



Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.



# The Long COVID Conundrum

Once the coronavirus disease 2019 (COVID-19) pandemic ebbs, attention will likely shift to the disease's long-term complications, dubbed "long COVID." Media narratives have characterized long COVID as a common, debilitating, multiorgan, and possibly lifelong chronic disease often with little connection to the severity of the acute illness. Yet greater nuance in the way we discuss and approach long COVID is warranted, particularly for patients who had mild or asymptomatic infections.

At the outset of the pandemic, research into the consequences of critical illness made it clear that survivors of severe respiratory disease due to severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) could face long-term adverse health effects. However, when defined as a report of 1 or more persistent symptoms, long COVID appears common even after mild infections. One study<sup>1</sup> found that 1 in 3 nonhospitalized adults report at least 1 symptom 6 months post-COVID-19. Although 1 study found eventual resolution of symptoms in children,<sup>2</sup> another found persistence among 57% of nonhospitalized children and 36% of initially asymptomatic children.<sup>3</sup> Such estimates fuel concerns that long COVID is the "next public health disaster in the making" that could afflict more than 1 in 20 Americans.<sup>4</sup>

There are important caveats, however. First, such estimates should be interpreted in the context of what we know about symptom persistence after other common respiratory infections and in other prevalent conditions. Three months after community-acquired pneumonia, 51% have fatigue and 28% have dyspnea.<sup>5</sup> An analysis of claims data reported "new clinical sequelae" among 13% following lower-respiratory tract infections, only slightly (yet significantly) lower than the 14% prevalence after COVID-19 (vs 9% among those without a pulmonary infection).<sup>6</sup> Even typical upper respiratory tract infections are a leading cause of a protracted cough. Meanwhile, fatigue and cognitive symptoms<sup>7</sup> are common among those with major

depression, the prevalence of which appeared to rise sharply in the United States in 2020<sup>8</sup> and which may even be a complication of COVID-19 itself.<sup>9</sup>

Other studies further problematize the interpretation of symptom prevalence after mild COVID-19. One preprint study found high rates of fatigue, memory loss, and difficulty concentrating in children with a previous mild SARS-CoV-2 infection ascertained serologically, but equivalent rates of these symptoms among seronegative children.<sup>10</sup> Another study found low yet similar rates of symptoms between children who were SARS-CoV-2 seropositive (with only mild infections) and those who were seronegative.<sup>11</sup> A survey that found a heavy symptom burden among those with self-reported Long COVID (>90% nonhospitalized) also found that most of these individuals reported negative SARS-CoV-2 antibody and polymerase chain reaction (PCR) testing, yet had a similar symptom burden.<sup>12</sup> The lack of difference in symptom prevalence between those with and without serological evidence of a prior SARS-CoV-2 infection in such studies suggests that for some, "long COVID symptoms" could arise from processes other than a prior SARS-CoV-2 infection.

Symptoms are, after all, common in the general population. This complicates interpretation of much long COVID literature because misattribution of the cause of symptoms, by both physicians and patients, is also common. For instance, side effects like fatigue were frequently reported by placebo recipients in COVID-19 vaccine trials. Similarly, the link between myalgia and statins has been undercut by n-of-1 randomized trials showing no correlation when patients are blinded to treatment.<sup>13</sup> And overdiagnosis of Lyme disease among those without evidence of *Borrelia burgdorferi* infection, even in nonendemic areas, is a longstanding problem.<sup>14</sup>

Meanwhile, the long-term impact of COVID-19 on the lung, where it does the most damage, is not fully understood. Multiple studies have found persistent imaging and pulmonary function deficits among patients in the months after hospitalization for severe COVID-19. A longer-term study of patients with severe COVID-19, however, found that decrements in forced vital capacity, lung diffusing for carbon dioxide (DLCO), and exercise capacity—and computed tomography (CT) abnormalities—all steadily improved over the course of a year, indeed to the normal

---

**Funding:** None.

**Conflicts of Interest:** None.

**Authorship:** The author is solely responsible for the content of this manuscript.

Requests for reprints should be addressed to Adam Gaffney, MD, 1493 Cambridge Street; Cambridge, MA, 02138.

E-mail address: [agaffney@challiance.org](mailto:agaffney@challiance.org)

range for most.<sup>15</sup> Still, a subpopulation has persistent abnormalities,<sup>15</sup> and interstitial lung disease as a rare complication remains a possibility necessitating monitoring and research.

Patients with severe COVID-19 are also at risk for the full spectrum of post-critical illness complications, including chronic organ failures. And all symptoms endured by those who have had COVID-19, regardless of severity, are real, impair quality of life, and deserve diligent clinical attention. Still, errant assumptions about etiological causality could lead to the misattribution of symptoms to SARS-CoV-2 rather than other processes; excessive testing and referrals and a potentially harmful cascade of care; and the provision of non-evidence-based therapies.

Indeed, although there are no therapies approved by the Food and Drug Administration (FDA) for long COVID, various nonevidence-based therapies are now being prescribed, ranging from ivermectin to antivirals directed against Herpesviridae, as described in media reports. Tenuous connections between COVID and such entities as mast cell activation syndrome (MCAS) and postural orthostatic tachycardia syndrome (POTS) are also being widely asserted. Researchers who contend that mast cell activation syndrome has a startlingly high prevalence of 17% in the general population (on the basis of surveys of nonspecific symptoms) have advocated for mast cell stabilizer therapy as a long COVID prophylactic.<sup>16</sup> Evidence connecting COVID-19 to POTS is, meanwhile, weak. In 1 of the largest case series linking the disorders (n = 20), most subjects had negative SARS-CoV-2 testing.<sup>17</sup> Regardless, low specificity of diagnostic testing for POTS<sup>18</sup> combined with the nonspecific nature of symptoms could lead to many patients exposed to specialized testing and pharmacotherapy of little value.

Ironically, 1 treatment with clear efficacy for patients with chronic lung disease—physical rehabilitation—is now among the most controversial in long COVID.<sup>19</sup> This controversy stems from a longstanding dispute about the use of exercise therapy for patients with chronic fatigue syndrome that culminated in its removal from Centers for Disease Control and Prevention (CDC) recommendations and National Institute for Health and Care Excellence (NICE) clinical draft guidelines. However, evidence from other chronic lung diseases suggests that pulmonary rehabilitation will likely prove useful in patients with respiratory impairment due to COVID-19.

Acknowledging such nuance does not diminish the destructive impact of COVID-19, nor does it undermine the imperative of controlling the pandemic with vaccination and public health interventions. Yet if long COVID is more akin to the damage left after a hurricane, rather than a novel disease process commonly instigated by even the mildest SARS-CoV-2 infection, it may well be that empathetic yet judicious care, focused on gradual recovery and rehabilitation while avoiding overtesting and overtreatment, will be the optimal approach for many or most patients.

Adam W. Gaffney, MD, MPH<sup>a,b</sup>

<sup>a</sup>Harvard Medical School,  
Boston, Mass

<sup>b</sup>Division of Pulmonary and Critical  
Care Medicine, Cambridge Health  
Alliance, Cambridge, Mass

## References

- Logue JK, Franko NM, McCulloch DJ, et al. Sequelae in adults at 6 months after COVID-19 infection. *JAMA Netw Open* 2021;4(2):e210830.
- Say D, Crawford N, McNab S, Wurzel D, Steer A, Tosif S. Post-acute COVID-19 outcomes in children with mild and asymptomatic disease. *Lancet Child Adolesc Health* 2021;5(6):e22–3.
- Buonsenso D, Munblit D, Rose CD, et al. Preliminary evidence on long COVID in children. *Acta Paediatrica* 2021;110(7):2208–11.
- Phillips S, Williams MA. Confronting our next national health disaster — long-haul COVID. *N Engl J Med* 2021;385(7):577–9.
- Metlay JP, Fine MJ, Schulz R, et al. Measuring symptomatic and functional recovery in patients with community-acquired pneumonia. *J Gen Intern Med* 1997;12(7):423–30.
- Daugherty SE, Guo Y, Heath K, et al. Risk of clinical sequelae after the acute phase of SARS-CoV-2 infection: retrospective cohort study. *BMJ* 2021;373:n1098.
- Pan Z, Park C, Brietzke E, et al. Cognitive impairment in major depressive disorder. *CNS Spectrums* 2019;24(1):22–9.
- Ettman CK, Abdalla SM, Cohen GH, Sampson L, Vivier PM, Galea S. Prevalence of depression symptoms in US adults before and during the COVID-19 pandemic. *JAMA Netw Open* 2020;3(9):e2019686.
- Taqet M, Geddes JR, Husain M, Luciano S, Harrison PJ. 6-month neurological and psychiatric outcomes in 236 379 survivors of COVID-19: a retrospective cohort study using electronic health records. *Lancet Psychiatry*, 8; 2021. p. 2021416–27.
- Blankenburg J, Wekenborg MK, Reichert J, et al. Mental health of adolescents in the pandemic: long-COVID19 or long-pandemic syndrome? *medRxiv*; 2021. <https://doi.org/10.1101/2021.05.11.21257037>.
- Radtke T, Ulyte A, Puhan MA, Kriemler S. Long-term symptoms after SARS-CoV-2 infection in children and adolescents [e-pub ahead of print]. *JAMA*. doi: 10.1001/jama.2021.11880, Accessed July 16, 2021.
- Davis HE, Assaf GS, McCorkell L, et al. Characterizing long COVID in an international cohort: 7 months of symptoms and their impact. *EClinicalMedicine* 2021;38:4101019.
- Herrett E, Williamson E, Brack K, et al. Statin treatment and muscle symptoms: series of randomised, placebo controlled n-of-1 trials. *BMJ* 2021;372:n135.
- Reid MC, Schoen RT, Evans J, Rosenberg JC, Horwitz RI. The consequences of overdiagnosis and overtreatment of Lyme disease: an observational study. *Ann Intern Med* 1998;128(5):354–62.
- Wu X, Liu X, Zhou Y, et al. 3-month, 6-month, 9-month, and 12-month respiratory outcomes in patients following COVID-19-related hospitalisation: a prospective study. *Lancet Respir Med* 2021;9:747–54.
- Afrin LB, Weinstock LB, Molderings GJ. COVID-19 hyperinflammation and post-COVID-19 illness may be rooted in mast cell activation syndrome. *Int J Infect Dis* 2020;100:327–32.
- Blihshteyn S, Whitelaw S. Postural orthostatic tachycardia syndrome (POTS) and other autonomic disorders after COVID-19 infection: a case series of 20 patients. *Immunol Res* 2021;69(2):205–11.
- Plash WB, Diedrich A, Biaggioni I, et al. Diagnosing postural tachycardia syndrome: comparison of tilt testing compared with standing haemodynamics. *Clin Sci (Lond)* 2013;124(2):109–14.
- Newman M. Chronic fatigue syndrome and long COVID: moving beyond the controversy. *BMJ* 2021;373:n1559.