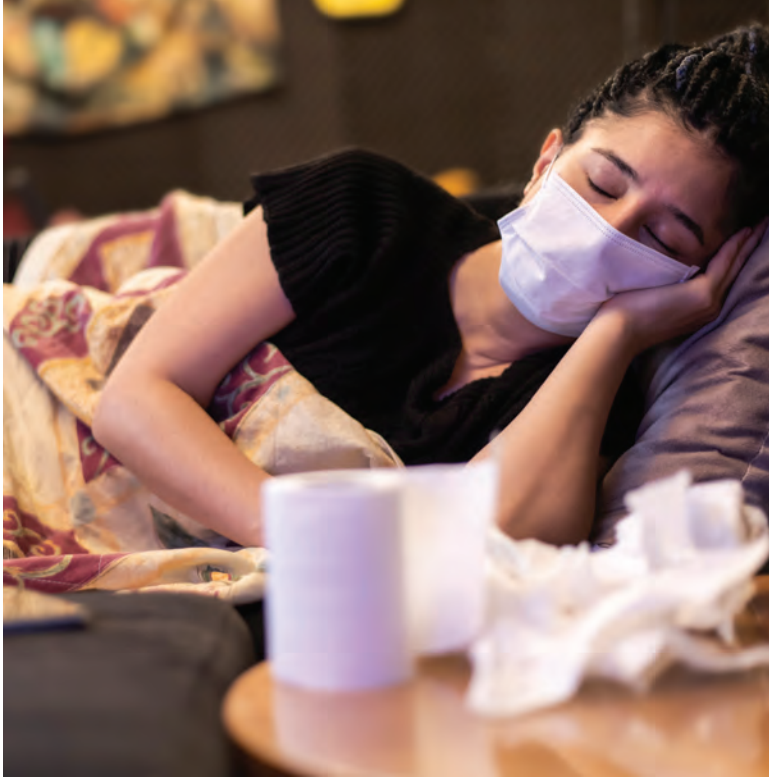
An update on long COVID and its management



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Long COVID is a multisystemic condition affecting five to 20% of individuals after SARS-CoV-2 infection. Although there is no cure, GPs can effectively support patients by managing symptoms, providing education and co-ordinating care. Evidence of the long-term health impacts, pathophysiology and potential treatments is rapidly evolving.

To date, over 11 million cases and 20,000 deaths from COVID-19 have been reported in Australia.[1] However, the true number of cases is likely higher, as seroprevalence surveys suggest over two-thirds of people in Australia had been infected with SARS-CoV-2 by December 2022.[2] Some patients continue to experience persistent symptoms of a physical, psychological or cognitive nature following SARS-CoV-2 infection. Evidence suggests this post-COVID-19 condition, commonly known as long COVID, poses a significant healthcare burden that will likely continue into the future.

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This article discusses the clinical presentations of long COVID, its pathophysiology, epidemiology and prognosis. A summary of long COVID management is presented, outlining the role of the GP, red flag symptoms and when to refer.

Definition of long COVID

In 2021, the WHO proposed a definition for long COVID, or the post-COVID-19 condition, that encompassed persistent symptoms occurring in individuals with probable or confirmed SARS-CoV-2 infection, usually three months from the onset of COVID-19 and lasting for at least two months, with no alternative diagnosis.[3] Common symptoms include fatigue, shortness of breath and cognitive dysfunction; however, systematic reviews have associated over 100 symptoms affecting a wide range of organ systems.[4,5] Symptoms may be new-onset following initial recovery from acute SARS-CoV-2 infection, or persist from initial illness. They frequently interfere with everyday functioning (including activities of daily living and employment) and may also fluctuate or relapse over time.

Clinical presentation

Long COVID is characterised by a wide constellation of symptoms affecting multiple organ systems (Table 1).[6] Symptoms may be general, such as fatigue, post-exertional malaise and myalgia, or organ specific. Sequelae affecting the cardiorespiratory system may manifest with dyspnoea, cough, chest pain or palpitations, whereas sequelae affecting the neurological system often feature insomnia, headache, dizziness, cognitive impairment (typically reported as 'brain fog') and smell and taste dysfunction. Red-flag symptoms that require urgent referral to a hospital emergency department are listed in Box 1.

Patients' symptoms tend to be characterised by at least one of three phenotypes or symptom clusters. A primary care-based study of electronic medical records from 486,149 nonhospitalised patients described three symptom clusters:[7]

TABLE 1. SYMPTOMS OF LONG COVID[6]

Organ system	Symptoms	Pathology
Heart	• Chest pain • Palpitations	• Cardiac impairment • Myocardial inflammation • Postural orthostatic tachycardia syndrome
Lungs	• Cough • Dyspnoea	Abnormal gas exchange
Pancreas		• Diabetes • Pancreatic injury
Immune system		• Autoimmunity • Mast cell activation syndrome
Gastrointestinal tract	• Abdominal pain • Nausea	• Gut dysbiosis • Viral persistence and viral reservoir
Neurological system	• Cognitive impairment • Fatigue • Disordered sleep • Memory loss • Tinnitus	• Dysautonomia • Myalgic encephalomyelitis/chronic fatigue syndrome • Neuroinflammation • Reduced cerebral blood flow • Small fibre neuropathy
Kidneys, spleen and liver		Organ injury
Blood vessels	Fatigue	• Coagulopathy • Deep vein thrombosis • Endothelial dysfunction • Microangiopathy • Microclots • Pulmonary embolism • Stroke
Reproductive system	• Erectile dysfunction • Increased severity and number of premenstrual symptoms • Irregular menstruation	Reduced sperm count

- 'fatigue' cluster (80% of patients) encompassing a wide range of symptoms such as fatigue, headache, chest pain, palpitations, abdominal pain and hair loss
- 'cognitive' cluster (14% of patients) including symptoms of brain fog, insomnia, anxiety and depression
- 'respiratory' cluster (6% of patients) including symptoms of cough, breathlessness and wheeze.

It should be emphasised that these clusters are not mutually exclusive, and many patients have multiple symptoms that do not necessarily fit into one cluster type.

Cardiovascular autonomic abnormalities, such as initial orthostatic hypotension (IOH) or postural orthostatic tachycardia syndrome (POTS), are common.[8] Although both forms manifest with symptoms of orthostatic intolerance, IOH is characterised by a transient drop in systolic (≥40 mmHg) or diastolic (≥20 mmHg) blood pressure within 15 seconds of standing, whereas POTS is classified by an excessive heart rate over 120 bpm, or an increase of 30 bpm or more within ten minutes of standing and in the absence of orthostatic hypotension.

Other manifestations, such as organising pneumonia, interstitial lung abnormalities and postintensive care syndrome, appear more frequently following hospitalisation for severe illness. Post-COVID pulmonary fibrosis is characterised by pulmonary function abnormalities and findings on CT such as parenchymal bands, ground-glass opacities and consolidation.[9] Postintensive care syndrome encompasses multidimensional impairments in cognitive, mental, physical and social function.[10]

1. RED-FLAG SYMPTOMS REQUIRING URGENT REFERRAL TO A HOSPITAL EMERGENCY DEPARTMENT

- Severe, worsening or new-onset breathlessness
- Syncope
- Unexplained chest pain, palpitations or arrhythmia
- Focal neurological signs or symptoms
- New-onset confusion
- Suicidal ideation

Pathophysiology

No one mechanism has been clearly associated with long COVID and it is likely that several different mechanisms are responsible for different phenotypes.[11] The pathophysiology of long COVID after community-managed initial infection may also have differences compared with abnormal recovery after severe initial infection. Multiple inflammatory mechanisms have been proposed as a common pathophysiology. Two leading hypotheses include:

- viral antigen persistence causing a sustained inflammatory response
- formation of microclots causing multiorgan dysfunction.

Delayed viral antigen clearance or possibly active viral reservoirs within the body may provoke chronic low-grade inflammation, autoimmunity, coagulation and fibrosis pathway activation and metabolic disturbances.[11] One study found 65% of participants with long COVID had detectable levels of SARS-CoV-2 spike protein in their plasma up to 12 months after infection.[12] Another study found combinations of proinflammatory cytokines, including interferon-beta,

interferon-gamma and interleukin-6, persisted up to eight months after infection and their presence predicted long COVID with about 80% accuracy.[13]

The hypothesis for the microclot mechanisms, which is awaiting further experimental validation, is that proteins within SARS-CoV-2 trigger the formation of amyloid fibrin-microclots, which inhibit the transport of red blood cells to capillaries, reducing oxygen transport to tissues.

Epidemiology

Prevalence

The diversity of study populations and methodologies has introduced bias and led to challenges in accurately determining the prevalence and natural history of long COVID. A recent meta-analysis showed that unresolved symptoms occurred in 35% of community-managed patients and 53% of hospitalised patients four months after infection.[14] However, many of the included studies did not include matched controls nor did they account for pre-existing symptoms. Prospective studies that included matched controls have suggested prevalence estimates of 12%, 13% and 38%.[15-17]

The Office for National Statistics in the UK inform our best estimates of long COVID prevalence in the postvaccine Omicron era. They found 4% of adults and 1% of children reported having long COVID 12 to 20 weeks after initial SARS-CoV-2 infection.[18] Vaccination was associated with a 29% lower risk of developing long COVID in one meta-analysis.[19] Similarly, the prevalence of long COVID following infection with the Omicron variant was about half that of earlier variants.[20,21]

Risk factors

The REACT-2 study (n=606,434) found that the severity of initial COVID-19 illness and hospitalisation carried the highest odds ratio for developing long COVID. In addition, the study found female sex, obesity, advanced age, smoking and low socioeconomic status were also significantly associated with long COVID.[17] Observational studies have consistently shown that women are more susceptible than men to developing long COVID, which may be because of differences in antiviral and autoimmune responses between the sexes.[22-24] The association between obesity and long COVID is less clear, with a potential explanation being an increase in the expression of angiotensin-converting enzyme 2 in adipocytes, proinflammatory cytokines and immune dysfunction associated with insulin and leptin resistance.[25] Other risk factors for developing long COVID include immunosuppression and comorbidities such as COPD, asthma and anxiety and depression.[7]

Treatment

Currently, no pharmacotherapies are approved for the treatment of long COVID. Numerous studies are underway to investigate potential drug therapies such as antivirals, HMG-CoA reductase inhibitors (statins), anticoagulants and immunosuppressants. Results from two large, randomised controlled trials investigating nirmatrelvir/ritonavir for the treatment of long COVID are expected by January 2024.[26,27] Primary prevention with early treatment of acute infection may be beneficial. One study demonstrated that treatment with nirmatrelvir within five days of COVID-19 diagnosis was associated with a 26% less risk of long COVID sequelae and 47% less risk of post-acute death among participants with at least one risk factor for severe illness.[28] The STIMULATE-ICP randomised trial is currently underway to evaluate the use of multiorgan MRI and a digitally enabled rehabilitation platform, in addition to pharmacotherapies such as colchicine, rivaroxaban and loratadine plus famotidine.[29]

Diagnosis

It is important to establish the timing of persistent symptoms in relation to the date of initial infection (preferably a confirmed SARS-CoV-2 diagnosis). If SARS-CoV-2 testing was not undertaken, a history consistent with COVID-19 infection may be sufficient to diagnose long COVID – even among patients with initially mild infective symptoms.

It is abnormal for almost any viral respiratory illness to cause persistent symptoms beyond one month. GPs may suspect long COVID in patients presenting with persistent, particularly disabling symptoms one month after COVID-19 infection, and are encouraged to initiate investigations early. Studies suggest only a small proportion of patients recover fully between one and three months postinfection (about 20% in the REACT-2 cohort).[17]

Given the lack of definitive biomarkers, long COVID remains a diagnosis of exclusion and it is important to consider alternative illnesses or coexisting pathologies that may present with similar symptoms. Initial investigations are ideally undertaken in primary care as GPs often have excellent knowledge of their patients' comorbidities and baseline test results.

Investigations

The history and examination will guide which investigations are appropriate for each patient (Table 2). Most patients should receive blood tests to identify anaemia, electrolyte abnormalities, kidney and liver dysfunction, lipid abnormalities, thyroid dysfunction, diabetes, nutritional deficiencies and inflammatory markers. An electrocardiogram (ECG) and chest x-ray are helpful to rule out serious conditions. Further complex investigations may be considered depending on the clinical presentation (e.g. echocardiogram, lung function tests, MRI brain).

Management

After excluding alternative pathology, management of long COVID usually involves controlling symptoms, optimising comorbidities, preventing reinfection and counselling. Box 2 provides useful information and resources on managing long COVID.

Symptom control

Patients are often required to adjust to a new baseline level of physical and mental

TABLE 2. SUGGESTED INVESTIGATIONS FOR PATIENTS WITH LONG COVID

	Investigation	Possible diagnosis	Further tests to consider if pre-test probability is appropriate
Suggested for most patients			
	• Full blood count • Electrolytes, urea and creatinine levels; liver function test • Thyroid function test • C-reactive protein level and erythrocyte sedimentation rate • Fasting blood sugar and glycated haemoglobin levels • Fasting lipid levels • Iron studies and vitamins B12 and D, folate levels	• Anaemia • Liver or kidney dysfunction • Thyroid status • Inflammation • New-onset diabetes • Cholesterol abnormalities • Nutrient deficiencies	
	ECG	• Arrhythmia • Pericarditis • Ischaemia	Holter monitor
	Chest x-ray	• Pericarditis • Heart failure • Pulmonary infiltrates	
	Mental health screen (e.g. Kessler Psychological Distress Scale; Depression, Anxiety and Stress Scale - 21 Items questionnaire)	Anxiety and depression	
Additional investigations			
Fatigue	Sleep apnoea screen	Obstructive sleep apnoea	Polysomnography
Chest pain	• Troponin and creatinine kinase levels • D-dimer level	• Myocardial damage • Pulmonary embolism	• Echocardiography • CT pulmonary angiogram
Breathlessness	• Pulse oximetry • Spirometry • D-dimer level	• Cardiorespiratory disease • Ventilation abnormalities • Pulmonary embolism	• Rapid exertional desaturation test (e.g. one minute sit to stand) • Complex lung function testing • CT pulmonary angiogram
Cognitive dysfunction	Montreal Cognitive Assessment (score: 0 to 30)	Dementia	• Dementia screen • MRI brain
Orthostatic intolerance	• Supine to standing blood pressure • NASA lean test	Postural orthostatic tachycardia	Autonomic studies (e.g. tilt table testing)

activity to prevent relapse. The WHO's *Support for Rehabilitation: Self-Management after COVID-19 Related Illness* report details multiple strategies to control symptoms, such as energy conservation or breathing techniques, and is an excellent resource for patients. Evidence also supports the use of supervised, tailored exercise programs, even among patients with initially mild COVID-19 illness.[30] One small randomised controlled trial demonstrated greater improvements in quality of life, cardiovascular fitness and muscle strength among participants who underwent an eight-week exercise program compared with those assigned self-management rehabilitation recommendations alone.[31]

Optimising comorbidities

Sleeping difficulties, life stressors and comorbidities, such as cardiorespiratory or musculoskeletal disorders, play a large role in mediating health-related quality of life among patients with long COVID.[32-34] Optimisation of comorbidities and lifestyle factors is likely to be beneficial.

Preventing reinfection

The Veterans Affairs study found that multiple COVID-19 infections were associated with cumulatively worse health outcomes and all-cause mortality.[35] Although causality cannot be inferred, it is sensible to limit patients' risk of repeat infections – consider vaccination, indications for antivirals and a COVID-19 action plan among high-risk patients. Vaccination may be delayed for three to six months after COVID-19 infection and we suggest following ATAGI recommendations

2. RESOURCES ON MANAGING LONG COVID

NSW Agency for Clinical Innovation
- Clinical practice guide for assessment and management of adults with post-acute sequelae of COVID-19: https://aci.health.nsw.gov.au/__data/assets/pdf_file/0011/726878/ACI-CPG-for-assessment-and-management-of-adults-with-post-acute-sequelae-of-COVID-19.pdf

World Health Organization
- Support for rehabilitation: self-management after COVID-19-related illness, second edition: https://www.who.int/europe/publications/i/item/WHO-EURO-2021-855-40590-59892

RACGP clinician resources
- Caring for patients with post-COVID-19 conditions: https://www.racgp.org.au/clinical-resources/covid-19-resources/clinical-care/caring-for-patients-with-post-covid-19-conditions/introduction

RACGP patient resources
- Patient resource: Managing post–COVID-19 symptoms: https://www.racgp.org.au/clinical-resources/covid-19-resources/patient-resources/patient-resource-managing-post-covid-19-symptoms/introduction
- Patient resource: Symptom diary: https://www.racgp.org.au/clinical-resources/covid-19-resources/patient-resources/managing-mild-covid-19-at-home/my-covid-19-action-plan-and-symptom-diary#:~:text=You%20can%20download%20the%20My,you%20are%20recoverign%20at%20home

BMJ visual summaries
- Long covid: a guide for primary care: https://www.bmj.com/content/378/bmj-2022-072117/infographic
- BMJ Orthostatic tachycardia visual summary: https://www.bmj.com/content/380/bmj-2022-073488/infographic

BMJ article
- Espinosa-Gonzalez AB, Master H, Gall N, et al. Orthostatic tachycardia after COVID-19. BMJ 2023; 380: e073488.

Australian Technical Advisory Group on Immunisation (ATAGI)
- ATAGI clinical guidance for COVID-19 vaccine providers: https://www.health.gov.au/our-work/covid-19-vaccines/advice-for-providers/clinical-guidance

Local HealthPathways
- https://www.healthpathwayscommunity.org/Home/Access-to-HealthPathways

Agency for Clinical Innovation
- Living Evidence - post acute sequelae of COVID-19 (long COVID): https://aci.health.nsw.gov.au/covid-19/critical-intelligence-unit/post-acute-sequelae

3. PRACTICE POINTS

- Long COVID is the persistence of symptoms at least three months from the onset of SARS-CoV-2 infection that are not otherwise explained.
- Five to 20% of individuals may develop long COVID after SARS-CoV-2 infection.
- Fatigue-, cognitive- or respiratory-dominant presentations may represent distinct long COVID phenotypes.
- Baseline investigations, including blood tests, ECG and chest x-ray, are optimally co-ordinated by the GP.
- Management involves exclusion of an underlying treatable pathology, symptom control, optimisation of comorbidities, prevention of reinfection and counselling.
- Most patients can be supported effectively in primary care and will improve over a course of months.
- Patients requiring intensive multidisciplinary rehabilitation may benefit from referral to a long COVID clinic.

for further vaccine scheduling (Box 2). Administering further doses of a COVID-19 vaccine to patients with ongoing long COVID may exacerbate symptoms, although most patients (75% in one meta-analysis) report either no change or improvement in symptoms.[36]

Counselling

Patients with long COVID require a nuanced and compassionate approach to care. Since many investigations will return normal results, patients may experience disbelief or stigma by their communities. Providing reassurance and education and addressing the uncertainties of prognosis can be a large focus of the consultation.

When to refer

For patients experiencing fatigue or deconditioning, consider referral for physiotherapy or occupational therapy, or to local rehabilitation services to assist with energy conservation strategies and to establish safe baseline levels of physical activity. Patients with mild breathlessness may benefit from referral to a community physiotherapist or exercise physiologist, which could be facilitated under a chronic disease management plan. However, patients with moderate to severe breathlessness limiting exercise tolerance may require pulmonary rehabilitation and assessment by a respiratory physician. For patients with suspected POTS that is not adequately controlled by conservative measures (liberal fluid and salt intake, avoidance of triggers, compression or physiotherapy), consider referral to a cardiologist for advice regarding use of off-label medications.

Mood disorders are common among patients with long COVID and may contribute to ongoing symptoms. Patients with a diagnosed mental health disorder are eligible to access Medicare rebates and should be considered for referral to a mental health clinician. Referral to a long COVID clinic should be reserved for patients with difficulty accessing a variety of specialists, patients with prolonged symptoms that are not improving, and patients who would

benefit from intensive multidisciplinary rehabilitation. Local HealthPathways offer clinical guidance and referral options to support care co-ordination.

Natural history and prognosis

Recovery from long COVID is variable and nonlinear. Patients who remain unwell at three months may still improve at a slower rate, although symptoms in many appear to plateau or fluctuate, with exacerbations during times of stress. A large study from Scotland (n = 31,486) assessing participants at six, 12 and 18 months after infection found minimal change in recovery status from full, partial or non-recovery, with only 13% of participants reporting improvement and 11% reporting deterioration between study visits.[37] The PHOSP-COVID (Post-hospitalisation COVID-19) study (n = 2468) also found minimal improvement across multiple robust measures of physical, mental and cognitive performance between five and 12 months.[38] There is some evidence to suggest hospitalised patients may experience a longer course of illness compared with nonhospitalised patients; however, further longitudinal studies are needed to inform prognosis.[39]

Large retrospective studies have also associated COVID-19 infection with increased risks of incident heart disease, new-onset diabetes, neurological disease and chronic kidney disease.[40-42] The effects of SARS-CoV-2 infection and long COVID on neurodegenerative disease or cancer remain to be determined.

Conclusion

Long COVID is a chronic postviral syndrome affecting five to 20% of individuals after SARS-CoV-2 infection. Patients often present to their GPs with symptoms of fatigue, breathlessness or cognitive impairment that often limit everyday functioning. Investigations for alternative causes of illness and appropriate management should be initiated as early as one month after infection, particularly for patients with debilitating symptoms. Although there is no cure for long COVID, most patients can be effectively supported in primary care using chronic disease management principles. Further research into the immunological mechanisms of long COVID may identify novel therapeutic targets. Larger studies with robust longitudinal methodology in the postvaccine Omicron era are needed to inform prognosis. Practice points for GPs are presented in Box 3. MT

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A list of references is included in the online version of this article (www.medicinetoday.com.au).

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