



Canadian Journal of Health Technologies

August 2023 Volume 3 Issue 8

CADTH Horizon Scan

Hyperbaric Oxygen Therapy: An Emerging Therapy for Post- COVID-19 Condition

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Key Messages

What Is the Issue?

- Post-COVID-19 condition presents an important challenge to health care decision-makers in Canada and across the world due to the high volume of potential patients, diverse presentations of symptoms, few clinical guidelines and treatments, and unknown pathophysiology.

What Is the Technology?

- Hyperbaric oxygen therapy (HBOT) is an established treatment for certain wound injuries, vascular conditions, and in specific medical emergencies. It is now being tested for post-COVID-19 condition, also known as long COVID. The therapy delivers a high concentration of oxygen inside specialized pressure chambers. HBOT has been proposed as a treatment to help resolve prominent symptoms of post-COVID-19 condition, such as fatigue and brain fog. The therapy may induce physiological changes that aid in recovering from the long-term effects and tissue damage due to severe acute respiratory syndrome coronavirus 2 (SARS-COV-2) infection.

What Is the Potential Impact?

- Results from early studies indicate that HBOT could improve a range of post-COVID-19 symptoms and its use is generally safe with few adverse effects. These results are based on 2 randomized control trials and small nonrandomized studies and case reports. However, published results have been based on studies with limited sample sizes and limited long-term follow-up.
- HBOT could offer a therapy option that could support millions of people around the world with post-COVID-19 condition if the ongoing and subsequent studies show efficacy.

What Else Do We Need to Know?

- As of now, there are uncertainties about how to effectively deliver and dose the therapy and the potential safety implications for people with post-COVID-19 condition. Implementation considerations, such as the number and location of hyperbaric oxygen chambers, will be important if HBOT is appropriate for a large number of people. As the evidence base develops, the potential role of HBOT in therapy for people with post-COVID-19 condition will become clearer and will provide an indication of what kind of health system planning may be needed to provide HBOT for those who can benefit.

Hyperbaric Oxygen Therapy: Potential Therapy for Post-COVID-19 Condition

Post-COVID-19 condition, also known as long COVID or post-acute sequelae of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, is a complex health condition associated with more than 100 different symptoms.^{1,2} Post-COVID-19 condition specifically refers to persisting symptoms lasting longer than 3 months after an initial SARS-CoV-2 infection or acute COVID-19 that cannot be explained by alternative diagnoses.² Although there is emerging work assessing different interventions, there are key challenges in developing treatments for the condition, such as uncertainties about the pathophysiology, the heterogeneity in presentation of symptoms, and the varying impact of different risk factors.³

A promising approach has been to assess existing interventions and therapies authorized for other health conditions that may share some aspects of the pathophysiology of post-COVID-19 condition.³ This Horizon Scan takes an early look at 1 such intervention – [hyperbaric oxygen therapy](#)⁴ – describing how it works, the state of existing evidence, and some potential issues to consider for health systems.

What Is Hyperbaric Oxygen Therapy and How Does It Work?

Hyperbaric oxygen therapy (HBOT) has been used in clinical practice for more than 50 years. The treatment delivers up to 100% oxygen concentration (ambient air has approximately 21% oxygen concentration) at 2 to 3 times atmospheric pressure (the air pressure at sea level) to patients inside specialized chambers.^{4,5} The treatment is primarily delivered in hospitals, but it may also be delivered in private clinics equipped with the specialized chambers. The higher oxygen concentration and increased air pressure environment can exert a range of physiological, cellular, metabolic, and genetic changes that may aid healing and recovery for certain health conditions affected by low oxygen (hypoxia).⁶ Short-term exposure of increased oxygen (hyperoxia) may activate or increase cellular signalling that promotes wound healing, regulates immune responses, or repairs vascular damage in different cells and tissues.⁶

The Undersea and Hyperbaric Medical Society (US) indicates that HBOT is a safe and effective treatment (often a complementary treatment) for 14 health conditions, including carbon monoxide poisoning, exceptional blood loss, necrotizing fasciitis (flesh-eating disease), and certain wound and burn injuries.⁴ For these health conditions, patients are placed in the specialized chamber for 1 to 2 hours with short breaks. They do this several times a week for 20 to 60 sessions.⁵ The specific physiological mechanisms HBOT promotes for recovery varies across these conditions. HBOT is sometimes touted as an effective treatment for other conditions; however, in many cases, there is limited evidence to support those claims.⁴ Health Canada has stated that it is important to be critical of such claims because HBOT can pose safety concerns, such as triggering claustrophobia or causing barotrauma (an adverse event in which tissue is damaged from differential air pressure), oxygen toxicity, vision changes, and respiratory symptoms.^{4,5}

Who Might Benefit?

Estimates from the Public Health Agency of Canada suggest that 1.4 million adults in Canada could be affected by post-COVID-19 condition.⁷ The most prominent symptoms are fatigue, muscle aches, shortness of breath, and cognitive impairment (sometimes referred to as *brain fog*).^{3,8,9} These symptoms are reported to affect between 20% to 50% of people with post-COVID-19 condition depending on the patient's risk factors.^{3,8,9} One hypothesis is that these symptoms may arise from poor oxygenation of blood vessels and misregulated immune responses, which contribute to reduced oxygenation in different tissues of the body, including the brain.¹⁰ There may also be other physiological changes from the viral infection that create oxidative stress, tissue damage, and inflammation that contribute to the systemic long-term effects reported by people with post-COVID-19 condition.^{3,10} HBOT has been proposed as a potential therapy to address the effects of hypoxia contributing to these symptoms.¹¹ An initial study was conducted in 2021; since then, more research is assessing the therapy with more rigorous study designs.¹²

Post-COVID-19 condition is a complex health condition that presents an important challenge to health care decision-makers in Canada

What Is the Evidence?

We identified 5 publications from randomized studies that assessed HBOT against sham controls as a treatment for post-COVID-19 condition.¹³⁻¹⁷ These publications were based on 2 randomized controlled trials (RCTs): 1 from Israel and 1 from Sweden. We also identified 4 nonrandomized studies and published abstracts that assessed HBOT, including 3 before-and-after studies^{12,18,19} and 1 case report.²⁰ All studies included participants who reported experiencing long-term symptoms for at least 3 months, which is in line with the clinical case definition of post-COVID-19 condition.¹

Emerging Evidence From Randomized Studies

We identified 2 RCTs that assessed HBOT for people with post-COVID-19 condition. One of these trials is ongoing in Sweden¹⁶ with a published interim safety analysis.¹⁷ The completed RCT is from Israel. Published studies from this trial have reported on neurocognitive and general post-COVID-19 symptoms,¹³ brain imaging results,¹⁴ and, most recently, myocardial function.¹⁵

The completed phase II trial ([NCT04647656](#)) from Israel was a sham-controlled (pressure delivered was similar to atmospheric pressure), double-blinded RCT in which adult participants received 40 sessions of either HBOT (n = 37) or control (n = 36) therapy for 8 to 10 weeks. The intervention group received HBOT with 100% oxygen at 2.0 ATA (absolute atmosphere) pressure for 90 minutes. The control group received 21% oxygen at atmospheric pressure and a slightly higher pressure (1.2 ATA) for the duration of each session. The results from the trial have been published in 3 publications.¹³⁻¹⁵

The evidence reported in these publications indicated that HBOT, when compared with control therapy, was associated with:

- significant improvements in physical activity levels, energy levels, sleep, and mental health outcomes as well as reduced pain¹³
- changes in brain connectivity and structural networks, measured by functional MRI, that were correlated with improvements in cognition and mental health outcomes¹⁴
- improved cardiac recovery, as measured by changes in global longitudinal strain.¹⁵

Authors cautioned that although the results of the trial across all 3 studies are indicative of positive associations and beneficial improvements in the HBOT group, the sample sizes were limited and there was heterogeneity in patient characteristics and their post-COVID-19 symptoms. The final outcomes were also assessed between 1 and 3 weeks after the last HBOT session; longer-term studies are needed to further assess and validate the trial's findings.¹³⁻¹⁵

The ongoing phase II trial from Sweden is also a sham-controlled, double-blinded RCT ([NCT04842448](#)) in which patients are administered either HBOT or a condition similar to air at atmospheric pressure.¹⁶ The trial aims to recruit 80 participants and provide either the intervention or control treatment (1:1 allocation) during 10 sessions over 6 weeks, with a 52-week follow-up period. At the time of writing this Horizon Scan, results from an interim safety analysis of 20 participants (HBOT: n = 9; control: n = 11) at 13 weeks was available.¹⁷ These early results reported that patients in both the intervention and control groups reported transient adverse events, but none were severe.¹⁷ The most common events included cough, chest pain, and respiratory symptoms.¹⁷

Emerging Evidence From Nonrandomized Studies

Four nonrandomized studies assessed HBOT in people with post-COVID-19 condition.^{12,18-20} All 4 studies reported the therapy may contribute to better clinical outcomes. However, the authors of all the studies also indicated that more rigorous studies are needed to evaluate clinical efficacy. These studies included:

- A study from the UK provided HBOT to 10 patients with post-COVID-19 condition with 10 HBOT sessions per patient. Participants reported statistically significant improvements in fatigue and a range of cognitive domains.¹²
- In a study from Poland, 31 patients received 15 HBOT sessions over 3 weeks and were assessed after every 5 sessions.¹⁹ Patients reported significant improvements in quality of life, mental health outcomes, performing daily activities, and general fitness after 15 sessions.
- In a study from Spain (abstract only), 5 patients received between 19 to 50 sessions of HBOT.¹⁸ Results indicated significant improvements in fatigue, cognitive scores, and quality of life before and 1 month after receiving HBOT.
- A case report study reported the evaluation of a patient from a clinic in Israel.²⁰ The patient received 60 sessions of HBOT over 3 months. The patient reported significant improvements in fatigue, cognition, and fitness. MRI scans of that patient's brain before and after HBOT indicated increased

brain perfusion (blood flow) to different brain regions that may be involved in memory, information processing, and executive functions.²⁰

Availability and Cost in Canada

Hyperbaric chambers require Health Canada's Medical Devices Regulations authorization. Several chambers are authorized in Canada according to the Medical Devices Active Licence Listings. However, at the time of this Horizon Scan, there were no clinical guidelines (either Canadian or international) identified specifically for post-COVID-19 condition that recommended the intervention as a treatment option. HBOT is available in limited Canadian centres, primarily at hospital-based sites. Different jurisdictions can have specific accreditation and licensing requirements of hyperbaric facilities. The [Canadian Undersea and Hyperbaric Medicine Association](#)²¹ lists 18 sites across Canada, but not all sites are available to general patient populations. There are also private clinics that offer HBOT, 1 of which lists a fee of \$365 for a single 90-minute session.²²

In the absence of clinical guidelines or reimbursement plans, it is likely that patients who are considering the treatment may need to bear the majority of costs through private insurance or pay out-of-pocket.

Issues to Consider

Dosing

Although the general protocol of HBOT across different indications includes delivering 100% oxygen at 2.0 to 2.5 ATA for 90-minute sessions, the frequency and total number of sessions required for clinically meaningful improvements is not well determined for people with post-COVID-19 condition.⁵ Studies report varied practices within and between studies, which could make comparing different results more complex. The study from Poland reported that at least 15 sessions were needed to observe clinically meaningful changes in symptoms.¹⁹ Establishing guidelines or protocols may help ensure consistent care across facilities.

Safety

Since the use of HBOT for post-COVID-19 condition is a new treatment option, assessing safety will be critical for informing clinical practice and ongoing evaluations. Although HBOT is generally safe for most people, it can be associated with safety risks, such as barotrauma, neurotoxicity, or respiratory symptoms.^{4,5,23} People with post-COVID-19 condition are already affected by a range of symptoms that can affect various aspects of their health and well-being. In the trial from Sweden, the study authors noted that, due to the poor health of participants, most would not be able to tolerate HBOT treatment over 2 consecutive days.¹⁷ Health care providers will need to ensure eligible patients are capable of receiving multiple sessions without exasperating their existing symptoms or leading to new symptoms. Since private clinics could offer

HBOT to people with post-COVID-19 condition outside of hospital settings, health systems may need to consider and develop approaches for monitoring safety, clinical outcomes, and patient experiences.

Implementation

HBOT chambers are large and expensive pieces of medical equipment. The cost of a new chamber can be approximately US\$100,000 with additional costs for maintenance and licensing.²⁴ It is uncertain whether existing public facilities have the capacity, both of staff and infrastructure, to take on the volume of patients with post-COVID-19 condition who could be eligible. Because people with post-COVID-19 condition present with highly diverse symptoms and characteristics, determining the eligibility criteria of for the people most likely to benefit from the treatment could help manage resource constraints. Considering the needs of people who may have to travel to HBOT sites will be important for providing equitable access. Additionally, should HBOT be available to people with post-COVID-19 condition outside of hospital settings for a fee, considerations regarding equitable access for people with all levels of income will be important.

Looking Ahead

As health systems continue to explore interventions that could support people with post-COVID-19 condition, the emerging evidence base for HBOT has so far provided encouraging results and warrants continued monitoring. There is currently at least 1 ongoing RCT assessing HBOT for people with post-COVID-19 condition, including 1 in Sweden.¹⁶ This trial is expected to conclude by September 2024. Monitoring the evidence from that trial and subsequent analyses from the RCT conducted in Israel, may help inform decision-makers in Canada and internationally considering treatment options for the condition. Should evidence of HBOT continue to suggest beneficial improvements in clinical outcomes, Canadian centres may consider evaluating the intervention as part of pan-Canadian research efforts. Supporting people's recovery from post-COVID-19 condition requires a multidisciplinary approach.³ With more than 300 trials under way assessing different pharmacological and nonpharmacological interventions to treat post-COVID-19 condition²⁵ (refer to [CADTH's scoping review](#)²⁶ for a detailed review on interventions), determining the most suitable treatment options will require better understanding of the condition's underlying pathophysiology (or pathophysiologies) and delivering care with a person-centred approach. HBOT could be a part of that treatment journey for some people, but more evidence from randomized trials and registry-based research is likely needed to determine its effectiveness and place in care.

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Appendix 1: Methods

Literature Search Strategy

An information specialist conducted a literature search on key resources, including MEDLINE, Embase, the Cochrane Database of Systematic Reviews, the International HTA Database, the websites of Canadian and major international health technology agencies, as well as a focused internet search. The search approach was customized to retrieve a limited set of results, balancing comprehensiveness with relevancy. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. Search concepts were developed based on the elements of the research questions and selection criteria. The main search concepts were post-COVID-19 condition and hyperbaric oxygen therapy. The following clinical trials registries were searched: the US National Institutes of Health's clinicaltrials.gov, WHO's International Clinical Trials Registry Platform (ICTRP) search portal, Health Canada's Clinical Trials Database, and the European Union Clinical Trials Register. No filters were applied to limit retrieval by study type. The search was completed on June 15, 2023, and limited to English-language documents published since January 1, 2020.

Selection Criteria

One author screened the literature search results and reviewed the full text of all potentially relevant studies. Studies were considered for inclusion if the intervention was hyperbaric oxygen therapy and not general oxygen therapy, specifically for post-COVID-19 condition. Studies that assessed the intervention for post-viral sequela less than the case definition of post-COVID-19 condition (i.e., symptoms persisting for at least 3 months after initial infection) were not included. Conference abstracts and grey literature were included when they provided additional information to that available in the published studies.

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ISSN: 2563-6596

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Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

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