Since April 2021, there are increasing reports of cases of myocarditis and pericarditis after mRNA COVID-19 vaccination (Pfizer-BioNTech BNT162b2 vaccine and Moderna mRNA-1233 vaccine). In Canada, there have been a small number of these reports, but no conclusive association has been established between myocarditis/pericarditis and mRNA vaccines at this point. The Public Health Agency of Canada (PHAC), Health Canada and Public Health Ontario (PHO) are closely monitoring these rare events, including those among youth.

Based on the reports received, Health Canada and PHAC are not yet seeing higher rates of myocarditis/pericarditis than would normally be expected in the general population. To date, PHO has received reports of a small number of cases of myocarditis/pericarditis in the 12 to 17 age group in Ontario through the provincial surveillance of Adverse Event Following Immunization (AEFI).

Preventing the spread of COVID-19 remains extremely important, and COVID-19 vaccines continue to be recommended for all eligible individuals, including youth. Countries using mRNA vaccines in young adults and adolescents are continuing to recommend their use but are following the emerging evidence on this topic very closely as further information is obtained.

The benefits of the mRNA vaccines continue to outweigh their risks in the authorized populations, as there are clear benefits of mRNA vaccines in reducing deaths and hospitalizations due to COVID-19 infections.

This document aims to provide interim guidance based on consensus opinion for clinicians who will be assessing pediatric patients who develop myocarditis or pericarditis after mRNA COVID-19 vaccination and should not replace best clinical judgment. This document will be revised as further information on this condition is gained. The management and clinical decision algorithm can be found at the end of this document.

1. How should cases be identified?

International and national reports of myocarditis/pericarditis following vaccination with COVID-19 mRNA vaccines have emerged. These reports indicate that:

- Cases have been seen after the first dose of a COVID-19 mRNA vaccine, but are more commonly reported after the second dose
- Symptom onset was typically within several days after vaccination, with most cases being reported within 7 days after vaccination
- Cases were mainly adolescents and young adults
- Cases were more often males compared to females
- Cases experienced mild illness, responded well to conservative treatment and rest, and their symptoms improved quickly.

Myocarditis and pericarditis involve inflammation of the myocardium or the pericardium, respectively, in response to an infection or some other trigger. Symptoms can include shortness of breath, chest pain, or the feeling of a rapid or abnormal heart rhythm. Until further data is gathered and a definition for an Adverse Event of Special Interest for myocarditis/pericarditis following COVID-19 vaccination has been established, patients who develop pericarditis or myocarditis up to 42 days (6 weeks) after vaccination should follow this guidance and should be reported to public health. It should be noted that the peak incidence occurs 1-3 days after vaccination and up to 7 days; cases beyond this are expected to be rare and other diagnoses should be considered.
Pericarditis:

The diagnosis of acute pericarditis can be made in the presence of at least two of the following four criteria, as described in the European Society of Cardiology and American College of Cardiology Guidelines for Pericardial Disease:

1. Pericarditic chest pain (sudden in onset, retrosternal, and pleuritic exacerbated by inspiration)
2. Pericardial rub found at auscultation
3. ECG changes including widespread ST-segment elevation or PR depression
4. New or worsening pericardial effusion at echocardiogram

Some of the supportive findings also include an elevation of inflammatory markers (CRP, ESR, white blood cell count). However, it should be noted that most of the reported cases of pericarditis after mRNA vaccination have had normal or mildly elevated inflammatory markers, and therefore a normal CRP, ESR and/or CBC does not rule out this diagnosis.

Myocarditis:

Myocarditis can present as different clinical syndromes that range from mild chest pain with transient ECG changes to heart failure and cardiogenic shock. Patients who present dyspnea, pericarditic chest pain, diaphoresis and/or palpitations in the days following COVID-19 mRNA vaccination should be evaluated for a suspicion of myocarditis. The Brighton collaboration case definitions for definitive, probable and possible cases of myocarditis are detailed in Box 1 in the supplementary information.

Other features and association with MIS-C (Multisystem Inflammatory Syndrome in Children):

Based on the reports received, patients who developed myocarditis/pericarditis after COVID-19 mRNA vaccination do not seem did not present the features of MIS-C. However, given the paucity of data available currently, it is important to ensure that these patients do not present any signs and symptoms of MIS-C. These symptoms include persistent fever, abdominal pain, vomiting, diarrhea, neurological symptoms (including altered mental status, lethargy, encephalopathy, focal neurological deficits and meningismus), skin rash, mucocutaneous lesions and in some severe cases, hypotension and shock.

All patients presenting symptoms concerning for pericarditis or myocarditis in the following days after COVID-19 mRNA vaccination should be rapidly assessed in-person by a physician. An ECG and serum troponin I, as well as a complete blood count (CBC) and differential, CRP, sodium and albumin should be performed in all patients with a clinical suspicion of post-vaccination myocarditis or pericarditis, based on the symptoms and criteria detailed above. A nasopharyngeal swab for SARS-CoV-2 PCR should be considered in these patients, depending on the presenting symptoms. A blood culture and peripheral IV insertion should be performed in patients who present with fever.

Patients with normal ECG and normal troponins do not require any further investigations, activity modifications or follow up. However, cases with a high clinical suspicion of myocarditis or pericarditis who have normal troponins and a normal ECG may be reviewed with cardiology to ensure that further investigations are not required, on a case-by-case basis.

For patients with an abnormal ECG (as detailed below) and/or elevated troponins (≥100 ng/L) should be discussed with cardiology regarding the indication and the timing for an echocardiogram based on the clinical presentation and the screening test result that is abnormal. Patients should also be discussed with infectious
diseases regarding any further investigations that may be required on a case-by-case basis and to organize the outpatient follow-up at the Special Immunization Clinic. SARS-CoV-2 serology testing (anti-SARS-CoV-2 IgG and anti-nucleocapsid antibodies) should also be performed for all patients with a confirmed diagnosis of pericarditis and/or myocarditis, in discussion with infectious diseases and the microbiologist on-call. The COVID-19 biobank study team may be notified about these patients as appropriate for possible enrolment.

**ECG changes that may be seen in pericarditis:**
- Widespread concave ST elevation and PR depression throughout most of the limb leads (I, II, III, aVL, aVF) and precordial leads (V2-6)
- Reciprocal ST depression and PR elevation in lead aVR (± V1)
- Sinus tachycardia
- Low voltages

**ECG changes that may be seen in myocarditis:**
- Paroxysmal or sustained atrial or ventricular arrhythmias (premature atrial or ventricular beats, and/or supraventricular or ventricular tachycardia, interventricular conduction delay, abnormal Q waves, low voltages)
- AV nodal conduction delays or intraventricular conduction defects (atrioventricular block (grade I-III), new bundle branch block)
- ST segment and T waves changes
- Prolonged QRS
- QT prolongation
- Diffuse T wave inversion

Patients with a normal echocardiogram, regardless of the ECG findings and troponin levels, do not require any additional investigations **UNLESS there is fever and/or features of MIS-C**. If so, please follow recommendations for the MIS-C pathway for expanded investigations (see below and link). **There is no role for serial troponin monitoring in the setting of a normal echocardiogram.**

For patients with an **abnormal echocardiogram and who are admitted under cardiology**, infectious diseases and rheumatology should be consulted. Further investigations for causes of myocarditis for patients with borderline or mildly reduced heart function may be considered, as clinically indicated and in consultation with cardiology, rheumatology and infectious diseases (See box 2 in the supplementary information). **Routine serial troponin monitoring is not recommended except in rare instances in consultation with Cardiology.**

Patients with an abnormal ECG and/or elevated troponins **and with any features of MIS-C** as detailed above should be discussed with rheumatology, and management should be in accordance with the COVID-associated hyperinflammation / Kawasaki Disease pathway (**SickKids SharePoint**). In addition to the bloodwork detailed above, expanded bloodwork for COVID-associated hyperinflammation also includes the following:

- Potassium, creatinine, ALT, LDH
- NT-pro-BNP
- Fibrinogen, D-dimers, PTT, INR
- Ferritin, triglycerides, ESR
3. What management should be initiated?

Pericarditis:

In general, most cases of acute pericarditis are self-limited and respond to nonsteroidal anti-inflammatory agents (NSAIDs). In cases of mild pericarditis, ibuprofen can be started using the dosing below, and patients can be followed in an ambulatory setting as detailed in the following section.

Ibuprofen: 10 mg/kg/dose q8h x 1 week (max 600mg), then 7.5 mg/kg/dose q8h x 1 week (max 400mg), then 5 mg/kg/dose q8h x 1 week (max 200mg).

In some cases, colchicine may be considered on a case-by-case basis and in discussion with cardiology. Colchicine has been observed to be effective in relieving pain and preventing recurrent pericarditis. However, no data is currently available on its use in the context of pericarditis occurring after COVID-19 mRNA vaccination.

Admission for observation and further investigations in consultation with cardiology, infectious diseases and rheumatology should be considered in cases who present high and persistent fevers, evidence of a large pericardial effusion at echocardiogram, clinical evidence of cardiac tamponade, and in the absence of response to NSAIDs and/or colchicine.

Corticosteroid use should be avoided as a first-line option in children given their association with increased risk of recurrences of pericarditis. In discussion with cardiology, steroids may be considered in select cases as a second-line option in the absence of response to NSAIDs or colchicine.

Myocarditis:

The treatment of myocarditis should be decided on a case-by-case as it is guided by the severity of the presentation. For mild cases without decreased heart function or features of heart failure, NSAIDs may provide symptomatic relief and patients may be followed in an ambulatory setting. In general, most cases of myocarditis following COVID-19 mRNA vaccination that have been reported have been mild and have been shown to be responsive to NSAIDs.

More severe cases with decreased heart function or displaying features of heart failure, arrhythmia or other complications of myocarditis require hospitalization for observation, investigations and further treatments. These patients may require supportive therapy that should be determined by cardiology, including pain control, hemodynamic and/or respiratory support, heart failure management, arrhythmia management and anticoagulation.

Immunomodulatory treatment may be considered in certain cases as per institutional practice and will be recommended by cardiology as clinically indicated. Further investigations in cases of severe myocarditis requiring hospitalization should also be discussed in consultation with cardiology, rheumatology and infectious diseases (see box 2 in supplementary information).

4. What follow-up is required?

All suspected cases should be followed by their primary care physicians (PCP). Patients with a diagnosis of pericarditis should be followed by their PCP; some may warrant cardiology follow-up, but this will be determined by cardiology on a case-by-case basis. Patients with a confirmed diagnosis of myocarditis should also be followed by a cardiologist at an interval and frequency that will be determined by cardiology based on clinical severity and course.
Patients with a confirmed diagnosis of pericarditis should refrain from high intensity or competitive sports for 3-4 weeks or until resolution of symptoms (if sooner). Patients with a confirmed diagnosis of myocarditis may require a modification in exercise which will be recommended by cardiology on a case-by-case basis, including duration.

Every patient with a confirmed diagnosis of pericarditis and/or myocarditis following COVID-19 mRNA vaccination should also be referred to the Special Immunization Clinic (SIC) to be assessed by an infectious diseases specialist. The SIC physician will look to find the causality of the AEFI and the risk of recurrence upon revaccination for any vaccination, including for a second dose of an mRNA COVID-19 vaccine, if applicable. Currently, until further data are generated, the decision to administer further doses of an mRNA vaccine should be made on a case-by-case basis. Factors that may influence the decision to revaccinate include evidence of prior infection with SARS-CoV-2 (history of COVID-19 and/or positive anti-nucleocapsid antibodies), the severity of the myocarditis/pericarditis, an individualized benefit-risk analysis and a discussion with the patient and their family.\textsuperscript{16,17} The SIC physician will also submit cases of myocarditis and pericarditis following COVID-19 vaccines to the public health unit using the Ontario AEFI reporting form. Public Health Ontario (PHO) is monitoring this issue as part of enhanced COVID-19 vaccine safety surveillance and produces a weekly summary of all COVID-19 AEFIs in Ontario, including myocarditis/pericarditis.
Myocarditis and Pericarditis after Receipt of mRNA COVID-19 Vaccines – V2.0. June 30th, 2021
Box 1: Myocarditis Brighton Collaboration case definition

Level of certainty 1 – Definitive case
- Histopathologic examination of myocardial tissue showing myocardial inflammation OR
- Elevated troponins AND
- Abnormal heart imaging study
  - Abnormal echocardiogram* OR
  - Abnormal cardiac magnetic resonance study

Level of certainty 2 – Probable case
- Clinical symptoms with no alternative diagnosis AND
  - Cardiac symptoms (at least one) OR
    - Acute chest pain
    - Palpitations
    - Dyspnea after effort or lying down
    - Diaphoresis
  - Non-specific symptoms (at least two)
    - Fatigue
    - GI symptoms
    - Dizziness/syncope
    - Edema
    - Cough
- Testing supporting the diagnosis
  - Elevated troponins OR
  - Abnormal echocardiogram OR
  - Abnormal ECG**

Level of certainty 3 – Possible case
- Clinical symptoms with no alternative diagnosis AND
  - Cardiac symptoms (at least one) OR
    - Acute chest pain
    - Palpitations
    - Dyspnea after effort or lying down
    - Diaphoresis
  - Non-specific symptoms (at least two)
    - Fatigue
    - GI symptoms
    - Dizziness/syncope
    - Edema
    - Cough
- Biomarkers supporting evidence of inflammation (at least one) AND
  - Elevated CRP
  - Elevated ESR
  - Elevated D-Dimers
- Non-specific ECG abnormalities (at least one)
  - ST-segment or T-wave abnormalities
  - Premature atrial or ventricular complex
*Includes new focal or diffuse ventricular function abnormalities, segmental wall motion abnormalities, global systolic or diastolic function depression, ventricular dilation, wall thickness change, intracavitary thrombi.

**Includes ST-segment or T-wave abnormalities (elevation or inversion), paroxysmal or sustained atrial or ventricular arrhythmias (premature atrial or ventricular beats, and/or supraventricular or ventricular tachycardia, interventricular conduction delay, abnormal Q waves, low voltages), AV nodal conduction delays or intraventricular conduction defects (atrioventricular block (grade I-III), new bundle branch block) or continuous ambulatory electrocardiographic monitoring that detects frequent atrial or ventricular ectopy.

---

**Box 2: Expanded investigation to consider in the investigation of select cases of myocarditis / pericarditis**

These investigations may be sent in consultation with infectious diseases, cardiology and rheumatology. Other investigations may be required as deemed appropriate and based on exposure history.

- **Blood lab:**
  - CBC & differential, CRP, blood gas, lactate, glucose, creatinine, urea, albumin
  - Calcium total, ionized calcium, magnesium, copper, selenium, ammonium
  - Bilirubin (conjugated/unconjugated), alkaline phosphatase, ALT, GGT, AST
  - CK, NT-proBNP
  - Cholesterol, 25-Hydroxyvitamin D, TSH
  - Acylcarnitines, anti-nuclear antibody, ASOT, DNA banking

- **Viral serologies:**
  - Mycoplasma pneumoniae IgM antibody
  - Parvovirus B19 IgG & IgM
  - EBV serology
  - CMV IgG and IgM
  - Toxoplasma serology
  - Bartonella serology (as applicable, depending on exposure history)
  - HIV serology (depending on risk factors)

- **Other microbiological testing:**
  - Blood enterovirus PCR
  - Blood HSV/VZV PCR
  - Blood Adenovirus quantitative PCR
  - Blood parvovirus B19 PCR
  - Blood CMV/EBV/HHV6 PCR
  - Nasopharyngeal swab for respiratory virus multiplex PCR
  - Throat bacterial culture
  - Throat mycoplasma/Chlamydophila pneumoniae PCR
  - Stool (GI) multiplex PCR and enterovirus PCR
  - Tuberculin skin test (TST) or IGRA (as applicable, depending on exposure history)

* Please refer to the EPIC order set for myocarditis
For additional information on myocarditis and pericarditis following COVID-19 mRNA vaccination and other useful documents, please visit the following links:


Diagnosis and Treatment of Myocarditis in Children in the Current Era (American Heart Association): https://www.ahajournals.org/doi/10.1161/circulationaha.113.001372

Coronavirus Disease 2019 (COVID-19) Vaccines (Centers for Disease Control and Prevention): https://www.cdc.gov/vaccines/acip/meetings/slides-2021-06.html

This document has been created by members of the COVID-19 working group, the Division of Cardiology, the Division of Emergency Medicine, the Division of Infectious Diseases and the Division of Rheumatology at The Hospital for Sick Children:

- Cardiology – Dr Lee Benson, Dr Anne Dipchand, Dr Émilie Jean-St-Michel, Dr Aamir Jeewa, Dr Brian McCrindle, Dr Luc Mertens, Dr Michael Seed
- Emergency Medicine – Dr Adrienne Davis, Dr Trent Mizzi
- Infectious Diseases – Dr Upton Allen, Dr Shaun Morris, Dr Pierre-Philippe Piché-Renaud
- Rheumatology – Dr Rae Yeung

Important Information and Disclaimers About This Document:

This Practice Advisory is intended to offer guidance to healthcare professionals at The Hospital for Sick Children (“SickKids”). Any use of this document must be subject to the professional judgment of a patient’s attending physician, taking into consideration the patient’s specific circumstances and all other available information and standards. The Practice Advisory is NOT intended for use by patients and is not intended to constitute medical advice.

SickKids does not recommend or endorse any information, procedure, or product that may be mentioned in this Practice Advisory. New and emerging research and experience may result in changes to the information in this document. You assume full responsibility for the use of any information in the Practice Advisory and are responsible for ensuring that the materials are current. SickKids assumes no liability for inaccurate or incomplete information, nor any actions taken in reliance on this Practice Advisory, which is provided “as is” with no representations or warranties of any kind, express, statutory or implied.

©The Hospital for Sick Children. All Rights Reserved. This Practice Advisory may not be used for publication, distributed, or reproduced without the consent of SickKids.


