Long COVID:
Sufferers can take heart

Robert Tindle

MILLIONS WORLDWIDE experience post-acute sequelae of COVID-19 (PASC or long COVID), according to the World Health Organization (WHO), European Union and the UK and US governments.[1-3] Long COVID symptoms >12 weeks after the initial severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection affecting 2–20% of patients with mild and severe acute COVID-19 are endemic in every jurisdiction with a competent health reporting system.[1] Although the Australian Bureau of Statistics and other health agencies in Australia do not survey the prevalence of long COVID, it is estimated that it affects hundreds of thousands,[2] presaging a parliamentary inquiry into long COVID[4] and repeated SARS-CoV-2 infection,[5] which reported to Federal Government in April 2023.[6] The 566 submissions to the Inquiry, including those from states, territories, professional bodies and the public, largely concur with the view that long COVID presents health management and sociological challenges to Australian society (conspicuously, the Queensland Government has a somewhat different perspective, attributing long COVID to a predominantly nocebo effect[7]). Furthermore, the submissions recognise significant wellbeing and financial challenges to individuals with long COVID.

Long COVID is a heterogeneous disease with variable cardiac, pulmonary, haematological and neurological involvement in which investigation of patient-reported symptoms is frequently unremarkable. Long COVID's overlap with myalgic encephalomyelitis/chronic fatigue syndrome, postural orthopaedic tachycardia syndrome (POTS) and other post-viral manifestations[8] predisposes to a diagnosis by exclusion.[9,10]

There is no consensus on what causes lingering COVID-19 symptoms long after the acute infection has cleared.[7] Indeed, there is no definition of what long COVID is. At present, public health officials are flying blind when it comes to long COVID and vaccination.[11]

Often unable to secure a diagnosis, patients are wont to seek multiple serial medical opinions, frequently being told their condition is due to anxiety or post-pandemic mental issues.[8]

The median duration of long COVID symptoms is five months, but 10% of patients still experience symptoms at 12 months.[12] Fatigue, shortness of breath and difficulty concentrating are reported at least up to two years after SARS-CoV-2 infection.[13] It is still too early to say whether some individuals with long COVID might never recover.

Long COVID patients present elevated inflammatory biomarkers (eg interleukin-6, C-reactive protein, tumour necrosis factor-α), which might function as a core set of blood biomarkers that can be used to diagnose and manage long COVID patients in clinical practice.[14,15]

Those subscribing to long COVID digital support groups report months of frustration at not being listened to, finding the health system woefully inadequate, with few primary or secondary care professionals knowing enough to offer much. The outcome for some of those experiencing long COVID is self-prescribed medication using over-the-counter remedies and dietary changes[16] based on potentially conflicting or misleading online information.[17] Some speak of a substantial proportion of their income being used in this way.[4]

Meanwhile, jobs, careers, incomes, community involvements, friendships, relationships, hope for a recovery and mental health are being destroyed. Those experiencing long COVID report that the long COVID digital support group is the '... only place they feel safe to share, the only place they feel understood, accepted, [and] supported'.[4]

One in five of those experiencing long COVID in the UK stopped working and was not back to work six months after disease onset.[18] In Australia, an estimated 240,000 of those with long COVID no longer work full time.[4] Work absenteeism might significantly impact the nation's economy, as in the UK.[19] In the US, long COVID has been declared a national emergency.[20]

Reduced to working part time to cope with unwellness, those with long COVID commonly report having to wait a year or more before receiving a diagnosis.[4] Without a definitive diagnosis, those with long COVID are not eligible for Job Seeker, the Disability Support Pension and National Disability Insurance Scheme (NDIS) protection under the *Fair Work Act*, thereby conferring long-term financial difficulties for themselves and their dependents. There is a need for guidelines on how those with long COVID can access social security and employment protection.

Primary healthcare providers need more guidance from the Federal and State Health Department authorities on handling the long COVID deluge,[4] and need to be educated on how to diagnose long COVID and best support those with the condition. Although some states have established long COVID clinics, some of these at least are of little help to the patient in providing substantive treatment guidelines or support and are little more than incident report centres. The waiting time for a long COVID clinic is typically several months or more.[4] Some general practitioners (GPs) were unaware of the clinics' existence in their area (R Tindle, pers. obs.). Clinics should be a resource to primary health providers, contribute to treatment plans and be able to refer to specialists.[4] Clinical management, including mental health, should be codesigned with patients' lived experiences. Specialised long COVID clinics now operate in numerous European countries; 1500 patients per week are referred to UK long COVID clinics, which provide online recovery platforms, hubs for children and GP training.[21]

There is concern that COVID-19 vaccination per se might contribute to long COVID, giving rise to the colloquial term 'Long Vax(x)'.[22] The spike protein of SARS-CoV-2 exhibits pathogenic characteristics and is a possible cause of post-acute sequelae after SARS-CoV-2 infection or COVID-19 vaccination. COVID-19 vaccines utilise a modified, stabilised prefusion spike protein that might share similar toxic effects with its viral counterpart.[22,23] A possible association between COVID-19 vaccination and the incidence of POTS has been demonstrated in a cohort of 284,592 COVID-19-vaccinated individuals, though at a rate that was one-fifth of the incidence of POTS after SARS-CoV-2 infection.[24] Multiple studies have shown an increased risk of myocarditis after vaccination with mRNA encoding SARS-CoV-2 spike protein.[25–27] mRNA vaccines can result in spike protein expression in muscle tissue, the lymphatic system, cardiomyocytes and other cells after entry into the circulation.[28] Recipients of two or more injections of the mRNA vaccines display a class switch to IgG4 antibodies. Abnormally high levels of IgG4 might cause autoimmune diseases, promote cancer growth, autoimmune myocarditis and other IgG 4-related diseases (IgG4-RD) in susceptible individuals.[29] There are clear implications for vaccine boosting where these and similar observations[8,22,30] relating to COVID-19 vaccination and the incidence of long COVID-like symptoms are substantiated, adding further to public health officials' concerns. Understanding the persistence of viral mRNA and viral protein and their cellular pathological effects after vaccination with and without infection is clearly required. Because COVID-19 vaccines were approved without long-term safety data and might cause immune dysfunction, it is perhaps premature to assume that past SARS-CoV-2 infection is the sole common factor in long COVID.[8] The Australian Government's promise of $50 million from the Medical Research Future Fund for long COVID research[31] will hopefully foment nationally coordinated long COVID and COVID-19 research programs encompassing basic science through to models of care.[6] The proposed development of a national centre for disease control[6] providing a national interrogative repository for hitherto fragmented incidence and outcome data for long COVID will aid in these investigations.

An encouraging step forward is the recent discovery in a preclinical model of a peptide inhibitor of nuclear angiotensin-converting enzyme 2 that reverses the persistent inflammation driving long COVID, reduces the latent viral reservoir in monocytes/macrophages and is associated with reduced SARS-CoV-2 spike protein expression in monocytes from individuals who have recovered from infection.[32] It also enhances immune protection against SARS-CoV-2 infection.[32] Clinical trials are pending.

The above initiatives, plus the recent listing of the antiviral drugs, Paxlovid (nirmatrelvir and ritonavir) and Lagevrio (molnupiravir) on the Pharmaceutical Benefits Scheme,[33] and the updated Royal Australian College of General Practitioners' guidelines for managing patients,[34] indicate that long COVID is, at last, receiving the attention it requires. Over time, the sentiment of those with long COVID has become more positive, reflecting increased knowledge, acceptance and awareness of long COVID and health system responses to the condition.[35]

Long COVID is not an easy medical condition for clinicians, health administrators, support systems or patients. The Australian health system is already stretched in coping with other chronic medical conditions.[36] Nevertheless, we must do better than in the approximate three years since long COVID was first reported.[37]

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