MULTI-SYSTEM INFLAMMATORY SYNDROME IN CHILDREN TEMPORALLY ASSOCIATED WITH COVID-19: INPATIENT WORKFLOW

DOCUMENT TYPE: GUIDELINE

Site Applicability

BC Children's Hospital – Inpatient Units

Guideline Statements

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.

Patients admitted to Pediatric Intensive Care Unit (PICU)

Isolation

Based on particular clinical features of the patient, please isolate as per routine PHSA IPAC guidelines which can be found at http://policyandorders.cw.bc.ca/ipac.

Resuscitation

Resuscitation with fluids should be provided rapidly if there is hemodynamic instability as most instability is likely to be fluid responsive and vasodilatory in nature, however because of the possibility of systolic cardiac compromise, monitor for signs and symptoms of fluid overload closely (new crackles, hepatomegaly, dilated cardiac silhouette). If shock is fluid-refractory, obtain echocardiogram early with early institution of inotropes as indicated.

Sepsis

Given the differential diagnosis of MIS-C patients includes sepsis, refer to the PICU Severe Sepsis or Septic Shock Order Set

Empiric antibiotic coverage: refer to BCCH Empiric Antibiotic Guide –
< 4 weeks old: Ampicillin + (Gentamicin or Cefotaxime) + Acyclovir*
> 4 weeks old: Cefotaxime +/- Vancomycin +/- Acyclovir (if neurologic abnormalities present)*
*If features of Toxic Shock syndrome present, add Clindamycin

Neurologic assessment

The following neurologic findings have been reported in children with MIS-C:

- Altered mental status (irritability, lethargy)
- Nuchal rigidity
- Aseptic meningitis
- Cerebral edema
- Cranial nerve palsies

Assessment of patient should include:

- History (if possible) of headache, neck stiffness, altered mental status, vision impairment, smell and/or taste impairment, balance/coordination problems, syncope
- Physical exam including mental status including GCS, cranial nerve exam (pupils, extraocular movements, cough/gag, bulbar function), strength in all 4 extremities, nuchal rigidity, finger- nose finger, gait (if possible)

If abnormal findings on neurologic exam, consider neurology consult, CSF sampling, EEG and brain imaging.

Consults

Consult Rheumatology, Cardiology, Infectious Diseases. **Early consultation** with rheumatology and infectious diseases is of particular importance to guide early treatment decisions and to ensure other infectious etiologies on differential have been ruled out. Consult Hematology with question of thromboprophylaxis in patients hospitalized for COVID-19, including those with MIS-C. Consider other services depending on patient's clinical features.

After initial consultation with cardiology, update the on-call cardiology team for relevant changes in the patient's status, including new/worsening cardiac laboratory or electrocardiogram abnormalities, concerns regarding cardiac clinical status, or when the diagnosis of MIS-C is confirmed.

MIS-C is associated with a high rate of severe/critical illness, and patients may experience mental health symptoms (ex: post-traumatic stress symptoms) that persist after discharge. Consider Psychology/Social work referral for inpatient cases, with goal of initiating support while in hospital to prevent or lessen acute mental health symptoms, and ensure appropriate resources are in place for family and community providers once the patient is discharged.

Investigations

The differential diagnosis of these patients includes infection, Kawasaki Disease, myocarditis and other inflammatory conditions, etc. Obtain relevant investigations based on clinical judgement of the patient's features (including cultures, imaging, etc.).
In addition to full work up for possible infection and alternative diagnoses, ensure Full MIS-C Evaluation complete:

- CBC with differential
- ESR, CRP
- Electrolytes, BUN, creatinine
- LFTs (AST, ALT, GGT, bilirubin), LDH, Albumin, lactate
- Ferritin, d-dimer, PT/PTT
- Troponin, BNP
- Urinalysis
- SARS-CoV2 testing:
  - SARS CoV2 PCR: respiratory (nasopharyngeal swab/saline gargle/sputum/BAL)
  - SARS CoV2 serology: obtain pre-IVIG whenever possible; contact medical microbiology on call for approval: if serology approved complete a SARS-CoV2 serology request form (available on ePOPs) and send by secure email to misc@cw.bc.ca. Serology not available publicly in BC (as of May 26, 2020) but will be performed for this indication.
- Type and screen (for those receiving IVIG)
- EKG
- CXR
- Echocardiogram
- **Consider** all usual bacterial or viral illnesses and alternative diagnoses and test as appropriate (ex: cultures, other infectious studies).

Additional biobanking of patient samples

This process will involve obtaining verbal or written consent from family prior to collection of extra tubes of blood for BioBanking/research, and if feasible, should occur prior to IVIG or other immunomodulatory therapies.Contact the BioBank team to coordinate blood sample collection:

- If Monday to Friday 9-5 call local 7497 and if no one answers, leave a message and page (604-877-3796). If after hours email: biobank@cw.bc.ca

Medications

- Antibiotics (see Sepsis section above). Given overlapping features of MIS-C with serious bacterial infections and toxic shock, infectious diseases should also be consulted to guide empiric antibiotic treatment when indicated.
- Immune-modulating and anti-inflammatory therapies:

  These could include IVIG, Steroids, Aspirin, biologic agents such as Anakinra or Tociluzumab. **Decisions regarding the use of any of these agents should be made in consultation with Rheumatology.** Based on recent literature supporting early use of adjunctive steroids in addition to IVIG in MIS-C, **Rheumatology should be consulted once the diagnosis is suspected** so this treatment can be instituted promptly in appropriate cases.
- Anticoagulation

  Registry data suggests an increased risk of symptomatic venous thromboembolism in patients with MIS-C. Decisions regarding anticoagulation should be made in discussion with hematology, taking into account the patient's age and risk factors for thrombosis based on guidelines. It is therefore recommended to consult hematology with question of thromboprophylaxis in patients hospitalized for COVID-19 or MIS-C.
- Antiviral medications

  Not routinely recommended in patients with suspected MIS-C.

Ongoing monitoring

Clinical response

- Resolution of shock, neurologic impairment, any other clinical features; AND improving markers of inflammation including fever.
- Lack of clinical response within the first 36-48 hours: Consider further immunomodulator as per Rheumatology recommendation

Laboratory testing

The following are recommended daily for the monitoring of hyperinflammation while patients have evidence of shock and/or fever and /or persistence of symptoms:

- CBC and diff
- CRP
- PT/PTT/INR
- D-dimer
- Troponin
- Ferritin
- LDH
- BNP
- Lactate
- SARS-CoV2 serology: if patient is admitted for more than 5 days and initial SARS-CoV2 serology was negative, send repeat SARS-CoV2 serology.

Follow-up Echocardiogram

Frequency of follow-up echocardiograms will depend on patient's particular clinical features and should be guided by Cardiology.

**IMPORTANT: MIS-C is a reportable condition in BC. Suspected cases seen at BCCH must have a serology case requisition form emailed to misc@cw.bc.ca, after receiving approval for serology from the medical microbiologist on call. If this form is not completed, then it will be the responsibility of the MRP to ensure the case gets reported to the medical health officer.

If patient being discharged home from PICU, please refer to "Discharge criteria instructions and Follow-up Plan" section at the end of this document.

Patients admitted to ward

Isolation

Based on particular clinical features of the patient, please isolate as per routine PHSA IPAC guidelines which can be found at http://policyandorders.cw.bc.ca/ipac.

Close monitoring of clinical stability

Patients with MIS-C have been found to deteriorate rapidly from a hemodynamic standpoint. Monitor vital signs frequently to assess stability, need for fluid resuscitation and need for elevation of care.

Consults

Consult Rheumatology, Infectious Diseases and Cardiology. **Early consultation** with rheumatology and infectious diseases is of particular importance to guide early treatment decisions and to ensure other infectious etiologies on differential have been ruled out. Consult Hematology with question of thromboprophylaxis in patients hospitalized for COVID-19, including those with MIS-C (see Anticoagulation section below). Consider other services based on clinical features.

After initial consultation with cardiology, update the on-call cardiology team for relevant changes in the patient's status, including new/worsening cardiac laboratory or electrocardiogram abnormalities, concerns regarding cardiac clinical status, or when the diagnosis of MIS-C is confirmed.

MIS-C is associated with a high rate of severe/critical illness, and patients may experience mental health symptoms (ex: post-traumatic stress symptoms) that persist after discharge. Consider Psychology/Social work referral for inpatient cases, with goal of initiating support while in hospital to prevent or lessen acute mental health symptoms upon discharge, and ensure appropriate resources are in place.

Investigations

It is imperative that clinicians give due consideration to sepsis and other life-threatening infections whose clinical presentations overlap MIS-C. Having MIS-C on the differential diagnosis **should not delay** empiric antibiotic coverage in patients whose clinical picture may be in keeping with a serious bacterial infection.

The differential diagnosis of these patients includes infection/sepsis, other inflammatory conditions, etc. Obtain relevant investigations based on clinical judgement of the patient's features (including blood culture for any patient with fever or concern of sepsis).

In addition to full work up for possible infection and alternative diagnoses, ensure Full MIS-C Evaluation complete:

- CBC with differential
- ESR, CRP
- Electrolytes, BUN, creatinine
- LFTs (AST, ALT, GGT, bilirubin), LDH, Albumin, lactate
- Ferritin, d-dimer, PT/PTT
- Troponin, BNP
- Urinalysis
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- EKG
- CXR
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Medications

- Immune-modulating and anti-inflammatory therapies:

  These may include IVIG, Steroids, Aspirin, Anakinra or Tocilizumab.

  - **Decisions regarding the use of any of these agents should be made in consultation with Rheumatology.**
  - Based on recent literature supporting early use of adjunctive steroids in addition to IVIG in MIS-C, **Rheumatology should be consulted once the diagnosis of MIS-C is suspected** so this treatment can be instituted promptly in appropriate cases. In patients preparing for transfer to BCCH from outside sites, discuss with Rheumatology whether treatment with steroids +/- IVIG should be initiated emergently prior to transfer.
  - For patients with typical Kawasaki Disease, the first dose of IVIG can be given by CTU. For doses and monitoring, refer to the BCCH KD Order Set. Consult rheumatology within 24 hours of admission, regardless of treatment effect.
  - For incomplete KD or other cases of suspected MIS-C, consult rheumatology prior to initiation of any treatment, as described above.

- **Antibiotics**

  Patients with bacterial sepsis can be easily mistaken for MIS-C based on overlapping clinical features. Bacterial sepsis can lead to similar laboratory abnormalities as those seen in MIS-C, including abnormal cardiac and coagulative parameters (ex: elevated BNP and d-dimer levels). These infections may occur in children with recent COVID-19. For patients presenting with fever and signs of severe illness/shock, strong consideration should be given to using empiric antibiotics, even when MIS-C is considered likely, until infection has been ruled out. Decisions regarding choice of antibiotics should be made based on presenting features and potential infectious etiologies being considered, in consultation with infectious diseases. Prior to initiating antibiotic therapy, obtain appropriate cultures.

- **Anticoagulation**

  Registry data suggests an increased risk of symptomatic venous thromboembolism in patients with MIS-C. Decisions regarding anticoagulation should be made in discussion with

hematology, taking into account the patient's age and risk factors for thrombosis. Hematology should be consulted for patients with confirmed MIS-C or in whom the condition is considered high on the patient's differential diagnosis.

- **Antiviral medications**

  Not routinely recommended in patients with suspected MIS-C.

Ongoing monitoring

Clinical response

- Resolution of fever, other clinical features and improving markers of inflammation
- Lack of clinical response within the first 36-48 hours: Consider further immunomodulation as per Rheumatology recommendation

Laboratory testing

Daily lab monitoring should be guided by Rheumatology recommendations.

The following may be considered for the monitoring of hyperinflammation while patients have evidence of fever and /or persistence of symptoms:

- CBC and diff
- CRP
- PT/PTT/INR
- D-dimer
- Troponin
- Ferritin
- LDH
- BNP
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Discharge criteria Instructions and Follow-up Plan

Discharge criteria

These will vary depending on the clinical scenario and severity of presenting illness but generally should include:

- Lack of fever for 48 hours without antipyretics (excluding steroids)
- Improvement in the presenting clinical symptoms (e.g. diarrhea, rash, etc.)
- Improvement in lab markers
- If during influenza season, patient should receive influenza vaccination prior to discharge if not already received

Particular considerations:

- Patients on Aspirin (ASA) – the continuation of this medication should be guided by Rheumatology and Cardiology. They should avoid NSAIDS while on ASA.
- Patients who received Steroids during admission – A tapering schedule should be established prior to discharge based on guidance from Rheumatology.

- Patients who received IVIG – should not receive live virus vaccines for 11 months

Outpatient Follow-up

- General Pediatrics – follow up with pediatrician or family physician within 1 week of discharge. The discharge summary should include a summary of investigations and reasons to return (see below). The follow up physician should be copied.
  Cardiology – follow-up with repeat echocardiogram, the timing of which will depend on patient's particular clinical features and should be guided by Cardiology.
- Patients with suspected MIS-C whose PCR and serologic testing was negative during admission should receive a lab requisition at the time of discharge to have serology repeated roughly 4-6 weeks from admission, or when they return to BCCH for their scheduled cardiology appointment.
- Rheumatology – Follow-up to be arranged depending on severity of illness, discharge medications, and availability of other physicians to see the patient. Rheumatology will provide follow up visit for patient prior to discharge.
- Immunology – Consider referral to immunology for patients with confirmed MIS-C for evaluation for an underlying primary immunodeficiency.
- Other services (ID, GI, Neuro, Surgery, etc.) – will depend on clinical features and course of the patient
- All appointments should be arranged prior to discharge where possible.

Reasons to return to Emergency Department

- Fever > 38 degrees Celsius
- Recurrence of presenting symptoms or child becomes unwell with other symptoms.
- New appearance of respiratory distress or shortness of breath.

Version History

DATE	DOCUMENT NUMBER and TITLE	ACTION TAKEN
09-Jun-2020	C-05-07-60677 Multi-System Inflammatory Syndrome In Children Temporally Associated With Covid-19: Inpatient Workflow	Developed by BCCH MIS-C Working Group; Approved by Professional Practice Director
17-Aug-2020	"	Updated; Approved by Professional Practice Director
10-Nov-2020	"	Approved by: Pharmacy, Therapeutics & Nutrition Committee
04-Jan-2021	"	Updated
03-Mar-2021	"	Updated
20-Apr-2021	"	Updated

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