign proteins, promoting mitophagy and improving mitochondrial health, as well as increasing stem cell production. [36-42] Intermittent fasting likely has an important role in promoting the breakdown and elimination of the spike protein.
- **Ivermectin; 0.2-0.3 mg/kg, daily for up to 4-6 weeks**. Ivermectin has potent anti-inflammatory properties. [43-45] It also binds to the spike protein, aiding in the elimination by the host. [46-48] It is likely that ivermectin and intermittent fasting act synergistically to rid the body of the spike protein. A trial of ivermectin should be considered as first line therapy. It appears that patients can be grouped into two categories: i) ivermectin responders and ii) ivermectin non-responders. This distinction is important, as the latter group are more difficult to treat and require more aggressive therapy.
- **Low dose naltrexone (LDN);** LDN has been demonstrated to have anti-inflammatory, analgesic and neuromodulating properties. [49,50] Begin with 1 mg/day and increase to 4.5 mg/day, as required. May take 2 to 3 months to see full effect.

- **Melatonin;** 2-6 mg *slow release/extended release* prior to bedtime. Melatonin has anti-inflammatory and antioxidant properties and is a powerful regulator of mitochondrial function. [51-55] The dose should be started at 750 mcg (μg) to 1 mg at night and increased as tolerated. Patients who are slow metabolizers may have very unpleasant and vivid dreams with higher doses.
- **Aspirin;** 81 mg/day.
- **Vitamin C;** 1000 mg orally three to four times a day. Vitamin C has important anti-inflammatory, antioxidant, and immune-enhancing properties, including increased synthesis of type I interferons. [56-60] Avoid in patients with a history of kidney stones. Oral Vitamin C helps promote growth of protective bacterial populations in the microbiome.
- **Vitamin D** and **Vitamin K2**; 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.
- **Quercetin;** 250-500 mg/day (or mixed flavonoids). Flavonoids have broad spectrum anti-inflammatory properties, inhibit mast cells, [61-65] and have been demonstrated to reduce neuroinflammation. [66] Due to the possible drug interaction between quercetin and ivermectin (see below) 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. [67] 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.
- **Nigella Sativa;** 200-500 mg twice daily. [68-71] It should be noted that thymoquinone (the active ingredient of Nigella Sativa) decreases the absorption of cyclosporine and phenytoin. Patients taking these drugs should, therefore, avoid taking Nigella Sativa. [72] Furthermore, two cases of serotonin syndrome have been reported in patients taking Nigella Sativa who underwent general anesthesia (probable interaction with opiates). [73]
- **Probiotics/prebiotics**; Patients with post-vaccine syndrome classically have a severe dysbiosis with loss of Bifidobacterium. [74-76] Kefir is a highly recommended nutritional supplement high in probiotics. [77] Suggested probiotics include Megasporebiotic (Microbiome labs) and TrueBifidoPro (US Enzymes).
- **Magnesium**; 500 mg/day.
- **Omega-3 fatty acids**: Vascepa, Lovaza or DHA/EPA; 4 g/day. Omega-3 fatty acids play an important role in the resolution of inflammation by inducing resolvin production. [78,79]

Adjunctive/Second Line Therapies (listed in order of importance)

- **Hydroxychloroquine (HCQ);** 200 mg twice daily for 1-2 weeks, then reduce as tolerated to 200 mg/day. HCQ is the preferred second line agent. HCQ is a potent immunomodulating agent and is considered the drug of choice for systemic lupus erythematosus (SLE), where it has been demonstrated to reduce mortality from this disease. Thus, in patients with positive autoantibodies or where autoimmunity is suspected to be a prominent underlying mechanism, HCQ should be considered earlier. Further, it should be noted that SLE and post-vaccine syndrome have many features in common. HCQ is safe in pregnancy; indeed, this drug has been used to treat preeclampsia. [80-84] With long term usage, the dose should be reduced (100 or 150mg/day) in patients weighing less than 61 kg (135 lbs).

- **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. [85-90] Wean IV Vitamin C as tolerated.
- **Fluvoxamine**; Start on a low dose of 12.5 mg/day and increase slowly as tolerated.
- **"Mitochondrial energy optimizer"** with pyrroloquinoline quinone (e.g., Life Extension Energy Optimizer or ATP 360®). [91-93]
- **N-acetyl cysteine (NAC)**; 600-1500 mg/day. [94-96]
- **Sulforaphane (broccoli extract)**; 400 mcg/day. [97-99]
- **Low dose corticosteroid**; 10-15 mg/day prednisone for 3 weeks. Taper to 10 mg/day and then 5 mg/day, as tolerated.
- **Behavioral modification, mindfulness therapy** [100] **and psychological support** may help improve patients overall well-being and mental health. [101] Suicide is a real problem in the vaccine-injured patient. Support groups and consultation with mental health professionals is important.
- **Tai Chi**; Tai Chi is a health-promoting form of traditional Chinese martial art, shown to be beneficial for preventing and treating diseases including long COVID. [102,103] It should be noted that long COVID is characterized by severe post-exertional fatigue and/or worsening of symptomology, therefore patients should be counseled to moderate exertion, increasing slowly only as tolerated. [104]

Third Line Therapy

- **Hyperbaric oxygen therapy** (HBOT) [105-113]; 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. While the optimal dose and dosing schedule is unclear, a pressure of between 1.5 and 2.0 ATM appears to be necessary to mediate the anti-inflammatory effects; however, others have reported improvements with a little as 1.3 ATM. Pressures above 1.3 ATM can only be achieved using hard shell chambers. While there is very limited published data on the treatment of long COVID and post-vaccine syndrome, remarkable life-saving benefits have been reported anecdotally. This therapy is limited by logistical issues and cost.

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. [115-122] Kiprov, et. al. have published a case report of a dramatic clinical improvement in a patient with long COVID. [123] 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.

- **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. [124] 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 above therapies, this drug can be considered. Note Maraviroc can be expensive and has risk for 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. [114]
- **Valproic acid** [125,126]; Depakote, 250mg 2-3 times daily. Valproic acid has anti-inflammatory effects and polarizes macrophages towards a M2 phenotype. [127] HDAC inhibitors are being studied for neural regeneration. In addition, valproic acid has important anticoagulant and anti-platelet effects. [128] Valproic acid may be helpful for neurological symptoms.
- **Sildenafil** with or without L-arginine-L-Citrulline [129-134]; Sildenafil doses titrated up from 25 to 100 mg 2-3 times daily with L-arginine/L-citrulline 5000 mg 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.
- **VEDICINALS® 9**; a unique phytopharmaceutical based therapeutic suspension that consists of nine bioactive compounds with antiviral, anti-inflammatory, immune modulatory, anti-pyretic and analgesic properties. The compounds include Baicalin, Quercetin, Luteolin, Rutin, Hesperidin, Curcumin, Epigallocatechin Gallate, Piperine and Glycyrrhizin. (https://www.vedicinals.com/vedicinals-9/). A number of these compounds are included in our protocol and the additional benefit of this 9 phytopharmaceutical combination over more widely available flavonoid combinations is unknown. [135]
- **C60 or C60 fullerenes** [136,137]; C60, short for Carbon 60, is composed of 60 carbon atoms forming something that looks like a hollow soccer ball and considered as a "free radical sponge." C60 is considered the single-most powerful antioxidant ever discovered. Robert Curl, Harold Kroto, and Richard Smalley were awarded the Nobel Prize for chemistry in 1996 for its discovery.
- **Cold Hydrotherapy** (e.g. cold showers) [138,139]; Avoid warm/hot water baths.

Disease-Specific Therapeutic Adjuncts

Small fiber neuropathy (SFN)/autonomic neuropathy
- Tricyclic antidepressants (start at low dose and increase as tolerated)
- Gabapentin; 300 mg twice daily and increase as tolerated
- Alpha lipoic acid; 600 mg/day

- POTS – ensure sufficient hydration and consider use of compression stocking 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. [21-28] 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.

Generalized Neurologic Symptoms/Injuries/"Brain Fog"/Fatigue
- LDN appears to play a pivotal role in treatment of many neurological symptoms
- 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.
- Nigella Sativa; 200-500 mg twice daily.
- Valproic acid and pentoxifylline may be of value in these patients.
- These symptoms may be mediated by Mast Cell Activation Syndrome (MCAS); see specific treatment below.

Patients with an elevated DIC and those with evidence of thrombosis
- These patients should be treated with a NOAC 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.
- Lumbrokinase activates plasmin and degrades fibrin. e.g., Lumbroxym (US Enzymes). [140] Lumbrokinase appears to be well absorbed from the GI tract. [141]
- Turmeric (Curcumin) 500 mg BID. Curcumin has anticoagulant, antiplatelet and fibrinolytic properties. [142]
- Triple anticoagulation should be considered in select patients. [143] 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. [124,144]

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.

- 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
- L-Lysine; 1000 mg twice daily [145,146]
- Valtrex; 500-1000 mg twice daily for 7-10 days

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. [147]
- 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: [147-149]
  - Cognitive behavioral therapy [150]
  - Specialized therapy including tinnitus retraining therapy, hearing aids, sound therapy, auditory perceptual training and repetitive transcranial magnetic stimulation. [147]
  - 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. [151,152] In addition, the SSRI sertraline has shown some efficacy. [153]
    - Clonazepam and or other benzodiazepines. These drugs may provide temporary relief, however, due to issue of dependence, long term use is not recommended. [154]
    - Melatonin slow release 2-6 mg at bedtime. [155]

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.

Patients with new onset allergic diathesis and those with features of Mast Cell Activation Syndrome (MCAS)
- The novel flavonoid lutein is reported to be a potent mast cell inhibitor. [61,62,64,65] Lutein 20-100 mg/day is suggested.
- Turmeric (curcumin); 500 mg/day. Curcumin has been reported to block H1 and H2 receptors and to limit mast cell degranulation. [156,157]
- H1 receptor blockers. Loratadine 10 mg/day, Cetirizine 5-10 mg/day, Fexofenadine 180 mg/day.
- H2 receptor blockers. Famotidine 20 mg twice daily as tolerated. [158]

- Montelukast 10 mg/day. Caution as may cause depression is some patients. The efficacy of montelukast as a "mast cell stabilizer' has been questioned. [29]
- 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.
- Low histamine diet.

IVIG treatment (Intravenous immunoglobulin treatment)

- Generally, treatment with IVIG is not recommended.
- 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 2to 3 weeks. Other patients report no benefit, while some appear worsened. Due to the presence of non-neutralizing anti-SARS-CoV-2 antibodies, 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 a RCT that enrolled patients with small fiber neuropathy. [159]
- 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).

Immunosuppressive Therapies

- As a rule, immunosuppressive therapy should be avoided, as these drugs may exacerbate the immune dysfunction in vaccine-injured patients and prevent 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.

References

1. Blaylock RL. COVID Update: What is the truth? Surgical Neurology International 2022; 13.
2. Rose J. A report on the U.S. Vaccine Adverse Events Reporting System (VAERS) of the COVID-19 messenger ribonucleic acid 9mRNA) biologicals. Science, Public Health Policy, and Law 2021; 2:59-80.
3. Neil M, Fenton N, Smalley J et al. Latest statistics on England mortality data suggest systematic mis-categorisation of vaccine status and uncertain effectiveness of Covid-19 vaccination. Research Gate 2021.
4. Colunga Biancatelli RM, Solopov P, Sharlow E et al. The SARS-CoV-2 spike protein subunit 1 induces COVID-19 like acute lung injury in K18-hACE2 transgenic mice and barrier dysfunction in human endothelial cells. Am J Physiol Lung Cell Mol Physiol 2021; 321:L477-L484.
5. Marik P, Iglesias J, Varon J et al. A Scoping Review of the pathophysiology of COVID-19. International Journal of Immunopathology and Pharmacology 2021.
6. Seneff S, Nigh G, Kyriakopoulos AM et al. Innate immune suppression by SARS-C-V-2 mRNA vaccinations: The role of G-quadruplexes, exosomes and microRNAs. Food & Chemical Toxicology 2022; 164:113008.
7. Chen BM, Cheng TL, Roffler SR. Polyethylene glycol immunogenicity: Theorectical, clinical and practical aspects of anti-polyethylene glycol antibodies. ASC Nano 2021; 15:14022-48.
8. Cadegiani FA. Catecholamines are the key trigger of mRNA SARS-CoV-2 and mRNA COVID-19 vaccine-induced myocarditis and sudden deahts: a compelling hypothesis supprted by epidemiological, anatomopathological, molecular and physiological findings. medRxiv 2022.
9. Schauer J, Buddhe S, Gulhane A et al. Persistent cardiac MRI findings in a cohort of adolescents with post COVID-19 mRNA vaccine myopericarditis. J Pediatr 2022.
10. Verma AK, Lavine KJ, Lin CY. Myocarditis after COVID-19 mRNA vaccination. N Engl J Med 2022; 385:1332-34.
11. Schiaffino MT, Di Natale M, Garcia-Martinez E et al. Immunoserologic detection and diagnostic relevance of cross-reactive autoantibodies in Coronavirus disease 2019 patients. J Infect Dis 2020; 222:1439-43.
12. Trahtemberg U, Fritzler MJ. COVID-19-associated autoimmunity as a feature of acute respiratory failure. Intensive Care Med 2021.
13. Woodruff MC, Ramoneli RP, Lee FE et al. Broadly-targeted autoreactivity is common in severe SARS-CoV-2 infection. medRxiv 2020.
14. Zuo Y, Estes SK, Ali RA et al. Prothrombotic autoantibodies in the serum from patients hospitalized with COVID-19. Sci Translation Med 2020.
15. Pascolini S, Vannini A, Deleonardi G et al. COVID-19 and immunological dysregulation: can autoantibodies be useful? Clin Trans Sci 2021; 14:502-8.
16. Wang EY, Mao T, Klein J et al. Diverse functional autoantibodies in patients with COVID-19. Nature 2021; 595:283-88.
17. Cabral-Marques O, Halpert G, Schimke LF et al. Autoantibodies targeting GPCRs and RAS-related molecules associated with COVID-19 severity. Nature Communications 2022; 13:1220.
18. Arthur JM, Forrest JC, Boehme KW et al. Development of ACE2 autoantibodies after SARS-CoV-2 infection. PloS ONE 2021; 16:e0257016.
19. Wallukat G, Hohberger B, Wenzel K et al. Functional autoantibodies against G-protein coupled receptors in patients with persistent Long-Covid-19 symptoms. Journal of Translational Autoimmunity 2021; 4:100100.

I-RECOVER: Post-Vaccine Treatment protocol (5/25/2022)

20. Levine TD, Kafaie J, Zeidman LA et al. Cryptogenic small-fiber neuropathies: Serum autoantibody binding to trisulfated heparin disaccharide and fibroblast growth factor receptor-3. Muscle & Nerve 2020; 61:512-15.
21. Oaklander AL, Mills AJ, Kelley M et al. Peripheral neuropathy evaluations of patients with prolonged long COVID. Neurol Neuroimmunol Neuroinflamm 2022; 9:e1146.
22. Burakgazi AZ. Small-fiber neuropathy possibly associated with COVID-19. Case Rep Neurol 2022; 14:208-12.
23. Shouman K, Vanichkachorn G, Chesire WP et al. Autonomic dysfunction following COVID-19 infection: an early experience. Clinical Autonomic Research 2021; 31:385-94.
24. Hinduja A, Moutairou A, Calvet JH. Sudomotor dysfunction in patients recovered from COVID-19. Clinical Neurophysiology 2021; 51:193-96.
25. Abdelnour L, Abdalla ME, Babiker S. COVID 19 infection presenting as motor peripheral neuropathy. Journal of the Formosan Medical Association 2020; 119:1119-20.
26. Abrams RM, Simpson DM, Navis A et al. Small fiber neuropathy associated with SARS-CoV-2 infection. Muscle & Nerve 2021.
27. Zhou L, Shin S. Small fiber neuropathy. Practical Neurology 2021;36.
28. Bednarik J, Bursova S, Dusek L et al. Etiology of small-fiber neuropathy. Journal of the Peripheral Nervous System 2009; 14:177-83.
29. Theoharides TC, Tsilioni I, Ren H. Recent advances in our understanding of mast cell activation-or should it be mast cell mediator disorders? Expert Rev Clin Immunol 2019; 15:639-56.
30. Weinstock LB, Brook JB, Walters AS et al. Mast cell activation symptoms are prevalent in Long-COVID. International Journal of Infectious Diseases 2021; 112:217-26.
31. Gold JE, Okyay R, Licht WE et al. Investigation of Long COVID prevalence and its relationship to Epstein-Barr Virus reactivation. Pathogens 2021; 10:763.
32. Chen T, Song J, Liu H et al. Positive Epstein-Barr virus detection in coronavirus disease 2019 (COVID-19) patients. Scientific Reports 2021; 11:10902.
33. Le Balc'h P, Pinceaux K, Pronier C et al. Herpes simplex virus and cytomegalovirus reactivations among severe COVID-19 patients. Crit Care 2020; 24:530.
34. Duma D, Collins JB, Chou JW et al. Sexually dimorphic actions of glucocorticoids provide a link to inflammatory diseases with gender differences in prevalence. Science Signaling 2010; 3:ra74.
35. Tomassetti F, Nuccetelli M, Sarubbi S et al. Evaluation of S-RBD and high specificity ACE-2 binding antibodies on SARS-CoV-2 patients after six months from infection. International Immunopharmacology 2021; 99:108013.
36. Fung J, Moore J. The complete guide to fasting. Victory Belt Publishing; 2016.
37. deCabo R, Mattson MP. Effects of intermittent fasting on health, aging, and disease. N Engl J Med 2019; 381:2541-51.
38. Hannan A, Rahman A, Rahman S et al. Intermittent fasting, a possible priming tool for host defense against SARS-CoV-2 infection: Crosstalk among calorie restriction, autophagy and immune response. Immunology Letters 2020; 226:38-45.
39. Zhao Y, Jia M, Chen W et al. The neuroprotective effects of intermittent fasting on brain aging and neurodegenerative diseases via regulating mitochondrial function. Free Radical Biology & Medicine 2022; 182:206-18.
40. Beckman JA. Thrombolytic therapy for pulmonary embolism. JAMA 2014; 311:2385-86.
41. Cheng CW, Adams GB, Perin L et al. Prolonged fasting reduces IGF-1/PKA to promote hematopoietic-stem-cell-based regeneration and reverse immunosppression. Cell Stem Cell 2014; 14:810-823.

I-RECOVER: Post-Vaccine Treatment protocol (5/25/2022)

42. Hine C, Mitchell JR. Saying No to drugs: Fasting protects hematopoietic stem cells from chemotherapy and aging. Cell Stem Cell 2014; 14:704.
43. Ci X, Li H, Yu Q et al. Avermectin exerts anti-inflammatory effect by downregulating the nuclear transcription factor kappa-B and mitogen activated protein kinase pathway. Fundamental & Clinical Pharmacology 2009; 23:449-55.
44. DiNicolantonio JJ, Barroso-Arranda J, McCarty M. Ivermectin may be a clinically useful anti-inflammatory agent for late-stage COVID-19. Open Heart 2020; 7:e001350.
45. Yan S, Ci X, Chen N et al. Anti-inflammatory effects of ivermectin in mouse model of allergic asthma. Inflamm Res 2011; 60:589-96.
46. Saha JK, Raihan J. The binding mechanism of ivermectin and levosalbutamol with spike protein of SARS-CoV-2. Research Square 2021.
47. Bello M. Elucidation of the inhibitory activity of ivermectin with host nuclear importin alpha and several SARS-CoV-2 targets. Journal of Biomolecular Structure and Dynamics 2021.
48. Lehrer S, Rheinstein PH. Ivermectin docks to the SARS-CoV-2 spike receptor-binding domain attached to ACE2. In Vivo 2020; 34:3023-26.
49. Younger J, Parkitny L, McLain D. The use of low-dose naltrexone (LDN) as a novel anti-inflammatory treatment for chronic pain. Clin Rheumatol 2014; 33:451-59.
50. Toljan K, Vrooman B. Low-dose naltrexone (LDN) - Review of therapeutic utilization. Med Sci 2018; 6:82.
51. Molina-Carballo A, Palacios-Lopez R, Jerez-Calero A et al. Protective effect of melatonin administration against SARS-CoV-2 infection: A systematic review. Current Issues in Molecular Biology 2022; 44:31-45.
52. Hasan ZT, AlAtrakji MQ, Mehuaiden AK. The effect of melatonin on thrombosis, sepsis and mortality rate in COVID-19 patients. International Journal of Infectious Diseases 2022; 114:79-84.
53. Reiter RJ, Sharma R, Ma Q et al. Plasticity of glucose metabolism in activated immune cells: advantages for melatonin inhibition of COVID-19 disease. Melatonin Res 2020; 3:362-79.
54. Reiter RR, Sharma R, Castillo R et al. Coronavirus-19,Monocyte/Macrophage glycolysis and inhibition by melatonin. J SARS-CoV2 COVID 2021; 2:29-31.
55. Colunga Biancatelli RM, Berrill M, Mohammed YH et al. Melatonin for the treatment of sepsis: the scientific rationale. J Thorac Dis 2020; 12 (Suppl 1):S54-S65.
56. Marik PE. Hydrocortisone, Ascorbic Acid and Thiamine (HAT therapy) for the treatment of sepsis. Focus on ascorbic acid. Nutrients 2018; 10:1762.
57. Marik PE. Vitamin C for the treatment of sepsis: The scientific rationale. Pharmacol Therapeut 2018; 189:63-70.
58. Colunga Biancatelli RM, Berrill M, Marik PE. The antiviral properties of vitamin C. Expert Rev Anti Infect Ther 2020; 18:99-101.
59. Miranda-Massari JR, Toro AP, Loh D et al. The effects of vitamin C on the multiple pathological stages of COVID-19. Life 2021; 11:1341.
60. Holford P, Carr AC, Zawari M et al. Vitamin C intervention for Critical COVID-19: A pragmatic review of the current level of evidence. Life 2021; 11:1166.
61. Theoharides TT, Cholevas C, Polyzoidis K et al. Long-COVID syndrome-associated brain fog and chemofog: Luteolin to the rescue. Biofactors 2021; 47:232-41.
62. Theoharides TC. COVID-19, pulmonary mast cells, cytokine storms, and beneficial actions of luteolin. Biofactors 2020; 46:306-8.
63. Bawazeer MA, Theoharides TC. IL-33 stimulates human mast cell release of CCL5 and CCL2 via MAPK and NF-kB, inhibited by methoxyluteolin. Eur J Pharmacol 2019; 865:172760.

64. Weng Z, Patel AB, Panagiotidou S et al. The novel flavone tetramethoxyluteolin is a potent inhibitor of human mast cells. J Allergy Clin Immunol 2015; 135:1044-52.
65. Patel AB, Theoharides TC. Methoxyluteolin inhibits neuropeptide-stimulated proinflammatory mediator release via mTOR activation from human mast cells. J Pharmacol Exp Ther 2017; 361:462-71.
66. Calis Z, Mogulkoc R, Baltaci AK. The roles of flavonols/flavonoids in neurodegeneration and neuroinflammation. Mini Rev Med Chem 2020; 20:1475-88.
67. Sathyapalan T, Manuchehri AM, Thatcher NJ et al. The effect of soy phytoestrogen supplementation on thyroid status and cardiovascular risk markers in patients with subclinical hypothyroidism: A randomized, double-blind, crossover study. J Clin Endocrinol Metab 2020; 96:1422-49.
68. Islam MT, Guha B, Hosen S et al. Nigellalogy: A review on Nigella Sativa. MOJ Bioequiv Availab 2017; 3:00056.
69. Barbash IJ, Davis BS, Yabes JG et al. Treatment patterns and clinical outcomes after the introduction of the Medicare Sepsis Performance Measure (SEP-1). Ann Intern Med 2021.
70. Ashraf S, Ashraf S, Ashraf M et al. Honey and *Nigella sativa* against COVID-19 in Pakistan (HNS-COVID-PK): A multi-center placebo-controlled randomized clinical trial. medRxiv 2021.
71. Fakhar-e-Alam Kulyar M, Li R, Mehmood K et al. Potential influence of *Nagella sativa (*Black cumin) in reinforcing immune system: A hope to decelerate the COVID-19 pandemic. Phytomedicine 2021; 85:153277.
72. Hannan MA. Black Cumin (Nigella sativa L.): A Comprehensive Review on Phytochemistry, Health Benefits, Molecular Pharmacology, and Safety. Nutrients 2021; 13.
73. Warner ME, Naranjo J, Pollard EM et al. Serotonergic medications, herbal supplements, and perioperative serotonin syndrome. Can J Anaesth 2017; 64:940-946.
74. Gutierrez-Castrellon P, Gandara-Marti T, Abreu AT et al. Probiotic improves symptomatic and viral clearance in Covid-19 outpatients: a randomized, quadruple-blinded, placebo-conttrolled trial. GUT Microbes 2022; 14:e2018899.
75. Zuo T, Wu X, Wen W et al. Gut microbiome alterations in COVID-19. Genomics, Proteomics & Bioinformatics 2021.
76. Chen Y, Gu S, Chen Y et al. Six-month follow-up of gut microbiota richness in patients with COVID-19. Gut 2021.
77. Rosa DD, Dias MM, Grzeskowiak LM et al. Milk kefir: nutritional, micobiological and health benefits. Nutrition Research Reviews 2017; 30:82-96.
78. Lee CR, Zeldin DC. Resolvin infectious inflammation by targeting the host response. N Engl J Med 2015; 373:2183-85.
79. Serhan CN. Novel pro-resolving lipid mediators in inflammation are leads for resolution physiology. Nature 2014; 510:92-101.
80. Shukla AM, Shukla AW. Expanding horizons for clinical applications of chloroquine, hydroxychloroquine and related structural analogues. Drugs in Context 2019; 8:2019-9-1.
81. Plantone D, Koudriavtseva T. Current and future use of chloroquine and hydroxychloroquine in infectious, immune, neoplastic and neurological diseases: A mini review. Clin Drug Invest 2018; 38:653-71.
82. Ruiz-Irastorza G, Khamashta MA. Hydroxychloroquine: the cornerstone of lupus therapy. Lupus 2008; 17:271-73.
83. de Moreuil C, Alavi Z, Pasquier E. Hydroxychloroquine may be beneficial in preeclampsia and recurrent miscarriage. Br J Clin Pharmac 2020; 86:39-49.

I-RECOVER: Post-Vaccine Treatment protocol (5/25/2022)

84. Siso A, Ramos-Casals M, Bove A et al. Previous antimalarial therapy in patients diagnosed with lupus nephritis: Influence on outcomes and survival. Lupus 2008; 17:281-88.
85. Fontana F, Cazzato S, Giovanella S et al. Oxalate nephropathy caused by excessive vitamin C administration in 2 patients with COVID-19. Kidney Int Rep 2020; 5:1815-22.
86. Auer BL. Relative hyperoxaluria, crystalluria and haematuria after megadose ingestion of vitamin C. Eur J Clin Invest 1998; 28:695-700.
87. Mashour S, Turner JF, Merrell R. Acute renal failure, oxalosis, and vitamin C supplementation: a case report and review of the literature. Chest 2000; 118:561-63.
88. McHugh GJ, Graber ML, Freebairn RC. Fatal vitamin C-associated acute renal failure. Anaesth Intensive Care 2008; 36:585-88.
89. Lawton JM, Conway LT, Crosson JT et al. Acute oxalate nephropathy after massive ascorbic acid administration. Arch Intern Med 1985; 145:950-951.
90. Fletcher RH. The risk of taking ascorbic acid. JAMA Intern Med 2013; 173:388-89.
91. Misra HS, rajpurohit YS, Khairnar NP. Pyrroloquinoline-quinone and its versatile roles in biological processes. J Biosci 2012; 37:312-25.
92. Akagawa M, Nakano M, Ikemoto K. Recent progress in studies on the health benefits of pyrroloquinoline quinone. Bioscience, Biotenchnology, and Biochemistry 2016; 80:13-22.
93. Hamilton D, Jensen GS. Nutraceutical support of mitochoncrial function associated with reduction of long-term fatigue and inflammation. Alternative Therapies in Health & Medicine 2021; 27:8-18.
94. Izquierdo JL, Soriano JB, Gonzalez Y et al. Use of N-Acetylcysteine at high doses as an oral treatment for patients with COVID-19. Science Progress 2022; 105.
95. Shi Z, Puyo CA. N-Acetylcysteine to combat COVID-19: an evidence review. Therapeutics and Clinical Risk Management 2020; 16:1047-55.
96. De Flora S, Balansky R, La Maestra S. Rationale for the use of N-acetylcysteine in both prevention and adjuvant therapy of COVID-19. FASEB J 2020.
97. Houghton CA, Fassett RG, Coombes JS. Sulforane: translational research from laboratory bench to clinic. Nutr Rev 2013; 71:709-26.
98. Kim JK, Park SU. Current potential health benefits of sulforaphane. EXCLI Journal 2016; 15:571-77.
99. Mokhtari RB, Baluch N, Homayouni TS et al. The role of sulforaphane in cancer chemoprevention and health benefits: a mini-review. J Cell Commun Signal 2018; 12:91-101.
100. Sanabria-Mazo JP, Montero-Marin J, Feliu-Soler A et al. Mindfulness-based program plus amygdala and inusla retraining (MAIR) for the treatment of women with fibromyalgia: A pilot ramdomized controlled trial. J Clin Med 2020; 9:3246.
101. Yong SJ. Long-haul COVID-19: Putative pathophysiology, risk factors, and treatments. medRxiv 2020.
102. Shu C, Feng S, Cui Q et al. Impact of Tai Chi on CRP, TNF-alpha and IL-6 in inflammation: a systematic review and meta-analysis. Ann Palliat Med 2021; 10:7468-6478.
103. Zhang Z, Ren JG, Guo JL et al. Effects of Tai Chi and Qigong on rehabilitation after COVID-19: a protocl for systematic review and meta-analysis. BMJ Open 2022; 12:e059067.
104. Brown JT, Saigal A, Karia N et al. Ongoing exercise intolerance following COVID-19: A magnetic resonance-Augmented Cardiopulmonary excercise Test Study. J Am Heart Assoc 2022; 11:e024207.
105. Robbins T, Gonevski M, Clark C et al. Hyperbaric oxygen therapy for the treatment of long COVID: early evaluation of a highly promising intervention. Clinical Medicine 2021; 21:e629-e632.

I-RECOVER: Post-Vaccine Treatment protocol (5/25/2022)

106. Oliaei S, Mehrtak M, Karimi A et al. The effects of hyperbaric oxygen therapy (HBOT) on coronavirus disease-2019 (COVID-19): a systematic review. Eur J Med Res 2021; 26:96.
107. Senniappan K, Jeyabalan S, Rangappa P et al. Hyperbaric oxygen therapy: Can it be a novel supportive therap in COVID-19? Indian Journal of Anaesthesia 2020; 64:835-41.
108. Kjellberg A, De Maio A, Lindholm P. Can hyperbaric oxygen safely serve as an inti-inflammatory treatment for COVID-19? Medical Hypotheses 2020; 144:110224.
109. Hadanny A, Abbott S, Suzin G et al. Effect of hyperbaric oxygen therapy on chronic neurocognitive deficits of post-traumatic brain injury patients: retrospective analysis. BMJ Open 2018; 8:e023387.
110. Han CH, Zhang PX, Xu WG et al. Polarization of macrophages in the blood after decompression in mice. 7 2017;240.
111. De Maio A, Hightower LE. COVID-19, acute respiratory distress syndrome (ARDS), and hyperbaric oxygen therapy (HBOT): what is the link? Cell Stress & Chaperones 2020; 25:717-20.
112. Buras JA, Holt D, Orlow D et al. Hyperbaric oxygen protects from sepsis mortality via an interleukin-10-dependent mechanism. Crit Care Med 2006; 34:2624-29.
113. Tezgin D, Giardina C, Perdrizet GA et al. The effect of hyperbaric oxygen on mitochondrial and glycolytic energy metabolism: the caloristasis concept. Cell Stress and Chaperones 2020; 25:667-77.
114. Patterson B, Yogendra R, Guevara-Coto J et al. Targeting the monocytic-endothelial-platelet axis with maraviroc and pravastatin as a therapeutic option to treat long COVID/Post-acute sequelae of COVID (PASC). Research Square 2022.
115. Jamme M, Mazeraud A. Plasmapheresis efficiency in Coronavirus disease 2019: More related to what you add and not what you take away? Crit Care Med 2021.
116. Patidar GK, Land KJ, Vrielink H et al. Understanding the role of therapeutic plasma exchange in COVID-19: preliminary guidance and practices. Vox Sanguinis 2021.
117. Hashemian SM, Shafigh N, Afzal G et al. Plasmapheresis reduces cytokine and immune cell levels in COVID-19 patients with acute respiratory distress syndrome (ARDS). Pulmonary 2021; 27:486-92.
118. Balagholi S, Dabbaghi R, Eshghi P et al. Potential of therapeutic plasmapharesis in treatment of COVID-19 patients: immunopathogenesis and coagulopathy. Transfusion and Apheresis Science 2020; 59:102993.
119. Keith P, Day M, Perkins L et al. A novel treatment approach to the novel coronavirus: an argument for the use of therapeutic plasma exchange for fulminant COVID-19. Crit Care 2020; 24:128.
120. Morath C, Weigand MA, Zeier M et al. Plasma exchange in critically ill COVID-19 patients. Crit Care 2020; 24:481.
121. Fernandez J, Gratacos-Gines J, Olivas P et al. Plasma exchange: An effective rescue therapy in critically ill patients with Coronavirus Disease 2019 infection. Crit Care Med 2020.
122. Gucyetmez B, Atalan HK, Sertdemir I et al. Therapeutic plasma exchange in patients with COVID-19 pneumonia in intensive care unit: a retrospective study. Crit Care 2020; 24:492.
123. Kiprov DD, Herskowitz A, Kim D et al. Case report. Therapeutic and immunomodulatory effects of plasmapheresis in long-haul COVID. F1000Research 2022; 10:1189.
124. Mostafa-Hedeab G, Al-kuraishy HM, Al-Gareeb AA et al. A raising dawn of pentoxifylline in the management of inflammatory disorders in Covid-19. Inflammopharmacology 2022.
125. Pitt B, Sutton NR, Wang Z et al. Potential repurposing of the HDAC inhibitor valproic acid for patients with COVID-19. Eur J Pharmacol 2021; 898:173988.

I-RECOVER: Post-Vaccine Treatment protocol (5/25/2022)

126. Unal G, Turan B, Balcioglu YH. Immunopharmacological management of COVID-19: Potential therapeutic role of valproic acid. Medical Hypotheses 2020; 14:109891.
127. Wu C, Li A, Leng Y et al. Histone deacetylase inhibition by sodium valproate regulates polarization of macrophage subsets. DNA and Cell Biology 2012; 31:592-99.
128. Larsson P, Alwis I, Niego B et al. Valproic acid selectively increases vascular endothelial tissue - type plasminogen activator production and reduces thrombus formation in the mouse. J Thromb Haemost 2016; 14:2496-508.
129. Santamarina MG, Boisier D, Contreras R et al. COVID-19: a hypothesis regarding the ventilation-perfusion mismatch. Crit Care 2020; 24:395.
130. Mario L, Roberto M, Marta L et al. Hypothesis of COVID-19 therapy with sildenafil. International Journal of Preventive Medicine 2020; 11:76.
131. Santamarina MG, Beddings I, Martinez Lomakin F et al. Sildenafil for treating patients with COVID-19 and perfusion mismatch: a pilot randomized trial. Crit Care 2022; 26:1.
132. Kniotek M, Boguska A. Sildenafil can affect innate and adaptive immune system in both experimental animals and patients. Journal of Immunology Research 2017; 2017:4541958.
133. Isidori AM, Giannetta E, Pofi R et al. Targeting the NO-cGMP-PDE5 pathoway in COVID-19 infection. The DEDALO project. Andrology 2021; 9:33-38.
134. Al-kuraishy HM, Ali-Gareeb AI, Al-Niemi MS et al. COVID-19 and phosphodiesterase enzyme type 5 inhibitors. J Microsc Ultrastruct 2022; 8:141-45.
135. Harasstaini OA, Moin S, Tham CL et al. Flavonoid combinations cause synergistic inhibition of proinflammatory mediator secretion form lipopolysaccharide-induced RAW 264.7 cells. Inflammation Research 2010; 59:711-21.
136. Marforio TD, Mattioli EJ, Zerbetto F et al. Fullerenes against COVID-19: Repurposing C50 and C70 to clog the active site of SARS-CoV-2 protease. Molecules 2022; 27:1916.
137. Hurmach Vv, Platonov MO, Prylutska SV et al. C60 fullerene against SARS-CoV-2 coronavirus: an in silico insight. Scientific Reports 2021; 11:17748.
138. Shevchuk N. Adapted cold shower as a potential treatment for depression. Medical Hypotheses 2008; 70:995-1001.
139. Mooventhan A, Nivethitha L. Scientific evidence-based effects of hydrotherapy on various systems of the body. North American Journal of Medical Sciences 2014; 6:199-209.
140. Wang YH, Li SA, Huang CH et al. Sirt1 activation by post-ischemic treatment with lumbrokinase protects against myocardial ischemia-reperfusion injury. Fronteirs in Pharmacology 2018; 9:636.
141. Yan XM, Kim CH, Lee CK et al. Intestinal absorption of fibrinolytic and proteolytic lumbrokinase extracted from earthworm, Eisenia andrei. Korean J Physiol Pharmacol 2010; 14:71-75.
142. Keihanian F, Saeidinia A, Bagheri RK et al. Curcumin, hemostasis, thrombosis, and coagulation. J Cell Physiol 2018; 233:4497-511.
143. Pretorius E, Venter C, Laubshder G et al. Combined triple treatment of fibrin amyloid microclots and platelet pathology in individuals with long COVID/Post -acute sequelae of COVID-19 (PASC) can resolve their persistent symptoms. Research Square 2021.
144. Ng WK, Rosenblatt Y, Brock GB et al. Phosphodiesterase inhibitors in vascular ischemia: A case report and review of their use in ischemic conditions. Can J Plast Surg 2010; 18:e5-e9.
145. Griffith RS, Wlash DE, Myrmel KH et al. Sucess of L-Lysine therapy in frequently recurrent Herpes simplex infection. Treatment and prophylaxis. Dermatologica 1987; 175:183-90.
146. Griffith RS, Norins AL, Kagan C. A multicentered study of Lysine therapy in Herpes simplex infection. Dermatologica 1978; 156:257-67.
147. Langguth B. Treatment of tinnitus. Curr Opin Otolaryngol Head Neck Surg 2015; 23:361-68.

I-RECOVER: Post-Vaccine Treatment protocol (5/25/2022)

148. Langguth B. Pharmacological approaches to the treatment of tinnitus. Drug Discovery Today 2010; 15:300-305.
149. Langguth B, Elgoyhen AB, Cederroth CR. Therapeutic approaches to the treatment of tinnitus. Ann Rev Pharmacol Toxicol 2019; 59:291-313.
150. MartinezDevesda P, Waddell A, Perera R et al. Cognitive behavioral therapy for tinnitus (Review). Cochrane Database of Syst Rev 2007.
151. Sullivan M, Katon W, Russo J et al. A randomized trial of nortriptyline for severe chronic tinnitus effects on depression, disability, and tinnitus symptoms. Arch Intern Med 1993; 153:2251-59.
152. Bayar N, Boke B, Turan E et al. Efficacy of amitriptyline in the treatment of subjective tinnitus. Journal of Otolaryngology 2001; 30:300-303.
153. Zoger S, Svedlund J, Holgers KM. The effects of sertraline on severe tinnitus suffering - A randomized, double-blind, placebo-controlled study. J Clin Psychopharmacology 2006; 26:32-39.
154. Bahmad FM, Venosa AR, Oliveira CA. Benzodiazepines and GABAergics in treating severe disabling tinnitus of predominantly cochlear origin. 12 2006;144.
155. Hosseinzadeh A, Kamrava SK, Moore BC et al. Molecular aspects of melatonin treatment in tinnitus: A review. Current Drug Targets 2019; 20:1112-28.
156. Jacob A, Wu R, Zhou M et al. Mechanism of the anti-inflammatory effect of Curcumin: PPAR-gamma activation. PPAR Research 2007; 2007:89369.
157. Kakavas S, Karayiannis D, Mastora Z. The complex interplay between immunonutrition, mast cells, and histamine signaling in COVID-19. Nutrients 2021; 13:3458.
158. Afrin LB, Weinstock LB, Molderings GJ. COVID-19 hyperinflammation and post-Covid-19 illness may be rooted in mast cell activation syndrome. Int J Infect DIs 2020.
159. Geerts M, de Greef BT, Sopacua M et al. Intravenous immunoglobulin therapy in patients with painful idiopathic small fiber neuropathy. Neurology 2022; 96:e2534-e2545.

I-RECOVER: Post-Vaccine Treatment protocol (5/25/2022)