



LONG COVID

Unpack Causes and Treatments at Length

More than five years have passed since the global COVID-19 pandemic began. From its initial outbreak in late 2019, the virus—described by the World Health Organization (WHO) as severe acute respiratory syndrome coronavirus 2, or SARS-CoV-2—spread rapidly worldwide. Declared an international public health emergency by WHO on January 30, 2020, the growing viral outbreak was subsequently characterized as a global pandemic within weeks.¹

The pandemic's impact was deeply felt throughout the world. The COVID-19 pandemic represents one of the most significant global public health events of modern times, with far-reaching social, economic, and health consequences. In fact, there have been more than 776 million cases reported worldwide, including more than 7 million deaths.² In the United States, COVID-19 has been identified by the Centers for Disease Control and Prevention (CDC) as the underlying cause (87%) or contributing cause (13%) of death for over 1,235,000 reported deaths.³

The global public health emergency officially ended on May 5, 2023.¹ Compared to the worst of the pandemic, when nearly half a million deaths were reported in 2021, life has improved. In 2025, although likely undercounted, fewer than 16,000 deaths related to COVID-19 have been reported as of October.³ The disease has become more manageable, with less risk of severe illness and hospitalization. More effective treatment options, increased public immunity from multiple vaccinations and previous infections, and other factors contribute to reducing public health risks.

An Enduring Legacy

While the worst of the pandemic may be behind us, the legacy of COVID-19 continues to impact society. Many people have lost family members and friends to the disease and endured economic hardship, mental health challenges, and other difficulties. And, COVID-19 remains endemic and poses a persistent infectious disease threat. It would be a mistake to dismiss the presence of COVID-19 as no longer of much concern

or comparable to a common cold.

Yet public concerns over COVID-19 have declined. In spring 2025, only 23% of adults reported having received the latest available COVID-19 vaccine. For children, the vaccination rate was 13%.⁴ Additionally, just about 4% of the public report regularly wearing a mask in public settings.⁵

One enduring effect of COVID-19 is found in the sizable population that contracts the SARS-CoV-2 virus who do not experience complete resolution of their illness following the infection's acute phase. Instead, these individuals experience persistent, new, or reemerging COVID-19 symptoms for weeks, months, or even years.

The condition is known as *long COVID*, a term first used by COVID-19 patients themselves in the early days of the pandemic.⁶ Long COVID refers to the wide range of conditions that can follow SARS-CoV-2 infection.

WHO describes long COVID as “the continuation or development of new symptoms three months after the initial SARS-CoV-2 infection, with these symptoms lasting for at least two months with no other explanation.”⁷

In 2024, the National Academy of Sciences, Engineering, and Medicine (NASEM) defined long COVID as “a chronic condition ... that occurs after SARS-CoV-2 infection and is present for at least three months as a continuous, relapsing and remitting, or progressive disease state that affects one or more organ systems.”⁸ As a newer disease phenomenon, more precise definitions of long COVID vary somewhat within the scientific community. However, the WHO and NASEM definitions are designed to reflect the broad understanding of long COVID based on current knowledge.

Measuring Causes

While research is ongoing, much has already been learned about what causes long COVID. One crucial contribution to unraveling the mysteries of long COVID comes from the Iwasaki Laboratory at Yale School of Medicine. Led by Akiko Iwasaki, PhD, an immunobiologist and the laboratory's director, four possible hypotheses have been proposed to explain the biological mechanisms underlying the onset and pro-

gression of long COVID following SARS-CoV-2 infection:

1. Persistent viral loads or remnants hidden away in tissue and causing chronic inflammation. These viruses may not be measurable via nasopharyngeal swabs because they might be “hiding” in other internal organs, such as the gut.
2. Our body's own disease-fighting B and T cells triggering an immune response—and subsequent inflammation—in a process called autoimmunity. The problem is [that] the stimulus that triggers autoimmunity in response to an acute infection is oftentimes occurring continuously in the body, making it difficult to pinpoint and shut down.
3. Dormant viruses reactivating, and/or dysbiosis of microbiome disturbing our body's homeostasis. Humans live with trillions of bacteria and a number of viruses that are latent. When acute infection disturbs the host, these bacteria lose [their] composition balance and dormant viruses can become reactivated. These viruses and microbes can cause inflammation and throw off [the] body's homeostasis.
4. Macroscopic and microscopic tissue damage resulting from the initial infection. COVID-19 impacts parts of our body that we don't commonly think about. Whether it's our lungs, ... our brains, or the endothelial tissue lining our blood vessels and supporting oxygen change, the virus—and the medication used to treat it—can lead to clotting or scarring in places that are difficult to reach and repair. In addition, inflammation that occurs in one tissue can trigger damage in other tissues.⁹

Individuals with long COVID may exhibit certain distinct immune characteristics, according to the Iwasaki Laboratory⁹:

- Amped or excessive humoral response to SARS-CoV-2
- An increased antibody response to other pathogens, such as the Epstein-Barr virus
- Lower cortisol levels
- Abnormal leukocyte (white blood cell) populations

In particular, lower cortisol levels are considered a key predictor or driver of long COVID.⁹

By the Numbers

While estimates vary, in 2023, the National Institutes of Health (NIH) found that as many as 23 million Americans may have long COVID, acknowledging also that many people were probably unaware their symptoms were linked to COVID-19.¹⁰

Approximately 6% of those who contract COVID-19 worldwide will develop long COVID, according to WHO.¹¹ Other estimates for percentages of those who experience long COVID come from a 2024 study published in *JAMA Network Open* (8% of U.S. adults),¹² a CDC 2024 Household Pulse Survey (18% of adults),¹³ and Massachusetts General Hospital (23% of the U.S. population).¹⁴

However, variables such as study design, the population under study, the source of data (whether from patient self-reporting or observational cohort studies), the predominant COVID-19 variant at the time of the study, and other factors can influence reported results.¹⁴

Likely, many cases of long COVID go unreported, as the NIH and other experts acknowledge. “As a researcher who studies these patients, I would argue that a lot of people have had long COVID; they have the symptoms, but they don’t connect it to COVID-19,” says Lauren Stiles, JD, president of Dysautonomia International and research assistant professor of neurology at Stony Brook University in New York. “They don’t realize the reason why they’re super fatigued or why their hair might be falling out is because they had COVID-19 three months before. Sometimes when people say they haven’t had COVID-19, they were probably asymptomatic and didn’t know they were infected. A very high rate of people can develop long COVID, or other postinfectious syndromes can occur similar to long COVID, even when the initial infection agent was asymptomatic.”

Closing the Distance

Undoubtedly, long COVID is a complex and challenging condition, not only for patients but for the clinicians working to assist their

Anyone can get long COVID, but you may be at higher risk if any of the following apply to you¹⁹:

- Older than 65
- Female
- Hispanic or Latino
- Do not have the COVID-19 vaccine
- Have experienced severe COVID-19 illness
- Have other health conditions

recovery. As research and treatment options still evolve, comprehensive, patient-centered care must guide the health system’s efforts in this area, according to experts.

“Long COVID is a real, disabling condition that deserves recognition and validation,” says Nikki Gentile, MD, PhD, medical director of the UW Medicine Long COVID Clinic in Seattle, Washington. “It affects people across all demographics, regardless of age, health history, or the severity of their initial COVID-19 illness. It can present as a wide range of symptoms—neurological, cardiopulmonary, gastrointestinal, musculoskeletal, and more—and may impair daily functioning, work, or relationships. Importantly, long COVID does not have a singular diagnostic test, making clinical understanding and patient-centered care critical for its recognition. Public messaging should emphasize that this condition can be disabling, often invisible, and that patients experiencing it are not exaggerating or imagining their symptoms. Validating these experiences is essential to reducing stigma and fostering trust in health care settings.”

As Dr. Gentile explains, the clinic offers an integrated array of patient care services. “Our clinic employs a multidisciplinary, patient-centered approach grounded in four key care anchors: psychosocial support, restorative movement, nutrition, and sleep/rest,” she says. “These anchors target modifiable aspects of health frequently disrupted by long COVID. By prioritizing individualized care through shared decision-making, this framework accounts for the variability of symptoms and severity among patients. We integrate both pharmacologic and non-pharmacologic

symptom management strategies tailored to each patient’s needs. Additionally, we collaborate closely with specialists, including physical therapists, speech-language pathologists, acupuncturists, and psychologists, to provide comprehensive and holistic care.”

As a relatively new area of specialized care, long COVID poses multiple treatment challenges, according to Dr. Gentile: “The biggest challenges include diagnostic uncertainty, as long COVID spans multiple systems and lacks definitive tests, and addressing post-exertional malaise in patients who experience symptom crashes after minimal activity, like [walking], taking a shower, or vacuuming. Additionally, navigating disability systems, fragmented referrals, and the psychosocial burden patients face due to stigma and misinformation about long COVID further highlight the need for comprehensive and coordinated care.”

Accordingly, treatment for long COVID is tailored to each patient’s unique clinical presentation, addressing concerns through a coordinated, stepwise approach to case management. “First, we identify patient goals and prioritize symptoms,” explains Caitlin McAuley, DO, a family medicine specialist who sees long COVID patients through the COVID Recovery Clinic at Keck School of Medicine of USC in Los Angeles. “I ask patients which are their top symptoms, ... [or which symptoms] interfere with their lives the most. Next, we want to make sure that other basic workups have been done, usually through their primary care provider, and, if needed, add a limited number of specific tests for co-occurring conditions. However, many patients do not need further testing by the time they reach the clinic, as they have already seen many specialists.”

“Since there is no established curative treatment for long COVID, we focus on symptomatic management,” adds Dr. McAuley. “I rely heavily on the American Academy of Physical Medicine and Rehabilitation guidance statement, most recently updated this year, for medications that help with different symptoms. I also rely on my occupational therapy and physical therapy colleagues to guide rehabilitation without causing worsening of symptoms from excessive exertion.”

In working with long COVID patients, Dr. McAuley identifies a few common barriers to recovery. “Challenges to recovery include limited response to medications, sensitivity to medications, and repeat infections,” she reports. “Repeat infections can lead to setbacks in symptom improvement and can also sometimes lead to new symptoms. Co-occurring conditions such as postural orthostatic tachycardia syndrome—POTS, mast cell activation syndrome—MCAS, and hypermobility can also be complicating factors for improvement.”

The Intersection of Dysautonomia and Long COVID

As a type of dysautonomia (a disorder of the autonomic nervous system), POTS deserves special consideration in our understanding of long COVID. As a generally unrecognized medical condition, estimates of its prevalence among patients with long COVID vary. One report in *Nature Reviews Cardiology* found POTS affects approximately 30% of highly symptomatic individuals with long COVID.¹⁵ Other studies suggest the impact may be even higher. For example, a report from Stanford University, Stony Brook University, and Dysautonomia International found 67% of long COVID cases involve symptoms of dysautonomia.¹⁶

While estimates of the exact extent of POTS or dysautonomia in long COVID differ, due to diagnostic and other study challenges, it is an important factor in many long COVID cases. “Dysautonomia, including POTS, is a common issue among patients with long COVID,” says Dr. Gentile. “There is an emerging body of research exploring the links between POTS and long COVID, though the underlying mechanisms are not yet fully understood. The connections are thought to involve dysregulation of the autonomic nervous system, chronic inflammation, and other systemic disruptions caused by

SARS-CoV-2 infection.

“POTS results from autonomic dysfunction, where the nervous system struggles to regulate blood flow and circulation, often triggered by upright posture,” explains Dr. Gentile. “Patients frequently experience symptoms such as tachycardia, shortness of breath, fatigue, dizziness, brain fog, and palpitations, all of which significantly impair daily functioning. Many patients report experiencing ‘crashes’ 24–72 hours after a full day of work or school due to post-exertional fatigue, post-exertional malaise, or post-exertional symptom exacerbation—PESE, which underscores the importance of managing activity levels and accommodating limitations in work, school, and extracurricular settings.”

Notably, a recent study links the COVID-19 pandemic to an unprecedented surge in POTS cases. A University of Toledo review of electronic medical records for over 65 million patients shows more than a five-fold increase in POTS cases since the pandemic’s onset. The study covers data from January 2018 to June 2024, with March 1, 2020, marking the beginning of COVID-19. To note, medical researchers have for some time suspected POTS is triggered by viral infections, such as the Epstein-Barr virus.¹⁷

Unfortunately, there is a shortage of specialists in autonomic disorders who treat POTS, and patients often endure long wait times for specialist appointments. “While it can be challenging to find a specialist, some testing, such as a NASA lean test, can be done in a primary care office or at home

with the right equipment,” says Dr. McAuley. “However, there is still a lack of knowledge and training in many medical settings, so the condition can go unrecognized.”

The NASA Lean test is a brief, straightforward point-of-care method that can help physicians diagnose and treat orthostatic intolerance.¹⁸

Despite the challenges, much can still be done to improve the health of patients with POTS. “Treatment for POTS can involve several therapies,” says Dr. Gentile. These involve a combination of supportive measures, including increased hydration, dietary sodium intake when medically appropriate, compression garments, and heart rate monitoring. Pacing is [also] emphasized as a critical strategy for managing activity within energy limits to avoid PEM/PESE [post-exertional malaise or post-exertional symptom exacerbation]. Pacing is a symptom management skill that [involves] purposefully scheduling or planning activities that require physical, cognitive, social, or emotional energy, alongside planned periods of rest, to allow for adequate recovery and energy conservation. Pacing with a gradual progression in activity—e.g., starting with recumbent exercises and gradually progressing to more upright activities as tolerable while remaining within the energy envelope—acknowledges the risk of symptom flares, particularly when first getting started. Ultimately, the goal is to learn to listen to your body’s cues that you are using too much energy and make changes to prevent overexertion.

“The activity progression here is patient-directed,” adds Dr. Gentile. “This approach differs from graded exercise therapy—GET, which systematically increases physical activity over time, often without consideration for symptom exacerbation, and operates on the assumption that symptoms are primarily due to deconditioning—a strategy that many patients have historically been encouraged to pursue. However, research has shown GET to be ineffective and potentially

Counting on You

“Don’t wait for a top-down mandate to learn: Seek out continuing education and practical tools now. *The Comprehensive Guide to Long COVID: Volume 2*, published by the COVID-19 Longhailer Advocacy Project, provides concrete assessment tools and clinician guidance. Partnering directly with people living with long COVID can strengthen empathy and care planning. This is one of the largest mass-disabling events of our lifetimes; the fastest way to improve outcomes is for providers outside the long COVID specialty community to engage, learn, and deliver patient-centered, evidence-informed care.”

—Karyn Bishof, COVID-19 Longhailer Advocacy Project Founder and President

harmful for individuals experiencing PEM and PESE, and, as a result, some patients remain cautious or skeptical of treatment plans that resemble GET due to its negative impact. We do *not* recommend GET for patients with long COVID.

“For more severe cases of POTS, medications such as beta blockers, pyridostigmine, or fludrocortisone may be used to alleviate symptoms,” notes Dr. Gentile. “Early identification, individualized pacing, and holistic care approaches are essential for reducing the impact of dysautonomia and improving patient outcomes.”

As issues with dysautonomia illustrate, improving treatment for long COVID requires identifying the underlying physical causes or disease subtypes that may occur in the disease.

“To find a ‘cure’ and more effective treatments, we really need to target a subset of the patients, because the biological mechanism in long COVID is probably not one thing,” explains Stiles. “For example, a person who has had COVID-19, was hospitalized, and had significant lung damage might have lifelong respiratory problems. [Their symptoms] would fit under the definition of long COVID. Another person might have had an asymptomatic initial infection, but they developed a neuropathy a month later. They will have a different diagnosis, a different biological mechanism causing their chronic health problem, but they’re also a long COVID patient. The treatment isn’t going to be the same. This is why researchers are tailoring or trying to find treatments for specific manifestations of long COVID. The underlying and most common mechanisms that we are seeing are neurological damage, inflammation, and autoimmunity issues. There’s still debate as to whether viral persistence plays a role, which I think is a good scientific debate to have.”

Stretch Your Skills

Many physicians may feel uncertain about diagnosing and treating long COVID because it is a newer medical condition. Experienced clinicians recognize and want to address the concern.

“Getting the diagnosis of long COVID from a provider can open doors for patients,”

says Dr. McAuley. “This is why there is a national effort amongst long COVID clinics to educate other providers, especially in primary care. My main message is to look at the timing of symptom onset, [which should occur] within two months of a COVID-19 infection or a COVID-like illness, paired with a workup for different symptoms [and] systems being normal. Instead of telling patients, ‘I don’t know what is wrong,’ we should be saying, ‘This meets criteria for long COVID.’ I also emphasize that we should start working on symptom management even while the workup is happening. I’ve seen many patients without treatment for over a year while they were being worked up by multiple specialists. One final challenge, which applies to the health care system in the United States, is [the] lack of comprehensive care coordination. Patients with long COVID and other chronic illnesses, especially those affecting cognition, fall through the cracks because they can’t coordinate their own care effectively.”

Dr. Gentile agrees that the health care system faces multiple challenges in improving care for long COVID patients. “Improving care begins with recognizing long COVID as a legitimate and multifaceted condition,” she suggests. “Clinicians and care team members should familiarize themselves with its common presentations—fatigue, cognitive dysfunction, dysautonomia, and multisystem symptoms—and validate patients’ lived experiences, even in the absence of conclusive diagnostic tests. Asking open-ended questions about how

symptoms impact daily life can help the care team better understand and document [changes] in the patient’s day-to-day functioning and their new limitations, which is often critical for accessing support such as disability insurance benefits. Supporting patients with practical guidance on work [or] school accommodations, ensuring equitable standards of care, and practicing thoughtful referral stewardship are key elements of effective care. Clinicians should also prioritize high-value testing to rule out reversible conditions—e.g., anemia—commonly associated with long COVID and avoid over-testing, which can lead to unnecessary costs and stress for patients.

“Health care systems can enhance support for clinicians by fostering interdisciplinary collaboration, streamlining referral pathways to specialists and ancillary services, promoting equitable access to care, providing continuing education focused on emerging guidelines and evidence, and incorporating longer visit times to address the complexities of long COVID,” explains Dr. Gentile. “Additionally, trauma-informed care approaches should be integrated into routine practice to address long COVID patients’ psychological burden and combat the skepticism that many face in medical settings. By combining patient-centered care with health system improvements, clinicians and care team members can help bridge the gaps in long COVID care and provide compassionate, effective support for this vulnerable population.”

In turn, within health systems, clinic staff should familiarize themselves with the needs of this patient population. As an educator, Latasha Ladd, BHCM, MEd, emphasizes the importance of medical assisting staff being attentive listeners when patients describe their symptoms or health issues during visits. This can be an especially vital skill in cases like long COVID, whose complex presentation and diagnostic challenges require thoughtful consideration by clinicians.

“You never want to minimize or downplay what someone is telling you,” says Ladd, who is the medical assisting program director at South University in Columbia, South Carolina. “Sometimes patients might find it

Patient Care Resources

UW Medicine Long COVID Clinic
University of Washington, Seattle
www.longcovidclinic.uw.edu

COVID Recovery Clinic, Keck Medicine of USC
University of Southern California, Los Angeles
<https://www.keckmedicine.org/covid-recovery-clinic>

hard to articulate what exactly is bothering them. The medical assistant can help them explain it to the provider [more effectively] once we get their chief [concern]. If patients are having new symptoms or [concerns] after [contracting] COVID-19, it's important for staff to be aware and listen carefully and with compassion. We can often help pull that information out of them."

In the Long Run

Undoubtedly, there are many hurdles and challenges to improving care for the long COVID patient community. With research funding cuts and public health leadership in turmoil, including the recent closure of the U.S. Department of Health and Human Services Office of Long COVID Research and Practice, future progress toward improved services, resources, and clinical care might appear uncertain.

Notably, as both a patient advocate and researcher, Stiles participated in NASEM's effort to develop a definition of long COVID. As such, she's aware of both the research progress already achieved and the roads still to be traveled for a fuller understanding of long COVID and how to treat it.

"When you meet long COVID patients, my advice is to believe them," says Stiles. "These patients need boots-on-the-ground help. Primary care offices are where most patients go, because there are not enough specialty centers. We need primary care, pediatrics, and general medicine [physicians] and clinicians to step up and try to help these patients. Patients and clinicians should know dedicated people [are] working to understand the biology of long COVID and related conditions and to find more effective treatments. Research endeavors are always difficult ... but I'm hopeful we are going to have some better answers soon."

Indeed, long COVID is perhaps already less a mystery disease than a condition whose complex, multifaceted presentation is now being methodically unraveled. Thanks to the many researchers, clinicians, and patients whose work and insights are contributing to a growing body of medi-

Advocacy Resources

Long COVID Alliance

<https://longcovidalliance.org>

Dysautonomia International

<https://www.dysautonomiainternational.org>

COVID-19 Longhailer Advocacy Project

<https://www.longhailer-advocacy.org>

cal knowledge about long COVID, future progress toward improved patient care is a realistic expectation. ♦

The CE test for this article can be found on page 28.



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