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Long COVID: A 'mysterious' syndrome with 'no clear pattern' of symptoms

Among the many health consequences of COVID-19, there remain a few mysteries, including what causes the long-term, postacute sequelae known as long COVID.

“It’s a mysterious mix of symptoms with no clear pattern,” **Sandra A. Fryhofer, MD**, chair-elect of the AMA board of trustees and a member of the CDC Advisory Committee on Immunization Practices COVID-19 vaccines work group, told *Infectious Disease News*. “There is much we still don’t know about COVID-19, and while many people with COVID-19 recover in the weeks following illness, we’re seeing patients experiencing symptoms that either last or appear many weeks or months after becoming infected.”



Symptoms of long COVID last or appear many weeks or months following infection, said Sandra A. Fryhofer, MD, chair-elect of the AMA board of trustees and member of the CDC Advisory Committee on Immunization Practices COVID-19 vaccines work group.

Source: *Mary Jane Starke*

Infectious Disease News spoke with experts about the questions surrounding long COVID and the patients it affects, known commonly as “long-haulers.”

Fryhofer noted that some of the more common symptoms of long COVID include cough, joint and muscle pain, chest pain and headaches — although the full list of symptoms is longer than that.

“In my practice, brain fog, fatigue, and dyspnea — often relayed as lack of stamina — have been most common,” she said.

John T. Brooks, MD, chief medical officer of the CDC’s COVID-19 emergency response, said patients with long COVID present around 4 weeks after initial infection with new symptoms or worsening initial symptoms.

“Interestingly, it’s not just people who’ve been in the hospital and very ill or who had a prolonged hospitalization, but also people who may have had mild illness, and even in some cases, people who didn’t know they were infected because they were asymptomatic,” Brooks told *Infectious Disease News*.

Researchers have learned that long COVID can affect nearly every organ system in the body.

“People say, ‘Oh, it’s just fatigue, you’ll rest and you’ll feel better,’ when that’s really almost laughable,” Ziyad Al-Aly, MD, FASN, director of the Clinical Epidemiology Center and chief of the research and development service at the Veterans Affairs Saint Louis Health Care System, said in an interview.

‘Substantial burden of health loss’

In addition to physical symptoms, patients with long COVID may experience “metabolic consequences” such as new-onset diabetes, depression or anxiety, Al-Aly said.



Ziyad Al-Aly

According to a study by Al-Aly and colleagues that was published in *Nature*, patients more than 30 days after a COVID-19 diagnosis can experience an excess burden of a variety of health conditions. Even patients who had what could be considered mild cases of COVID-19 face an increased risk for death in the ensuing 6 months, they reported.

The results are from a study of more than 86,000 people who had COVID-19 — believed to be the largest study of COVID-19 long-haulers to date, the researchers said.

“We have been hearing a lot about and seeing patients who did not fully recover from acute COVID-19. Some people were complaining about shortness of breath, some about memory problems, and some were having blood clots months after the initial infection,” Al-Aly said. “So, we decided to take a comprehensive look at all the clinical manifestations that may be encountered in 30-day survivors of COVID-19 — people who survive the acute phase of the illness.”

They used the national health care databases of the U.S. Department of Veterans Affairs to identify 6-month incident sequelae, including diagnoses, medication use and laboratory abnormalities among 30-day survivors of COVID-19.

The cohort included 73,435 nonhospitalized patients with COVID-19 who survived at least the first 30 days after diagnosis and 4,990,835 matched controls, and 13,654 hospitalized patients with COVID-19 and 13,997 hospitalized patients with seasonal influenza.

Overall, the study demonstrated that beyond the first 30 days of illness, nonhospitalized COVID-19 survivors had a nearly 60% increased risk for death (HR = 1.59; 95% CI, 1.46-1.73) and a 20% increased risk for an outpatient care encounter (HR = 1.2; 95% CI, 1.19-1.21). The researchers estimated that 8.39 excess deaths occurred per 1,000 people (95% CI, 7.09-9.58) in this cohort at 6 months. Beyond the first 30 days, hospitalized patients with COVID-19 faced a 51% increased risk for death (HR = 1.51; 95% CI, 1.3-1.76), and excess deaths at 6 months in this group were measured to be approximately 29 per 1,000 people (95% CI, 19.51-36.85).

Al-Aly and colleagues evaluated the patients to determine their risk for 379 diagnoses of diseases occurring beyond the first 30 days that could be related to COVID-19. Overall, they found that COVID-19 survivors faced a “substantial burden of health loss” involving nearly every organ and regulatory system in the body.

They faced an excess burden of respiratory conditions more so than any other set of conditions, including respiratory failure, insufficiency, arrest and lower respiratory disease. Excess burden of nervous system disorders, cardiovascular conditions and gastrointestinal problems were evident, including neurocognitive disorders and headache, hypertension, cardiac dysrhythmias, circulatory signs and symptoms, chest pain, esophageal disorders, abdominal pain and an increased use of laxatives, histamine antagonists, antacids and antidiarrheal agents, the researcher reported.

Additionally, survivors faced an excess burden of mental health issues, including sleep disorders, anxiety and fear-related disorders and trauma- and stress-related disorders.

“We do not yet know the precise explanation for this prolonged recovery. Some have theorized that it represents persistent infection that has not been cleared, but this seems less likely,” **Brian L. Block, MD**, assistant professor of medicine in the division of pulmonary and critical care at the University of California, San Francisco, told *Infectious Disease News*.

“It seems more likely that the virus triggers a maladaptive immune response causing persistent inflammation, and that blood vessels, in particular, may be affected,” Block said. “This is similar to the presumed pathophysiology of another postviral syndrome called chronic fatigue syndrome.”

No definitive case definition

According to Al-Aly, the most agreed upon timeline is that symptoms that persist or emerge after the 4th week of COVID-19 are considered post-acute sequelae.

Unfortunately, experts have not definitively determined who is at a higher risk for long COVID, although there is some evidence that it might be more common among women aged 20 to 60 years, Block said.

“Does the burden of long COVID differ by age? Is it more common in older adults or younger adults? Is it more common in Black people or white people? Males or females? We don’t know the answer to this,” Al-Aly said. “Remember, this is a fairly new disease that we’re trying to understand.”

In addition to not being able to pinpoint exactly who is at highest risk, experts are unsure of the incidence of long COVID for several reasons.



John T. Brooks

“There isn’t yet a definitive case definition, so it makes it hard to count cases,” Brooks said. “Having said that, we know from a review of the literature [that] anywhere from 5% to 80% of people who survived COVID can have these [symptoms]. I know that’s a very big range, but the reason it’s so large is that it all depends on how you define what you’re looking at.”

One thing experts seem to agree on is that patients who experienced a more severe acute illness may be at an increased risk for long COVID.

However, “As more studies come out, it is increasingly clear that patients can go on to develop prolonged recovery from COVID-19 regardless of initial illness severity,” Block said. “Those who had very severe illness — for instance, those requiring a mechanical ventilator — are more at risk for organ damage and scarring than those who had mild acute illness, but all are at risk for developing persistent symptoms of fatigue, shortness of breath and brain fog.”

National effort to address long COVID

To help solve some of the mysteries surrounding long COVID, the NIH announced an early initiative to identify cases and ultimately a means of prevention and treatment for long-haulers.

“We do not know yet the magnitude of the problem, but given the number of individuals of all ages who have been or will be infected with SARS-CoV-2, the public health impact could be profound,” NIH Director **Francis S. Collins, MD, PhD**, said at the time of the announcement.

Some of the initial underlying questions the initiative hopes to answer are what the spectrum of recovery from SARS-CoV-2 infection looks like, how many people continue to have symptoms of COVID-19 or develop new symptoms after acute SARS-CoV-2 infection, what the underlying biological cause of the prolonged symptoms is, what makes some people vulnerable to it and whether SARS-CoV-2 infection triggers changes in the body that increase the risk for other conditions, such as chronic heart or brain disorders.

“We are learning about it in real time,” Fryhofer said.

In December 2020, before the announcement of the NIH initiative, Congress provided the NIH \$1.15 billion in funding over 4 years to support research into the prolonged health consequences of COVID-19.

“We don’t know exactly what the underlying causes are but we’re really grateful to our legislators who have given both the NIH and CDC such generous funding to really try and understand this condition, characterize it, and understand who’s at risk for it, why people are getting it and what we can do to help them,” Brooks said.

Fryhofer said the AMA has begun “to advocate for legislation to provide funding for research, prevention, control and treatment of post-viral syndromes and long-term sequelae associated with viral infections, such as COVID-19.”

“The AMA believes ongoing and future long-haul COVID research results that are inclusive of all populations, including people with disabilities and underlying health conditions, are needed in real time to support providers through development and dissemination of best practices for long-haul COVID care,” she said. “As part of its new policy, the AMA will provide physicians and medical students with accurate and current information on post-viral syndromes and collaborate with other medical and educational entities to promote education among patients about post-viral syndromes, which should help minimize the harm and disability current and future patients face.”

‘Let’s not drop the ball’

Al-Aly said he has seen “a bit of medical gaslighting” when it comes to long COVID — medical professionals who are not taking the syndrome seriously.

“Patients are hurting and it’s unnecessary,” he said. “It’s not a fake condition. It’s not in their heads. They’re not imagining the shortness of breath, or imagining weakness, or imagining diabetes. This is happening to them. They’re having strokes and getting diabetes. They’re getting blood clots, and they’re weak and tired and exhausted and just wiped out.”

“We dropped the ball on COVID,” he added, “Let’s not drop it on long COVID.”

FAST FACTS

1. Consequences of long COVID may include new-onset diabetes, depression, anxiety, chronic pain and heart disease.
2. Between **5%** and **80%** of people who survive COVID-19 have long COVID symptoms.
3. Congress provided the NIH **\$1.15 billion** over 4 years to support research into the prolonged health consequences of COVID-19.

Sources:

1. Ziyad Al-Aly, MD, FASN.
2. John T. Brooks, MD.
3. NIH.



The best approach to handling long COVID “would be to centralize care in centers of excellence where clinicians have experience working with this population,” Block said. “This would lead to the highest chance of effective treatment and the lowest risk of misdiagnosis or over-testing.”

Block said long COVID presents such a challenge to the U.S. health care system for several reasons, including that “many people, particularly early in the pandemic, were not able to get tested for COVID, so we do not have objective confirmation of their infection,” Block said.

“Some of them undoubtedly did have COVID, others may not have,” he said. “This makes it all the more challenging when meeting people in the office setting, with an outcome — long COVID — that is not well defined, and an exposure — initial SARS-CoV-2 infection — that we lack confirmation of.”

Another challenge, Block said, is that long COVID is new and manifests in many ways.



Aaron E. Glatt

“The health care system in the United States is quite robust. Readiness for long COVID depends on what is available to treat these people,” **Aaron E. Glatt, MD**, chairman of the department of medicine and chief of infectious diseases at Mount Sinai South Nassau in Oceanside, said in an interview.

Because COVID-19 long-haulers experience a variety of symptoms that are not covered by one specialty, Brooks said they should have access to a “variety of specialists” who can collaborate to determine the best plan for rehabilitation.

“Physiatry and rehabilitation medicine, neurology, rheumatology, and pulmonary medicine clinicians need to be involved,” he said. “Then, depending on the other problems the person is experiencing, other specialists may need to be involved. This is a condition that would benefit from a multidisciplinary approach.”

There is one other way to address long COVID, Brooks noted.

“The most important thing you can do to prevent post-COVID conditions is don't get COVID-19 — get vaccinated,” he said.

References:

[Al-Aly Z, et al. *Nature*. 2021;doi:10.1038/s41586-021-03553-9.](#)

NIH. NIH launches new initiative to study “Long COVID.” <https://www.nih.gov/about-nih/who-we-are/nih-director/statements/nih-launches-new-initiative-study-long-covid>. Accessed on June 11, 2021.

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