CME

Emerging research on postacute COVID-19 complications

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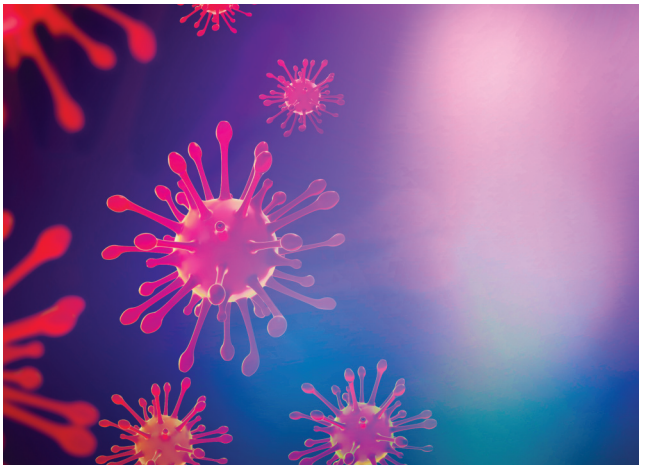
ABSTRACT

An estimated 21.5% of patients in the United States who have had COVID-19 report development of a prolonged postviral syndrome that has been called postacute sequelae of COVID-19 (PASC). Symptoms can range from very mild to debilitating damage to organ systems caused directly by the virus and indirectly by the body's inflammatory response. Research into defining PASC and discovering effective treatments is ongoing. This article discusses the common presentations of PASC in patients who have had COVID-19; describes specific effects on the pulmonary, cardiovascular, and central nervous systems; and identifies potential treatments based on current literature.

Keywords: COVID-19, complications, postacute, long COVID, postacute sequelae of COVID, PASC

Learning objectives

- Recognize the common symptoms associated with PASC.
- Understand the potential long-term effects of COVID-19 on the pulmonary, cardiovascular, and central nervous systems.
- Identify recommended treatment options for PASC as defined by current literature.



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According to the CDC, more than 104 million cases of COVID-19 and more than 1.1 million related deaths have occurred in the United States since COVID-19 first emerged in December 2019.[1] With more than 230 million people (69.4% of the total population) fully vaccinated in the United States, life has returned to some semblance of normalcy for most, even as new and some more virulent variants of COVID-19 continue to emerge and circulate.[1] The constellation of symptoms that make up postacute sequelae of COVID-19 (PASC) was identified early in the pandemic through social media support groups by patients who had recovered from COVID-19 but experienced new or persistent symptoms.[2] PASC was not recognized in peer-reviewed literature until several months into the pandemic and was only identified in case reports at that time because of limited scientific knowledge of COVID-19.[2] Since then, PASC has become a more well-defined syndrome that can be diagnosed when symptoms persist at least 4 weeks after infection with COVID-19.[3] Although anyone infected with COVID-19 can develop PASC, data suggest that patients who have more severe acute illness are more likely to develop PASC than those who experience mild acute illness.[3] Different patterns of onset of PASC demonstrate the variability of post-COVID-19 conditions.[4] Early studies on patients who recovered from an acute COVID-19 infection have shown inflammatory infiltration in the heart, lungs, intestines, and kidneys, supporting the hypothesis that the systemic inflammatory response syndrome associated with COVID-19 leads to persistent injury to multiple organ systems.[5] Some patients may experience persistence or evolution of symptoms that originated during the acute phase of COVID-19.[4] Others may develop new-onset conditions following a period of remission or asymptomatic infection, and some develop worsening of preexisting symptoms or conditions.[4] Some patients with PASC may share similar clinical presentations as those with other postinfectious syndromes, including myalgic

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Key points

- PASC is a syndrome with a wide variety of symptoms, ranging from mild to debilitating.
- PASC can affect adults and children, many of whom were previously healthy.
- Treatment for PASC should be individualized, multidisciplinary, and patient-focused based on each patient's constellation of symptoms.

encephalomyelitis/chronic fatigue syndrome (ME/CFS), postural orthostatic tachycardia syndrome (POTS) and other forms of dysautonomia, or mast cell activation syndrome.[4]

Although some patients experience mild postviral symptoms such as persistent cough and fatigue, others suffer severe irreversible damage to the heart, lungs, and central nervous system (CNS). The pathophysiologic mechanism by which the SARS-CoV-2 virus causes PASC likely is multifactorial, as evidenced by the variability in clinical presentation.[6] Pathophysiologic theories include direct effects of the SARS-CoV-2 virus causing organ injury, persistence of the virus in body tissues, new autoimmunity, altered coagulation, autonomic dysfunction, reactivation of other latent pathogens (such as Epstein-Barr virus), iatrogenic effects of treatment (mechanical ventilation, supplemental oxygen, corticosteroids), and exacerbation of comorbid health conditions.[6]

About 10% of patients with a history of COVID-19 experience PASC, also referred to as long COVID or post-COVID-19 syndrome.[3] According to the National Institutes of Health (NIH) RECOVER (Researching COVID to Enhance Recovery) initiative, commonly reported symptoms include cough, dyspnea, body aches, headaches, fevers, disturbance in taste/smell, altered sleep, fatigue, and mood changes.[7] Symptoms may be intermittent, and duration may be weeks, months, or longer.[7] The duration of PASC is unknown and will be defined over time with additional studies. Some studies have shown persistence of at least one symptom in more than half of patients at 110-day follow-up.[3] PASC can even affect young adults who experienced mild symptoms during infection and did not require hospitalization for COVID-19; PASC also can manifest in children, many of whom had asymptomatic COVID-19 infections.[8] Although COVID-19 and PASC are still relatively new phenomena, they have shown similarities to other well-documented viral respiratory illnesses, such as Middle East respiratory syndrome (MERS) and severe acute respiratory syndrome (SARS), which caused similar postviral disorders including ME/CFS. Of patients with PASC, an estimated 50% meet criteria for ME/CFS.[6]

Studies of survivors of SARS or MERS have shown that even 15 years after acute illness, some patients, mostly under age 40 years, still had lung and bone radiologic complications.[8] If PASC follows a similar pattern, clinicians will be treating the complications of this illness for many years to come.

PULMONARY COMPLICATIONS

Pulmonary manifestations are among the most reported symptoms of PASC in adults.[9] As more people are infected with and recover from COVID-19, clinicians are faced with a growing number of patients who have persistent breathing problems and radiologic abnormalities for months after recovery.[10] In a nationwide survey in the United Kingdom, 40% of patients reported five or six persistent symptoms, with breathing problems being among the most commonly reported.[10] Radiologic abnormalities are prevalent in post-COVID-19 lung disease; residual ground-glass opacities were seen in 63% of patients and fibrotic lesions were seen in 19% of patients at 4 months in one study.[10] Several studies following post-COVID-19 patients have found regression of radiologic abnormalities over time.[10] Additionally, pulmonary function testing may show diffusion abnormalities and restrictive patterns (decreased forced vital capacity and decreased total lung capacity), which stabilize or improve over time.[10] Postviral lung disease has been studied in relation to other respiratory illnesses including influenza, SARS, and MERS. This information may be useful for predicting the biologic mechanisms and treatments for post-COVID-19 lung disease. Development of post-COVID-19 lung disease may be related to direct viral effects on the lungs, iatrogenic effects, and deconditioning.[10] Specific pathophysiologic theories include upregulation of proinflammatory cytokines and increased oxidative stress on lung tissue, viral interaction with the renin-angiotensin system, oxygen toxicity, and ventilator-induced lung injury.[11] Risk factors for post-COVID-19 lung disease may include preexisting comorbidities, length of ICU or hospital stay, obesity, invasive and noninvasive mechanical ventilation, and elevation of inflammatory biomarkers (C-reactive protein, lactate dehydrogenase, and fibrinogen).[10]

Definitive treatment recommendations for post-COVID-19 lung disease are still uncertain and research is ongoing. Because post-COVID-19 conditions are poorly understood, clinicians are encouraged to engage in shared decision-making conversations with patients and to set goals based on achieving better daily functioning and quality of life.[4] Progress and goals should be reassessed as new treatment recommendations emerge.[4] Care of patients with PASC should involve an interprofessional team that may include medical management; physical and occupational therapy; speech/language therapy; neurologic rehabilitation; physical rehabilitation; and counseling to address nutritional, sleep, and stress problems.[4] Some potential medical treatments include corticosteroids; antifibrotic agents; pulmonary rehabilitation; vaccination against COVID-19, influenza, and pneumonia; and lung transplantation.[11] Corticosteroids are part of the standard

of care for hospitalized patients with severe COVID-19, often as moderate to high doses of dexamethasone. Few studies have investigated the efficacy of continuing lower-dose corticosteroids after discharge, but this has been suggested to prevent evolution into organizing pneumonia.[10] One observational study of 30 patients selected to receive corticosteroid taper over 3 weeks reported subjective improvement in symptoms, which was correlated with improved CT findings and pulmonary function testing.[12] This study is limited by the small cohort of patients and lack of control group for comparative analysis. Therefore, further research is necessary to develop recommendations for the use of corticosteroids for post-COVID-19 lung disease.

Antifibrotic agents such as pirfenidone and nintedanib (which are approved for idiopathic pulmonary fibrosis) may be useful during or after COVID-19 infection to prevent pulmonary fibrosis, but further investigation is warranted before these drugs can be recommended for antifibrotic use in all patients with post-COVID-19 lung disease.[10]

Pulmonary rehabilitation is recommended in the hospital and after discharge for patients with moderate to severe COVID-19 infection, based on multiple observational studies showing improved pulmonary function and quality of life.[10] The American Thoracic Society recommends assessment 6 to 8 weeks postinfection and comprehensive rehabilitation for patients experiencing new or persistent breathing symptoms.[10] Lung transplantation may be an option in select patients who fail to wean off of ventilatory support or in patients with significant limitations and oxygen dependence, but criteria for transplantation are controversial.[10] Some transplant physicians suggest that if other treatments are not effective, patients with post-COVID-19 interstitial lung disease or other forms of progressive interstitial lung disease can be considered for lung transplant.[13] Lung transplant should be reserved for patients with progressive disease or significant disability.[13]

CARDIOVASCULAR COMPLICATIONS

Patients who have had COVID-19 are susceptible to developing persistent cardiac injury after infection.[5] Manifestations of COVID-19-related cardiac injury include myocarditis, dysrhythmias, acute coronary syndrome, systolic heart failure, and cardiogenic shock.[14] Viral infections are a common cause of acute myocarditis through direct interaction with cardiomyocytes and indirectly via cytokine release, inflammation, and immune response.[5] Myocarditis is now recognized as a complication of COVID-19 and affects a significant number of patients during and after acute illness.[14] Patients who develop myocarditis are at risk for severe complications because of myocardial inflammation, which can lead to decompensation.[14] Patients may experience dysrhythmias and cardiogenic shock, ultimately requiring treatment with inotropic medications and other circulatory support such as extracorporeal membrane oxygenation.[14] Patients who develop myocarditis may require longer hospital stays, need mechanical ventilation, and have higher mortality.[14]

Even after patients with serious acute complications are stabilized, they are at risk for developing chronic heart failure caused by myocardial injury and inflammatory cardiomyopathy.[5] The prothrombotic state associated with severe COVID-19 infection also is thought to lead to pulmonary embolism, resulting in acute right-sided heart failure.[15] The acute respiratory distress syndrome and parenchymal lung disease caused by COVID-19 also lead to pulmonary hypertension and new right-sided heart failure.[15] Overall, a new diagnosis of heart failure was seen in up to a quarter of patients hospitalized for COVID-19 who did not have a history of heart failure.[15]

Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) may affect the course of COVID-19.[16] This is because the SARS-CoV-2 spike protein binds to ACE2 in the lungs, small intestine, and heart.[15] Because ACE inhibitors upregulate ACE2 receptors, researchers were initially concerned that ACE inhibitors might make patients more prone to worse outcomes if they contracted the virus.[15] This association was investigated in a multicenter observational study of hospitalized patients with COVID-19 who continued ACE inhibitor/ARB treatment during hospitalization.[16] The study found that taking an ACE inhibitor or ARB was associated with lower levels of inflammation and better in-hospital outcomes.[16] Current guidelines recommend continued use of ACE inhibitors or ARBs in patients with an indication for their use.[16]

CNS AND NEUROCOGNITIVE COMPLICATIONS

COVID-19 infection also can cause acute and long-term neurologic symptoms including headache, insomnia, and psychosis.[17] The virus is thought to cause neurologic impairment directly by damaging the neuronal pathway and indirectly through hypoxia, hypertension, coagulopathy, cytokine storm in the CNS, and worsening preexisting conditions.[18] Headache is a common symptom of COVID-19 infection and often is resistant to typical treatment methods including acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), and classic migraine medications.[19] Headache also is a prevalent symptom in PASC, affecting 10.6% of patients at 90 days after acute infection.[20] A recent meta-analysis showed that the prevalence of persistent headache in patients who have recovered from COVID-19 infection was 8% to 15% in the first 6 months.[20] These headaches can present as new daily persistent headaches and migraine-type headaches in patients with or without a history of primary headache disorders.[21] COVID-19 also has been shown to trigger new migraine syndromes in patients without a history of migraines.[21] A

recent study found SARS-CoV-2 proteins in the trigeminal nerves, suggesting that the virus activates the trigeminovascular system.[21] Headaches in patients with PASC often are associated with other neurologic symptoms including insomnia, dizziness, brain fog, and fatigue.[18,21] No consensus exists about effective treatment for headaches related to COVID-19 because they often are refractory to typically recommended treatments. Headache associated with COVID-19 has been shown to have only a partial response to first-line analgesics.[19]

In addition to persistent headache, several other neurologic symptoms have been noted in patients with COVID-19 and PASC; the most common are mental fog, persistent anosmia and ageusia, and fatigue.[17] Less commonly and in more severe cases, patients can experience delirium, psychosis, encephalitis, and ischemic and hemorrhagic strokes.[17] COVID-19 can act indirectly and directly on the CNS. Indirectly, COVID-19 activates the inflammatory cascade and causes a cytokine storm that can damage healthy organs as it fights the virus.[17] COVID-19 RNA and COVID-19 antibodies also have been found in cerebrospinal fluid, suggesting that the virus is able to enter the CNS directly.[17] One hypothesis is that the virus can travel through the olfactory nerves to the brain and reach the ACE2 receptors on neurons.[17]

Patients who recover from their initial infection may be left with persistent anosmia and ageusia, which can continue to disrupt their eating habits and quality of life. Up to 10% of patients report persistent dysfunction of smell and taste sensation after COVID-19 infection.[22] Patients who experience these persistent symptoms often report decreased appetite, weight loss, social stress, and altered relationship with food.[22] Patients may experience a lack of enjoyment or even a repulsion toward food and beverages because of their altered senses. These patients may even develop dietary deficiencies related to decreased oral intake of nutrients.[22] Many aspects of our social lives revolve around sharing meals, so these patients may feel frustrated, depressed, or isolated.[22] Anosmia and ageusia often are overlooked as less serious complications of COVID-19, especially compared with severe complications related to the cardiovascular and pulmonary systems. Sensory deficits may lead to physical and psychosocial issues for patients with these persistent symptoms.

COMPLICATIONS IN CHILDREN

Children infected with COVID-19 tend to be asymptomatic or have only mild symptoms associated with the illness.[23] Fewer than 0.2% of children infected with COVID-19 were hospitalized and fewer than 0.03% died.[23] Hospitalization rates were doubled in children who were not vaccinated compared with those who were vaccinated.[24] CDC data report an incidence of multisystem inflammatory syndrome in children (MIS-C) of 1 in 3,000 to 4,000 children diagnosed with COVID-19.[25] Persistent postviral symptoms consistent with PASC have been reported in children; the World Health Organization defines pediatric PASC as one or more new or persistent physical symptoms lasting at least 12 weeks after COVID-19 infection; these symptoms fluctuate and impair daily function.[26] A recent meta-analysis found that 25% of children experienced PASC symptoms lasting more than 4 weeks post-infection; another study found a prevalence of PASC symptoms lasting more than 90 days in children of 2% to 5%.[26] Evaluation of children with PASC should focus on returning them to healthful lifestyle habits as well as ruling out other causes of reported symptoms such as thyroid dysfunction, anemia, Epstein-Barr virus, or vitamin D deficiency.[26] Consultation with a multidisciplinary team or post-COVID-19 clinic may be considered for patients whose symptoms persist beyond 12 weeks and affect normal function.[26]

CONCLUSION

COVID-19 continues to have a large effect on the US healthcare system and will affect many aspects of healthcare for years to come. Studies and programs such as the NIH RECOVER initiative continue to work to understand symptomatology, pathophysiology, and treatment of PASC.[7] Treating patients with PASC requires a holistic approach and multidisciplinary team to address the wide variety of symptoms that patients may experience.[4] Treatment decisions should involve shared decision-making with patients and should be reevaluated as new research emerges.[4] Patients may benefit from self-care, traditional medications, various modalities of therapy, and post-COVID-19 clinics.[4] Knowledge of the long-term effects and possible treatments for the various symptoms will likely be evolving for years to come and will be important for the continuing care of these patients. **JAAPA**

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