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An update on Long COVID

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ABSTRACT

'Long COVID' is a major dilemma, difficult to diagnose and even more challenging to treat. Millions are still being affected globally and ~10% of people experience Long COVID following acute infection. Many complain about fatigue, brain fog and mental difficulties, and ~200 symptoms are described making diagnosis difficult. Both acute COVID-19 and Long COVID can cause organ damage – involving the heart, lungs, kidneys, and brain; as well as inflammation, and studies suggest that severe COVID-19 is dominated by endothelial and immunological dysfunction, and immunothrombosis. Diagnostic tests for Long COVID are largely in development and finding effective therapies for Long COVID has been a major challenge; however, it is likely that antivirals have a role in preventing and treating Long COVID. Real-world data support the effectiveness of COVID-19 vaccines in reducing the risk of Long COVID. Long COVID remains a major challenge that needs considerable on-going research to determine effective treatments. The global public health emergency may be over but the fallout of Long COVID will be with us for some time.

Keywords: antiviral drugs, coronavirus, COVID-19, Long COVID, PASC, SARS-CoV-2.

'Long COVID' is a major dilemma, difficult to diagnose and even more challenging to treat. Millions are still being affected globally by Long COVID and many thousands have succumbed in the USA alone. Australian research suggests that some 10% of COVID-19 cases are affected, based on symptoms being present 3 months after onset of acute COVID-19 (a diagnostic requirement); some suffer for years, though most cases are likely to resolve within 1 year.[1] In a recent review, it is estimated that at least 65 million individuals worldwide have Long COVID, and that ~10% of people experience Long COVID following acute infection, with 50–70% of people experiencing lasting symptoms following severe infection.[2]

Although a universal definition has yet to be determined, the World Health Organization (WHO) defines Long COVID as the continuation of symptoms, or the development of new symptoms, 3 months after the initial SARS-CoV-2 infection (COVID-19), with these symptoms lasting for at least 2 months with no other explanation. Long COVID can occur after any COVID-19 infection including subclinical infection.[3]

The Australian government Standing Committee on Health Report relating to COVID-19[4] has recommended the establishment and funding of a single COVID-19 database by our new Australian Centre for Disease Control to *inter alia*, document post COVID-19 complications (post-acute sequelae, PASC, of COVID-19) and establish a nationally co-ordinated research program involving basic science, clinical trials and implementation science. Evidence-based guidelines for diagnosis and treatment are needed and are in development.[4,5]

Long COVID can be debilitating. Many complain about fatigue, brain fog and mental difficulties, and ~200 symptoms are described. This makes diagnosis difficult. Nervous system disorders, such as postural orthostatic tachycardia syndrome (POTS) are commonly reported, often comorbidly with chronic fatigue syndrome (CFS). There are increasing reports of cognitive sequalae post COVID-19 infection, e.g. 6 months after acute symptoms have gone. Using magnetic resonance imaging (MRI), changes have been reported to the brain stem and front lobe in areas associated with fatigue, insomnia, anxiety, depression, headaches, and cognitive issues. Lasting lung damage has also been seen in children and teens with Long COVID using MRI technology.[6] Furthermore, many symptoms can be caused by another malady, making it vital to obtain a full understanding of symptoms, signs, and underlying conditions. Importantly, CFS, though separate, shares several similarities with Long COVID and often follows a viral respiratory condition.

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Severe COVID-19 disease can increase 'the risk of cardiac arrest, death, diabetes, heart failure, pulmonary embolism and stroke', as determined by analysis of the US Department of Veterans Affairs databases. Cases of severe acute COVID-19 disease, that require admission, have a higher risk of developing Long COVID. However, the majority of COVID-19 cases only have mild symptoms but can still develop Long COVID: the fact is that patients – who had mild to moderate acute illness – make up most people who go on to suffer from Long COVID.[2] In a small US study, 41% of patients with Long COVID had never tested positive for the virus except that they were found to have specific antibodies in their blood that indicated exposure to COVID-19.[7]

What risk factors predispose patients to Long COVID? Those with a history of allergies, anxiety, depression, arthritis, autoimmune diseases, nervous system disorders, chronic infections, diabetes (types 1 and 2), and obesity are more likely to be affected. There is also a higher prevalence of Long COVID in women – especially in perimenopausal and menopausal women and those under 50 years are also much more likely to develop PASC than men of similar age.[8] Research has also shown that being overweight negatively affects the body's immune response, impairing antibodies to fight the virus.[9] Having said that, being overweight does not seem to affect the immune response generated by COVID-19 vaccines. People cannot be blamed for developing Long COVID because exposure to the infection is almost impossible to prevent. Vaccination, adequate ventilation, as well as masking and other hygiene interventions are helpful but render imperfect protection.

The pathology of the virus is under intense scrutiny. Both acute COVID-19 and Long COVID can cause organ damage – including the heart, lungs, kidneys and brain – as well as inflammation, potentially leading to other issues, such as diabetes. Putative mechanisms underlying Long COVID's pathogenesis include abnormal neurological signalling, autoimmunity and immune dysregulation (including decreased production of SARS-CoV-2 antibodies), disruption of the microbiota, abnormal clotting, persistent reservoirs of virus or spike antigen, reactivation of underlying pathogens (e.g. Epstein–Barr Virus, Herpes Zoster or Shingles, and Herpes Simplex or Bell's palsy), priming of the immune system by molecular mimicry, endothelial and immunological dysfunction, and immunothrombosis.[10,11] However, studies suggest that severe COVID-19 is dominated by endothelial and immunological dysfunction, and immunothrombosis.

There is no clear understanding why SARS-CoV-2 can result in severe outcomes or why symptoms persist, whereas other human coronaviruses just cause common colds. However, one recent study, which used artificial intelligence methodology, has shown that fragments of the SARS-CoV-2 virus may drive inflammation by mimicking the action of specific immune molecules in the body.[12] It is likely that viral protein fragments, generated after the SARS-CoV-2 virus can mimic a key component of the body's machinery for amplifying immune signals (RECOVER: Researching COVID to Enhance Recovery, see https://recovercovid.org, accessed 2 March 2024).

Diagnostic tests for Long COVID are largely in development and focus predominantly on biomarkers such as proteins, hormones, endothelial/vascular biomarkers, and inflammatory monocytes to name a few.[13,14] However, results from a recent study suggest that complement biomarkers could facilitate the diagnosis of Long COVID, which also raises the possibility of using available inhibitors of complement activation to treat Long COVID.[15]

Finding effective therapies for Long COVID has been a major challenge and there is no broadly effective treatment. An important issue is that there are, almost certainly, multiple deleterious 'paths of destruction' so no one-fits-all-treatment can be applied. Specific medications (like inhaled steroids for shortness of breath), the application of cognitive strategies for brain fog, dietary changes, optimising sleep and the use of antiviral drugs may each be helpful. A few studies have shown that Paxlovid is useful to help resolve Long COVID more quickly in some cases.[16,17] More generally, in people at high risk of progression to severe COVID-19, Molnupiravir use within 5 days of SARS-CoV-2 infection may reduce the risk of Long COVID.[18] Both Paxlovid and Molnupiravir were associated with lower all-causes mortality risk compared with no antiviral use for the treatment of acute COVID-19.[19]

It is worth noting that Paxlovid is authorised for use in children as young as 12 years old but Molnupiravir isn't authorised for people younger than 18 years as it may affect bone and cartilage growth. Molnupiravir, is not recommended for pregnant individuals because animal studies suggest it could cause foetal harm. Simnotrelvir (a protease inhibitor) has also been shown to reduce symptoms of COVID-19 for those with mild infections.[20,21]

'COVID rebound' (recurrent symptoms), shortly after Paxlovid treatment was completed, has also been described, but is mild and short-lived, resolving on average in 3 days without additional antiviral treatment.[22] Paxlovid contains both Nirmatrelvir, a protease inhibitor that blocks SARS-CoV-2 from replicating, and Ritonavir, which boosts Nirmatrelvir by slowing its metabolism in the liver. However, care must be taken with the use of Paxlovid as Ritonavir can slow the metabolism of several important other drugs, thereby increasing their concentration in the blood. In some patients, drug interactions can occur but these can be managed by several means: temporarily withholding treatment, adjusting the dose or using an alternative concomitant medication. This can be time consuming the first few times the physician reviews a patient's current medications.

It is likely that antivirals have a role in preventing and treating Long COVID.[23,24] In other studies, various treatments have been effective for population subsets[2] and a variety of treatments to relieve Long COVID symptoms have been tried with mixed success, including: low-dose naltrexone,[25] antihistamines, anticoagulant regimens and apheresis.[26] Using specific monoclonal antibodies as therapy may also reduce infection risk – with the greatest benefit in immunocompromised persons including those receiving organ transplants. Such antibodies may also help immunocompromised patients with Long COVID.[27] Additionally, Coenzyme Q_{10} and D-ribose supplements have shown promise in treating Long COVID.[28] Ideally, to tackle any pandemic and its aftermath requires the availability of not only

effective vaccines but also accessible effective drugs that target excessive inflammation using inexpensive repurposed generic drugs. A recent review focusing on statins, ACE inhibitors and angiotensin receptor blockers suggests that these drugs help maintain or restore endothelial barrier integrity.[29,30] Many patients have turned to alternative medical treatments (including plasma exchange) but evidence for benefit is limited. Finally, it is worth noting that exercise use can assist mild–moderate cases but may be harmful in more severe cases (e.g. POTS), where pacing may be more effective and the input of a specialist program of rehabilitation is important.

Can Long COVID be avoided? It is best prevented by not getting COVID-19 in the first place. It is likely that by the end of 2024, more than 90% of people will have been exposed to COVID-19 at least once, but many repeatedly, so, clearly, PASC and Long COVID cases will keep on emerging. Many people have become blasé about annual vaccination even though vaccination can reduce the risk. In early studies the Australian Institute of Health and Welfare reported that, if you still catch COVID19 after two vaccination doses, there is a 13–47% lower risk of symptoms persisting beyond 4 weeks, compared to unvaccinated people who catch COVID-19.[1] Furthermore, in a recent study in Hong Kong, involving over 1 million patients, real-world data supported the effectiveness of COVID-19 vaccines in reducing the risk of post-COVID-19 long-term health consequences in patients who had a primary vaccination course or a booster dose.[31] This is encouraging and further highlights the importance of receiving booster vaccines, especially for those vulnerable to severe disease from COVID-19, but also for those not at risk and wanting some protection, albeit imperfect, against the development of Long COVID.

It is important to return to the recent development in Australia of a national plan for Long COVID, which recognises the chronic nature of Long COVID and the need for multidisciplinary team-based healthcare. The plan is focused on; strengthening primary healthcare services, improving COVID-19 vaccination communications, educational support for healthcare providers, and has a national research program involving an A$50 million investment. It also seeks to ensure all people with Long COVID and their families and carers can readily access support and treatment to achieve the best possible outcomes.[32]

Long COVID remains a major challenge that needs considerable on-going research to determine effective treatments. The global public health emergency may be over but the fallout of Long COVID will be with us for some time. Long COVID cases are increasing daily.

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