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REVIEW

Long Covid in Year 5: Some Progress, Still Many Questions

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Long Covid was first described in 2020. Five years later, progress in disease characterization has been considerable, and definitions continue to evolve. Several disease mechanisms are under study, and evidence for multiple endotypes is accumulating. No clinical biomarker has been identified, nor has an effective therapy been developed. Overlap with other post-infectious syndromes, particularly myalgic encephalomyelitis/chronic fatigue syndrome, is now more evident. For most individuals, symptoms of long Covid progressively disappear over time. Recurrent Covid-19 infections are now an important contributor to the pool of affected individuals. While symptoms limit activity in as many as 20%, inability to work is less common. The anticipated surge of disability claims from insured individuals has not materialized.

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EVOLVING DEFINITIONS

Multiple definitions of long Covid now exist. Each definition differs slightly and some are lengthy, underscoring both the heterogeneity of long Covid and the lack of consensus about its phenotypic expression. The definitions mostly differ in the duration of symptoms required (1 vs 3 months) and/or whether incident medical diagnoses are included. The 2024 definition proposed by the National Academies of Sciences, Engineering and Medicine's (NASEM) is the most comprehensive and lengthy definition to date.[1] In addition to sanctioning the term 'long Covid' (and reducing Covid to lower-case) it includes a catalogue of 'single or multiple diagnosable conditions' that may be considered manifestations of long Covid. This includes common cardiovascular, mental health and endocrine disorders, amongst others. Thus, new onset atrial fibrillation, diabetes mellitus or anxiety disorder, occurring 3 months after Covid-19 infection, can be considered long Covid. This seems odd; many of these diagnoses will not have been triggered by SARS-CoV-2 infection. Even more curious, these 'diagnosable conditions' include myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), suggesting that any de-novo diagnosis of ME/CFS following a Covid-19 infection can also merit the label long Covid. A dual label of long Covid and ME/CFS risks creating diagnostic ambiguity and is unlikely to curry favour with patients. The authors acknowledge the definition's 'intentional inclusivity' and write that it will lead to 'high diagnostic sensitivity and low diagnostic specificity.' This seems likely; assigning a long Covid label to common illnesses is

problematic. However, the NASEM definition is unlikely to be the final one. As clarity around phenotypic expression improves and as biomarkers emerge, the definition will become shorter and more precise.

DISEASE MECHANISMS

No single mechanism has emerged to explain the multiple symptoms of long Covid. This is not surprising; long Covid likely has multiple endotypes, with either unique or shared mechanisms. Amongst 6 possible pathogenic pathways, persistence of virus or viral fragments has attracted most attention. Viral remnants have been detected in various tissues, including the gut, brain, and endothelium, months to years following Covid-19 infection. These may provoke chronic immune activation, triggering long Covid symptoms. However, caution is needed; a persistent virus may be an incidental finding, rather than a direct cause.

Autoimmunity is the second proposed mechanism. While autoimmunity is a well-documented feature of acute Covid-19, growing evidence suggests it also plays a role in long Covid. Various antigens may be involved, with molecular mimicry potentially playing a key role.

Reactivation of Ebstein-Barr virus (EBV) is a third mechanism under scrutiny. In many individuals with long Covid, EBV antibody pattens suggest EBV reactivation. Whether symptoms are a consequence is less clear. Reactivation of EBV and human herpes viruses has long been implicated in ME/CFS, but causality has not been proven; the situation in long Covid may be similar.

Clotting abnormalities is the fourth proposed mechanism. These may be precipitated by endothelial damage, platelet activation, or by autoantibodies to clotting factors. Tissue hypoxia may result and could explain many of the multi-site long Covid symptoms.

Gut microbiome dysbiosis, characterized by an imbalance between beneficial and pathogenic bacteria, is the fifth mechanism. Dysbiosis has a series of downstream effects: it disrupts the intestinal barrier, allowing microbial metabolites to enter the systemic circulation, triggering systemic inflammation. Metabolites may ultimately cross the blood brain barrier, causing neuroinflammation. Dysbiosis may also alter the gut-brain axis, via local damage to vagal nerve endings and disruption of vagal pathways in the brainstem. Damage to the hypothalamic-pituitary axis may also be a consequence.

Finally, mitochondrial dysfunction is now recognized as a potential explanation for long Covid symptoms.[2] SARS-CoV-2 infection alters mitochondrial structure and function. The resulting metabolic perturbations, such as elevated lactic acid levels, may explain the marked fatigue and post-exercise malaise that is characteristic of long Covid.

DIAGNOSTICS

Multiple initiatives are underway to develop a diagnostic test for long Covid. As long Covid has multiple endotypes a single diagnostic test seems unlikely. More likely, patterns of abnormal biomarkers will emerge, based on blood proteins or multi-omics analyses. While not yet at the point of diagnostic utility, abnormal patterns of biomarkers, particularly markers of inflammation and complement activation, have advanced the identification of different subtypes of long Covid.[3] Multi-omics analyses are also underway and will likely provide additional clarity. Sophisticated imaging technologies, such as diffusion magnetic resonance imaging (MRI) to map glial activity, imaging flow cytometry to detect fibrin microclots and whole-body positron emission tomography (PET) to detect activated lymphocytes, have also been evaluated,[4] and while less likely to have diagnostic utility will add to the understanding of disease mechanisms.

SIMILARITIES WITH ME/CFS

The similarities between long Covid and myalgic encephalitis/chronic fatigue syndrome (ME/CFS) are striking. ME/CFS is perhaps

the best described of the 'post-acute infection syndromes' (PAIS). Common to all PAISs is a history of acute infection- viral, bacterial or rickettsial- although prior infection is not always proven. Chronic symptoms that may last months to years, and even lifetimes, are a hallmark. Long Covid distinguishes itself amongst the PAISs by virtue of its emergence during a pandemic, thus permitting a clear causative link to a prior viral infection. It has also provided an exceptionally large cohort of cases, creating a comprehensive catalogue of its clinical features and facilitating extensive research into its pathophysiology.

Are long Covid and ME/CFS the same illness, or variants of the same? The list of symptoms is remarkably similar, particularly the cardinal symptoms of fatigue, post-exertional malaise, cognitive disturbance and dysautonomia. But the lists are not identical. For example, anosmia, dysgeusia and alopecia are rare in ME/CFS, but common in long Covid, whereas painful lymph nodes are common in ME/CFS, but not seen in long Covid.[5]

All PAISs exhibit a strong female predominance, a pattern also seen in long Covid, where the female-to-male ratio is approximately 3:1. It is postulated that in addition to different immune signatures in females, a more vigorous adaptive immune response to infections may favour the development of long Covid and other PAISs.[6] Lower androgen levels may also contribute. Determining the precise reason for the sex-based prevalence difference in long Covid could provide key insights into all PAISs, including ME/CFS.

PREVALENCE OF LONG COVID AND LONG COVID DISABILITY

Global estimates of long Covid prevalence range from 3% of the population in the United Kingdom to 50% in Brazil and Saudi Arabia.[7] Variance is explained by the definition used, population and time period studied, SARS-CoV-2 variant, and vaccination status. Based on self-reports, the prevalence of long Covid in the United States in 2023 was 6.4%, varying by state from 2.9% in the US Virgin Islands to 9.7% in West Virginia.[8] In Canada, 6.9% of Canadians self-reported long Covid in 2023,[9] and in the United Kingdom, the equivalent number was 2.9%.[10]

Of those reporting long Covid symptoms, how many are unable to work? Of the 6.4% of Americans reporting long Covid symptoms, 20% reported "significant activity limitation."[8] Of the 2.9% reporting long Covid in the UK, 20% reported that day-to-day activities had been "limited a lot."[9] Neither figure adequately addresses the question of employment. Statistics Canada reports that among employed Canadian adults reporting long-term symptoms, only 5.3% applied for disability benefits or workers' compensation, and of these, 93.8% received benefits or compensation.[10] While this suggests that only 0.3% of Canadians with long Covid were unable to work, caution is in order. Some individuals with long Covid, although eligible for benefits will opt, for a variety of reasons, not to claim. Among those working Canadians reporting long-term symptoms, the most common industries represented were healthcare and social assistance (17.5%), professional, scientific and technical services (17.1%), and educational services (10.3%).[10]

To date, life insurers have not experienced the once-anticipated increase in long Covid disability claims. The reasons are likely multiple: insured populations are younger and healthier and are less likely to have had severe Covid-19, both major risk factors for long Covid. And they are more likely to be vaccinated, which reduces the long Covid risk by as much as 40%.[11] They are also more likely to have received booster doses, which lower the risk of recurrent Covid-19 infections– a newly recognized and ongoing risk factor for long Covid.

TREATMENT

There is presently no cure for long Covid. Physical therapies have gained some popularity, as have therapies directed at specific

symptoms of long Covid, eg, ivabradine for postural orthostatic tachycardia syndrome (POTS), olfactory training for loss of smell and melatonin for hypersomnia. Short-course antivirals, antiplatelets and steroids have not proven beneficial. All told, for the majority of long Covid patients, treatment options are limited.

Thus, the intense interest in the research agenda. At time of writing, using the search term 'long Covid' over 500 trials were registered with the US National Library of Medicine's ClinicalTrials.gov, of which 350 were listed as 'interventional'. The World Health Organisation's International Clinical Trial Registry Platform similarly lists over 500 studies, of which over 300 are testing potential therapies.[12] Many of these are exploratory evaluations, involving small numbers of subjects, examining a vast variety of interventions.

The results of the studies in the National Institutes of Health (NIH) RECOVER initiative are the most eagerly anticipated (https://recoverCovid.org). These will evaluate interventions that address 4 symptom clusters that characterize the long Covid cohort: autonomic symptoms, disordered sleep, postexertional malaise, and neurocognitive dysfunction. A further study will evaluate interventions to reduce viral persistence, considered the possible root cause of long Covid. All told, 8 clinical trials are presently underway evaluating 13 different interventions (https://trials.recoverid.org). Interventions include prolonged courses of nirmatrelvir/ritonavir, intravenous gamma globulin, transcranial brain stimulation to improve cognitive function, modafinil for hypersomnia, cardiopulmonary rehabilitation, and pacing protocols. Results are expected in 2025 and beyond. The wide range of interventions being tested highlights the persisting uncertainty about disease mechanisms, the lack of useful biomarkers and the urgent need for remedies that can alleviate symptoms and help restore a sense of normalcy for millions.

CONCLUSION

After 5 years, long Covid remains largely unsolved. Although clearer clinical phenotypes and distinct disease mechanisms are emerging, the absence of useful biomarkers remains a major obstacle to both defining long Covid and to the implementation of large-scale clinical trials. Nevertheless, the results from RECOVER and similar trials hold hope for both progress in disease understanding and effective treatments. In the meantime, disability claims from insured individuals remain infrequent.

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