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Recognizing the Clinical Sequelae of COVID-19 in Adults: COVID-19 Long-Haulers

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ABSTRACT

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As the numbers of acute severe acute respiratory syndrome coronavirus 2 infections continue to rise, we are learning that symptoms do not resolve quickly in all patients. Although why some patients experience persistent symptoms is not clear, these individuals suffer. Long-hauler is the term that is associated with these persistent symptoms, and this review of the literature provides information to nurse practitioners working in primary care about symptoms, risk factors, and resources for disease management.

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Coronavirus disease 2019 (COVID-19) is caused by an infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Patients infected with SARS-CoV-2 exhibit a wide spectrum of clinical manifestations, ranging from asymptomatic to severe, during the acute phase of illness. The focus of research and publications has been the acute illness; however, as we enter the second year of the COVID-19 pandemic, it is becoming more apparent that COVID-19 has lingering effects. This article provides the nurse practitioner (NP) with a general overview of these persistent symptoms and resources for the clinical management of these patients.

Long-Haulers

Not all patients who are diagnosed with COVID-19 completely recover; some experience persistent symptoms that wax and wane.¹ Approximately 10% of people who experience mild COVID-19 symptoms will become long-haulers.² There is a higher incidence of persistent symptoms in patients with comorbidities^{3,4} or more severe SARS-CoV-2 infection.²⁻⁵ These persistent symptoms wax and wane.¹ While no standard time frame has been established to identify when symptoms become persistent, it is generally agreed that symptoms lasting longer than 3 to 4 weeks after the initial diagnosis of mild, moderate, and severe illness and lasting longer than 6 weeks in critical illness are considered persistent.⁶

The physical and psychologic symptoms experienced by COVID-19 long-haulers are similar to the symptoms survivors of sepsis or other critical illness experience when there is immune dysregulation.⁷ At this time, why symptoms persist is unclear. It is possible that the symptoms are the result of chronic fatigue syndrome or myalgic encephalomyelitis, which has been associated with other viral infections.⁸ It is also possible that the persistent symptoms are

related to persistent inflammation or damage due to direct viral entry into tissues. Researchers have discovered evidence that patients with persistent symptoms have signs of vessel wall inflammation on imaging⁹ and elevated biomarkers consistent with inflammation.¹⁰ During the SARS-CoV-1 outbreak in 2003, the SARS-CoV-1 virus was detected in myocardial tissue during autopsy, providing evidence of direct viral entry into tissues.¹¹

Clinical Sequelae of COVID-19

The cellular entry point for SARS-CoV-2 is the angiotensin converting enzyme 2 (ACE2) receptor.¹¹ Attachment of the virus to the ACE2 receptor is associated with increased levels of angiotensin leading to inflammation, vasoconstriction, and thrombosis.¹¹ In addition to the ACE2 receptor, SARS-CoV-2 requires a protease to prime the spike protein before the virus can enter the cell.^{11,12} The ACE2 receptor and the required protease are both expressed in lung, heart, gut smooth muscle, liver, kidney, neurons, and immune cells, which provide an explanation for the symptomatology of COVID-19.¹¹ Long-haulers may experience sequelae from 1 or multiple systems. The sequelae are discussed below, and a summary is also provided in [Table 1](#).^{1,4,13-29}

Mental Health Sequelae

The uncertainty surrounding long-haul COVID-19 leaves patients feeling helpless and alone in managing their symptoms.¹ In interviews, long-haulers report feeling frustrated by the lack of assistance and empathy they receive from family and health care providers.¹ Previously healthy and independent functioning individuals now, as long-haulers, have difficulty completing basic

Table 1
Sequelae of COVID-19

System	Sequelae	Source
Mental Health	Anxiety Depression Insomnia Posttraumatic stress disorder (PTSD)	Mazza et al (2020) ¹³
Pulmonary	Dyspnea Cough Impaired exercise capacity Lung fibrosis Impaired diffusing capacity	Carfi et al (2020) ¹⁴ Kingstone et al (2020) ¹ Higgins et al (2020) ¹⁵ Tenforde et al (2020) ¹⁶ Mandal et al (2020) ⁴
Central nervous system	Stroke Polyneuropathy Headaches Hyposomnia Mental fatigue & confusion —"Brain fog" Delirium	Higgins et al (2020) ¹⁵ Amenta et al (2020) ¹⁷ Cognitive Assessment Group (2021) ¹⁸ LaHue et al (2020) ¹⁹ Manca et al (2020) ²⁰ Tenforde et al (2020) ¹⁶
Cardiovascular	Chest pain Myocardial infarction Cardiomyopathy Arrhythmias Heart failure LV dysfunction and myocardial inflammation Coagulopathies and thrombosis	Carfi et al (2020) ¹⁴ Kingstone et al (2020) ¹ Liu et al (2020) ¹¹ Madjid et al (2020) ²¹ Amenta et al (2020) ¹⁷ Higgins et al (2020) ¹⁵ Vechi et al (2020) ²² Dani et al (2021) ²³
Gastrointestinal	Orthostatic hypotension Abdominal pain Gastrointestinal bleeding Nausea, vomiting, diarrhea Hepatitis Pancreatitis	Carfi et al (2020) ¹⁴ Tenforde et al (2020) ¹⁶
Renal	Glomerular disease	NIH VideoCast (2020) ²⁴
Musculoskeletal	Myalgias Arthralgias	Carfi et al (2020) ¹⁴ Kingstone et al (2020) ¹ NIH (2020) ²⁵ Amenta et al (2020) ¹⁷ Mikkelsen et al (2021) ²⁶ Tenforde et al (2020) ¹⁶ Feldman et al (2021) ²⁷ Sachdeva et al. (2020) ²⁸
Cutaneous	Skin lesions Chilblain-like acral lesions "COVID toes"	Carfi et al (2020) ¹⁴ NIH (2020) ²⁵ Amenta et al (2020) ¹⁷ Mikkelsen et al (2021) ²⁶ Tenforde et al (2020) ¹⁶ Mandal et al (2020) ⁴
Constitutional symptoms	Fatigue Fever	Carfi et al (2020) ¹⁴ NIH (2020) ²⁵ Amenta et al (2020) ¹⁷ Mikkelsen et al (2021) ²⁶ Tenforde et al (2020) ¹⁶ Mandal et al (2020) ⁴

COVID-19 = coronavirus disease 2019; LV = left ventricular.

daily activities and are unable to work due to limited endurance and other symptoms.^{26,29}

The changes in mental health experienced by many long-haulers have many etiologies. Multiple psychologic stressors have emerged as a result of the COVID-19 pandemic, including financial, social isolation, and uncertainty and fear regarding the infection.¹³ Long-haulers experience additional psychologic stressors related to prolonged changes in physical functioning and the perception that family and health care providers are not supportive.¹ The inflammatory response to the virus itself may also cause an increased amount of psychologic symptoms.¹³ Regardless of the cause, survivors of COVID-19 experience a significant impact on mental health to include anxiety, depression, insomnia, and posttraumatic stress disorder.¹³

Pulmonary Sequelae

Cough and dyspnea are common complaints among long-haulers.^{1,14} The pulmonary sequelae include impaired exercise

capacity, fibrotic lung tissue, and impaired diffusing capacity.¹⁵ Pulmonary function can improve over time, but fibrosis is irreversible.¹⁵ At this time, the duration of pulmonary symptoms associated with long-haul COVID-19 is unknown. However, patients with SARS-CoV-1, which is similar to SARS-CoV-2, the infection that causes COVID-19, have experienced impaired pulmonary function up to 15 years after infection.¹⁵

Central Nervous System Sequelae

Sequelae of the central nervous system include stroke, polyneuropathy, headaches, and hyposomnia.¹⁵ New or worsened concentration problems are commonly seen among long-haulers.¹⁷ The term brain fog has been used to describe the mental fatigue and confusion occurring after COVID-19.¹⁸ Patients hospitalized with acute COVID-19 have additional risk factors for delirium due to physical isolation measures instituted to prevent the spread of disease. Physical isolation measures, such as facial coverings and personal protective equipment, create a physical and emotional barrier between providers and patients. Hospital staff cluster care to minimize exposure time, which has decreased the number of interactions staff have with patients. Visitation by friends and families has also been restricted for all patients to prevent disease transmission. These infection control measures have increased the social isolation for all patients, but older individuals, in particular, are at increased risk for mental health issues and cognitive decline as a result of social isolation.^{19,20}

Cardiovascular Sequelae

Survivors of COVID-19 are also at increased risk for cardiovascular complications to include myocardial infarction, cardiomyopathy, arrhythmias, and heart failure.^{11,15,21} Some long-haulers also have evidence of impaired lower left ventricular ejection fraction and myocardial inflammation on cardiac magnetic resonance imaging.¹⁷

Long-haulers have an increased incidence of coagulopathies and thrombosis.¹⁵ Pulmonary embolus has been reported 3 to 4 weeks after the acute illness.²² Patients presenting with symptoms consistent with embolus need to have this condition ruled out even in patients who had mild acute illness.

Viral illnesses such as COVID-19 can also affect the autonomic nervous system. Affected individuals may display orthostatic hypotension along with tachycardia in response to position changes.²³ Individuals with these findings are at risk for injury due to vasovagal syncope. These symptoms should be evaluated to rule out other causes for their symptoms, and patients should be educated on how to avoid injury and to manage symptoms.²³

Gastrointestinal, Renal, and Musculoskeletal Sequelae

The gastrointestinal system may also be affected. Complaints of abdominal pain, gastrointestinal bleeding, nausea and vomiting, diarrhea, hepatitis, and pancreatitis may be experienced by long-haulers. Long-haulers who experienced kidney dysfunction during the acute illness period are more likely to have continued kidney dysfunction after discharge.¹⁷ The development of acute kidney injury is associated with worse long-term outcomes in other diseases, but we are uncertain how this will affect COVID-19 long-haulers.²⁴ The musculoskeletal symptoms of myalgias and arthralgias are also common complaints among long-haulers.^{17,25,26}

Cutaneous Sequelae

Skin lesions may develop up to 2 weeks after acute COVID-19 infection²⁸ and normally resolve within 2 to 8 weeks.²⁷ Common cutaneous manifestations of COVID-19 include morbilliform rash and chilblain-like acral lesions, “COVID toes.”²⁷ Dermatologic findings may be the only symptom associated with COVID-19 infection. The etiology of dermatologic lesions associated with COVID-19 is uncertain, and iatrogenic causes cannot be ruled out.²⁷

Constitutional Symptoms

Fatigue is one of the most common symptoms reported by COVID-19 survivors.^{4,14,16} This symptom can be debilitating for some individuals, particularly when other symptoms are present. Fever, while less commonly reported than fatigue, is another symptom that long-haulers experience but is not associated with acute infection.¹⁶

Implications for Primary Care NPs

The diagnosis of long-haul COVID-19 is a diagnosis of exclusion, and there is uncertainty regarding symptom duration.²⁵ Long-term data regarding COVID-19 survivors are not currently available; however, current reports indicate that symptoms may persist months after the acute illness.⁵ The list of sequelae discussed above is not exclusive. As the pandemic continues, we learn more about long-haulers, and with that knowledge, we improve management.

NPs are recommended to approach each patient as an individual and to perform a comprehensive history and physical examination to rule out serious complications and comorbidities as causes for symptoms.³⁰ Physical, cognitive, psychologic, psychiatric, and functional status needs to be evaluated in patients with persistent symptoms.^{26,31} As explained earlier, long-haul COVID-19 is a diagnosis of exclusion, and alternative explanations for symptoms need to be ruled out before deciding that a patient is presenting with the sequelae of COVID-19. After serious complications and comorbidities have been ruled out as a cause for symptoms, most symptoms can be managed symptomatically.² A list of resources and guidelines for managing persistent symptoms is presented in Table 2.

Long-haul COVID-19 is a relatively unknown syndrome and one that benefits from multidisciplinary management. Post-COVID-19 care centers are opening at many academic medical centers,³² and if available, long-haulers should be referred.¹³ If a post-COVID-19 care center is not available in your area, specialty consultation is another option.^{13,30}




When these patients are evaluated, it is important to remember that the disease has a high emotional impact and that the emotional dimension of COVID-19 should not be ignored in patients who present with persistent symptoms.¹³ Most patients with persistent symptoms can be evaluated via telemedicine or in person. However, in interviews, people with persistent symptoms indicated a desire to be assessed face-to-face, when possible.¹

Conclusion

The persistent symptoms associated with COVID-19 are frustrating for patients who just want to be normal and to return to their previous level of function before COVID-19. Unfortunately there are no clear answers for them at this time, and NPs should share this with them. Alternative explanations for symptoms need to be ruled out before associating the symptoms with long-haul COVID-19. If a COVID-19 care center is available, patients should be referred. If a COVID-19 care center is not available, specialists

Table 2

Resources for Managing Persistent Symptoms of COVID-19

Resource	Synopsis
NIH COVID-19 Treatment Guidelines Available for download from https://www.covid19treatmentguidelines.nih.gov/ 	Section on persistent symptoms or illnesses after recovery from acute COVID-19
Management of post-acute COVID-19 in primary care Available for download from https://www.bmj.com/content/bmj/370/bmj.m3026.full.pdf 	Guidance on symptom evaluation and management
NICE COVID-19 guideline Available for download from https://www.nice.org.uk/guidance/ng188/resources/covid19-rapid-guideline-managing-the-longterm-effects-of-covid19-pdf-66142028400325 	General guidance on the identification, assessment, investigation, and management of persistent symptoms

COVID-19 = coronavirus disease 2019; NICE = National Institute of Health and Care Excellence; NIH = National Institutes of Health.

Note: Scan the QR code with your mobile device.

need to be consulted. Given the impact on mental health, evaluating the mental health of long-haulers is a priority.

More research is needed regarding the long-haulers of COVID-19. More than 27 million Americans have already been infected with COVID-19, and there have been more than 106 million cases globally.³³ Given that 10% of patients with acute COVID-19 are predicted to become long-haulers,² the number of patients presenting to primary care with persistent symptoms will be the next wave of the pandemic. NPs who are knowledgeable about the long-term effects of COVID-19 will improve the quality of care that long-haulers receive while minimizing frustration for these individuals.

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