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Long COVID as an Infection-Associated Chronic Condition: Implications

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In-brief

A link between infection and chronic illness has been recognized, along with the complexities of interactions between pathogen, environment, host genetics, route of exposure, and timing of outcomes. The COVID-19 pandemic has brought this issue to the forefront and Long COVID is recognized to be an infection associated chronic condition. However, given the wide range of Long COVID presentations, the singular expression gives a false sense of simplicity. Long COVID is best considered as a group of infection associated conditions requiring developing research studies and treatment trials that address the inherent heterogeneity.

Keywords

Long COVID; COVID-19; infection-associated chronic condition; myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS); post-treatment Lyme disease; dysautonomias; chronic disease; post-viral syndrome; infection-associated chronic illness

Introduction

The COVID-19 pandemic has had a profound effect on all aspects of our lives. While the impact will inevitably fade with the passage of time, and eventually it may seem no more relevant than the 1918 ‘Spanish flu’ did prior to 2019, I am hopeful that the message that infections can have long-term health consequences, like Long COVID, will remain clear and strong. Prior to Long COVID, patients living with myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), post-treatment Lyme disease, dysautonomias, and other poorly understood illnesses triggered by sporadic infections, faced disbelief, stigma, and denial of support from health care providers, social support services, and employers. Some were even abandoned by families and friends. Recognizing that Long COVID is an infection-associated chronic condition needs to be a call to action to marshal the multi-disciplinary resources needed to address these neglected conditions.

Background

Shortly after the start of the COVID-19 pandemic, groups of patients who recovered from the acute illness recognized that their health and functioning were far from normal and were not improving after many months of waiting and being told that there was nothing to be done. Healthcare workers struggling to keep up with the onslaught of critically ill COVID-19 patients were a bit slower to appreciate the problem. However, the healthcare workforce, regularly exposed and not uncommonly affected by COVID-19 themselves, also began reporting a variety of long-term health problems that prevented them from returning to work. Considered ‘reliable’ reporters, the post-acute illness descriptions given by healthcare workers gave credibility to the self-reported systemic symptoms that could not be readily explained by routine clinical tests. Slowly, the problem was recognized and given a variety of names including post-COVID condition (WHO), post-COVID conditions (CDC), Post-acute sequelae of SARS CoV-2 (PASC, NIH), and Long COVID (patient community).

Post-COVID clinics eventually began opening their doors, scattered across the country, largely in academic settings. Originally envisioned to care for and rehabilitate patients with pulmonary and cardiovascular damage from severe acute COVID-19, they also began seeing patients who had no abnormalities on routine tests but were crippled by systemic symptoms including cognitive impairment, severe fatigue, sleep problems, and illness relapse from minimal activity that could have been tolerated prior to illness (i.e., post-exertional malaise). The patients themselves coalesced around the need to fully describe their situation and raise awareness among the general public and health care providers. Arising from Body Politic, a networking and support group, the Patient Led Research Collaborative published the first large international description of Long COVID symptoms and their impact¹.

Led by the American Academy of Physical Medicine and Rehabilitation, a multi-disciplinary group of clinicians gathered to share their experience and develop treatment and management guidelines based on expert opinion, the Multi-Disciplinary PASC Collaborative². Importantly, they involved those with lived experience and promoted patient-centeredness and health equity. The collaborative benefitted from the experience of patients living with ME/CFS as well as clinicians with expertise in ME/CFS.

While questions remained about frequency, severity, risk factors, symptoms, latency, and duration of the illness experienced by people following COVID-19, it seemed clear that this was triggered by SARS-CoV-2. The published literature used a variety of case definitions and studied different populations (i.e., hospitalized, clinic based, general population), and not unexpectedly, came up with different conclusions about the nature of the problem. Agreeing on a definition seemed to be essential for raising awareness, improving clinical care, generating reproducible research findings on pathogenesis, and gathering public health data.

The US Department of Health and Human Services asked the National Academies of Sciences, Engineering, and Medicine (NASEM) to develop a definition of Long COVID based on the best scientific evidence and input from those with lived experience. Their report

is an excellent summary of the state of knowledge, and their definition is an important starting place³. The 2024 NASEM Long COVID definition states that “Long COVID is an infection-associated chronic condition that occurs after SARS-CoV-2 infection”. This suggests that Long COVID is best viewed and understood from what we know about other infection-associated chronic conditions.

Infection and Chronic Illness

NASEM (formerly the Institute of Medicine) has considered the link between infections and chronic illness in two prior reports. The first in 2004, “The infectious etiology of chronic diseases: linking infectious agents and chronic diseases”⁴ along with further discussion in the follow-up publication⁵, emphasized the breadth and complexity of the link between infections and chronic diseases. The report noted the wide range of infectious pathogens (parasites, bacteria, viruses, and prions) that have been associated with chronic diseases and conditions. The kinds of associations between infections and long-term illness also differ. One infection may produce one chronic outcome, such as polio resulting in flaccid paralysis, or may have many outcomes affecting many organs, such as hepatitis B virus and chronic liver disease, hepatocellular carcinoma and polyarteritis nodosa. In addition, different infections may also produce the same or similar chronic conditions, such as reactive arthritis following Salmonella, Shigella, or Klebsiella infections. [Figure 1A]

These reports also recognized that there were a wide variety of mechanisms in play. These could include direct impact of acute infection damaging tissue or inducing genetic changes through integration into cellular DNA; persistent active or latent infection as well as reactivation of other latent infections resulting in ongoing tissue damage as a result of inflammation and immune activation; and indirect effects predisposing to chronic illness. The complexity of the situation also includes interactions between the environment, and host and viral genetic factors, as well as age and route and severity of infection. [Figure 1B]

Importantly, these reports note the many challenges with making the link between infection and illness. These include the time between infection and illness, and limitations in methods detecting the triggering infection. The longer the time interval between infection and detection of the condition, the harder it is to exclude other factors. In addition, the agent causing acute illness and triggering chronic effects may no longer be present or detectable. The triggering infection may be asymptomatic, or associated with mild symptoms that did not prompt diagnostic testing, or the infection may be hidden in a protected site not easily sampled, or simply missed by the assays used.

Moving to Infection Associated Chronic Illnesses

The second NASEM consideration of infection and chronic illnesses, “Toward a Common Research Agenda in Infection-Associated Chronic Illnesses,” was reported in 2024⁶. This workshop focused on the unexplained syndromic illnesses that follow acute infection. These were first recognized simply as the failure to follow the expected recovery from acute infection, resulting in prolonged illness over many years or months. A review in 2022 used the term ‘unexplained post-acute infection syndromes’ (PAIS)⁷, while NASEM used the

term ‘infection-associated chronic illness’ (IACI), in recognition of the uncertainty about whether the original triggering infection had indeed been cleared, but both terms refer to the same group of syndromic illnesses. Many viral and non-viral infectious agents are recognized to be associated with these syndromes that have similar symptoms as well as considerable overlap with myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), a poorly understood multisystemic illness often suspected to have an infectious trigger. The syndromic illnesses following a specific or, in the case of ME/CFS, unknown infection have been challenging to understand. Specific diagnostic tests and treatments have not been identified, leaving both the diagnosis and clinical care to be based on symptoms. It could be argued that, given the significant symptom overlap between these conditions and failures of the siloed approach, considering these conditions as a whole or including several different conditions as comparison groups may be needed to identify the underlying causal pathways that may be shared. The workshop also emphasized the importance of a patient-centered view of these illnesses, as the patients suffering from any of these conditions have frequently faced delays in diagnosis, stigma, and lack of understanding from the medical community.

Long COVID Heterogeneity

Both the 2003 and 2024 NASEM discussions of how infections result in chronic diseases and conditions play out in the challenge that NASEM faced in defining Long COVID. The 2024 NASEM definition states that it is an infection-associated chronic condition and then goes on to list the single or multiple symptoms and single or multiple conditions presentations that patients with Long COVID may have. The report indicates that none of these are unique to SARS-CoV-2 infection, so it is the link to SARS-CoV-2 infection that makes any of these presentations into Long COVID.

As an infection associated condition, the challenges in defining Long COVID are understandable. The symptoms and conditions are strikingly diverse. All these outcomes of SARS CoV-2 are important to recognize as they will be increased because of the pandemic and result in the need for more health care services and social support for those affected. However, the complexity of the overall picture of Long COVID requires stepping back and thinking realistically about what can be achieved with a case definition. Is Long COVID really a condition or would we be better served recognizing that it is a group of conditions (and their associated symptoms) that could be grouped when considering how to approach Long COVID in terms of surveillance, clinical care, and research? Recognizing the heterogeneity of patients with Long COVID, a variety of approaches have been used to phenotype or subgroup patients using a variety of clustering algorithms based on symptoms, co-morbidities, and/or biomarkers ⁸⁻¹¹.

The NASEM Long COVID definition emphasizes that the long list of Long COVID presentations as diagnosable conditions and symptoms is not complete. Focusing on the listed diagnosable conditions, a proposed grouping based on presumed mechanisms is shown in Table 1. Group 1 conditions are likely attributable to direct organ damage from the infection, (e.g., interstitial lung disease). Group 2 conditions are recognized autoimmune conditions (e.g., Sjögren’s syndrome), whereas the mechanisms for the unexplained systemic syndromes in Group 3 conditions (e.g., ME/CFS) are unknown. Both Group 1

and 2 conditions have diagnostic abnormalities in clinical tests, and treatment is not altered based on knowledge of the triggering infection. However, diagnosis of Group 2 conditions is often delayed as recognition requires a combination of biomarkers and clinical history, and until a diagnosis is made, patients face skepticism and stigma about their symptoms. Both Group 1 and Group 2 conditions are established and likely to be coded in the medical record. The Group 3 conditions, while listed as separate diagnosable conditions, such as dysautonomia, mast cell activation syndrome, fibromyalgia, and POTS, are challenging, complex and overlapping conditions. They are often not diagnosed, irrespective of prior COVID infection, because they are symptom-based, have no or few routine test abnormalities and limited treatment options. These are the syndromic ‘unexplained’ PAISs that have stymied researchers and clinicians for years. Patients with these syndromes face frequent stigma and medical neglect and may not be diagnosed for many years¹². Medical coding for these conditions is not reliable¹³. Not grouped are the diagnosable conditions of mood disorders and anxiety that are common in persons experiencing any chronic illness and cognitive impairment that may be attributable to conditions within any of the three groups. Of note, the presenting symptoms of Long COVID listed in the NASEM report are frequently associated with more than one of the conditions in more than one group, although post-exertional malaise is more specific for ME/CFS (Table 1).

While a Long COVID diagnosis is helpful to patients in understanding what they are experiencing, at the moment there is little evidence that, for an individual patient, linking the condition to COVID-19 will impact treatment or management. For the recognized conditions in Group 1 and 2, established therapies and management will be followed. For example, diagnosing Long COVID in a patient presenting solely with new onset diabetes mellitus type 1 or type 2, or with new onset of rheumatoid arthritis would clarify the long-term burden of the COVID-19 infection, but would not influence the patient’s care or require a new Long COVID clinic infrastructure. For the syndromic conditions in Group 3, the limited treatment and management options are directed towards symptoms irrespective of the trigger infection, known or unknown. The approach to these conditions has been developed over the years by those caring for patients with ME/CFS, POTS, dysautonomia, post-treatment Lyme disease and related conditions, and has been incorporated into current clinical guidance developed by the PASC collaborative¹⁴.

Being recognized as Long COVID may have advantages in allowing access to multi-disciplinary Long COVID clinics or circumstances that require a linkage to COVID-19. However, with a view to health equity, it can be asked where this leaves patients with similar conditions who either have a different triggering infection or completely unknown infection with respect to access to care through resources and networks established for Long COVID patients. As noted in the 2024 NASEM definition, the ability to definitively link any condition or symptom to COVID-19 remains a subjective clinical decision, and as time progresses, fewer patients will be tested for SARS-CoV-2 during their acute illness and more will have experienced other infections, such as RSV and influenza. The clinical approach to Long COVID patients has been patterned after that developed for patients with ME/CFS. The PASC collaborative compendium of recommendations is being prepared and will include language indicating the same approach to patient care can be used regardless of the known or unknown infectious trigger [personal communication].

Admittedly, patients do not always fall neatly into one group of conditions and the symptoms may not fulfill all diagnostic criteria of any condition. Knowledge that the patient had a prior SARS-CoV-2 infection may prompt clinicians to screen for relevant conditions and increase understanding of patient reports of symptoms that don't fit the usual profile of any recognized condition. In addition, it is possible that symptoms and conditions may be perpetuated by latent or occult SARS-CoV-2 infection or residual antigens so that treatment to specifically eradicate SARS-CoV-2 could be helpful. To date there is little evidence that this is the case. In addition, while removal of the agent could reduce ongoing organ damage, most conditions in group 1 are unlikely to be reversible (e.g., lung fibrosis, cardiac damage and diabetes are recognized as chronic conditions).

Research Design for Infection Associated Chronic Conditions (IACCs)

An understanding of the complexity of Long COVID and other IACCs must inform how research is designed to advance understanding and identify therapies targeting the underlying pathogenesis. Including patients with Long COVID presenting with all three groups of conditions in one study of biomarkers, pathogenesis, or treatment would be challenging.

From the start it has been suspected that Long COVID encompasses a variety of pathogenic pathways, and several reviews have summarized these^{15,16}. Insights from how SARS-CoV-2 triggers lung fibrosis or thrombosis, for example, may suggest mechanisms that may be involved in triggering unexplained PAIS or recognized autoimmune conditions. However, it can't be emphasized enough that any one of the group 2 or 3 conditions is, in and of itself, heterogeneous. For example, patient heterogeneity is a major challenge in systemic lupus erythematosus in clinical management and research¹⁷. In the field of ME/CFS, extensive work has demonstrated a wide variety of multi-organ pathologies and laboratory abnormalities, but none have been specific enough for diagnosis or to be used as biomarkers to direct treatment, and patient heterogeneity is recognized¹⁸.

Recognizing the heterogeneity of these illnesses calls for research study designs and therapeutic trials that accommodate the complexity of the situation. For example, therapeutic interventions may identify important subsets of responders and non-responders. Significant associations between biomarkers and illness groups should be presented in a way that allows the distribution of data to be observed and so that those that fail to follow the trend can be further characterized. Research could also be advanced by changing the paradigm from studying an illness following a specific infection to trying to understand common features of the underlying pathogenesis of symptoms regardless of the triggering infection. This would suggest that the Long COVID syndromic illnesses would be best studied in the context of similar syndromic illnesses following other or unknown infections¹⁹.

Conclusion

The 2024 NASEM Long COVID definition is an important starting point. In addition to level setting that Long COVID is an infection associated chronic condition following SARS-CoV-2, it spells out what we can standardize, the requirement for symptom duration

of 3 months. Beyond that it is justifiably descriptive, recognizing the wide variety of presentations, the waxing and waning of symptoms, the profound impact that it can have on the lives of those affected and their families, and that it can affect anyone, all ages, genders, races, ethnicities, and economic groups. Note should be made that use of singular expressions – Long COVID is an infection associated condition - gives a false sense of simplicity. As with other infection associated conditions, Long COVID is best considered as a group of infection associated chronic conditions.

Despite the many years that it has been recognized that infections can have multiple long term-impacts on health, we are still unraveling the extent of the complexity of the intersection of genetics, environment, and infections. We need to be realistic about the speed at which we can expect progress in diagnostics and interventions. A great deal of humility is required as we move forward, as there is so much that we don't understand. This is particularly important for those providing healthcare, as patients need to be supported and believed, even when there are no definitive answers. The attention that Long COVID has brought to this field has stimulated research into causes and targeted therapies, bringing hope that in the future we will understand how to detect, diagnose, treat, and hopefully prevent Long COVID and other IACCs with known or unknown infectious triggers.

Disclaimer -

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

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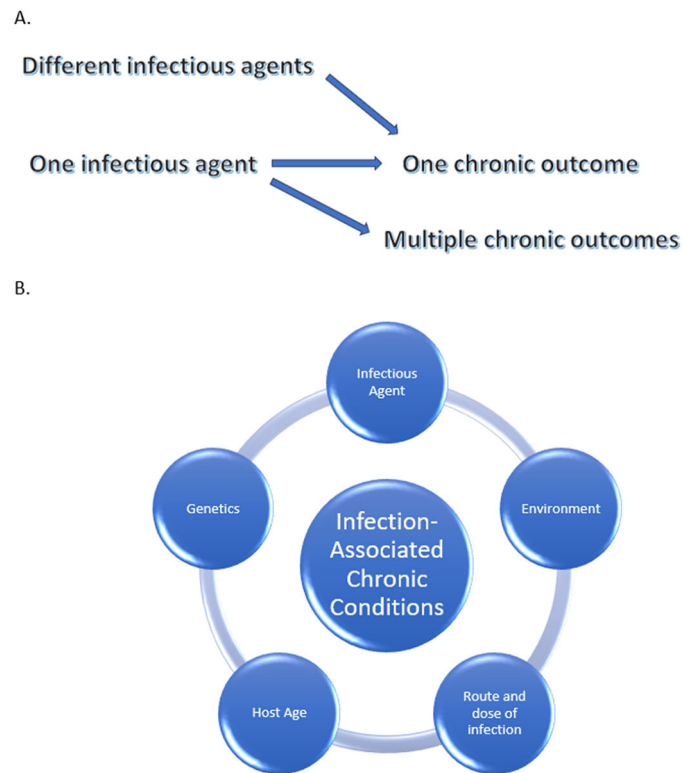


Figure 1 –.

Complexity of Infections and chronic illnesses

A. One infection may result in one outcome, such as poliovirus resulting in flaccid paralysis, or multiple chronic outcomes, such as SARS CoV-2 leading to lung fibrosis, lupus, or ME/CFS. On the other hand, multiple infections may lead to a single chronic outcome such as Salmonella, Shigella, Klebsiella infections resulting in reactive arthritis.

B. A wide variety of factors play a role in the development of infection-associated chronic conditions, such as host age, genetics of host and infection, type of infection, environmental toxins and stress, and the route and dose of infection.

Table 1 –
Proposed Grouping of Long COVID Presentations - Diagnosable Conditions

Manifestations of Long COVID		
Group 1 - Organ Damage	Group 2 - Autoimmune Conditions	Group 3 - Unexplained Syndromes
interstitial lung disease and hypoxemia	systemic lupus erythematosus	ME/CFS
cardiovascular disease and arrhythmias	rheumatoid arthritis	postural orthostatic tachycardia syndrome
chronic kidney disease	Sjögren's syndrome	dysautonomia
stroke	connective tissue diseases	mast cell activation syndrome
blood clots		fibromyalgia
hyperlipidemia		migraine

Mood disorders, and anxiety are diagnosable conditions that are common in persons experiencing any chronic illness. Cognitive impairment may be attributable to conditions within any of the three groups.

Presenting symptoms of Long COVID are associated with one or more of these diagnoses or groups. For example, fatigue is associated with conditions in all three groups, whereas post-exertional malaise is more characteristic of ME/CFS.