

Long COVID—ACOEM Guidance Statement

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Abstract: Persistent symptoms are common after acute COVID-19, often referred to as long COVID. Long COVID may affect the ability to perform activities of daily living, including work. Long COVID occurs more frequently in those with severe acute COVID-19. This guidance statement reviews the pathophysiology of severe acute COVID-19 and long COVID and provides pragmatic approaches to long COVID symptoms, syndromes, and conditions in the occupational setting. Disability laws and workers' compensation are also addressed.

Keywords: long COVID, ADLs, occupational health, COVID-19 research

LEARNING OUTCOMES

- Discuss the most frequent symptoms and potential pathophysiology associated with long COVID.
- Assess the impact of long COVID on fitness for work.
- Recommend COVID vaccines to workers as a way to reduce the risk of severe disease and long COVID.
- Discuss the approach to analyzing workers' compensation claims for long COVID.

The COVID-19 pandemic, caused by the novel coronavirus SARS-CoV-2, began in China in late 2019, with clinical cases first identified in the United States (US) in early 2020. By late 2022, it was estimated that 70% of adults in the United States had been infected with SARS-CoV-2.^{1,2} The pandemic

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has gone through a series of peaks driven by variants that have become increasingly contagious and the trajectory of the disease continues to evolve. People who become infected with SARS-CoV-2 may be asymptomatic and may have mild illness, or the infection may lead to a series of complications and for some may be fatal. Hypoxemia due to viral pneumonia is a prominent feature among those requiring hospitalization.

Soon after the pandemic began, it was recognized that some individuals continued to have persistent symptoms after recovery from the acute COVID-19 infection. Persistent symptoms are more likely after severe illness, although they may occur even after mild illness. Patients who were admitted to intensive care units (ICUs) have higher risks of persistent symptoms, including fatigue, chest tightness, anxiety, dyspnea, and myalgia.³ Patients with mild illness have a lower rate of ongoing symptoms most of which resolve within a year from diagnosis.⁴ Reinfection also carries an added risk for persistent symptoms.^{5,6} Ongoing symptoms can range from unpleasant to disabling and may affect the ability to perform activities of daily living as well as work.

PERSISTENT SYMPTOMS: DEFINITIONS AND PREVALENCE

Persistent symptoms, including those that emerge later and those that may remit and relapse, are commonly referred to as long COVID.⁷ This term was coined by a patient and is a useful shorthand descriptor. Several organizations have developed slightly varying definitions for ongoing symptoms after the acute illness including the National Institutes of Health (NIH), which uses the term postacute sequelae of SARS-CoV-2 infection (PASC),⁸ the Centers for Disease Control and Prevention (CDC), which uses post-COVID conditions,⁹ and the World Health Organization, which uses the term post-COVID.¹⁰ A limitation of these definitions is that they group conditions that may be triggered by different pathophysiologic processes as well as conditions seen in patients admitted to ICUs such as post-ICU syndrome¹¹ and posttraumatic stress disorder.

Estimates of the incidence and prevalence of long COVID vary widely. This may be due to varying time course and symptom definitions, reliance on self-selection for reporting, or studies in nonrepresentative populations. Surveys may also fail to distinguish between symptoms caused by COVID-19 and those

due to comorbid conditions. The CDC Household Pulse Surveys indicate that approximately 15% of US adults reported ever having experienced long COVID symptoms.¹² The CDC Household Pulse Survey in June 2023 revealed that 6% of US adults had long COVID, a decrease from 7.5% in June 2022.¹³ This overall prevalence includes adults who did not report having COVID-19. Among respondents indicating that they had COVID-19, 11% reported that they had ongoing symptoms of long COVID, a decrease from 18.9% in 2022.^{12,13} Of those with long COVID, approximately 25% indicated that they had significant impairment.^{12,13}

WORKFORCE AND WORKPLACE IMPACT

Long COVID is associated with an overall decrease in workforce participation. In 2022, it was estimated that between 1.8 and 4.1 million full-time equivalent workers were out of work in the US because of long COVID.¹⁴ Time out of work varies considerably depending on the time from the initial infection, severity of the initial infection,¹⁵ type of work, and professional categories¹⁶ (blue vs white collar workers). It may also differ based on other social determinants of health.

Among those previously employed, rates of permanent employment loss due to long COVID range from approximately 11% to approximately 14%.^{17,18} Early retirement has also been reported in relation to long COVID.¹⁹ Persons with long COVID who are seeking to re-enter the workforce are less likely to be employed full time, especially if they present with persistent cognitive symptoms.²⁰

Workers with long COVID may have decreased productivity, also known as dysfunctional presenteeism, and continue to work despite their symptoms, or return to work too early, sometimes against their physician's advice.^{19,21} Some may have to reduce their workload. Self-employed workers may need to hire additional staff to help them.¹⁹

Working relationships may deteriorate for workers presenting with long COVID.¹⁸ Some workers have reported lack of support from their coworkers or supervisors, dismissal of the reality of their symptoms, unfair treatment including harassment, or threats of disciplinary action.^{18,19} On one survey, almost 30% of workers with long COVID reported that they thought their condition affected their chances for promotion.¹⁸

PATHOPHYSIOLOGY OF SEVERE COVID-19

Many factors have been identified that increase the risk of severe acute COVID-19. These include older age,²² male sex,²³ elevated body mass index,^{24,25} diabetes,²² liver disease,²³ immunocompromised state,^{26–28} and genetic factors.^{29,30} Genetic associations include genes that affect immune functioning, inflammatory signaling, and endothelial permeability.^{29,30}

Severe acute COVID-19 increases the risk for long COVID, and the pathophysiology of severe illness may also contribute to persistent symptoms. This includes a high level of autoantibodies, some of which inhibit anti-inflammatory mediators and interferons,³¹ and high levels of antiphospholipid antibodies^{32,33} which may affect coagulation, worsen respiratory disease, and decrease kidney function.³³

SARS-CoV-2 also causes suppression of mitochondrial gene transcription. Even after lung mitochondrial function recovers, mitochondrial function in the heart, kidney, liver, and lymph nodes remained impaired.³⁴ Many cytokines are elevated in severe disease, including IL-6, which induces synthesis of several acute phase proteins.³⁵ These include amyloid and fibrinogen, which may contribute to thrombosis. In addition, the viral spike (S) glycoprotein may inhibit fibrinolysis and contribute directly to a hypercoagulable state with persistent microthrombi.³⁶ It can also cause vascular leakage³⁷ and endothelial damage.^{38–40}

PATHOPHYSIOLOGY OF LONG COVID

A variety of factors have been theorized to contribute to long COVID, including organ damage, direct viral toxicity, inflammation including vasculitis and endothelialitis, thrombosis, autoantibodies, decreased serotonin levels, and persistent replicating virus or viral fragments.^{40–46} Inflammatory mediators are elevated in many patients with long COVID including elevated markers of monocyte inflammation and complement activation² as well as type I interferon (IFN- β) and type III interferon (IFN- λ 1).⁴⁷ Elevated levels of IL-6 during acute illness may cause long-lasting changes in gene expression leading to ongoing production of inflammatory cytokines.⁴² Plasma samples from many patients contain large amyloid deposits in microthrombi, which are resistant to fibrinolysis.⁴⁸ Autoantibodies associated with severe acute COVID-19 may persist.

VACCINES, MONOCLONAL ANTIBODIES TREATMENTS, AND MEDICATIONS MAY REDUCE RISK OF PERSISTENT SYMPTOMS

COVID-19 vaccination and administration of anti-SARS-CoV-2 monoclonal an-

tibodies (mAbs) reduce the risk of severe acute infections.⁴⁹ They may also play a role in reducing the risk of persistent symptoms, possibly by reducing the incidence of severe COVID-19. Among more than half a million people in the two largest regions of Sweden, one, two, and three or more vaccine doses reduced post-COVID condition by 21%, 59%, and 73%, respectively.⁵⁰ In an observational analysis of more than 50,000 patients at eight Houston area hospitals, vaccines reduced the diagnosis of postacute sequelae of SARS-CoV-2 by more than 60% and mAbs by more than 50%.⁴⁹ However, mAbs are not currently available due to mutations of the SARS-CoV-2 virus, which have rendered them ineffective.

Medication treatment of acute illness has also been associated with a reduced risk of persistent symptoms. Treatment of patients with COVID-19 with oral nirmatrelvir:ritonavir within 5 days after a positive test for COVID-19 was associated with a 25% reduction of postacute sequelae in a large VA study.⁵¹ Reductions were seen for “people who were unvaccinated, vaccinated, and boosted, and in people with primary SARS-CoV-2 infection and reinfection.”⁵¹

In a clinical trial of adults aged 30 to 85 years with overweight or obesity who were treated as outpatients, individuals receiving a new prescription for metformin during the period of acute infection had a reduced incidence of long COVID of more than 40%.⁵² The observed benefits of metformin might be related to its *in vitro* activity against SARS-CoV-2, the inhibition of the release of interleukin-1 β and interleukin-18, or neuroprotective effects on dopaminergic neurons. In the same study, there was no benefit from the administration of fluvoxamine or ivermectin.⁵²

POSTINFECTION SYNDROMES

Postinfection symptoms and syndromes occur after a variety of infections and occur more often after severe infection. Many syndromes associated with SARS-CoV-2 infection are similar to those seen with other agents and pathogens. These include chronic fatigue, cognitive decline, olfactory dysfunction, thromboembolism, and insulin resistance.

A relatively uniform fatigue syndrome followed infection with the diverse agents Epstein-Barr virus, *Coxiella burnetii*, and Ross River virus affected a significant minority of patients for 6 months or more after infection.⁵³ The likelihood of this fatigue syndrome was associated with acute illness severity and not with demographic, psychological, or microbiological factors.⁵³ The severe acute respiratory syndrome (SARS) outbreak of 2002–2004, caused by SARS-CoV-1, also resulted in a chronic post-SARS syndrome including chronic fatigue, pain, weakness, depression, and sleep disturbance.^{54,55} Survivors

of Middle East respiratory syndrome (MERS), caused by another coronavirus, MERS-CoV, experienced a high rate of chronic fatigue.^{55,56}

Cognitive decline can occur after hospitalization for pneumonia.^{57,58} Among adults hospitalized for community-acquired pneumonia, moderate-to-severe impairment in multiple cognitive domains affected 38% of patients older than 65 years and 19% of younger patients 1 year later.⁵⁷

Postviral olfactory dysfunction has been described in association with rhinovirus, coronavirus, parainfluenza virus, and Epstein-Barr virus.⁵⁹ Olfactory dysfunction is often transient and resolves with the acute viral respiratory illness, but some may have protracted symptoms, and some may not regain their sense of smell.⁵⁹

Venous thromboembolism is increased by a variety of infections. Pneumonia, urinary tract, oral, intra-abdominal, and systemic blood stream infections were associated with substantially increased odds of venous thromboembolism in a case control study adjusted for common venous thromboembolism risk factors.⁶⁰

Several viruses increase systemic insulin resistance including influenza A, cytomegalovirus, and herpes simplex during acute infection.⁶¹ Beyond acute infection, a variety of respiratory and gastrointestinal infections increase insulin resistance, sometimes for more than 3 months after infection.⁶¹

Comparing patients with persistent symptoms after COVID-19 with patients who had influenza, nine symptoms (abnormal breathing, fatigue/malaise, chest/throat pain, headache, other pain, abdominal symptoms, myalgia, cognitive symptoms, and anxiety/depression) were reported after influenza and COVID-19 but were more frequent after COVID-19.⁶²

LONG COVID SYMPTOMS, SYNDROMES, AND CONDITIONS

An extensive list of symptoms may be associated with long COVID. Persons with long COVID may also have symptoms related to comorbid conditions, including post-ICU syndrome or posttraumatic stress disorder among those with severe acute COVID-19. Mental health disorders may also be present and need to be assessed and treated. It may be helpful to apply the biopsychosocial model, which suggests that “(l)ong COVID could be explained as an embodied condition with heterogeneous biological, psychological (experiential), and social (or environmental) factors integrated in complex relationships.”⁶³ Critics of this model raise the concern that this approach may lead to disregard of patient complaints that are perceived as primarily psychological.⁶⁴ However, properly applied, this approach should lead to more holistic care.

While patients may have clusters of symptoms, from a pragmatic perspective, it

is helpful to separate conditions to provide guidance related to specific aspects of long COVID.

Fatigue and Myalgic Encephalomyelitis/Chronic Fatigue Syndrome

Fatigue is frequently reported among those with continuing symptoms after acute COVID-19. It is important to distinguish whether fatigue is associated with myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) as recommendations for rehabilitation and accommodations may differ. Myalgic encephalomyelitis/chronic fatigue syndrome is also known as systemic exertional intolerance disease and the terminology is sometimes shortened to CFS. The diagnostic criteria for ME/CFS were defined by the Institute of Medicine (now the National Academy of Sciences) in 2015⁶⁵ and requires the following:

1. A substantial reduction or impairment in the ability to engage in preillness levels of occupational, educational, social, or personal activities that persists for more than 6 months and is accompanied by fatigue, which is often profound, is of new or definite onset (not life-long), is not the result of ongoing excessive exertion, and is not substantially alleviated by rest AND
2. Postexertional malaise AND
3. Unrefreshing sleep

At least one of the two following manifestations is also required:

1. Cognitive impairment OR
2. Orthostatic intolerance

Persons with ME/CFS may have a variety of additional symptoms including muscle or joint pain, headaches, lymphadenopathy, sore throat, night sweats, and sensitivity to odors.⁶⁶ Symptoms may vary over time.

Postural orthostatic tachycardia syndrome may occur as a component of ME/CFS or separately. Postural orthostatic tachycardia syndrome is a form of dysautonomia that “is characterized by an increase in heart rate of at least 30 beats per minute within 10 minutes of standing and symptoms of orthostatic intolerance, such as presyncope, palpitations, light-headedness, generalized weakness, headache and nausea, with symptom duration exceeding three months.”⁶⁷ Symptoms may be delayed with first occurrence 6 to 8 months after acute infection.⁶⁷

Several abnormalities have been identified in patients with CFS, including downregulation of the hypothalamic-pituitary-adrenal axis; a widespread state of neuroinflammation (particularly activation of microglial cells); autonomic nervous system abnormalities; im-

paired cellular energy generation; elevated blood cytokine levels; and a lower anaerobic threshold with exercise.⁶⁸ Increased levels of three plasma proteins that promote inflammation were observed in patients with fatigue 6 months after hospitalization for COVID-19. This set of elevated markers were also seen in patients with cardio-respiratory symptoms, and with anxiety and depression.²

Occupational medicine physicians may be asked to evaluate workers with fatigue after acute COVID-19 to assess their ability to work or recommend accommodations. Workers with fatigue should be evaluated with a thorough history, physical examination, and appropriate laboratory tests to determine whether there are other or additional causes of fatigue besides long COVID, including depression or sleep apnea.⁶⁹ As people may not be familiar with ME/CFS diagnostic criteria, some people who believe they have ME/CFS may not meet criteria, while others who do not recognize that they meet criteria may not be aware of the diagnosis.⁷⁰ Whether a worker meets criteria, it is important to determine whether they have exertional intolerance and postexertional malaise because this may affect performance and recommendations for rehabilitation. The American Academy of Physical Medicine and Rehabilitation Multi-Disciplinary PASC Collaborative developed consensus guidance for the assessment and treatment of fatigue after SARS-CoV-2 infection.⁸ The key elements of treatment programs include the following: (1) an individualized and structured, titrated return to activity program; (2) energy conservation strategies, (3) a healthy diet and hydration, and (4) treatment of any underlying medical conditions.⁸ Cognitive behavioral therapy was helpful to reduce severe fatigue in a small trial, although it is unclear whether any participants met criteria for ME/CFS.⁷¹

For workers with postural orthostatic tachycardia syndrome, nonpharmacologic approaches include volume repletion, compression hosiery, and exercise conditioning as tolerated.^{67,72} If symptom control is not achieved, medications that control heart rate, increase peripheral vasoconstriction, and increase intravascular volume may be helpful.⁶⁷

Accommodations should be individualized. The Job Accommodation Network publishes an extensive online list of accommodation ideas for workers with ME/CFS by limitations and by work-related functions.⁶⁶

“Brain Fog,” Neurological Symptoms, and Cognitive Impairment

While brain fog is not a medical diagnosis, the term is associated with a variety of medical conditions and treatments (eg, chemotherapy) and is widely used to describe a variety of cognitive symptoms, including issues

with memory, concentration, focus, and mental clarity.⁷³ Persistent cognitive dysfunction after acute SARS-CoV-2 infection is more likely in those with severe illness or who were admitted to the ICU, those with respiratory problems at the onset of infection, those with longer symptom duration, and for women.^{74–76} Among those hospitalized, moderate or severe cognitive deficits assessed with the Montreal Cognitive Assessment test were associated with elevated inflammatory markers 5 months after the acute illness.⁷⁷ Cognitive changes in those who did not feel that they had recovered from the initial illness persisted through almost 2 years of follow-up.⁷⁵

Brain imaging using magnetic resonance imaging and magnetic resonance imaging with diffusion tensor imaging have identified differences in brain structures between patients who have recovered from acute COVID-19 and controls.^{78–80} In one study, self-reported memory loss correlated with changes in total gray matter volume in general and at specific sites, along with global mean diffusivity of white matter.⁷⁹

Patients with neurologic symptoms after acute COVID-19 infection had “blood-brain barrier (BBB) impairment, elevated microglia activation markers, and a polyclonal B cell response targeting self-antigens and non-self-antigens”⁸¹ along with significantly higher median interferon γ in cerebrospinal fluid.^{81,82} Cognitive impairment after recovery from COVID-19 was associated with several elevated plasma markers that suggest neuroinflammation and tissue repair.²

Wong et al⁴⁴ hypothesize that some people with neurocognitive symptoms have reduced serotonin levels as a result of diminished intestinal absorption of the serotonin precursor tryptophan, and possibly other mechanisms. Reduced serotonin could impede the activity of the vagus nerve, resulting in impaired hippocampal responses and memory.⁴⁴

In some patients who report cognitive symptoms associated with COVID-19, standard cognitive tests may be normal. This may be because the tests are not sufficiently sensitive to detect their specific deficits or because the symptoms are driven by other mechanisms. In a small study involving 29 patients with persistent symptoms after acute COVID-19, including 79% reporting problems with memory and 93% with concentration complaints, the symptomatic group had similar performance on the NIH Toolbox batteries for cognition as the controls.⁸³ However, the symptomatic patients had poorer dexterity and endurance and higher scores for negative affect and perceived stress.⁸³ Similarly, in a study of 200 patients, an average of 125 days since a positive COVID-19 test, “self-reported neurologic dysfunction did not correlate with dysfunction on quantitative neurologic testing.”⁸⁴ However, self-reported cognitive symptoms were associated with depression and anxiety.⁸⁴

Occupational medicine physicians may be asked to evaluate workers who self-report cognitive issues and are requesting accommodations, for concerns about job performance problems that may be due to cognitive impairment, or because of safety concerns. Assessments should be individualized based on symptoms and time course. Testing of employees with performance concerns is permissible under the Americans with Disabilities Act and may be considered. Standard neurologic testing may be helpful. If standard testing is unrevealing, additional neuropsychological testing may be helpful. Regardless of whether cognitive testing is performed, assessment for depression, anxiety, and sleep disturbance should be pursued if indicated by history. Accommodations for employees with cognitive impairment might include “memory aids, changing work hours, or adjustment of work duties.”⁸⁵

Cardiovascular, Chest Pain, and Dyspnea

A variety of cardiovascular problems may occur during acute COVID-19 or less commonly with COVID-19 vaccination, which may result in ongoing health issues. These include myocarditis, myocardial infarction, coronary artery disease, Takotsubo syndrome, and heart failure.⁸⁶⁻⁹¹ There is also an increase in new diagnoses of hypertension.⁹² As with other conditions and symptoms, ongoing symptoms occur more frequently in those with more severe disease.⁸⁷ Among patients with severe COVID-19 requiring mechanical ventilation, the risk for arrhythmias, including ventricular tachycardia, atrial fibrillation, tachyarrhythmias, and bradycardia requiring pacemaker implantation, was substantially increased within 6 months of acute illness.^{86,93}

Chest pain is common among those with persistent symptoms and has a broad differential diagnosis.⁹⁴ While it is important to consider that cardiovascular disease may be the cause for chest pain, symptoms may arise from any structure in the chest and possibly the abdomen.⁹⁴

Chest pain and dyspnea may occur separately or together and may arise from the same or different processes. The differential diagnosis of dyspnea is also broad. In some cases, it may be due to pulmonary injury from the acute infection. Among patients hospitalized early in the pandemic, more than half had pulmonary scarring, thickening, or fibrosis on computed tomography scans at 6 months and one-third still had lung abnormalities 2 years later.⁹⁵ Many patients also have decreased diffusing capacity.^{95,96} Another possible cause of exertional dyspnea is diaphragm muscle weakness, which has been reported in patients who did and did not require mechanical ventilation.⁹⁷

Along with treatment for diagnosable conditions, cardiac rehabilitation⁹⁸ or pulmonary rehabilitation⁹⁸ is recommended for appropriate patients.⁹⁹ Rehabilitation usually involves gradually increasing exercise, although patients with myocarditis may require a 3- to 6-month period of complete rest.⁹⁹ Rehabilitation interventions have been associated with improved quality of life.¹⁰⁰

Workers with cardiovascular or pulmonary disease may have substantial limitations in their ability to perform some job functions effectively or safely. In determining the need for restrictions, it is important to have full information on the specific diagnosis (or diagnoses), medications, treatments, and time course. While most workers may be able to perform sedentary jobs, there may be limitations for jobs that require exertion or the ability to respond quickly during emergencies. For workers with pulmonary disease who are required to wear a respirator, powered air-purifying respirators may be a good alternative to N95 respirators.¹⁰¹

Anosmia/Parosmia/Ageusia

Loss of or distorted sense of smell (anosmia, parosmia) and loss of sense of taste (ageusia) have been frequently reported in association with COVID-19. The mechanism of injury seems to involve systemic inflammation and infection of cells surrounding olfactory neurons, which results in downregulation of olfactory receptors and their signaling components,¹⁰² and endothelial injury of the microvasculature in olfactory tissue.¹⁰³

In 2021, approximately 60% of those infected from the beginning of the pandemic reported experiencing smell or taste disturbance.¹⁰⁴ Full recovery of smell and taste was reported by 72% and 58%, respectively, while 3.7% and 2.6% had not improved.¹⁰⁴ In another study, 88% of patients with anosmia or ageusia completely recovered within 2 years, including 11% with a late recovery.¹⁰⁵ By 3 years, half of those who had anosmia at 2 years had resolution of symptoms.¹⁰⁶ Those infected with more recent Omicron variant of SARS-CoV-2 are at a significantly lower risk of developing chemosensory loss than those infected with the initial virus or the alpha or the delta variants.¹⁰⁷

Workers may require the ability to smell/taste to perform job tasks or to detect hazardous conditions. Jobs that require an average or heightened sense of taste include food scientists, food analysts, food technicians, food tasters, food critics, sommeliers, chefs, and others involved in food preparation. Workers with impaired olfactory function may also be unable to smell gas leaks or fires.¹⁰⁸

For workers who require the ability to taste or smell, accommodations may be challenging. They may need to perform a different role until they recover. Workers who require

the ability to smell to detect hazardous chemicals may be able to be accommodated by having a coworker present when odor detection is essential or using an alternative detection system that does not require the sense of smell.

If needed, workers can be referred to an otolaryngologist for smell or taste testing and olfactory training.¹⁰⁹ Olfactory training was associated with improved smell scores for approximately half of COVID-19 patients in 3 weeks, which was not further improved by the addition of intranasal steroids.¹¹⁰ In a clinical trial, gabapentin was also found not to be effective.¹¹¹

Diabetes

Type 2 diabetes is diagnosed more often in patients after COVID-19 than in those who were not infected. Estimates vary widely, with studies suggesting an increase in new diagnoses of 20% to 100%.¹¹²⁻¹¹⁵ Increased severity of infection is associated with a greater risk of developing diabetes.¹¹³ Reinfection is also associated with an increase in diagnoses.⁶ It is unclear to what extent these new diagnoses represent an acceleration of the clinical manifestations of diabetes in those who would have eventually developed diabetes.⁴¹

While some new diagnoses may be opportunistic because of increased contact with the healthcare system, there are several possible mechanisms that could underlie a real increase in incidence.¹¹⁵ These include insulin resistance caused by proinflammatory cytokines,⁶¹ elevation of hormones like GP73, which can cause hyperglycemia through increased hepatic glucose production,¹¹⁵ and a direct effect of the virus on pancreatic β -cells.¹¹⁵

Workers with diabetes may need accommodations based on the specific circumstances of their condition and treatment. Because this is newly diagnosed diabetes, they may not have the complications of chronic diabetes, including ophthalmopathy, neuropathy, and nephropathy. However, they may have poorly regulated blood glucose levels, including medication-related hypoglycemia. This may create a safety risk, depending on the job, which needs to be assessed. Workers may also need accommodations for breaks, meals, schedules, and time off for medical visits.

Gastrointestinal Disorders

Approximately one in six patients with acute COVID-19 experience nausea, vomiting, diarrhea, or abdominal pain.¹¹⁶ Fecal tests for SARS-CoV-2 RNA were positive in approximately half of patients.^{117,118} Even after patients no longer shed RNA from the oropharynx, approximately one in eight patients were shedding SARS-CoV-2 RNA in the feces at 4 months and approximately 4% were still shedding RNA at 7 months.¹¹⁷ However, it is unclear to what extent this indicates the presence of replication-competent viruses.¹¹⁹

In a large study of Veterans Health Administration patients in the postacute phase of COVID-19, Xu et al¹²⁰ reported “increased risks and 1-year burdens of incident gastrointestinal disorders spanning several disease categories including motility disorders, acid related disorders (dyspepsia, gastroesophageal reflux disease, peptic ulcer disease), functional intestinal disorders, acute pancreatitis, hepatic and biliary disease.” The likelihood of persistent symptoms increased with increasing severity of the acute illness.¹²⁰ In another study of hospitalized patients 12 months after hospital discharge, a diagnosis of irritable bowel syndrome was six times higher than for hospitalized patients without COVID-19.¹²¹ In patients with gastrointestinal symptoms 6 months after hospitalization for COVID-19, increased levels of three plasma proteins were observed that promote inflammation and are associated with dysregulation of the brain-gut axis.²

Workers with inflammatory bowel disease or irritable bowel syndrome may need accommodations for schedules and breaks. If a worksite has a cafeteria, it would be helpful if available options include foods compatible with a low FODMAP (fermentable oligosaccharides, disaccharides, monosaccharides, and polyols) diet. Because some workers with inflammatory bowel disease may be taking immunosuppressive medications, restrictions or accommodations may be needed if there is potential for concerning exposure.

Thromboembolic Disorders

SARS-CoV-2 infection induces a prothrombotic state. The incidence of arterial thrombosis and venous thromboembolic events after the diagnosis of COVID-19 are relatively high soon after COVID-19 diagnosis.¹²² The risk declines for arterial thrombosis; however, the risk for venous thromboembolic events remains elevated for at least 49 weeks after the COVID-19 diagnosis.¹²² This prolonged increase in risk is primarily seen in hospitalized patients.^{122,123}

Thromboembolic disorders associated with acute COVID-19 can lead to ongoing symptoms. These include arterial or venous thrombosis that can cause ischemic stroke, myocardial infarction, mesenteric ischemia, limb ischemia, deep vein thrombosis, and pulmonary embolism (PE).¹²⁴

The pathophysiology of the thromboembolic events in long COVID is mediated in part by extracellular vesicles released intravascularly by various cells harboring SARS-CoV-2 virus that can affect distant tissues and organs.¹²⁵ The extracellular vesicles can also release tissue factor and phosphatidylserine, which increase thrombosis.¹²⁵ With viral persistence, chronic inflammation, and endothelial damage, pulmonary structural changes occur, which can result in hypertension, embolism, and fibrosis.¹²⁵ Chronic hypoxemia

can further exacerbate vascular inflammation and induce coagulation abnormalities.¹²⁵

The NIH Treatment Guidelines for COVID-19 recommends against routinely prescribing venous thromboembolism (VTE) prophylaxis for nonhospitalized patients with COVID-19 or continuing VTE prophylaxis in patients with COVID-19 after hospital discharge unless there is another indication for anticoagulation.¹²⁶ It is possible that selected high-risk patients who have a low risk of bleeding may benefit from postdischarge anticoagulation if they have a history of VTE, peak D-dimer level greater than 3 $\mu\text{g/mL}$, and predischARGE C-reactive protein level greater than 10 mg/dL .¹²⁷

Workers on anticoagulants should avoid tasks that can potentially increase the risk of bleeding. Substitution of jobs or tasks is recommended. For workers with deep vein thromboses, prolonged sitting should be avoided, and adequate hydration should be maintained.

Autoimmune Disease

Acute COVID-19 is associated with development of a wide variety of autoantibodies.¹²⁸ These include many autoantibodies that are associated with autoimmune diseases.¹²⁹

In a study of 33 patients with severe acute COVID-19, one third tested positive for antinuclear antibodies and one-fourth tested positive for anti-antiphospholipid antibodies.¹³⁰ In another study, patients had higher detectable antinuclear antibodies at 3 months after developing COVID-19, compared with age- and sex-matched healthy controls.⁴³

Along with the development of autoantibodies, COVID-19 is associated with an increased risk of developing new-onset autoimmune diseases.^{131–133} Among those without a preexisting autoimmune disease, higher rates of new diagnoses of many autoimmune conditions were made 3 to 15 months after acute COVID-19 compared with those without SARS-CoV-2 infection. Increased risks were seen for Graves disease, Hashimoto thyroiditis, rheumatoid arthritis, systemic lupus erythematosus, ankylosing spondylitis, systemic sclerosis, Sjögren syndrome, mixed connective tissue disease, Behçet disease, dermatomyositis, polymyalgia rheumatica, and vasculitis.^{131,132} Risk increased with increasing severity of the acute illness.¹³² Persons with preexisting autoimmune disease and COVID-19 also had an increased chance of being diagnosed with another new autoimmune disease.¹³²

Workers with autoimmune diseases may or may not need accommodations or restrictions. This will depend on the disease status, nature of the job (including, but not restricted to, exposure to biological hazards), the specific diagnosis, comorbid conditions, the presence of any disease specific functional limitations, and whether they are taking immunosuppressive medications.

DISABILITY LAWS AND REGULATIONS

Long COVID may be considered a disability under civil rights laws that protect people with disabilities from discrimination. Administration of these laws is overseen by the Equal Employment Opportunity Commission.¹³⁴ They include the Americans with Disabilities Act¹³⁵ as amended,¹³⁶ which applies to employers including state and local governments, and Section 504 of the Rehabilitation Act of 1973,¹³⁷ which applies to the federal government. Under these laws and regulations, a person with a disability is an individual with a physical or mental impairment that substantially limits one or more of the major life activities.¹³⁸ This includes having an actual disability, having a record of a disability, or being regarded as having a disability.¹³⁸ Employers covered under these acts must make reasonable accommodations for persons with a disability.^{135–137}

The analysis of whether a person with long COVID has a disability and the process for determining whether requested accommodations are reasonable is the same as for any form of disability. Requests for accommodations are initiated by employees, who may be asked to provide medical documentation. Guidance on long COVID as a disability under antidiscrimination laws has been released by the US Department of Health and Human Services.¹³⁸ In some cases, occupational medicine physicians may be asked about accommodations or restrictions. The Job Accommodation Network publishes an online guide that provides suggestions for accommodations based on symptoms, limitations, and job functions for persons with long COVID.¹³⁹

WORKERS' COMPENSATION AND COVID-19

Workers' compensation laws provide coverage for work-related injuries and illnesses that arise out of and occur in the course of employment. Benefits cover the medical costs and partial salary replacement for time lost from work. Coverage and rules vary by state, and it is important to note the compensability under these statutes do not necessarily equate to medical or scientific causation. There are also separate federal programs for federal employees and some industries such as railroad workers, covered under the Federal Employers Liability Act, and maritime industries, covered under the Longshore and Harbor Workers' Compensation Act. Workers' compensation is no-fault insurance, meaning that employees do not have to prove negligence on the part of the employer. However, employers can challenge claims based on whether they meet the legal requirements.

In the early phases of the COVID-19 pandemic, many states used legislation, directives,

emergency rules, and/or executive orders to create presumptions that workers who developed COVID-19 were covered by workers' compensation.¹⁴⁰ However, these presumptions were rebuttable, meaning that employers can still challenge coverage, but they "shift the burden of proof to employers, who must present evidence that a covered employee did not contract COVID-19 in the workplace."¹⁴¹

From 2020 through 2022, many states established presumptions, including some that established a more general "infectious disease presumption."^{140,142} There is wide variation in which workers are covered by the presumption and how long the changes would remain in effect. Many of the state-based presumptions incorporated a statute of limitations and have expired. The presumptions also did not extend the filing time for claims, which vary by state and are often 1 or 2 years. Workers in states without presumptions can still file claims but may have a greater challenge in demonstrating that their infection was acquired at work.

A study of the Workers' Compensation Research Institute's Benchmark Evaluation database assessed workers' compensation claims for long COVID from 31 states from March 2020 and September 2021.¹⁴³ The average cost of a long COVID claim was approximately \$29,000, approximately 10 times greater than the cost for claims for acute COVID-19. Between 2% and 8% of claimants had long COVID in 29 states, while 10% of claimants in California and Oregon had long COVID.¹⁴³

An analysis of COVID-19 workers' compensation claims in New York State initiated by March 2022 identified 977 accepted claims for long COVID of 3139 paid COVID-19 claims.¹⁴⁴ Most of these occurred during the first peak of the pandemic. While 40% returned to work within 60 days of infection, 18% of workers with long COVID could not return to work for more than 1 year. The majority of workers with long COVID claims were employed in healthcare, law enforcement, or public administration.¹⁴⁴

CAUSATION ANALYSIS FOR LONG COVID IN THE CONTEXT OF WORKERS' COMPENSATION

Workers may file a workers' compensation claim seeking to demonstrate that long COVID is due to COVID-19 acquired in the workplace. Employers or their representatives may argue that the condition was acquired in the community or that a worker's symptoms are not due to COVID-19. When these situations arise, whether in the context of a treating physician role, independent medical evaluation, or independent file review, a medically sound and scientific approach should be taken for the occupational medicine physician to provide a rational opinion.

There are several steps for the determination of work-relatedness of a patient's disease. The National Institute for Occupational Safety and Health,¹⁴⁵ the American Medical Association,¹⁴⁶ and American College of Occupational and Environmental Medicine^{147,148} have adopted a six-step approach to these questions:

- 1) Identify evidence of disease,
- 2) Review and assess the available epidemiological evidence for a causal relationship,
- 3) Obtain and assess the evidence of exposure,
- 4) Consider other relevant factors,
- 5) Judge the validity of testimony, and
- 6) Form conclusions about the work-relatedness of the disease in the person undergoing evaluation.

To satisfy these criteria, verifying the diagnosis of acute COVID-19, determining whether the infection was acquired at work, and ascertaining that the symptoms are a consequence of COVID-19 are critical.

Verifying the diagnosis of COVID-19 may be straightforward if positive test results are available and more challenging if they are not. The availability of PCR testing early in the pandemic was limited and home-based antibody tests became widely available later, which may not have been verified or memorialized. In the absence of verified test results, a documented medical diagnosis may be helpful. The presence of antibodies to the SARS-CoV-2 nucleocapsid protein (anti-N Abs) is also evidence of prior infection because vaccines available in the US targeted only the spike (S) protein, but a negative test does not rule out past infection. An observational study showed that anti-N Abs median levels peak between 90 and 119 days after infections and wane afterward.¹⁴⁹ Waning can occur earlier, especially in females and in younger age categories. Anti N-Abs have an estimated half-life of approximately 283 days.¹⁵⁰ Only 80% of individuals with a positive PCR test up to 269 days before serology sampling were found to test positive for anti-N Abs.¹⁴⁹

Once the diagnosis has been confirmed, the determination of whether the infection was acquired at work is analyzed. Factors to consider include:

- 1) A known exposure to a co-worker or patient who tested positive, particularly in a closed or indoor setting.¹⁵¹
- 2) Whether there were clusters of employees infected with COVID-19 at the time the worker became infected.¹⁵²
- 3) Whether an exposure was identified through contact tracing.¹⁵³
- 4) Whether work practices could have produced exposure to SARS-CoV-2.¹⁵⁴
- 5) Whether the specific occupation has a higher risk of SARS-CoV-2 infections

compared with other occupations (eg, personal care and services workers, health-care practitioners and support staff, and protective services workers).¹⁵⁵

6) Absence of an alternative non-work exposure at home or in the community, although an alternate exposure source does not negate the possibility of a work-acquired infection.¹⁵⁶

After establishing the work-relatedness of an infection, a determination must be made whether current symptoms are the result of long COVID. This can be a challenge because many medical conditions can mimic long COVID symptoms.¹⁵⁷ Medical records, including those from a long COVID clinic, that contain a diagnosis of long COVID, or conditions associated with long COVID, may be helpful.

FUTURE RESEARCH

Long COVID presents a significant challenge for workers and employers. Future research could address how often workers are fully disabled, how often workers require accommodations, and what accommodations are provided. Because the SARS-CoV-2 virus is continually mutating, it would be of interest to understand how long COVID changes over time and is affected by different variants. It would also be helpful to understand how workers' compensation systems address long COVID claims and how often workers with long COVID utilize short- and long-term disability. In addition, because some patients have improvement in symptoms, it would be valuable to track return to work status for these individuals over time.

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