How to Treat Quiz

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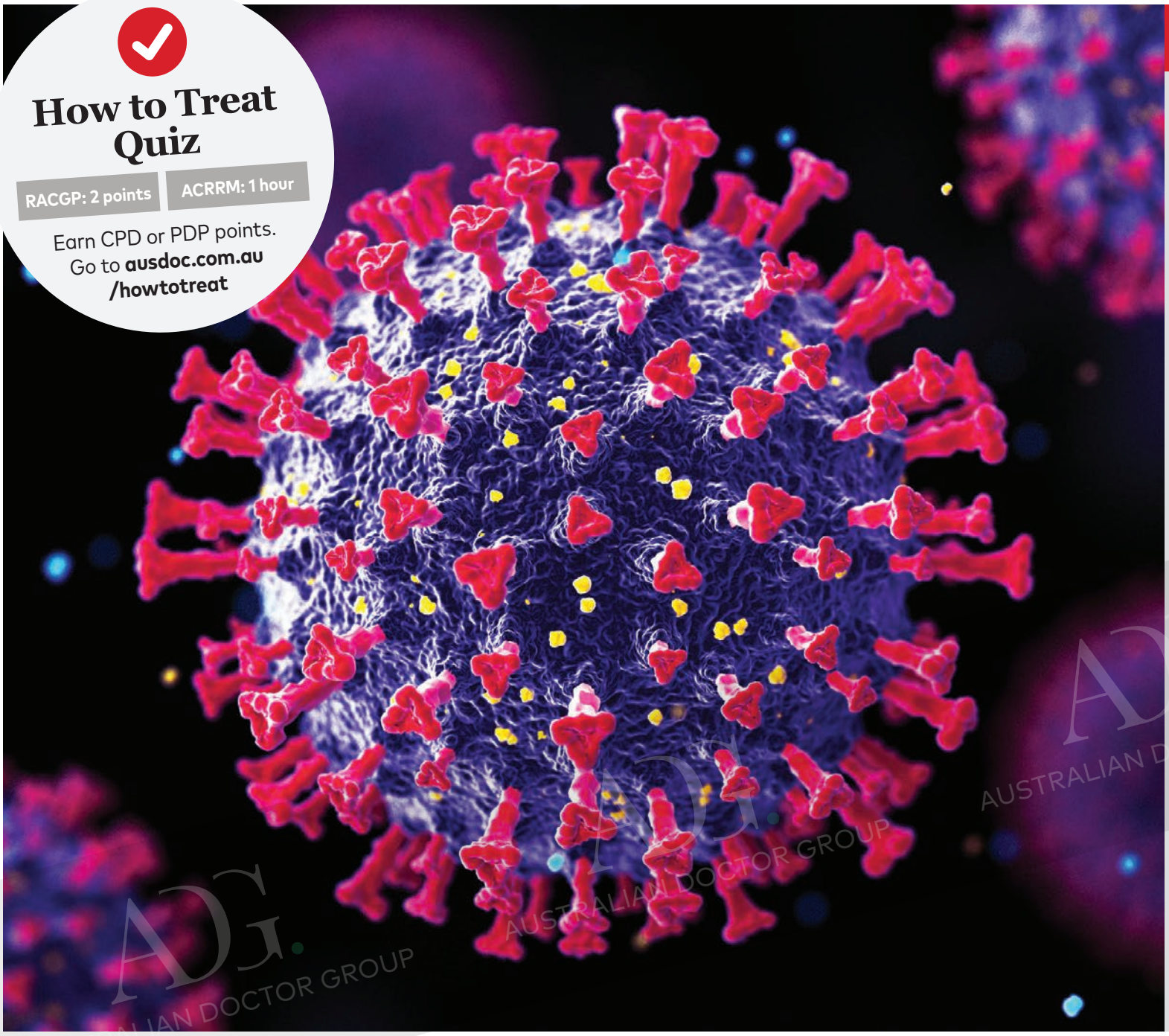

NEED TO KNOW

Long COVID is the persistence of symptoms 12 weeks or more from SARS-CoV-2 viral infection that are not otherwise explained.

Knowledge of the patient's pre-COVID health status is essential in the diagnosis of long COVID.

Fatigue, dyspnoea and cognitive dysfunction are common long COVID symptoms.

Early identification of long COVID patients is possible using known risk factors such as severe acute COVID disease (requiring hospitalisation), more than five acute symptoms, female gender and comorbid disease, including diabetes.

Baseline assessments with questionnaires (COVID-19 Yorkshire Rehabilitation Scale), blood tests, ECG and chest X-ray can be easily performed by GPs.

While no specific treatments are currently available, optimising existing or newly diagnosed conditions will benefit patients.

Red flag symptoms of chest pain, dyspnoea at rest, syncope and suicidal ideation require prompt inpatient or specialist referral.

Patients with long COVID require a multidisciplinary chronic care plan.

Long COVID

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BACKGROUND

IN 2019 the novel coronavirus SARS-CoV-2 was found to cause an acute respiratory distress syndrome (ARDS) among the first patients identified in Wuhan, China.[1] As with other respiratory viruses causing ARDS (including SARS-CoV-1 and Middle East respiratory syndrome), the mortality rate for COVID-19 disease was high. However, the infectiousness of this new virus allowed it to rapidly infect new hosts via droplet and aerosol transmission. The virus rapidly spread around the world and was declared a global pandemic at the start of 2020 by the WHO. There are now more than six million deaths from over 500 million cases of COVID-19, although the true numbers are probably much higher.[2]

Persistent symptoms following severe acute COVID-19 were expected among patients recovering from severe pneumonia, ARDS and intensive care admissions. However, the literature began reporting COVID-19 survivors with a wide spectrum of symptoms across several organ systems, including those not thought to be directly affected by the virus.[3] The chronicity of this reported "post-acute" syndrome among "long haulers" was also surprising, particularly among previously healthy individuals with a non-severe (community managed) initial acute COVID-19 illness.[4] The recognition of a variety of chronic symptoms among people with a history of SARS-CoV-2 virus eventually led to the formal definition of "long COVID" by the WHO in October of 2021, now defined as "the persistence of symptoms beyond 12 weeks" not otherwise explained by an alternative diagnosis.[5]

This How to Treat discusses the known pathophysiology of the acute SARS-CoV-2 viral infection that leads to long COVID in some people. It explains who is most likely to have long COVID, how this is diagnosed, and aims to ensure GPs can identify high-risk patients, confirm a long COVID diagnosis with simple baseline investigations and then begin the (often long) process of management to minimise debilitating symptoms. Also discussed are the red flag symptoms of long COVID and when to refer to specialists.

AETIOLOGY

COVID-19 disease is caused by inhalation and subsequent entry of the novel enveloped betacoronavirus SARS-CoV-2 into the host's respiratory tract, causing an acute respiratory infection. While much (80%) of new RNA virus' genes are similar to the original SARS-CoV-1 virus, there are important differences in SARS-CoV-2 surface proteins and viral load kinetics that most likely explain its greater transmissibility, which has led to much more widespread global disease.[6] In the common respiratory form of COVID, the spike protein subunit of SARS-CoV-2 binds to the ACE-2 receptor of the respiratory epithelial cells lining the upper airway before gaining entry into the cell via the surface airway vascular cell transmembrane serine protease 2. The viral genome is then released into the host cytoplasm where viral replication, assembly and release into the host begin the first of the biphasic pattern of acute illness (see figure 1).

The peak SARS-CoV-2 viral load is typically at the time of symptom onset in the host, before declining, with positive viral cultures (as opposed to detectable RNA) uncommon beyond nine days.[6] The second phase of the acute COVID-19 illness (after 5-10 days, with shorter times for later viral variants) is dominated by a profound inflammatory response of the host's immune system characterised by activated cytokines, including tumour necrosis factor and IL-6 detectable in peripheral blood. It is thought that the severity of the host inflammatory response correlates with the severity of the acute illness, at least for pulmonary severity and pneumonitis.[7]

Treatments to limit acute lung injury (ALI) and ARDS are directed at reducing this overactive immune response (see management).

Following acute COVID-19 disease, most people will fortunately recover completely within 28 days. Those with persistent symptoms beyond this are said to have post-acute sequelae of COVID; it is this group of patients who require careful scrutiny to identify early those requiring investigations and further management for a chronic or long COVID condition.[5,8]

There are more than 40 symptoms associated with long COVID.[9] The most commonly experienced symptoms in order of prevalence are fatigue, dyspnoea, myalgia, joint pain, headache, cough and chest pain.[10] However, worsening mental health, insomnia, word-finding difficulty and 'brain fog' with difficulty maintaining concentration and performing complex tasks are also prevalent but less easily identified, especially by self-report.

Long COVID symptoms can affect almost any body organ and are sometimes rather unexpected, such as hair loss, rashes and red eyes. Symptoms may be constant or variable, mild or severe, but they are almost always noticed by the patient and frequently ▸

◂ interfere with both quality of life and the ability to perform usual activities (including employment).

The recent Australian ADAPT study of mostly community-managed patients with a history of SARS-CoV-2 virus found one in four experienced not just cognitive impairment in the months following acute COVID-19 disease, but a decline in cognitive function over 12 months.[11] Interestingly, cognitive decline was not associated with the severity of the initial disease (requiring hospitalisation) nor the presence of a mood disorder (anxiety or depression), which is common among patients with chronic and disabling symptoms.[11]

EPIDEMIOLOGY

THERE have been almost 10 million reported cases of COVID-19 in Australia since the start of the pandemic, and over 13,000 (acute) deaths associated with COVID-19.[12] The true number of cases is likely higher, as many asymptomatic infections will go undetected, and there have been periods of limited test accessibility, and variable reporting of community cases. Most of the positive cases in Australia have been since December 2021, coinciding with the Omicron wave. From that time, case numbers grew quickly, with confirmed cases peaking in early January – more than 450,000 cases were diagnosed in the week ending January 2022.[13] Comparatively, in the week ending 28 June 2022, there were approximately 48,000 confirmed cases.[12] The Omicron variant remains the dominant lineage in Australia at the time of writing. In July 2022, BA.2 was the most common circulating sub-lineage; however, the proportion of BA.4 and BA.5 has recently increased, and these are now the dominant sub-lineages of the virus, with overall case numbers rising because of their increased transmissibility.[14,15]

Globally, the total number of COVID-19 cases stands at nearly 596 million, with more than 6.4 million deaths (as of 25 August 2022).[2] The global death rate is approximately 10 times that of the death rate in Australia, reflective of our access to and high uptake of vaccines and the relatively low case numbers during the early stages of the pandemic, which was achieved through other public health measures. More than 95% of Australians over the age of 16 have received two doses of a COVID-19 vaccine, and 70% of the eligible population has received three or more doses.[12] Vaccination is known to provide protection against severe illness, hospitalisation and death from COVID-19, and research suggests the risk of long COVID is reduced.[16] In addition, cohort studies demonstrate an improvement in long COVID symptoms following a first (13%) and second (9%) vaccination in those infected with the virus prior to vaccination.[16] Overall, 10-20% of acute SARS-CoV-2 viral infections go on to experience prolonged symptoms consistent with a diagnosis of long COVID.[4,17] This means between 0.8 and 1.6 million Australians may already be affected by the condition. The impact of different variants on the development of long COVID remains unclear; however, UK data suggests the Omicron variants may be less likely than Delta to result in long COVID, with 5% and 11% of respondents reporting symptoms beyond 12 weeks.[18]

Risk factors for the development of long COVID (beyond 12 weeks) include older age, hospitalisation for acute COVID-19 disease, being unvaccinated (for SARS-CoV-2), comorbidities such as diabetes, and the presence of more than five symptoms at the time of initial diagnosis. Interestingly, female gender is also a significant risk factor for long COVID, with a greater than three times increased risk among hospitalised patients in Spain and 1.5 times risk for a community-based population from the UK.[19, 20]

A genetic basis for long COVID is also suspected; however, this is far from being completely understood. The OAS1/2/3 gene cluster on chromosome 12 (12q24.13) has been identified as a point of risk for severe acute COVID-19 disease. This block of DNA (haplotype) that spans these three genes is derived from Neanderthals, and confers an approximately 23% increased risk of becoming critically unwell with acute COVID-19.[21] Whether this locus also provides protection against long COVID is unclear, but we know that severe acute COVID-19 (requiring intensive care admission) is a strong risk factor for subsequent long COVID.

PATHOPHYSIOLOGY

THE underlying pathophysiology of long COVID is incompletely understood (see figure 2). There are three popular theories to account for the development of a post-COVID syndrome: first, sustained host inflammatory response; second, microclots causing multi-organ dysfunction; and third, the persistence of viral antigen or stimulation of autoimmunity through molecular mimicry.

Cohort and case control studies demonstrate highly active innate immune cells producing pro-inflammatory cytokines over several months compared with healthy controls or other coronaviruses. While no single cytokine was identified, combinations of type I interferon (IFN-B), PTX-3, IL-6 and type III interferon (IFN-gamma 1) remained high at eight months and predicted long COVID with approximately 80% accuracy.[22] Certain chemokines that help regulate white cell immune responses have also been found in higher levels among long COVID patients. Chemokine ligand 2 (CCL2), which is secreted by macrophages and smooth muscle cells, promotes inflammation and has been implicated in ARDS, and chemokine receptor type 5 also appears to be important in mediating respiratory and vascular sequelae.[23]

Coagulopathies are a recognised feature of both COVID and long COVID. The activation of complement mediated endothelial inflammation results in a pro-coagulant state with thrombotic micro-angiopathy demonstrated in patients with severe acute COVID-19 disease.[24]

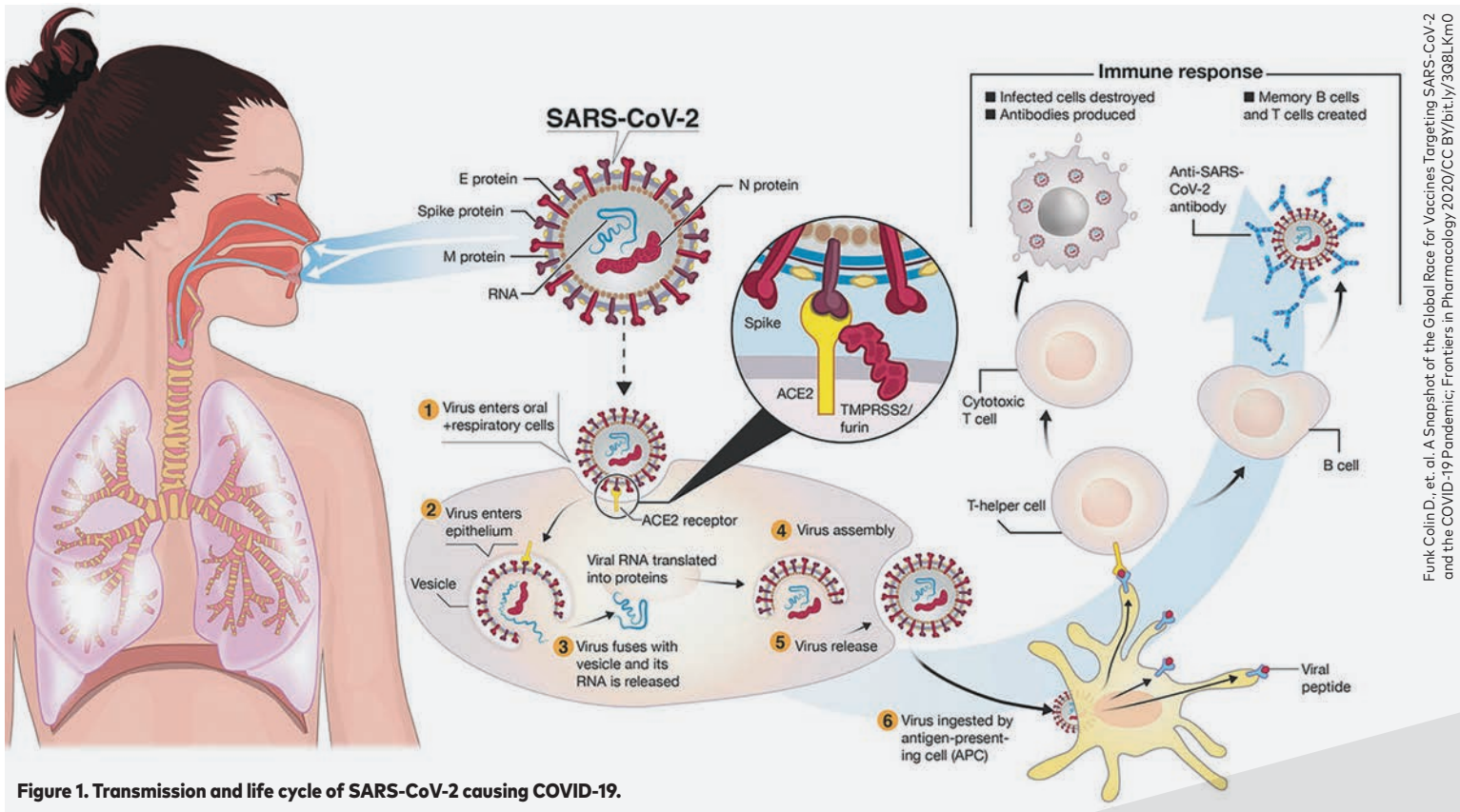
The microclot theory attributes the aetiology of long COVID to the formation of aberrant amyloid fibrin microclots, triggered by the SARS-CoV spike protein. Amyloid microclots can inhibit the transport of red blood cells to capillaries, thus inhibiting the transport of oxygen to the tissues.[25] These abnormal clots may be resistant to natural fibrinolysis and result in the multi-organ dysfunction encountered in long COVID. While multiple explanations are proposed for the pathophysiology of long COVID, none is yet able to satisfactorily explain the phenomena.

DIAGNOSIS AND INVESTIGATIONS

LONG COVID or a post-COVID condition is diagnosed in accordance with the Delphi consensus definition of the WHO in October 2021.[5] The condition is defined by the acquisition of confirmed or probable SARS-CoV-2 viral infection that leads to the persistence of symptoms beyond 12 weeks. Persistent symptoms can affect most organ systems (see figure 3) and should not be due to an alternative medical condition.

Before a patient can be said to have long COVID, the clinician must be confident that the diagnosis of SARS-CoV-2 has been correctly made. If the method of detection of the virus was made by polymerase chain reaction (PCR), this can be easily confirmed with the laboratory along with the date of detection. However, if a rapid antigen test (RAT) was used, these diagnostic details will usually not be recorded with a laboratory but may have been registered by the patient in their state of residence. Regardless of whether the PCR or RAT was used to detect the SARS-CoV-2 virus, the clinician should be satisfied that the history of symptom onset, disease progression and recovery (complete or partial) is consistent with a history of COVID-19 disease, noting that a spectrum of disease severity is possible.

In cases where there is doubt, a blood test can be ordered requesting COVID-19 serology (to differentiate natural infection from vaccination utilising the nucleocapsid and spike proteins). While false negative tests can PAGE 22 ▸



Funk Colin D., et. al. A Snapshot of the Global Race for Vaccines Targeting SARS-CoV-2 and the COVID-19 Pandemic; Frontiers in Pharmacology 2020/CC BY/bit.ly/3Q8LKm0

Figure 1. Transmission and life cycle of SARS-CoV-2 causing COVID-19.

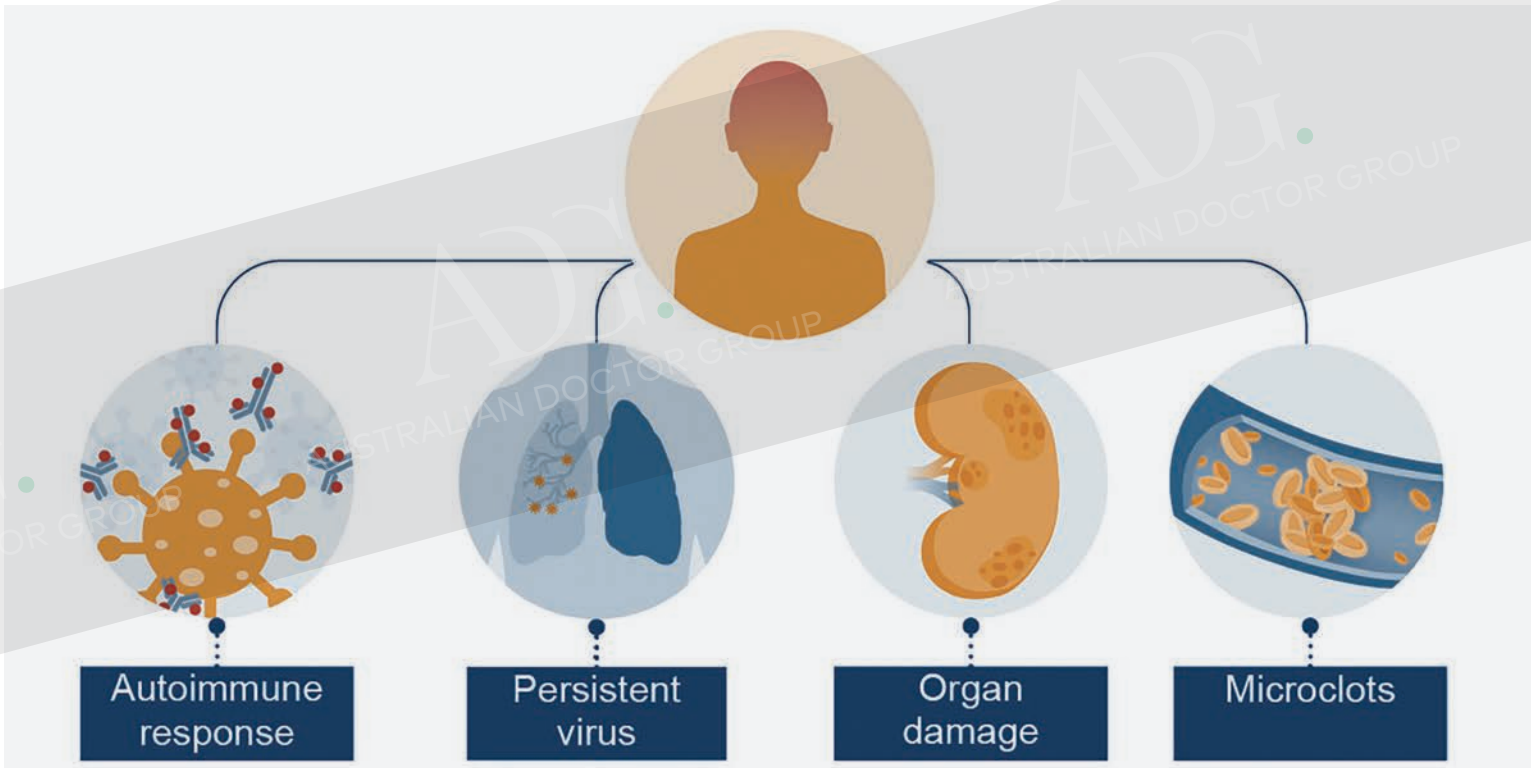


Figure 2. Possible causes of long COVID.

Government Accountability Office (GAO) analysis of medical literature. GAO-22-105666

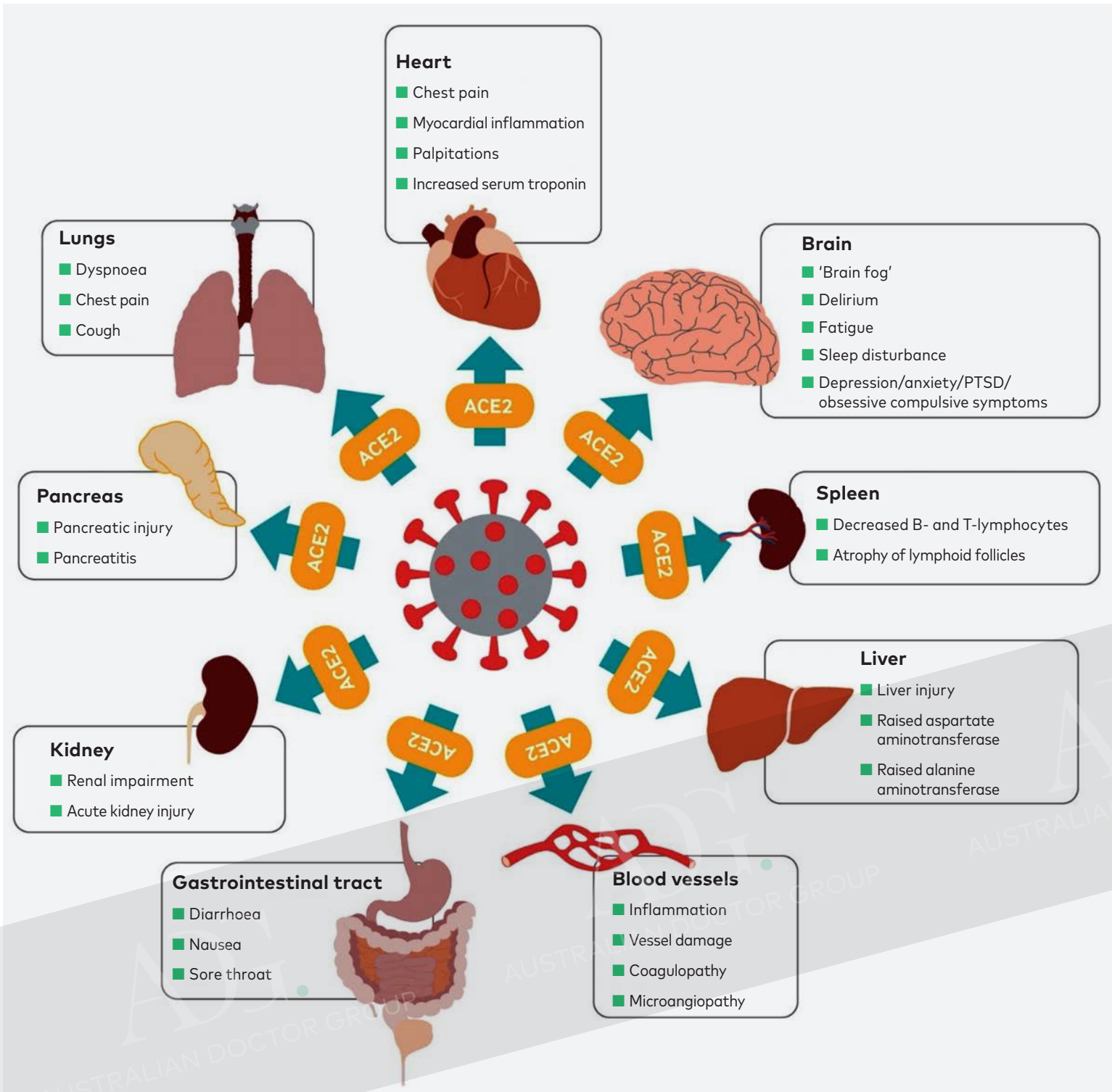


Figure 3. Multi-organ complications of COVID-19 and long COVID.

Box 1. Indications for specialist referral

- A large variety of symptoms that require a range of therapists, which may be difficult to co-ordinate in the community.
- Where deterioration in symptoms or lack of improvement is noted.
- When patients have been referred to several specialists who have not been able to find treatable causes for the symptoms.
- When treating therapists recommend more intensive therapy.
- When financial constraints make managing the patient in the community or through the private sector difficult.

◂PAGE 20 occur, a positive nucleocapsid antibody confirms a history of natural COVID-19 disease.

Once the history of COVID-19 disease is established, the clinician must then calculate the time that has passed with persistent symptoms and then investigate whether these symptoms are explained by alternative diagnoses. Twelve weeks after the onset of acute COVID symptoms (or diagnosis) is necessary for a diagnosis of long COVID. This is also referred to as eight weeks of symptoms beyond the acute period of the initial illness (four weeks). The exclusion of alternative conditions or diagnoses that could explain persistent symptoms require baseline investigations and a knowledge of the patient's comorbid disease. GPs are well placed to initiate these tests, as they are likely to have a record of their patients' pre-COVID status, including pre-existing medical conditions, blood tests and imaging results performed before the onset of acute COVID illness.

The history and physical examination will determine which investigations are most appropriate for each individual patient. In general, order blood tests to exclude electrolyte disturbance, anaemia, renal, liver dysfunction or thyroid dysfunction as well as inflammatory markers in most people. In those with dyspnoea or chest pain, the addition of CK, troponin and D-dimer are useful in excluding important cardio-pulmonary causes. The D-dimer is frequently elevated in patients post COVID and does not always indicate venous thromboembolism, but a negative result makes that diagnosis unlikely in most patients. Table 1 lists a suggested approach to baseline investigations for GPs.

An ECG and chest X-ray are simple to perform and, if normal, provide reassurance among those with predominant neurological and generalised symptoms of long COVID. For patients with persistent chest pain, dyspnoea or the suggestion of possible arrhythmia or autonomic dysfunction, more sophisticated testing is required; specialist referral is usually appropriate at this point. Undertake further investigation in consultation with a specialist because of the variable yield of clinically relevant information and significant cost to patients. In rural settings and/or after discussion with a specialist, some of the following tests may be required: CT pulmonary angiogram, 24-hour Holter monitor, transthoracic echocardiogram or ventilation/perfusion (V/Q) lung scanning.

MANAGEMENT

PREVENTION is better than cure. GPs and clinicians are encouraged to do everything possible to reduce the probability of infection and severe disease from SARS-CoV-2 to reduce the likelihood of long COVID. Vaccination (against COVID-19) has been shown to reduce the risk of viral acquisition (symptomatic and asymptomatic) as well as progression to hypoxic respiratory failure and the need for hospitalisation.[26,27] While certain variants of concern (particularly Omicron) are more able to evade vaccinated individuals (46.7% vaccine efficacy of Astra Zeneca course at 5-9 weeks), the number of vaccines received and the durability of the individual's immune response are important variables.[28] Among adults who have breakthrough infection following two COVID-19 vaccines, the risk of long COVID is reduced by approximately 15%.[29]

The widespread availability of oral antiviral medication for certain high-risk populations also limits severe disease, hospitalisation and therefore long COVID.[30] The rapid initiation of these medications (within five days of the onset of the illness) is not without its challenges. Eligible patients may not be aware of their availability, and access to primary or specialist care for an unwell and infectious COVID-19 patient is often difficult at short notice. Strategies to facilitate virtual communication between patients and healthcare professionals such as email and telehealth are essential. A COVID action plan for high-risk patients, including those with disabilities and/or with comorbid conditions, is of critical importance.

The presence of red flags, such as active suicidal ideation, dyspnoea with poor oxygen saturations at rest or exercise, acute deterioration in cognitive function, focal neurological signs or falls with injury, requires urgent referral to ED to exclude life-threatening conditions.

Clinical management of symptoms

Table 2 outlines the clinical management of symptoms.

Education and reassurance are vital for those with post-acute symptoms that have not persisted for more than 12 weeks. Natural recovery occurs in up to 80% of those who have had COVID. It is abnormal and unusual for symptoms to persist beyond 28 days for almost all respiratory viruses. Therefore, if a patient with acute COVID has persistent symptoms after 28 days that are causing disabling symptoms, investigations and management are appropriate; do not delay till 12 weeks to investigate. All patients (acute, post-acute and chronic) need advice and assistance.

Our service directs patients to use the WHO's resource document *Support for Rehabilitation: Self-Management after COVID-19 Related Illness*.[31] A number of online education and therapy programs are available through state health departments and mental health websites; these offer tools for the management of insomnia, health anxiety and depression. NSW Health offers online resources through the HealthPathways portal. The use of the COVID-19 Yorkshire Rehabilitation Scale available on the NSW Health's Health Outcomes and Patient Experience (HOPE) platform allows clinicians to track recovery and is the only validated tool to measure long COVID recovery.[32,33]

This involvement of therapists requires co-ordination through a case conference at 4-6 weeks to ensure that goals are being attained. A Medicare billing item number is now available for allied health to attend a community case conference initiated by the GP. In some instances, there is a need for referral to a local rehabilitation physician for more intense therapy or to enhance goal attainment probability.

The NSW ACI *Clinical Practice Guide for Assessment and Management of Adults with Post-Acute Sequelae of COVID-19* outlines the management of other symptoms.[34] Phone and online support from long COVID clinics are available to assist GPs who are managing patients with long COVID symptoms in the community. However, in some situations, referral to a specialist long COVID clinic for a multidisciplinary rehabilitation assessment and treatment program may be required (see box 1).

PROGNOSIS

WHILE the prognosis for long COVID is speculative, we do have more than two years of clinical and research experience. Markers of recovery have been identified and may allow for some prognostication, as in the case with quinolinic acid and cognitive impairment following acute COVID-19 disease, but these are currently only available in the context of research studies.[11]

In an Australian cohort of mostly community managed COVID-19 patients recruited in 2020, adults with symptoms of long COVID reduced from 40% at four months to 30% by eight months.[39] Importantly, these were unvaccinated individuals with no specific treatment interventions, so this likely reflects the natural history of COVID-19 disease with the original strains of the SARS-CoV-2 virus.

If we look at prognostic information from other similar viruses with the ability to cause severe disease such as SARS-CoV-1 and Middle East respiratory syndrome coronavirus (MERS-CoV), we see that symptoms

Table 1. Suggested baseline assessments for patients with long COVID

Investigation or assessment	Domain assessed	Possible diagnosis	Abnormal threshold	Suggested further testing
C19-YRS * (0-190)	Overall COVID-19 impairment	Long COVID	Variable**	Yes
mMRC dyspnoea scale (0-4)	Breathlessness severity	Heart lung dysfunction	2**	Chest X-ray CT chest
FACIT-F scale (0-52)	Fatigue severity (lower = worse)	Fatigue	Less than 30**	Yes
MOCA (0-30)	Cognitive impairment	Dementia	Less than 26**	Dementia screen
HADS (0-21)	Mood	Anxiety Depression	Sub-scale score more than 8	Psychologist Psychiatrist
Stop BANG (0-8)	Obstructive sleep apnoea risk	Obstructive sleep apnoea	More than 3	Diagnostic sleep study (home)
Epworth Sleepiness Score (0-24)	Hypersomnolence	Poor sleep hygiene Obstructive sleep apnoea Secondary	More than 10	Sleep hygiene Sleep study Sleep physician
FBC	Abnormalities of blood cells	Anaemia Inflammation	See laboratory reference ranges	Anaemia screen Infection screen
EUC	Abnormalities of renal function and electrolytes	Renal impairment Deficiency or excess in electrolytes	See laboratory reference ranges	Kidney disease screen Gastrointestinal
LFT	Abnormalities of liver function	Liver injury Steatosis Cirrhosis	See laboratory reference ranges	Liver specific
Fasting BSL and HbA1C	Endocrine	Diabetes Impaired glucose tolerance	See laboratory reference ranges	Diabetes specific
TFT	Thyroid dysfunction	Hypothyroidism Hyperthyroid	See laboratory reference ranges	Thyroid screen
Iron studies, B12, folate, vitamin D	Nutritional	Deficiency	See laboratory reference ranges	Micronutrient specific
Chest X-ray	Cardio-respiratory	Pulmonary infiltrates Heart failure Pleural effusion	Any abnormality (unexplained)	CT chest Echocardiogram
Spirometry pre/post	Respiratory (lung mechanics)	Obstructive (asthma/COPD) Restrictive	Any abnormality (unexplained)	Complex lung function testing
ECG	Cardiology	Atrial fibrillation Heart block Pericarditis Ischaemia	Any abnormality (unexplained)	Holter monitor Autonomic studies Cardiologist review

**C19-YRS, COVID-19 Yorkshire Rehabilitation Screening Tool*
***An abnormal threshold also requires consideration for what the patient's level of disability was pre-COVID and how the current disability impacts usual activities*

Table 2. Clinical management of symptoms

Symptom	Management
Fatigue This is a common symptom and affects nearly 60% of patients at three months and requires a multimodal approach[35] This may be physical, cognitive and/or emotional, affecting function, ability to work or drive, and can have a fluctuating course[36]	Exclude other treatable causes of fatigue; perform a medication review, and optimise sleep, mental health and comorbidity Several patients with long COVID at the St Vincent's clinic have been incidentally diagnosed with iron deficiency Once all other causes and contributors are excluded, attempt a multidisciplinary approach with a case conference for goal setting and to review outcomes: • An individualised, physiotherapy designed activity/movement program using patient-reported fatigue and breathlessness scores as feedback (such as the Borg scale) — This is critical, as many with fatigue also have post-exertional malaise that can temporarily worsen physical outcomes; the latter needs to be carefully avoided through pacing and supervision of activity • Pain management • Psychology-directed pacing skills and management of breathlessness during daily activities, as well as psychoeducation around activity modification and the management of distress — An occupational therapy review for energy conservation strategies, assistance with return to work, and driving programs through task training and liaison with the workplace • Nutritional review for patients with dysgeusia and weight loss, with review of blood levels of iron, vitamins B12, D and folate, so that an eating plan can be designed • An ambulatory sleep study in patients at risk of sleep disordered breathing to rule out obstructive sleep apnoea
Cognitive dysfunction This is reported by almost 30% of patients with long COVID[35] Symptoms are variable but may include executive dysfunction, deficits in attention, working memory and word-finding difficulties, and are strongly linked with fatigue	Cognitive screening using MMSE or MoCA may be indicated, as well as neuroimaging and referral to a neurologist in some cases Focus management around optimising underlying conditions such as pain or sleep disorders, medication review, enforcing sleep hygiene strategies, developing a return to activity and movement program[37] A referral to an occupational therapist or speech pathologist may also be indicated
Dyspnoea This affects 25% of patients with post-acute long COVID and may reflect breathing discomfort or an awareness of breathing[35]	Refer patients who are desaturating on room air or have abnormal respiratory examination findings to a respiratory physician[38] Lung function tests may be indicated if symptoms persist, and a bronchodilator may be indicated based on these findings Perform a chest X-ray Several patients in our post-acute and long COVID clinic have been diagnosed with pulmonary embolism (PE); an elevated D-dimer in a patient with new onset of breathlessness warrants a V/Q scan or CTPA to rule out PE Medications may be prescribed for ongoing evidence of pneumonitis, or the patient may be referred to their local pulmonary rehabilitation program
Cardiovascular symptoms	Cardiovascular symptoms including chest pain, palpitations or autonomic dysfunction may require further investigation and referral to a cardiologist Some of our long COVID clinic patients have subsequently been diagnosed with postural orthostatic tachycardia syndrome
Mood disorders Mood disorders post COVID-19 infection are present in more than 10% of patients and may include symptoms of PTSD from hospitalisation[35]	Supportive counselling and an appropriate referral to clinical psychology with the development of a Mental Health Care Plan are recommended Some patients may require pharmacological treatment

can persist for several years.[40] Most of these patients were hospitalised for their acute illness, often requiring intensive care, which is quite different from most patients, with SARS-CoV-2 patients currently managed in the community in Australia. Nonetheless, it appears that many patients with long COVID will have a slow diminution of symptoms over time. GPs and clinicians should therefore approach long COVID in the same way as a chronic medical illness, one that requires a multidisciplinary management plan and ongoing review.

THE FUTURE

BECAUSE long COVID symptoms are often subjective and heterogenous, attempts to quantify functional impairment and disability are important in measuring both the health and economic impact of the condition and the evaluation of response to treatment. It is hoped that future biomarkers will allow the rapid identification of people most likely to progress to long COVID from their acute infection with the SARS-CoV-2 virus.

With an improved understanding of the pathophysiological basis of this common and debilitating post-viral condition, specific and targeted treatments that demonstrate objective benefit to important clinical and functional outcomes will be able to be employed. As with other complex, multisystem diseases, it is expected that the future management of long COVID will include targeted pharmacotherapy with attention to lifestyle and environmental factors that may be protective or harmful. Like the virus itself, long COVID management is rapidly evolving and requires constant vigilance to ensure clinical practice follows the best available evidence combined with clinical acumen.

CASE STUDIES

Case study one

PAULA, a 65-year-old ex-smoker of 35 pack years, was functionally independent with mild breathlessness on exertion and no exercise limitation before contracting SARS-CoV-2 in January 2022. She was unvaccinated at the time of acute infection and experienced fever, fatigue, cough, sputum production and severe breathlessness, which resulted in hypoxic respiratory failure and a hospital admission. She was treated with intravenous dexamethasone and remdesivir with oral baricitinib. Following clinical improvement and weaning off supplemental oxygen, she was discharged after 10 days.

She presented again with worsening breathlessness and recurrent hypoxia two weeks later. A CT pulmonary angiogram (see figures 4, 5 and 6) excluded a pulmonary embolism but demonstrated worsening pulmonary infiltrates with areas of consolidation peripherally in the bases, suggesting an organising pneumonia. She was started on prednisone 50mg daily for five days, with clinical improvement, and was discharged on a weaning course of oral steroids.

Unfortunately, Paula experienced persistent symptoms of grade 4 breathlessness with severe fatigue and bronchitis over subsequent weeks while at home. She was reviewed in the St Vincent's Hospital Post-Acute and Long COVID Clinic. Her oxygen saturation was 93% on room air, and other vital signs were normal. There were crackles at the right lung base on auscultation of the chest but no wheeze. There were no clinical signs of DVT or right heart failure. Laboratory investigations revealed a normal C-reactive protein, renal function and electrolytes. The blood sugar was 6.9mmol (random 3.0-7.7mmol/L), D-dimer was elevated, and liver function tests were mildly abnormal with a raised ALT and AST, but stable.

Lung function tests with spirometry demonstrated a fixed, moderate severity obstructive deficit with a FEV1 of 1.4L.

A subsequent V/Q scan (see figure 7) showed a subsegmental pulmonary embolism, and Paula was started on therapeutic anticoagulation (apixaban 10mg twice daily). The transthoracic echocardiogram demonstrated normal biventricular systolic function with a mild elevation in resting pulmonary pressure (25mmHg plus right atrial pressure). A thoracic CT scan showed resolution of the basal predominant organising pneumonia and COVID pneumonitis with persistent upper lobe paraseptal emphysema.

Azithromycin (250mg thrice weekly) was added to her usual combination inhaler (fluticasone furoate/umeclidinium/vilanterol) and sputum expectoration techniques as management of her moderate severity ▸

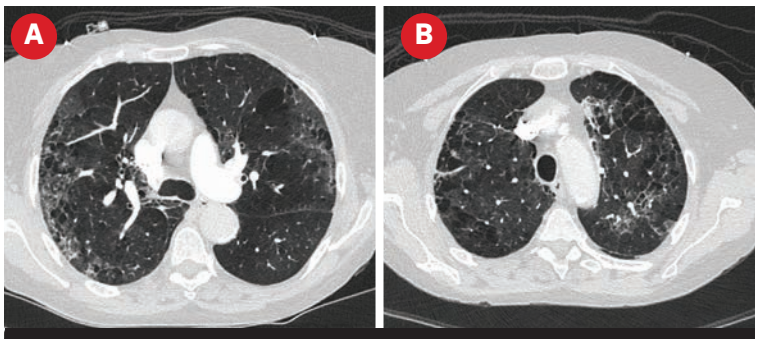


Figure 4. Serial non-contrast CT scans with transaxial slices.
Figures 4A and 4B. Initial CT scan with peripheral ground glass opacities of COVID-19 pneumonia.

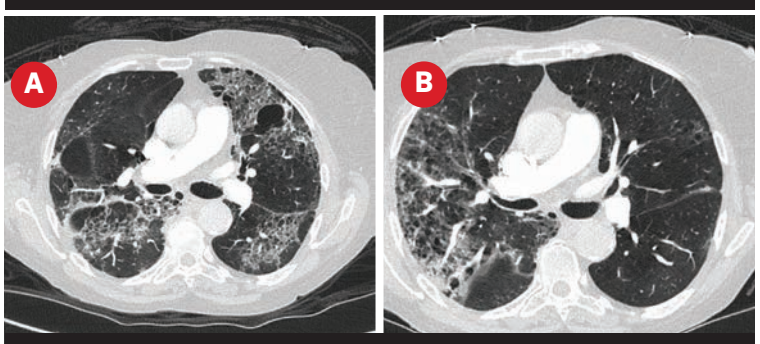


Figure 5. Progress CT.
Figures 5A and 5B. CT with peripheral areas of consolidation consistent with organising pneumonia.

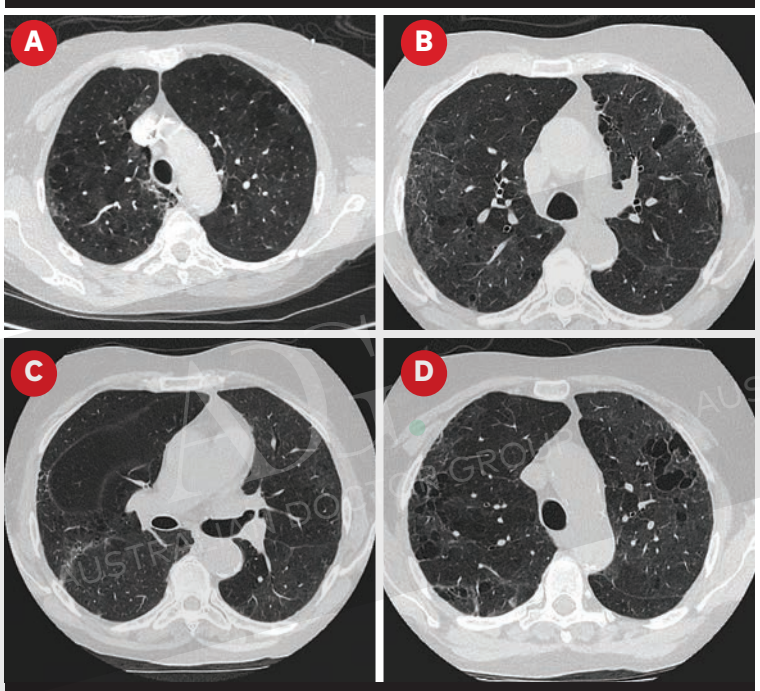


Figure 6. Final CT.
Figures 6A, 6B, 6C and 6D. CT with resolution of basal inflammatory changes but persistence paraseptal emphysema.

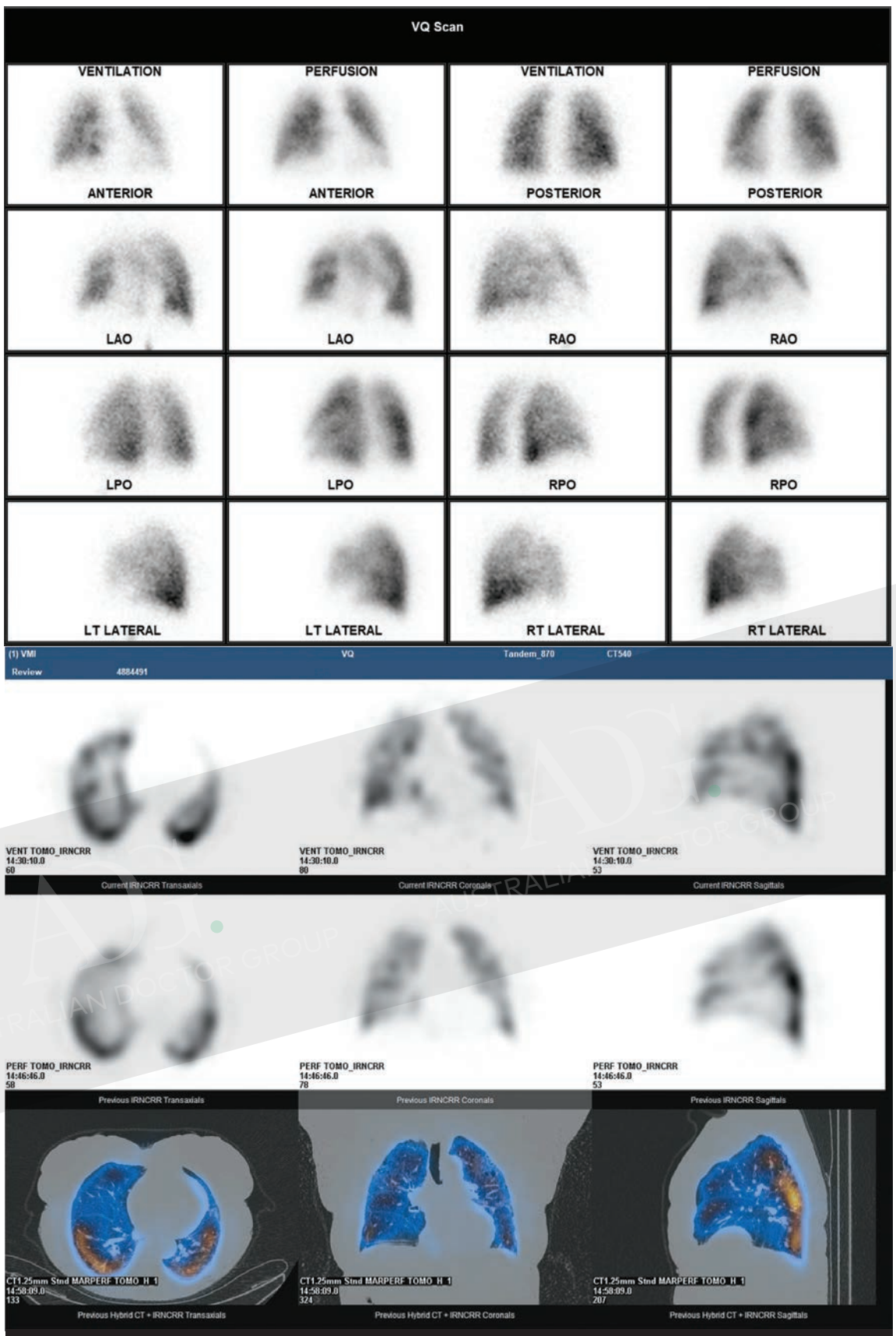


Figure 7. Nuclear medicine V/Q lung scan demonstrating subsegmental pulmonary embolism.

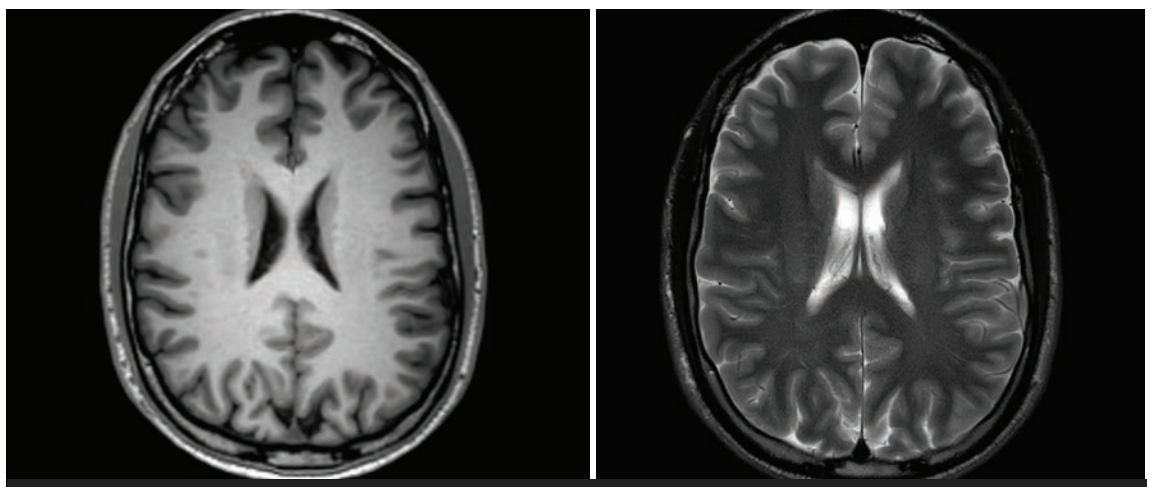


Figure 8. MRI showing mild inflammatory change in the frontal white matter and brainstem.

◂ COPD. She is referred for rehabilitation, physiotherapy and psychology review.

Paula experienced a gradual improvement in her breathlessness (grade 2 from 4) and fatigue over the next month. Her exercise tolerance also improved, but she had not quite recovered to her pre-morbid level five months post-acute COVID-19 disease.

Case study two

Sean, a 34-year-old corporate lawyer, was diagnosed with SARS-CoV-2 viral infection in December 2021. He was previously well, with a history of gastro-oesophageal reflux disease and insomnia, for which he was taking melatonin SR 2mg at night. Sean was double vaccinated against COVID-19. He was previously functionally independent and working 60 hours per week. He was also very active, including cycling to work each day, as well as running up to 6km several times a week.

Sean had multiple symptoms (more than five acute symptoms) during his acute infection, including fever, myalgias, awareness of breathing, cough with minimal sputum production, fatigue, dizziness and palpitations, but he did not require hospitalisation.

Four months after his acute infection, he was reviewed at the St Vincent's Hospital Post-Acute and Long COVID Clinic; he was predominantly affected by debilitating fatigue and persisting cognitive symptoms and had not been able to return to work. Sean had difficulty maintaining sleep, with early morning waking and non-refreshing sleep of up to six hours per night. Despite this, he was fatigued throughout the day and needed to nap for up to two hours during the day. He was able to manage his own personal activities of daily living, very light domestic tasks as well as a very short walk each day. He also had cognitive dysfunction related to deficits in attention and working memory, including dual tasking. He was struggling to read anything beyond a simple article, follow a television program or compose a text message. These symptoms had a significant impact on his mood, causing him to feel overwhelmed and anxious; he had a reactive affect, demonstrated insight into his medical condition and was highly motivated to improve his health.

His vital signs were within normal range and his physical examination was normal, apart from brisk reflexes. A Montreal Cognitive Assessment (MoCA) was performed, and he scored 28 out of 30, which is within normal limits, losing two points in delayed recall. An MRI brain (including perfusion and spectroscopy, see figures 8 and 9) was performed and showed mild inflammatory change in the frontal white matter and brainstem. A chest X-ray was normal, and a diagnostic sleep study showed mild obstructive sleep apnoea (OSA). He was referred for lung function tests to be completed.

Sean's management involved multidisciplinary input from the Post-Acute and Long COVID Clinic. He was advised to trial an increase in melatonin dose to 4mg nocte and a trial of CPAP for mild OSA. He was reviewed by a neurologist and will undergo progress neuroimaging. A physiotherapist provided guidance on a graded exercise program, and advised the incorporation of breathing exercises into his daily exercise, including walking and tai chi. A clinical psychologist supported Sean with the management of his anxiety through regulating his breathing, symptom awareness and

PAGE 26 ▸

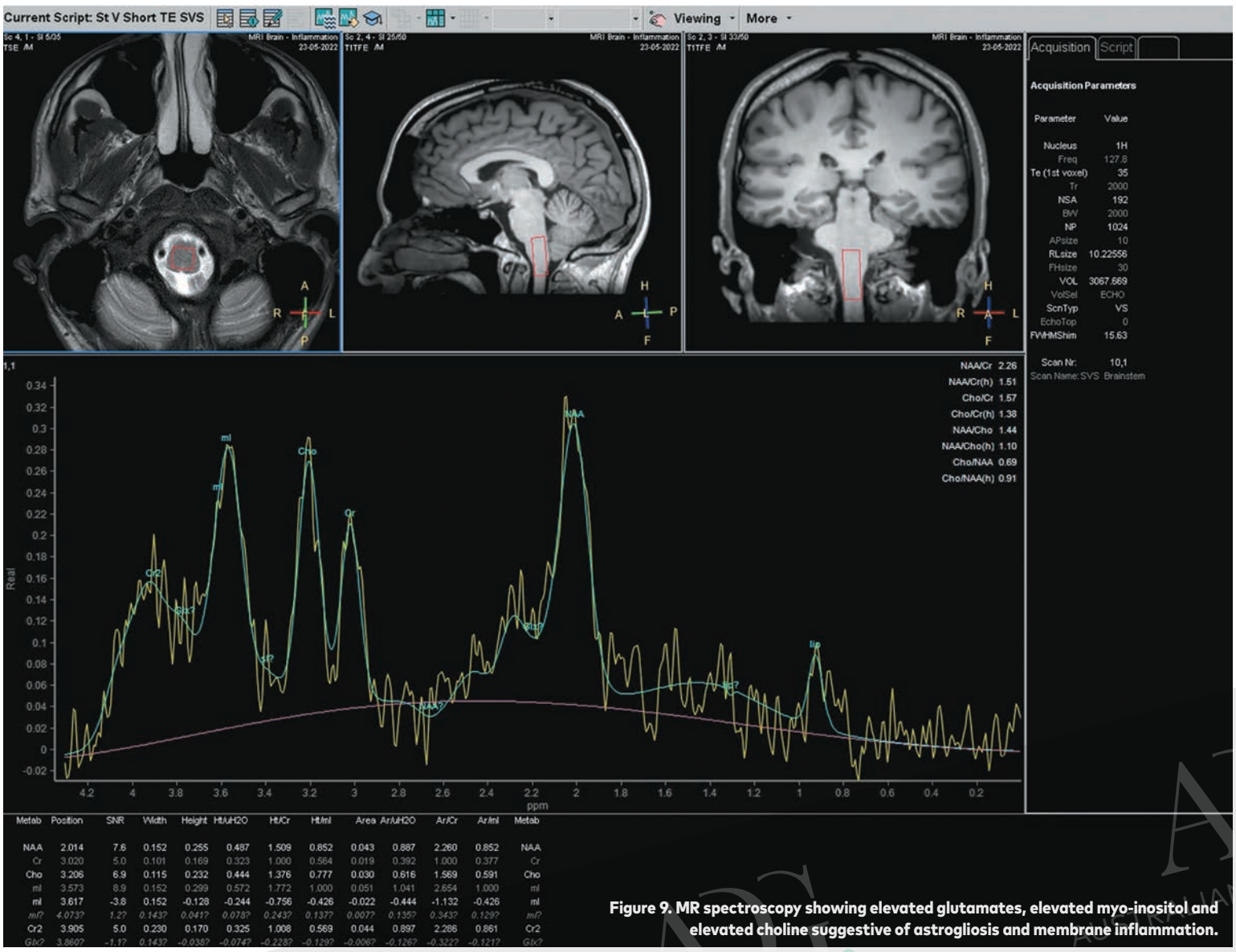


Figure 9. MR spectroscopy showing elevated glutamates, elevated myo-inositol and elevated choline suggestive of astrogliosis and membrane inflammation.

◂PAGE 24 self-management strategies. More general advice was also offered around maintaining a consistent gentle degree of physical activity to manage his fatigue, education around pacing and maintaining a routine. His cognitive symptoms were also mediated by his levels of fatigue, but could be assisted by planning, making notes and lists.

Six months post COVID-19 infection Sean has returned to working from home, up to nine hours per week, with modification of his job tasks in this initial period. A structured and gradual return to work has allowed him flexibility for pacing.

CONCLUSION

LONG COVID, a chronic post-viral condition that affects hundreds of thousands of Australians, is now common. Knowledge of risk factors and common symptoms of long COVID is critical for all healthcare professionals. Prevention of COVID-19 disease as well as limiting severe disease with existing therapies is likely to also reduce the incidence of long COVID. GPs are well placed to confirm the diagnosis based on their pre-existing knowledge of the patient combined with standardised, baseline assessments. Treatment strategies include optimising new and existing medical conditions identified on screening, and specialist and multidisciplinary referral for complex or persistent cases.

Future and more targeted pharmacotherapy is anticipated following a more complete understanding of the complex pathophysiology of long COVID and appropriate clinical trials demonstrating objective benefit with reasonable cost-effectiveness and negligible harm. Until these medications arrive, we must utilise best practice guidelines and clinical judgement. Listening to and caring for our patients with persistent symptoms is also important.

RESOURCES

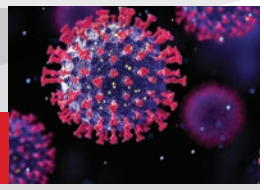
- **NICE guidelines, UK, Long COVID**
  bit.ly/3Bbka38
- **NSW Health**
  - **NSW Agency for Clinical Innovation, 'Living Evidence – post acute sequelae of COVID-19 (long COVID)'**
    bit.ly/3Pkvq1G
  - **HealthPathways**
    bit.ly/3OA6eTt
  - **Health Outcomes and Patient Experience (HOPE) IT platform**
    bit.ly/3PD0QjK
  - **Agency for Clinical Innovation Clinical practice guide for assessment and management of adults with post-acute sequelae of COVID-19**
    bit.ly/3cV6n7b

  WHO
  - **Post COVID-19 condition**
    bit.ly/3OMZoua
  - **Support for Rehabilitation: Self-Management after COVID-19 Related Illness**
    bit.ly/3OfqB8x
- **Borg Rating of Perceived Exertion Scale**
  bit.ly/3Q0vB2b
- **This Way Up: online tools and programs for mental health**
  bit.ly/2L7xFVM

References
Available on request from howtotreat@adg.com.au

How to Treat Quiz.

LONG COVID



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1. **Which THREE statements regarding the aetiology of COVID-19 are correct?**
   - **a** The peak SARS-CoV-2 viral load is typically at the time of symptom onset in the host.
   - **b** Following acute COVID-19 disease, most people will recover completely within 12 weeks.
   - **c** The second phase of the acute COVID-19 illness is dominated by a profound host inflammatory response.
   - **d** The severity of the host inflammatory response correlates with the severity of the acute illness.

2. **Which ONE is the most commonly experienced symptom in long COVID?**
   - **a** Cough.
   - **b** Myalgia.
   - **c** Fatigue.
   - **d** Dyspnoea.

3. **Which TWO are risk factors for the development of long COVID?**
   - **a** Older age.
   - **b** Acute illness lasting longer than seven days.
   - **c** Being unvaccinated for SARS-CoV-2.
   - **d** Male gender.

4. **Which THREE theories may account for the development of a post-COVID syndrome?**
   - **a** Systemic coagulopathy with widespread micro haemorrhages.
   - **b** Sustained host inflammatory response.
   - **c** Microclots causing multi-organ dysfunction.
   - **d** The persistence of viral antigen or stimulation of autoimmunity through molecular mimicry.

5. **Which THREE features are required to make a diagnosis of long COVID?**
   - **a** The acquisition of confirmed or probable SARS-CoV-2 viral infection.
   - **b** Persistence of symptoms beyond 12 weeks.
   - **c** X-ray changes.
   - **d** Persistent symptoms are not caused by an alternative medical condition.

6. **Which THREE investigations may be appropriate in the diagnosis of long COVID?**
   - **a** ECG and chest X-ray in those with predominant neurological and generalised symptoms of long COVID.
   - **b** Laboratory tests to exclude electrolyte disturbance, anaemia, renal, liver or thyroid dysfunction and inflammatory markers in most people.
   - **c** CK, troponin and D-Dimer in suspected cardio-pulmonary causes.
   - **d** A 24-hour Holter monitor in all patients with fatigue.

7. **Which TWO statements regarding the management of long COVID are correct?**
   - **a** Vaccination reduces the risk of viral acquisition, progression to hypoxic respiratory failure and the need for hospitalisation.
   - **b** Oral antiviral medications do not impact on the development of long COVID.
   - **c** Natural recovery occurs in up to 50% of those who have had COVID.
   - **d** Red flags, such as active suicidal ideation, among others, require urgent referral to ED.

8. **Which THREE are appropriate in the management of symptoms of long COVID?**
   - **a** Exclude other treatable causes of fatigue.
   - **b** Cognitive screening, neuroimaging and referral to a neurologist as required.
   - **c** An activity/movement program that will tire the patient, so they sleep well.
   - **d** Pain management.

9. **Which THREE are appropriate in the management of symptoms of long COVID?**
   - **a** Chest X-ray if dyspnoea persists.
   - **b** V/Q scan or CTPA to exclude PE if new breathlessness and an elevated D-dimer.
   - **c** Referral to a cardiologist or respiratory physician as required.
   - **d** Pharmacological treatment for mood disorders.

10. **Which THREE are indications for referral to a long COVID specialist clinic?**
    - **a** When treating therapists recommend more intensive therapy.
    - **b** When patients have been referred to several specialists who have found treatable causes for the symptoms.
    - **c** Where deterioration in symptoms or lack of improvement is noted.
    - **d** A large variety of symptoms requiring a range of therapists, which may be difficult to co-ordinate in the community.

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- Read this article and take the quiz via **ausdoc.com.au/howtotreat**
- Each article has been allocated 2 RACGP CPD points and 1 ACRRM point.
- RACGP points are uploaded every six weeks and ACRRM points quarterly.