

Multisystem Inflammatory Syndrome in Children (MIS-C) Temporally Associated with COVID-19: Guidance for Clinicians in B.C.

Updated: December 8, 2020

What is multisystem inflammatory syndrome in children (MIS-C)?

Multisystem inflammatory syndrome in children (MIS-C) is a newly described rare condition associated with COVID-19. Evidence supports that MIS-C is a post-infectious illness, occurring between two to six weeks following SARS-CoV-2 infection. A preliminary case definition has been developed by the World Health Organization and amended for use in B.C. (see Appendix A).

What are the features of MIS-C?

Children with MIS-C present with symptoms of systemic inflammation, and can have clinical similarities to Kawasaki disease, toxic shock syndrome and macrophage activation syndrome. Prominent features include fever, abdominal pain, vomiting, diarrhea, mucosal inflammation (e.g., conjunctival erythema), rash, and cardiac involvement. Respiratory and neurological symptoms are seen in a minority of patients. Abnormal inflammatory, cardiac, renal and coagulative markers are typical laboratory findings. Reported echocardiogram findings include depressed ejection fraction and coronary abnormalities. There may be a spectrum of disease severity and phenotypes in children affected by COVID-19-associated inflammation.

When to consider MIS-C?

Appendix B shows a sample algorithm for evaluating a child with features that could be in keeping with MIS-C. There should be a low threshold to consider and evaluate for MIS-C in children who present with an acute inflammatory illness within two months following a known COVID-19 infection or exposure, even if they are well-appearing on initial presentation. Children with unexplained fever and inflammation (elevated white blood cell count, C-Reactive Protein), and those in early phases of an acute COVID-19 illness should be followed closely for progression of their illness. The initial infection with SARS-CoV2 may have been asymptomatic, therefore MIS-C should still be considered in children without a previous history of infectious or respiratory symptoms.

Consider sepsis and other serious illnesses

When evaluating patients for MIS-C, consider sepsis and other life-threatening infections (e.g, toxic shock syndrome) whose clinical presentations overlap with MIS-C. Evaluation for MIS-C



should not delay empiric antibiotic coverage in patients whose clinical picture may be consistent with a serious bacterial infection. Bacterial sepsis can lead to similar laboratory abnormalities as those seen in MIS-C, including abnormal cardiac and coagulative parameters (e.g., elevated brain natriuretic peptide and d-dimer levels). These infections may also occur in children with recent COVID-19. Additionally, other serious pediatric illnesses (e.g., leukemia, systemic onset juvenile idiopathic arthritis, among others) can present with fever and signs of systemic inflammation, and should also be considered in the differential diagnosis.

What is the general approach for patients with possible MIS-C?

Children with possible MIS-C require evaluation by a pediatric specialty team experienced in the diagnosis of Kawasaki Disease and other inflammatory conditions of childhood.

Consultation with pediatric rheumatology, cardiology, infectious disease, and critical care is recommended, ideally at a tertiary pediatric centre. Evidence for the optimal management of MIS-C is evolving and should be guided by pediatric subspecialists caring for MIS-C patients, with consideration given to early use of Intravenous immunoglobulin and other immunomodulatory therapies as indicated. Care may involve serial monitoring of clinical and laboratory parameters, cardiac imaging, therapies targeting inflammation, and close follow up post-discharge (see Appendix B). Children admitted to a general pediatrics ward for MIS-C require close monitoring for clinical deterioration. Affected patients can become critically ill quickly and there have been deaths reported. In addition, confirmed cases warrant consultation with hematology for guidance on whether anticoagulation is indicated.

If you have a possible case of MIS-C, page the infectious diseases or rheumatology physician on call at BC Children's Hospital for further discussion and triaging. If cardiac imaging is needed, liaise with the pediatric cardiologist at BC Children's Hospital. Both specialists can be reached through central paging at 1-604-875-2000. These providers can help make informed decisions with you regarding whether a child needs urgent cardiac evaluation, or whether they may be safely monitored at their local institution.

Cases of MIS-C are reportable under the Reporting Information Affecting Public Health Regulation and *Public Health Act*. Please contact your local medical health officer to report cases of MIS-C. They can provide guidance regarding further testing required to confirm COVID-19 and liaise with the consultant pediatric specialists. They can be reached through your local public health department or hospital switchboard.



Appendix A: Case Definition for MIS-C

Person under investigation

Children 0-19 years of age with fever ≥ 3 days

And two of the following:

- a) Acute gastrointestinal symptoms (abdominal pain, vomiting, diarrhoea)
- b) Rash or bilateral non-purulent conjunctivitis or muco-cutaneous inflammation signs (oral, hands or feet)
- c) Hypotension or shock
- d) Features of myocardial dysfunction, or pericarditis, or valvulitis, or coronary abnormalities: ECHO findings or elevated troponin/ brain natriuretic peptide (BNP)/ Natriuretic peptide tests (NT-proBNP)
- e) Evidence of coagulopathy: abnormal prothrombin time/ partial thromboplastin time (PT/PTT), elevated d-dimer

And

Elevated markers of inflammation such as erythrocyte sedimentation rate, C-reactive protein, or procalcitonin

And

No other obvious microbial cause of inflammation, including bacterial sepsis, staphylococcal or streptococcal shock syndromes and no alternative plausible obvious diagnosis

Confirmed case

Meets criteria for a MIS-C person under investigation

And

Evidence of SARS-CoV-2 infection (positive PCR test or serology), or close contact¹ with a confirmed or probable (lab-probable or epi-link probable) COVID-19 case²

¹ Close contacts include individuals who lived with or had close contact (within 2m) with a COVID-19 case for more than 15 minutes up to 48 hours prior to symptom onset. See a full definition of close contacts here:

http://www.bccdc.ca/resource-gallery/Documents/Guidelines%20and%20Forms/Guidelines%20and%20Manuals/Epid/CD%20Manual/Chapter%201%20-%20CDC/2019-nCoV-Interim_Guidelines.pdf

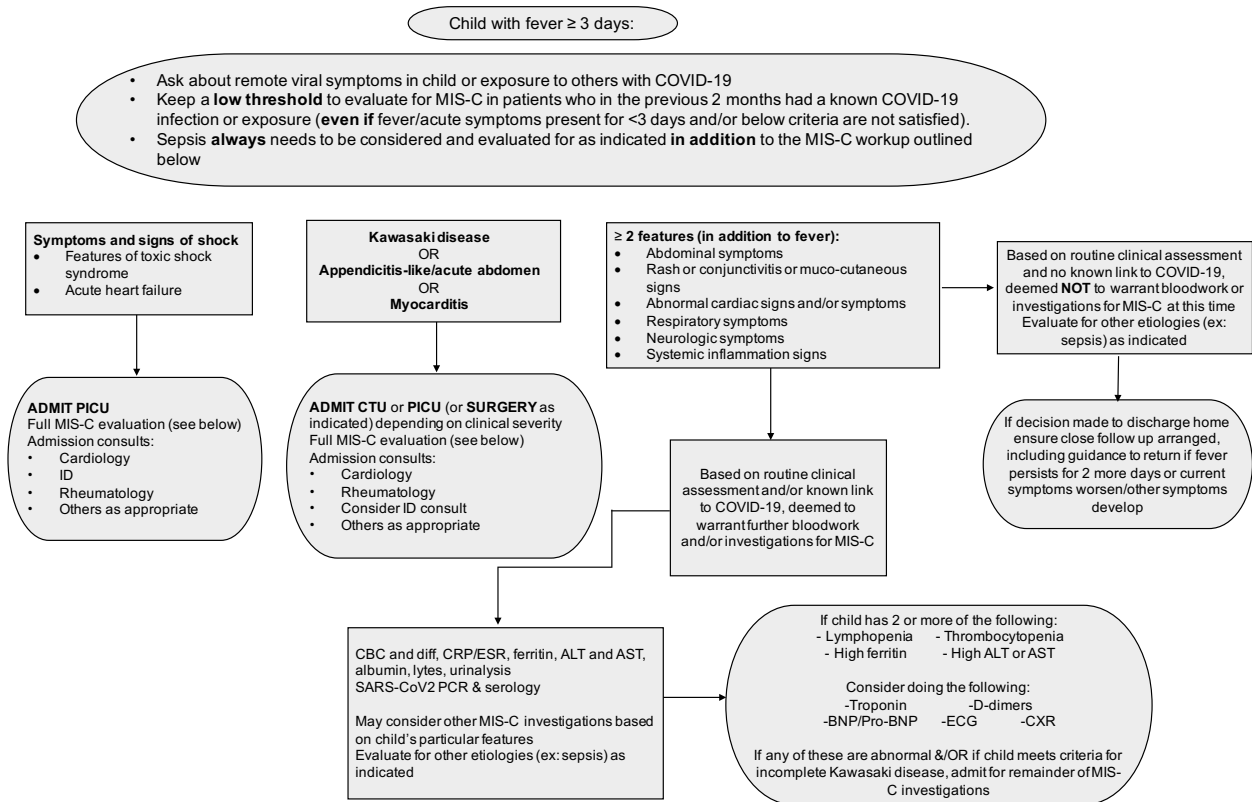


² Confirmed and lab-probable cases have positive or indeterminate NAAT results, respectively. COVID-19 cases are further defined here: [http://www.bccdc.ca/health-professionals/clinical-resources/case-definitions/covid-19-\(novel-coronavirus\)](http://www.bccdc.ca/health-professionals/clinical-resources/case-definitions/covid-19-(novel-coronavirus))



Appendix B: Sample algorithm for evaluation of a patient with possible MIS-C. See reference sections for alternative published evaluation/management pathways for MIS-C.

To be performed in addition to routine (including infectious) workup. This document provides guidance for the identification of and investigations for MIS-C only. It **DOES NOT** include the work-up and management of other entities on the differential diagnosis, including **sepsis**, which still need to be considered and managed according to clinical judgment.



+Full MIS-C evaluation:

- Complete Blood Count (CBC) with differential
- Erythrocyte sedimentation rate (ESR), C-reactive protein (CRP)
- Electrolytes, blood urea nitrogen (BUN), creatinine
- Liver function tests (LFTs), Lactate dehydrogenase (LDH), albumin
- Ferritin, d-dimer, prothrombin time/ partial thromboplastin time (PT/PTT)
- Troponin, brain natriuretic peptide (BNP)
- Urinalysis
- SARS-CoV-2 testing:
 - SARS CoV-2 polymerase chain reaction (PCR): respiratory (nasopharyngeal swab/saline gargle/ sputum/ bronchoalveolar lavage)
 - SARS CoV-2 serology: obtain pre-IVIG (pre-intravenous immunoglobulin)



whenever possible; contact local medical microbiology on call for approval.

- Type and Screen (for those receiving IVIG)
- Electrocardiogram (EKG)
- Chest X-ray (CXR)
- Echocardiogram
- **Consider** all usual bacterial or viral illnesses and alternative diagnoses and test as appropriate (ex: cultures, other infectious studies).

Patient Presentation with Clinical Suspicion of COVID-19 MIS-C	
Systemic Inflammation <ul style="list-style-type: none"> • Myalgias • Tachycardia • Hypotension • Hypoperfusion or hyperperfusion • Lymphadenopathy/lymphadenitis 	Cardiopulmonary <ul style="list-style-type: none"> • Respiratory distress • Chest Pain
Mucocutaneous <ul style="list-style-type: none"> • Rash: reticular, morbiliform, purpuric • Lip swelling/cracking • Strawberry tongue • Extremity swelling/peeling • Conjunctivitis • Blisters or erosions 	Neurologic <ul style="list-style-type: none"> • Headache • Altered mental status • Meningismus • Focal deficits • Seizure
Gastrointestinal <ul style="list-style-type: none"> • Nausea/vomiting • Diarrhea • Abdominal Pain 	

Adapted from: NY Presbyterian / Columbia University guidance document

For further clinical guidance on COVID-19 in children, see [Clinical Reference Group Recommendation: Pediatric Clinical Guidance for COVID-19](#).



Resources:

BCCDC Pediatric Clinical Guidance for COVID-19:

http://www.bccdc.ca/Health-Professionals-Site/Documents/COVID-19_Pediatric_clinical_guidance.pdf

American College of Rheumatology Clinical Guidance for Multisystem Inflammatory Syndrome in Children Associated With SARS–CoV-2 and Hyperinflammation in Pediatric COVID-19 including diagnostic pathway and treatment algorithm for MIS-C:
<https://onlinelibrary.wiley.com/doi/epdf/10.1002/art.41454>

Canadian Pediatric Society Practice Point on MIS-C (referred to as Pediatric Inflammatory Multisystem Syndrome in document):
<https://www.cps.ca/documents/position/pims>

World health organization scientific brief on multisystem inflammatory syndrome in children and adolescents with COVID-19:
<https://www.who.int/publications-detail/multisystem-inflammatory-syndrome-in-children-and-adolescents-with-covid-19>

Royal College of Paediatrics and Child Health UK Guidance on pediatric multisystem inflammatory syndrome temporally associated with COVID-19:
<https://www.rcpch.ac.uk/sites/default/files/2020-05/COVID-19-Paediatric-multisystem-%20inflammatory%20syndrome-20200501.pdf>

CDC guidance on MIS-C with alternative case definition:
<https://emergency.cdc.gov/han/2020/han00432.asp>

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Preliminary guidance for clinicians in British Columbia about:
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