I-RECOVER

Management Protocol for Long Haul COVID-19 Syndrome (LHCS)

The approach outlined below is a consensus protocol based on a collaboration led by Dr. Mobeen Syed ("Dr. Been"), Dr. Tina Peers, and the FLCCC Alliance. Given the lack of clinical treatment trials of Long Haul COVID-19 Syndrome, these recommendations are based on the pathophysiologic mechanisms of COVID-19 and post-viral illnesses along with our collective experience observing profound and sustained clinical responses achieved with the treatment approaches below.

This protocol has also been used to treat **post-vaccine inflammatory syndromes** with similar success. As with all FLCCC Alliance protocols, the components, doses, and durations will evolve as more clinical data accumulates.

If the patient presents with shortness of breath or low oxygen levels: Refer to lung specialist if available, otherwise perform chest imaging (CT preferred) to assess for secondary organizing Pneumonia (OP). If findings consistent with secondary OP found, initiate Corticosteroid Therapy as below. May need to repeat or prolong course of treatment if symptoms or oxygen needs persist.

1. FIRST LINE THERAPIES

- **IVERMECTIN**: 0.2 mg/kg body weight. Once daily for 1 week.[1]
- **PREDNISONE**: 10–15 mg daily for 3 weeks. Taper to 10 mg for three days, then 5 mg for three days and then stop.[2]
- Low dose **NALTREXONE** (LDN): Begin with 1 mg daily and increase to 4.5 mg as required. May take 2–3 months for full effect.
- **OMEGA-3 FATTY ACIDS**: **Vascepa**, **Lovaza** or **DHA/EPA** 4 g per day. Omega-3 fatty acids play an important role in the resolution of inflammation by inducing resolvin production
- **VITAMIN D**: The majority of those with post-COVID-19 syndrome continue to have hypovitaminosis D.
  See tables 1 or 2 for vitamin D supplementation.

If symptoms do not improve after 1–2 weeks continue steroids, omega-3 fatty acids and Naltrexone and add second line medications.

2. SECOND LINE THERAPIES

- **FLUVOXAMINE** (low dose): 25 mg once daily. Stop if the symptoms increase. Caution with the use of other antidepressants and psychiatric drugs. Taper and discontinue once symptoms improve.
- **ATORVASTATIN**: 20–40 mg once daily. Caution in patients with Postural Orthostatic Tachycardia Syndrome (POTS); may exacerbate symptoms.

3. THIRD LINE THERAPY

- **MARAVIROC**: 300 mg PO twice a day

  If 6–8 weeks have elapsed and significant symptoms persist, consider either getting an InCellDx test to assess long hauler index profile prior to initiating or can consider initiating empirically. Note maraviroc can be expensive and it has risk for significant side effects and drug interactions.

4. OPTIONAL ADJUNCTIVE THERAPIES (in order of priority)

- **Curcumin:** has anti-inflammatory and immunomodulating properties and has been demonstrated to repolarize macrophages.
- **Nigella Sativa:** which like curcumin has anti-inflammatory and immunomodulating properties.
- **Vitamin C:** 500 mg BID (vitamin C inhibits histamine and repolarizes monocytes).
- **Melatonin:** 2–8 mg at night (slow release/extended release) with attention to sleep hygiene. Increase dose from 1 mg as tolerated (may cause severe nightmares at high dosages).
- **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.
- **Behavioral modification**, **mindfulness therapy** and **psychological support** may help improve survivors' overall well-being and mental health.
- **Luteolin** 100–200 mg day or **Quercetin** 250 mg day (or mixed flavonoids). Luteolin and quercetin have broad spectrum anti-inflammatory properties. These natural flavonoids inhibit mast cells, and have been demonstrated to reduce neuroinflammation.
- **H1 receptor blockers** (for mast cell activation syndrome): **Loratadine** 10 mg daily, or **Cetirizine** 5–10 mg daily, or **Fexofenadine** 180 mg — daily.
- **H2 receptor blockers** (for mast cell activation syndrome): **Famotidine** 20–40 mg, or **Nizatidine** 150 mg — twice daily as tolerated.
- **Montelukast:** 10 mg/day (for mast cell activation syndrome). Caution as may cause depression is some patients.
- **Anti-androgen therapy: Spironolactone** 50–100 mg twice a day, and **Dutasteride** 1 mg daily.

1. Relative contraindications: 1) Patients on Warfarin require close monitoring and dose adjustment.
   2) Pregnant or lactating women require a more in-depth risk/benefit assessment.
2. Side effects may include: Increased appetite, mood changes, insomnia, raised blood glucose, dyspepsia.

I-RECOVER

Management Protocol for Long Haul COVID-19 Syndrome (LHCS)

Tables

Table 1. Guidance on upfront loading dose regimens to replenish Vitamin D stores in the body

Achieving serum 25(OH)D concentrations above 50 ng/mL based on serum 25(OH)D concentration in non-emergency situations in a 70 kg adult *				
Serum vitamin D (ng/mL) **	Vitamin D dose, 50,000 IU capsules: Initial and weekly ***		Duration (weeks)	Total amount for deficit correction (IU, in millions) ****
	Initial Dose (IU)	Weekly dose (50,000 IU caps)		
< 10	300,000	x 3	8 – 10	1.5 – 1.8
11–15	200,000	x 2	8 – 10	1.0 – 1.2
16–20	200,000	x 2	6 – 8	0.8 – 1.0
21–30	100,000	x 2	4 – 6	0.5 – 0.7
31–40	100,000	x 2	2 – 4	0.3 – 0.5
41–50	100,000	x 1	2 – 4	0.2 – 0.3

* A suitable daily or weekly maintenance dose should start after completing the schedule.
** For conversion of ng/mL to nmol/L, multiply by 2.5.
*** Mentioned replacement doses can be taken as single cumulative doses or spread out through the week.
**** Estimated deficit of vitamin D needed to replenish body stores.

(Table adapted with permission from S.J. Wimalawansa)

Table 2. Vitamin D dosing in the absence of a baseline Vitamin D level

Longer-term maintenance of serum 25(OH)D concentrations above 50 ng/mL based on body weight *			
Body-weight category	Dose (IU) kg/day	Dose (IU)/day	
		Daily dose (IU)	Once a week
BMI ≤ 19 (under-weight)	40 – 70	≃ 2,000 – 4,000	~ 25,000
BMI 20–29 (non-obese person)	70 – 100	≃ 5,000 – 7,000	~ 50,000
BMI 30–39 (obese persons)	100 – 150	≃ 9,000 – 15,000	~ 75,000
BMI ≥ 40 (morbidly obese persons)	150 – 200	≃ 16,000 – 30,000	~ 100,000

(Table adapted with permission from S.J. Wimalawansa)

I-RECOVER

Management Protocol for Long Haul COVID-19 Syndrome (LHCS)

The Long Haul COVID-19 Syndrome (also "Post-COVID-19 Syndrome")

Excerpt from the "Guide to the Management of COVID-19" by Dr. Paul Marik / FLCCC Alliance (version 65 from Jan 13, 2022)
Please see latest version on www.flccc.net/flccc-protocols-a-guide-to-the-management-of-covid-19

The Long Haul COVID-19 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. [500–512] Up to 80% of patients experience prolonged illness after Covid-19. LHCS is not only seen after the COVID infection, but it is being observed in some people that have received vaccines (likely due to monocyte/microglia activation by the spike protein from the vaccine). LHCS 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. [509,513] A puzzling feature of the LHCS syndrome is that it is not predicted by initial disease severity; post-COVID-19 frequently affects mild-to-moderate cases and younger adults that did not require respiratory support or intensive care. [511]

The symptom set of LHCS is in the majority of the cases very similar to the chronic inflammatory response syndrome (CIRS)/ myalgic encephalomyelitis/ chronic fatigue syndrome. [511] An important differentiating factor from CIRS is the observation that LHCS continues to improve on its own albeit slowly in the majority of cases. Another important observation is that LHCS includes more young people compared to severe COVID, which affects older people or persons with comorbidities. Furthermore, the similarity between the mast cell activation syndrome and LHCS has been observed, and many consider post-COVID to be a variant of the mast cell activation syndrome. [514]

The LHCS syndrome is highly heterogeneous and likely results from a variety of pathogenetic mechanisms. Furthermore, it is likely that delayed treatment (with ivermectin, etc.) in the early symptomatic phase will results in a high viral load which increase the risk and severity of LHCS. The following theories have been postulated to explain LHCS: [511]

1. Ongoing respiratory symptoms (SOB, 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 micro- and/or macrovascular thrombotic disease which appears to be common in severe COVID-19 disease.[515] Brain MRIs' 3 months post-infection demonstrated microstructural changes in 55% of patients. [516] In addition, features of encephalopathy may be related to encephalitis and auto-reactive brain antibodies [517] as well as severe cerebral vasoconstriction. [518] The brain microvasculature expresses ACE-2 receptors and SARS-CoV-2 "pseudovirions" may bind to the microvascular endothelium causing cerebral microvascular inflammation and clotting.[519].
4. An unmasking of mast cell activation syndrome (MCAS), or triggering of mast cell activation syndrome. 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.[520] Following stimulation, mast cells release proinflammatory mediators such as histamine, tryptase, chemokines and cytokines which may result in neurovascular inflammation.[520] The "brain-fog", cognitive impairment and general fatigue reported in long-COVID may be due to mast cell related neurovascular inflammation.

Clinical signs and symptoms can be grouped in the following clusters. The reason for this grouping is to allow organ specific targeted therapy/individualized therapy.

1. Respiratory: shortness of breath, congestion, persistent cough, etc.
2. Neurological/psychiatric: brain fog, malaise, tiredness, headaches, migraines, depression, inability to focus/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 (ADL's).
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.

Approach to Treatment

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.) during the acute symptomatic phase and adequate anti-inflammatory/macrophage repolarization therapy (e.g. corticosteroids, statins, omega-3 fatty acids, fluvoxamine, ivermectin, etc.) during the acute phase of COVID-19 are much more likely to develop the Post-COVID-19 Syndrome.

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. [521] 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.[506] These patients should be referred to a pulmonologist with expertise in pulmonary fibrosis. Anti-fibrotic therapy may have a role in these patients, [473–476] however additional data is required before this therapy can be more generally recommended. As discussed above, the serotonin receptor blocker cyproheptadine may reduce the risk of pulmonary fibrosis. [364]

Similar to patients who have recovered from septic shock, [522] a prolonged (many months) immune disturbance with elevated pro- and anti-inflammatory cytokines may contribute to the LHCS. This is likely the consequence of monocyte activation syndrome and monocyte repolarization therapy is therefore indicated. Activated microglia may contribute to the neurological symptom's characteristic of LHCS. A cytokine panel may allow targeted anti-inflammatory therapy (Maraviroc in patients with high CCR5 levels). 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. [523]

I-RECOVER

Management Protocol for Long Haul COVID-19 Syndrome (LHCS)

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 upregulating endogenous opioid signaling by transient opioid-receptor blockade. [315,524] LDN typically in a dose of 4.5 mg has been used successfully to treat fibromyalgia, Crohn's disease, multiple sclerosis, and complex chronic pain syndromes as well as many chronic pain syndromes. [315,524] LDN may be particularly useful in the treatment of LHCS as is inhibits activated macrophages/monocytes and microglia. [524,525] 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; clinical features typical of those found with LHCS.

References

315. Toljan K, Vrooman B. Low-dose naltrexone (LDN) - Review of therapeutic utilization. Med Sci 2018; 6:82.
500. Carfi A, Bernabei R, Landi F. Persistent symptoms in patients after acute COVID-19. JAMA 2020.
501. Prescott HC, Girard TD. Recovery from Severe COVID-19. Leveraging the lessons of survival from sepsis. JAMA 2020.
502. Greenhalgh T, Knight M, A'Court C et al. Management of post-acute COVID-19 in primary care. BMJ 2020.
503. Chopra V, Flanders SA, O'Malley M. Sixty-day outcomes among patients hospitalized with COVID-19. Ann Intern Med 2020.
504. Mandal S, Barnett J, Brill SE et al. 'Long-COVID': a cross-sectional study of persisting symptoms, biomarker and imaging abnormalities following hospitalization for COVID-19. Thorax 2020.
505. Michelen M, Manoharan L, Elkheir N et al. Characterising Long-Term COVID-19: A rapid living systematic review. medRxiv 2020.
506. Huang C, Huang L, Wang Y et al. 6-month consequences of COVID-19 in patients discharged feom hospital: a cohort study. Lancet 2021.
507. Logue JK, Franko NM, McCulloch DJ et al. Sequelae in adults at 6 months after COVID-19 infection. JAMA Network Open 2021; 4:e210830.
508. Janiri D, Carfi A, Kotzalidis GD et al. Posttraumatic stress disorder in patients after severe COVID-19 infection. JAMA Psychiatry 2021.
509. Voruz P, Allali G, Benzakour L et al. Long COVID neuropsychological deficits after severe, moderate or mild infection. medRxiv 2021.
510. Al-Aly Z, Xie Y, Bowe B. High-dimensional characterization of post-acute sequalae of COVID-19. Nature 2021.
511. Yong SJ. Long-haul COVID-19: Putative pathophysiology, risk factors, and treatments. medRxiv 2020.
512. Bek LM, Berentschot JC, Huijts S et al. Symptoms persisting after hospitalization for COVID-19: 12 month interim results of the COFLOW study. medRxiv 2021.
513. Taquet M, Geddes JR, Husain M et al. 6-month neurological and psychiatric outcomes in 236 379 survivors of COVID-19: a retrospective cohort study using electronic health records. Lancet Psychiatry 2021.
514. 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.
515. Bryce C, Grimes Z, Pujadas E et al. Pathopysiology of SARS-CoV-2: targeting of endothelial cells renders a complex disease with thrombotic microangiopathy and aberrant immune response. The Mount Sinai COVID-19 autopsy experience. medRxiv 2020.
516. Lu Y, Li X, Geng D et al. Cerebral micro-structutal changes in COVID-19 patients - An MRI-based 3-month follow-up study. EClinicalMedicine 2020.
517. Franke C, Ferse C, Kreye J et al. High frequency of cerebrospinal fluid autoantibodies in COVID-19 patients with neurological symptoms. Brain,Behavor, and Immunity 2021.
518. Sirous R, Taghvaei R, Hellinger JC et al. COVID-19-associated encephalopathy with fulminant cerebral vasoconstriction: CT and MRI findings. Radiology Case Reports 2020; 15:2208-12.
519. Magro CM, Mulvey JJ, Laurence J et al. Docked severe acute respiratory syndrome coronavirus 2 proteins within the cutaneous and subcutaneous microvasculature and their role in the pathogenesis of severe coronavirus disease 2019. Human Pathology 2020; 106:106-16.
520. 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.
521. Dhooria S, Chaudhary S, Sehgal IS et al. High-dose versus low-dose prednisolone in symptomatic patients with post-COVID-19 diffuse parenchymal lung abnormalities: an open-label, randomised trial (COLDSTER). Eur Respir J 2021.
522. Riche F. Protracted immune disorders at one year after ICU discharge in patients with septic shock. Crit Care 2018; 22:42.
523. Andreakos E, Papadaki M, Serhan CN. Dexamethasone, pro-resolving lipid mediators and resolution of inflammation in COVID-19. Allergy 2020.
524. 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.
525. Liu SL, Li YH, Shi GY et al. A novel inhibitory effect of naloxone on macrophage activation and atherosclerosis formation in mice. J Am Coll Cardiol 2006; 48:1871-79.

Disclaimer

The I-RECOVER protocol is borne of clinical experience only and thus is meant solely for educational purposes to health care providers regarding potentially beneficial empiric treatment approaches for Long Haul COVID-19 Syndrome. Never disregard professional medical advice because of something you have read on our website and releases. This is not intended to be a substitute for professional medical advice, diagnosis, or treatment in regards to any patient. Treatment for an individual patient is determined by many factors and thus should rely on the judgement of your physician or qualified health care provider. Always seek their advice with any questions you may have regarding your medical condition or health.

Please check our homepage www.flccc.net regularly for updates of our COVID-19 Protocols! –
New medications may be added and/or dose changes to existing medications may be made as further scientific studies emerge.