

Episode #48 – Update on Post COVID-19 Condition (Long COVID)

November 12, 2021

Overview

As of November 6, 2021, over 249 million cases of COVID-19 and over 5.0 million deaths have been reported globally. Canada has reported over 1.7 million cases and over 29 thousand deaths. Ontario has reported over 602,000 cases and over 9,800 deaths. Despite the prevalence of this disease, the natural history, clinical course, and long-term consequences are still not completely understood. [1] [2] [3]

Depending on the severity of symptoms, most individuals with COVID-19 fully recover within 3-4 weeks after contracting SARS-CoV-2, but some experience long-term effects on several organ systems, including respiratory, cardiovascular, neurological, gastrointestinal, and musculoskeletal systems, as well as enduring psychological effects. These effects can occur regardless of age or initial severity of infection, but develop more frequently, for example, in the female sex, older age, and in individuals with more symptoms initially. [4] [5] [6]

Long COVID or post-COVID-19 are umbrella terms that refer to COVID-19 symptoms that persist for weeks to months beyond the initial phase of a severe, mildly symptomatic, or asymptomatic SARS-CoV-2 infection. Several other terms have also been utilized to describe this condition. For example, Public Health Ontario utilizes the term post-acute COVID-19 to describe persistent symptoms that develop or last beyond 3 weeks since COVID-19 symptom-onset. [4] [7]

The United States National Institutes of Health (NIH) introduced the term post-acute sequelae of SARS-CoV-2 infection (PASC) to refer to the constellation of symptoms and other effects experienced by individuals who do not return to their baseline health status after COVID-19. [8]

The lack of a single terminology and clinical case definition have been continually indicated as obstacles in advancing research and managing individuals experiencing post COVID-19 sequelae. [6]

On October 6, 2021, the World Health Organization (WHO) published a clinical case definition of post COVID-19 condition according to input from a panel of researchers, patients, clinicians, and other stakeholders from forty-four countries in the 6 WHO

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regions (i.e., Africa, Americas, Eastern Mediterranean, Europe, South-East Asia, Western Pacific). [6] [9] [10]

Through consensus, the panel identified 12 domains to be included in the clinical case definition:

- History of SARS-CoV-2 infection
- Laboratory-confirmed SARS-CoV-2 infection
- Minimum time period from the onset of symptoms (or from date of positive test for asymptomatic) of 3 months
- Minimum duration of symptoms of at least 2 months
- Symptoms (e.g., cognitive dysfunction, fatigue, shortness of breath)
- Minimum number of symptoms
- Clustering of symptoms
- Time course of symptoms
- Sequelae of well-described complications of COVID-19 (e.g., stroke, heart attack)
- Symptoms cannot be explained by alternative diagnosis
- Application of definition to different populations
- Impact on everyday functions [6]

WHO's clinical case definition states:

> *Post COVID-19 condition occurs in individuals with a history of probable or confirmed SARS CoV-2 infection, usually 3 months from the onset of COVID-19 with symptoms and that last for at least 2 months and cannot be explained by an alternative diagnosis. Common symptoms include fatigue, shortness of breath, cognitive dysfunction but also others and generally have an impact on everyday functioning. Symptoms may be new onset following initial recovery from an acute COVID-19 episode or persist from the initial illness. Symptoms may also fluctuate or relapse over time. A separate definition may be applicable for children.* [6]

WHO encourages all national authorities, policy makers, and clinicians to adopt the definition to enhance recognition of the condition, measure the burden of illness, and understand global prevalence. Further, a standardized definition of post COVID-19 condition will help advance research, facilitate awareness and acceptance, and aid diagnosis and management. WHO notes the definition may change as new evidence emerges and as understanding of COVID-19 consequences continues to evolve. [6] [11]

Prevalence of post COVID-19 condition[1]

The number of individuals affected with long-term sequelae after acute COVID-19 remains unknown. Some published reports have indicated approximately 10-20% experience lingering symptoms for weeks to months following acute SARS-CoV-2 infection. However, some studies suggest the prevalence is 31-51%, with incident rates over 80% among those hospitalized with COVID-19. [4] [6] [12]

[1] Refer to Episodes #28 and #38 for additional information on long-term sequelae and post COVID-19 condition (long COVID).

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As of September 14, 2021, the Ontario COVID-19 Science Advisory Table conservatively estimated between 57,000 to 78,000 individuals had or are currently experiencing post COVID-19 condition in Ontario. [7]

A rapid systematic review published in June 2021 estimated more than 150,000 Canadians were living with post COVID-19 condition. [13]

Furthermore, research has shown onset of post COVID-19 condition maybe delayed. For example, a retrospective cohort study by Taquet et al. (2021) revealed 37% of 273,618 individuals with COVID-19 had at least one long-term symptom 90 to 180 days after diagnosis, of whom 40% did not experience post sequalae in the first 3 months. [14]

Several studies have shown the prevalence of persistent symptoms lessened as time increased since symptom-onset. For example, Sudre et al. (2021) noted persistent symptoms decreased from 13.3% at 28 days after symptom-onset, to 4.5% at 8 weeks, and 2.3% at 12 weeks (n=558 patients). [15] In a United Kingdom (UK) study of 20,000 individuals, 21.0% experienced at least one persistent symptom 5 weeks after symptom-onset and 13.7% at 12 weeks. [16] Havervall et al. (2021) conducted a cohort study of 323 seropositive (mild disease) and 1,072 seronegative healthcare workers in Sweden to investigate long-term symptoms. At least one moderate to severe persistent symptom was reported at 56 days since initial serological test in 26.0% of seropositive cases (seronegative cases: 8.9%), 21.4% (7.2%) at 112 days, and 14.9% (3.4%) at 224 days. [17]

Risk factors for developing post COVID-19 condition

Potential risk factors include the presence of comorbidities (e.g., obesity, asthma), female sex, older age, increased disease severity, and having more acute symptoms. [4] [7] [18] [19]

For example, Rohrer-Meck et al. (2021) found females (63.5%) were more likely than males to have a diagnosis of post COVID-19 condition. There was also a higher prevalence in individuals who had been hospitalized for COVID-19. [18]

A prospective cohort study by Wynberg et al. (2021) based in Amsterdam found COVID-19 symptoms persisted for one year after illness onset, even in some individuals with mild disease. Their study showed recovery after 6 months from the onset of disease was uncommon, suggesting individuals who remain symptomatic beyond this point may require more intensive support and care. Female sex and obesity were the most important determinants of speed of recovery from symptoms. Female participants experienced a 35% slower recovery than males and participants who were obese recovered 38% slower than those of normal weight, when adjusted for age, sex, and comorbidities. [20]

Munblit et al. (2021) found similar results with 47% of adults admitted to hospital due to COVID-19 reported persistent symptoms 6 to 8 months after discharge. Fatigue and

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respiratory symptoms were most common, and female sex was associated with persistent symptoms. [21]

Sudre et al. (2021) found persistent symptoms over 28 days was significantly associated with age, rising from 9.9% in the individuals aged 18-49 years to 21.9% in those aged ≥70 years. [15]

A longitudinal cohort study by Huang et al. (2021) reported 20% to 30% of patients who had been moderately ill and up to 54% of those who were critically ill were still having lung problems (e.g., lung diffusion impairment and radiographic abnormalities) 12 months after leaving the hospital. [22]

In addition, experiencing more than five symptoms during the first week of illness was associated with post COVID-19 condition regardless of age or sex. [15] [19]

Interestingly, a longitudinal prospective cohort study by Augustin et al. (2021) of non-hospitalized individuals with COVID-19 found a lower baseline level of SARS-CoV-2 immunoglobulin G (IgG),[2] anosmia, and diarrhea during acute COVID-19 were predictors for post COVID-19 condition after seven months. [23]

Oral health and disease severity[3]
Periodontitis appears to increase COVID-19 severity, a risk factor for developing post COVID-19 condition. In a case-control study of 568 COVID-19 patients, Marouf et al. (2021) found individuals with periodontitis were 3.5 times more likely to be admitted to intensive care, 4.5 times more likely to require assisted ventilation, and had an almost 9 times higher risk of death then individuals without periodontitis. Levels of white blood cells, C-reactive protein, and D-dimer (indicative of blood clotting) were also significantly higher in the blood of individuals with COVID-19 and periodontitis. [24]

Symptoms
More than 200 different symptoms across multiple organ systems have been associated with post COVID-19 condition. Symptoms can fluctuate in prevalence and intensity over time. Relapses have been reported, primarily triggered by exercise, physical or mental activity, and stress. Some of the most reported symptoms include:

- Dyspnea or increased respiratory effort
- Fatigue
- Post-exertional malaise[4] and/or poor endurance
- "Brain fog" or cognitive dysfunction
- Cough
- Chest pain
- Headache
- Anxiety
- Depression
- Palpitations and/or tachycardia

[2] Refer to Episodes #44 & #45 for information on immunoglobulins.
[3] Refer to Episodes #13 & #31 for more information on oral health, periodontal disease, and COVID-19.
[4] Post-exertional malaise (PEM) is the worsening of symptoms following even minor physical or mental exertion, with symptoms typically deteriorating 12 to 48 hours after activity and lasting for days or even weeks. PEM can be lessened by pacing activities. The goal is to avoid PEM flare-ups and illness relapses by balancing rest and activity. [86]

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- Arthralgia
- Myalgia
- Paresthesia
- Abdominal pain
- Diarrhea
- Insomnia and other sleep disturbances
- Fever
- Lightheadedness (postural orthostatic tachycardia syndrome)[5]
- Impaired daily function and mobility
- General pain or discomfort
- Mood changes
- Anosmia or dysgeusia
- Menstrual cycle irregularities
- Rash (e.g., urticaria) [7] [25] [26]

Davis et al. (2021) conducted an online survey of individuals with suspected or confirmed COVID-19. Data was collected from September 2020 to November 2020. The researchers analyzed responses from 3,762 individuals from 56 countries (including Canada). Their analysis estimated the prevalence of 203 symptoms lasting more than 28 days in 10 organ systems, 66 of which were traced over 7 months. More than 91% of individuals needed at least 35 weeks to recover. Participants experienced on average 55.9 symptoms across 9.1 organ systems.

The most frequent symptoms after month 6 were fatigue (98.3%), post-exertional malaise (89%), and cognitive dysfunction (85.1%). Other symptoms included:

- Visual hallucinations
- Tremors
- Sexual dysfunction
- Bladder control issues
- Hair loss
- Shingles
- Blurred vision
- Tinnitus
- Night sweats

In addition, 96% of participants indicated their symptoms lasted more than 90 days, and 65% stated their symptoms lasted for at least 180 days. [26]

A retrospective electronic health record cohort study by Estiri et al. (2021) was conducted involving 52,491 individuals with mild or asymptomatic SARS-CoV-2 infections. Sequalae experienced for over 2 months included anosmia, dysgeusia, alopecia, chest pain, and dyspnea, as well as a variety of new diagnoses, such as diabetes mellitus and neurological disorders. However, more than 63% of sequalae were observed in individuals under 65 years of age. The authors stressed the importance of younger adults opting for vaccination to minimize the risk of debilitating post-acute sequelae of COVID-19 since long-term effects of COVID-19 are not limited to older individuals. [27]

[5] Refer to Episode #38 for more information on postural orthostatic tachycardia syndrome.

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Overview of complications by body system [26] [28] [29]

Body system	Complications*
Neurologic	Olfactory deficits Gustatory deficits Headache Cognitive impairment Hearing loss, earache, tinnitus
Psychological or psychiatric	Insomnia Post traumatic stress disorder Depression Anxiety Obsessive compulsive syndromes
Cardiovascular	Dyspnea Tachycardia, palpitations Myocarditis Cerebrovascular disease Postural tachycardia orthostatic syndrome (POTS)
Respiratory	Dyspnea Cough Pulmonary fibrosis Impaired pulmonary function Pulmonary hypertension
Gastrointestinal	Loss of appetite Acid reflux Diarrhea, vomiting, nausea Constipation Abdominal distension & pain
Musculoskeletal	Bone aches, joint pain Muscle aches Muscle spasms Tightness of chest
Dermatologic	Skin rash Hair loss
Other	Chronic fatigue Kidney injury, chronic kidney disease Hyperglycemia, diabetes Multisystem inflammatory syndrome in children (MIS-C) Fever

* List is not comprehensive

Increase use of medications

Post COVID-19 condition has been associated with increased incident use of numerous medications. Al-Aly et al. (2021) conducted research to identify 6-month incident sequelae, including diagnoses, medication use, and laboratory abnormalities in hospitalized and nonhospitalized individuals with COVID-19 who survived for at least 30 days after diagnosis. In addition, identifying multiple sequalae, the research revealed

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increased use of numerous medications in 380 medication classes, such as pain medications (opioids and non-opioids), anxiolytics, antidepressants, antihypertensives, antihyperlipidemic agents, oral hypoglycemics, antimicrobials, insulin, laxatives, histamine antagonists, antacids, antiasthma medications, bronchodilators, vitamins, minerals, decongestants, and antidiarrheal agents. [30]

Pediatric population

Systematic reviews of SARS-CoV-2 infection in children have described mild disease and generally good outcomes in this population.[6] [31] However, the prevalence and characteristics of the post COVID-19 condition in children is less understood. Similar to adults, even children who had mild initial symptoms, or who were asymptomatic have experienced long-lasting post COVID-19 effects. [7] [32] [33]

In a review of 14 international studies on long COVID in children and adolescents involving 19,426 children and adolescents, Zimmermann et al. (2021) found the prevalence of persisting symptoms ranged from 4 to 66%. The most common symptoms reported 4-12 weeks after acute infections were:

- Fatigue (3-87%)
- Concentration difficulties (2-81%)
- Headache (3-80%)
- Abdominal pain (1-76%)
- Sleep disturbance (2-63%)
- Myalgia or arthralgia (1-61%)
- Rash (2-52%)
- Loss of appetite or weight (2-50%)
- Chest tightness or weight (1-31%)
- Cough (1-30%)
- Disturbed sleep or anosmia (3-26%)
- Congested or runny nose (1-12%)

The authors noted in the majority of reviewed studies, symptoms did not persist longer than 12 weeks but pointed out even if only a small number of children and youth have persisting symptoms, the overall impact would be considerable. The study emphasized why children who are eligible for vaccinations should be vaccinated. The authors stressed the need for additional research into the risk, impact, and underlying immunological mechanisms of post COVID-19 condition in children and adolescents. [34]

Molteni et al (2021) conducted a prospective UK cohort study of 1,734 children aged 5 to 17 years with positive SARS-CoV-2 test results from September 1, 2020 to January 24, 2021. The study revealed 4.4% (77) experienced prolonged symptoms 28 days after infection, and 1.8% (25) experienced symptoms 56 days after infection. Age correlated with illness duration as the median illness duration was longer in older children versus younger children (7 vs 5 days, respectively). The most common prolonged symptoms reported were fatigue, headache, anosmia, and sore throat. [35]

Notably, the study contained data from September 2020 to January 2021, which preceded the arrival in the UK of the more infectious Delta variant. More pediatric COVID-19 cases have emerged in countries where the Delta variant is the predominant strain (e.g., UK, U.S., Canada). Ultimately, the Delta variant or other more transmissible

[6] Refer to Episodes #33 and #34 for additional information on the pediatric population and COVID-19.

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variants may impact the prevalence of post COVID-19 in the pediatric population. [35] [36] [37] [38] [39] [40] [41]

On November 5, 2021, Chief Public Health Officer Dr. Theresa Tam stated those under 12 years currently represent over 20% of daily cases, despite only representing 12% of the country's population. Dr. Tam explained it was not a surprising or unexpected pattern, given the high level of vaccination in the other age groups, schools re-opening, and children under 12 are so far not eligible for vaccination against SARS-CoV-2. [42]

A review by Zimmermann et al. (2021) noted vaccination, in addition to protecting children from severe illness, can protect against post COVID-19 condition including multisystem inflammatory syndrome in children (MIS-C). Another advantage of vaccinating children is to help decrease viral transmission and thus reduce spread to vulnerable adults and the risk of new virus variants emerging. Vaccination can also protect children against indirect harms caused by repeat testing, quarantines, and school closures. [43]

Multisystem inflammatory syndrome in children (MIS-C)[7]

Children are at risk for multisystem inflammatory syndrome in children (MIS-C)[8] after SARS-CoV-2 infection. MIS-C is a Kawasaki-like disease with toxic shock syndrome and myocarditis. It is a potentially serious illness in children that appears to be a delayed, post-infectious immunologic response to SARS-CoV-2 infection. Symptoms can begin days to weeks after recovery from acute COVID-19 infection, with reports of fatigue, fever, gastrointestinal symptoms (e.g., abdominal pain, diarrhea, vomiting), dyspnea, headache, Kawasaki-like disease, and toxic shock syndrome. [28] [44] [45]

A cross-sectional study by Buonsenso et al. (2021) found 2.3% of children with COVID-19 developed MIS-C. Without early diagnosis and treatment, MIS-C can lead to severe complications to organs, such as the heart, lungs, and kidneys. In rare cases, MIS-C could result in permanent damage or even death. The exact cause of MIS-C is not known yet, but it appears to be an excessive immune response related to COVID-19. [33]

Risk factors for post COVID-19 condition in children

Osmaov et al. (2021) investigated risk factors for developing enduring symptoms in children (≤18 years old) hospitalized with COVID-19. The prospective cohort study found age was significantly associated with persistent symptoms, with children above ≥6 years of age being at higher risk. Specifically, those aged 6-18 years had 2.7 times higher odds of long-term symptoms, compared to those below 2 years. Also, for children with more than one persistent symptom, the odds were 2.5 times higher for those aged 6-11 years, and 3.2 times higher among 12-18 years, relative to those younger than 2 years. This concurs with increasing age being a risk factor for adults.

[7] Refer to Episode #33 for additional information on MIS-C.
[8] MIS-C is also known as pediatric inflammatory multisystem syndrome (PIMS).

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The study also found children with a history of allergic disease had 1.7 times higher odds of delayed resolution. This agrees with adult studies reporting asthma to be associated with development of long-term symptoms. Recent data suggested COVID-19 consequences may be linked with the mast cell activation syndrome (MCAS)[9] and the T helper type 2 cells (Th2) biased[10] immunological response in children with allergic diseases may be responsible for an increased risk of long-term consequences. [46]

Pathogenesis of post COVID-19 condition

The pathogenesis of post COVID-19 condition may include the direct effects of infection and factors related to any severe illness that requires hospitalization and/or critical care admission.

Post-intensive care syndrome (PICS) is a well-documented condition of acquired disability after critical illness and ICU admission. These critically ill patients may develop health problems related to their illness, injury, mechanical ventilation, or other treatments. These problems cannot be totally prevented and may persist after hospital discharge. PICS can lead to impairment of cognitive (e.g., difficulties remembering, problem solving, paying attention), psychological (e.g., sleep disturbances, nightmares, depression, anxiety, posttraumatic stress disorder [PTSD]), and physical health (e.g., skeletal muscle wasting and weakness due to bed rest and immobilization leading to difficulty with daily living, including dressing, feeding, bathing, walking). [7] [47] [48]

Several hypotheses have been proposed to explain the long-term outcomes of SARS-CoV-2 infection, such as:

- Virus reservoirs harboured across the body, which may not be identified by nasopharyngeal swabs.
- Delayed viral clearance due to immune exhaustion resulting in chronic inflammation[11] and impaired tissue repair.
- Cross reactivity of SARS-CoV-2-specific antibodies with host proteins resulting in autoimmunity.
- Abnormal immunometabolism.
- Imbalance in renin-angiotensin system (RAS) leading to the long-term health consequences of COVID-19.
- Reactivation of previously acquired viruses.
- Alterations in the microbiome.
- Disruption of epithelial barrier function by microbiome dysbiosis. [49] [50]

[9] MCAS is a condition where mast cells mistakenly release high levels of mediators causing an individual to have repeated severe allergy symptoms, such as hives, swelling, low blood pressure, difficulty breathing, and severe diarrhea. Much of COVID-19 hyperinflammation is consistent with mast-cell-driven inflammation and dysfunctional mast cells of MCAS may underlie acute and chronic COVID-19 illness. [87] [88] [89]

[10] Substantial evidence supports the concept that allergic asthma is an immune-mediated disease, driven in part by T-cells directed against aeroallergens and viruses. [90]

[11] Refer to Episode #44 for information on inflammation.

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Hidden viral reservoirs

SARS-CoV-2 may drive chronic symptoms by persisting in certain body sites or tissue reservoirs after acute infection. A postmortem pathologic study by Yao et al. (2020) presented evidence of persistent residual virus in the lungs, suggesting the possibility of SARS-CoV-2 virus may cause lasting lung damage. [51] Puelles et al. (2020) in an autopsy study of 22 patients who died from COVID-19 detected viral presence in multiple organs, including the heart, brain, liver, kidneys and blood, in addition to the respiratory system. [52] Several studies have shown the presence of gastrointestinal reservoirs of SARS-CoV-2 nucleic acids even after recovery from COVID-19. [53] [54] [55] Studies have also demonstrated long-term SARS-CoV-2 viral shedding among individuals with COVID-19, which continued for 3 months or longer. [56] [57] This viral persistence could then trigger chronic inflammation which may underlie the chronic COVID-19 symptoms experienced by some individuals. [49]

Immune exhaustion

Immune exhaustion is a phenomenon that is frequently associated with chronic viral infections. Immune exhaustion is defined as the dysfunction of antigen-specific immune cells due to prolonged antigen stimulation. Viral persistence and its associated immune response may lead to immune exhaustion which may further explain the long-term consequences resulting in post COVID-19 condition. [49]

Viral-induced autoimmunity[12]

COVID-19 is associated with a wide range of clinical manifestations, including autoimmune features and autoantibody[13] production. A study by Bastard et al. (2021) found autoantibodies that existed before infection with SARS-CoV-2 may account for 20% or more of serious or fatal COVID-19 cases. [49] [58]

Thus, researchers contemplated if SARS-CoV-2 infection could also result in the production of autoantibodies in people who did not have them prior to infection. To answer this question, Chang et al. (2021) screened for a range of autoantibodies in blood samples from 147 individuals hospitalized with COVID-19 and 41 healthy volunteers. The researchers found approximately 50% of the people hospitalized with severe COVID-19 had at least one type of autoantibody circulating in their bloodstream. In contrast, only 15% of healthy controls had such antibodies. Also, 51 of the individuals with COVID-19 had blood samples drawn on more than one day, including the day they were first hospitalized. Results showed about 20% of these individuals did not have any autoantibodies upon hospital admission but developed them over the course of their illness. Some had very high levels of autoantibodies, close to levels seen in autoimmune diseases. [59]

The mechanisms behind the autoantibody production are not yet clear. Widespread and long-term inflammation during severe COVID-19 may cause the immune system[14] to produce antibodies to pieces of the virus it would not normally recognize. Some of those

[12] Refer to Episode #45 for information on autoimmunity.

[13] Autoantibodies are antibodies (immune proteins) that mistakenly target and react with a person's own tissues.

[14] Refer to Episodes #44 & #45 for information on the immune system.

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pieces might resemble human proteins enough to trigger the production of autoantibodies. Excessive inflammation could also boost production of autoantibodies that had previously only existed in the body at very low levels. Vaccination against COVID-19 is much less inflammatory than infection with the virus. [49] For example, in a study by Arunachalam et al. (2021) that investigated COVID-19 vaccination, none of the healthy volunteers developed autoantibodies. More research is needed to determine if autoantibodies contribute to the symptoms of post COVID-19 condition or cause late-term problems (e.g., autoimmune disease development later in life). [60]

Abnormal immunometabolism

Abnormal immunometabolism maybe implicated in the development of post COVID-19 condition. For example, elevated cytokine levels caused by SARS-CoV-2 infection may cause pancreatic beta cell hyperstimulation and damage, and insulin resistance leading to the onset of metabolic changes. [49] Montefusco et al. (2021) documented abnormalities in beta cell function, insulin resistance, and glycometabolic control in a cohort of patients hospitalized with COVID-19, without prior history or diagnosis of diabetes. The glycemic abnormalities persisted for at least 2 months suggesting metabolic alterations play an important role in the development of post COVID-19 condition. Abnormal immunometabolism could, consequently, be triggered by the hyperinflammatory state observed in some individuals with COVID-19. [61]

Imbalance in renin-angiotensin system (RAS)

The renin-angiotensin system (RAS) plays an important role in maintaining blood pressure as well as electrolyte and fluid homeostasis, thereby influencing the function of many organs (e.g., kidneys, lungs, blood vessels, brain). Dysregulation of RAS has been implicated in multi-organ injury (e.g., lung, heart, kidney, small intestine) associated with COVID-19, causing long-term multi-organ impairments observed in post COVID-19 condition. [49] [62] [63] [64]

Reactivation of previously acquired viruses

SARS-CoV-2 may dysregulate the host immune response during acute COVID-19 allowing previously harbored pathogens to reactivate, infect new body sites, and drive new chronic symptoms. Humans accrue enduring viruses over a lifetime. These viruses generally persist in dormant, latent, or non-cytolytic forms, but may reactivate with stress, immunosuppression, or immune dysregulation. Reactivated viruses might also infect new body sites and cell types, allowing them to drive new symptoms.

Studies have demonstrated reactivation of viruses, such as herpes simplex virus type 1 (HSV-1), human herpesvirus 6 (HHV-6), human herpes virus 7 (HHV-7), varicella-zoster virus (VZV), and Epstein-Barr virus (EBV) in individuals with COVID-19. For example, Gold et al. (2021) conducted EBV antibody tests on individuals recovered from COVID-19, comparing EBV reactivation rates of those with persistent COVID-19 symptoms to those without. The majority of those with enduring symptoms were positive for EBV reactivation, yet only 10% of controls indicated reactivation. These findings suggest many persistent COVID-19 symptoms may not be a direct result of the SARS-CoV-2

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virus but may be the result of COVID-19 inflammation-induced EBV reactivation. [50] [65]

Altered microbiome

The gut microbiota of the gastrointestinal tract is essential for regulating immune homeostasis. [66] Research by Yeoh et al. (2021) showed gut microbiota composition was altered in patients with COVID-19, and together with inflammatory cytokines and blood markers (e.g., C-reactive protein) reflected disease severity and dysfunctional immune response. The dysbiotic gut microbiota persisted for up to 30 days after disease resolution which suggested a role in the persistent symptoms of post COVID-19 condition. [49] [67]

Epithelial barrier function disruption by microbiome dysbiosis

Microbiome dysbiosis is often accompanied by inflammation that can lead to dysfunction or breakdown of oral epithelial barriers, such as the gingiva, the epithelial lining of the gut, or related barriers. This increased epithelial permeability allows oral pathogens to translocate into the blood, where their presence and products can sustain a range of systemic inflammatory processes. Epithelial barrier permeability due to microbiome dysbiosis could contribute to persistent COVID-19 symptoms. [50]

Further, systemic inflammatory processes caused by translocation of oral bacteria to distal sites in combination with SARS-CoV-2 activity could result in more severe pathology. Adams et al. (2019) showed *Porphyromonas gingivalis* and bacteria translocated into blood can fuel hypercoagulation. [68] Similarly, SARS-CoV-2 also secretes substances that activate coagulation cascades. [69] Pretorius et al. (2021) identified fibrinolytic resistant amyloid microclots in plasma samples collected from 11 individuals with post COVID-19 condition. Microclots that are resistant to fibrinolysis can block capillaries and inhibit oxygen exchange. [70] This may contribute to lingering symptoms, such as recurring fatigue, muscle weakness, and dyspnea. This suggests individuals who have both periodontal disease and COVID-19 might be disproportionally impacted by long-term symptoms that could result from blood inflammatory/coagulation cascades. [50]

Diagnosis

Currently, post COVID-19 condition is primarily diagnosed based on previous SARS-CoV-2 infection and presenting with post COVID-19 symptoms. There is no minimal number of symptoms required for diagnosis. Testing or a positive test is not required for a diagnosis of post COVID-19. The condition can be diagnosed clinically based on history alone. A negative antibody test does not exclude post COVID-19 condition. [6] [29] [71]

Treatment and management

Published guidelines from the National Institute for Health and Care Excellence (NICE), the Centers for Disease Control and Prevention (CDC), and other research groups provide various treatment courses primarily focused on symptom management. Common foci across different care models include multidisciplinary teams (e.g.,

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pulmonary, cardiovascular, psychiatry, psychology, physiotherapy, occupational therapy, social work, neurology, primary care, nutrition, speech and language therapy), self-management (e.g., education and support), standardized symptom assessment, referral systems, and follow-up care. [29]

Impact on daily living

Post COVID-19 condition generally has an impact on everyday living. For example, limitations in the ability to perform activities of daily living, such as walking, dressing or bathing, reduced ability to care for family members or dependents, and difficulty returning to work, have been reported. Physical weakness can be attributed to myopathy, neuropathy, cardio-respiratory impairments, cognitive impairment, or a combination of these conditions. Factors such as age, frailty, and presence of comorbidities may also modulate the long-term impact of the condition. [7] [49]

A international cohort study by Davis et al. (2021) showed at 7 months post-SARS-CoV-2 infection approximately half of respondents (45.2%) needed a limited work schedule compared with their pre-COVID-19 schedule, and an additional 22.3% were not working due to illness. [26] Post COVID-19 condition may also impact children's ability to learn, attend school, and participate in extracurricular activities, including sports and clubs. [72]

COVID-19 vaccination[15]

COVID-19 vaccination decreases the probability of developing post COVID-19 condition by lessening the chance of becoming infected. In addition, vaccination may reduce the chance of developing the post COVID-19 condition among those with post vaccine ("breakthrough") infections. [7]

For example, Bergwerk et al. (2021) conducted a prospective cohort study of 1,497 fully vaccinated Israeli healthcare workers. Results showed 39 (2.6%) had confirmed post-vaccine SARS-CoV-2 infections, and 7 (0.4% of sample; 19% of post-vaccine infection cases) had post COVID-19 symptoms at 6 weeks. [73]

Antonelli et al. (2021) conducted a prospective community-based case-control study examining post-vaccine infections (7 days after second dose) in the UK. The researchers found the odds of having post COVID-19 condition for 28 days or more were approximately halved by being fully vaccinated with a two-dose series vaccine (i.e., Pfizer-BioNTech Comirnaty, AstraZeneca Vaxzevria, or Moderna Spikevax COVID-19 vaccines[16]) compared to infected unvaccinated control participants. They also reported breakthrough infections among fully vaccinated individuals was 0.2%. [74]

Furthermore, receiving a COVID-19 vaccine after the acute infection phase may help reduce post-COVID-19 symptoms in unvaccinated individuals who develop post-COVID-19 condition. [29] A survey study by the LongCovidSOS group of individuals

[15] Refer to Episodes #15, #39, and #40 for information on vaccination and COVID-19.
[16] The brand names of these COVID-19 vaccines were changed in September 2021. [91]

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enduring symptom who subsequently received at least their first dose, found 56.7% saw an overall improvement, 24.6% saw no change, and 18.7% saw some symptoms worsen. They further analyzed how individuals experienced changes in their symptoms. They grouped participants into 6 categories according to the pattern of improvement or deterioration of their symptoms. They found among vaccine recipients, 11.4% reported all their symptoms had improved, while a further 15.8% showed some symptoms had improved, and others were unchanged. Only 2.9% indicated all their symptoms had worsened, and a further 3.8% had a mixture of decline and no change. The remainder saw no change (42.3%) or a mixture of improvement and decline (23.7%). The latter group nevertheless reported almost 20% symptom improvement overall. [75]

An observational study by Raw et al. (2021) found individuals with prior COVID-19 infections, receipt of COVID-19 vaccination was not associated with a worsening of long-term COVID-19 symptoms or increased reactogenicity following immunization. [76]

A preprint study of individuals with persistent COVID-19 symptoms 8 months after hospital discharge, receipt of at least one dose of either an mRNA or viral vector vaccine was not associated with symptom exacerbation and a small improvement in persistent symptoms. [77]

Expected burden of post COVID-19 condition in Ontario

The Ontario COVID-19 Science Advisory Table conservatively estimated between 57,000 to 78,000 Ontarians had or are currently experiencing post COVID-19 condition 12 or more weeks beyond their COVID-19 diagnosis. [7] However, the Public Health Agency of Canada (PHAC) estimated approximately 60% reported 1 or more symptoms more than 12 weeks beyond initial infection. [78] This would result in a crude estimate of over 350,000 Ontarians who have or had the post COVID-19 condition. [2]

In Ontario, COVID-19 has been disproportionately concentrated in populations who are racialized, have lower socioeconomic status, are recent immigrants or essential workers. Therefore, it is likely the burden and disability associated with the post COVID-19 condition will also be unequally distributed with greater prevalence in these populations. [7] [79]

Individuals with the post COVID-19 condition have a multitude of complex health and supportive needs. For example, individuals with severe illness during initial infection, especially those who require intensive care unit (ICU) admission, are expected to have significant long-term health consequences. [7]

A study by Melnick & O'Leary (2021) found that even though the majority of individuals with COVID-19 did not require hospitalization, many adults with post COVID-19 condition continued to seek medical care for up to 6 months or more. [80]

Millet et al. (2021) conducted a follow up study on individuals diagnosed with COVID-19. They found nearly half of all participants (47.9%) still experienced at least one

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symptom 12 months after their initial infection. This suggests COVID-19 may carry a risk of developing long-term and possibly permanent sequelae. [81]

Thus, health resource planning, management strategies, and relevant government policies will be required to manage the burden of long-term consequences on patients, caregivers, the health care system, and the province overall. [7]

Oral health considerations

Post COVID-19 condition consist of a collection of signs and symptoms that may interfere with daily life and the ability to undergo routine oral healthcare. The wide variety of symptoms, such as fatigue, shortness of breath, chronic pain, and risk of developing neurologic and psychiatric complications may necessitate modifying routine oral healthcare interventions. For example, some clients may have decreased ability to withstand treatment and thus require shorter appointments. Fatigue may also affect their ability to perform daily oral selfcare. Others may be taking multiple medications impacting their oral health (e.g., decreased salivary flow increasing caries and periodontal disease risks) or may interact with medications administered and prescribed for oral health conditions. Careful positioning of the dental chair may be necessary for clients experiencing postural orthostatic tachycardia. Cognitive changes may impact ability to remember appointments or post care instructions.

A throughout medical, dental, and social history is therefore imperative to understand the client's condition, how it impacts their daily living, and their ability to tolerate treatment. It will also be important to work with the client's healthcare providers to understand the nature of their current and previous conditions, including any medical interventions. Interprofessional collaboration will also be essential to help monitor symptoms, progress, and recovery and to refer for further evaluation and treatment as required. [82]

Post COVID-19 condition may increase caries and periodontal disease risk and impact ability to perform daily selfcare. Thus, some clients my need increased recare frequency, nutritional counselling to promote oral health, strategies to manage xerostomia, and enhancement of homecare routines with products, such as power toothbrushes, oral irrigators, fluoride mouth rinses, and high fluoride toothpastes as required. [83]

Prevention of post COVID-19 condition

The best way to prevent post-COVID condition is to prevent SARS-CoV-2 infection. Research demonstrates getting vaccinated against COVID-19 is the best way to prevent contracting SARS-CoV-2 and spreading the virus. [84]

It is also important to consistently follow personal preventive practices and public health advice (e.g., masking,[17] avoiding crowded places, improving ventilation, practising hand hygiene and respiratory etiquette). [85]

[17] Refer to Episode # 25 for information on community use of face masks.

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Take home messages

- Post COVID-19 condition is associated with a broad range of persistent symptoms and morbidity, increased use of healthcare resources, and adverse impact on work, activities of daily living, mental health, and quality of life. It has the potential to cause significant harms to individuals impacted by the condition, their families, caregivers, health systems, and society.
- More research is required to understand risk factors of post COVID-19 condition, including the role of variants, the impact on specific populations, such as children, and to develop strategies for prevention and treatment.
- Post COVID-19 condition will require a multidisciplinary approach to monitor symptoms, identify potential complications, provide care and treatment, along with mental health and social services support. Oral healthcare professionals will be part of this team and therefore, must understand post COVID-19 condition and be prepared to treat and support individuals experiencing its impacts and refer as required.
- Oral healthcare professionals may be sought out as advisors for complications, such as parosmia and dysgeusia because of their education, knowledge, and expertise of related structures.

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Client Resources

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https://www.covidlonghaulcanada.com/
Facebook: https://www.facebook.com/groups/920314451799658/
Survivors Corp https://www.survivorcorps.com/pccc-canada

Long Covid Kids
https://www.longcovidkids.org/

Long COVID-19 clinics
https://esnetwork.ca/wp-content/uploads/2021/04/Evidence-Synthesis-BN-on-Long-COVID-19-Clinics-27-April-2021.pdf

Long COVID Clinics in Ontario

- London Health Sciences Centre
  https://www.lhsc.on.ca/urgent-covid-19-care-clinic
- Toronto Rehabilitation Institute (established in association with the University Health Network
  https://www.uhn.ca/TorontoRehab
- Halton Post COVID-19 Syndrome Clinic
  https://www.haltonhealthcare.on.ca/services_/28763/s29703-outpatient-rehabilitation/t80512-post-covid-19-syndrome-clinic

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https://www.cdc.gov/coronavirus/2019-ncov/long-term-effects/index.html

Caring for People with Post-COVID Conditions, Centers for Disease Control and Prevention
https://www.cdc.gov/coronavirus/2019-ncov/long-term-effects/care-post-covid.html

Long COVID Resources for Patients and Families, University Health Network
https://guides.hsict.library.utoronto.ca/c.php?g=716817&p=5171775

CAN COV – Patient Resources
https://cancov.net/patient-resources/

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http://www.phsa.ca/health-info/post-covid-19-care-recovery

What Is Anosmia? *JAMA* Patient Page
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https://www.who.int/news-room/events/detail/2021/06/15/default-calendar/expanding-our-understanding-of-post-covid-19-condition-webinar-2

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