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Long COVID Revisited

Richard Simoneaux Steven L. Shafer, MD, FASA
Editor-in-Chief

Shortly after SARS-CoV-2 began spreading worldwide in early 2020, clinicians noted that some seemingly recovered patients had prolonged neurological, cardiovascular, and metabolic sequelae. The syndrome was given various names, including “long-haul COVID,” “long COVID,” and “post-acute COVID-19.” Over the past two years, it has become evident that the sequelae of COVID-19 represent a significant disease burden for the world’s popula-

tion. A recent review estimated that the prevalence may be as high as 40% in adults and 3.5% in children (*Public Health Rev* 2022;43:1604501). The study concluded that there will be a “substantial public health impact” from long COVID.

Online surveys: an important tool for assessing long COVID

Investigators from the United Kingdom conducted an online survey among
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Cutting-Edge Technology in Perioperative Blood Glucose Monitoring

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Diabetes mellitus is one of the top 10 causes of mortality and morbidity worldwide. Additionally, annual worldwide health care expenditure due to diabetes is \$726 billion or more (*Diabetes Res Clin Pract* 2019;157:107843). Advancements in technologies that support diabetes management have greatly

increased in recent years (*Lancet Diabetes Endocrinol* 2018;7:657). Hardware and software developments offer patients and physicians tools to better facilitate glycemic control, decrease hypoglycemia, and reduce the everyday burden of diabetes self-management in patients’ lives. Perioperative insulin management can
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Today’s Initiative, Tomorrow’s Leaders: Introducing ASA’s New Leadership Academy

Laura K. Berenstain, MD, FASA, ACC Crystal C. Wright, MD, FASA

The future of our specialty lies in the hands of today’s anesthesiology leaders ... and tomorrow’s. Anesthesiologists already command health care teams in every corner of the country, but prioritizing and providing opportunities for education in leadership skills and techniques for current and future leaders will make the specialty, our practices, and our patient care even stronger.

“Advancing a robust bench of trained leaders – leaders adept at communications, conflict management, negotiations and more – is a worthy investment,” said Jeff Mueller, MD, FASA, ASA Vice President for Professional Affairs. “Leadership skills must be learned and honed. That’s why the society is introducing our new Leadership Academy to support members who want

to grow their skills. Leadership is, in part, about empowering others, which is exactly what this initiative aims to do.”

ASA’s new Leadership Academy invites anesthesiologists at all career stages to get more intentional about developing performance-enhancing skills and professional qualities. We’ve trained to be excellent anesthesiologists. Now we can access professional training in a range of leadership skills designed to maximize opportunities throughout our careers.

The Leadership Academy includes four modules, all targeted to meet your needs, wherever you currently are in your career journey. If you are not already in a formal leadership role, there is content to prepare you. If you hold a leadership position, it will maximize your abilities and
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SPECIAL SECTION

Ambulatory Anesthesia and NORA: Anesthesia in the Room Where It Happens 24-34

Guest Editor: Girish P. Joshi, MBBS, MD, FFARCSI

In the Know: Long COVID Revisited*Continued from page 1*

patients who had lab-confirmed (antibody or PCR) COVID-19 in order to assess the prevalence and nature of long COVID (*PLoS One* 2022;17:e0264331). These researchers tallied self-reported clinical data via an online survey portal using “non-probability sampling.” The analyses included only non-hospitalized adults (first two weeks of illness) who reported

“Long COVID had a strongly detrimental impact on the participants’ well-being. Approximately one-third were unable to live without assistance at six weeks after illness onset. More than a third reported income loss, and two-thirds were unable to perform their usual activities or duties. Significant portions of participants reported illness-affected self-care issues (50%), mental health issues (64%), and work issues (75%).”

a suspected or antibody/PCR-confirmed case of COVID-19 with long COVID. Most patients (roughly 90%) characterized their health as excellent, very good, or good prior to COVID-19. The median duration of long COVID was 7.6 months. Initial symptoms included chest pressure/tightness, dyspnea, exhaustion, and headache. Later in the course of long COVID, subjects presented with cognitive dysfunction and heart palpitations. Over half of the subjects described fluctuation in their symptoms. Exacerbations were triggered

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by physical activity, sleep disturbance, and stress.

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Another online survey performed by U.S. and U.K.-based researchers assessed the symptoms and impacts of long COVID in an international cohort of patients for seven months (*EClinicalMedicine* 2021;38:101019). Their online survey was disseminated through social media and COVID-19 support groups to those with confirmed or suspected cases of COVID-19. Data were collected from September 6, 2020, to November 25, 2020. There were a total 3,762 participants from 56 countries. Sixty-six symptoms were tracked over the course of seven months. More than 90% of participants had recovery times that exceeded 35 weeks. Frequently cited symptoms after six months included cognitive dysfunction, fatigue, and post-exertional malaise. The authors identified three symptom clusters, each of which had distinct temporal profiles. As with the previously described online survey, approximately 86% of participants experienced relapses that were often triggered by exercise, physical/mental exertion, or stress. A majority of participants had altered work schedules; almost half of the

participants required a reduced work schedule, and an additional 22% were not working due to illness.

These authors also noted multisystem involvement leading to disability. “Patients with long COVID report prolonged, multisystem involvement and significant disability. By seven months, many patients have not yet recovered (mainly from systemic and neurological/cognitive symptoms), have not returned to previous levels of work, and continue to experience significant symptom burden.”

Post-COVID neurological symptoms

A recent literature review documented involvement of both the central and peripheral nervous systems in long COVID (*The Adv Chronic Dis* 2022;13:20406223221076890). The authors noted that “neurological symptoms are often inextricable from ‘long COVID’ manifestations that involve other organ systems, while nonspecific symptoms, including fatigue, ‘brain fog,’ post-exertional malaise, and sleep disorders, may comprise epiphenomena of underlying respiratory, cardiovascular, endocrine, renal, hematologic, autoimmune, or psychiatric diseases.”

A systematic review/meta-analysis in *Scientific Reports (Nature)* incorporating data from 47,910 patients estimated that 80% (yes, 80%, that is not a typo) of patients have at least one symptom for a minimum of two weeks following infection (*Sci Rep* 2021;11:16144). The most common symptoms were fatigue (58%), headache (44%), and attention disorder (27%). Other neurological sequelae included ageusia (23%), anosmia (21%), memory loss (16%), and hearing loss or tinnitus (15%).

A recent comprehensive review of fatigue following COVID-19 found that “persistent fatigue was reported by a significant minority of patients, ranging from 13% to 33% at 16-20 weeks post-symptom onset” (*Open Forum Infect Dis* 2021;8:ofab440).

The neurological effects of SARS-CoV-2 are probably not a result of direct infection of brain tissue, since available evidence strongly suggests that the virus does not directly infect brain parenchyma (*Nature* 2021;595:565-71). As suggested in a recent paper in *Molecular Neurobiology*, the neurological sequelae of COVID-19 could instead be due to toxic effects of the SARS-CoV-2 spike protein itself on neural tissue (*Mol Neurobiol* 2022;59:1850-61).

A paper in *Nature Communications* documented direct toxicity of the spike protein on brain tissue (*Nat Commun* 2022;13:1745). Eight non-human primates (four Rhesus macaques and four wild-caught African green monkeys) were inoculated with SARS-CoV-2 via aerosol and by multi-route exposure (conjunctival, intratracheal, nasal, and pharyngeal mucosa). All SARS-CoV-2-exposed animals developed infec-

“Substantial evidence suggests that the protean neurological manifestations of long COVID are not a result of brain infection, but instead reflect a toxic response to the spike protein. The neurological sequelae may develop even when the initial presentation of SARS-CoV-2 is clinically unremarkable.”

tion within the first week of exposure. Microscopic analysis of the brains on autopsy documented hemorrhages, microinfarcts, vascular leakage, neuronal injury, and cell death consistent with hypoxic injury in all animals. The autopsy results were consistent with reports of human brains following death from COVID-19. Brain injury was seen even in the absence of severe respiratory

disease. There was no evidence that SARS-CoV-2 infected neuronal tissue.

Similarly, a paper in *Scientific Reports (Nature)* found that direct injection of the spike protein into the mouse hippocampus induced cognitive deficits and anxiety-like behavior, accompanied by neuronal cell death (*Sci Rep* 2022;12:5496). Cell death was not directly mediated by the spike protein, but rather by the glial cell activation.

Thus, substantial evidence suggests that the protean neurological manifestations of long COVID are not a result of brain infection, but instead reflect a toxic response to the spike protein. The neurological sequelae may develop even when the initial presentation of SARS-CoV-2 is clinically unremarkable.

Post-COVID diabetes

A recent paper in *Lancet Diabetes & Endocrinology* looked at the relative risk of diabetes in 181,280 patients following a laboratory-confirmed diagnosis of COVID-19 compared to a contemporary control cohort (N = 4,118,441) (*Lancet*

Diabetes Endocrinol March 2022). The cohort with laboratory-diagnosed COVID-19 had an elevated risk (hazard ratio [HR] = 1.40) of diabetes compared with the control cohort, associated with an excess disease burden at 12 months of 13.46 patients per 1,000. The hazard ratio for diabetes or anti-hyperglycemic drug use at 12 months was 1.46, with an excess burden of 18.03 per 1,000 at 12 months. The authors concluded that “Post-acute COVID-19 care should involve identification and management of diabetes.”

Presidential long COVID initiative

On April 5, 2022, the White House issued a Presidential Memorandum that directed the Secretary of Health and Human Services (HHS) to develop and coordinate the first interagency research plan for long COVID (asamonitor.pub/3k6UmLP). This effort will address many areas involving long COVID and its associated conditions, including prevention, treatment, support, and services. In addition, the memorandum also orders

HHS to outline the services available to those directly or indirectly affected by long COVID.

One aspect of this directive is the “delivery of high-quality care for individuals experiencing long COVID.” To that end, actions to be taken include launching centers of excellence for the promotion of evidence-based care models; establishing and expanding clinics for long COVID; promoting provider education and clinical support where needed; and bolstering insurance coverage for the extensive medical costs associated with long COVID.

The memorandum includes recommendations for supporting individuals experiencing long COVID. Recommendations include the raising of awareness of long COVID as a disability; protecting individuals with long COVID from discrimination; translating research into an effective and inclusive disability policy; connecting people with the appropriate resources available; and strengthening support for workers experiencing long COVID.

The Presidential Memorandum promotes advancing knowledge concerning long COVID. Toward this goal, the Secretary of HHS will coordinate federal efforts for the first interagency research action plan on long COVID, increase investments in long COVID research and surveillance, and leverage the use of federal health care databases (e.g., U.S. Department of Veterans Affairs). Lastly, enrollment in the RECOVER initiative, a \$1.5 billion program to enhance the “understanding of and ability to predict, treat, and prevent long COVID,” will be accelerated.

Long COVID is a new disease. The long-term trajectory and prognosis of long COVID remain unknown. Long COVID will challenge patients, physicians, and health care providers in the coming years. However, the challenges arising from long COVID extend well beyond medicine. Long COVID will affect the cost of health care, the productivity of the workforce, and the well-being of patients, families, colleagues, businesses, and institutions for many years. ■

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FEATURED ARTICLE

Quantitative Neuromuscular Monitoring in Clinical Practice

Background: Residual neuromuscular blockade can be avoided with quantitative neuromuscular monitoring. The authors embarked on a professional practice initiative to attain documented train-of-four ratios greater than or equal to 0.90 in all patients for improved patient outcomes through reducing residual paralysis.

Conclusion: In this professional practice initiative, documentation of train-of-four ratios greater than or equal to 0.90 occurred for 93% of patients in a busy clinical practice. Return-of-strength documentation is an intermediate outcome, and only one of many factors contributing to patient outcomes.

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