



# COVID-19: A New Wave of Chronic Disease

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**Abstract:** While the number of deaths and hospitalizations caused by the novel coronavirus SARS-CoV-2 and the disease it causes (COVID-19) have captured public attention, a wave of chronic disease is also resulting from the pandemic. Some survivors of COVID-19, even those whose symptoms were too mild to warrant hospitalization, have struggled with persistent symptoms months after initial infection. SARS-CoV-2 affects several body systems and generates a wide variety of symptoms including dyspnea, myalgia, fatigue, and brain fog. It is yet unknown who is at risk of long-term disease, how long these symptoms may last, and what the long-term sequelae of the damage inflicted by this virus may be.

NDs must adapt their practices to include consideration of COVID-19 as a differential diagnosis or root cause for a wide range of clinical presentations. The purpose of this article is to review the evidence of some of the longer-term effects and symptoms of COVID-19 that NDs may encounter in clinical practice, with background information on other post-infection syndromes for context.

Around the world, millions have now been infected by SARS-CoV-2, the novel coronavirus that causes the illness known as Coronavirus Disease 2019 (COVID-19).<sup>1,2,3</sup> As of this writing, hundreds of thousands of those infected have died. Understandably, much of the attention this pandemic has commanded has been on the dramatic struggle for survival in overwhelmed intensive care units (ICUs) and emergency rooms. It is a mistake, however, especially for practitioners, to measure the impact of COVID-19 by deaths only.<sup>4</sup> It is now clear that many will face significant health challenges for a prolonged and unknown period of time, regardless of how severe their initial acute infection.<sup>5</sup> This prolonged symptomatic period is becoming known as the “long tail” of this disease.<sup>5</sup> As more data emerges about longer-term health implications of COVID-19, and experts share their experiences of the long-term health implications of other infectious diseases, it’s becoming obvious that we will be witnessing a significant new wave of chronic disease.<sup>6</sup>

While it is critical that all healthcare providers recognize signs of acute SARS-CoV-2 infection, naturopathic doctors (NDs) may be more likely to see patients after the acute infectious stage. These patients may have symptoms that do not fit the current popular understanding of COVID-19 (its course, demographics affected, and body systems involved), and they may be struggling to find adequate health care related to these issues or even a health care provider who believes that they are genuinely sick. There is also the possibility that COVID-19 may trigger health issues that may appear to be unrelated. Moving forward, NDs must adapt their

practices to include consideration of COVID-19 as a differential diagnosis or root cause for a wide range of clinical presentations. The medical and scientific communities’ understanding of this pandemic - its risks, wide range of effects, mechanisms, and long-term health implications - is rapidly developing. The purpose of this article is to review the evidence of some of the longer-term effects and symptoms of COVID-19 that NDs may see in their clinical practice, to review the effects of other viruses and relevant syndromes in order to provide important context, and to highlight the relevance of this information to a naturopathic clinical practice. The article concludes with some suggested general approaches to treatment, but specific recommendations are beyond the scope of this article.

## Chronic disease following acute infections

Post-infection syndromes are seen after an acute infection with a number of different microbes. Examples include fatigue, myalgias, orthostatic intolerance and headache caused by *borrelia burgdorferi* (Lyme)<sup>7</sup> bacterium and West Nile virus,<sup>8</sup> myalgic encephalomyelitis/chronic fatigue syndrome caused by Epstein-Barr virus and human herpesvirus-6,<sup>9</sup> and similar syndromes following the 1918 H1N1 flu, Ebola, and the virus causing Severe Acute Respiratory Syndrome (SARS).<sup>10</sup> Fatigue and exercise intolerance resulting from mitochondrial oxidative stress are common features of post-infection syndromes.<sup>10,11</sup> Although mechanisms of action are not yet clear, some predictors of the development of these chronic syndromes include severity of infection, the degree to which microbes induce “cytokine storms”, and Th2 dominant immune responses.<sup>10</sup>

Post-viral syndromes have been documented for the two previous coronavirus epidemics, SARS and Middle East acute respiratory syndrome (MERS)<sup>12-14</sup>. A wide range of persistent symptoms has been reported with each of these infections, including respiratory compromise, decreased quality of life, psychiatric symptoms<sup>12-15</sup> and autonomic dysfunction.<sup>16,17</sup> Although there is little information on the typical course of prolonged illness in non-hospitalized patients, emerging data suggests that persistent symptoms of unknown length may also occur in some people following COVID-19 infection.<sup>18</sup>

Prolonged recovery is common in hospitalized patients with COVID-19, especially among those who experienced Acute Respiratory Distress Syndrome (ARDS).<sup>2,4</sup> While the general course of COVID-19 in outpatients with “milder” symptoms is believed to be recovery within two to three weeks, extended debility is also being observed among this population. In a survey of 294 patients recovering from COVID-19 from multiple US medical centers, 35% of respondents reported persistent symptoms at 14-21 days, with mean symptom count of seven, and more than half reporting at least one persistent symptom.<sup>18</sup> Consistent with data from hospitalized patients, older age and number of comorbid diagnoses were significantly associated with prolonged illness.<sup>18</sup>

One of the more striking findings in this survey was that among adults age 18 to 34 years of age without comorbidities, one out of every 5 patients exhibited prolonged symptoms, with fatigue, dyspnea, and cough being the most common.<sup>18</sup> Among those without comorbidities, there is as yet no indicator who may be more at risk of developing these sequelae.<sup>18</sup>

Since the common narrative of COVID-19 has been that patients who do not require hospitalization will fully recover in two to three weeks, those with persistent symptoms are often not believed by their families or even their doctors.<sup>19</sup> Thousands of people are now participating in “long-hauler” online support groups and symptom tracking apps<sup>19-21</sup> created to support those who’ve had confirmed or suspected cases of mild COVID-19 (not requiring hospitalization), but whose symptoms have been debilitating and have continued beyond 2 weeks.<sup>20</sup> *Body Politic* surveyed 640 long-haulers and found: “... about three in five are between the ages of 30 and 49. About 56 percent have not been hospitalized, while another 38 percent have visited the emergency room but were not admitted. About a quarter have tested positive for COVID-19 and almost half have never been tested. Some became sick in mid-March, when their home countries were severely short on tests (most survey respondents live in the U.S. and the U.K.). Others were denied testing because their symptoms didn’t match the standard set.”<sup>19,20</sup>

Preliminary studies suggest that up to 85% of patients have symptoms beyond 2 weeks, and up to 55% have 3 or more symptoms.<sup>4</sup> Reported post-acute symptoms include fatigue, headache, brain fog or difficulty thinking despite normal brain scans, poor concentration, anosmia, pharyngitis, dyspnea, cough, chest pain, post-exertional fatigue, heart palpitations, dizziness, headaches, seizures, intense muscle pain, and

various neurological symptoms, many of which fall under autonomic dysfunction.<sup>5,16,19,20,22</sup> These symptoms sound remarkably like chronic fatigue immune deficiency syndrome (CFIDS), and while there are many similarities, it would be errant to label this as such. It’s important that clinicians and researchers consider and address the possible ways in which the SARS-CoV-2 virus might be causing this specific post-viral syndrome.<sup>13,14</sup> The mechanisms to explain this range of signs and symptoms are not yet known, although possible explanations are inflammation, maladaptive changes to the immune response,<sup>15</sup> persistent or cyclical microvascular issues reducing oxygen delivery to tissues, and disruption to the gut microbiome.<sup>6,13,14</sup> Prospective studies of recovery from COVID-19 are needed to elucidate symptom duration and time of return to baseline function, as well as who is at risk of extended debility. Clinicians will need to consider prolonged recovery from COVID-19 in the differential for the above symptoms.

## Systems

SARS-CoV-2 enters cells via the ACE2 receptor,<sup>6,16,17</sup> which is present in multiple organs including lung, heart, gut, kidney, vasculature, and nervous system.<sup>16,17</sup> Organs with these receptors appear to be differentially affected by COVID-19, which may suggest that cell infection is multifactorial,<sup>23-25</sup> and differentiates this from previous coronaviruses. Several systems affected by SARS-CoV-2 are detailed here.

### *Pulmonary*

COVID-19 was first described as a pneumonia of unknown origin,<sup>26,27</sup> and caused alarm due to its potential to lead to ARDS.<sup>28</sup> Chest CT scans of COVID-19 patients have shown a distinctive pattern of ground-glass opacities (GGOs), and consolidation to be the most common findings, both of which can appear within days of symptom onset.<sup>28,29</sup>

Lingering dyspnea is a common post-acute complaint; an Italian study of 179 previously hospitalized COVID-19 patients found that dyspnea was reported by 43.4% of patients at 60 days after symptom onset.<sup>4</sup> GGOs have also been noted in imaging of SARS, MERS, and avian flu patients; these were observed to begin to improve within 6 months of infection, though the presence of such visible lesions had stronger correlation with some loss of pulmonary function compared to those who had none.<sup>30</sup>

Importantly, two studies have documented GGOs in asymptomatic individuals infected with SARS-CoV-2 who did not progress to overt illness.<sup>31,32</sup> While it is likely that COVID-19 patients hospitalized for pulmonary symptoms of the disease will have subsequent lung damage that will affect their ongoing health, further research will determine how prevalent asymptomatic lung changes are in the larger population, whether these lesions resolve, and whether these asymptomatic findings may subtly impact pulmonary function and long-term health.<sup>33</sup>

***Cardiovascular***

Rich in ACE2 receptors, the heart muscle is affected by SARS-CoV-2. Direct myocardial viral invasion has been shown by postmortem myocyte inflammation in autopsy samples,<sup>6,34</sup> and several studies have documented elevated troponin levels in hospitalized patients, indicating virus-induced myocardial invasion and inflammation.<sup>22,34,35</sup>

While patients with risk factors such as hypertension, obesity, and advanced age are more vulnerable to severe outcomes from COVID-19, the adverse effects of this virus on the heart has been observed in younger people without known underlying conditions.<sup>22</sup> An Italian study compared cardiac findings of 100 COVID-19 patients (mean age 49, two-thirds of whom had not required hospitalization) with those of healthy controls.<sup>22</sup> Two months post-infection, cardiovascular magnetic resonance imaging showed significant differences between cases and healthy controls in structural changes and cardiac blood markers.<sup>22</sup> The concern is that some of this damage may be long-term and lead to decreased cardiac capacity, chronic heart disease, or heart failure.<sup>22</sup> Further study will help to clarify long-term effects.

A cardiovascular risk of COVID-19 that was not immediately understood is the unique propensity of the virus to initiate blood clots. It's now known that SARS-CoV-2 acts on the endothelial lining of blood vessels (perhaps via ACE2 receptors), triggering thrombi throughout the body that impair local and regional circulation or travel via the circulatory system to trigger organ damage, pulmonary emboli, strokes, and myocardial infarctions.<sup>36</sup>

***Neurological***

The neurological COVID-19 sequelae dubbed “NeuroCOVID”<sup>16</sup> may be the most complex and variable. Neurological symptoms that have been documented in association following SARS-CoV-2 infection include headache, altered consciousness, ataxia, acute cerebrovascular disease, hyposmia, seizure, hypoguesia, neuralgias, and mood disorders as well as the secondary effects due to stroke and ischemia associated with this infection.<sup>12,16,37,38</sup> Similarly, sequelae of SARS and MERS coronavirus infections included encephalopathy, encephalitis, ischaemic and haemorrhagic stroke attributed to hypercoagulability, sepsis and vasculitis, and GBS.<sup>12,16</sup>

Other than ischemia, processes by which the nervous system is affected in COVID-19 are currently unproven. Suspected mechanisms of injury include direct attack on neurons by the virus, incidental damage from hypoxia or fever, and induced autoimmune disease.<sup>12,39</sup> How the virus gains entry to the CNS is unclear. Possible mechanisms of entry include entry via damage to the vascular endothelium of the blood-brain barrier (BBB), and retrograde transmission via the olfactory nerve.<sup>16,32,38,39</sup> Other coronaviruses have been shown to spread via neuronal retrograde, through ascending the cranial nerves or through the chemo- and mechanoreceptors of the lung, crossing synapses and ultimately reaching the brainstem.<sup>16,39</sup>

Neurologists in the U.K. identified 4 categories of NeuroCOVID as early as March 2020, based on 43 patient cases: a) encephalopathies with psychosis or delirium but normal brain MRIs and CSF analyses; b) inflammatory syndromes of the CNS, including acute disseminated encephalomyelitis (ADEM), a demyelinating autoimmune disease affecting the CNS; c) ischemic strokes; and d) disorders of the peripheral nervous system (including Guillain-Barré syndrome, a demyelinating autoimmune disease affecting the PNS).<sup>12</sup> SARS-CoV-2 viruses were present in the CSF of approximately half these cases.<sup>12</sup>

Several studies have documented the association of COVID-19 with dysregulation of the autonomic nervous system.<sup>40–42</sup> Dysautonomia (DA) results from the over- or under-reaction of the sympathetic or parasympathetic nervous systems. Symptoms of DA are wide-ranging, including: orthostatic hypotension, unstable blood pressure<sup>40</sup>, erectile dysfunction, bladder and bowel problems,<sup>40</sup> non-epileptic seizures,<sup>41</sup> gastric motility issues,<sup>43</sup> and postural orthostatic tachycardia syndrome (itself a constellation of symptoms, including fatigue, dizziness, tachycardia, light-headedness, anxiety, tremors, and exercise intolerance).<sup>44</sup> DA has also been associated with other infections, including the viruses HIV, coxsackie B, hepatitis C, mumps,<sup>40</sup> Epstein-Barr,<sup>40,43</sup> herpes,<sup>43</sup> SARS, and MERS.<sup>17</sup>

SARS-CoV-2 invasion of the CNS may also be associated with new onset or worsening anxiety and depression.<sup>38</sup> One study that tracked symptoms in 114 patients who had tested positive for COVID-19 found that olfactory dysfunction (OD) had a stronger correlation with anxiety and depression than did upper respiratory symptoms of cough, dyspnea, or fever, all of which are presumably represented more severe disease and therefore presumed to be more challenging to mental health.<sup>38</sup> Further studies to validate the finding and examine causality and duration of effect are needed to fully understand the implications of this research. Given that OD is estimated to be even greater than the reported prevalence of 34–68% of patients with COVID-19,<sup>32</sup> an infectious etiology of depression and anxiety, may further compound the concerning mental health trends associated with social and financial losses resulting from the pandemic. Clinicians should remain aware of the increasing need of mental health supports, as well as a potential infectious etiology of new or exacerbated mental illness symptoms in patients.

***Endocrine***

Diabetes is a major international health issue.<sup>45</sup> Patients with pre-existing type 2 diabetes (T2DM) have a greater risk of severe COVID-19 outcomes and death.<sup>46–50</sup> Worsening glycemic control in existing T2DM as well as new onset type 1 diabetes (T1DM) has been observed with current and previous coronavirus infections including SARS.<sup>50–52</sup> Although the mechanism of action is yet unclear, direct medication interactions, impaired glycemic control, direct pancreatic injury via ACE2 receptor binding, and new development of auto-antibodies in genetically predisposed individuals, have been shown.<sup>47–50,53–55</sup>

**Other systems**

Unfortunately, long-term effects of COVID-19 are likely not isolated to just the pulmonary, cardiac, neurological, and endocrine issues outlined above. There is also emerging evidence of sequelae related to the kidneys, male fertility, and possibly more<sup>56-60</sup>. This is a rapidly evolving area of research to follow in the months and years to come.

**What can be applied to naturopathic clinical care?**

As naturopaths, a large focus of our care is on disease prevention and health promotion. Anyone, regardless of age or health status, can become gravely ill from COVID-19. Still, it's important to maintain and improve health to support patients and reduce risk of poor outcomes due to comorbidities. It's also critical for NDs to recognize and properly diagnose sequelae from previous or undetected SARS-CoV-2 infections. Prevention and generally supportive naturopathic therapies will likely be helpful. Recommended patient management approaches include: Establish the foundations for health, including good nutrition, sleep, and physical activity. This may include various immune supportive supplemental nutrients and herbs. Practitioners should be prepared to support patients within the realm of patients' available resources.

1. Monitor and manage patients' conditions recognized as risk factors for poorer COVID-19 outcomes (e.g., diabetes, chronic kidney disease, hypertension, obesity), and routinely screen patients for comorbidities where applicable.
2. Educating healthy patients that although the risk is less, they can still become very ill from a COVID-19 infection and experience long-lasting, debilitating symptoms. Fear-mongering isn't helpful, but there is a great deal of complacency regarding this virus among young and healthy people. NDs must help all patients understand the potential risks of COVID-19.
3. Encourage patients to follow public health guidance to reduce risk of COVID-19 exposure and transmission including mask-wearing, physical distancing, and sensible hand hygiene.<sup>61-67</sup> Remind patients that reducing spread and "flattening the curve" is not just about infection prevention, but also about buying science time to learn more about how this virus infects and how to prevent severe/long-term outcomes.
4. Teach patients with confirmed or suspected COVID-19 how to recognize early signs of dangerous conditions such as stroke, heart attack, ketoacidosis, or new onset neurological symptoms, and to report or seek prompt medical attention should these symptoms arise.
5. Upgrade your knowledge and skills as necessary to provide healing support for patients who may be experiencing the "long tail" of COVID-19. Monitor reports from post-infection clinics.<sup>4,57</sup> Be prepared to see patients dealing with these sequelae.

Review what you know about the many treatment options we have in the naturopathic toolkit for decreasing inflammation, treating chronic fatigue, and for supporting mitochondrial function. Learn about post-viral autonomic dysfunction and supportive interventions to resolve or cope with the various expressions of dysautonomia.

6. Monitor patients who have tested positive for or possibly been exposed to COVID-19 as needed for potential sequelae (strokes, heart and lung function compromise, depression). It may take months or years to understand the consequences of these exposures for some people.
7. Take seriously any patient concern regarding brain fog, fatigue, and especially diminished exercise tolerance. Especially with abrupt or prolonged complaints, consider cardiac/pulmonary workup. Do not dismiss the experience of these patients. Autonomic dysfunction especially is very hard to "see" via any known testing.
8. Validate your patients who are finding their recovery difficult. Patients often do not get the support they need from family and friends who don't understand why they're "still sick". Help your patients understand that recovery may be gradual, even with continued treatment.
9. Recognize that patients with persistent symptoms may need consistent support and assistance with advocacy, especially in light of an already burdened health care system now facing chronic sequelae due to COVID-19.

It has long been clear that COVID-19 is infectious and deadly. Months after the initial outbreak in Wuhan, China, we are still learning about acute and chronic multi-organ implications resulting from COVID-19, and understand that disease sequelae may impact the quality of life for patients for extended periods. Naturopathic medicine aims to identify the root cause of disease and remove obstacles to cure, and we are well-positioned to be especially useful as thousands of recovering patients will be dealing with complex and frustrating symptoms and chronic disease. Helping all patients (regardless of their age or health status) understand the seriousness of this virus is of utmost importance. This should be done without fear mongering, but instead, in the true nature of *docere*. This is an opportunity for NDs to provide kind guidance and leadership — to their patients in clinical practice, to their communities through social media and educational offerings, and to the profession through continued research and development of evidence for effective and evidence-informed naturopathic management of the various aspects of this new wave of chronic disease. 🌱

