Scientific Advisory Group

COVID-19 Scientific Advisory Group Rapid Evidence Report

What is known about the optimal management for patients with post-COVID conditions or complications occurring after acute COVID-19 infection?

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Lay Summary

BACKGROUND

- In Alberta, COVID-19 infections were first documented in March 2020. By July 2021 (18 months later), over 232,000 Albertans have been infected, resulting in 9,600 hospitalizations and 2,300 deaths. (https://www.alberta.ca/stats/covid-19-alberta-statistics.htm)
- While most people survived their infection, varied potential long term complications of COVID-19 have been described. Sometimes the term “Long COVID” has been used for these post COVID conditions. Some people have experienced symptoms for more than weeks or months.
- This review summarizes what is currently known about how common post COVID conditions are, how long they seem to last, whether we can predict what will happen for people with these issues, and what medical care may be useful in treating people with these conditions.
- It is important to consider how the health care system might plan care for potentially a large number of people, and this will be an important area for research.
- This review is meant to be useful for primary care providers, hospital based physicians and staff, health systems decision makers, and scientists.

KEY FINDINGS

- “Post-COVID conditions” or PCC include symptoms that do not go away after COVID infection and new medical issues and symptoms that occur during or after COVID-19 infection.
- Current health services include three specialty post-COVID clinics, two in Calgary and one in Edmonton. Primary Care continues to be the main place that most people get their care after COVID infection. Post-COVID conditions will add to the demand for health care. Patients tend to have complex care needs and many health care specialists may need to be involved to help them effectively, in a team approach.
- So far there are no specific treatments for PCC compared to similar problems that happen to people without COVID (see Recommendations).
- PCC is an area of active research and new studies are published frequently. Many of the available studies have focused on patients who were hospitalized and/or admitted to intensive care units. Less information is available about patients in the community, how the virus causes long term symptoms, the best way to treat different PCC symptoms, what patients can expect longer term, and how best to deliver health care services.

RECOMMENDATIONS

- As PCC is relatively new and there is not a lot of evidence available, currently people with PCC should be assessed and treated using current standards of medical care, which include the following:
- People who may have PCC should be seen by a physician for a full examination. Detailed history of the symptoms, when they started, what helps or worsens them, and how they are changing should be discussed. How the PCC are affecting people in their daily life is a very important discussion. Some medical testing or functional testing may be recommended for some people but testing will not be needed for everyone with suspected PCC.
- Although post-COVID symptoms are common, those caring for them should keep an open mind to non COVID related conditions that may need diagnosis and treatment to

make sure they are not missed, and appropriate testing and treatment for these conditions should be done as needed.

- Patients with concerning medical features, especially heart, breathing, nervous system, or kidney issues that are worsening or not improving may need to see a specialist, or access emergency care, at the discretion of their treating physician.
- Some people may be helped by exercise-based rehabilitation programs, however before starting any exercise program, care providers should make sure there are no heart or lung symptoms, blood pressure drops, low oxygen with exercise, or major problems with stamina.
- Further research regarding many aspects of PCC is needed and this review will need to be updated as new research study results become available. These include expanding the populations studied, disease processes, effects of therapies, what patients can expect, and how to optimize care delivery. Recommendations may change as new studies are done.

Authorship and Committee Members

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Jeffrey Schaefer	Writing – introduction, overall key messages and recommendations
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Note: Authors, librarians, and scientific reviewers of post-COVID condition groups are listed in each section of this report

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Topic: What is known about the optimal management for patients with post-COVID conditions or complications occurring after acute COVID-19 infection?

1. What is the prevalence and duration (if known) of complications of acute COVID-19 and symptoms that persist after 30 days (Long COVID) assigned to your review?
2. Are there factors that predict the outcomes of these post-COVID conditions?
3. What is the recommended management of post-COVID conditions?
4. What health care services are currently available for patients with these post-COVID conditions?
5. What impacts do these post-COVID conditions have on the health care system?
6. What are the pressing research questions related to your area of concern?

Context

- Approximately 10% of COVID-19 patients experience prolonged symptoms (https://www.bmj.com/content/370/bmj.m3026). Given that 230,000 Albertans have been infected, this pandemic has had an enormous effect on the population, providers, and the health care system.
- Post-COVID conditions (PCC), which is sometimes informally called “Long COVID”, have received considerable attention by patients, providers, and media. With the knowledge that the science related to PCC is in its early stages, it was felt important to provide a review at this time and plan to update it with new evidence.
- Alberta Health Services has sponsored a review of the available literature regarding post-COVID conditions.

Key Messages from the Evidence Summaries

- A summary of prevalence, adverse predictive factors (risk factors and negative prognostic factors), and management is presented below.
- The evidence base around these conditions is evolving quickly but is generally quite preliminary, subject to bias, and of low to very low quality. Most studies have been done in hospitalized or critical care cohorts with much less data around PCC manifestations in outpatients. In the absence of evidence, there is a paucity of known effective management strategies compared with current standard of care in the non-COVID setting.
- Hyperlinks to the Key Messages for each topic are provided.

	Prevalence estimates (studies are mostly of hospitalized patients, at 1 to 6 months post-infection)	**Possible risk factors (sample size and findings varied among individual studies)**	**Management (note- there is a lack of studies evaluating effectiveness of treatment strategies)**
Cardiovascular			
Chest Pain	16%	no data	same as non-COVID patients
Shortness of Breath	85%	no data	same as non-COVID patients
Palpitations	11%	no data	same as non-COVID patients
Orthostatic Light Headedness	case reports	no data	same as non-COVID patients
			when to refer

Hematological			
Venothrombotic Disease	1-2.5%	> 75 yr, co-morbidities, IMPROVE-DD VTE score ≥4, ICU stay	same as non-COVID patients, studies underway regarding post-discharge prophylaxis
Neurological			
Headache	7-50%	pre-existing conditions, > 65 yr, BMI >30, female sex, COVID severity, ICU stay	same as non-COVID patients
Cognitive Impairment	12-40%		same as non-COVID patients, supportive care, med review
Peripheral Neuropathy	2-6%		same as non-COVID patients
Fatigue & Post-Exertional Malaise	13-63%	female sex, co-morbidity, illness severity, trop-I	consider myalgic encephalomyelitis / chronic fatigue syndrome guidelines, pace activity to match energy level, exclude non-COVID conditions
Psychiatric			
Anxiety	6-63%	co-morbidity, younger, illness severity, others	same as non-COVID patients
Depression	4-42%	prior depression, female sex	same as non-COVID patients
Post-Traumatic Stress Disorder	12-47%	anxiety, depression, length of stay	same as non-COVID patients
Sleep Disturbance	30-44%	co-morbidity, female sex, low mood, anxiety	attention to sleep hygiene with multidisciplinary care, community support groups, self-management strategies for more severe cases
Pulmonary			
Dyspnea	36%	hospitalization, pre-existing lung disease	multidisciplinary, patient-centred care including pulmonary specific investigations as indicated
Cough	17%		
Sputum	1-43%		
Pulmonary Complications	Abnormal chest CT 55%, abnormal pulmonary function test 44%, pulmonary hypertension 7%	> 60 yr, ICU stay	
Diminished Exercise Capacity	25-55%	length of stay, O2 needs	
Renal			
Acute Kidney Injury & Chronic Kidney Disease	Acute Kidney Injury 10-46%	age, African ancestry, male, co-morbidities, illness severity, invasive ventilation	same as non-COVID patients
Assessment prior to possible rehabilitation program start			
Pre-screening	Per Canadian Cardiovascular Society Guidelines: pre-screen for post-exertional symptom exacerbation, cardiac symptoms, exertional oxygen desaturation, autonomic nervous system dysfunction. Screening includes history & physical examination, as well as monitoring symptoms and vital signs during a sub-maximal exercise test, such as the 6-minute walk test or the 1-minute sit-to-stand test. Several recommendations & practical considerations are presented.		
Type 1 Diabetes Mellitus			
Incidence	Currently there is insufficient evidence to confirm COVID-19 is a risk factor for new type 1 Diabetes Mellitus		

Committee Discussion

The committee achieved consensus on the recommendations and provided feedback for the final document draft. Overall, it was felt that the medical literature regarding PCC is in its early stages and thus all recommendations are based on lower quality medical evidence, and in some areas the evidence base was too thin to support recommendations so practical guidance was offered instead. The topics covered were diverse which required high-level summaries. The audience is encouraged to refer to individual reviews and be mindful that new developments may have occurred.

Recommendations

It is suggested to approach post-COVID conditions in a similar manner to current standards of care. Note that the medical literature is nascent; the reader is cautioned that rapidly evolving new information and evidence may modify recommendations.

1. Patients suspected of having post-COVID conditions should undergo a history and physical examination. Symptom onset, location (if applicable), progression, and aggravating/relieving factors should be sought. Knowledge of past conditions, effects on daily function, and functional testing may be important for occupational considerations.
2. Although post-COVID symptoms are common, maintain a broad differential diagnosis including those with potentially serious outcomes (e.g. unstable angina in the patient with chest pain). Investigations should be ordered as indicated.
3. Indications for specialist assessment are similar to the non-post-COVID setting, and include clinical concern along with respiratory, cardiac, neurological symptoms, or findings of kidney failure that are new, persistent, or progressive.
4. For patients in whom an exercise-based rehabilitation program is being considered, pre-screen patients for cardiopulmonary symptoms, exertional desaturation, orthostatic hypotension, and consider functional testing (e.g. 6-minute walk test).
5. Multi-disciplinary clinics have been launched in Calgary and Edmonton in conjunction with the Strategic Clinical Networks and Universities. Those interested in developing clinics or engaging in research activity are encouraged to liaise with these clinics.

Research Gaps

- Research gaps are numerous. There is a lack of descriptive epidemiology especially in community cohorts with rigorous followup, there is little known about the pathophysiology of specific PCCs, screening and assessment tools have not been fully developed and validated, clinical effects of specific interventions have not been studied (including the effect of vaccination), and optimal models of care have not been fully defined.
- Examples of research needs include broadening the populations studied to include population based samples of virologically confirmed COVID-19 patients in the community, assessment of impacts on vulnerable populations, larger well defined patient cohorts followed for longer periods, pathophysiology, effects of therapies, and optimal models of care. The reader is referred to individual reviews for additional potential research directions.

Strength of Evidence

- The literature on post-COVID conditions is growing rapidly and is mostly observational.

- Subjects are often selected from those who were hospitalized or admitted to the ICU, findings may be influenced by the length of time from the initial infection or hospital discharge, subject response rates, self-selection, self-report with or without confirmation of disease, and other biases.
- Interventional trials are lacking and recommendations in the medical literature are mostly the opinion of authorities or reports of expert committees.

Cardiovascular Symptoms

Key messages

1. Cardiac symptoms associated with post-COVID conditions include chest pain and palpitations.
2. Symptoms should be investigated per usual standard of care.
3. Patients with new cardiac findings, symptoms or exacerbation of pre-existing COVID should be managed using current treatments, similar to patients without a history of COVID-19 infection.
4. Close surveillance is important for those with pre-existing cardiac conditions or multi-system disease.

What is the prevalence and duration of these post-COVID conditions?

There is a lack of high-quality data on the prevalence of cardiac symptom subtypes in patients with post-COVID conditions. Fatigue and shortness of breath are commonly reported, affecting up to 98% and 85% of patients respectively. Chest pain or palpitations have been reported in 10-73% of cases at 4-12 weeks post confirmed COVID-19 infection in cohort studies. No clear relationship between chronicity of symptoms and severity of initial COVID-19 illness has been observed. (Dennis et al., 2021; López-León et al., 2021; National Institute for Health and Care Excellence, 2020) Excessive orthostatic tachycardia, associated with a diagnosis of postural tachycardia syndrome (POTS) post-COVID-19 has been anecdotally reported (Raj et al., 2021; Raj et al., 2020).

Are there factors that predict the outcomes of these post-COVID conditions?

At present, there are no data available to identify factors to predict outcomes of cardiac-specific post-COVID conditions. Current factors predictive of cardiac disease outcomes should be applied to post-COVID cardiac conditions. The following recommendations are largely based on expert opinion and current collective experience.

What is the recommended management of these post-COVID conditions?

Suggested Cardiac Investigations

The Canadian Cardiovascular Society has placed an emphasis on physical examination and non-invasive assessment utilizing local expertise and continued close surveillance, especially among those with pre-existing cardiac conditions or multi-system disease (Table 1) (Paterson et al., 2021).

Table 1. Symptom-guided investigations for possible cardiac-related post-COVID conditions. (Paterson et al., 2021) ©CCS

Symptom	Suspected Etiologies	Suggested Investigations
Chest pain	• Myopericarditis • Ischemic heart disease	• ECG, cardiac troponin, echo, cardiac magnetic resonance • ECG, functional test for ischemia
Shortness of breath	• Congestive heart failure • Deconditioning • Pulmonary scarring, thromboembolic disease, pulmonary hypertension	• ECG, BNP/NT-proBNP, echo • Pedometer, cardiopulmonary exercise test • Chest X-ray, pulmonary functiontesting, computed tomography
Palpitations	• Arrhythmia • Inappropriate sinus tachycardia • Cardiac dysautonomia	• ECG, Holter • ECG, active standing test

Orthostatic light headedness	• Cardiac dysautonomia	• Postural vital signs • Active standing test

Recommended Treatment
Although there are no specific recommendations for managing cardiac symptoms in patients presenting with post-COVID conditions, there is considerable support for maintaining guideline-based goal-directed therapy in patients with pre-existing cardiovascular disease. Patients with new cardiac findings or symptoms should be managed using contemporary treatments, similar to patients without a history of COVID-19 infection (Table 2).

Table 2. Suggested treatments of cardiac-related post-COVID conditions. (Paterson et al., 2021) ©CCS

Diagnosis	Possible Treatments
Established cardiovascular disease	Continue with guideline-based goal-directed therapy
Myopericarditis	Nonsteroidal anti-inflammatory drug, colchicine
Cardiac dysautonomia (orthostatic hypotension, persistent sinus tachycardia, Postural Orthostatic Tachycardia Syndrome (POTS)-like syndrome)	Hydration, salt supplementation, compression garments Selective use of pharmacotherapies, including midodrine, beta blockers, ivabradine, fludrocortisone

Potential Post-COVID Cardiac Scenarios Warranting Consultation with Cardiac Specialists
Patients with diagnosed COVID-19 more than 4 weeks ago and:

1. Persistent or new unexplained chest pain. A cardiac etiology is more likely with multiple cardiac risk factors, documented cardiac injury and/or new Q waves or ST-T wave abnormalities on ECG, during or after initial COVID-19 illness.
2. Shortness of breath. A cardiac etiology is more likely with elevated BNP, left ventricular dysfunction on imaging and/or radiographic evidence of pulmonary edema.
3. Frequent palpitations. A cardiac etiology is more likely if associated with pre-syncope or syncope and/or a significant arrhythmia is detected on Holter or other cardiac monitoring device. For patients with persistent sinus tachycardia, consider a cardiac etiology in the absence of systemic causes (e.g., fever, anemia, hypoxia).
4. Postural light headedness. A cardiovascular etiology is more likely if orthostatic hypotension is documented (Paterson et al., 2021).

What health care services are currently available for patients with these post-COVID conditions?
Calgary and Edmonton have post-COVID clinics. Local PCNs can provide specific information for post-COVID rehabilitation and specialist referral.

What impacts do these post-COVID conditions have on the health care system?
Post-COVID conditions will contribute additional burden of disease to already stretched resources in specialist cardiac services. The magnitude of long-term cardiac disease requiring medical management has yet to be determined. The wide spectrum of multi-system symptoms associated with post-COVID conditions may require multi-disciplinary clinics and rehabilitation services that align provider skills with severity of patient multimorbidity.

What are the pressing research questions related to this area of concern?
Management strategies proposed for post-COVID conditions have not yet been evaluated in clinical trials.

Future work on post-COVID conditions should evaluate:

- incidence and prevalence of de novo (or worsening of pre-existing) cardiac conditions
- risk factors for developing late cardiac complications
- knowledge gaps related to consistent assessment and clinically effective management of cardiac conditions

Authors

This review was written by Carmel Montgomery, RN, PhD, and scientifically reviewed by Ian Paterson, MD. The literature search was conducted by Joycelyn Jaca.

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Long-term Venous Thromboembolic Risk Following COVID-19

Key Messages

- The rate of VTE is estimated to be around 1-2.5% within 1-6 months following the diagnosis of acute Covid-19.
- There is no high-quality evidence to definitively support recommendations for long-term VTE prophylaxis in COVID patients discharged from hospital or being treated in the outpatient setting.

Recommendations

- Currently VTE prophylaxis post hospital discharge or in outpatients post COVID is not recommended outside of clinical trials.

What is the prevalence and duration of this post-COVID condition?

- Multiple observational studies have demonstrated that rate of VTE is ~1-2.5% within 1-6 months following diagnosis of acute COVID-19 (Rashidi et al., 2021).
- Patients with COVID-19 treated in the outpatient setting demonstrated a higher VTE risk after 31 days compared to matched controls, that persisted for up to 6 months of follow-up. (Chevinsky et al., 2021; Lund et al., 2021)
- In the inpatient setting, a matched analyses demonstrated that rate of VTE after hospital discharge was 4.8/1000 discharges after COVID admissions, which was not significantly different from that after non-COVID admissions at 3.1/1000 discharges (OR 1.6; 95% CI 0.8-3.1) (Roberts et al., 2020). Similar results were observed in other matched cohorts (Chevinsky et al., 2021)

Are there factors that predict the outcomes of this post-COVID condition?

- Identified risk factors for post-discharge VTE include: advanced age >75 years, cardiovascular risk factors (personal history of VTE, coronary artery disease, carotid occlusive disease, and peripheral arterial disease), CKD, IMPROVE-DD VTE score ≥4, and ICU stay (Giannis et al., 2021)

What is the recommended management of this post-COVID condition?

- Currently VTE prophylaxis post hospital discharge or in outpatients post COVID is not recommended outside of clinical trials.
- Retrospective observational data suggests that use of VTE prophylaxis in patients with COVID-19 discharged from hospital may be associated with a reduction in the composite endpoint of VTE, arterial thromboembolic events and death (Giannis et al., 2021)
- However, there is no high-quality evidence to definitively support recommendations for long-term VTE prophylaxis in COVID patients discharged from hospital or being treated in the outpatient setting.
- Numerous ongoing clinical trials and prospective cohort studies ongoing will soon be able to provide robust evidence to guide post-discharge thromboprophylaxis's decision making.

What impacts does this post-COVID condition have on the health care system?

- The VTE risk of patients recovering from COVID-19 is unclear and as such optimal resources for screening and follow-up are unknown.

What are the pressing research questions related to this area of concern?

1. Compared to non-COVID19 patients discharged from hospital, what is the long-term risk of VTE in those discharged post COVID-19 infection?
2. If COVID-19 patients are at higher long-term risk of VTE, how long does that risk persist?

3. What is the role of VTE prophylaxis in preventing VTE after acute COVID-19 including in those with defined post-COVID conditions?
4. What is the role of coagulation parameter testing, (including d-dimer, fibrinogen), screening ultrasounds and lung imaging post discharge?

For more information on screening and preventing VTE in patients with COVID-19, see the Scientific Advisory Group review.

Authors

This review was written by Tania Pannu and Pishoy Gouda and scientifically reviewed by Elizabeth MacKay, Leslie Skeith, and Cynthia Wu. The literature search was conducted by Nicole Loroff.

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Neurological: Headache, Cognitive Impairment, and Peripheral Neuropathies

Key Messages

1. Neurologic symptoms such as headache and cognitive impairment are common in post-COVID condition patients
    a. Risk factors for the development of post-COVID neurological symptoms include an age over 65, female sex, a BMI greater than 30, and the severity of underlying COVID infection.
2. Headaches appear to improve over time and treatment is largely supportive.
    a. Red flag features that warrant referral include those with progressive headaches, focal neurological features, or signs/symptoms of increased intracranial pressure should be referred to the emergency department for evaluation
3. Cognitive impairment is also a common symptom associated with post-COVID conditions and while there may be some improvement in symptoms over time, it is unclear whether people fully return to the pre-morbid baseline.
4. Neuropathy is less common than headaches and cognitive impairment in those with post-COVID conditions, but it is reported, and it tends to mirror the typical presentation of acute illness neuropathy. The degree of resolution over time is still unclear.

Recommendations

1. Post-COVID conditions with neurologic features are common and should be screened for after a patient has contracted COVID-19. Common neurologic symptoms include headaches, cognitive impairment, and neuropathic pain.
2. Management of headache is supportive and centres around identifying the subtype of headache, i.e., tension type, migraine etc. and treating in the usual fashion.
3. Management of cognitive impairment is also broadly supportive and includes patient expectation setting and daily cognitive stimulation.
4. Management of neuropathic symptoms is also largely supportive and includes the use of agents such as TCAs, SNRIs and gabalin/pre-gabalin compounds.

What is the prevalence and duration of these post-COVID conditions?

There is significant heterogeneity in the published data around post-COVID conditions and neurologic sequalae, although there may be a correlation between more severe COVID infections and the risk of developing symptoms compatible with post-COVID conditions. Neurologic conditions associated with post-COVID conditions include fatigue, headache, neuropathies (typically small fiber and relatively mild, but there are reports of more severe disease such as Guillain-Barre), cognitive impairment, autonomic dysfunction (including postural orthostatic tachycardia syndrome), fibromyalgia, chronic fatigue, anosmia and ageusia. This review will focus on headache, cognitive impairment, and peripheral neuropathies.

Headaches are very common symptoms associated with both acute COVID infections and post-COVID conditions. Typical features are similar to tension-type headaches; migraine type and new daily persistent headaches have also been reported[1,3-5,18]. The prevalence of headache is unclear but has been reported in between 15-50% of individuals at 4-6 weeks post infection; the prevalence drops to 7-22% at 8-12 weeks post infection. Over time, the prevalence of individuals with headache and post-COVID conditions appears to decrease, but it is unclear how long these symptoms might last, or if they resolve in all patients[1,3,4,14,15]. Unsurprisingly, COVID infection can also worsen headaches with the same or similar symptoms/signs as patient's pre-existing headache conditions which can outlast the acute COVID infection[3,17].

Cognitive impairment and cognitive fog are also commonly reported in the post-COVID condition population. There appears to be a correlation with disease acuity, with incidence and symptom severity correlating with disease severity, or need for ICU treatment. Most reported deficits are in verbal learning and executive function and subjective complaints are typically an inability to focus, complete tasks at work, or be as 'quick' as they once were. The prevalence at four weeks post infection has been reported to range from 12-25% with similar prevalence at 8- and 12-weeks post-infection, respectively. Nuclear medicine studies have shown a gradual reduction in inflammation/activity in the brain over time (up to 3 months), but whether that translates to a clinical improvement and/or a return to baseline is less clear[1,2,4,9,10,12]. Prolonged cognitive impairment has been documented to be 20-40% in post critical illness setting discharged from the ICU, which is not COVID specific. It would be expected that patients who were critically ill from COVID with an ICU stay would have a similar outcome. Additionally, complications such as stroke or hypoxic/anoxic brain injuries can lead to long lasting or permanent neurocognitive symptoms that can require extensive rehabilitation[1,16,17].

Neuropathic symptoms are also reported in the post-COVID population, although at a much lower incidence than headache, or cognitive impairment. Post-COVID condition neuropathic symptoms can range from mild tingling and neuropathic pain to severe peripheral nerve dysfunction resulting in autonomic dysfunction. There are also case reports for significant peripheral nerve dysfunction disorders like Guillain-Barre, but they are more typically associated with acute COVID infections [1,3,4,8,9]. Both demyelination and axonopathy syndromes have been characterized with post-COVID conditions. The prevalence is much lower, with 2.3-6% of COVID patients reporting neuropathic symptoms at 4-weeks post-infection. This population has been followed less closely in the literature, so is unclear whether prevalence drops over time, or if symptom severity wanes with time[1,5,14].

Are there factors that predict the outcomes of these post-COVID conditions?

There are several risk factors associated with the development of the post-COVID condition with neurologic findings, these risk factors are the same for those who develop headaches, cognitive impairment, and/or peripheral neuropathy. Risk factors include age greater than 65, a BMI greater than 30, the female sex, a more severe COVID infection, with the greatest risk in those in ICU. There also seems to be an association with comorbidities; those with more comorbidities being more likely to develop one, or all, of these symptoms[1,4,5,14,15]. It is important to note, however, that even young healthy adults with no comorbid conditions and mild disease have been noted to have these post-COVID conditions[3,4,5].

What is the recommended management of these post-COVID conditions?

Unfortunately, not much has been established in the treatment of these post-COVID symptoms beyond supportive and usual management for these symptoms.

For headaches, standard therapy should be implemented for post-COVID headaches without significant red flags. This includes approaches starting with trigger identification and behavior modification progressing to preventative therapies, both non-prescription and prescription, in keeping with the predominant primary headache semiology (migraine vs tension type). Appropriate abortive therapy should be prescribed, avoiding medication overuse. Referral or consideration of the need for further investigation with imaging should be reserved for refractory cases. Those with red flag features such as progressive headaches, focal neurological features, or signs/symptoms of increased intracranial pressure should be referred to the emergency department for evaluation.

The management for cognitive fog and cognitive impairment is largely supportive and includes setting patient expectations (that the individual may never return to their pre-infection baseline) and ensuring patient safety, particularly if they had a lower baseline function prior to the

infection. Remaining management should be directed at reviewing medications and trying to reduce opioids, benzodiazepines, anticholinergic, and other high-risk Beers criteria medications, which may exacerbate cognitive fog/impairment. Clinicians should also review the patient's alcohol, cannabis, and stimulant intake and counsel on minimization of these. Clinicians should also promote other aspects of healthy eating including sleep hygiene, eating well, and exercising most days of the week.

Peripheral neuropathies have been managed in the typical fashion with gabapentin/pregabalin, SNRIs, and TCAs[14].

What health care services are currently available for patients with these post-COVID conditions?

1. Information and resources for post-COVID cognitive impairment can be found at: https://myhealth.alberta.ca/after-covid/brain-health-and-mental-health/brain-fog-trouble-with-memory-and-concentration
   Additional supports for managing post-COVID cognitive impairment, including potential rehabilitation and strength building opportunities, can be found through the Alberta living well program: https://www.albertahealthservices.ca/info/page13984.aspx

What impacts do these post-COVID conditions have on the health care system?

Estimating the impact of the neurologic symptoms of post-COVID conditions, i.e., headaches, cognitive impairment, and peripheral neuropathies are difficult to capture as these presentations can have a significant impact on quality of life rather but rarely precipitate urgent admissions to hospital, or require extensive physiotherapy, or rehabilitation time/resources. However, these symptoms are common presenting complaints to the emergency department, primary care practices, and walk-in clinics and so over time there may be a significant 'cost' to the system from post-COVID conditions. It remains to be seen whether symptoms such as post-COVID headache are lifelong or time limited. Experience with new daily persistent headache resulting from other systemic viruses has shown it to be refractory to treatment and often requiring specialist care, which will further stress outpatient subspecialty resources and increase current wait times.

Furthermore, complications of cognitive impairment and neuropathic injury can be an increased tendency for mechanical falls, orthostasis and syncope, which are all associated with increased morbidity and mortality. However, estimating the impact, or risk, of these neurologic sequelae is less clear and will be determined retrospectively.

What are the pressing research questions related to this area of concern?

1. What is the natural course for these neurologic sequalae? Do they resolve? And can these individuals return to their pre-COVID baseline? This information will allow for better expectation setting with patients and provide a clearer sense of who is diverging from the 'typical course'.
2. Pathophysiology and mechanism understanding behind these neurologic symptoms. What is the process driving these symptoms and how is it different than in non-COVID circumstances? Knowledge around mechanisms should help elucidate more targeted management.
3. True prevalence of these neurologic sequalae in the Alberta population? This will allow us to better deploy healthcare personnel, resources, and follow-up to the post-COVID condition population.

Authors

This report was written by Simon M. Taylor MD MSc(c) FRCPC, and scientifically reviewed by Katie Wiltshire MD MHA FRCPC, and Chris White MD FRCPC. The literature search was conducted by Rachel Zhao.

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Neurological: Fatigue/Post Exertional Malaise

Key Messages

- Fatigue is a prevalent symptom for individuals experiencing post-COVID conditions as studies show a reported prevalence range of 13.3-63%, six months' post diagnosis.
- Screening tools for fatigue and post exertional malaise (PEM) that have been used in post-COVID condition patients include Multidimensional Fatigue Inventory Score, Brief Fatigue Inventory the Functional Assessment of Chronic Illness Therapy-Fatigue Scale (FACIT-F) and DePaul Symptom Questionnaire-Post-Exertional Malaise. These tools may assist in understanding the burden of fatigue and post exertional malaise for individuals experiencing post-COVID conditions.

Practical Guidance

- There is no evidence regarding specific management strategies for fatigue and post exertional malaise specific to post-COVID conditions, as this is an emerging area of research. Clinical guidance from post-viral fatigue and myalgic encephalomyelitis (ME)/chronic fatigue syndrome (CFS) may provide strategies for management, but require further research. A complete fatigue assessment, including functional and physical assessment, patient history, and testing to rule out differential diagnoses is warranted. Screening for post exertional malaise will assist in tailoring management strategies.
- Rehabilitation programs have been suggested for the management of post-COVID conditions. There is insufficient evidence to clearly recommend these approaches. Patient education and engagement should focus initially on balance between engaging in modified daily activity and adopting strategies to limit exertion associated with daily tasks to reduce potential exacerbation of fatigue and PEM; strategies may include encouraging frequent short rests, energy conservation and reconditioning approaches, managing quality sleep, creating self-awareness and in particular, pacing activities to maximize energy and participation in daily activities.
- Research is ongoing comparing ME/CFS to post-COVID conditions to determine if they are similar conditions and to better understand the rehabilitation needs of individuals with post-COVID conditions experiencing fatigue and/or PEM.

What is the prevalence and duration of these post-COVID conditions?

Fatigue associated with post-COVID condition is defined as "the decrease in physical and/or mental performance that results from changes in central, psychological, and/or peripheral factors due to the COVID-19 disease" (Rudroff et al., 2020). Data are evolving but currently it is the most commonly cited symptom of post-COVID condition (Goërtz et al., 2020; Logue et al., 2021; Maltezou et al., 2021; Office for National Statistics, 2021; Pavli et al., 2021; Shah et al., 2021; Shanbehzadeh et al., 2021; Zapatero & Hanquet, 2021), and the main symptom unresolved at six months (22% of patients in a cohort with mild COVID) (Klein et al., 2021). Post exertional malaise (PEM) is the worsening of multiple symptoms after mental, physical or emotional activity that was previously well tolerated. The onset can be immediate or delayed and recovery is greater than 24 hours.

A total of 23 studies (20 cohort studies, two cross sectional studies, and one survey based study) identified fatigue as a symptom of post-COVID condition (Table 1). Fatigue was reported in 9.7% to 98% of patients with post-COVID condition. There is considerable heterogeneity in the study populations (age, severity of illness, etc.), the duration of follow-up, and the approach to measuring fatigue, primarily measured by self-reports. Six systematic reviews and/or meta-analyses have been conducted since November 2020 that included prevalence of fatigue as an

outcome. In summary, they identified fatigue as a symptom of post-COVID condition in 6.6-87% of patients (Cabrera Martimbianco et al., 2021; Cares-Marambio et al., 2021; Iqbal et al., 2021; Nasserie et al., 2021; Shanbehzadeh et al., 2021; Willi et al., 2021). In a pragmatic literature review, PEM was reported in one cross-sectional internet survey of 3,762 patients, with up to 89% of individuals' experience PEM six months' post COVID diagnosis (Zapatero & Hanquet, 2021). This high prevalence of PEM can be associated with other immunological manifestations such as persistent sore throat or lymphadenopathy (Gaber, 2021).

While duration of fatigue is not yet completely known, studies that assessed symptoms at six months or more had a reported prevalence range of 13.3-63%, suggesting post-COVID condition symptoms may improve over time based upon existing knowledge that those diagnosed with myalgic encephalomyelitis (ME)/chronic fatigue syndrome (CFS) post-infection continue to recover in the first year (Augustin et al., 2021; Hopkins et al., 2021; Huang et al., 2021; Klein et al., 2021; Logue et al., 2021; Wu et al., 2021). Standardized measures of fatigue used to assess post-COVID condition include: The Multidimensional Fatigue Inventory Score (Morin et al., 2021), the Brief Fatigue Inventory (Venturelli et al., 2021), the Functional Assessment of Chronic Illness Therapy-Fatigue Scale (FACIT-F), and the DePaul Symptom Questionnaire-Post-Exertional Malaise (Twomey et al., 2021).

Are there factors that predict the outcomes of these post-COVID conditions?

Post-COVID condition fatigue has been associated with:

- Female patients (Fernández-de-las-Peñas et al., 2021; Shanbehzadeh et al., 2021; Stavem et al., 2021; Sykes et al., 2021; Townsend et al., 2020; Venturelli et al., 2021)
- Co-morbidities including pre-existing psychological issues and/ or diagnosis of depression or anxiety (Pavli et al., 2021; Shanbehzadeh et al., 2021; Townsend et al., 2020; Zapatero & Hanquet, 2021)
- Hospitalized/ICU patients, and those with more severe illness/longer hospital stays, those with ongoing lung difficulties (Goërtz et al., 2020; Maltezou et al., 2021; Osikomaiya et al., 2021; Shanbehzadeh et al., 2021; Stavem et al., 2021)
- Serum troponin-I levels during the acute illness show high correlation with the symptom of fatigue after hospital discharge(Liang et al., 2020)
- Proinflammatory cytokines, low grade endothelitis, intracortical GABAergic dysfunction may be factors associated with fatigue and long-COVID (Korompoki et al., 2021)
- Increased perception of exertion (Townsend et al., 2021)

What is the recommended management of these post-COVID conditions?

The recommended management of fatigue associated with post-COVID condition is currently being researched as there is insufficient evidence in the primary literature to offer clear guidance.

Assessment/Diagnosis

A complete fatigue assessment, including functional and physical assessment, patient history, and testing to rule out differential diagnoses (Lapp & John, 2021; Scordo et al., 2021) is warranted. The patient history should include the onset date and specific questions about fatigue and PEM (signs and symptoms, medical issues, psychosocial and emotional factors, related to medication and substance use, sleep patterns and potential toxin exposures) (Sisó-Almirall et al., 2021). Routine laboratory testing including CBC, electrolytes, creatinine, glucose, Ca, Mg, albumen, PO4, ALT, ALP, bilirubin, TSH, CK, and ferritin (hemochromatosis), hepatitis C, CRP, HgbA1C, and urinalysis may be considered (Gaber, 2021; Sisó-Almirall et al., 2021). Additional testing should focus on the individuals' symptoms, co-morbidities and possible

differential diagnosis. For suspected ME/CFS secondary to post-COVID condition, the US ME/CFS guidelines provide laboratory testing suggestions: https://drive.google.com/file/d/1Yu79EYxQIwNVER5tErp7LH7KY8pI8S_e/view (US ME/CFS Clinician Coalition, 2021).

Management

While management of COVID-related symptoms such as fatigue is advocated, the efficacy of outcomes from rehabilitative programming are lacking (Vehar et al., 2021). Patient education and engagement should focus initially on balance between engaging in modified daily activity and adopting strategies to limit exertion associated with daily tasks to reduce potential exacerbation of fatigue and PEM; strategies may include encouraging frequent short rests, energy conservation and reconditioning approaches, managing quality sleep, creating self-awareness and in particular, **pacing activities to match energy level** (Center for Disease Control and Prevention, 2021; Frota et al., 2021; Gaber, 2021; Lapp & John, 2021). The "four-P" approach to energy conservation (Planning, Pacing, Prioritizing, and Positioning) may be of value (Mikkelsen & Abramoff, 2021). For individuals that do not experience PEM, an exercise program under the guidance and/or monitoring of health care professionals may provide value (with caution, as may also exacerbate symptoms) (Scordo et al., 2021). Pulmonary rehabilitation programs have been hypothesized as a mechanism to reduce exertional fatigue and improve clinical outcomes for individuals recovering from post-COVID condition (Daynes et al., 2021), however there remains little evidence of its utility.

It may be plausible to consider existing approaches for the treatment of ME/CFS for individuals experiencing burdensome fatigue related to post-COVID condition (Center for Disease Control and Prevention, 2021; Friedman et al., 2021; Gaber, 2021). In a comparative review of ME/CFS symptoms to post-COVID condition symptoms, 25 of 29 ME/CFS symptoms were reported by at least one post-COVID condition study (Wong & Weitzer, 2021). Further, a case study of three young adults/adolescents in the United States were found to have ME/CFS triggered by COVID, with symptoms persisting six months post-diagnosis (Petracek et al., 2021). For individuals with suspected ME/CFS consider the Diagnosing and Treating ME/CFS guidelines: https://drive.google.com/file/d/1SG7hlJTCSDrDHqvioPMq-cX-rgRKXjfk/view (US ME/CFS Coalition, 2020). It is suggested patients with persistent symptoms (especially those with several ongoing symptoms) lasting beyond 12 weeks, they are referred for an evaluation in a COVID-19 follow-up clinic (if available), or alternatively a subspecialty clinic specific to their symptoms (such as fatigue/PEM) (Mikkelsen & Abramoff, 2021).

What health care services are currently available for patients with these post-COVID conditions?

No resources specific to post-COVID fatigue were identified by the Post-COVID Task Force's review of available healthcare services.

What impacts do these post-COVID conditions have on the health care system?

Utilization of healthcare practice to include early screening, early interventions with clear directives for resource allocation, and specialist consultations should be available to address the ongoing challenges (Korompoki et al., 2021). Sisó-Almirall and colleague (2021) have developed proposed guidelines for the diagnosis and management of post-COVID conditions in primary care, and suggest pursuing further diagnostic testing is fatigue is present after four weeks. Individuals that experience post-COVID conditions may require ongoing care, and if warranted, should be evaluated for ME/CFS (Simani et al., 2021). Rehabilitative programming is well-suited to address the ongoing rehabilitation needs of individuals with post-COVID condition, however, programs may require tailoring to best match individual needs, taking into account the

availability and use of healthcare resources, the attention to symptom management over time, screen for PEM, and the functional and sustainable occupational goals for activities of daily living (Singh et al., 2020).

What are the pressing research questions related to this area of concern?

1. Improving our understanding of risk factors for post-COVID condition symptoms, contributors to fatigue and the disease trajectory including ongoing functional deficits and health care needs (Overview | COVID-19 Rapid Guideline: Managing the Long-Term Effects of COVID-19 | Guidance | NICE, 2020; Rudroff et al., 2020)
2. Research is ongoing comparing ME/CFS to post-COVID condition to determine if they are similar conditions (Komaroff & Bateman, 2021; Scordo et al., 2021).
3. Ongoing research evaluating the natural history of post-COVID condition, and defining the risk factors, prevalence, and possible management strategies to establish COVID-19 as a potential infectious trigger of ME/CFS (Poenaru et al., 2021).
4. Further research relating to exercise rehabilitation programming for improvement of post COVID condition (Overview | COVID-19 Rapid Guideline: Managing the Long-Term Effects of COVID-19 | Guidance | NICE, 2020)

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Appendix A

Table 1. Reported prevalence of fatigue as a symptom of post-COVID conditions in research published since November, 2020.

Study	Population	Follow-Up Period	Fatigue Prevalence- (self-report unless otherwise indicated)
(Arnold et al., 2021)	110 hospitalized patients	8–12 weeks post admission	39%
(Augustin et al., 2021)	442 (4 month follow up) 353 (7 month follow up) patients with mild, non-hospitalized patients	4 & 7 months	4 months-9.7% 7 months-14.2%
(Boari et al., 2021)	94 hospitalized patients	Mean of 4 months	52%
(Darley et al., 2021)	78 patients (69 community-based care, 9 hospitalized)	Median 113 days post-diagnosis	22%
(Dennis et al., 2021)	201 community patients	141 days post-infection	98%
(Graham et al., 2021)	100 individuals (50 SARS Co-V-2 positive, 50 SARS Co-V-2 negative) seen at a neuro COVID-19 clinic	Mean of 5.27 months	85% overall (84% for SARS CO-V-2 + and 86% for SARS CO-V-2 -) (P=1.0).
(Hopkins et al., 2021)	434 participants in an online survey of patients that lost sense of smell due to COVID-19	6 months	24%
(**Huang et al., 2021)**	1733 Patients discharged from hospital	6 months	63% (1038 of 1655 reported fatigue)
(Klein et al., 2021)	103 mild COVID-19 patients	6 months	22%
(Leth et al., 2021)	49 hospitalized patients	6 & 12 weeks	6 weeks-65% 12 weeks-63%
(Liang et al., 2020)	76 hospitalized patients	3 months	59%
(Logue et al., 2021)	177 patients (16 inpatient, 150 outpatients, 11 asymptomatic patients)	6 months	13.6%
(Mandal et al., 2021)	384 hospitalized patients	Median 54 days post discharge	69%
(Morin et al., 2021)	478 hospitalized patients	4 months	31% Multidimensional Fatigue Inventory score (n = 130) was 4.5

			(interquartile range, 3.0-5.0) for reduced motivation and 3.7 (interquartile range, 3.0-4.5) for mental fatigue (possible range, 1 [best] to 5 [worst]). T
(O'Sullivan et al., 2021)	155 patients referred by primary care to a rehabilitation program	Median 13 weeks post illness	70.3%
(Petersen et al., 2020)	180 patients with history of COVD-19	Mean of 125 days	28%*
(Shang et al., 2021)	1174 patients with severe disease	6 months	25.3%
(Simani et al., 2021)	120 hospitalized patients	6 months	17.5%
(Stavem et al., 2021)	458 non-hospitalized patients	Median of 117.5 days	46%
(Sykes et al., 2021)	134 hospitalized patients	Median 113 days	39.6% "extreme fatigue"
(van den Borst et al., 2021)	124 patients (27 mild, 51 moderate, 26 severe and 20 critical disease)	Mean 13 weeks	69%
(Venturelli et al., 2021)	767 hospitalized patients	Median time of 81 days after discharge	Brief Fatigue Inventory 44.1% had new-onset fatigue
(Wu et al., 2021)	54 hospitalized patients	6 months	24.1%

Psychiatric: Anxiety

Key Messages

- Most of what is published relies on measuring anxiety symptoms through self-reported surveys, which is not equivalent to clinically diagnosed anxiety disorders requiring specialized treatment.
- Anxiety should be treated in post-COVID patients using the same techniques as other patients, with the knowledge that it often decreases over time.

What is the prevalence and duration of this post-COVID condition?

When considering the prevalence and duration of anxiety in patients with COVID multiple issues need to be detangled. The first is to differentiate the impact of having the infection from the impact of the pandemic globally (isolation, unemployment, fear of infection). The second issue is that measuring anxiety symptoms through self-reported surveys is not equivalent to clinically diagnosed anxiety disorders that require specialized treatment. This does not diminish the impact that anxiety has on patients diagnosed with COVID, but does need to be considered when discussing the current literature.

An important lesson from the SARS outbreak in 2004 was that anxiety symptoms do decrease over time. Specifically, from in hospital (mean of 50.21 on the SCL-90 anxiety subscale) to below the clinical cut off 12 months later (29.72 mean) (Liu, Baumeister, & Zhou, 2021).

A systematic review of studies on patients admitted with COVID-19 reported ranges from 6.5% to 63% of anxiety symptoms in people 1-3 months post-discharge (or reporting of symptoms) with higher prevalence in patients admitted to ICUs than to wards (Shanbehzadeh, Tavahomi, Zanjari, Ebrahimi-Takamjani, & Amiri-Arimi, 2021). This study highlighted that cultural differences may impact mental health reporting, and so results may not be applicable universally. Further variation may have been the result of variety in the tools for mental health diagnoses in the studies (HADS, GAD-7 and surveys designed for the individual studies were all reported).

A study using administrative data reported that compared with other respiratory tract infections, patients with COVID had a hazard ratio of 1.59 – 2.62 for anxiety 14 – 90 days post COVID, and a 4.7% probability of anxiety symptoms at 90 days (Taquet, Geddes, Husain, Luciano, & Harrison, 2021). This study also reported an increased likelihood of first anxiety diagnoses 1-180 days post COVID diagnosis (HR 1.78 (1.66 – 1.91) compared to someone diagnosed with influenza. This risk was higher for patients admitted to intensive treatment units (ITU), which was unsurprising given the known impact of ICU admittance (similar to ITUs) (Taquet et al., 2021).

Daugherty et al. published a study using United States administrative data (merged with laboratory and hospital inpatient data) with 3 propensity matched control groups (2020 comparators, non-COVID; 2019 comparators; and historical group with lower respiratory tract illness). They investigated mental health diagnoses at 21 days post lab-confirmation of SARS-CoV-2 and calculated a hazard ratio of 1.24 – 1.54 and a risk difference of 0.83 (0.60 – 1.02) between COVID positive patients and non-COVID 2020 control group (Daugherty et al., 2021).

Another study of clinical and non-clinical health care workers in the UK who were recruited at the start of the pandemic that included a prospective control group (pre-print) reported that rates of anxiety assessed by online questionnaire were not significantly different between people who had anti-bodies for COVID and those who did not, however the rates were high in both groups

(51.4% in COVID positive samples; 47.2% in the control group) (Amin-Chowdhury et al., 2021). This study may not be representative of the general population and the researchers created a study specific screening tool.

Many of the reports of elevated anxiety in post-COVID patients did not include relevant control groups and so interpretation is limited. Specifically, it is not possible to unequivocally determine what proportion (if any) of the increases in anxiety symptoms is due to the COVID-19 infection, rather than other factors. However, there were reports that anxiety declined over the 45 days post-admission (hospitalized patients) (Matalon et al., 2021). Interestingly, one study reported lower rates of anxiety in those admitted to intensive care units (23%) versus general wards (31.4%), however that group only included patients who had reported new symptoms in the 4 months post-diagnosis (Morin et al., 2021).

The study with the highest reported rate (47% depression or anxiety) also reported that 42% of the study population reported pre-COVID diagnosis of depression or anxiety, which is significantly higher than the population average of 21% (Graham et al., 2021). The authors did not hypothesize on the cause of this discrepancy, further work may demonstrate inequitable vulnerability to COVID, or simply that this population was not representative of the general population for a different reason.

A recent study on PTSD symptoms 3 months after a COVID diagnosis reported that anxiety symptoms (State-Trait Anxiety Inventory form Y) decreased between the 1 month and 3 month timepoints (Mazza et al., 2021). The same study measured anxiety through clinical interviews (N=20) and the State-Trait Anxiety Inventory form Y (N=51) demonstrating the variation possible due to differing measurement techniques (Mazza et al., 2021).

Are there factors that predict the outcomes of this post-COVID condition?

A recent systematic review of studies of hospitalized and non-hospitalized patients (33 studies included) with COVID-19 reported risk factors for anxiety including: illness severity; medical comorbidities; younger age; reduced quality of life; close relatives with COVID; prior psychiatric history; and decreased sense of smell (Vanderlind et al., 2021). The authors highlighted that most of the included studies were completed during the first wave of infections and the results may change during different waves of infections.

Most studies identified admission to an intensive care unit as a risk factor for measurable symptoms of anxiety 3 weeks to 12 months later (Daugherty et al., 2021; Shanbehzadeh et al., 2021). One systematic review identified treatment with corticosteroids as a potential risk factor for anxiety (after 21 days post-symptom onset) (Michelen et al., 2020) and studies also found that being female increased the risk of anxiety (Beck et al., 2021) and/or psychiatric morbidity(Shanbehzadeh et al., 2021).

What is the recommended management of this post-COVID condition?

Anxiety should be treated in post-COVID patients using the same techniques as other patients, with the knowledge that it often decreases over time.

What health care services are currently available for patients with this post-COVID condition?

- Brain health and mental health: Depression, anxiety, stress (alberta.ca)
- Mental Health Tip sheet: https://www.albertahealthservices.ca/assets/info/amh/if-amh-mhpip-disaster-pandemic-covid-19-and-your-mental-health.pdf
- Mental Health Toolkit: https://www.albertahealthservices.ca/assets/info/amh/if-amh-mhpip-disaster-pandemic-covid-19-and-your-mental-health.pdf

- Togetherall: Togetherall | A safe community to support your mental health, 24/7
- Text4Hope: https://www.albertahealthservices.ca/topics/Page17019.aspx
- Mental Health Helpline: 1-877-303-2642

What impacts does this post-COVID condition have on the health care system?
The impact of post-COVID mental health diagnoses on the health care system may not be able to be isolated from the population level mental health impacts of over a year of pandemic response. The Provincial Addiction and Mental Health team is working with zone Addiction and Mental Health teams to create a robust recovery plan that will respond to increases in demands for services.

What are the pressing research questions related to this area of concern?
Studies with rigorous control groups and that take into consideration the external context of isolation, increased unemployment and societal changes during the pandemic should be pursued. However, this research would be useful for future planning, rather than in addressing the current patient needs. One study measured a protective effect of 'resilience' which is a promising area of research that may have impact far beyond COVID (Beck et al., 2021). Due to anxiety diagnoses being most common before or during early adulthood, and COVID infections not, research should monitor if first episode anxiety is diagnosed more commonly in older age groups.

The current studies have used a variety of survey tools (one included clinical interviews) and none investigated the type of anxiety patients were experiencing more completely. This would allow for differentiation of types of disorders, such as generalized anxiety disorder, panic disorder, or a phobia, which have different appropriate treatments.

Further work should also investigate if the symptoms and rates change based on: timing of surveys; changes due to differences in knowledge about the disease; the current rate of infection in the population; or the impact of variants of concern.

As with all AMH research, investigations into disaggregated data that can investigate differences in marginalized populations is valuable and important, especially in this situation, where the impact of COVID has been inequitable.

Authors
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Psychiatric: Depression

Key Messages

- Most data is from self-reported surveys, which have inherent biases and is not equivalent to clinically diagnosed major depressive disorder that requires specialized treatment.
- It is unclear at this time if depression symptoms are due to COVID infection or to the impact of the pandemic globally (isolation, unemployment, fear of infection).
- Depression in post-COVID patients should be treated using the same techniques as other patients, including pharmacotherapy and psychotherapy.

What is the prevalence and duration of this post-COVID condition?

When considering the prevalence and duration of depression in patients with COVID multiple issues need to be detangled. The first is to differentiate the impact of having the infection from the impact of the pandemic globally (isolation, unemployment, fear of infection). The second issue is that measuring depression symptoms through self-reported surveys is not equivalent to clinically diagnosed major depressive disorder that require specialized treatment. This does not diminish the impact that depression symptoms have on patients diagnosed with COVID, but does need to be considered when discussing the current literature.

There were large ranges in the prevalence of depressive symptoms measured in COVID-19 patients after 30 days. This is partially due to the variety of tools used to assess symptoms and the range of timeframes measured (Vanderlind et al., 2021). Recent pre-prints are also highlighting significant publication bias and heterogeneity of studies, with one meta-analysis calculating small-study effects for 56% of symptoms (Hoshijima et al., 2021), and another reporting an I^2 of 79.6% to 98.6% (Badenoch et al., 2021). Moderate to severe depression ranged from 10.0 – 42.0% in community dwelling COVID-19 patients 2-3 months post discharge (Vanderlind et al., 2021). In a systematic review of 10 studies prevalence ranged from 4 – 31% after one month (33 – 41.3% had symptoms of both depression and anxiety) (Shanbehzadeh, Tavahomi, Zanjari, Ebrahimi-Takamjani, & Amiri-Arimi, 2021).

Interestingly, one large administrative data study reported that the rate of depression diagnoses in COVID-19 patients (87 day median follow up) was not statistically different than the rate reported in the control group of people diagnosed with other lower respiratory virus infections (Daugherty et al., 2021). A recent (pre-print) prospective, longitudinal cohort of health care workers reported non-statistically significant differences in depression symptoms of people who had COVID (7.5 months prior on average) and a control group (Amin-Chowdhury et al., 2021); both groups reported depression symptoms of over 21%. Another large administrative data study (United States based) documented that the hazard ratios for a first diagnosis of a mood disorder in the 6 months following a COVID-19 diagnosis were 1.78 (1.61 – 1.96) in those not hospitalized, and 2.06 (1.57 – 2.71) for those with an intensive treatment unit admission compared to people with other respiratory tract infections (Taquet, Geddes, Husain, Luciano, & Harrison, 2021).

In contrast to the high percentages reported above, a study on patients with COVID-19 admitted to intensive care units before June, 2020, recorded only 5% abnormal and 10.2% borderline abnormal depression scores on the Hospital Anxiety and Depression Scale (HADS) three months after discharge (Gonzalez et al., 2021).

Several studies reported around 20% of patients with significant depressive symptoms: 18% (95% CI 11.7 – 23.5) a median of 61 days from discharge (D'Cruz et al., 2021); 18.8% average 48 days between infection and survey (Poyraz et al., 2021); 19% at 16 weeks (Peluso et al.,

2021); 18% average 54 days (Silva et al., 2021); 21% - 23.5% 7 months post diagnosis (Fernandez-de-Las-Penas et al., 2021); and 18% in former ICU patients and 20.6% in complete group at 4 month follow up (Morin et al., 2021). In contrast, a large study in South Korea that included matched controls (matched for age, sex and residence) and excluded anyone with a psychological diagnosis in the past 5 years, reported 1.3% newly diagnosed depression in the total cohort, but people who had COVID had significantly higher rate (4.9%) compared to the matched controls (1.0%) (Oh, Park & Song, 2021).

Are there factors that predict the outcomes of this post-COVID condition?
Those with prior psychiatric history, that perceived higher stigma related to COVID-19 or underwent quarantine post-hospitalization had higher rates of depressive symptoms (Vanderlind et al., 2021). One review suggested that better lung function at follow up may correlate to fewer depression symptoms (Shanbehzadeh et al., 2021). Several articles highlighted that female patients had higher rates of psychological diagnosis (Beck et al., 2021; Islam et al., 2021; Oh et al., 2021; Shanbehzadeh et al., 2021; Vanderlind et al., 2021) and those with prior psychological diagnosis (Naidu et al., 2021), which is to be expected based on literature regarding depression diagnoses in the general population.

What is the recommended management of this post-COVID condition?
Depression in post-COVID patients should be treated using the same techniques as other patients, including pharmacotherapy and psychotherapy. In one meta-analysis of the impact of SARS long-term, depression symptoms showed the most improvement over 12 months, though they were still higher than the general population (Liu, Baumeister, & Zhou, 2021). One study specifically recommended internet-based CBT, but did not investigate the effectiveness (Shanbehzadeh et al., 2021).

When appropriate, patients should be screened for risk of suicide; most AHS facilities use the Columbia short screen (available in Connect Care), the two children's emergency departments use the ASQ (also available in Connect Care) and long-term care use questions related to the inter-Rai.

What health care services are currently available for patients with this post-COVID condition?
- Brain health and mental health: Depression, anxiety, stress (alberta.ca)
- Mental Health Tip sheet: https://www.albertahealthservices.ca/assets/info/amh/if-amh-mhpip-disaster-pandemic-covid-19-and-your-mental-health.pdf
- Mental Health Toolkit: https://www.albertahealthservices.ca/assets/info/amh/if-amh-mhpip-disaster-pandemic-covid-19-and-your-mental-health.pdf
- Togetherall: Togetherall | A safe community to support your mental health, 24/7
- Text4Hope: https://www.albertahealthservices.ca/topics/Page17019.aspx
- Mental Health Helpline: 1-877-303-2642

What impacts does this post-COVID condition have on the health care system?
The impact of post-COVID mental health diagnoses on the health care system may not be able to be isolated from the population level mental health impacts of over a year of pandemic response. The Provincial Addiction and Mental Health team is working with zone Addiction and Mental Health teams to create a robust recovery plan that will respond to increases in demands for services.

What are the pressing research questions related to this area of concern?
The most pressing question to address will be if depression symptoms related to COVID-19 resolve completely over time or become chronic in nature. Research into a possible physiological mechanism due to COVID-19 infection will also be of interest.

Further work should also investigate if the symptoms and rates change based on: timing of surveys; changes due to differences in knowledge about the disease; the current rate of infection in the population; symptoms of infection that last past 4 weeks; or the impact of variants of concern.

As with all AMH research, investigations into disaggregated data that can investigate differences in marginalized populations is valuable and important.

Authors

This review was written by Katherine (Kay) Rittenbach, PhD, and scientifically reviewed by Scott Patten, Nicholas Mitchell, and Michael Trew. The literature search was conducted by Rachel Zhao.

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Psychiatric: Post Traumatic Stress Disorder

Key Messages

- COVID infection may or may not be the event resulting in Post Traumatic Stress Disorder (PTSD), even in patients who were infected and go on to develop PTSD symptoms.
- Not all people who are diagnosed with COVID will develop PTSD; patients who are admitted to the ICU may experience Post-Intensive-Care-Syndrome (PICS), a non-ICD/DMS diagnosis related to Acute Stress Disorder, which is not COVID specific.
- PTSD should be treated in post-COVID patients using the same techniques as other patients. The preferred initial approach is psychotherapy with a focus on addressing triggers and managing the impact of symptoms. Pharmacotherapy may play a role in selected patients.

What is the prevalence and duration of this post-COVID condition?

When considering the prevalence and duration of PTSD in patients with COVID multiple issues need to be detangled. The first is to differentiate the impact of having the infection from the impact of the pandemic globally (isolation, unemployment, fear of infection). The second issue is that measuring PTSD symptoms through self-reported surveys is not equivalent to clinically diagnosed PTSD that requires specialized treatment. Finally, some of the surveys used will also measure PTSD symptoms due to other events in the patient's life rather than the COVID infection, only one publication attempted to minimize this impact by specifying that the infection was the "event". This does not diminish the impact that PTSD has on patients diagnosed with COVID, but does need to be considered when discussing the current literature.

It is hard to disentangle post-COVID psychiatric symptoms from Post-Intensive-Care-Syndrome (PICS), which is a non-ICD/DMS diagnosis related to Acute Stress Disorder that is characterized by long-term physical, psychological and cognitive disabilities that can occur in patients who have previously been hospitalized in intensive care units (ICU). Studies on the sequela of COVID-19 that include populations that were treated in ICUs may be reporting PICS symptoms, rather than a specific manifestation of post-COVID conditions. A meta-analysis from 2019 reported that the rate of PTSD in patients discharged from ICUs is 19.83% regardless of the reason of admittance (Righy et al., 2019). This is a natural outcome of the fact that perceived life threat and fear of death play a key role in the development of PTSD.

One systematic review, that included 33 studies, reported that at 3-4 months post-hospitalization for COVID-19, 25.6% of participants reported mild symptoms of PTSD, 11.3% reported moderate symptoms and 5.9% reported severe symptoms of PTSD (Vanderlind et al., 2021). Another systematic review that included 7 studies assessed prevalence between 12.1 and 46.9%, and noted that it was more prevalent in patients admitted to intensive care units than to wards (Shanbehzadeh, Tavahomi, Zanjari, Ebrahimi-Takamjani, & Amiri-Arimi, 2021). It was noted that patients experiencing post-COVID 19 symptoms had an increased risk of reporting PTSD symptoms. Interestingly, one study reported no statistical difference in PTSD among patients hospitalized (9.5%) and non-hospitalized (7.0%) (Einvik, Dammen, Ghanima, Heir, & Stavem, 2021). This study in Norway suggested that the lower proportions observed may be a consequence of high trust in the health system and accessibility of adequate medical treatment (Einvik et al., 2021).

A well designed, large administrative database study that included 266,586 SARS-CoV-2 positive patients and multiple propensity matched control groups, found that the risk difference between participants who had been diagnosed with COVID and those who had not (in 2020) was only 0.08 (0.03 – 0.15) (Daugherty et al., 2021).

Interestingly, a study of both hospitalized and non-hospitalized patients showed that the percentage of participants reporting PTSD symptoms increased over time (week 16: 6%; week 32: 11%) which is concerning, however they hypothesized that the participants motivated to continue participating where ones who suffered more symptoms (Peluso et al., 2021), potentially enriching the sample and making interpretation complicated.

Overall, the rates of positive screens for PTSD in patients who had tested positive for COVID-19 ranged significantly, potentially due to variety in the inclusion criteria and screening tools used. One study that excluded anyone who had received psychiatric medications in the year prior to diagnosis with COVID-19 measured PTSD as 5.8% using the PCL-5 survey (Simani et al., 2021), which is lower than many other studies. Demonstrating that the measurement tool has significant impact, a study that used both the IES-R and the PCL-5 measured PTSD rates of 22% with the IES-R and 13% with the PCL-5 in the same participants (Mazza et al., 2021).

Are there factors that predict the outcomes of this post-COVID condition?
Surprisingly, severity of COVID did not predict the likelihood of reporting PTSD symptoms in one study of hospitalized patients (Matalon et al., 2021), however increased anxiety and depression at hospital admission, along with hospitalization length, did.

Studies reported that people with prior psychiatric diagnoses were more likely to report moderate to severe PTSD symptoms (Poyraz et al., 2021; Tarsitani et al., 2021), and that male sex was protective (Tarsitani et al., 2021). However, sex differences were not found in all studies (Einvik et al., 2021)

What is the recommended management of this post-COVID condition?
PTSD should be treated in post-COVID patients using the same techniques as other patients. The preferred initial approach is psychotherapy with a focus on addressing triggers and managing the impact of symptoms. Pharmacotherapy may play a role in selected patients.

What health care services are currently available for patients with this post-COVID condition?
- Brain health and mental health: Depression, anxiety, stress (alberta.ca)
- Mental Health Tip sheet: https://www.albertahealthservices.ca/assets/info/amh/if-amh-mhpip-disaster-pandemic-covid-19-and-your-mental-health.pdf
- Mental Health Toolkit: https://www.albertahealthservices.ca/assets/info/amh/if-amh-mhpip-disaster-pandemic-covid-19-and-your-mental-health.pdf
- Togetherall: Togetherall | A safe community to support your mental health, 24/7
- Text4Hope: https://www.albertahealthservices.ca/topics/Page17019.aspx
- Mental Health Helpline: 1-877-303-2642

What impacts does this post-COVID condition have on the health care system?
The impact of post-COVID mental health diagnoses on the health care system may not be able to be isolated from the population level mental health impacts of over a year of pandemic response. Though by definition PTSD is caused by traumatic events rather than the elevated stress, the increase in ICU admissions and the increase in exposure to mortal risk due to COVID may result in increased diagnoses that result in higher demands on the health care system. The Provincial Addiction and Mental Health team is working with zone Addiction and Mental Health teams to create a robust recovery plan that will respond to increases in demands for services.

What are the pressing research questions related to this area of concern?
Studies with rigorous control groups that take into consideration the external context of isolation, increased unemployment and societal changes during the pandemic should be conducted. In

addition, because PTSD is a response to a traumatic event and studies have shown that ICU admissions can trigger the symptoms, control groups of patients diagnosed with PTSD triggered by non-COVID events and by non-COVID ICU admissions would help determine if PTSD due to COVID infection has unique features.

PTSD can have delayed onset, so longitudinal studies are needed to assess the full impact of COVID infections.

Further work should also investigate if the symptoms and rates change based on: timing of surveys; changes due to differences in knowledge about the disease; the current rate of infection in the population; or the impact of variants of concern.

As with all AMH research, investigations into disaggregated data that can determine differences in marginalized populations is valuable and important.

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Post-COVID Sleep Disturbances

Key Messages

- Sufficient evidence on the development, prevalence, and specific sleep symptoms or disorders in the post-COVID population has not been reported in the literature to date.
- Observational data, primarily from follow-up of individuals hospitalized for COVID-19, suggest that sleep disturbances are commonly reported following COVID-19 infection in adults; however, it is unclear whether this is related to COVID-19 or other factors known to affect sleep quality such as increase in stressors, concurrent mental health disorders, change in work situation and isolation from support systems.
- There is limited evidence concerning what risk factors may be associated with persistent sleep disturbances or disorders post-COVID.
- The evidence base regarding optimal management of individuals with persistent sleep symptoms following acute COVID-19 is limited and there are no recommendations specific to the management of post-COVID sleep disturbances.

What is the prevalence and duration of these post-COVID conditions?

Sufficient evidence on the development, prevalence, and specific sleep disorders in the post-COVID population has not been reported in the literature to date. Observational data in adult populations suggest that sleep disturbances, insomnia, poor sleep quality, or sleep disorders (not otherwise specified; hereafter referred to as sleep problems), are commonly reported following hospitalization due to COVID-19 infection in prospective cohort studies. There are limited data describing details of patient-reported sleep problems (e.g., presence of concurrent symptoms) in the post-COVID setting. In a systematic review of available data, Nasserie et al. (2021) identified 45 studies evaluating a variety of persistent conditions at least 60-days after COVID-19 diagnosis, symptom onset, or hospital admission. Persistent sleep problems or symptoms of insomnia among adults (mean ages: 47 to 65.5 years) hospitalized due to acute COVID-19 were reported in 8 studies, with a median prevalence of 29.4% (interquartile range [IQR]: 24.4-33.0%) (Nasserie et al., 2021). From a meta-analysis of participants in 4 cohort studies (n=3 hospitalized patients; n=1 non-hospitalized patients) at least 12-weeks after COVID-19 infection, the pooled prevalence of sleep disturbances was 44% (95% confidence interval [CI], 8-85%) (Iqbal et al., 2021).

Post-COVID sleep problems have primarily been evaluated among individuals previously hospitalized due to acute COVID-19 (Nasserie et al., 2021; Iqbal et al., 2021). There is insufficient evidence to indicate whether prevalence estimates differ in non-hospitalized COVID-19 survivors. There is also no data comparing post-discharge sleep problems between patients hospitalized due to acute COVID-19 infection and patients hospitalized due to other reasons. Variability in prevalence may be due to a number of factors including differing follow-up periods, lack of detailed characterization of sleep disturbances or sleep problems, lack of serial measurements over time, and lack of data on sleep disturbances or sleep disorders that predate COVID-19 infection in affected individuals. This literature has limited incorporation of validated questionnaires or objective sleep diagnostic testing to assess for sleep disorders. Further, evidence concerning post-COVID sleep problems among pediatric populations was not identified in the peer-reviewed literature.

The duration of sleep disturbances or sleep complaints after having a COVID-19 infection is unclear. Iqbal et al. (2021) reported that sleep disturbances were highly prevalent in the ‘chronic post-COVID’ stage (i.e., 12-weeks or more after COVID-19 infection). Post-COVID sleep disturbances have been documented up to 6-months following initial COVID-19 infection (Nasserie et al., 2021; Iqbal et al., 2020; NICE 2020a; Mahmud et al., 2021, Huang et al., 2021); there is no data on sleep disturbances beyond 6-months in this population. However, published

follow-up data are limited due to recency of cases and thus, the duration of the sleep disturbance in affected individuals is unknown.

Notably, an increased prevalence of sleep problems in healthcare workers (pooled prevalence: 36.0%, 95% CI: 21.1-54.2%) and the general population (pooled prevalence: 32.3%, 95% CI: 25.3-40.2%) has been reported during the pandemic (Jahrami et al., 2021). Furthermore, critical illness or hospitalization is associated with disturbances in sleep even in the absence of COVID-19 (range: 22-57%, 3 and 6-months post-hospitalization or ICU stay) (Altman et al., 2017). These findings support the supposition that factors beyond COVID-19 infection itself may influence prevalence of sleep disturbances since the pandemic began. In addition to COVID-19, other factors that influence sleep quality such as social isolation, psychological stress, substance abuse, or mental health disorders, may co-exist. It is, therefore, not possible to conclude at this time whether COVID-19 infection itself has a direct impact on sleep.

Are there factors that predict the occurrence of these post-COVID conditions?

There is a lack of high-quality evidence around the risk factors associated with persistent sleep disturbances or disorders post-COVID (Vanderlind et al., 2021). In a cross-sectional study of 1021 COVID-19 survivors, a higher proportion of those with multiple comorbidities experienced long-term sleep disturbances (41.3%), relative to those who did not (24.8%) (Mannan et al., 2021). In contrast, a small prospective cohort study (n=119) by D'Cruz et al. (2021) reported no associations between the presence or absence of pre-existing comorbidities and sleep disturbances at least 51 days after acute COVID-19 hospitalization. Sykes et al. (2021) found that females (50%, 23/46) were more likely to experience post-COVID sleep disturbances compared to males (27.3%, 24/88; p=0.009) and that persistent sleep disturbances were commonly reported by COVID-19 survivors with low mood and anxiety.

What is the recommended management of these post-COVID conditions?

There are no recommendations specific to the management of post-COVID sleep disturbances due to a lack of evidence in this population; however, there are general patient education resources:

- Canadian Sleep and Circadian Network CSCN - Canadian Sleep and Circadian Network (cscnweb.ca)
- Canadian Sleep Society Podcasts - Canadian Sleep Society (CSS) (css-scs.ca)
- American Academy of Sleep Medicine Patient Information | Sleep | American Academy of Sleep Medicine (aasm.org)

As a general approach to the care of patients with sleep complaints, not specific to COVID-19, comprehensive clinical history is important to identify and manage co-existing mental health concerns, medications that may cause sleepiness or affect sleep duration, substance use that affects sleep duration and quality, and medical conditions that cause symptoms such as chronic pain or dypsnea that affect sleep quality. Identification of sleep disorders that may have been unrecognized prior to COVID-19 or have symptoms that are more pronounced following COVID-19 such as obstructive sleep apnea, restless leg syndrome or bruxism should be assessed for clinically through history and physical examination and addressed. General advice surrounding sleep hygiene may be useful in patients where difficulties initiating or maintaining sleep is a concern. Care planning, including specialist referrals, should employ shared decision-making and individuals should be advised of peer-to-peer groups, caregiver support and education, and relevant self-management strategies (WHO, 2021; NICE, 2020b; Greenhalgh et al., 2020).

What health care services are currently available for patients with these post-COVID conditions?

The majority of sleep disturbances are identified and managed in primary care with the involvement of sleep subspecialist when needed. Self-management resources for sleep hygiene after COVID-19 are available to patients from MyHealth.Alberta.ca Network: Self-care: Sleeping well (alberta.ca).

Referral to a sleep disorders program may be prompted when primary care resources are insufficient to resolve patient concerns, there is a suspected underlying sleep disorder that is not identified through ambulatory testing, polysomnography is required for funding for patient access to therapy, or at the treating physicians' discretion. There are three adult sleep disorders programs in the province located in the Calgary zone (Foothills Medical Centre; Alberta Children's Hospital), Edmonton zone (University of Alberta Hospital [UAH]; Stollery Children's Hospital), and South zone (Lethbridge, Lacidem building). For patients with post-COVID sleep disturbances, primary care and other community providers should consult the provincial and zone-specific referral pathways and information for these sleep services:

- Primary Care Pathway for Uncomplicated Obstructive Sleep Apnea (OSA) OSA Pathways (albertahealthservices.ca);
- Calgary zone – Sleep Centre referral Calgary Zone Sleep Centre Referral Quick Reference (albertahealthservices.ca); Pediatric Sleep Clinic Alberta Referral Directory - Service At Facility Data Entry
- Edmonton zone – UAH Sleep Disorders Program Alberta Referral Directory - Service At Facility Data Entry; Pediatric Sleep Lab Alberta Referral Directory - Service At Facility Data Entry
- South zone – Sleep Clinic Alberta Referral Directory - Service At Facility Data Entry.

What impacts might these post-COVID conditions have on the healthcare system?

Coordinated, multi-disciplinary follow-up and care for individuals with post-COVID conditions would require the development of new service delivery models and/or expansions of existing services in Alberta. Development of coordinated care pathways would also help ensure continuity of care (WHO, 2021; NICE, 2020b). For individuals with post-COVID sleep disturbances, these pathways should integrate primary care and community providers, sleep specialists, multidisciplinary teams that support evidence-based behavioural management of insomnia (e.g., providers of cognitive behavioural therapy for insomnia), and mental health and psychosocial services. Further, expansion of existing sleep services, such as sleep testing facilities and outpatient sleep clinics for patients that may have an unrecognized sleep disorders, are likely required to address the increased capacity from, and the potentially unique needs of, individuals with sleep disturbances after having COVID-19.

What are the pressing research questions related to this area of concern?

- What is the prevalence and duration of new or worsened sleep disturbance following COVID-19 infection?
- What are the characteristics of the sleep disturbance reported following COVID-19 infection (e.g. sleep initiation or sleep maintenance insomnia, hypersomnolence, other).
- What factors influence the risk and severity of developing persistent sleep problems after COVID-19?
- Does COVID-19 affect the prevalence or manifestations of sleep disorders including sleep-related breathing disorders, circadian sleep-wake disorders, insomnia, disorders of hypersomnolence, parasomnias or sleep-related movement disorders?
- What are the most clinically relevant and cost-effective interventions for managing persistent sleep disturbances or disorders post-COVID? Does effectiveness vary for

different populations (e.g., never hospitalized due to acute COVID-19, ethnicity, sex, or age)?
- What is the most clinically- and cost-effective service delivery model for a multi-disciplinary post-COVID conditions assessment clinic?

Please provide key references in support of your findings and recommendations.

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Pulmonary Symptoms: Dyspnea, Cough, Sputum

Key Messages

- Persistent dyspnea and cough are common after COVID-19 infection, occurring in 36% and 17% of patients, respectively
- Pulmonary function tests and chest imaging are recommended for individuals with persistent pulmonary symptoms post-COVID, but evidence to guide management of post-COVID pulmonary symptoms is limited.
- Referral pathways and multidisciplinary teams should be created to evaluate and follow patients with post-COVID pulmonary symptoms, with clear processes to evaluate resource utilization and outcomes.

What is the prevalence and duration of these post-COVID conditions?

Persistent pulmonary symptoms, particularly dyspnea and cough, are frequently reported by individuals experiencing long-term effects of COVID-19. In one of the largest systematic reviews to date (Nasserie et al., 2021), 45 studies examined persistent symptoms at least 60 days after COVID-19 diagnosis or 30 days after hospital discharge. The median prevalence of persistent dyspnea was 36% (interquartile range [IQR], 27.6%-50.0%; n=26 studies) (Nasserie et al., 2021). Persistent cough was reported in 18 studies with a median prevalence of 16.9% (IQR, 14.4%-25.1%) (Nasserie et al., 2021). While sputum production was less frequent, there was greater variability in reported prevalence: estimates from two cohort studies ranged from 0.8% (of 131 participants) (Wang et al., 2020) to 43% (of 76 participants) (Liang et al., 2020).

There was some variability in the prevalence of dyspnea and cough between those who required hospitalization for acute COVID-19 infection and those who did not. A rapid review by the National Institute for Health Care and Excellence (NICE) in the United Kingdom (UK) found that in hospitalized patients 4 weeks post-COVID-19 diagnosis, dyspnea was reported by 33%-74.3% (n=6 studies) and cough was reported by 33%-42.6% (n=2 studies) (NICE, 2020a). Among individuals who were not hospitalized due to acute COVID-19 infection, 7.7%-71% reported dyspnea (n=4 studies) and 25.9%-39.7% (n=3 studies) reported persistent cough at least 4 weeks following their COVID-19 diagnosis (NICE, 2020a).

Based on the reported prevalence estimates available to date, post-COVID dyspnea and cough may persist between 30 days and 1 year following COVID-19 diagnosis (Nasserie et al., 2021; Iqbal et al., 2020; NICE 2020a; Ceravolo et al., 2020; UK National Statistics; Fernández-de-las-Peñas et al., 2021).

Are there factors that predict the occurrence of post-COVID pulmonary symptoms?

The evidence is limited, with mixed results regarding potential factors associated with developing post-COVID pulmonary symptoms. Individuals who experienced dyspnea in the acute phase of infection, were hospitalized (i.e., increased severity of illness) due to acute COVID-19, and/or have a history of asthma or other chronic pulmonary disease, may be at higher risk for post-COVID dyspnea, relative to those without (AHS SAG review 2020; NICE, 2020b; Iqbal et al., 2021). In contrast, a 1-year follow-up study found no association between persistent post-COVID cough and having acute dyspnea or cough, age, sex, existing comorbidities, previous hospitalization with or without ICU admission, or other concomitant post-COVID symptoms (e.g., persistent fatigue or chest pain) (Fernández-de-las-Peñas et al., 2021).

What is the recommended management of post-COVID pulmonary symptoms?

Evidence concerning routine management of individuals with persistent pulmonary symptoms after acute COVID-19 is limited. Broadly, guidance from the World Health Organization (WHO, 2021a) as well as NICE and others in the UK (NICE, 2020c) recommend a multi-disciplinary, person-centred approach for managing individuals with post-COVID symptoms. This approach

should be tailored to the patient, employ shared-decision-making, and may involve a comprehensive clinical history (i.e., physical, cognitive, psychological) and diagnostic testing (WHO 2021a; NICE 2020c). For those with post-COVID pulmonary symptoms, general practitioners could consider a chest radiograph as well as standard bacterial cultures for sputum. Pre-existing conditions, such as asthma and gastroesophageal reflux disease, contributing to post-COVID pulmonary symptoms may be identified and managed according to other guidelines (e.g., Irwin et al., 2006). Patients should also be advised on relevant strategies for self-management of symptoms (WHO, 2021a; NICE, 2020c; Greenhalgh et al., 2020).

Consensus opinion from the Swiss Society for Pulmonology (Funke-Chambour et al., 2021) suggests pulmonary follow-up for those with persistent pulmonary symptoms after acute COVID-19 infection. There is no literature to inform referral criteria to a pulmonary specialist for individuals with post-COVID pulmonary symptoms. Pulmonary follow-up may include: pulmonary function tests (e.g., spirometry, plethysmography, diffusion capacity measurement); blood gases analysis; functional exercise assessments (e.g., 6-min walk test, cardio-pulmonary exercise test); and/or chest computed tomography (Funke-Chambour et al., 2021). Access to a specialized, multi-disciplinary post-COVID clinic and rehabilitation program are also suggested (Funke-Chambour et al., 2021). There is limited evidence, however, to support multi-disciplinary pulmonary rehabilitation for individuals with post-COVID pulmonary symptoms (Funke-Chambour et al., 2021; Ceravolo et al., 2020).

What health care services are currently available for patients with these post-COVID conditions?

There are currently 3 post-COVID pulmonary clinics in the province located in the Edmonton zone (Kaye Edmonton Clinic) and the Calgary zone (Peter Lougheed Centre and Rockyview General Hospital).

In addition, the following resources are available to patients with pulmonary symptoms post-COVID-19 and their support team:

- Symptoms: Feeling short of breath (alberta.ca)
- Symptoms: Coughing (alberta.ca)
- Alberta Wide - Rehabilitation Advice Line | Alberta Health Services
- Self-care (alberta.ca)
- Find Healthcare | Alberta Health Services

What impacts do these post-COVID conditions have on the health care system?

Given the complex needs of individuals with post-COVID symptoms, those with persistent pulmonary symptoms will require coordinated access to multi-disciplinary services. Care for these patients should, therefore, draw on diverse health professionals' expertise and patients should have access to a variety of appropriate assessments and diagnostic tests (World Health Organization [WHO], 2021a; NICE, 2020c).

Delivery of such services may require creation of a centralized multi-disciplinary assessment clinic, multiple locations, or a virtual platform (WHO, 2021a; NICE, 2020c). Development of integrated referral pathways between primary care, specialist services including pulmonary services, multi-disciplinary rehabilitation services, and if present, multi-disciplinary assessment clinics, are also recommended (WHO, 2021a; NICE 2020c). Ongoing exchange of knowledge, skills, and training would benefit primary care and other healthcare providers in the community to identify appropriate assessments and interventions (NICE, 2020c). Currently there is insufficient pulmonary rehabilitation capacity to support patients with chronic respiratory conditions (i.e., chronic obstructive pulmonary disease, asthma, interstitial lung disease) in Alberta. Therefore, substantial adaptation or expansion of existing services, such as to

pulmonary rehabilitation programs, are required to support individuals with post-COVID pulmonary symptoms (Spruit et al., 2020).

What are the pressing research questions related to this area of concern?

- What factors influence the risk of developing persistent pulmonary symptoms and their trajectory post-COVID? For instance, what factors are associated with either less or more severe dyspnea or cough?
- What are the most clinically and cost-effective interventions for managing post-COVID pulmonary symptoms? Does effectiveness vary for different populations (e.g., hospitalization due to acute COVID-19, ethnicity, sex, or age)?
- What is the most clinically- and cost-effective service delivery model for a multi-disciplinary post-COVID assessment clinic?
- What is the clinical effectiveness of pulmonary rehabilitation and/or exercise interventions for people with post-COVID pulmonary symptoms? Does effectiveness vary for different populations (e.g., hospitalization due to acute COVID-19, ethnicity, sex, or age) or timing of initiation?

Please provide key references in support of your findings and recommendations.

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Pulmonary Complications: Lung Function Impairment, Respiratory Failure, Pulmonary Vascular Dysfunction, Interstitial Lung Disease, and Airway Disease

Key Messages

- Pulmonary complications after COVID-19 include persistent radiographic abnormalities, abnormal pulmonary function testing, and a higher risk of pulmonary embolism.
- Long-term pulmonary complications occur in in approximately 50% of patients who have been hospitalized for acute COVID-19, which warrants appropriate follow-up and referral to multidisciplinary post-COVID care centres. Long-term pulmonary complications also occur in non-hospitalized COVID-19 survivors; this evidence is limited.
- Evidence for specific therapies, including rehabilitation, to manage pulmonary complications of COVID-19 is limited.

What is the prevalence and duration of these post-COVID conditions?

Evidence of long-term pulmonary complications of acute COVID-19 is emerging. A recent, large systematic review and meta-analysis conducted by So et al., (2021) identified 15 studies (n=3066 participants) evaluating radiological and functional pulmonary assessments of COVID-19 survivors post-hospitalization, and, of whom, less than 4% had pre-existing chronic lung disease. Among patients previously hospitalized due to acute COVID-19, the pooled prevalence of abnormal chest computed tomography (CT) post-COVID was 55.7% (95% confidence interval [CI]: 41.2-70.1, n=13 studies) at least 30 days after discharge or 40 days after symptom onset (So et al., 2021). The CT abnormalities included, but were not limited to, ground glass opacities, interstitial fibrotic changes, signs of airway damage, and pleural thickening (So et al., 2021). Post-COVID pulmonary function test (PFT) abnormalities were also common, with a pooled prevalence of 44.3% (95% CI: 32.2-56.4) based on 10 studies, where patients were followed-up at least 30 days post-hospital discharge or 74 days following symptom onset (So et al., 2021). Specifically, the pooled prevalence of impaired diffusion capacity, restrictive pattern, and obstructive pattern were 34.8% (95% CI 25.8–43.8, n=9 studies), 16.4% (95% CI 8.9–23.9, n=8 studies), and 7.7% (95% CI 4.2–11.2, n=7 studies), respectively. These studies, however, did not account for pulmonary findings pre-COVID-19 infection; thus, post-COVID CT and PFT abnormalities may not necessarily be related to acute COVID-19. One study in non-hospitalized COVID-19 patients showed impaired forced vital capacity (11%; n=201 participants) at least 141 days following acute COVID-19 symptom onset; this impairment was identified in only 3% of healthy controls (n=36) (Dennis et al., 2021).

Few studies have evaluated the prevalence of pulmonary vascular sequelae of COVID-19. In a small prospective cohort study (n=171) of ICU patients with respiratory failure secondary to acute COVID-19 infection, pulmonary hypertension was identified in 7% of individuals at 4 months post-COVID diagnosis (as evaluated by point of care cardiac ultrasound and after ruling out pulmonary embolism) (Alharthy et al., 2020). Further, a large matched-cohort study of nearly 150,000 participants in the United Kingdom reported that, relative to those without a previous COVID-19 diagnosis, the likelihood of acute pulmonary embolism was 2.8 times greater (adjusted odds ratio [OR]: 2.8; 95% CI: 1.6-6.0) among post-COVID patients who were 31-60 days post-infection (Chevinsky et al., 2021).

Based on the available prevalence estimates to date, pulmonary complications may persist between 30 days and 12 months following acute COVID-19 infection (So et a., 2021; Torres-Castro et al., 2020; Wu et al., 2021a; Alharthy et al., 2020; Chevinsky et al., 2021).

Are there factors that predict the occurrence of these post-COVID conditions?

Early evidence regarding risk factors associated with post-COVID pulmonary complications indicate that age above 60 years and intensive care unit (ICU) admission (with or without need for mechanical ventilation) due to acute COVID-19 may be associated with impaired lung function (Ekbom al., 2021) and persistent abnormal CT findings (Sonnweber et al., 2021). These risk factors have also been associated with more severe acute COVID-19 infection (National Institute for Health and Care Excellence [NICE], 2020a). Impaired diffusion capacity among COVID-19 survivors 12 months post-hospitalization was also positively associated with being female in one study (Wu et al., 2021a). In a small 6-month follow-up study of patients hospitalized due to acute COVID-19 (n=54), 52.6% of individuals with either multiple pulmonary symptoms, impaired lung function, or abnormal lung imaging during hospitalization were more likely to present with persistent abnormal lung CT findings post-COVID, relative to those who did not (3.4%) (Wu et al., 2021b). So et al., (2021), in contrast, noted that the high prevalence of chest CT abnormalities at least 30 days post-discharge or 40 days after symptom onset (>50%) was apparent despite 77% (2211/2849) of cases being mild (few pulmonary symptoms and no evidence of pneumonia in imaging) or moderate (fever, some pulmonary symptoms, and pneumonia on radiographic imaging) in this pooled dataset.

What is the recommended management of these post-COVID conditions?

High-quality evidence concerning routine management of and specialist referral criteria for individuals with pulmonary complications post-COVID is limited. Available guidance is, therefore, based on consensus of expert opinion and limited observational study data. The British Thoracic Society (British Thoracic Society, 2020), the National German S3 (Kluge et al., 2021), and the Swiss Society for Pulmonology (Funke-Chambour et al., 2021) recommend pulmonary specialist follow-up for hospitalized COVID-19 patients within 3 months post-discharge. In fact, the Swiss guidance suggests pulmonary follow-up for all COVID-19 patients, including those who experienced mild acute infection, by 3 months post-diagnosis (Funke-Chambour et al., 2021). Based on consensus of expert opinions, pulmonary follow-up for post-COVID patients may include history of the acute COVID-19 illness, physical examination, lung function testing, and diagnostic imaging (e.g., chest radiograph) (Funke-Chambour et al., 2021). In addition, supplementary generic and disease-specific quality of life questionnaires and other laboratory investigations (e.g., SARS-CoV2 antibody confirmation) may be included in the assessment.

Currently, there is limited guidance pertaining to therapeutic recommendations for individuals with long-term pulmonary complications post-COVID. The Swiss guidance suggests empiric inhaled or systemic steroid treatment be offered to those with obstructive lung disease and a trial of systemic steroids in individuals who present with persistent interstitial abnormalities, after exclusion of an active infection and even in the absence of hypoxemia is also suggested (Funke-Chambour et al., 2021). There was no recommendation on the exact steroid dose and duration with case by case risk benefit assessment suggested. To date, there is insufficient evidence to recommend routine use of antifibrotic drugs among those with post-COVID pulmonary fibrosis (Funke-Chambour et al., 2021). For post-hospital COVID-19 survivors with pre-existing or persistent lung function impairment, the European Respiratory Society- and American Thoracic Society-coordinated international task force suggests a comprehensive pulmonary rehabilitation program at 6-8 weeks post-hospitalization (Spruit et al., 2020). There is, however, limited evidence specific to the post-COVID population to support this suggestion (Funke-Chambour et al., 2021; Ceravolo et al., 2020; Barker-Davies et al., 2020; Spruit et al., 2020).

What health care services are currently available for patients with these post-COVID conditions?

There are currently 3 post-COVID pulmonary clinics in the province located in the Edmonton zone (Kaye Edmonton Clinic) and the Calgary zone (Peter Lougheed Centre and Rockyview General Hospital).

In addition, the following resources are available to patients with pulmonary complications post-COVID and their support team:

- Symptoms: Feeling short of breath (alberta.ca)
- Symptoms: Coughing (alberta.ca)
- Alberta Wide - Rehabilitation Advice Line | Alberta Health Services
- Self-care (alberta.ca)
- Find Healthcare | Alberta Health Services

What impacts do these post-COVID conditions have on the health care system?

The capacity for pulmonary specialist resources to manage patients with post-COVID conditions is likely to fluctuate and may be strained if a limited number of specialists are associated with post-COVID clinics and are balancing other clinical commitments. Capacity to assess patients with post-COVID conditions could be limited if a large referral demand exceeds the number of specialist resources available. Programs may need to offload specialists working in post-COVID clinics from other duties in order to meet the demand for post-COVID referrals in a timely manner. Additionally, booking a PFT, 6 minute walk test, or cardiopulmonary exercise test can also be delayed given reductions in testing capacity due to varying local pandemic restrictions and increasing numbers of people needing those tests. Demand and capacity for patients with post-COVID conditions and access to specialized testing must also be balanced against the care deficits and needs that may have arisen for patients with other (non-COVID related) pulmonary conditions during the pandemic.

Please see other potential impacts outlined in the “Post-COVID Pulmonary Symptoms: Dyspnea, Cough, Sputum” document.

What are the pressing research questions related to this area of concern?

- What factors specifically influence the risk of developing persistent pulmonary complications and their trajectory post-COVID?
- What are the most appropriate diagnostic imaging tests, and timing of assessment, for individuals with pulmonary complications post-COVID? What factors affect appropriateness (e.g., severity of acute COVID-19 illness, presence of other comorbidities)?
- What are the most clinically and cost-effective interventions for managing pulmonary complications post-COVID? Does effectiveness vary for different populations (e.g., hospitalization due to acute COVID-19, ethnicity, sex, or age)?
- What is the most clinically- and cost-effective service delivery model for a multi-disciplinary post-COVID syndrome assessment clinic?
- What is the clinical effectiveness of pulmonary rehabilitation and/or exercise interventions for people with post-COVID pulmonary complications? Does effectiveness vary for different populations (e.g., hospitalization due to acute COVID-19, ethnicity, sex, or age) or timing of initiation?

Please provide key references in support of your findings and recommendations.

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Pulmonary: Diminished Exercise Capacity

Key Messages

- Diminished exercise capacity occurs in 25-55% of patients after a hospitalization for acute COVID-19 infection.
- Hospitalized patients requiring supplemental oxygen are most likely to have impaired exercise capacity.
- Evaluation of dyspnea and reduced exercise capacity should be evaluated in multi-disciplinary post-COVID clinics or networks and should include objective measurements of exercise capacity such as cardiopulmonary exercise testing or six-minute walking distance.

What is the prevalence and duration of this post-COVID condition?

Diminished exercise capacity due to cardiopulmonary causes is increasingly observed as a long-term sequela of COVID-19 infection among previously hospitalized patients. Of the small cohort studies that have evaluated exercise capacity in COVID-19 survivors through cardiopulmonary exercise testing (CPET), indicators of diminished capacity were observed in 29%-55% of participants between 2 and 6 months after hospitalization for acute COVID-19 (Debeaumont et al., 2021; Dorelli et al., 2021; Raman et al., 2021; Rinaldo et al., 2021; Walsh-Messinger et al., 2020). In particular, ventilatory inefficiency and reduced peak oxygen consumption (VO_2) below 80-85% of predicted values were observed among those with persistent dyspnea post-COVID (Dorelli et al., 2021; Debeaumont et al., 2021). Studies that evaluated functional capacity with the 6-minute walking test (6MWT) also found that 23.2%-79% of patients demonstrated diminished capacity (e.g., distance less than age-adjusted predicted values) between 6 weeks and 6 months following hospitalization for acute COVID-19 (Bardacki et al., 2021; Huang et al., 2021; Daher et al., 2020).

Based on the reported prevalence estimates to date, diminished exercise capacity may persist between 30 days and 6 months following acute COVID-19 infection (Debeaumont et al., 2021; Dorelli et al., 2021; Raman et al., 2021; Rinaldo et al., 2021).

Are there factors that predict the occurrence of this post-COVID condition?

There is very limited evidence concerning what factors are associated with diminished exercise capacity post-COVID. However, available evidence suggests a relationship between acute disease severity and reduced functional capacity. From a small cross-sectional study conducted by Townsend et al. (2021), longer inpatient length of stay for acute COVID-19 infection was positively associated with reduced 6-minute walking distance (6MWD) at least 6-weeks post-hospitalization. Furthermore, patients who were hospitalized due to acute COVID-19 and required supplemental oxygen (e.g., non-invasive or invasive mechanical ventilation, extracorporeal membrane oxygenation) were 2.18 times more likely to have a lower 6MWD at 6-months post-discharge, relative to hospitalized patients who did not (odds ratio [OR]: 2.18; 95% confidence interval [CI]: 1.18-4.03); these findings were adjusted for age, sex, smoking status, comorbidities, medication use (Huang et al., 2021).

What is the recommended management for this post-COVID condition?

There is insufficient evidence regarding routine management of individuals with diminished exercise capacity post-COVID. Given early evidence that exercise intolerance tends to present concomitant to persistent dyspnea (Dorelli et al., 2021; Debeaumont et al., 2021), guidance for managing individuals with post-COVID pulmonary symptoms (e.g., dyspnea and cough) may apply (see “Post-COVID-19 Pulmonary Symptoms: Dyspnea, Cough, Sputum” document). For instance, consensus opinion from the Swiss Society for Pulmonology (Funke-Chambour et al., 2021) suggests pulmonary follow-up, which may include: pulmonary function tests (e.g.,

spirometry, plethysmography, diffusion capacity measurement); blood gases analysis; functional exercise assessments (e.g., 6MWT, CPET); and/or chest computed tomography, if appropriate (Funke-Chambour et al., 2021). There is no literature to inform referral criteria to a pulmonary specialist for individuals with post-COVID pulmonary symptoms, with or without diminished exercise capacity. The Swiss consensus also suggests access to a specialized multi-disciplinary post-COVID assessment clinic and rehabilitation program (Funke-Chambour et al., 2021). However, the evidence to support multi-disciplinary pulmonary rehabilitation for individuals with diminished exercise capacity post-COVID is limited (Funke-Chambour et al., 2021; Ceravolo et al., 2020).

What health care services are currently available for patients with this post-COVID condition?
There are currently 3 post-COVID pulmonary clinics in the province located in the Edmonton zone (Kaye Edmonton Clinic) and the Calgary zone (Peter Lougheed Centre and Rockyview General Hospital).

In addition, the following resources are available to patients with pulmonary complications post-COVID-19 and their support team:

- Symptoms: Feeling short of breath (alberta.ca)
- Symptoms: Coughing (alberta.ca)
- Alberta Wide - Rehabilitation Advice Line | Alberta Health Services
- Self-care (alberta.ca)
- Find Healthcare | Alberta Health Services

What impacts do these post-COVID conditions have on the health care system?
Currently there is insufficient pulmonary rehabilitation capacity to support patients with chronic respiratory conditions (i.e., chronic obstructive pulmonary disease, asthma, interstitial lung disease) in Alberta. As such, substantial adaptation or expansion of existing pulmonary rehabilitation programs are required to support individuals with diminished exercise capacity post-COVID (Spruit et al., 2020). Many COVID-19 survivors experience persistent dyspnea and diminished exercise capacity, despite no substantial impairment in lung function in the post-COVID phase (Personal Communication: University of Alberta Department of Medicine Grand Rounds, Drs. M. Smith and G. Lam; February 12, 2021). Therefore, other multidisciplinary rehabilitation or out-patient exercise programs may be more appropriate for those with diminished exercise capacity post-COVID.

Please see other potential impacts outlined in the “Post-COVID Pulmonary Symptoms: Dyspnea, Cough, Sputum” document.

What are the pressing research questions related to this area of concern?

- What factors influence the risk of developing diminished exercise capacity post-COVID? What are the most common mechanisms for diminished exercise capacity post-COVID?
- What are the most clinically and cost-effective interventions for managing diminished exercise capacity post-COVID? Does effectiveness vary for different populations (e.g., hospitalization due to acute COVID-19, ethnicity, sex, or age)?
- What is the most clinically- and cost-effective service delivery model for a multi-disciplinary post-COVID syndrome assessment clinic?
- What is the clinical effectiveness of pulmonary rehabilitation and/or exercise interventions for improving exercise capacity post-COVID? Does effectiveness vary for different populations (e.g., ethnicity, sex, or age), timing of initiation, or clinical history (e.g., presence of pre-existing lung disease, severity of acute infection)?

Please provide key references in support of your findings and recommendations.

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Renal Complications

Key Messages

- Acute kidney injury (AKI) is common in acute COVID-19 and may result in chronic kidney disease (CKD).
- Current suggested approach to AKI and CKD is to follow guidelines for post-discharge management of AKI (measure kidney function and proteinuria at 90 days following discharge), and follow guidelines for CKD management (see www.ckdpathway.ca).

What is the prevalence and duration of these post-COVID conditions?

Within the multisystem nature of acute COVID-19, acute kidney injury (AKI) is recognized as a common complication in those with severe disease (Berlin, Gulick, & Martinez, 2020), and AKI is a known risk factor for chronic kidney disease (CKD) (Venkatachalam et al., 2010). Reported incidence of AKI associated with COVID-19 varies substantially. Initial data from the first wave in New York reported that 46% of all patients hospitalized for COVID-19 had AKI (Chan et al., 2021). Subsequent meta-analyses have reported the pooled incidence of AKI among hospitalized patients to be in the range of 10-35% (Lin et al., 2020; Robbins-Juarez et al., 2020; Silver et al., 2021) although the range of AKI incidence in the included was broad (0.5% to 80%). It is unclear if the variability of AKI incidence relates to differences in assessment, thresholds for hospitalization, ICU care (e.g., concomitant use of mechanical ventilation and fluid management), or the prevalence of AKI risk factors in the population studied (Wald & Bagshaw, 2021).

The etiology of AKI in COVID-19 is uncertain but it may be due to hemodynamic changes and cytokine release or direct viral cytotoxicity (Palevsky PM, Radhakrishnan J, & Townsend RR, 2021). Kidney biopsies and autopsies indicate that acute tubular necrosis (ATN) is the primary finding noted (Kudose et al., 2020; Su et al., 2020), suggesting that COVID-19 associated AKI may be similar to other forms of AKI causing ATN.

While burden of dialysis dependent AKI at the time of discharge appears to be low, the extent of recovery of renal function and the subsequent impact on the development of CKD is not yet clear. In a longitudinal study comparing in-hospital AKI, those with COVID-19 associated AKI had a greater rate of eGFR decrease after discharged compared to AKI in patients without COVID-19 (median follow-up: 93 days), independent of underlying comorbidities or AKI severity (Nugent et al., 2021). These findings speak to the importance of monitoring kidney function after COVID-19-associated AKI for CKD.

Are there factors that predict the outcomes of these post-COVID conditions?

Independent risk factors reported for AKI in acute COVID-19 include: age, African ancestry, male, obesity, diabetes, hypertension, cardiovascular disease, CKD, higher interleukin-6 level, and requiring mechanical ventilation (Bowe et al., 2020; Chan et al., 2021). While less common, an associated glomerular disease labeled COVID-19-associated nephropathy (COVAN) has been reported. Similar to HIV-associated nephropathy, COVAN is more common in individuals of African descent with a high proportion of those tested possessing high-risk APOL1 genotypes; it is characterized by collapsing glomerulopathy and presentation with nephrotic-range protein urea and AKI (Peleg et al., 2020; Velez, Caza, & Larsen, 2020).

While AKI alone may not be considered a post-COVID condition, there is an increased risk of CKD secondary to AKI. Among subjects with AKI, the prediction of who will develop advanced CKD remains to be determined. The following variables have been associated with a higher risk of advanced chronic kidney disease in patients with AKI (not specific for COVID-19): older age,

female sex, CKD, albuminuria, greater acute kidney injury severity, and higher discharge serum creatinine values (James et al., 2017).

What is the recommended management of these post-COVID conditions?
There is currently no data to suggest that management of patients with COVID-19-associated AKI should differ from established guidelines for post-discharge management of AKI in general. Follow-up is important to ensure that full kidney recovery has occurred and to appropriately manage subsequent CKD.

Key points for the general management of AKI:

- **Ensure measurement of eGFR, albumin to creatinine ratio (ACR) and urinalysis at 90 days post discharge.** Emerging evidence suggests that measurement of ACR after an episode of AKI may allow for identification of patients who are at the highest risk of kidney disease progression or development of end stage renal disease (Liu et al., 2020).
- **Continue to monitor for CKD and refer to nephrology as appropriate.** Patients with AKI are at increased risk for subsequent development of CKD even after apparent resolution of AKI. The Alberta CKD pathway (http://www.ckdpathway.ca/) serves as a guide on how often to test kidney function and when to refer to nephrology.
- **Ensure blood pressure control and education.** Target should be < 140/90 mmHg (<130-80 mmHg for people with diabetes).
- **Review medications.** Avoid the use of medications that may have nephrotoxic effects (NSAIDS, COX-2 inhibitors, etc. –see also the CKD pathway).
- **Sick day protocols.** Educate patients on medications that need monitoring during acute illness and consider protocols to withhold kidney-excreted nephrotoxic drugs.

Further details on a suggested post-AKI care bundle of KAMPs (Kidney function, Advocacy, Medications, Pressure, Sick day protocol) are available here (Kashani et al., 2019).

What health care services are currently available for patients with these post-COVID conditions?
Current management of CKD is by primary care providers in conjunction with nephrologists; more advanced CKD requiring multidisciplinary care and renal replacement therapy is provided by Alberta Kidney Care within Alberta Health Services. Referral criteria and process are outlined here: www.ckdpathway.ca/referral

What impacts do these post-COVID conditions have on the health care system?
Given the incidence of AKI varies across the literature, projections of future impact on kidney outcomes such as progression of chronic kidney disease and subsequent dialysis requirement remains difficult. If we were to use a conservative estimate of ~15% of people who were hospitalized experience AKI, this could translate to around 1440 people at increased risk of CKD related to COVID-19 (Alberta data indicate that 9607 people have been hospitalized; with 1800 admitted to ICU due to COVID-19, date June 27, 2021). However, an examination of the renal data on the impacts of COVID using local Alberta data would give better estimate of the actual burden.

What are the pressing research questions related to this area of concern?
While severe renal complications of COVID-19 tend to be in the acute phase and tend to be less common within post-COVID syndrome, the long-term effects and burden of COVID-19-associated AKI are unclear. Whether recovery from COVID-19 AKI differs from other forms of AKI is unknown.

Future research and local surveillance is needed to better understand the impact of COVID-19 on long-term outcomes and the effects of the pandemic specific to Alberta.

Key research questions include:

- What is the incidence of AKI associated with acute COVID-19 in Alberta?
- What proportion of patients with COVID-19 or COVID-19 associated AKI develop CKD (with or without the need for chronic kidney replacement therapy) in Alberta?
- Among those with COVID-19 associated CKD, what proportion will require: 1) long term nephrologist care; 2) multidisciplinary kidney care; 3) have progressive CKD; 4) require kidney replacement therapy?
- Are there unique aspects of COVID-19 associated AKI and subsequent CKD that differ from what is known of AKI and CKD in general (non-COVID associated)?

Authors

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What are the contraindications to commencing exercise training in adults with post-COVID conditions?

Key Messages

- Very little primary literature exists on this topic. Recommendations are derived from patient experience and expert opinion.
- Patients with post-COVID conditions (defined as symptoms beyond the acute period or more than 4 weeks, as per the Canadian Cardiovascular Society) should undergo screening for the following prior to commencing exercise: 1) post-exertional symptom exacerbation, 2) cardiac symptoms, 3) exertional oxygen desaturation and 4) autonomic nervous system dysfunction. Screening includes a patient interview and physical examination, as well as monitoring symptoms and vital signs during a sub-maximal exercise test, such as the 6-minute walk test or the 1-minute sit-to-stand test.
- Any patients presenting with cardiac symptoms during screening or exercise testing should be referred to a cardiologist before commencing exercise.
- Exercise programs should be progressed gradually, avoiding exacerbation of symptoms. Monitoring of vital signs (heart rate, blood pressure, and oxygen saturation) as well as symptoms (dyspnea, fatigue, chest pain/pressure, or heart palpitations) should continue before, during, and after exercise training sessions.
- Patients with post-COVID condition(s) will need to increase their exercise workload gradually. Pacing and energy conservation strategies are very important in this population. Patients may need to prioritize activities of daily living over a return to exercise if they do not have the energy to manage both.

Note: Patients who do not present with post-COVID conditions may still need to return to exercise gradually after recovering from COVID-19. Screening is not required for those who have recovered fully from COVID-19 and do not have any underlying medical pathology.

Recommendations/Practical Considerations

1) Patients should be medically stable before beginning a rehabilitation or exercise program (Barker-Davies et al. 2020; Calabrese et al. 2021; Halle et al. 2021; Kurtais et al. 2020; Salman et al. 2021; Siddiq et al. 2020; Yong et al. 2021)
2) Patients should be referred to a cardiologist for further testing prior to beginning rehabilitation or exercise if any cardiac symptoms are present, such as chest tightness or pain, palpitations, difficulty breathing, or syncope/presyncope (Barker-Davies et al. 2020; Calabrese et al. 2021; Canadian Cardiovascular Society 2021; O'Sullivan et al. 2021; Phelan et al. 2020; Salman et al. 2021)
3) Patients with confirmed myocarditis should avoid high-intensity activity for 3-6 months and return to exercise should be guided by the patient's cardiologist (Barker-Davies et al. 2020; Calabrese et al. 2021; Salman et al. 2021)
4) Patients presenting with post-COVID conditions should undergo submaximal exercise testing, such as a 6-minute walk test or a 1-minute sit-to-stand test, prior to returning to exercise. Oxygen saturation, respiratory rate, rate of perceived exertion, dyspnea, and blood pressure should be monitored during initial testing and throughout rehabilitation/exercise (Barker-Davies et al. 2020; Calabrese et al. 2021; Frota et al. 2021)
5) Patients with the following may not be suitable for exercise: oxygen saturation of less than 90%, respiratory rate greater than 30-40 breaths/minute, very low (<90) or very high (>180) systolic blood pressure, or heart rate less than 40 beats per minute or more than 120 beats per minute (Brika et al. 2020; Kurtais et al. 2020; Siddiq et al. 2020)

6) Discontinue exercise if respiratory rate increases to more than 30 breaths per minute, oxygen saturation falls below 90% (88% for those with known lung pathology) or more than 4-5% compared to baseline, or if the patient has onset of fever, chest pain/pressure, vertigo, profuse sweating, tinnitus or palpitation (Alberta Health Services 2021; Kurtais et al. 2020)
7) Patients presenting with post-exertional malaise, a worsening of symptoms after minimal physical or mental exertion, may need to avoid exercise and focus on symptom management and activity pacing (Alberta Health Services 2021; Torjesen et al. 2020; World Physiotherapy 2021)
8) Start at a low level of activity and progress slowly. Pacing and energy conservation are important (Alberta Health Services; Barker-Davies et al. 2020; BC Provincial Health Authority 2021; Canadian Cardiovascular Society 2021; C.S. Mott Children's Hospital 2020; de Lira et al. 2021; Kho, 2021; NIHR 2021; Salman et al. 2021; Shepherd, C. 2021; Silva et al. 2021; Torjesen et al. 2020; Yong 2021)
9) Consider the impact of other sequelae such as dysphagia (Cervolo et al. 2020), orthostatic hypotension (American Academy of Physical Medicine and Rehab 2021; Yong 2021), post-traumatic stress disorder (Salman 2021).

Summary of the evidence

The research databases MEDLINE, Embase, and PubMed were searched for articles related to post-COVID conditions. Post-COVID conditions were defined as symptoms beyond the acute period of more than 4 weeks (Canadian Cardiovascular Society 2021). Synonyms, such as post-COVID-19 or long COVID, were used to maximize the number of articles retrieved. The search was limited to English language studies published from July 2020 to present. Over 2000 abstracts were identified. Only articles focusing on exercise or rehabilitation for Post COVID condition(s) were included. Google was searched for grey literature sources; an additional 13 relevant sources identified.

Evidence from secondary and grey literature

29 secondary literature sources were included in this review: 14 expert opinion articles, 5 narrative reviews, and 11 grey literature sources.

Secondary evidence was primarily expert opinion. In addition to the recommendations listed above, authors recommend that patients with cardiac symptoms undergo exercise testing and ECG monitoring (Barker-Davies et al. 2020; de Lira et al. 2021; Halle et al. 2021; O'Sullivan et al. 2021; Phelan et al. 2020; Salman et al. 2021)

Thorough testing, including ECG, echocardiography, and biomarker assessment, may be required for those returning to very intense activity (O'Sullivan et al. 2021; Phelan et al. 2020), although asymptomatic athletes or those with very mild symptoms may not require cardiovascular screening before returning to activity (Phelan et al. 2020).

Evidence from the primary literature

13 primary literature sources were included in this review: 3 prospective cohort studies, 1 retrospective cohort study, 8 case series, and 1 case report,

Several observational studies explored exercise intolerance 1-3 months after diagnosis of COVID-19. Arnout and colleagues found that patients with exertional dyspnea had significant exercise intolerance 3 months after a diagnosis of acute COVID-19 (Arnout et al. 2020). Three observational studies found that 1-3 months after COVID-19 symptom onset, patients presented with significantly reduced exercise capacity (Barratto et al. 2021; Cassar et al. 2021; Dorelli et

al. 2021). A retrospective cohort study by Debeaumont suggested that persistent dyspnea is likely caused by persistent breathing disorder and ventilatory inefficiency (Debeaumont et al. 2021).

Madrid-Mejia studied patients 6 months after COVID-19 and found that almost half of the patients in their observational study experienced oxygen desaturation during exercise testing and delayed heart rate recovery one minute after exercise testing (Madrid-Mejia et al. 2021). Fuglebjerg et al. reported that nearly half of the patients in their study had silent hypoxia during exercise testing (Fuglebjerg et al. 2020). Nunez-Cortez used 1-minute sit-to-stand testing and found that 32% of patients experienced desaturation of 4% or more 4 weeks after hospital discharge (Nunez-Cortez et al. 2021).

Malek and colleagues found that athletes who were asymptomatic or had mild COVID-19 symptoms showed a lack of ECG changes and normal troponin concentration (Malek et al. 2021).

There are a limited number of studies exploring the safety and efficacy of exercise or rehabilitation programs. After following screening protocols, the limited number of studies to date have reported no adverse events (Betschart et al. 2021; Brika et al. 2020; Daynes et al. 2021; Maniscalo et al. 2021).

What are the pressing research questions related to this area of concern?

Further study is required to determine:

1) the safety of high-intensity exercise training programs (Christiansen et al. 2021; Keech et al. 2021)
2) the effectiveness of rehabilitation and physical exercise interventions for post-COVID conditions
3) the optimal methods of screening patients with post-COVID conditions prior to rehabilitation and physical exercise interventions
4) the optimal methods of monitoring patients with post-COVID conditions to detect adverse events, patient's lived experiences during rehabilitation and recovery from Post COVID conditions

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Type 1 Diabetes during COVID-19

Key Messages

- Incidence of new-onset type 1 diabetes has remained predominantly stable during the pandemic in children and youth.
- Rates of DKA in new-onset type 1 diabetes have increased during the pandemic as well as its severity in children and youth.

Recommendations

- Need for public and provider education/awareness campaign on symptoms of diabetes for earlier detection to type 1 diabetes in children and youth (Dzygalo et al. 2020; Dayal, 2020).

What is the incidence of in Type 1 diabetes during the COVID-19 pandemic?

Over the last two decades, there has been an increase in the incidence of type 1 diabetes (T1D) in children and youth (Mayer-Davis et al., 2017; Tittel et al., 2020). However, the incidence of T1D appears to have remained stable during the COVID-19 pandemic in children and youth. Specifically, research from Alberta, Canada across two tertiary care pediatric hospitals reported that the incidence of new-onset of T1D (10.6 per 100,000 persons in 2019 compared to 9.9 per 100,000 persons in 2020) has been stable (Ho et al., 2021). Similarly, literature from many other countries have reported that the incidence of new-onset pediatric T1D has been similar during the pandemic (in 2020) when compared to previous years (Alaqeel et al., 2021; Atlas et al., 2020; Lawrence et al., 2021; Tittel et al., 2020). There is a paucity of information of new-onset of T1D in adults.

Some public media reports have raised the query of a possible interplay between new-onset T1D and COVID-19; since literature has suggested a signal that COVID-19 infection in adults may be associated with new-onset diabetes (Rubino et al., 2020). However, at present there is insufficient evidence to comment on changes in incidence. Nevertheless, this is a line of ongoing inquiry and recent literature reviews have noted that a causal relationship is questionable (Atkinson & Powers, 2021; Drucker, 2021).

What are the rates of diabetic ketoacidosis at presentation with new onset of diabetes during the Covid-19 pandemic?

Several studies have shown that both diabetic ketoacidosis (DKA) rates at presentation of pediatric T1D have increased as well as rates for severe DKA (Ho et al., 2021; Kamrath et al., 2020; Sellers & Pacaud, 2021). Studies from across the globe, as well as Canada, have examined data from pediatric care centers and/or a registry and the reported rates of DKA at presentation of newly diagnosed pediatric T1D ranged from 26% to 73% during pandemic vs 13.4% to 45.6% pre-pandemic; indicating that presentation of DKA in newly diagnosed children with T1D increased during the COVID-19 period in 2020 (Alaqeel et al., 2021; Ho et al., 2021; Kamrath et al., 2020; Lawrence et al., 2021; Sellers & Pacaud, 2021). Similarly, the proportions of children and youth with severe DKA were notably higher during the pandemic and ranged from 19.4% to 48.3% in 2020 vs 5% to 37% pre-COVID-19 period (Ho et al., 2021; Kamrath et al., 2020; Lawrence et al., 2021; Sellers & Pacaud, 2021). Moreover, a recent study from the U.S. reported that the number of children with new-onset type 2 diabetes that presented with DKA had also increased since March 2020 than previous years (DKA increased from <10% in 2018–2019 to 20% in 2020 (Chao, Vidmar, & Georgia, 2021).

Some studies have found no variations in the rate of DKA and/or severity and new-onset T1D diagnosis pre- COVID-19 and during COVID-19 time periods in children and youth (Bogale,

Urban, Bangalore Krishna, & Schaefer, 2021; Rabbone, Schiaffini, Cherubini, Maffeis, & Scaramuzza, 2020). Taken together, there is evidence indicating the rate and severity of DKA has been heightened during the pandemic; however, the evidence is not unanimous.

Guidelines on the immediate assessment and management of DKA in children and youth can be found at Diabetic Ketoacidosis, Pediatric - Emergency and Inpatient (ahsnet.ca). The rate of DKA at presentation in new-onset diabetes in adults during COVID-19 is currently being investigated by international researchers who focus on diabetes and are developing a Global Registry of COVID-19-related diabetes (*CoviDiab Registry (e-dendrite.com)*.

What are the impacts of delayed presentation with new onset type 1 diabetes on the healthcare system?

During the COVID-19 pandemic, delayed presentation of new-onset T1D can result in preventing a timely diagnosis of T1D and prevention of DKA, including severe DKA (Cherubini et al., 2020; Dayal, 2021; Ho et al., 2021; Sherif et al., 2021). Several reasons that may have contributed to delayed presentation include concern of contracting COVID-19 at the hospital or urgent care; problems in accessing healthcare services due to the stay-at-home orders; and rejection by hospitals where clinical attention shifted to COVID-19 infections. Moreover, when seeking primary care appointments, potential barriers may have also involved: fewer face-to-face visits, redeployment of health care providers to COVID-19 related activities, misdiagnosis of diabetes symptoms, and reduced laboratory testing to decrease the burden on laboratory resources from COVID-19 (Ho et al., 2021); all suggesting missed opportunities for diagnosis.

Individuals with symptoms of T1D and/or DKA are guided by health care providers to seek immediate medical attention at emergency departments or urgent care. Management of DKA often requires hospitalization and possibly the intensive care unit. Notably, DKA is associated with increased length or stay, morbidity and mortality (Li et al., 2020; Nyenwe & Kitabchi, 2016) and thus causes a significant impact to individuals and families with a new diagnosis of T1D as well as to the health care system with already limited resources.

What are the pressing research questions related to your area of concern?

While the relationship between diabetes and COVID-19 is not well understood; further research of new-onset T1D during COVID-19 may include:

1) Additional qualitative studies that assess the reasons for delayed presentations of T1D to support both the public and health care providers to improve the prevention of severe presentation of T1D (Lawrence et al., 2021).
2) Improving our understanding of new-onset diabetes development during the pandemic and potential relationships of T1D, DKA, SARS-COV-2; and if a relationship exists explore possible mechanism(s) (Rubino et al., 2020; Suwanwongse & Shabarek, 2021). Currently there is a Global registry that is collecting data and investigating the phenotype, management and several short and long-term outcomes of new-onset COVID-19 -related diabetes *CoviDiab Registry (e-dendrite.com)*.
3) Understand the role of educational programs for prevention of DKA in the presentation of type 1 diabetes (Vanelli et al., 1999; Vanelli, Chiari, Lacava, & Iovane, 2007).

Authors

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