The Race to Understand Post–COVID-19 Conditions

Paul G. Auwaerter, MD

For more than a decade after the 1918 influenza pandemic, a mysterious Parkinson-like syndrome with sleep disturbance, hypomimia, and a high mortality rate developed in thousands of people across the globe. In 1920 the U.S. Surgeon General declared that the syndrome, popularly termed "encephalitis lethargica," was caused by influenza. However, opinions varied, mainly as cases of encephalitis lethargica frequently differed from respiratory infections thought to represent influenza (1). More than a century later, questions remain regarding the cause, transmission, and availability of effective treatments, and lastly, will it happen again?

While still amid the COVID-19 pandemic globally, postinfectious sequelae may again be a thorny and more long-lasting issue with little current understanding or treatment to offer patients. The pandemic's terrible human impact has been most frequently measured in deaths and hospitalizations. However, consequences affect both those with and those without COVID-19, with spillover effects not only on postponed health care and prevention but socioeconomic disruption that may prompt anxiety, depression, and post-traumatic stress disorder. In studies of SARS-CoV-2 infections, up to 61% of patients have experienced symptoms that persist for months after COVID-19, occurring in hospitalized and nonhospitalized adults, adolescents, and children. However, the absence of well-defined control groups or reliance on serologic testing or self-reporting will limit improving our current understanding (2–5).

Even if only 10% of patients experience persistent symptoms after COVID-19, the number afflicted will easily be tens of millions. Described symptoms are wide-ranging from depression and anxiety to rashes, cardiac issues, and gastrointestinal distress. The Centers for Disease Control and Prevention lists 18 new or ongoing, and mostly subjective, symptoms that may arise even after asymptomatic infection (6). Many patients could be easily diagnosed with common disorders other than COVID-19, such as myalgic encephalomyelitis or chronic fatigue syndrome, fibromyalgia, irritable bowel syndrome, migraine disorder, or anxiety or depression.

How to tease out directly what is a post–COVID-19 disorder versus the indirect impact of the pandemic on human life is more than a tall order. Simple explanations are unlikely for wide-ranging disease manifestations (7). For example, the hope of precision medicine to offer a straightforward approach to acute SARS-CoV-2 infection means subtyping that may include differences in viral variants, host responses, and treatment effects. Factor then additional influences in recuperation, premorbid health, and external stressors may mean galactic complexities for enumerating post–COVID-19 phenotypes. Despite these challenges, opportunities exist to leverage the already substantial knowledge and scientific resources gained from the coronavirus to understand mechanisms that produce such problems as fatigue and pain. Perhaps there are common mechanisms, whether an aberrant response to viral infection or loss of a job?

Many postinfectious disorders have defied detailed scientific understanding or precise diagnosis, causing contention among clinicians, researchers, and patients. Some, such as the common cold due to rhinovirus infection, appear to have little effect on health. In contrast, others, such as primary Epstein–Barr virus infection and *Coxiella burnetii* (Q fever), precipitate a postinfectious syndrome infection in 11% to 12% of patients (8). Both infectious mononucleosis and Lyme disease may cause persistent symptoms after the resolution of acute illness in the minority. Frustration frequently arises in these often marginalized patients with symptoms that some clinicians dismiss as only nonphysiologic or related to mental health. On another angle, some alternative practitioners offer false hope with antibiotic treatments, using Lyme disease as a stand-in for chronic, medically unexplained symptoms without a basis in demonstrable infection. Moreover, desperate patients seek information through social media and take non–evidence-based treatments for chronic Lyme disease, partly due to modern mainstream medicine's lack of effective approaches (9).

As a clinician who has evaluated patients who may or may not have Lyme disease, Epstein–Barr virus, or other infections as causes for their symptoms, I see there are gaps in the field's knowledge that should inform research priorities into the aftermath of COVID-19. More important, if science does not move with dispatch in addressing post–COVID-19 care in a multidisciplinary manner, the vacuum will be quickly filled by pseudoscience and quackery. Moreover, engagement of patients and advocates early in the design of studies, clinical guidelines, and public messaging may lessen the development of a parallel universe of care through a cottage industry.

Studies that lead to clear case definitions for a post–COVID-19 diagnosis may well be split into objective pathologic findings and those with only apparent subjective symptoms. Then, understanding risk factors leading to post–COVID-19 problems will also help guide vaccine-hesitant people toward immunization or greater care to avoid contracting the infection. While diagnostic tests that solidly confirm prior SARS-CoV-2 infection are essential for those without such documentation, the diagnostic Holy Grail would be biomarkers that could implicate a postviral explanation or, better yet, a predisposition to such an outcome. Validated assays may then help inform appropriate interventions. Regardless, prospective longitudinal studies should lead to key findings, including patient cohorts with asymptomatic, mild, and severe COVID-19. Accompanying biorepositories that include viral and human samples of well-characterized cohorts will also facilitate research and aid U.S. Food and Drug Administration approval of diagnostic tests.

While a basic understanding of postinfectious fatigue may inform novel approaches to treatment, effective interventions

This article was published at Annals.org on 31 August 2021.

are needed now. Clinical trial design should repurpose existing drugs or other interventions through studies that examine both medium- and long-term outcomes. Incorporating a placebo control is highly desirable because interventional studies of patients with long-term symptoms after Lyme disease have found up to a 36% response rate in placebo groups (10).

Novelty tends to spur new resources and investigators in infectious diseases. The National Institutes of Health has committed more than $1 billion to post–COVID-19 research, and the World Health Organization is coordinating global efforts. All are more than welcome infusions that will hopefully invigorate the study of postinfectious syndromes. Undoubtedly, the challenges to understand and treat postinfectious complications of SARS-CoV-2 will be daunting, but never have such resources been allocated. Understanding the basis of postinfectious sequelae will garner greater legitimacy and spur the prospect of successful treatments. The race is on, and it should not only focus on quality science and clinical trials but address head-on human behavior and anticipate controversy. Operation Warp Speed is by all accounts a success in developing effective vaccines for COVID-19. A similar program is long overdue to help those with postinfectious complications. Let not post–COVID-19 sequelae become our encephalitis lethargica of this century.

From The Sherrilyn and Ken Fisher Center for Environmental Infectious Diseases, Johns Hopkins University School of Medicine, Baltimore, Maryland (P.G.A.).

Disclosures: Disclosures can be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M21-3072.

Corresponding Author: Paul G. Auwaerter, MD, The Sherrilyn and Ken Fisher Center for Environmental Infectious Diseases, Johns Hopkins University School of Medicine, 725 North Wolfe Street, #231, Baltimore, MD 21205; e-mail, pauwaert@jhmi.edu.

Author contributions are available at Annals.org.

Ann Intern Med. doi:10.7326/M21-3072

References

1. **Dourmashkin RR.** What caused the 1918-30 epidemic of encephalitis lethargica. J R Soc Med. 1997;90:515-20. [PMID: 9370993]
2. **Morin L, Savale L, Pham T, et al; Writing Committee for the COMEBAC Study Group.** Four-month clinical status of a cohort of patients after hospitalization for COVID-19. JAMA. 2021;325:1525-1534. [PMID: 33729425] doi:10.1001/jama.2021.3331
3. **Radtke T, Ulyte A, Puhan MA, et al.** Long-term symptoms after SARS-CoV-2 infection in children and adolescents. JAMA. 2021. [PMID: 34264266] doi:10.1001/jama.2021.11880
4. **Blomberg B, Mohn KG, Brokstad KA, et al; Bergen COVID-19 Research Group.** Long COVID in a prospective cohort of home-isolated patients. Nat Med. 2021. [PMID: 34163090] doi:10.1038/s41591-021-01433-3
5. **Nehme M, Braillard O, Chappuis F, et al.** Prevalence of symptoms more than seven months after diagnosis of symptomatic COVID-19 in an outpatient setting. Ann Intern Med. 2021. [PMID: 34224254] doi:10.7326/M21-0878
6. **Centers for Disease Control and Prevention.** Post-COVID conditions. 2021. Accessed at www.cdc.gov/coronavirus/2019-ncov/long-term-effects.html on 18 July 2021.
7. **Lerner AM, Robinson DA, Yang L, et al.** Toward understanding COVID-19 recovery: National Institutes of Health workshop on post-acute COVID-19. Ann Intern Med. 2021;174:999-1003. [PMID: 33780290] doi:10.7326/M21-1043
8. **Hickie I, Davenport T, Wakefield D, et al; Dubbo Infection Outcomes Study Group.** Post-infective and chronic fatigue syndromes precipitated by viral and non-viral pathogens: prospective cohort study. BMJ. 2006;333:575. [PMID: 16950834]
9. **Feder HM Jr, Johnson BJ, O'Connell S, et al; Ad Hoc International Lyme Disease Group.** A critical appraisal of "chronic Lyme disease.". N Engl J Med. 2007;357:1422-30. [PMID: 17914043]
10. **Klempner MS, Baker PJ, Shapiro ED, et al.** Treatment trials for post-Lyme disease symptoms revisited. Am J Med. 2013;126:665-9. [PMID: 23764268] doi:10.1016/j.amjmed.2013.02.014