

Post-COVID-19 Syndrome: Theoretical Basis, Identification, and Management

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ABSTRACT

As COVID-19 continues to spread, with the United States surpassing 29 million cases, health care workers are beginning to see patients who have been infected with SARS-CoV-2 return seeking treatment for its longer-term physical and mental effects. The term long-haulers is used to identify patients who have not fully recovered from the illness after weeks or months. Although the acute symptoms of COVID-19 have been widely described, the longer-term effects are less well known because of the relatively short history of the pandemic. Symptoms may be due to persistent

chronic inflammation (eg, fatigue), sequelae of organ damage (eg, pulmonary fibrosis, chronic kidney disease), and hospitalization and social isolation (eg, muscle wasting, malnutrition). Health care providers are instrumental in developing a comprehensive plan for identifying and managing post-COVID-19 complications. This article addresses the possible etiology of postviral syndromes and describes reported symptoms and suggested management of post-COVID syndrome.

Key words: long-haulers, post-COVID syndrome, symptom management

As COVID-19 continues to spread, with the United States surpassing 29 million cases,¹ health care workers are beginning to see patients who have been infected with SARS-CoV-2 return seeking treatment for the physical and mental effects of the virus. The term *long-haulers* is applied to patients who have not fully recovered from the disease after weeks or months.² Although the acute symptoms of COVID-19 have been widely described, the longer-term effects are less well known because of the relatively short history of the pandemic. Symptoms may be due to persistent chronic inflammation (eg, fatigue), sequelae of organ damage (eg, pulmonary fibrosis, chronic kidney disease), and hospitalization and social isolation (eg, muscle wasting, malnutrition).³ Health care providers are instrumental in developing a comprehensive plan

for identifying and managing post-COVID-19 complications. This article addresses the possible etiology of postviral syndromes and describes reported symptoms and suggested management of post-COVID syndrome.

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Theoretical Pathophysiology

Coronavirus affects multiple systems, including the nervous, respiratory, cardiovascular, musculoskeletal, and gastrointestinal systems.⁴ Thus, symptoms of COVID-19 are numerous, vary from person to person, and may include fatigue, hallucinations, “brain fog,” delirium, memory loss, numbness and tingling, tachycardia, and shortness of breath.⁴ In trying to develop a pattern for diagnosis, experts are comparing these symptoms to a postviral syndrome that emerged with the first severe acute respiratory syndrome (SARS) that appeared in 2002, which was also caused by a coronavirus.² Anthony Fauci, MD, director of the National Institute of Allergy and Infectious Diseases, has suggested that the long-hauler presentation is similar to myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS).² Exploring the etiology of ME/CFS can provide insight into post-COVID syndrome.

Myalgic encephalomyelitis/chronic fatigue syndrome is defined by the Institute of Medicine as

an acquired, chronic multi-systemic disease characterized by significant relapse after physical, cognitive, or emotional exertion of any sort. The disease includes immune, neurological and cognitive impairment, sleep abnormalities, and autonomic dysfunction, resulting in significant functional impairment accompanied by a pathological level of fatigue.⁵

This syndrome is thought to be due to complex dysregulation of the immune and autonomic nervous systems.⁶ The hallmark of ME/CFS is postexertional malaise, an inappropriate loss of physical and mental stamina following any physical or emotional exertion. Multiple metabolic changes noted in ME/CFS include exercise-induced reduction in oxygen supply of muscles, skeletal muscle acidosis or dysregulation of protons, and impaired glucose uptake and reduced adenosine triphosphate levels in skeletal muscle cells during or after exercise.⁶ These changes are believed to be due to β_2 -adrenergic receptor and M3 acetylcholine receptor autoantibodies.⁶ Removal of these autoantibodies by IgG apheresis leads to improvement in patient fatigue.⁷

Normal functioning of β_2 -adrenergic receptors is complex and beyond the scope of this article. In general, these receptors are found in various tissues, the most important of which are liver, smooth muscle, skeletal muscle, and the myocardium.⁸ The receptors are responsible

for vasodilation of vascular smooth muscle tissue in the periphery and bronchodilation in the lungs. Stimulation of β_2 receptors in the myocardium has positive inotropic and chronotropic effects (increased contractility and heart rate, respectively). The M3 acetylcholine receptors are also located in many areas of the body, including the brain, smooth muscles, and endocrine and exocrine glands. Generally, when stimulated, these receptors cause smooth muscle contraction and increased glandular secretions.⁸ Although β_2 -adrenergic receptors and M3 acetylcholine receptors have other functions, these functions are pertinent to understanding the theoretical cause of ME/CFS. These receptors balance each other's activity to maintain physiological stability. The production of autoantibodies for β_2 -adrenergic receptors and M3 acetylcholine receptors theoretically would lead to the reversal of these receptor actions and result in significant smooth muscle dysfunction with consequent fatigue as well as other significant functional impairments.⁷ Chronotropic incompetence during exercise in patients with ME/CFS suggests impaired activation of cardiac β_2 receptors. Mental fatigue and “brain fog” may be due to reduced cerebral blood flow secondary to excessive sympathetic vasoconstriction in the presence of dysfunctional β_2 receptors.⁶ Polymorphisms and desensitization of β_2 -adrenergic receptors by chronic high sympathetic tone also contribute to the pathophysiology of ME/CFS.⁶ These abnormalities may play a role in the continued symptoms of patients after the acute phase of COVID-19.

An additional finding that may explain the fatigue and behavioral symptoms associated with COVID-19 is that the SARS 2002 virus invades multiple tissues, including the central nervous system.⁹ Viral particles were isolated from the cytoplasm of neurons; however, how the virus crossed the blood-brain barrier remains unclear.¹⁰ It may be that the virus crosses the blood-brain barrier into the hypothalamus via the olfactory pathway, similar to what has been suggested in ME/CFS patients who have disturbances of lymphatic drainage from the microglia in the brain.^{11,12} This lymphatic system drains spaces around the olfactory nerve through the cribriform plate into the nasal mucosa.^{11,13} If the current coronavirus pathogenesis follows the same pathway, this could be a possible cause of the taste and smell

disorders noted with COVID-19.¹² Abnormalities of this lymphatic system may lead to an accumulation of proinflammatory cytokines that eventually affect the autonomic nervous system with resultant cognitive dysfunction and severe fatigue, which are also noted in ME/CFS patients.^{12,14} Although more research is needed, understanding ME/CFS may facilitate understanding of post-COVID-19 syndrome.

Post-COVID-19 Symptoms

In addition to the wide variation of symptoms seen in post-acute COVID-19 syndrome, patients with the condition who initially had mild to moderate acute symptoms and were not hospitalized continue to have long-term symptoms.^{15,16} These symptoms include fatigue, cough, headache, shortness of breath, chest pains, joint pains, brain fog, gastrointestinal issues, and loss of taste and smell, along with neuropsychiatric symptoms such as insomnia, anxiety, depression, and delirium.¹⁷ In addition, a wide variety of skin manifestations, substantially more than seen with other viral infections, have been reported.¹⁸

These symptoms are similar to those seen in patients affected by previous outbreaks of viral disease. A systematic review of data collected from patients hospitalized with SARS and Middle Eastern respiratory syndrome revealed long-term complications including depressed mood (10.5% of patients), insomnia (12.1%), anxiety (12.3%), irritability (12.8%), memory impairment (18.9%), and fatigue (19.3%).¹⁹ A meta-analysis of the same data set found high prevalence rates for posttraumatic stress disorder (32.2%), depression (14.9%), and anxiety disorders (14.8%) during the postillness stage. Such findings are useful for developing treatment approaches and research foci while the complete picture of the COVID-19 pandemic is still unfolding.²⁰

Regardless of ethnicity or body mass index, females report more fatigue than males weeks after being discharged from an intensive care unit.^{17,21,22} In Paris, France, clinicians reported that after the lockdown ended, they saw an average of 30 individuals per week who remained symptomatic, with young women (mean age of 40 years) outnumbering males in a ratio of 4:1.²² Fatigue was reported more frequently in females with a preexisting diagnosis of depression.²³ Interestingly, the degree of fatigue was unrelated to the severity of initial acute symptoms.

Five cutaneous patterns have been noted in patients with COVID-19: maculopapular, urticarial, pseudochilblain, vesicular, and livedoid (see Table).²⁴ Characterizing these skin changes may help to identify mechanisms involved. For instance, livedoid changes are associated with occlusion of cutaneous vessels that may portend systemic thrombosis.¹⁸

Neuropsychiatric manifestations of COVID-19 are abundant, with evidence of impact on both the central nervous system (CNS) and the peripheral nervous system.⁴ The virus is known to be neurotropic, meaning that it replicates in neurons.²⁵ Factors involved in the emergence of neuropsychiatric symptoms are similar to those that cause fatigue and cognitive difficulties and include cytokine storm, blood clotting dyscrasias, and hypoxic events related to the respiratory symptoms.²⁶ A small case study of patients with neurologic symptoms resulting from COVID-19 (N = 127) was completed in the United Kingdom. The researchers examined the breadth of complications that affected the brain.²⁷ In addition to the acute occurrence of altered mental status and new-onset psychosis, significant physiological events were also reported. Cerebrovascular events were reported in 62% of patients, and 31% experienced altered mental status related to encephalopathy with evidence of CNS inflammation. A small segment of study participants experienced peripheral neurologic symptoms. Although the long-term consequences of cerebrovascular events have been extensively studied,^{2,3} the impact of the inflammatory process, both in the CNS and peripherally, is much less understood.

As the long-term picture of COVID-19 gradually unfolds, a clearer understanding of the long-hauler syndrome will emerge. Other surveys performed in conjunction with social media sites such as Facebook and Survivor Corps²⁸ have yielded similar findings, including fatigue, muscle or body aches, shortness of breath, difficulty concentrating, headache, psychological effects, and loss of smell and taste after recovery from COVID-19.²⁹ Some of these findings, particularly fatigue, are similar to those noted with post-intensive care syndrome and other postviral syndromes such as Epstein-Barr virus infection.²⁹ Data gathered thus far are largely patient collected and indicate a common and disabling condition with a wide variety of symptoms that can persist for many months.

Table: Skin Change Patterns Seen in Patients With COVID-19^a

Skin Change	Description and Distribution Pattern	Additional Considerations
	<p>Flat or raised red rash May be perifollicular</p>	<p>Lasts for a shorter period of time Frequently appears concurrently with other symptoms Associated with more severe disease Sometimes involves itching</p>
	<p>Red, raised welts (eg, hives) Truncal or widespread; some palmar</p>	<p>Lasts for a shorter period of time Frequently appears concurrently with other symptoms Associated with more severe disease Usually involves itching</p>
	<p>Painful, swollen red bumps with some vesicles or pustules Typically appears on fingers and toes; may be asymmetrical</p>	<p>Tends to occur in younger patients Occurs later in disease Associated with less severe disease</p>
	<p>Blister, monomorphic lesions Appears on trunk, limbs</p>	<p>Tends to occur in middle-aged patients Associated with medium severity of disease May appear before other symptoms Frequently involves itching</p>
	<p>Necrotic Truncal or on fingers/toes</p>	<p>Uncommon Usually occurs in elderly patients Associated with severe disease Suggestive of coagulopathies or vascular changes</p>

^a Data were derived from Casas et al²⁴ Sources of images: Microsoft Bing images (pseudochilblain, vesicular), National Institutes of Health (urticaria), authors' files (maculopapular, livedoid). Vesicular image republished under the Creative Commons Attribution-Share Alike 3.0 (<http://creativecommons.org/licenses/by-sa/3.0/deed.en>). Urticaria image republished under the Creative Commons Attribution Share Alike 2.0 (<https://creativecommons.org/licenses/by/2.0/>).

Post-COVID Symptom Assessment and Management

How long symptoms last and whether they are exclusive to COVID-19 or due to existing comorbidities or other disease states is unknown. What is known is that the pandemic has led to a major decrease in the use of health care services unrelated to COVID-19.³⁰ In addition, continued symptoms may limit patients' ability to work, with resultant loss of employer-based health insurance. This situation, coupled with the increasing number of patients with post-COVID symptoms, places a further burden on the health care system and presents clinicians with increasing challenges. Post-COVID-19 clinics have opened in a few states and provide a multidisciplinary approach to management of symptomatic individuals.²⁸ However, many areas lack these resources.

Patients with persistent symptoms should first consult their primary care provider for an initial evaluation and appropriate referrals, as needed. It is important that these patients' concerns are taken seriously. One female patient who experienced symptoms of post-COVID syndrome relayed to one of the authors of this article that she was told by health care providers that her symptoms might be "all in her head" (imaginary), despite the fact that she had been hospitalized with documented COVID-19 for 15 days. Thus, emotional support is crucial. A careful history and physical examination are paramount and can help determine differential diagnoses along with appropriate initial testing. For instance, are complaints of cough and shortness of breath in a patient with uncontrolled asthma due to an increase in asthma symptoms or to post-COVID syndrome? Is a complaint of chest pain related to increasing myocardial ischemia or due to post-COVID syndrome? Comorbidities such as diabetes, hypertension, renal disease, or heart disease must be managed in conjunction with COVID-19 symptoms. With respect to physical assessment, new murmurs or gallop rhythm might suggest cardiac involvement, pulmonary crackles or rhonchi could suggest continued lung infection, neurologic testing may indicate cognitive impairment, or palpable tenderness or engorgement of lymph nodes could suggest immune system abnormalities.¹⁰

To determine if patient symptoms are related to COVID-19, serologic testing has been suggested.³¹ Serologic testing involves the detection of specific antibodies to SARS-CoV-2 in blood,

serum, or plasma, which are usually measurable a minimum of 7 to 14 days after symptom onset.³¹ Negative results, however, do not rule out acute or previous SARS-CoV-2 infection.³¹ In mild cases, antibody response may not reach a level high enough to be detected.³² In addition, recent data have not shown that detectable antibodies confer durable immunity against reinfection. Serologic testing may be useful to identify patients who were infected with SARS-CoV-2 and whose symptoms may be related to post-COVID syndrome. The findings may offer some reassurance to patients.

Fatigue Assessments and Interventions

Fatigue, along with shortness of breath, may be multifactorial and shares features with chronic fatigue syndrome described after other serious viral or bacterial infections.¹⁶ A complete blood count to rule out anemia as one cause, along with chest radiography, chest computed tomography, and/or pulmonary function testing to rule out residual lung disease, may be required. Pulse oximeters may be helpful to monitor respiratory symptoms. For chest pains, measurement of erythrocyte sedimentation rate, C-reactive protein level, and troponin level, along with an electrocardiogram and transthoracic echocardiography (2-dimensional echo), can help to rule out myopericarditis or acute coronary syndrome. Further testing may require cardiac magnetic resonance. A 2-dimensional echocardiogram is valuable to determine whether dyspnea is due to a reduced ejection fraction, along with N-terminal pro-brain natriuretic peptide for diagnosis of heart failure. A complete blood count with differential can also identify lymphopenia or leukocytosis possibly indicative of reinfection or secondary infection. Increased ferritin levels may indicate inflammation and a continued prothrombotic state. If the patient was diagnosed with a thrombotic event, such as a pulmonary embolus, anticoagulation should be continued per current guidelines. How long patients remain in a hypercoagulable state, or if anticoagulation therapy is beneficial after acute COVID-19, is currently being studied.

Fatigue secondary to physical disability may be improved through rehabilitation programs with assistance from physical therapists and exercise physiologists. An exercise program should involve strengthening, flexibility exercises, aerobic exercises, and exercises

intended to improve gait and balance.³³ Patients should start slowly and be monitored for worsening symptoms such as breathlessness and muscle aches. In addition to exercise training, patients with significant respiratory symptoms may also benefit from pulmonary rehabilitation programs. Many programs offer various virtual models, including video-linked classes, printed materials, and telephone support.

Additional System Assessments and Interventions

Older patients are at higher risk for sarcopenia, depression, malnutrition, and delirium.³⁴ Nutritional assessment should include serum albumin and prealbumin levels and lymphocyte counts. SARS-CoV-2 infection may induce or exacerbate anorexia and worsen malnutrition, leading to a poor recovery. Detailed information on the nutritional management of patients with COVID-19 can be found in the recently published guidance of the European Society for Clinical Nutrition and Metabolism.³⁵ In cases of continued gastrointestinal symptoms, such as anorexia, nausea, vomiting, diarrhea, or abdominal discomfort, referral to a gastroenterologist may be needed.

Because physiological damage to the central and/or peripheral nervous systems may include neuropsychiatric sequelae—and given the psychological impact of COVID-19 and the socio-economic impact of a pandemic—a thorough psychological assessment is required. Patients should be screened for acute psychiatric complications such as suicidality as well as insomnia, anxiety, depression, and delirium.^{36,37} Long-term follow-up is crucial, not only to monitor and treat these patients, but also to fully understand the long-term impact of infection with the virus.

Clearly, the severity of symptoms affects recovery. A systematic review indicated that 76.9% of patients who had severe illness related to SARS or Middle Eastern respiratory syndrome had returned to work at a follow-up time of 3 years.¹⁹ Such long-term data are not yet available for those recovering from COVID-19; however, it can be predicted that the well-documented fatigue and cognitive deficits will affect recovery. Rehabilitation therapies should be used for patients with severe disease. Patients experiencing long-term psychological consequences of the disease should be referred for treatment consisting of counseling and/or medication.

As always, patients with persistent symptoms should be referred to an appropriate specialist (eg, cardiologist, pulmonologist, psychologist, infectious diseases specialist, neurologist, nephrologist). For example, advanced neuroimaging may be needed to fully investigate cognitive impairment, unresolved depression should be addressed by a mental health practitioner, and persistent abnormal chest radiography and oximeter readings require referral to a pulmonologist.¹⁶

Summary

Evidence suggests that acute COVID-19 symptoms are attributable to a severe inflammatory response and cytokine storm syndrome triggered by dysregulated cytokine production, particularly involving interleukin 6.¹⁴ Regardless of the exact mechanism, it is now well known that relapse or reinfection, weak or absent antibody response, and other factors may contribute to the degree and type of symptoms.¹⁵ Although the acute effects of SARS-CoV-2 infection have been widely described, the long-term effects are less well understood. How many individuals will have continued or new symptoms after infection with the virus is unknown. Patients who were healthy before their illness are now facing unexpected symptoms, while others with comorbidities must manage new or worsening symptoms. Many have avoided seeking health care during the pandemic. While clinicians continue to battle COVID-19 on the front lines, we also need to develop comprehensive, evidence-based plans to manage post-COVID-19 symptoms and encourage those affected to seek appropriate care. Patients and families who experience these debilitating symptoms require targeted treatment as well as ongoing support.

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CE Evaluation Instructions

This article has been designated for CE contact hour(s). The evaluation tests your knowledge of the following objectives:

1. Describe the theoretical pathophysiology of long-term symptoms following infection with SARS-CoV-2.
2. Relate post-COVID-19 symptoms to pathophysiologic mechanisms.
3. Identify at least 2 strategies for managing patients with post-COVID-19 symptoms.

Contact hour: **1.0**

Synergy CERP Category: **A**

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