I-RECOVER℠

LONG COVID TREATMENT

# AN APPROACH TO TREATING LONG COVID

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FLCCC ALLIANCE

FRONT LINE COVID-19 CRITICAL CARE ALLIANCE
PREVENTION & TREATMENT PROTOCOLS FOR COVID-19

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# Disclaimer

The information in this document is our recommended approach to COVID-19 based on the best (and most recent) literature. It is provided as guidance to healthcare providers worldwide on the early treatment of COVID-19. Our guidance should only be used by medical professionals in formulating their approach to COVID-19. Patients should always consult with their provider before starting any medical treatment. As this is a highly dynamic topic, we will update these guidelines as new information emerges. Please check to ensure you are using the latest version of this protocol.

# About Long COVID

Long COVID, also known as Long Haul COVID Syndrome (LHCS), is characterized by prolonged malaise, headaches, generalized fatigue, sleep difficulties, hair loss, smell disorder, decreased appetite, painful joints, dyspnea, chest pain and cognitive dysfunction. [1-13] Up to 80% of patients experience prolonged illness after COVID-19. Long COVID is not only seen after the COVID infection, but it is being observed in some people who have received vaccines (likely due to monocyte/microglia activation by the spike protein from the vaccine). Long COVID may persist for months after the acute infection and almost half of patients report reduced quality of life. Patients may suffer prolonged neuropsychological symptoms, including multiple domains of cognition. [10;14] A puzzling feature of long COVID is that it is not predicted by initial disease severity; long COVID frequently occurs in people who had mild-to-moderate cases and in younger adults who did not require respiratory support or intensive care. [12]

The symptom set of long COVID is, in the majority of cases, very similar to chronic inflammatory response syndrome (CIRS)/myalgic encephalomyelitis/chronic fatigue syndrome. [12] An important differentiating factor from CIRS is the observation that long COVID continues to improve on its own, albeit slowly in the majority of cases. Another important observation is that long COVID includes more young people compared to severe COVID, which affects older people or persons with comorbidities. Furthermore, the similarity between mast cell activation syndrome (MCAS) and long COVID has been observed, and many consider long COVID to be a variant of MCAS. [15]

## Theories for why long COVID occurs

Long COVID is highly heterogeneous and likely results from a variety of pathogenetic mechanisms. Furthermore, it is likely that delayed treatment in the early symptomatic phase results in a high viral load (high spike protein load), which increase the risk and severity of long COVID. The following theories have been postulated to explain long COVID: [12]

1. Ongoing respiratory symptoms (shortness of breath, cough, reduced effort tolerance) may be related to unresolved organizing pneumonia (activated pulmonary macrophages).
2. Monocyte and microglia activation. Persistence of viral debris (? Spike protein) in monocytes and microglia results in an ongoing inflammatory response in an attempt by the immune system to clear the offending protein(s) and viral RNA fragments.
3. The neurological symptoms may be related to micro- and/or macrovascular thrombotic disease, which appears to be common in severe COVID-19 disease. [16] The brain microvasculature expresses ACE-2 receptors and SARS-CoV-2 “pseudovirions” may bind to the microvascular endothelium causing cerebral microvascular inflammation and clotting. [17] Brain MRIs 3 months post-infection demonstrated micro-structural changes in 55% of patients. [18]

4. Due to molecular mimicry, the spike protein results in a vast spectrum of autoantibodies, many of which are associated with neurological complications. In particular, features of encephalopathy may be related to encephalitis and auto-reactive brain antibodies. [19] Small fiber neuropathy and autonomic neuropathy (POTS) are directly associated with the presence of autoantibodies. Antibodies against the ACE2 receptor and G-coupled membrane receptors are commonly found in long COVID patients. [20-22]
5. An unmasking or triggering of MCAS. Mast cells are present in the brain, especially in the median eminence of the hypothalamus, where they are located perivascularly close to nerve endings positive for corticotropin releasing hormone. [23] Following stimulation, mast cells release proinflammatory mediators such as histamine, tryptase, chemokines, and cytokines, which may result in neurovascular inflammation. [23] The "brain fog," cognitive impairment and general fatigue reported in long COVID may be due to mast cell related neurovascular inflammation.
6. Immune suppression with reactivation of dormant viruses and/or reactivation of chronic bacterial infections (i.e., Lyme disease, etc.).

## Phenotypes

As a consequence of the varied but overlapping pathogenetic mechanism, long COVID may be grouped into a number of phenotypes:

- Inflammatory phenotype (with high C-Reactive Protein) — likely due to persistent spike protein and immune activation
- Microvascular and macrovascular clotting syndrome (with high D-dimer and antiphospholipid antibodies)
- Predominantly CNS syndrome with microinfarcts and neural loss, especially of frontal lobes and hippocampus (diagnosed by MRI) — likely poorly reversible
- Mast cell activation syndrome (in those with genetic predisposition)
- Autoimmune syndromes including Lupus-like syndrome, adrenal insufficiency (anti-ACTH antibodies), ITP, TTP, GBS, small fiber neuropathy, POTS and dysautonomic syndromes
- Pulmonary phenotype with a) ongoing organizing pneumonia; b) a fibrotic form
- Reactivation of dormant viruses, (i.e., Epstein-Barr virus, Herpes type I/II and Zoster, Herpes VI, CMV — likely due to low CD8+ levels)

## Groups of symptoms

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

1. **Respiratory**: shortness of breath, congestion, persistent cough, etc.
2. **Neurological/psychiatric**: brain fog, malaise, tiredness, headaches, migraines, depression, inability to focus or concentrate, altered cognition, insomnia, vertigo, panic attacks, tinnitus, anosmia, phantom smells, etc.
3. **Musculoskeletal**: myalgias, fatigue, weakness, joint pains, inability to exercise, post-exertional malaise, inability to perform normal activities of daily life
4. **Cardiovascular**: Palpitations, arrhythmias, Raynaud-like syndrome, hypotension, and tachycardia on exertion
5. **Autonomic**: Postural tachycardia syndrome (POTs), abnormal sweating
6. **Gastrointestinal disturbance**: anorexia, diarrhea, bloating, vomiting, nausea, etc.

7. **Dermatologic**: itching, rashes, dermatographia
8. **Mucus membranes**: running nose, sneezing, burning and itchy eyes

# Treatment Strategy for Long COVID

## Initial screening tests

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

***The following basic tests are recommended:***

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

***Specific Phenotypic tests***

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

## Approach to treatment

Although numerous reports describe the epidemiology and clinical features of long COVID, [1-11] studies evaluating treatment options are glaringly sparse. [312] Indeed, the NICE guideline for managing the long-term effects of COVID-19 provide no specific pharmacologic treatment recommendations. [36] Patients with long COVID should be managed by clinicians who have experience treating this troublesome disorder.

The treatment approach should be individualized to the grouping of clinical signs and symptoms. However, in general, it is likely that patients who did not receive adequate antiviral treatment (e.g**.,** ivermectin, etc.) and adequate anti-inflammatory/macrophage repolarization therapy (e.g., corticosteroids, Omega-3 fatty acids, fluvoxamine, etc.) during the acute symptomatic phase of COVID-19 are much more likely to develop long COVID.

In patients with ongoing respiratory symptoms, chest imaging is suggested (preferably a chest CT scan). Those with unresolved pulmonary inflammation (organizing pneumonia with ground glass opacification) should be treated with a course of corticosteroids. Low-dose prednisolone/methylprednisolone (10 mg/day) for six weeks is suggested. [25] However, the patients' symptoms and CRP should be followed closely, as a dose escalation may be required in those who respond poorly. An unknown number of patients who have recovered from COVID-19 organizing pneumonia will develop pulmonary fibrosis with associated limitation of activity. Pulmonary function testing demonstrates a restrictive type pattern with decreased residual volume and DLCO. [7] These patients should be referred to a pulmonologist with expertise in pulmonary fibrosis. Anti-fibrotic therapy may have a role in these patients, [26-29] however additional data is required before this therapy can be more generally recommended. The serotonin receptor blocker cyproheptadine may reduce the risk of pulmonary fibrosis. [30]

Similar to patients who have recovered from septic shock, [31] a prolonged (many months) immune disturbance with elevated pro- and anti-inflammatory cytokines may contribute to long COVID. This is likely the consequence of monocyte activation syndrome and monocyte repolarization therapy is therefore indicated. Activated microglia may contribute to the neurological symptoms characteristic of long COVID. It should be noted that, much like Omega-3 fatty acids, corticosteroids have been demonstrated to increase expression of pro-resolving lipids including Protectin D1 and Resolvin D4. [32]

Naltrexone is a well-known opioid antagonist used in chronic opiate abuse. Naltrexone is classically prescribed in daily doses of at least 50 mg taken orally. Paradoxically, low dose naltrexone (LDN) — in a dose between 1 to 5 mg — has been demonstrated to have anti-inflammatory, analgesic and neuromodulating properties. Specifically, LDN has been shown to reduce glial inflammatory response by modulating Toll-like receptor 4 signaling in addition to systemically up-regulating endogenous opioid signaling by transient opioid-receptor blockade. [33;34] LDN — typically in a dose of 4.5 mg — has been used successfully to treat fibromyalgia, Crohn's disease, multiple sclerosis, as well as many chronic pain syndromes. [33;34] LDN may be particularly useful in the treatment of long COVID, as it inhibits activated macrophages/monocytes and microglia. [33;35] Once activated, microglia produce inflammatory and excitatory factors that can cause sickness behaviors such as pain sensitivity, fatigue, cognitive disruption, sleep disorders, mood disorders, and general malaise; these are clinical features typical of those found with long COVID.

**In general, while the treatment of long COVID should be individualized, the following treatments may have a role in the treatment of this disorder.**

## First Line Therapies

- **Prednisone**: 10-15 mg daily for 3 weeks. Taper to 10 mg for three days, then 5 mg for three days, then stop.
- **Ivermectin**: 0.2–0.3 mg/kg daily for 2-3 weeks.
- **Low dose naltrexone (LDN)**: Begin with 1 mg daily, increase to 4.5 mg daily as required. May take 2-3 months for full effect.
- **Intermittent daily fasting and/or periodic daily fasts**: Fasting promotes autophagy, the body's evolutionary preserved protective mechanism to remove misfolded, foreign and damaged proteins. It also promotes mitophagy and the release of stem cells. [37-43] It is likely that promoting autophagy will aid in the removal of the spike protein. NOTE: Hydroxychloroquine inhibits autophagy and should be avoided in patients undergoing intermittent fasting.
- **Spermidine and/or Resveratrol:** These compounds have been demonstrated to augment autophagy. [44-53] Spermidine and resveratrol promote autophagy by acting via different metabolic pathways, and are therefore likely to have additive or synergistic effects. [52] Furthermore, it is likely that both spermidine and resveratrol potentiate autophagy induced by intermittent fasting. Wheatgerm, mushrooms, grapefruit, apples and mango are high natural sources of spermidine. [54] Wheatgerm supplements contain high amounts of spermidine. Generally, the oral bioavailability of resveratrol is poor. [55] However, a bio-enhanced formulation containing trans-resveratrol from Japanese Knotwood Root appears to have improved bioavailability.
- **Melatonin:** 2-8 mg at night (slow release/extended release preferred). Patients should pay attention to good sleep habits. Increase dose from 1 mg as tolerated (may cause severe bad dreams at high dosages).
- **Vitamin D**: The majority of those with long COVID continue to have Vitamin D deficiency. Patients may require a loading dose based on baseline Vitamin D levels.
- **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. [56;57]
- **Aspirin**: 81 mg daily.
- **Curcumin (turmeric)**: 500 mg twice daily. Curcumin has anti-inflammatory and immunomodulating properties and has been demonstrated to repolarize macrophages. [58]

**If symptoms do not improve after 1-2 weeks continue steroids, Omega-3 fatty acids and LDN and add second line therapies as below.**

## Second Line Therapies

- **Fluvoxamine**: 50 mg twice daily. Start on a low dose of 12.5 mg/day and increase slowly as tolerated. Stop if the symptoms increase. Caution with the use of other antidepressants and psychiatric drugs. Taper and discontinue once symptoms improve.
- **Hydroxychloroquine (HCQ)**: 200 mg twice daily for 1-2 weeks, then reduce as tolerated to 200 mg daily. 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. 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. [59-63] With long term usage, the dose should be reduced (100 mg or 150 mg daily) in patients weighing less than 61 kg (135 lbs.).
- **Intravenous Vitamin C**: 25 g/week, together with oral Vitamin C 1000 mg (1 gram) 2-3 times daily. Oral Vitamin C is important to provide nutrients for the microbiome. 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. [64-69] Wean IV Vitamin C as tolerated.
- **"Mitochondrial energy optimizer"** with pyrroloquinoline quinone (e.g., Life Extension Energy Optimizer or ATP 360®). [70-72]
- **N-acetyl cysteine (NAC)**: 600-1500 mg/day. [73-75]

## Third Line Therapies

- **Maraviroc:** 300 mg by mouth twice daily. If 6-8 weeks have elapsed and significant symptoms persist despite first and second line treatment, this drug can be considered. Note maraviroc can be expensive and it has risk for significant side effects and drug interactions. Maraviroc is a C-C chemokine receptor type 5 (CCR5) antagonist. CCR5 receptors are expressed on macrophages and dendritic cells. CCR5 interacts with multiple ligands, notably the chemokines CCL3 (macrophage inflammatory protein-1), CCL4 (macrophage inflammatory protein-1), and CCL5 (RANTES). CCR5 and its ligands are overexpressed in COVID-19. [76-78] The activated CCR5 pathway may partly explain the persistence of activated monocytes in long-COVID. [79;80]
- **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. [109-116] 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/)

## Optional adjunctive therapies

- ***Nigella sativa*** which, like curcumin, has anti-inflammatory and immunomodulating properties.
- **Kefir, probiotic yogurt and/or Bifidobacterium Probiotics** (e.g., Daily Body Restore) together with Prebiotics (e.g. XOS Prebiotic, Bio Nutrition Pre-Biotic) to normalize the microbiome. Prolonged dysbiosis has been reported following COVID-19 infection. [81]
- **Sulforaphane (broccoli sprout powder):** 500 mcg – 1g twice a day. While sulforaphane has many potential benefits in patients with long COVID, [82-84] there is limited clinical data to support this intervention. Sulforaphane has immunomodulatory effects by targeting monocytes/macrophages, suggesting a benefit in chronic inflammatory conditions. [82-84] Sulforaphane is a beneficial supplement that may be useful for reducing microglial mediated neuroinflammation and oxidative stress. 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. [85;86] We recommend a 100% whole broccoli sprout powder, which maximally retains both glucoraphanin and myrosinase whilst, at the same time, deactivates the inhibitors.
- **Behavioral modification, mindfulness therapy** [87] and **psychological support** may help improve overall well-being and mental health. [12]
- **Luteolin:** 100-200 mg daily or **quercetin** 250 mg daily (or mixed flavonoids). Luteolin and quercetin have broad spectrum anti-inflammatory properties. These natural flavonoids inhibit mast cells, [23;88-91] and have been demonstrated to reduce neuroinflammation. [92]
- **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. [93] 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 long COVID.
- **Valproic acid**: [94;95] Depakote, 250 mg 2-3 times daily. Valproic acid has anti-inflammatory effects and polarizes macrophages towards a M2 phenotype. [96] HDAC inhibitors are being studied for neural regeneration. In addition, valproic acid has important anticoagulant and anti-platelet effects. [97] Valproic acid may be helpful for neurological symptoms.
- **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. [98] 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).
- **H1 receptor blockers** (for mast cell activation syndrome). Loratadine 10 mg daily, Cetirizine 5-10 mg daily, Fexofenadine 180 mg daily.
- **H2 receptor blockers** (for mast cell activation syndrome). Famotidine 20 mg – twice daily, as tolerated. [15]
- **Montelukast** 10 mg daily (for mast cell activation syndrome). Caution as may cause depression in some patients.
- **Anti-androgen therapy**. Spironolactone 50-100 mg twice daily and dutasteride 1 mg daily.

**Macrophage/monocyte Repolarization Therapy for COVID-19 and long COVID**

- Corticosteroids [99]
- Omega-3 fatty acids [100-102]
- Melatonin [103]
- Vitamin C
- Anti-androgen therapy [104-106]
- Curcumin (turmeric) [58]
- Valproic acid [96]

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