

## CLINICAL UPDATE

# Long-COVID: An evolving problem with an extensive impact

M Mendelson,<sup>1</sup> MBBS, PhD; J Nel,<sup>2</sup> MB ChB; L Blumberg,<sup>3</sup> MB BCh, MMed (Clin Micro); S A Madhi,<sup>4</sup> MB BCh, PhD; M Dryden,<sup>3</sup> MB ChB; W Stevens,<sup>5</sup> MB BCh, MMed (Haem); F W D Venter,<sup>6</sup> MB BCh, PhD

<sup>1</sup> Division of Infectious Diseases and HIV Medicine, Department of Medicine, Groote Schuur Hospital and Faculty of Health Sciences, University of Cape Town, South Africa

<sup>2</sup> Division of Infectious Diseases, Helen Joseph Hospital and Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa

<sup>3</sup> Division of Public Health Preparedness and Response, National Institute of Communicable Diseases, South Africa

<sup>4</sup> South African Medical Research Council Vaccines and Infectious Diseases Analytical Research Unit, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa

<sup>5</sup> National Priority Programmes, National Health Laboratory Service, South Africa

<sup>6</sup> Ezintsha, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa

**Corresponding author:** M Mendelson (marc.mendelson@uct.ac.za)

Persistence of symptoms or development of new symptoms relating to SARS-CoV-2 infection late in the course of COVID-19 is an increasingly recognised problem facing the globally infected population and its health systems. 'Long-COVID' or 'COVID long-haulers' generally describes those persons with COVID-19 who experience symptoms for >28 days after diagnosis, whether laboratory confirmed or clinical. Symptoms are as markedly heterogeneous as seen in acute COVID-19 and may be constant, fluctuate, or appear and be replaced by symptoms relating to other systems with varying frequency. Such multisystem involvement requires a holistic approach to management of long-COVID, and descriptions of cohorts from low- and middle-income countries are eagerly awaited. Although many persons with long-COVID will be managed in primary care, others will require greater input from rehabilitation medicine experts. For both eventualities, planning is urgently required to ensure that the South African public health service is ready and able to respond.

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Despite much now being known about the clinical presentation and management of acute COVID-19,<sup>[1]</sup> less is known about the duration, clinical manifestations, and risk factors for development of prolonged COVID-19 sequelae, commonly referred to as 'long-COVID' or 'COVID long-haulers'. Despite long-term symptoms being recognised as manifestations of other coronavirus infections, including severe acute respiratory syndrome coronavirus (SARS) and Middle East respiratory syndrome coronavirus (MERS),<sup>[2,3]</sup> knowledge of SARS-CoV-2's sequelae remains incomplete, particularly in low- and middle-income countries. Much emphasis has been placed on people who have died or 'recovered' from SARS-CoV-2 infection, with less recognition given to those with persisting symptoms. The term 'recovered' can be a misnomer, and confuses the public, politicians and clinicians.

## What is long-COVID, and how does it manifest?

Currently there is no internationally recognised definition of long-COVID. A generally accepted time frame that differentiates the duration of the acute and post-acute infection from long-COVID is 28 days. At this stage, there is some uncertainty as to which symptoms of acute COVID-19 will persist up to 1 month, which may continue as long-COVID, and which may only start during the long-COVID time frame. Individuals with severe acute COVID-19 who require hospital admission often have residual fatigue and shortness of breath.<sup>[4]</sup> However, persisting symptoms for durations of up to 3 weeks are clearly not restricted to hospitalised persons alone. A study from the

US Centers for Disease Control and Prevention,<sup>[5]</sup> which interviewed 274 individuals with proven COVID-19 who had not been admitted to hospital, demonstrated that even in young adults, symptoms may be slow to resolve; 26% of interviewees aged 18 - 34 years reported not having returned to their usual state of health within 14 - 21 days of their test, the figure rising to 47% in those aged ≥50 years. The greater the number of pre-existing chronic conditions, the greater was the likelihood that symptom resolution would be delayed.

Similar to acute COVID-19, patients with long-COVID can experience multiple symptoms that involve the lungs and other parts of the body.<sup>[6]</sup> These may include, but are not limited to, fatigue, muscle pains, weakness and low-grade fever; cough, shortness of breath and chest pain ('lung burn'); headaches, cognitive blunting ('brain fog') and pins and needles; rashes such as chilblain-like lesions (e.g. 'COVID toe') and vesicular or maculopapular rash; mental health conditions including mood swings; and thromboembolic disease. Some symptoms such as fatigue may be continuous, while others are intermittent.

The unprecedented levels of stress triggered by COVID-19, spanning fears about the future, anticipation anxiety, loss of jobs, and fear for, and the death of, loved ones from the virus, in addition to the psychological effects of lockdown, have adversely affected the mental health of many living through the last 10 months. However, there is accumulating evidence that SARS-CoV-2 infection itself can result in persisting cognitive impairment. A recent study published online prior to peer review reported cognitive function in 84 285 participants in the Great British Intelligence Test.<sup>[7]</sup> This

study showed that COVID-19 has consequences for prolonged cognitive dysfunction even in persons who had relatively mild symptoms that were managed at home. For the most severely affected participants with COVID-19, i.e. those who had been hospitalised and required mechanical ventilation, the study found a significant loss of function, equivalent to an average 10-year decline in global cognitive performance between the ages of 20 and 70 years. Linguistic problem-solving and visual selective attention were most notably affected. Although we have known from studies predating COVID-19 that people admitted to hospital requiring mechanical ventilation for other causes demonstrate persisting cognitive deficit, sometimes lasting up to 5 years,<sup>[8]</sup> the fact that reduced cognitive performance in this study was protracted in people not requiring ventilation was 'unexpected'. In short, COVID-19 is capable of causing persisting loss in cognitive function, even in individuals who were mildly affected during the acute infection. Exactly how long this may last is still to be determined.

### How many people with acute COVID-19 go on to suffer from long-COVID?

This too is unknown, and partly relates to whether the diagnosis requires a laboratory confirmation of SARS-CoV-2 infection or not. In the study by Sudre *et al.*,<sup>[6]</sup> using a COVID Symptoms Study App to study the symptoms of over 4 million persons from the UK, the USA and Sweden, 4 182 persons were identified who had a positive SARS-CoV-2 polymerase chain reaction test, logged their symptoms prospectively, and scored themselves as 'feeling physically normal' before the onset of their illness. Of these persons with confirmed COVID-19, 13% had symptoms lasting >28 days, and of these, 4.5% had symptoms lasting >8 weeks and 2.3% >12 weeks. However, these results were only for persons with confirmed SARS-CoV-2 infection. Global testing coverage for SARS-CoV-2 has varied considerably, not just between countries but also within countries,<sup>[9]</sup> and may have changed over time as testing capacity is reached. For example, in SA, the number of persons infected with SARS-CoV-2 over and above the current figure of 759 658 since the start of our epidemic (as at 20 November 2020),<sup>[10,11]</sup> is estimated to be over 10 times that number.<sup>[12]</sup> Many people have therefore not been officially diagnosed with a laboratory-confirmed SARS-CoV-2 infection but were symptomatic during the first wave. Owing to this variance in testing, we need to accept that not having had a test for COVID-19 should not exclude a diagnosis of long-COVID in someone who experienced acute COVID-19-compatible symptoms during this epidemic and is experiencing persisting symptoms, a position supported internationally.<sup>[13]</sup>

### Can we predict who will get long-COVID?

Fatigue and headache were almost universal in persons with long-COVID identified by the COVID Symptoms Study App. Three-quarters experienced shortness of breath and anosmia, which was particularly common in the older age groups, and approximately two-thirds had persistent cough, sore throat, fever or myalgia. Persons with more than five symptoms in the first week of their illness were four times more likely to develop long-COVID than those with fewer symptoms. The five most predictive symptoms of long-COVID in the first week of illness were fatigue, headache, shortness of breath, hoarse voice and myalgia. Long-COVID was also more likely to occur in women, older people, and those with obesity.

The findings of this study applied equally in each of the three participating countries. However, that does not automatically mean

that exactly the same findings would result from a similar study in SA, which has very different health and socioeconomic profiles. Furthermore, whether the same findings are true for those who did not have a positive confirmatory test for SARS-CoV-2, remains unknown. Despite these limitations, this study provides our best current evidence for predicting who will get long-COVID and which symptoms are most likely to persist.

### What determines whether long-COVID will develop?

This remains unknown at present, and there may not be a single pathogenesis in light of the variable symptoms that may manifest and the interplay with the psychological impact of COVID-19 and the deconditioning that occurs during prolonged illness. The interplay with genetic predisposition is unknown, and the role of ongoing viral replication in driving long-term symptoms is equally uncertain. A study following 100 German patients at a median of 10 weeks from diagnosis found ongoing myocardial inflammation in 60%, irrespective of whether they had any pre-existing heart disease and independent of severity and overall course of the acute COVID-19 illness.<sup>[14]</sup> Biopsies from affected heart muscle in three patients with a severe ischaemic pattern on cardiovascular magnetic resonance imaging showed acute lymphocytic infiltration but no signs of the coronavirus, suggesting a potential autoimmune inflammatory pathogenesis rather than one driven by viral replication. Whether this translates to all patients or to the mechanism(s) causing brain, gut, and musculoskeletal system involvement, requires further research to illuminate the driver(s) of long-COVID, and therefore how we might treat them.

### How should we manage long-COVID?

If our best guess that ~10% of people displaying symptomatic acute COVID-19 do go on to experience long-COVID, the morbidity from long-COVID and its public health implications for SA will be considerable. In view of the involvement of multiple systems, management would benefit from a holistic approach. Although this phase of illness may be managed by a primary care physician in many instances, in some cases where resources allow, a multidisciplinary team could be of benefit – clinician(s), occupational therapists/rehabilitation medicine specialists, physiotherapists and mental health practitioners may be just some of those who could bring expertise to bear, when appropriate. Furthermore, peer support groups have largely led the way in addressing long-COVID up to now, and as for other persisting illnesses, their importance should not be underestimated to patients manifesting long-standing symptoms, whether or not they require a multidisciplinary team.

However protracted its course, and despite the reported remitting and relapsing nature of symptoms experienced by some patients, it is important to provide reassurance that the majority of persons suffering from long-COVID will get better in time.<sup>[15-17]</sup>

General considerations to consider include optimising the treatment of significant coexisting conditions, e.g. diabetes, high blood pressure and mental health issues, to ensure that they are not contributing to symptoms. A healthy, balanced diet should be encouraged. Although two studies showed that vitamin D deficiency was over-represented in hospitalised patients with acute COVID-19,<sup>[18,19]</sup> there is no current scientific evidence demonstrating that supplementation with vitamins or minerals such as vitamin D, zinc, etc. reduces the risk for COVID-19 or improves long-COVID symptoms. The association of vitamin D deficiency and COVID-19 hospitalisation does not prove causation, and further studies are needed. Over-investigation

of patients' symptoms is largely unnecessary and unhelpful, while being costly for the patient. However, specialist referral should be considered if symptoms worsen, particularly if the pulmonary, cardiovascular or neurological systems are affected. Some patients with COVID-19 will manifest severe pulmonary involvement and may require specialist management and a pulmonary rehabilitation programme. Common symptoms such as lung burn and other aches and pains or fevers should be treated with simple analgesia and anti-inflammatories, as required.

Anosmia is debilitating, but reassurance should be given that it will recover with time. If it is persistent, repeated sniffing of a set of odorants (olfactory training) may help to speed recovery.<sup>[20]</sup> Chronic cough or shortness of breath may benefit from breathing control exercises.<sup>[17,21]</sup> Fatigue is often one of the most difficult symptoms to manage, not only in COVID-19, but also in non-COVID-related fatigue syndromes. Careful pacing and goal setting are a pragmatic approach.<sup>[22]</sup> Start with low-intensity exercise, increasing gradually. The Stanford Hall consensus statement for post-COVID-19 rehabilitation gives more detailed rehabilitation advice for patients and their healthcare providers.<sup>[23]</sup> Stress reduction is important at any time, but in the context of the SARS-CoV-2 pandemic and in the management of long-COVID, it becomes doubly so.<sup>[24]</sup> Involving mental health professionals in care may be necessary for those experiencing mental health issues that cannot be managed at primary care. The National Institute for Health Research in the UK has published a helpful dynamic review of the evidence around long-COVID, which contains links to many websites for healthcare practitioners caring for long-COVID patients.<sup>[25]</sup>

## Summary

Although long-COVID may be short on evidence for optimal management, this rapidly evolving clinical problem has important public health considerations as the pandemic continues apace. An expectation of recovery and a pragmatic, holistic approach to management are required, and plans must be made to accommodate the needs of this group of patients in the SA health system. What's more, further research is clearly needed into all aspects of this condition,<sup>[26]</sup> especially in our local context with our high burden of comorbid infectious and non-communicable diseases, potentially complicating both the manifestations of long-COVID and our approach to its holistic management.

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