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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. Ram Yogendra, Dr. Bruce Patterson, 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. For the most up-to-date information on optional treatments, go to: flccc.net/flccc-protocols-a-guide-to-the-management-of-covid-19 (see LHCS section).

Initial therapy of Long-haul Covid Syndrome:

IVERMECTIN

0.2–0.4 mg/kg dose once daily with meals* for 3–5 days (higher doses are sometimes needed in anosmia).

* Take on empty stomach if presenting with nausea/diarrhea/anorexia.

After 3–5 days, change to once or twice weekly depending on the time to symptom recurrence/persistence.

Discontinue after 2–4 weeks if all symptoms have resolved and do not recur.

Relative Contraindications:
- Patients on Warfarin require close monitoring and dose adjustment.
- Pregnant or lactating women require a more in-depth risk/benefit assessment.

If not all symptoms resolve with ivermectin:

CORTICOSTEROID THERAPY

A tapering dose of **prednisone** as follows:

1. 0.5 mg/kg daily for 5 days
2. 0.25 mg/kg daily for 5 days
3. 0.12 mg/kg daily for 5 days

Take in morning to lessen impact on sleep.

Side effects may include: Increased appetite, mood changes, insomnia, raised blood glucose, dyspepsia.

For use in all patients:

MACROPHAGE/MONOCYTE REPOLARIZATION THERAPY

- Vitamin C — 500 mg twice daily
- Omega-3 Fatty Acids — 4 gm/daily (Vascepa, Lovaza, or DHA/EPA)
- Atorvastatin — 40 mg daily
- Melatonin — 2–10 mg nightly, start with low dose, increase as tolerated in absence of sleep disturbance.

Additional Supplement

- Vitamin D3 — 2,000–4,000 IU daily

DHA Docosahexaenoic acid
EPA eicosapentaenoic acid
IU international units
mg/kg dose in mg per kg body weight

If presenting with neurologic symptoms, i.e. poor concentration, forgetfulness, mood disturbance:

FLUVOXAMINE

50 mg – twice daily for 15 days.

Reduce dose or discontinue if side effects develop. Doses as low as 9 mg twice daily have shown efficacy.

Monitor closely as some patients may respond poorly. Teens/young adults can experience acute anxiety; monitor and treat to prevent rare escalation to suicidal or violent behavior.

If presenting with shortness of breath or low oxygen levels:

PULMONARY EVALUATION

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.

CT computed tomography scan
OP organizing pneumonia

If symptoms still unresolved or recur after ivermectin and corticosteroid regimens:

TREATMENT OF SUSPECTED MAST CELL ACTIVATION

Choose a Type I and a Type II antihistamine along with a mast cell stabilizer – for example, Loratadine, Famotidine, and Rupatadine. Change medicines if poor response. United States FDA approved doses of many of the below medicines are once daily but can use up to three times daily with caution and close monitoring if poor response or side effects.

First-line Therapy

- Low histamine diet
- *Type I antihistamines:* Loratadine 10 mg, or Cetirizine 10 mg, or Fexofenadine 180 mg – three times daily as tolerated.
- *Type II antihistamines:* Famotidine 20 mg, or Nizatidine 150 mg – twice daily as tolerated.
- *Mast cells stabilizers:*
  - Rupatadine 10 mg – once daily, or Ketotifen 1 mg – once daily at night (increase as tolerated).
  - May add: Sodium Cromoglycate 200 mg three times daily (increase slowly), or Quercetin 500 mg three times daily.

Second-line Therapy

- Montelukast 10 mg (beware depression in some) – once daily.
- Low Dose Naltrexone (LDN) – start with 0.5 mg daily, increasing by 0.5 mg weekly up to 4.5 mg daily. Avoid if on opiates.
- Diazepam 0.5–1 mg twice daily.
- SSRIs.

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The Long-haul COVID syndrome = LHCS (post-COVID syndrome)

Excerpt from the "Guide to the Management of COVID-19" by Dr. Paul Marik / FLCCC Alliance
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 [400-411] Up to 80% of patients experience prolonged illness after COVID-19. LHCS is not only seen after the COVID-19 infection but it is being observed in some people that have received vaccines (likely due to monocyte activation by the spike protein from the vaccine). LHCS may persistent 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. [409,412] 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. [411] The symptom set of LHCS is in majority of the cases very similar to the chronic inflammatory response syndrome (CIRS) / myalgic encephalomyelitis/chronic fatigue syndrome. [411] An important differentiating factor from CIRS is the observation that LHCS continues to improve on its own albeit slowly in majority of the cases. Another important observation is that LHCS includes more young people compared to severe COVID-19 that 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-19 to be a variant of the mast cell activation syndrome. [413]

The LHCS syndrome in highly heterogenous and likely results from a variety of pathogenetic mechanisms Furthermore, it is likely that delayed treatment (with ivermectin) 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: [411]

1. Ongoing respiratory symptoms (SOB, cough, reduced effort tolerance) may be related to unresolved organizing pneumonia (activate pulmonary macrophages).
2. Monocyte activation syndrome. Persistence of viral debris in monocytes results in an ongoing immune 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. [414] Brain MRIs' 3 months post-infection demonstrated micro-structural changes in 55% of patients. [415] In addition, features of encephalopathy may be related to encephalitis and auto-reactive brain antibodies [416] as well as severe cerebral vasoconstriction. [417] The brain microvasculature expresses ACE-2 receptors and SARS-CoV-2 "pseudovirons" may bind to the microvascular endothelium causing cerebral microvascular inflammation and clotting. [418].
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 corticotrophin releasing hormone. [419] Following stimulation, mast cells release proinflammatory mediators such as histamine, tryptase, chemokines and cytokines which may result in neurovascular inflammation. [419] The "brain-fog", cognitive impairment and general fatigue reported in long-COVID-19 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. GIT 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 received inadequate antiviral treatment (ivermectin) during the acute symptomatic phase and inadequate anti-inflammatory/macrophage repolarization therapy (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) should be treated with a course of corticosteroids (prednisone) and closely followed. A CRP should be measured, and extended corticosteroids (titrated to the CRP) offered to these patients. Similar to patients who

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have recovered from septic shock, [420] 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. In addition, 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. [421] 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. [406] These patients should be referred to a pulmonologist with expertise in pulmonary fibrosis. Anti-fibrotic therapy may have a role in these patients, [380-383] 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. [256]

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