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COVID-19 – MEDICAL DIRECTOR CHALLENGES

Long COVID - An Early Perspective

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A new syndrome called "Long COVID" has emerged amongst the survivors of acute COVID-19 infection. Its protracted and debilitating nature will almost certainly result in many short and long-term disability claims. Insurers need to understand the nature of Long COVID, including its definition, its prevalence, its natural history, and underlying risk factors. This article will summarize current knowledge of Long COVID and provide a perspective on its evolution and its impact.

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Long COVID is a widely used term to describe an array of symptoms and signs that are present weeks and months following acute COVID-19 infection. The term was introduced by an Italian physician on Twitter, in May 2020.[1] Although it is now prevalent in mainstream medical literature, it has not been universally accepted. The UK's National Institute for Health and Care Excellence (NICE) has suggested that Long COVID be described as "ongoing symptomatic COVID-19" (symptoms between 4 to 12 weeks) and "post-COVID syndrome" (symptoms lasting longer than 12 weeks).[2] Individuals who have persistent symptoms may also be referred to as "long haulers," another social media term[3] that, although popular, has been neither fully defined or widely accepted.

Whilst the terminology to describe the symptom complex will evolve, there is considerable pressure from patient advocate groups not to abandon the descriptor Long COVID. Indeed, the emergence and recognition of Long COVID as a potentially major public health problem is largely due to advocacy groups such as the Body Politic COVID-19 Support Group, and Patient Led Research For COVID-19, both developed on social media platforms. As a result of their efforts, Long COVID has been recognized by the World Health Organization as an international health care concern and an "emergency-use" ICD code has been issued (U09.9 Post-COVID condition).[4]

More than 100 different symptoms have been reported, underscoring the heterogene-

ity of Long COVID. The most common are fatigue, dyspnea, chest tightness, headache, palpitations, chills or sweats, mild body aches, dry cough, fever, headache and brain fog. Other symptoms include anosmia, ageusia, arthralgias, evanescent rashes and mood disturbance. Multiple symptoms are the rule and groupings of symptoms are common, raising the possibility of different phenotypes. Symptoms frequently remit and relapse, such that individuals feel "cured," only to relapse days or weeks later. Early analyses of risk factors suggest that older age, elevated BMI, female sex, seasonal allergies, vitamin D deficiency and asthma are risk factors, but the research results are open to substantial bias.

Symptom duration is variable, ranging from 4 weeks up to 7 months, according to published accounts.[5-8] However, social media exchanges at time of writing suggest that symptoms have now extended to 10 months. Thus, there is a high likelihood that cohorts with symptoms lasting more than a year will soon be reported.

Most individuals with Long COVID are disabled to various degrees. Some are unable to work; others are unable to cope with daily tasks. Access to appropriate health care has presented a substantial problem as many practitioners are unaware of Long COVID as an entity. Further, due to the wide variety of clinical manifestations, multidisciplinary care, including rehabilitation and mental health support are often required. Long COVID units have now opened in major medical centers in North America, and in December 2020, the UK National Health Service announced the opening of 60 Long COVID clinics across the country.[9]

Long COVID was initially thought to be limited to survivors of hospital care and to those admitted to an intensive care unit. However, it is now evident that most cases are described in individuals who were not hospitalized or who did not immediately seek medical care. Similarly, while a positive reverse-transcriptase, polymerase chain reaction (PCR) nasal swab was originally required to establish the presence of Long COVID, this is no longer a requirement. Many individuals with symptomatic acute COVID-19 infections, particularly at the outset of the pandemic, were not tested and access to testing remains limited in many countries. Further, PCR nasal swab sensitivity is less than perfect. Thus, many individuals in the reported cohorts do not have a confirmatory PCR test.

HOW COMMON IS LONG COVID?

It is frequently proposed that 10% of COVID-19 survivors have developed symptoms of Long COVID. However, the data is conflicting. An early Italian study reported that at 60 days post discharge, 87% of 143 patients discharged from a Rome hospital had at least 1 symptom, and 55% had 3 or more symptoms.[10] The UK Office of National Statistics recently reported that 1 in 5 questionnaire respondents who tested positive for COVID-19 reported symptoms for a period of 5 weeks or longer, and 1 in 10 reported symptoms for 12 weeks or longer.[11] However, in a UK preprint of a prospective cohort study of 4182 cases, 13.3% had symptoms lasting more than 28 days, 4.5% more than 8 weeks and 2.3% had persistent symptoms after 12 weeks.[5] Lastly, in a web-based survey that followed 3762 individuals for 7 months, the majority of respondents reported symptoms at 6 months.[6]

The substantial variance in these studies is most likely explained by differences in the populations being studied (eg, hospitalized and/or non-hospitalized, confirmatory test and/or no confirmatory test), the time criteria being applied (eg, 4 weeks vs 3 months) and the wide variety of study instruments (eg, web questionnaire vs hospital records). Further, these studies report the presence of symptoms rather than a confirmed diagnosis. Until such time as diagnostic criteria have been developed, estimates of disease prevalence will continue to vary. Similarly, until such time as the correct number of acute COVID-19 infections can be established (which one might argue is an impossible task),

it will be difficult to determine the percentage of individuals progressing to Long COVID.

Whatever the correct prevalence, there is little doubt that the absolute number of individuals with Long COVID is substantial. If prevalence is between 2% and 10%, one could anticipate between 380,000 and 1.9 million cases in the United States (19 million COVID-19 infections at time of writing), 10,000 to 50,000 in Canada (500,000 COVID-19 infections), and 1.6 to 8 million worldwide (80 million infections). As the pandemic continues this number will increase. The final number will be determined by the duration of the pandemic, the effectiveness of mitigation measures and the success of vaccine rollouts. It will certainly be higher.

QUESTIONS ABOUT LONG COVID

Uncertainty abounds about many aspects of Long COVID. For example: Is it a unique syndrome? What is the underlying pathogenesis and pathophysiology? How is it clinically defined? Who is at risk? How long does it last? Are there multiple phenotypes? Can it be prevented, or treated? What types of rehabilitation are effective? Will vaccination have an impact?

While studies to address these questions are being formulated, comparisons are being drawn with post-viral fatigue syndrome, post intensive care syndrome and with myalgic encephalitis/chronic fatigue syndrome (ME/CFS), all of which share some of the symptoms of Long COVID.[12]

Comparisons are also drawn with SARS and MERS; two different coronavirus infections that are characterized by protracted physical and psychologic symptoms following recovery from acute infection.[13-15] Both SARS and MERS viruses are similar in structure to the COVID-19 virus and all three gain cellular entry via the ACE2 receptor, suggesting that all three might have similar long-term consequences. Similarly, the chronic autoimmune features, which persist many years following infection with Ebola and Chikungunya viruses, may prove instructive when investigating pathogenesis.[16]

Undoubtedly there are lessons to be learned from the experience of other viral infections. However, the vast array of symptoms involving different organs suggest that Long COVID differs substantially and may be unique. Or indeed, it may include more than one discrete pathology.

RESEARCH AGENDA

Not surprisingly, the research agenda is extensive. Parallels are drawn with the arrival of HIV disease in the 1980s, and the research initiative it jumpstarted. Long COVID presents, as did HIV, a confusing array of symptoms and signs, a new virus, an unknown pathogenesis, and substantial suffering. Long COVID and HIV disease also share effective patient advocacy. However, Long COVID advocates include many physicians, nurses and other healthcare workers, many of whom understand how medical research is conducted and will insist on patient participation in the research agenda, to a degree not previously seen.

Research will be collaborative and international. Two major symposia in December 2020, the first sponsored by the US National Institutes of Health,[17] the second a joint venture between the UK-based International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC) and the Global Research Collaboration for Infectious Disease Preparedness (GloPID-R),[18] outlined the research agenda. Both emphasized the necessity of international collaboration, a common vocabulary, robust data collection methods and well-designed cohort studies.

Basic research will evaluate the different pathophysiologic mechanisms that are currently under consideration. These include ongoing organ damage, persistence of virus due to an inadequate antibody response, a persisting inflammatory/immune response and/or a chronic lupus-like autoimmune process. Multiple strategies will likely be employed,

utilizing animal models and stem cell-derived human tissue, such as pneumocytes and cardiomyocytes, in an effort to elucidate the culprit mechanism(s).

Clinical research will involve the creation of Long COVID cohorts, often with case-controls. Their objective will be to decipher the epidemiology of Long COVID, in particular its incidence and prevalence, its natural history, its demographics and risk factors. A number of these studies, such as the NIH-sponsored Longitudinal Study of COVID-19 Sequelae and Immunity (RECON_19),[19] the UK ISARIC COVID-19 follow-up study[20] and the Canadian COVID-19 Prospective Cohort Study (CANCOV)[21] are already underway.

Ultimately, just about every discipline in medicine will be involved, each with its different questions. Cardiologists will ask: can the abnormal cardiac resonance images noted many months following an acute COVID-19 infection explain ongoing dyspnea and palpitations? Or, are such images also seen in asymptomatic individuals recovering from pneumonia? Pulmonologists will ask: can acute COVID-19 lung damage explain the dyspnea of Long COVID and if so, will it follow a similar path to the well documented long-term SARS damage? Intensivists will ask: are the symptoms of Long COVID different to those of Post-Intensive Care Unit syndrome? Neurologists will ask: are the fatigue, 'brain fog' and postural disturbance of Long COVID unique in any way? Rheumatologists will enquire: are the muscle aches and joint pains of Long COVID typical of fibromyalgia? Dermatologists will ask: are the multiple skin rashes, including 'COVID-toe', unique to Long COVID or are they transient phenomena common to viral infections? Pediatricians will ask: is pediatric Long COVID a sequela of Multisystem Inflammatory Syndrome of Children (MIS-C)? Gastroenterologists will attempt to explain the ongoing abdominal pains and lack of appetite and will enquire whether changes to the microbiome induced by viral invasion of the intestinal wall can explain the myriad GI symptoms.

There will be no quick answers to these questions. Basic and clinical studies will likely take years to complete. In the meantime, individuals with symptoms of Long COVID are frustrated with the lack of care options. Thus, there is pressure to quickly evaluate different therapeutic approaches. Questions that could be quickly addressed include: What are the most clinically effective interventions? Are multimodality/multidisciplinary post-COVID-19 clinics effective? Are rehabilitation programs effective? Do exercise programs work? What pharmacologic treatments are effective?

CHALLENGES FOR INSURERS

Given the current prevalence estimates, there will likely be many disability claims. Disability will be ascribed to both physical and mental health disorders. The duration of these claims is unknown and while comparison with other coronavirus infections is of interest it may also be misleading. Claims will arrive before many of the fundamental questions about COVID-19 have been answered. Without clear diagnostic criteria, adjudicators will be challenged. Claimants will provide a vast array of symptoms. These will be supplemented by abnormal pulmonary function tests, renal function tests, pulmonary CT scans, and heart magnetic resonance imaging. Abnormal immunologic panels will generate further questions. Some claimants will have confirmatory COVID-19 diagnostic tests; others will not. Some will have predominantly physical symptoms; neuropsychological symptoms will predominate in others. In some, both will feature. Some claimants will be enrolled in physical rehabilitation programs, others not, as such programs will not be widely available. Objective measures of disability will be few and far between.

Medical directors will be asked to opine on many of these claims and will struggle to do so. They may also be asked to develop criteria for disability and will find this difficult, too. However, despite the obvious challenges,

medical directors possess a skillset that is ideally suited to the task. They understand the impact of a symptom, the relevance of a physical finding, the significance of an abnormal blood test and the pertinence of an imaging abnormality. More than most, they can understand a psychosocial context and read between the lines of an attending physician report. Built on their clinical experience, they can gauge the burden of disability and estimate the likelihood of return to work. In the climate of uncertainty that will surround Long COVID, such skills are invaluable. As the results of basic and clinical research studies arrive, the task will become easier. But the interim period will be busy, lengthy and challenging.

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