I-RECOVER℠

LONG COVID TREATMENT

An approach to treating long COVID

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Disclaimer

The information in this document is our recommended approach based on the best (and most recent) literature. It is provided as guidance to healthcare providers worldwide. Our guidance should only be used by medical professionals in formulating their approach to patients. 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

Due to the marked overlap between long COVID and post-vaccine syndrome, please refer to the *I-RECOVER Post-Vaccine Treatment* protocol for detailed treatment strategies. This document highlights the differences between these two syndromes.

Long COVID, also known as Long Haul COVID Syndrome (LHCS) and more recently by the terminology "Post-acute sequelae of COVID-19 (PASC), is a heterogenous syndrome 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. Furthermore, many of the symptoms of are common to COVID-19 vaccine-injured patients; indeed, both disorders are considered manifestations of "spike protein-related disease," with a significant overlap in symptoms, pathogenesis, and treatment.

To complicate this issue further, many long COVID patients are vaccinated, and the symptomatology of vaccine-injured patients is often exacerbated by an acute COVID-19 infection.

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 increases 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 Spike protein in monocytes, macrophages, pericytes and microglia results in an ongoing inflammatory response in an attempt by the immune system to clear the offending protein(s) and viral RNA fragments.

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 microstructural 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.).

Groups of symptoms

Further, the clinical signs and symptoms can be grouped into 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

Initial screening tests for long COVID

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

Healthcare providers are referred to *I-RECOVER: Post-Vaccine Treatment* protocol for specific guidance regarding the treatment of long COVID. This document outlines the major differences between the management of long COVID and vaccine injury, namely ongoing organizing pneumonia.

Furthermore, although numerous reports describe the epidemiology and clinical features of long COVID, [1-11] studies evaluating treatment options are glaringly sparse. [25] Indeed, the NICE guidelines for managing the long-term effects of COVID-19 provide no specific pharmacologic treatment recommendations. [26] Patients with long COVID should be managed by clinicians who have experience treating this troublesome disorder.

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

The major difference between long COVID and post-vaccine syndrome patients is unresolved organizing pneumonia with persistent respiratory symptoms. Therefore, chest imaging is suggested in patients with ongoing respiratory symptoms (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. [27] 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, [28-31] 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. [32]

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