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

July 5, 2021

This guidance is intended for health-care providers. It is based on known evidence as of June 8, 2021.

Summary of Key Changes in This Update

1. Updates to features of MIS-C based on recent literature.
2. Minor changes to consideration of other disease entities.
3. Updates to treatment and management of MIS-C.
4. Addition of the B.C. Working Group's MIS-C email address for reporting purposes.
5. Addition of recommendations for disposition planning.
6. Addition of serology request form link in appendix B.

What is Multisystem Inflammatory Syndrome in Children (MIS-C)?

Multisystem inflammatory syndrome in children (MIS-C) is a 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 child can develop MIS-C regardless if their acute infection was asymptomatic or symptomatic.

What are the Features of MIS-C?

The case definition of a person under investigation or a confirmed case of MIS-C used in B.C. is adapted from the case definition developed by the World Health Organization (see appendix A).

There is likely a spectrum of disease severity and phenotypes in children affected by MIS-C. However, the majority of children with MIS-C are usually sick enough to require hospitalization and, often, intensive care. Children with MIS-C may initially present with mild symptoms, which can progress quickly. Presenting symptoms usually reflect systemic inflammation and often have similarities to Kawasaki disease (KD), toxic shock syndrome (TSS) and macrophage activation syndrome. Prominent features include:

- Kawasaki-like symptoms: Polymorphous rash, bilateral non-purulent conjunctivitis, cracked lips, strawberry tongue, peripheral extremity changes, cervical lymphadenopathy.
- TSS-like symptoms: Shock/haemodynamic instability, sunburn like rash.
- Gastrointestinal symptoms: Abdominal pain, vomiting, diarrhea.
- Neurologic symptoms: Headache, seizures, meningismus, focal neurological deficits.
- Cardiac symptoms: Dysfunction, myocarditis.
- Respiratory symptoms (less common).

Common laboratory abnormalities include:

- Neutrophilia.
- Lymphopenia.
- Thrombocytopenia.
- Elevated markers of inflammation (e.g., C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), ferritin).
- Evidence of coagulopathy: Elevated D-dimer, international normalized ratio (INR), partial thromboplastin time (PTT).
- Elevated cardiac markers: Troponin and brain natriuretic peptide (BNP).
- Transaminitis.
- Elevated creatinine.

Some laboratory values may be normal on presentation but can worsen if the child has clinical progression. Reported echocardiogram findings include depressed ejection fraction and coronary artery abnormalities.

MIS-C can affect children of any age but typically affects those older than seven years old. This is in contrast to the typical age group affected by classic KD which is under 5 years old. When compared to children with

severe acute COVID-19, children with MIS-C were more likely to be in the six to 12 year old age group. Many cases of MIS-C have disproportionately affected children of Black, Hispanic or South Asian ethnicity. It is unclear if this is related to a genetic susceptibility or to socioeconomic risk factors. Most children with MIS-C will not have co-morbidities.

When to Consider MIS-C?

There should be a low threshold to consider and evaluate for MIS-C in children who present with unexplained fever for three days or more, even if they are well-appearing on initial presentation and especially within two months following a known COVID-19 infection or exposure. 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 symptoms.

Consider sepsis and other serious illnesses

When evaluating patients for MIS-C, clinicians should always consider other overlapping diagnosis, especially sepsis. Bacterial sepsis can lead to similar laboratory abnormalities as those seen in MIS-C, including abnormal inflammatory, cardiac and coagulative parameters. **Evaluation for MIS-C should not delay empiric antibiotic administration** in patients whose clinical picture may be consistent with a serious bacterial infection.

Other overlapping diagnosis include severe acute COVID-19 infection, KD, TSS, viral illness, malignancies and inflammatory rheumatological conditions. Similar to TSS and severe acute COVID-19, children with MIS-C can present with multi-organ dysfunction and respiratory distress. When compared to classic KD, children with MIS-C are more likely to present with shock, cardiac dysfunction and gastrointestinal symptoms. Children who present with rash and/or meningo-encephalitic symptoms should be prescribed antivirals if clinically indicated.

What is the General Approach for Patients with Possible MIS-C?

General management

Children with MIS-C may appear well initially but can deteriorate within hours to days. Providers should be vigilant around the potential of MIS-C and, if suspicious, should proceed with the work-up outlined in appendix B in addition to any other relevant investigations for overlapping diagnosis. Caregivers of children who appear well and are therefore discharged should be counselled about symptoms of MIS-C and to return to the emergency department if they worsen, do not improve within 48 hours or fever does not abate after five days.

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. Clinicians outside of BC Children's Hospital (BCCH) who are caring for children with possible MIS-C requiring hospitalization should consult the paediatric or the critical care team on call at BCCH for consultation and to potentially facilitate

transfer to BCCH. **Children with possible MIS-C require evaluation by a pediatric specialty team experienced in the diagnosis of KD and other inflammatory conditions of childhood.** Consultation with pediatric rheumatology and infectious disease is recommended if querying MIS-C. If cardiac imaging is needed outside of BCCH, liaise with the pediatric cardiologist at BCCH. Any of these specialists can be reached through central paging at 1-604-875-2000 or toll free 1-888-300-3088.

Confirmed cases warrant consultation with hematology for guidance on whether anticoagulation is indicated. **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 be reached through your local public health department or hospital switchboard. Clinicians should also report MIS-C cases to the B.C. MIS-C working group by emailing MISC@cw.bc.ca.

Treatment

The management of MIS-C differs from that of severe acute COVID-19. Severe acute COVID-19 infection remains rare in pediatrics and any suspected cases of COVID-19 should be discussed with specialists at BCCH as this is a separate entity from MIS-C but may require active therapy.

Evidence for the optimal management of MIS-C should be guided by these specialists. The majority of children require early fluid resuscitation. The mainstay of treatment has been early use of intravenous immunoglobulin (IVIg) with or without intravenous steroids. Some children have required immunomodulatory therapy (biologic treatments) for refractory symptoms as guided by a rheumatologist. Low dose aspirin is recommended in children with MIS-C who have features of KD or coronary aneurysms seen on echocardiogram, in consultation with rheumatology. Even with treatment, children with MIS-C require serial monitoring of clinical and laboratory parameters, cardiac imaging and close follow up post-discharge (see disposition section).

Disposition

All follow up appointments should be made and clearly communicated to families prior to discharge. Discharge documentations should be sent to all relevant specialist involved in the patient's care. The long-term sequalae of MIS-C is still unknown but being studied.

- **Primary care provider:** All patients evaluated for MIS-C should be seen by their primary care provider within one week of discharge, regardless if they were a confirmed case or not.
- **Pediatrics:** Children hospitalized with MIS-C should be referred to a pediatrician on discharge for follow up. For those with abnormal inflammatory markers or laboratory findings at discharge, repeat bloodwork should be considered prior to this visit.
- **Cardiology:** Confirmed cases of MIS-C will require a repeat echocardiogram, typically four to six weeks after discharge, as guided by cardiology.
- **Rheumatology:** Follow up will depend on the severity of illness and discharge medications, as guided by rheumatology.

- **Haematology:** For children who were started on prophylactic/therapeutic anticoagulation in hospital, the dose and duration of therapy should be clearly communicated to the family prior to discharge, if applicable. Follow up will be guided by haematology.
- **Mental health:** Families with children who were hospitalized for MIS-C should be offered mental health support in the community as needed.
- **Others:** Follow up with other specialties (e.g., neurology, immunology) will depend on their clinical features and course in hospital.
- **Return to emergency department:** Families should be counselled on when to bring their child back to the emergency department. Reasons to return include:
  - Persisting fever > 38 degrees Celsius.
  - Recurrence of presenting symptoms or child becomes unwell with other symptoms.
  - New appearance of respiratory distress or shortness of breath.

Appendix A: Case Definition for MIS-C

Confirmed case

Children 0-19 years of age requiring hospitalization with fever for three days or more **and two** of the following:

a) Acute gastrointestinal symptoms (abdominal pain, vomiting, diarrhea);
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;

And
Evidence of SARS-CoV-2 infection (positive NAAT test, antigen test and/or serology) or close contact[1] with a confirmed or probable (lab-probable or epi-link probable) COVID-19 case.[2]

[1] Close contacts include individuals who lived with or had close contact (within two metres) with a COVID-19 case for more than 15 minutes up to 48 hours prior to symptom onset. Refer to the BCCDC for a full definition of close contacts.
[2] Refer to the BCCDC for further information on confirmed and lab-probable COVID-19 cases.

Appendix B: Full MIS-C Evaluation

To be performed in addition to workup of alternative diagnosis, including sepsis.

- 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 CoV2 antigen
    - SARS CoV-2 serology: Contact local medical microbiology on call for approval and fill out serology request form. Obtain serology pre-IVIG whenever possible.
- 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 (e.g., cultures, other infectious studies).

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.

American College of Rheumatology Clinical Guidance for Multisystem Inflammatory Syndrome in Children Associated With SARS–CoV-2 and Hyperinflammation in Pediatric COVID-19.

Canadian Paediatric Society Practice Point on MIS-C (referred to as Pediatric Inflammatory Multisystem Syndrome in document).

World Health Organization Scientific Brief on Multisystem Inflammatory Syndrome in Children and Adolescents with COVID-19.

Royal College of Paediatrics and Child Health Guidance on Paediatric Multisystem Inflammatory Syndrome Temporally Associated with COVID-19.

CDC Guidance on MIS-C with Alternative Case Definition.