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The authors reported no potential conflict of interest relevant to this article.

doi: 10.12788/jfp.0517

The family physician's role in long COVID management

A paucity of both data and therapeutics presents obstacles to care and makes your role in symptom management, psychological support, and referral—all described here—essential.

PRACTICE RECOMMENDATIONS

› Acknowledge and address the persistence of COVID-19 symptoms when meeting with patients. **C**

› Continue to monitor persistent, fluctuating symptoms of COVID-19 well after hospital discharge or apparent resolution of initial symptoms. **C**

› Provide psychological support and resources for mental health care to patients regarding their ongoing fears and frustrations with persistent COVID-19 symptoms. **C**

Strength of recommendation (SOR)

- A** Good-quality patient-oriented evidence
- B** Inconsistent or limited-quality patient-oriented evidence
- C** Consensus, usual practice, opinion, disease-oriented evidence, case series

Several years into the pandemic, COVID-19 continues to deeply impact our society; at the time of publication of this review, 98.8 million cases in the United States have been reported to the Centers for Disease Control and Prevention (CDC).¹ Although many people recover well from infection, there is mounting concern regarding long-term sequelae of COVID-19. These long-term symptoms have been termed *long COVID*, among other names.

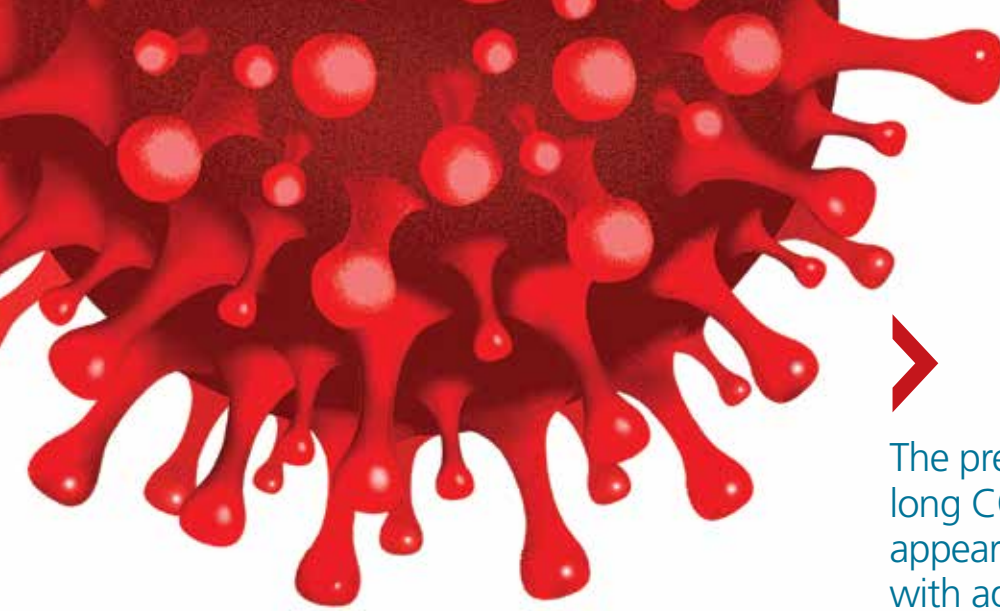
What exactly is long COVID?

The CDC and National Institutes of Health define long COVID as new or ongoing health problems experienced ≥ 4 weeks after initial infection.² Evidence suggests that even people who have mild initial COVID-19 symptoms are at risk for long COVID.

Available data about long COVID are imperfect, however; much about the condition remains poorly understood. For example, there is little evidence regarding the effect of vaccination and viral variants on the prevalence of long COVID. A recent study of more than 13 million people from the US Department of Veterans Affairs database did demonstrate that vaccination against SARS-CoV-2 lowered the risk for long COVID by only about 15%.³

Persistent symptoms associated with long COVID often lead to disability and decreased quality of life. Furthermore, long COVID is a challenge to treat because there is a paucity of evidence to guide COVID-19 treatment beyond initial infection.

Because many patients who have ongoing COVID-19 symptoms will be seen in primary care, it is important to understand how to manage and support them. In this article, we discuss current understanding of long COVID epidemiology, symptoms that can persist 4 weeks after initial infection, and potential treatment options.



The prevalence of long COVID symptoms appears to increase with age.



Prevalence and diagnosis

The prevalence of long COVID is not well defined because many epidemiologic studies rely on self-reporting. The CDC reports that 20% to 25% of COVID-19 survivors experience a new condition that might be attributable to their initial infection.⁴ Other studies variously cite 5% to 85% of people who have had a diagnosis of COVID-19 as experiencing long COVID, although that rate more consistently appears to be 10% to 30%.⁵

A study of adult patients in France found that self-reported symptoms of long COVID, 10 to 12 months after the first wave of the pandemic (May through November 2020), were associated with the *belief* of having had COVID-19 but not necessarily with having tested positive for anti-SARS-CoV-2 antibodies,⁶ which indicates prior COVID-19. This complicates research on long COVID because, first, there is no specific test to confirm a diagnosis of long COVID and, second, studies often rely on self-reporting of earlier COVID-19.

As such, long COVID is diagnosed primarily through a medical history and physical examination. The medical history provides a guide as to whether additional testing is warranted to evaluate for known complications of COVID-19, such as deep vein thrombosis, pulmonary embolism, myocarditis, and

pulmonary fibrosis. As of October 1, 2021, a new International Classification of Disease (10th Revision) code went into effect for *post COVID condition, unspecified (U09.9)*.⁷

The prevalence of long COVID symptoms appears to increase with age. Among patients whose disease was diagnosed using code U09.9, most were 36 to 64 years of age; children and adults ages 22 years or younger constituted only 10.5% of diagnoses.⁷ Long COVID symptoms might also be more prevalent among women and in people with a pre-existing chronic comorbidity.^{2,7}

Symptoms can be numerous, severe or mild, and lasting

Initially, there was no widely accepted definition of long COVID; follow-up in early studies ranged from 21 days to 2 years after initial infection (or from discharge, for hospitalized patients).⁸ Differences in descriptions that have been used on surveys to self-report symptoms make it a challenge to clearly summarize the frequency of each aspect of long COVID.

Long COVID can be mild or debilitating; severity can fluctuate. Common symptoms include fatigue, dyspnea or other breathing difficulties, headache, and cognitive dysfunction, but as many as 203 lasting symptoms have been reported.^{2,8-12} From October

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1, 2021, through January 31, 2022, the most common accompanying manifestations of long COVID were difficulty breathing, cough, and fatigue.⁷ Long COVID can affect multiple organ systems,^{13,14} with symptoms varying by organ system affected. Regardless of the need for hospitalization initially, having had COVID-19 significantly increases the risk for subsequent death at 30 days and at 6 months after initial infection.¹⁵

Symptoms of long COVID have been reported as long as 2 years after initial infection.⁸ When Davis and colleagues studied the onset and progression of reported symptoms of long COVID,⁹ they determined that, among patients who reported recovery from COVID-19 in < 90 days, symptoms peaked at approximately Week 2 of infection. In comparison, patients who reported *not* having recovered in < 90 days had (1) symptoms that peaked later (2 months) and (2) on average, more symptoms (mean, 17 reported symptoms, compared to 11 in recovered patients).⁹

■ **Fatigue**, including postexertion malaise and impaired daily function and mobility, is the most common symptom of long COVID,^{8-10,14} reported in 28% to 98%¹⁴ of patients after initial COVID-19. This fatigue is more than simply being tired: Patients describe profound exhaustion, in which fatigue is out of proportion to exertion. Fatigue and myalgia are commonly reported among patients with impaired hepatic and pulmonary function as a consequence of long COVID.¹³ Patients often report that even minor activities result in decreased attention, focus, and energy, for many hours or days afterward. Fatigue has been reported to persist from 2.5 months to as long as 6 months after initial infection or hospitalization.^{9,16}

Postviral fatigue has been seen in other viral outbreaks and seems to share characteristics with myalgic encephalomyelitis/chronic fatigue syndrome, or ME/CFS, which itself has historically been stigmatized and poorly understood.¹⁷ Long COVID fatigue might be more common among women and patients who have an existing diagnosis of depression and antidepressant use,^{10,11,16,18} although the mechanism of this relationship is unclear. Potential mechanisms include

damage from systemic inflammation to metabolism in the frontal lobe and cerebellum¹⁹ and direct infection by SARS-CoV-2 in skeletal muscle.²⁰ Townsend and colleagues¹⁶ found no relationship between long COVID fatigue and markers of inflammation (leukocyte, neutrophil, and lymphocyte counts; the neutrophil-to-lymphocyte ratio; lactate dehydrogenase; C-reactive protein; serum interleukin-6; and soluble CD25).

■ **Neuropsychiatric symptoms** are also common in long COVID and can have a significant impact on patients' quality of life. Studies have reported poor sleep quality or insomnia (38% to 90%), headache (17% to 91.2%), speech and language problems (48% to 50%), confusion (20%), dementia (28.6%), difficulty concentrating (1.9% to 27%), and memory loss or cognitive impairment (5.4% to 73%).^{9,10,14,15} For some patients, these symptoms persisted for ≥ 6 months, making it difficult for those affected to return to work.⁹

Isolation and loneliness, a common situation for patients with COVID-19, can have long-term effects on mental health.²¹ The COVID-19 pandemic itself has had a negative effect on behavioral health, including depression (4.3% to 25% of patients), anxiety (1.9% to 46%), obsessive compulsive disorder (4.9% to 20%), and posttraumatic stress disorder (29%).²² The persistence of symptoms of long COVID has resulted in a great deal of frustration, fear, and confusion for those affected—some of whom report a loss of trust in their community health care providers to address their ongoing struggles.²³ Such loss can be accompanied by a reported increase in feelings of anxiety and changes to perceptions of self (ie, “how I used to be” in contrast to “how I am now”).²³ These neuropsychiatric symptoms, including mental health conditions, appear to be more common among older adults.⁴

Other neurologic deficits found in long COVID include olfactory disorders (9% to 27% of patients), altered taste (5% to 18%), numbness or tingling sensations (6%), blurred vision (17.1%), and tinnitus (16%).¹⁴ Dizziness (2.6% to 6%) and lightheadedness or presyncope (7%) have also been reported, although these symptoms appear to be less

common than other neurocognitive effects.¹⁴

The mechanism of action of damage to the nervous system in long COVID is likely multifactorial. COVID-19 can directly infect the central nervous system through a hematogenous route, which can result in direct cytolytic damage to neurons. Infection can also affect the blood-brain barrier.²⁴ Additionally, COVID-19 can invade the central nervous system through peripheral nerves, including the olfactory and vagus nerves.²⁵ Many human respiratory viruses, including SARS-CoV-2, result in an increase in pro-inflammatory and anti-inflammatory cytokines; this so-called *cytokine storm* is an exaggerated response to infection and can trigger neurodegenerative and psychiatric syndromes.²⁶ It is unclear whether the cytokine storm is different for people with COVID-19, compared to other respiratory viruses.

■ **Respiratory symptoms** are very common after COVID-19¹⁵: In studies, as many as 87.1% of patients continued to have shortness of breath \geq 140 days after initial symptom onset, including breathlessness (48% to 60%), wheezing (5.3%), cough (10.5% to 46%), and congestion (32%),^{14,18} any of which can persist for as long as 6 months.⁹ Among a sample of previously hospitalized COVID-19 patients in Wuhan, China, 22% to 56% displayed a pulmonary diffusion abnormality 6 months later, with those who required supplemental oxygen during initial COVID-19 having a greater risk for these abnormalities at follow-up, compared to those who did not require supplemental oxygen (odds ratio = 2.42; 95% CI, 1.15-5.08).¹¹

■ **Cardiovascular symptoms.** New-onset autonomic dysfunction has been described in multiple case reports and in some larger cohort studies of patients post COVID-19.²⁷ Many common long COVID symptoms, including fatigue and orthostatic intolerance, are commonly seen in postural orthostatic tachycardia syndrome. Emerging evidence indicates that there are likely similar underlying mechanisms and a significant amount of overlap between long COVID and postural orthostatic tachycardia syndrome.²⁷

A study of patients within the US Department of Veterans Affairs population found that, regardless of disease severity, patients

who had a positive COVID-19 test had a higher rate of cardiac disease 30 days after diagnosis,²⁸ including stroke, transient ischemic attack, dysrhythmia, inflammatory heart disease, acute coronary disease, myocardial infarction, ischemic cardiopathy, angina, heart failure, nonischemic cardiomyopathy, and cardiac arrest. Patients with COVID-19 were at increased risk for major adverse cardiovascular events (myocardial infarction, stroke, and all-cause mortality).²⁸ Demographics of the VA population (ie, most are White men) might limit the generalizability of these data, but similar findings have been found elsewhere.^{5,10,15}

Given that, in general, chest pain is common after the acute phase of an infection and the causes of chest pain are broad, the high rate of cardiac complications post COVID-19 nevertheless highlights the importance of a thorough evaluation and work-up of chest pain in patients who have had COVID-19.

■ **Other symptoms.** Body aches and generalized joint pain are another common symptom group of long COVID.⁹ These include body aches (20%), joint pain (78%), and muscle aches (87.7%).^{14,18}

Commonly reported gastrointestinal symptoms include diarrhea, loss of appetite, nausea, and abdominal pain.^{9,15}

Other symptoms reported less commonly include dermatologic conditions, such as pruritus and rash; reproductive and endocrine symptoms, including extreme thirst, irregular menstruation, and sexual dysfunction; and new or exacerbated allergic response.⁹

Does severity of initial disease play a role?

Keep in mind that long COVID is *not* specific to patients who were hospitalized or had severe initial infection. In fact, 75% of patients who have a diagnosis of a post-COVID-19 condition were not hospitalized for their initial infection.⁷ However, the severity of initial COVID-19 infection might contribute to the presence or severity of long COVID symptoms²—although findings in current literature are mixed. For example:

- In reporting from Wuhan, China, higher position on a disease severity



The high rate of cardiac complications post COVID-19 highlights the importance of a thorough evaluation and work-up of chest pain in patients who have had COVID-19.

➤ **Long COVID–associated fatigue is more than simply being tired. Patients describe profound exhaustion, in which fatigue is out of proportion to exertion.**

scale during a hospital stay for COVID-19 was associated with:

- greater likelihood of reporting ≥ 1 symptoms at a 6-month follow-up
- increased risk for pulmonary diffusion abnormalities, fatigue, and mood disorders.¹¹
- After 2 years' follow-up of the same cohort, 55% of patients continued to report ≥ 1 symptoms of long COVID, and those who had been hospitalized with COVID-19 continued to report reduced health-related quality of life, compared to the control group.⁸
- Similarly, patients initially hospitalized with COVID-19 were more likely to experience impairment of ≥ 2 organs—in particular, the liver and pancreas—compared to nonhospitalized patients after a median 5 months post initial infection, among a sample in the United Kingdom.¹³
- In an international cohort, patients who reported a greater number of symptoms during initial COVID-19 were more likely to experience long COVID.¹²
- Last, long COVID fatigue did not vary by severity of initial COVID-19 infection among a sample of hospitalized and nonhospitalized participants in Dublin, Ireland.¹⁶

No specific treatments yet available

There are no specific treatments for long COVID; overall, the emphasis is on providing supportive care and managing preexisting chronic conditions.⁵ This is where expertise in primary care, relationships with patients and the community, and psychosocial knowledge can help patients recover from ongoing COVID-19 symptoms.

Clinicians should continue to perform a thorough physical assessment of patients with previous or ongoing COVID-19 to identify and monitor new or recurring symptoms after hospital discharge or initial resolution of symptoms.²⁹ This approach includes developing an individualized plan for care and rehabilitation that is specific to presenting

symptoms, including psychological support. We encourage family physicians to familiarize themselves with the work of Vance and colleagues,³⁰ who have created a comprehensive table^a to guide treatment and referral for the gamut of long COVID symptoms, including cardiovascular issues (eg, palpitations, edema), chronic cough, headache, pain, and insomnia.

This new clinical entity is a formidable challenge

Long COVID is a new condition that requires comprehensive evaluation to understand the full, often long-term, effects of COVID-19. Our review of this condition substantiated that symptoms of long COVID often affect a variety of organs^{13,14} and have been observed to persist for ≥ 2 years.⁸

Some studies that have examined the long-term effects of COVID-19 included only participants who were not hospitalized; others include hospitalized patients exclusively. The literature is mixed in regard to including severity of initial infection as it relates to long COVID. Available research demonstrates that it is common for people with COVID-19 to experience persistent symptoms that can significantly impact daily life and well-being.

Likely, it will be several years before we even begin to understand the full extent of COVID-19. Until research elucidates the relationship between the disease and short- and long-term health outcomes, clinicians should:

- acknowledge and address the reality of long COVID when meeting with persistently symptomatic patients,
- provide support, therapeutic listening, and referral to rehabilitation as appropriate, and
- offer information on the potential for long-term effects of COVID-19 to vaccine-hesitant patients. **JFP**

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^a“Systems, symptoms, and treatments for post-COVID patients,” pages 1231-1234 in the source article (www.jabfm.org/content/jabfp/34/6/1229.full.pdf).³⁰

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