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MEDICINE

COVID-19 Long-Haulers

For twenty percent of patients,
a long hard journey to recovery



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COVID-19 Long-Haulers

Twenty percent of patients report mental health symptoms, notably anxiety, insomnia and dementia, posing huge public health implications

By Delia O'Hara

WITH COVID-19 a frightening fixture of life, and a vaccine still in the future for most, a substantial minority of people who test positive for the disease are finding it can have lasting, debilitating effects. These COVID long-haulers are experiencing symptoms ranging from fatigue to skin rashes to shortness of breath.

Long-haulers have symptoms that last weeks to months. The Centers for Disease and Prevention (CDC) reported 35% still had symptoms two to three weeks after testing positive for COVID-19. One British study put the percentage of patients who become long-haulers at 10%. Other estimates are much higher.

Many of the afflicted are healthcare workers; many were in excellent health before they contracted SARS-CoV-2, the virus that causes COVID-19, and many did not get very sick in the early phase. Symptoms are “a mixed bag” involving many organ systems, but neurological symptoms are prominent, says Avindra Nath, MD, clinical director of the National Institute of Neurological Disorders and Stroke in Bethesda, Maryland. A number of studies are underway to follow these long-haulers, Dr. Nath says.

“Some people do get better on their own,” he says, though the conditions some long-haulers have could become chronic. In general, with sequelae, “most recoveries occur within six months, so once you have that six-month data, you’ll have a better idea of the crux of the problem.” Dr. Nath added that it’s important not to take away patients’ hope. “There is a lot of research being done.”

Long-Haulers Report More Than 100 Symptoms

In a survey conducted last summer of more than 1,500 long-haulers by the Survivor Corps Facebook group and Natalie Lambert, PhD, a researcher at the Indiana University School of Medicine, long-haulers reported nearly 100 symptoms. The most common are fatigue, muscle or body aches, shortness of breath, difficulty concentrating, inability to be active, and headache. More than a quarter of symptoms are painful—body aches, nerve pain, and joint pain. Many respondents reported their pain is frequent, extreme and difficult to manage.

Other common long-haul symptoms, according to a different study published this fall by researchers at the University of California at Davis, include

cough, difficulty sleeping, brain fog, and loss of taste and/or smell. With brain fog, “patients report being unusually forgetful, confused or unable to concentrate even enough to watch TV,” according to the study.

“People should be aware that COVID is not just a pulmonary disease,” says Eric Liotta, MD, a neurological critical care specialist at Northwestern Medicine. [See “Study: Encephalopathy Linked to Worse Outcomes”]. “It affects other organs—the GI [gastrointestinal] system, the cardiac system—and it affects the neurological system in ways that have impacts beyond the hospital stay.”

Pathogens typically do not get past the body’s blood-brain barrier, but SARS-CoV-2 is being found in the brains of some—not all—COVID-19 patients. It’s simply too early to say what is causing neurological symptoms, says Vishnu Chundi, MD, an infectious disease specialist with AMITA Health in Oak Park. Dr. Chundi chairs the Chicago Medical Society COVID-19 Taskforce. “We may not have a complete explanation for this anytime soon,” Dr. Chundi says, and identifying or developing treatments will take even longer.

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A National Study is Underway

Rush University Medical Center will be part of a national study, INSPIRE, designed to gather data on long-haulers that will be shared with the patients themselves, according to Bala Hota, MD, chief analytics officer at RUMC.

INSPIRE, funded through the CDC, is enrolling now at Rush and seven other medical centers—300 patients at Rush who have recently tested positive for COVID-19, plus 100 control patients who had concerning symptoms but tested negative. In all, an estimated 4,800 patients will be enrolled nationwide at a 3-1 ratio positive to negative, and

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LEFT TO RIGHT: Drs. Avindra Nath, clinical director of the National Institute of Neurological Disorders and Stroke; Eric Liotta, a neurological critical care specialist at Northwestern Medicine; Vishnu Chundi, an infectious disease specialist with AMITA Health.

followed for two years.

“We’re going to see how they are doing from a symptom point view,” Dr. Hota says. Symptoms can range from subtle to obvious, Dr. Hota notes; the problem with subtle symptoms is that the patients may not have been reporting them to their physicians. The study hopes to capture those, among other findings. “We may not be fully appreciating the extent of the ongoing impact,” Dr. Hota says.

COVID-19 causes horrific lung damage in some cases, often from organizing pneumonias, which can respond well to corticosteroids.

One goal of INSPIRE will be to see if some long-haulers develop a condition resembling myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), Dr. Hota explains. Common symptoms of that chronic condition are debilitating fatigue and a worsening of symptoms after physical or mental exertion, or even standing upright. Others are joint pain, muscle pain and headaches, which figure among the symptoms long-haulers report. The cause of ME/CFS is unknown, but one conjecture is that it lays people low who have previously had a virus of some type. Some people describe its onset as being similar to the flu.

Secondary Symptoms Are Nothing New

Even though COVID-19 is a new and, in many ways, enigmatic disease, there’s nothing new

about secondary symptoms showing up in the wake of outbreaks of infectious diseases. Up to 90% of survivors of Ebola have post-Ebola syndrome, for example.

Ian Lipkin, MD, director for the Center for Infection and Immunity at the Mailman School of Public Health at Columbia University in New York City, speculates that in the case of COVID-19, some as-yet-unknown mechanism of the disease triggers innate immunity, resulting in damage to the metabolism and perhaps to the central nervous system as well.

At present, “there is no way to know who will be affected,” Dr. Lipkin says. He is an expert on ME/CFS, which he says appears to have some things in common with the syndrome that is hitting COVID-19 survivors. West Nile virus is another disease that leaves a fatiguing illness in its wake, he says, and research into that syndrome has suggested patterns of cytokine abnormalities as a cause. “We don’t entirely understand the mechanism yet. We don’t have enough data,” Dr. Lipkin adds.

Mark Yoder, MD, chief of pulmonary medicine at RUMC, says some symptoms COVID long-haulers have are ones he sees in patients who have recovered from acute respiratory distress syndrome (ARDS). COVID-19 causes horrific lung damage in some cases, often from organizing pneumonias, which Dr. Yoder says can respond well to corticosteroids. Those were discouraged when COVID-19 first appeared but are being used now, he says.

Blood clots in the lungs and elsewhere are also a known feature of the disease. Those can be hard to detect, and they can take months to resolve, Dr. Yoder says.

An Austrian study last summer showed that



LEFT TO RIGHT: Drs. Bala Hota, chief analytics officer, Rush University Medical Center; Ian Lipkin, director, Center for Infection and Immunity, Mailman School of Public Health, Columbia University; Mark Yoder, chief of pulmonary medicine at Rush.

damage to the lungs and heart does improve over time in many cases, and that rehabilitation helps. “Some people are recovering; there are so many different trajectories to the disease. This virus is different from anything I’ve ever seen,” Dr. Yoder says.

Who Are Long-Haulers?

Research is under way to differentiate among patients damaged by severe acute COVID-19 infections or by treatments for the disease, and designated long-haulers, some of whom were not very sick in the beginning.

COVID-19 can be lethal in its acute phase, perhaps killing up to 1% of infected people overall, though official counts are probably low. Mortality risk varies considerably, depending on age, ethnicity, socioeconomic status, access to care and underlying health conditions. The illness itself can last for weeks; the damage it does to patients who get really sick can take months to heal—and has not been resolving consistently. De-conditioning can lay patients low; some procedures and treatments, and the effects of long-term intensive care, can be harmful as well.

Specialists at the Shirley Ryan AbilityLab, an NM-affiliated rehabilitation hospital, were among the NM researchers who flagged nerve damage that can occur when COVID-19 patients are put in a prone position (PP) for long periods of time to help them breathe, as an alternative to a ventilator.

To an extent, the AbilityLab is bridging infection-caused, treatment-induced and long-haul symptoms of COVID-19, according to Leslie Rydberg, MD, an AbilityLab physiatrist. Concerned about containing infection, the facility has dedicated an entire unit, with its own therapy space,

for those COVID patients in recovery who need rehab services.

“Some of our patients have been hospitalized for months,” Dr. Rydberg says. Most have been damaged during the acute phase by the infection or by measures, like PP, deployed to save their lives. Treatment in a dedicated unit makes it possible for these patients to begin walking and doing other rehab activities as soon as possible, and for their caregivers to work as a team.

A team of researchers at Northwestern Medicine has shown that the brain is often affected in a serious bout of COVID-19, and that outcomes for those patients may be worse than in cases where the brain is not involved.

The AbilityLab staff works with clinics at NM to get patients, including long-haulers, assessed and their medical and functional needs addressed. Many academic centers around the country, and in Chicago, are setting up multi-disciplinary COVID-19 sections as well.

Huge Public Health Implications

The persistence of ill effects from the disease for some patients “is a little scary,” Dr. Rydberg says. “It does have huge public health implications.”

Mental health symptoms, notably anxiety, insomnia and dementia, affect nearly 20% of COVID long-haulers, according to a recent study



LEFT TO RIGHT: Drs. Leslie Rydberg, a physiatrist at the Shirley Ryan AbilityLab; Meeta Shah, an emergency medicine physician at Rush University Medical Center.

in the *Lancet*. As with other symptoms, this aspect will require research to understand, but Meeta Shah, MD, an RUMC emergency department physician, says physicians should be aware of how demoralizing it is for long-haulers to be dealing with often painful or debilitating conditions that make it impossible for them to work, meet other obligations and enjoy life.

Treating people who come into the ER with these symptoms is a challenge. “There’s not much we can do in the emergency department,” Dr. Shah says. “You can understand why people are frustrated. They’re over the infection, but they’re continuing to deal with these symptoms.”

Patients Need Empathy and Support

Dr. Chundi says it’s important for physicians to believe their patients and to empathize with their frustration. “We believe most people will start to get better on their own. Rule out the possibility of other conditions, like hypothyroidism, support the patient, get them moving and help them get the help they need. With luck, the end is in sight.”

Delia O’Hara is a Chicago-based freelancer who frequently writes about healthcare and science topics. She was previously a longtime features reporter for the Chicago Sun-Times. [C](#)

Study: Encephalopathy Linked to Worse Outcomes

A team of researchers at Northwestern Medicine (NM) has shown that the brain is often affected in a serious bout of COVID-19, and that outcomes for those patients may be worse than in cases where the brain is not involved.

Of 509 hospitalized patients the team studied, 82% had neurological symptoms, most frequently muscle pain; headaches (38%); encephalopathy, a spectrum of altered mental function

ranging from mild confusion to coma (32%); dizziness (30%); disorder of taste (16%); and disorder of smell (11%).

Nearly one-quarter (22%) of the patients who had encephalopathy died, compared with 3% of patients without encephalopathy. And only about one-third (32%) of patients who had encephalopathy were able to care for themselves after they recovered and went home, compared with 89% of those without encephalopathy. The study was published in October in the *Annals of Clinical and Translational Neurology*.

“This suggests that people aren’t having bad outcomes necessarily because they had just really bad pulmonary disease, but that there is this additional

neurological component that is detrimental on top of the pulmonary disease and being older,” says Eric Liotta, MD, a NM specialist in neurological critical care and a member of the research team that did the study. The team saw stroke in only about 1.5% of patients studied.

“What’s important is this concept of encephalopathy. That is the neurological manifestation that’s going to have the most public health impact in terms of COVID-19,” Dr. Liotta says.

The study didn’t explore whether people who weren’t sick enough to go to the hospital might have had a milder version of the neurological process Dr. Liotta’s team saw occurring in hospitalized patients, he says.