

# LONG COVID

## INTRODUCTION

Long COVID, also referred to as post-acute sequelae of COVID-19 (PASC), long-haul COVID-19, post-acute COVID-19, or simply Post-COVID conditions, encompasses a constellation of new, recurrent, or persistent symptoms that endure beyond 3 months following the acute phase of SARS-CoV-2 infection.[1]

Although substantial progress has been made in gaining better insight into this condition, a comprehensive understanding of Long COVID is still evolving and continue to impose a significant burden on individuals and society worldwide. The majority of individuals make a complete recovery after SARS-CoV-2 infection, yet some previously healthy individuals develop symptoms that persist after acute illness.

Exact prevalence figures vary due to diverse reporting methodologies, but most studies have suggested that anywhere from 20% to 80% of adults previously diagnosed with SARS-CoV-2 have persistent health issues stemming from the acute infection.[1-3] Although Long COVID has been observed to occur more frequently in those with severe infection, anyone who has been infected may develop Long COVID symptoms.[2,3]

People with disabilities or barriers to accessing health care, who are experiencing homelessness or in correctional facilities, or who belong to racial and ethnic minority populations who experience disproportionate chronic conditions have experienced a higher burden of COVID-19 which has led to a higher number of people being impacted by Long COVID in some of these same populations.[16]

## PATHOPHYSIOLOGY

The underlying pathophysiology of Long COVID is still unclear.[4] There are most likely multiple causes that overlap with various diagnoses, which share similar biological factors. Long COVID presents as a constellation of symptoms that intersect with other post-viral conditions including myalgic encephalomyelitis and chronic fatigue syndrome, mast cell activation syndrome (MCAS), postural orthostatic tachycardia syndrome (POTS), along with autoimmune disorders.[5-7] It remains to be determined whether Long COVID constitutes a distinct condition or represents a reactivation of underlying conditions, with significant variations stemming from unique and individual immune responses.

Currently, several hypothesized mechanisms exist for Long COVID, including chronic inflammation, immune cell dysfunction, dysregulated energy metabolism/mitochondrial dysfunction, endothelial dysfunction, and gut dysbiosis.[4,5,8] Studies have consistently observed abnormalities across cell lines of both the innate and adaptive immune responses.[4,9,10] Studies have also documented circulating autoantibodies in a substantial number of Long COVID patients in addition to reduced peak oxygen consumption utilizing cardiopulmonary exercise testing.[5,8,10,11] Furthermore, studies

have identified the microbiome as a target for SARS-CoV-2 infection, given that the angiotensin-converting enzyme-2 (ACE2) is expressed in the gut.[5,11] The pathogenicity of the SARS-CoV-2 spike protein and its interaction with ACE2 receptors may potentially offer a link into the heterogeneous manifestations of Long COVID, however, this research remains in its infancy.[4,5,9]

## **SYMPTOMS**

Clinical manifestations of Long COVID can include fatigue, post-exertional malaise, cough, cardiac arrhythmia, chest pain, shortness of breath, myocarditis, thromboembolism, headache, insomnia, “brain fog”, dizziness, neuropathy, depression, anxiety, abdominal pain, musculoskeletal pain, weakness, arthralgia, rash, changes in menstrual cycles, diarrhea, paresthesia, and sleep dysfunction, among others.[4-6,8-10]

While effectively identifying and diagnosing Long COVID is crucial, there are several challenges that stand in the way of proper diagnosis:

- There is no laboratory test to definitively diagnose Long COVID
- Symptoms can be hard to explain
- Symptoms can be multi-systemic
- Symptoms can be relapsing
- Symptoms may be present at initial infection or emerge weeks/months after initial infection, even if asymptomatic at time of initial infection

## **DIAGNOSTIC TESTING**

The absence of diagnostic testing poses a significant challenge in establishing a clear diagnosis of Long COVID. Nevertheless, laboratory testing and imaging can play a crucial role in investigating the possible mechanisms of Long COVID symptoms.[4-6,10]

- General: Complete Blood Count (CBC), Comprehensive Metabolic Panel (CMP), Urinalysis (UA)
- Endocrine: Thyroid Function, Hemoglobin A1c, Fasting AM Cortisol, Dehydroepiandrosterone Sulfate (DHEAS), Free Testosterone
- Autoimmune/Inflammatory: High-Sensitivity C-Reactive Protein (hs-CRP), Erythrocyte Sedimentation Rate (ESR), Antinuclear antibodies (ANA), Homocysteine, Procalcitonin
- Cardiopulmonary: Orthostatic vital signs, Chest X-ray, Electrocardiogram (EKG), Pulmonary Function Tests, Echocardiogram
- Gastrointestinal: Celiac Panel, Small Intestinal Bacteria Overgrowth (SIBO) testing
- Micronutrient Deficiencies: Vitamin D, Magnesium, Vitamin B12, Folate, Thiamine, Ferritin
- Endothelial Dysfunction: Thrombotic Marker Panel, Factor VIII

- Consider Epstein-Barr virus (EBV), Cytomegalovirus (CMB), and Lyme titers if there is concern for reactivation of endogenous latent viruses
- Consider workup for MCAS if there is concern for a dysregulated inflammatory response

## TREATMENT

Even three years after the emergence of SARS-CoV-2, guidelines for Long COVID management remain sparse. Most studies conducted thus far have been small-scale studies, highlighting the challenge posed when treating patients with Long COVID.

It is crucial to provide a comprehensive clinical assessment, targeting individual symptoms in addition to the underlying physiology, supported by a multidisciplinary approach, including appropriate referrals, community support, rehabilitation, and education.[8] The ultimate aim of this integrated approach is to enhance functional capacity and quality of life. Evidence indicates that holistic support for the patient throughout their illness course can be beneficial.[16]

The following is a comprehensive, albeit not exhaustive, summary of targeted therapies that have been studied for Long COVID.

## SUPPLEMENTS

Several pilot studies have supported use of the following supplements:

- Probiotics for gut dysbiosis [4,5]
- Pycnogenol for systemic inflammation and endothelial dysfunction [4]
- Coenzyme Q10, N-acetylcysteine (NAC), alpha-lipoic acid (ALA) for mitochondrial support[4,5,8]
- L-arginine with Vitamin C for endothelial dysfunction[13]
- *Panax ginseng* and *Eleutherococcus senticosus* for fatigue and post-exertional malaise[5]

Other supplements including nicotinamide ribose, a form of vitamin B3, omega-3 fatty acids, resveratrol, and Vitamin D are currently being investigated in clinical trials.

## MEDICATIONS

The following medications have shown promising results in initial research and studies:

- H1 and H2 histamine antagonists such as levocetirizine and famotidine if there is a concern for MCAS [4-6,8]
- $\beta$ -blockers to mitigate symptoms from exaggerated sympathetic and adrenergic responses to orthostasis[4,8]

- Low-dose naltrexone for neuroinflammation[4]
- Intravenous immunoglobulin for immune dysfunction[4]

Other medications including several anti-viral medications, antibody therapies, Metformin, and Vortioxetine are currently being investigated in clinical trials.

## **LIFESTYLE INTERVENTIONS**

Several lifestyle and complementary and integrative health strategies may help manage symptoms. These include:

- Adhering to an anti-inflammatory diet
- Limiting caffeine/alcohol intake
- Maintaining adequate hydration and considering salt repletion
- Addressing sources of stress
- Maintaining a regular sleep/wake cycle supported by timed sunlight exposure
- Developing a therapeutic connection with a counselor or therapist

For more information, refer to the [Choosing a Diet](#), [What We Drink](#), [Bringing Mindful Awareness into Clinical Work](#), and [Working With Our Thinking](#) Whole Health Tools. For more information on complementary and integrative health research, approaches, and strategies, refer to [Complementary and Integrative Health](#).

## **OTHER TREATMENT MODALITIES**

Additional treatment methods not covered above include:

- Energy conservation strategies. This can be accomplished through keeping a diary that outlines daily activities, perceived level of stress, and associated amount of energy.[10]
- Individualized, paced return to activity that can start with supine exercise. Graded exercise therapy and exercise may not be appropriate as a treatment, as they have the potential to exacerbate symptoms.[4,8,10,14,15]
- Heart rate variability (HRV) biofeedback training[8]
- Stellate ganglion block[4]

For more information, refer to the [Prescribing Movement](#), [Breathing](#), [The Power of Breath: Diaphragmatic Breathing](#), and [Biofeedback](#) Whole Health Tools.

## **RESOURCE LINKS**

- [Biofeedback](https://www.va.gov/WHOLEHEALTHLIBRARY/docs/Biofeedback.pdf). <https://www.va.gov/WHOLEHEALTHLIBRARY/docs/Biofeedback.pdf>
- [Breathing](https://www.va.gov/WHOLEHEALTHLIBRARY/docs/Breathing.pdf). <https://www.va.gov/WHOLEHEALTHLIBRARY/docs/Breathing.pdf>

- [Bringing Mindful Awareness into Clinical Work.](https://www.va.gov/WHOLEHEALTHLIBRARY/docs/Bringing-Mindful-Awareness-into-Clinical-Work.pdf)  
https://www.va.gov/WHOLEHEALTHLIBRARY/docs/Bringing-Mindful-Awareness-into-Clinical-Work.pdf
- [Choosing a Diet.](https://www.va.gov/WHOLEHEALTHLIBRARY/docs/Choosing-A-Diet.pdf) https://www.va.gov/WHOLEHEALTHLIBRARY/docs/Choosing-A-Diet.pdf
- [Complementary and Integrative Health.](https://www.va.gov/WHOLEHEALTH/professional-resources/clinician-tools/cih.asp)  
https://www.va.gov/WHOLEHEALTH/professional-resources/clinician-tools/cih.asp
- [Prescribing Movement.](https://www.va.gov/WHOLEHEALTHLIBRARY/docs/Prescribing-Movement.pdf)  
https://www.va.gov/WHOLEHEALTHLIBRARY/docs/Prescribing-Movement.pdf
- [The Power of Breath: Diaphragmatic Breathing.](https://www.va.gov/WHOLEHEALTHLIBRARY/docs/The-Power-Of-Breath-Diaphragmatic-Breathing.pdf)  
https://www.va.gov/WHOLEHEALTHLIBRARY/docs/The-Power-Of-Breath-Diaphragmatic-Breathing.pdf
- [What We Drink.](https://www.va.gov/WHOLEHEALTHLIBRARY/tools/index.asp) https://www.va.gov/WHOLEHEALTHLIBRARY/tools/index.asp
- [Working With Our Thinking.](https://www.va.gov/WHOLEHEALTHLIBRARY/docs/Working-with-Our-Thinking.pdf)  
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## AUTHORS

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