Long COVID poses a conundrum for physicians and researchers alike. Representing a wide range of new, returning or ongoing health problems that arise about a month after initial infection, it can affect 20% to 30% of patients after recovery from even mild illnesses and about half of COVID-19 patients who required hospitalization.

More than 200 symptoms associate with long COVID, but no universal clinical case definition exists.

Long-haulers often don’t know what to do about their lingering symptoms, which can include fatigue, shortness of breath, memory impediments, and gastrointestinal symptoms. Many different organ systems are involved, said Akiko Iwasaki, PhD, professor of immunobiology at Yale University and a principal investigator at the Howard Hughes Medical Institute.

“We really need a guidance for the physicians to be able to diagnose properly long COVID because not every patient has obviously all these symptoms,” Iwasaki said during a recent episode of “AMA COVID-19 Update.”

“At the hypothesis stage”

Long COVID likely comprises multiple diseases under one umbrella, said Iwasaki. The task ahead is to disassociate and disentangle the conditions.

Causes of long COVID have eluded clinicians and researchers, but several hypotheses exist.
Persistent virus or viral remnants in tissues, such as viral RNA or protein could be triggering chronic inflammation. Another hypothesis is autoimmunity, noted Iwasaki. An acute respiratory infection can induce autoimmune conditions in some patients. Once this happens, it's very difficult to reverse. “And that could be happening in a subset of long COVID patients.”

Dysregulated gut microbiome, dysbiosis and latent reactivation of viruses such as Epstein-Barr are other possibilities. “Currently we are at the hypothesis stage,” she said.

Find out what doctors wish patients knew about long COVID.

**Two types of long COVID**

Research to date suggests that long COVID might fall into “two bins,” said Iwasaki.

There’s the patient who had a severe case of COVID, was hospitalized and then discharged. Long COVID has been appearing in about half of these patients.

Long COVID has also been seen in patients with mild or asymptomatic infections who develop symptoms over time, within three months of infection. Prevalence in this group tends to be between 5% to 30%. “They vary because we don't have a universal definition of long COVID,” said Iwasaki.

British researchers have also found definitive physical changes in long COVID patients. Compared with uninfected matched controls, they have a greater reduction in gray matter thickness and global brain size, and bigger changes in markers of tissue damage in regions connected to the primary olfactory cortex.

It’s unclear what’s causing these kinds of brain mass reduction, “but I believe inflammation is involved,” said Iwasaki.

Not enough data is available right now to advise physicians on treatment. “What we really need to do is to understand these different endotypes that underlie the disease called long COVID,” suggested Iwasaki.

Read about answers to common questions patients have about long COVID.

**A plan for long COVID**


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Iwasaki joined other public health experts to issue a road map about strategies for living with COVID-19. Long COVID was one of 12 key focus areas.

The road map calls for the establishment of a task force to coordinate interagency activities. “We also need to create scientific and regulatory responses for characterizing and then counting really long COVID and also understanding the basic disease pathogenesis so we can start doing planning for clinical trials based on that understanding,” she said.

Physicians need a consensus-based guideline for interdisciplinary care models for clinical treatment and management of long COVID. “And of course, we need to ensure adequate health and social support is provided to the patients,” said Iwasaki.

Get the latest news on the COVID-19 pandemic, vaccines and variants, and more reliable information directly from experts and physician leaders with the “AMA COVID-19 Update.”

You can catch every episode by subscribing to the AMA’s YouTube channel or the audio-only podcast version.