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Postacute Sequelae of Severe Acute Respiratory Syndrome Coronavirus 2 Infection

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KEYWORDS

• COVID-19 • SARS-CoV-2 • Postacute sequelae of SARS-CoV-2 infection (PASC) • Long COVID • Long-haul COVID • Postacute COVID-19

KEY POINTS

- Postacute sequelae of SARS-CoV-2 (PASC) infection or long COVID is a heterogeneous, multisystem, relapsing and remitting illness that can affect patients infected with SARS-CoV-2 regardless of the severity of the acute infection.
- Estimates of the incidence and prevalence of long COVID symptoms vary widely across published studies.
- The diagnosis of long COVID is currently primarily based on history and physical examination and may require a multidisciplinary approach to care.
- The overall approach to the treatment of long COVID is to focus on symptom management, functional goals, and improvements in the quality of life.

INTRODUCTION

The clinical spectrum of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection ranges from asymptomatic to critical illness, which may include severe sepsis and acute respiratory failure.[1] When symptomatic, acute coronavirus disease 2019 (COVID-19) illness will typically last days to weeks, and most of the symptoms are thought to be mediated by the replication of the virus and the initial immune response to the infection.[2] As the COVID-19 pandemic continues, it has become increasingly clear that clinical sequelae and symptoms may persist for weeks to months beyond the acute stage of SARS-CoV-2 infection for a significant proportion of patients. This chronic illness has been termed postacute sequelae of SARS-CoV-2 (PASC) infection, post-COVID syndrome, or long COVID. A less common postacute hyperinflammatory illness (multisystem inflammatory syndrome in children [MIS-C] and multisystem

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inflammatory syndrome in adults [MIS-A]) has also been characterized. MIS-C and MIS-A will typically occur 2 to 5 weeks after the initial SARS-CoV-2 infection and are thought to be mediated by a dysregulated immune response.[1] Patients with these syndromes may suffer from cardiovascular, gastrointestinal, neurologic, dermatologic, and mucocutaneous manifestations like Kawasaki disease,[3,4] and this is discussed further in Chapter 12. This review highlights what is known about the epidemiology, clinical features, pathophysiology, and risk factors of long COVID and summarizes current rational approaches for the diagnosis, prevention, and treatment of this new syndrome based on emerging literature and expert opinion.

Definitions and Epidemiology

As of this writing, there is no universally accepted case definition for long COVID.[5] The Centers for Disease Control and Prevention defines post-COVID conditions as a range of health problems or symptoms experienced 4 or more weeks after initial infection with SARS-CoV-2.[6] The United Kingdom National Institute for Health and Care Excellence (NICE) guidance classifies acute infection as lasting up to 4 weeks, classifies ongoing symptomatic COVID-19 as lasting up to 12 weeks, and then defines post-COVID syndrome as a cluster of overlapping signs and symptoms across multiple systems that has developed during or after the initial infection and continues for more than 12 weeks after SARS-CoV-2 infection.[7] Using a time frame similar to NICE, the World Health Organization (WHO) proposes a clinical case definition in which long COVID begins 3 months from the onset of probable or confirmed SARS-CoV-2 infection.[8] All current case definitions do, however, acknowledge that long COVID encompasses a wide range of symptoms and can persist, fluctuate, or relapse following the initial SARS-COV-2 infection or can newly appear after initial symptom resolution.

Estimates of the incidence and prevalence of long COVID symptoms vary widely across published studies. The reasons for this variability include the overall severity and spectrum of SARS-CoV-2 infection in the study population, participant sociodemographics and geographic location, the health system, and the public health infrastructure within which the study is completed, the follow-up period from the initial SARS-CoV-2 infection, the spectrum of symptoms on which the reports are based, the methods and tools for data collection, and the chosen study outcome measure.[9] In addition, most studies describing the prevalence and clinical manifestations of long COVID are cross-sectional or observational and are subject to various types of selection or reporter bias that make it difficult to generalize the results beyond the population studied.[10] As an example, participation in app-based self-report surveys requires motivated participants with adequate computer literacy to download the app and track their COVID-19 symptom, thus influencing the responding cohort.[11,12]

Acknowledging the heterogeneity of these studies, in general, for those patients evaluated or treated for acute COVID-19 in the outpatient setting, the reported incidence of long COVID ranges from 10% to 35%[13–15] and can exceed 80% for those treated in the hospital with more severe initial illness.[16,17] In one of the earliest attempts to define the clinical course of COVID-19, a cross-sectional study of symptomatic adults tested in outpatient settings reported that 34% had not returned to their usual state of health 14 to 21 days after SARS-CoV-2 infection.[14] In light of the prolonged course of long COVID, multiple studies have since followed participants for longer durations in a variety of settings. An illustrative selection of those studies is summarized in **Table 1**. Taken together, these studies reveal the global scope of the syndrome and suggest the potential for a significant proportion of patients who are infected with SARS-CoV-2 regardless of severity of the initial infection to develop long COVID.

Table 1
Select publications highlighting long coronavirus disease prevalence

Authors	Population	Participants (n)	Severity of Initial Illness	Evaluation Time Point	Outcome Measure	Prevalence
Carvalho-Schneider et al,[18] 2021	Patients at Tours University Hospital (France)	150	Mild-moderate COVID-19 (n = 116); severe COVID-19 (n = 34)	30 d and 60 d after initial infection	≥ 1 persistent symptom	69% and 66%, respectively
Carfi et al,[19] 2020	Postacute outpatient service in Italy	143	Hospitalized; ICU admission (13%)	60 d since symptom onset (mean)	≥1 persistent symptom	87%
Huang et al,[20] 2021	Hospitalized adults in Wuhan, China	1733	Hospitalized	186 d after symptom onset (median)	≥1 symptom	76%
Goertz et al,[21] 2020	Members of Facebook groups for patients with COVID-19 with persistent complaints in the Netherlands and Belgium, and a panel of individuals registered on a Web site of the Lung Foundation Netherlands	2113	Hospitalized (n = 112); nonhospitalized adults (n = 2001)	79 d after symptom onset (mean)	≥1 symptom from a 29-symptom list	87% fatigue and 71% dyspnea
Sudre et al,[11] 2021	Respondents from United Kingdom, United States and Sweden, self-reporting symptoms in the COVID Symptom Study app	558	Mild to moderate COVID-19 illness based on the low rates of hospitalizations in the cohort	≥28 d, ≥8 wk, and ≥12 wk	≥ 1 symptom	13.3%, 4.5%, and 2.3% had persistent symptoms ≥28, ≥56 and ≥ 84 d, respectively
Blomberg et al,[22] 2021	Prospective cohort of patients testing positive for SARS-CoV-2 in Norway	312	Home-isolated (n = 247); hospitalized (n = 65)	6 mo	Any persistent symptom	61% (189/312)

Abbreviation: ICU, intensive care unit.

Clinical Manifestations

Current literature suggests that long COVID is a heterogeneous, multisystem, relapsing and remitting illness that can affect patients infected with SARS-CoV-2 regardless of the severity of the acute infection.[23]

Although not universal, most patients presenting with long COVID will report a prior history of a viral syndrome with symptoms consistent with an acute COVID-19 infection such as fever, shortness of breath, cough, or change in taste or smell. Several recent review papers or meta-analyses describe the ability of long COVID to manifest across multiple body systems including constitutional,[24] cardiovascular,[25–27] pulmonary,[28] neurologic,[29] neuropsychiatric,[30] musculoskeletal,[31] and gastrointestinal.[32] A recent meta-analysis that included international studies that defined long COVID as ranging from 14 to 110 days postviral infection and included hospitalized and ambulatory treated infections found that the most common symptoms were fatigue (58%), headache (44%), attention disorder (27%), hair loss (25%), difficulty breathing (24%), and loss of taste (23%) or smell (21%).[33] Incidence of gastrointestinal symptoms (eg, diarrhea, nausea, pain) ranged from 3% to 79%.[33] Another recent systematic review and meta-analysis comprising 81 studies of individuals reporting fatigue and cognitive impairment 12 or more weeks after COVID-19 infection revealed the proportion of affected individuals to be 32% and 22%, respectively.[24] Other reported symptoms include cardiac impairments, muscle weakness, and poor exercise tolerance.[34] **Table 2** summarizes common clinical signs and symptoms reported in the long COVID literature, as well as associated differential diagnoses for consideration in patients presenting for evaluation.

Beyond signs and symptoms, long COVID may also be associated with new or worsening difficulties completing activities of daily living and difficulty returning to work. In an observational cohort study of 448 individuals contacted via telephone approximately 60 days after discharge from hospitals across Michigan, persistent symptoms related to the acute COVID-19 illness were present in 159 of 448 (35.5%) and 58 of 488 (11.8%) reported new or worsening difficulties completing activities of daily living.[35] Furthermore, among 195 patients who were employed before hospitalization, 117 had returned to work, whereas 78 could not return because of ongoing health issues or job loss.[35] Similarly, in a large multicenter cohort study of 253 adults previously hospitalized in the United States for COVID-19 who completed 1-month telephone follow-up after hospital discharge, a majority (139 [53.8%]) reported at least 1 new or worsened cardiopulmonary symptom, 130 (52.8%) reported new limitations in activities of daily living or instrumental activities of daily living, and 213 (84.2%) reported that they were not fully back to their pre-COVID level of health and well-being. Importantly, this study suggests a complex relationship between the level of symptoms, degree of disability, and degree of perceived recovery.[36]

Although long COVID is a newly emerging illness, it is worth noting that postinfectious syndromes that share a similarly diffuse degree and constellation of symptoms have been previously described. For example, postinfectious fatigue syndromes have been reported following infections with *Giardia lamblia*, *Coxiella burnetii*, and *Borrelia burgdorferi,* the causative agent of Lyme disease. Postviral fatigue syndromes have also been described after other viral infections such as Epstein-Barr virus.[50] In a classic paper on the identification and management of postviral fatigue syndromes, a postviral fatigue syndrome was characterized by (1) generalized, relapsing fatigue exacerbated by minor exercise that was associated with disruption of usual daily activities for at least 3 months and (2) subjective cognitive complaints including

Table 2
Postacute sequelae of severe acute respiratory syndrome coronavirus 2 clinical signs and symptoms

Systems	Symptom or Sign	Differential Diagnosis for Consideration
Constitutional[37,38]	Fatigue, fevers, malaise, exercise intolerance	Postviral fatigue, deconditioning, electrolyte imbalance
Cardiovascular[25,27]	Tachycardia, chest pain, chest tightness, palpitations, exercise intolerance	Anemia, heart failure, myocarditis, pericarditis, thromboembolic disease, hypoxemia, pulmonary fibrosis, pulmonary vascular disease, chest wall pain, gastrointestinal source, coronary artery disease, small fiber neuropathy, autonomic impairment
Respiratory[19,20,37,39,40]	Shortness of breath, cough, exercise intolerance	Residual lung disease, reactive airway disease, cryptogenic organizing pneumonia, myocardial involvement, pulmonary embolism, angina variant
Neurologic[29,41]	Headache, dizziness, ataxia, vertigo, nerve pain, smell and taste impairment, seizure like activity	Cerebrovascular disease, migraines, traumatic brain injury, concussion, allergic rhinitis, functional neurologic disorder
Gastrointestinal[32,42]	Abdominal pain, nausea, vomiting, diarrhea, constipation, bloating	Irritable bowel syndrome, inflammatory bowel disease, gluten sensitivity, dysautonomia, parasitic infection
Musculoskeletal and skin[42–44]	Joint pain, myalgia, increased pain and tenderness, numbness and tingling in upper or lower extremities, COVID toes, balance problems, upper back pain	Small fiber neuropathy, ICU-acquired neuromuscular weakness, dysautonomia, reactive arthritis, chronic fatigue syndrome, autoimmune disorders, central desensitization syndromes[41,42]
Neuropsychiatric[30,45]	Anxiety, depression, posttraumatic stress symptoms	Premorbid mood or anxiety disorder, secondary impact from neurologic injury from acute illness (eg, stroke), dysautonomia

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Table 2
(continued)

Systems	Symptom or Sign	Differential Diagnosis for Consideration
Sleep[46]	Insomnia, hypersomnia	Premorbid sleep disorder, polypharmacy, mood disorder, hypersomnolence disorders includding narcolepsy, obstructive sleep apnea, restless leg syndrome, circadian rhythm sleep-wake disorders, substance/ medication-induced sleep disorder
Autonomic nervous system[26,27,47]	Disequilibrium, dizziness, pre-syncope, blurred vision, chest pain palpitations, positive tilt table, hypotension, difficult-to-control hypertension, breathlessness	Dehydration, autonomic failure, POTS, autoimmune disorders, mast cell activation syndrome, orthostatic hypotension, myocarditis, pulmonary embolism
Neurocognitive[24,37,48,49]	Cognitive changes, light sensitivity, personality changes, change in taste or smell, balance change, gait changes	Premorbid mild cognitive impairment, delirium, depression, anxiety, psychosis, traumatic brain injury, post-ICU syndrome[47]

Abbreviations: ICU, intensive care unit; POTS, postural tachycardia syndrome.

disturbances in concentration and/or short-term memory impairment, with no other "obvious, organic causes for a similar syndrome."[51] In this proposed definition, other supporting criteria could include (1) symptoms such as "myalgias, gastrointestinal disturbances, headache, depression, tinnitus, paresthesias, tinnitus, sleep disturbance, cardiovascular complaints, adverse effects of alcohol, adverse effect of heat"; (2) clinical signs of lymphadenopathy, localized muscle tenderness, or pharyngitis; and (3) laboratory evidence of viral infection and abnormalities in immune function.[51] Myalgic encephalomyelitis or chronic fatigue syndrome (ME/CFS) is a chronic complex disease that has often been described as beginning after a viral infection, although the cause remains unknown. ME/CFS is estimated to affect between 836,000 and 2.5 million people in the United States alone[52] and is characterized by fatigue, postexertional malaise, sleep problems, cognitive impairment, pain, autonomic dysfunction, and neuroendocrine symptoms.[52] These examples demonstrate the ubiquity of postinfectious syndromes that share some similarities with the clinical presentations we now see with long COVID.

Risk Factors for Long Coronavirus Disease

Although the pathophysiology is still to be elucidated and likely includes multiple phenotypes, studies thus far suggest that long COVID may be a syndrome with predisposing, precipitating, and perpetuating factors.[53]

Nonmodifiable and modifiable characteristics such as older age and female sex, obesity, and the presence of multiple preexisting medical comorbidities including immunosuppressive and psychiatric conditions may all be factors associated with an increased risk of protracted symptoms after COVID-19 infection.[11,14] In their neurocognitive evaluation of 106 patients (mean age 64.9 years, 26.7% female) 6 months after discharge from a pulmonary COVID-19 unit, Cristillo and colleagues[54] found that more severe pulmonary disease during the acute COVID-19 illness and a measure of prehospital vulnerability captured by the National Health System COVID-19 Decision Support Tool were associated with abnormal levels of cognitive function as determined by age- and education-adjusted Montreal Cognitive Assessment scores. These findings support the hypothesis that premorbid vulnerability and older age play an important role in predicting long-term cognitive sequalae of SARS-CoV-2 infection.[54]

In multiple cross-sectional studies[11,37] as well as in multiple observational studies of long COVID in treatment settings,[55,56] women appear more likely to develop long COVID symptoms than men.[57] In addition, the largest cross-sectional studies of long COVID symptoms in adults have typically shown a predominance of female participants[11,37]; however, it remains unclear if this reflects a true biologic predisposition to long COVID, because reporter bias may also play a role.

In terms of precipitating factors, perhaps not surprisingly, several studies report that the severity of the initial COVID-19 infection seems to be associated with an increased risk of developing long COVID.[11] Similarly, the length of hospitalization and intensive care unit (ICU) admission have also been identified as independent predictors of long COVID at 6 months of follow-up.[58] In a large, prospective cross-sectional study of 558 adults who self-reported their symptoms in the COVID Symptom Study app[59] adults with more than 5 symptoms during the first week of their COVID-19 illness were more likely to experience symptoms beyond 28 days (odds ratio [OR] 3.95 [95% confidence interval (CI) 3.10–5.04]).[11] In this study, in adults older than 70 years, loss of smell, fever, and hoarse voice were symptoms most predictive of developing long COVID, with odd ratios ranging from 4.03 to 7.35.[11] In a prospective multicenter study of 991 patients with COVID-19 requiring ICU admission, persistent post-COVID-19 symptoms were reported in more than two-thirds of patients at 3 months. Among this cohort, independent risk factors for persistent poor health post-COVID-19 included female sex, development of ICU-acquired pneumonia, duration of ICU stay, and acute respiratory distress syndrome.[60] Taken together, the severity of the acute COVID-19 infection whether classified by the number of symptoms, the duration of the hospital stay, or the need for ICU care have all been associated with an increased risk of long COVID.

Few studies have looked at perpetuating factors in protracted recovery in patients diagnosed with long COVID.

Pathophysiology

Both viral direct and indirect mechanisms have been hypothesized to play a role in the pathogenesis of long COVID symptoms, although the pathophysiology is still largely unknown. SARS-CoV-2 uses angiotensin-converting enzyme 2 (ACE2) for cellular entry,[61] and ACE2 is widely expressed on pulmonary and extrapulmonary tissues throughout the body, allowing for the potential of widespread direct virally mediated issue damage.[42] The possibility that there may be persistent viral replication in localized sites has not been excluded. In one recent study that analyzed intestinal biopsies obtained from asymptomatic persons 4 months after COVID-19 onset, there was persistence of SARS-CoV-2 nucleic acids and immunoreactivity in the small bowel of 7 of 14 participants.[62] In addition, in a small meta-analysis of patients with

COVID-19 in Hong Kong, the stool appeared to have a high prevalence of viral RNA, even though 70% of these samples were collected after the respiratory specimens were no longer positive for the virus.[63] Other pathophysiologic mechanisms of COVID-19 that may have lasting adverse effects beyond the acute phase of infection phase include endothelial damage and hypercoagulability/thrombosis and maladaptation of ACE2-related pathways.[2,42] Endothelial dysfunction, small vessel microangiopathy, and fibrin clotting within small capillaries may also contribute to decreased effective oxygen carrying capacity and contribute to shortness of breath and exercise intolerance.[64] A hyperinflammatory syndrome with persistent immune activation and dysregulation of the immune response has also been suggested as a possible mechanism for some of the symptoms.[65,66] The histopathological detection of autoreactive T cells in autopsy samples from individuals infected with COVID-19 supports this latter mechanism.[67,68] Similarly, measures of overt and latent autoimmunity have been demonstrated to persist in some individuals with long COVID.[69]

Impairment in mitochondrial function could be an important contributor to the exercise intolerance and fatigue symptoms in patients with long COVID. A study in which patients with long COVID were tested with Cardio pulmonary exercise testing (CPET) found a lower level of impaired fatty acid oxidation and increased levels of lactate accumulation during exercise regardless of their baseline comorbidities.[70] These results are consistent with impaired energy utilization contributing to the fatigue and functional impairment reported in patients with long COVID.

CONSIDERED APPROACH TO THE EVALUATION OF PATIENTS WITH LONG CORONAVIRUS DISEASE

History

An important part of the evaluation for long COVID is a review the patient's acute COVID-19 illness history, including the effect of the illness and the pandemic on their interpersonal relationships and their social and financial vulnerability. A thorough history should review the main symptoms including fatigue and postexertional malaise.[71] Patients may describe severe exhaustion after minimal exertion, a lack of stamina, or feeling "weighted down." Postexertional malaise may be described as "crashing" after several good days, or several days of worsening symptoms after stressors or triggers. Cognitive difficulties or "brain fog" can include impaired attention, concentration, reduced ability to multitask, difficulty with short-term memory, and word-finding difficulties.[72] Some patients may describe increased irritability or emotionally vulnerability. Reports of unrestful or nonrestorative sleep, often with delayed sleep onset or frequent awakening, are common. Orthostatic intolerance has been reported in long COVID[39,45] and may manifest as syncope, dizziness, lightheadedness, blurred vision, weakness, fatigue, gastrointestinal symptoms (nausea, abdominal pain, bloating, constipation, diarrhea), palpitations, headache, dyspnea, chest pain, temperature intolerance, labile blood pressure, new-onset hypertension, and neck and shoulder pain. Typically, symptoms are triggered or worsened by upright posture. As with other respiratory infections, some patients may experience a persistent breathing discomfort and other respiratory sequelae including chronic cough.[73] Some patients will describe generalized pain in joints, muscle, and soft tissues. Exercise intolerance, burning chest pain, numbness and tingling in the hands or feet, and muscle cramps are also reported.

Clinical Examination

Most patients with long COVID may present with a normal physical examination. Some patients may show signs of fatigue or being generally unwell. Signs of weight loss may

be evident in some patients with months of gastrointestinal symptoms. Others may show signs of slow thinking, poor attention, short memory, and impaired word finding. In patients in whom some degree of autonomic dysfunction is suspected, screening patients using the 10-minute NASA Lean Test (NSL) or active stand test may be reasonable.[24,45] The active stand test measures blood pressure and heart rate after 5 minutes of lying supine and then 3 minutes after standing. Orthostatic hypotension is defined as a decrease of greater than 20 mm Hg systolic and greater than 10 mm Hg diastolic after standing for 3 minutes, or during or after a head up tilt to at least 60°.[74] Ten-minute orthostatic vital signs may show a heart rate increase greater than 30 beats per minute (bpm) after standing (or in those aged 12–19 year, more than 40 bpm).[75] Patients with cognitive complaints may benefit from a thorough neurologic examination to identify focal neurologic deficits. Balance and gait may be assessed and compared with age-based norms. For patients with changes in visual acuity or eye pain, a low threshold for a post-COVID-19 retinal examination seems reasonable given that the eyes are known to have ACE2, and such examinations can be a window into microvascular alterations affecting the whole body.[76,77]

Laboratory Testing

Laboratory testing should focus on ruling out comorbid conditions, contributory factors, and common conditions that may explain reported symptoms. It may help to prepare the patient for the fact that most of these test results will be normal. Examples of useful screening tests for initial investigations include complete blood cell count with differential, iron and ferritin levels, comprehensive metabolic panel, urinalysis, thyroid function, vitamin B12 and 25-hydroxy vitamin D levels, and high-sensitivity C-reactive protein, erythrocyte sedimentation rate, and antinuclear antibodies (ANA). More extensive laboratory evaluation may be ordered to identify less common alternative diagnoses and comorbidities, including newly emergent autoimmune conditions.[69,78] Pulmonary function testing and chest imaging are reasonable in patients with chronic breathlessness and/or evidence of oxygen desaturation on exertion.[73] Brain imaging in most cases may be best reserved for patients with focal neurologic deficits or a history of head trauma.Transthoracic echocardiography, cardiac stress testing, and cardiopulmonary exercise testing should be considered on an individual basis based on the patient's associated symptoms and treatment plan.

PREVENTION

Prevention of long COVID can best be achieved through consistent use of established tools for the prevention of COVID-19, including vaccination, the appropriate use of personal protective equipment, hand hygiene, and social distancing. Studies are underway to understand if early use of effective antiviral therapies (eg, monoclonal antibodies or other antiviral therapies) can mitigate or prevent long COVID in patients infected with COVID-19. Reports of the mitigating effects of vaccination on long COVID are intriguing. This includes a large UK prospective, community-based, nested, case-control study using self-reported data that found that when compared with unvaccinated participants, vaccination before SARS-CoV-2 infection was associated with reduced likelihood of symptomatic acute COVID-19, and reduced odds of long-duration ($\geq$28 days) symptoms following the second vaccine dose.[79] Intriguing results from a prospective, single-center study of 449 discharged hospital patients suggest a significant, 35.9% reduction in long COVID at 6 months in those treated with the antiviral remdesivir during the acute period, with multivariate analysis identifying the drug as an independent predictor of the syndrome (OR = 0.641; 95%

CI = 0.413–0.782; $P < .001$).[58] Although confirmatory, randomized, placebo-controlled trails are needed, these studies support the possibility that a host of interventions, including early effective antiviral interventions and vaccination, may have a substantial mitigating effect on long COVID.

Treatment

Although there are few studies of treatment in long COVID that have shown efficacy or effectiveness, consensus guidance on best approaches to treat these patients based on the lived experience of patient and clinicians are emerging.[71–73,80] The overall approach to treatment of long COVID is to focus on managing symptoms, improving function, and working with the patient to settle on reasonable treatment targets that have the potential to improve their quality of life. Given the wide array and varying magnitude of presentation of long COVID symptoms, multiprong approaches may be needed. Providing patients with the tools for self-management is crucial early in the disease course because patients are often dealing with isolation and uncertainty. The goal of self-management is to help the patient be in control of their disease and healing process. The primary care providers or generalists should remain integrated in the care of these patients to facilitate access to local physiotherapy, occupational therapy, dieticians, or home care. In addition, the primary care provider has an important role in searching for alternative diagnoses, so that not all the patient's symptoms are automatically attributed to this syndrome.

Titrating physical activity: The evaluation may first focus on the patient's medical history, diagnostic tests, pre-COVID-19 level of physical activity, and social determinants of health. Patients should be screened for postexertional symptom exacerbation through careful monitoring of their symptoms both during physical activity and in the days following the activity. Signs of exertional oxygen desaturation, orthostatic intolerance, or autonomic dysfunction may also be important to titrate the appropriate level and type of physical activity during the recovery process. Importantly, telling patients to push through their pain or discomfort during the early periods may lead to worsening postexertional malaise and may prolong recovery. It is important to individualize the patient-reported outcome measure to each patient and to consider the reality of post-exertional malaise and energy conservation in the educational interventions. NICE guidelines do not recommend graded exercise therapy or any physical activity program that uses a fixed incremental increase in physical activity. Rather, more recent guidelines recommend a symptom-titrated physical activity approach in which physical activity is continuously monitored an adjusted according to symptoms.[7,71] Educational materials can focus on teaching patients how to recognize when they are crossing their anaerobic threshold, which is often much lower than their pre-COVID-19 baseline. In patients who are limited by dizziness, imbalance, and headache symptoms, adjusting mode of exercise to be recumbent may be beneficial along with compression stockings and use of isometric exercises. Vestibular rehabilitation or balance programs may be appropriate in patients demonstrating vestibular impairment or poor balance.

Accommodating cognitive symptoms: For patients with significant impairments in their well-being due to cognitive symptoms, a referral to a specialist who can complete a thorough assessment of the domains of impairment (eg, speech language pathologist, occupational therapist, neuropsychologist) seems a reasonable treatment approach.[72] The evaluation may focus on the assessment of memory, attention, language, energy and cognitive endurance, sleep, and other symptoms. Patients should be asked about their living situation, their work or school status, and what cognitive symptoms are most troubling them. Educational materials may focus on memory, attention, communication strategies, helping patients understand what types of

cognitive activities use up the most cognitive energy, and helping patients to assess factors that may be affecting their cognitive energy such as mood, stress, sleep, pain, or medication changes.

Dysautonomia: For patients with dysautonomia symptoms, the education materials may focus on the 4 pillars of active nonpharmacologic management: liberalizing salt intake, increasing hydration, low level of physical activity, and the use of compression garments. For patients with gastrointestinal symptoms of dysautonomia, eating small and frequent meals and eating slowly in a low-stress environment may help alleviate some of the symptoms. For patients with heat intolerance, cold showers and ice packs applied to the face and neck may be important.

Referral to post-COVID or other subspecialty clinics: In response to the growing numbers of individuals presenting with long-COVID, multidisciplinary outpatient clinics have been formed throughout the United States and other countries. Using their experiences in the formation of such academic health clinics centers at Johns Hopkins and the University of California, San Francisco, Santhoth and colleagues suggest a framework focused on addressing clinical needs through coordination across multiple subspecialties to address impairments in physical function, cognitive function and mental health, longitudinal follow-up, and integration of research efforts to foster greater understanding of evolving disease processes.[51] As the pandemic continues, addressing optimal resource allocation, the focus of care (primary vs specialty), and the ability to scale-up will also become increasingly challenging.[81] Earlier referral may be appropriate in younger patients, more complex patients in whom the diagnosis is unclear and the treatment challenging, in patients for whom the disability impact of illness is severe, and in patients in whom local clinical support is limited.

DISCUSSION OF NEXT STEPS, CHALLENGES, AND UNANSWERED QUESTIONS

In recognition of the significant public health impact of long COVID, the National Institutes of Health launched a major initiative in February 2021 to support research efforts to better understand the cause of long COVID, and to identify best methods of prevention and treatment for affected individuals.[82] Additional efforts toward systematic collection of large-scale clinical data to examine the medium- and long-term consequences of COVID-19 have also come from the WHO, through their creation of a post-COVID case report form.[83]

Collections of individuals afflicted with long COVID have made an important contribution to the research response. Key initial reports of the defining symptoms of long COVID have come from such groups of citizen scientists and the large-scale surveys to which they have contributed. The first detailed patient surveys of long COVID came from efforts from the international Patient-Led Research Collaborative born out of the Body Politic support group.[37] The study sample in this study consisted predominately of white females between the ages 30 and 49 years. . A higher proportion of females has since been documented in subsequent peer-reviewed survey studies of long COVID symptoms[11]More research is needed to better understand the biological and psychosocial factors that may explain any differences in risk of long COVID symptsom by sex and/or gender. Another important challenge in long COVID research is that across many of the studies, the proportion of the study sample with laboratory confirmed SARS-CoV-2 infection will vary depending on the phase of the pandemic, the local availability of COVID-19 testing, the sensitivity and specificity of the specific COVID-19 tests used. Challenges with attribution of reported symptoms to the sequelae of COVID-19 infection were further revealed in a recent cross-sectional analysis of 26,823 individuals participating in the French population-based CONSTANCES

cohort.[84] After adjusting for key metrics, including age, sex, income, self-reported health, level of education, and depressive symptoms, linear regression models revealed that the presence of a persistent long COVID symptom lasting for greater than 8 weeks was more strongly associated with a belief in having had COVID-19 than with having serologically confirmed COVID-19 infection. The limited sensitivity of COVID-19 serology performed after a long delay from symptom onset should, however, be kept in mind in interpreting this study.[84]

As of this writing, little of the published research on long COVID has been conducted in low- and middle-income countries. In addition, despite the disproportionate impact of COVID-19 on historically disadvantaged populations in the United States, the impact of long COVID in Black, Indigenous, and People of color community settings have been underexplored.

SUMMARY

The long-term sequelae of COVID-19 are protean, impacting multiple organ systems to varying degrees. The multiorgan dysfunction induced by COVID-19 has the potential to result in significant morbidity in affected individuals. The growing proportion of patients recovering from COVID-19 makes an improved understanding of risk factors, mechanistic pathways, sequelae, and potential mitigating factors important research and clinical goals.

CLINICS CARE POINTS

- Provide patients with physical fatigue, cognitive symptoms, and/or postexertional malaise educational materials about the importance of energy conservation
  - 4 *P's*: pacing, prioritization, planning, positioning.[71]
- Consider referring patients with cognitive complaints to specialist with expertise in cognitive rehabilitation therapies (eg, speech therapist, occupational therapist, neuropsychologist).[72]
- Assess the impact of the symptoms on the patient's ability to return to normal daily activities and consider early disability accommodations to facilitate recovery.
- For individuals with autonomic dysfunction without evidence or history of congestive heart failure, pericarditis, myocarditis, coronary artery disease, or essential hypertension, nonpharmacologic management can include[75]:
  - Liberalizing salt and electrolyte intake
  - Increase fluid intake
  - Compression garments
  - Individualized return to physical activity including consideration of recumbent or supine exercises.

DISCLOSURE

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