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Long COVID: defining the role of rheumatology in care and research

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The global pandemic of COVID-19 has had an impact on the profession of rheumatology from many perspectives, including its effects on our patients with immune-mediated conditions and immunocompromised states, the disruption of care pathways, and beyond. There also are lingering questions about how the next phase of the pandemic will evolve, with the continuing emergence of new viral variants posing a continuing threat to our patients. Beyond these formidable challenges is the uncertainty around the long-term effects of COVID-19—referred to as long COVID among other names—in the rheumatology patient population, and the role of the rheumatology practitioner in care of and research among this population. Given the current global impact of long COVID and our early stages of understanding of the condition, we pose a series of questions for the rheumatology profession, to stimulate reflection and discussion around how to address long COVID.

The first question involves the definition of long COVID. It is both surprising and disappointing that long COVID remains poorly defined. At the simplest level, long COVID is the state of not recovering completely following acute infection with SARS-CoV-2, the precise duration of which is unclear but is generally considered to be within a timeframe of 1–3 months.[1] Long COVID, in the context of this Comment, must be differentiated from the broad umbrella of post-COVID-19 conditions. The term post-COVID-19 conditions describes all maladies occurring after the acute infection period, including those that are probably byproducts of critical illness that have clear, pathologically defined sequelae (such as cardiopulmonary scarring and vital organ infarction), as well as psychological stress typical of post-intensive care unit syndromes that was well recognised before COVID-19. We define long COVID as the sequelae generally experienced after mild to moderate COVID-19, most often characterised by a mixture of symptoms—predominantly fatigue, neurocognitive dysfunction, breathlessness, and pain—that often occur with a waxing and waning clinical course and cannot be explained by an alternative diagnosis.

Another question is whether long COVID is unique from other syndromes that occur after acute infectious illness. We and others contend that there should be little surprise at the emergence of long COVID, because similar syndromes have been described after numerous infectious illnesses.[2] We also argue that many, but not all, of these post-infectious syndromes (including myalgic encephalomyelitis, which bears strong similarities to long COVID[3]) remain largely unexplained and represent a collective of syndromes. Finally, until now, these disorders have been understudied and are often attended by a collective sense of frustration on behalf of both practitioners and patients.

The epidemiology of long COVID is poorly understood. On a global scale, long COVID is common and, although methods differ, is estimated to affect 10–35% of people at 28 days post infection.[1,4] A prospective longitudinal cohort analysis from the Netherlands approximated the incidence of long COVID at one (13%) in eight.[5] Given the global burden of COVID-19, this percentage translates into tens of millions of patients worldwide, with potentially detrimental effects on quality of life and productivity. At a minimum, rheumatologists will be obliged to care for patients with rheumatic diseases who develop long COVID, and many are already doing so. Currently, we do not know whether patients with immune-mediated diseases are more or less susceptible to long COVID, or whether their clinical phenotype differs in severity from patients without such underlying conditions. A recent study showed that post-acute COVID-19 symptoms are common among patients with rheumatic disease;[6] however, additional and more granular studies across diverse geographical sites are urgently needed.

Studies of patients with putative long COVID have reported a broad array (>50) of subjective symptoms, making long COVID extremely difficult to define on purely clinical grounds. Most studies have revealed similar findings, reporting symptoms that include new-onset fatigue or exacerbation of pre-existing fatigue, often with post-exertional features (ie, enhanced by mild to moderate exercise or emotional or intellectual tasks), neurocognitive complaints (often referred to as brain fog), and musculoskeletal pain (eg, myalgia and arthralgia).[1] As described in this Comment, although the underlying pathobiology of most of

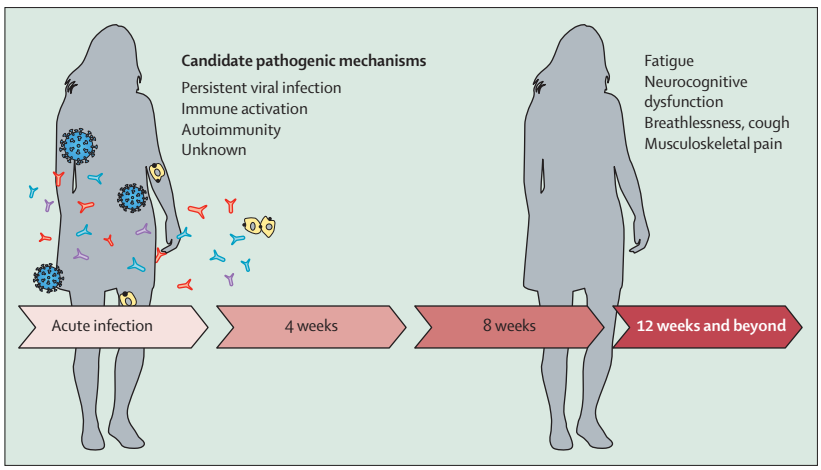

Figure: **Long COVID at a glance**
Acute infection with SARS-CoV-2 (left) is self-limited in most patients, but recovery times vary. Persistence of symptoms or the onset of new symptoms in the post-acute stage is the entry point for a diagnosis of long COVID; however, the required time is not universally agreed on (eg, 4 weeks, 8 weeks, 12 weeks, or longer). Potential pathogenic pathways currently of high interest are noted in the centre of the figure, whereas representative and common symptoms are noted on the right.

the clinical symptoms of long COVID remain poorly understood, there are ongoing efforts on a global scale to investigate these and other domains. Given rheumatologists' familiarity with chronic fatigue states in both inflammatory and non-inflammatory diseases,[7] the frequent presence of neurocognitive complaints in many rheumatic disorders, and rheumatologists' particular expertise in musculoskeletal pain, our field has potential to contribute meaningfully to these efforts.

The pathobiology of long COVID is another matter of ongoing investigation. Per the working definition of long COVID, a majority of the ascribed complaints are medically unexplained, and given the lack of consensus classifications or diagnostic criteria, effective laboratory biomarkers are urgently needed. A rapidly growing body of research is revealing evidence of persistent viral infections (with SARS-CoV-2 as well as reactivation of other latent viruses), immune activation of both innate and adaptive arms of the immune response, loss of tolerance and autoantibody formation, and dysfunction of neuropsychoimmunological pathways, providing iterative steps toward our understanding of the pathobiology of long COVID, as well as revealing potentially treatable targets (figure).[8] Other studies, however, have postulated that the power of suggestion, strong beliefs, and the framing effect might produce many similar symptoms, even in individuals without confirmed COVID-19.[9] Rather than diminish the clinical significance of long COVID, we believe such data reflect our incomplete understanding of how neurophysiological systems are integrated and influence clinical domains such as fatigue, neurocognition, pain, and other complaints seen in both inflammatory and non-inflammatory disorders. These data also underscore the urgent need for biomarker discovery. The field of rheumatology can bring extensive experience in research and therapy to many of these areas relevant to long COVID.

Not surprisingly, the optimal treatment of long COVID is unclear for now, but multispecialty long COVID clinics are growing in number, primarily at large tertiary care centres throughout the world. These long COVID clinics mostly offer extensive diagnostics to rule out other conditions, which can and do occur. Rehabilitation to improve physical function is also standard in these clinics, but the type of rehabilitation (eg, graded exercise *vs* pacing, with a more individualised approach advocated for patients with myalgic encephalomyelitis) is not universally agreed on.[1,3] Finally, given the global burden of neuropsychological stress and mood disorders associated with long COVID and the pandemic, a role for general mental health support is crucial.

Unfortunately, at present, there are no approved therapies for long COVID, but numerous candidate therapies have been widely discussed, including antivirals, immunomodulators, metabolomic modifiers, and a host of integrative medicine approaches. With regards to immune-based therapies, rheumatologists' extensive clinical trial experience with agents now being considered candidate therapies for long COVID make them particularly suited for the task.[10]

There are currently many more questions than answers regarding long COVID and the evolving role of rheumatology in treating this patient population. Overall, given the many unknowns surrounding the syndrome, rheumatologists are well positioned to contribute to basic and clinical research, as well as to care pathways for patients with long COVID, including patients with underlying rheumatic diseases and those with rheumatic complaints. At present, rheumatologists and other subspecialists are limited to some of the foremost tools in our armamentarium (ones that we have long offered to legions of patients with incurable chronic diseases): careful listening, providing validation, and offering empathy. These tools, although in themselves not curative, for now could help patients with long COVID.

We declare no competing interests.

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