Guidelines for the Evaluation and Management of Multisystem Inflammatory Syndrome in Children (MIS-C)

This guideline was developed by the Saint Louis Children's Hospital MIS-C Working Group:

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I. Background:

- In April 2020, the Paediatric Intensive Care Society in the United Kingdom issued a warning about children presenting with an unusual clinical picture with overlap between toxic shock and atypical Kawasaki disease, including prominent GI symptoms and myocardial involvement (1), shortly thereafter, additional cases were reported throughout Europe and the United States (2-5).
- The Centers for Disease Control named the syndrome Multisystem Inflammatory Syndrome in Children (MIS-C) and released a case definition in 2020, updated in 2023 (below) (6). It is recognized as a post-infectious inflammatory syndrome related to SARS-CoV-2. The case definition is not diagnostic criteria, and may not capture the full range of presentations of MIS-C.
- This clinical guideline is intended to assist clinicians with the evaluation and management of patients suspected to have MIS-C. It is based on expert opinion and will be updated as evidence in this field continues to emerge.

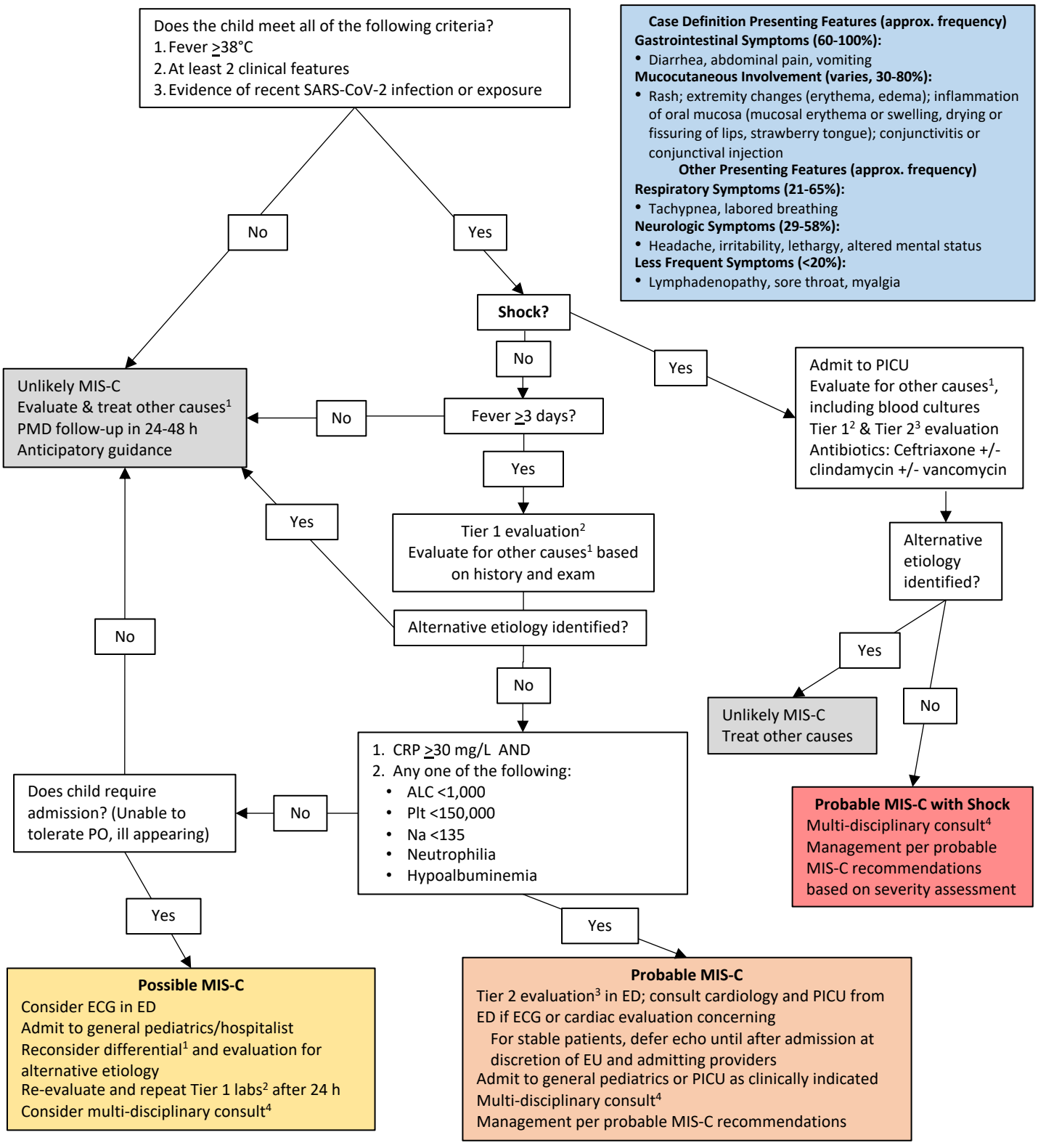
CDC Case Definition: https://www.cdc.gov/mis/mis-c/hcp_cstecdc/index.html

• An individual aged <21 years presenting with **all** of the following, in the absence of a more likely alternative diagnosis:
  ○ subjective or documented fever (>=38.0 C)
  ○ laboratory evidence of inflammation as indicated by elevated C-reactive protein (>=30mg/L)
  ○ evidence of clinically severe illness requiring hospitalization or resulting in death
  ○ new onset multisystem (2 or more categories) involvement (cardiac, mucocutaneous, GI, hematologic, shock)[1] **AND**
• Evidence of SARS-CoV-2 infection or exposure: detection of SARS-CoV-2 RNA or SARS-CoV-2 specific antigen in a clinical specimen up to 60d prior to or during hospitalization, **or** detection of SARS-CoV-2 specific antibodies in serum, plasma or whole blood with current illness resulting in or during hospitalization; **or** close contact with a confirmed or probable case of COVID-19 disease in the 60d prior to hospitalization (probable case)
[1] *Cardiac*: LVEF <55% **or** coronary artery dilation, aneurysm, or ectasia, **or** elevated troponin; *mucocutaneous*: rash **or** inflammation of oral mucosa **or** conjunctivitis/ conjunctival injection **or** extremity findings; *GI*: abdominal pain **or** vomiting **or** diarrhea; *Hematologic*: platelet count <150,000 cells/μL **or** ALC <1000cells/ μL; *shock*: clinical documentation

II. General Principles for Evaluation and Management:

- The definition and differential diagnosis of MIS-C is broad, it remains rare, particularly in vaccinated children and after infection with the Omicron variant (7, 8). It is important to consider alternative diagnoses.
- The majority of patients with MIS-C, especially those with cardiac manifestations, merit ICU admission (9). Clinicians should have a low threshold to discuss patients with possible MIS-C with the PICU.

III. Algorithm for Evaluation of Suspected Multisystem Inflammatory Syndrome in Children (MIS-C)



Notes:

[1] Possible alternative diagnoses should be assessed throughout evaluation. Differential diagnosis includes, but is not limited to: other viral infection (EBV/CMV, adenovirus, enterovirus), sepsis, toxic shock syndrome, Kawasaki disease, hemophagocytic lymphohistiocytosis (HLH)/macrophage activation syndrome (MAS), rickettsial disease (Ehrlichiosis, Rocky Mountain Spotted Fever), malignancy

[2] Tier 1 evaluation: CBC w/diff, CMP, ESR, CRP, Respiratory panel w/SARS-CoV-2 (RP.2.1), urinalysis

[3] Tier 2 evaluation: SARS-CoV-2 Antibodies; Cardiac evaluation: Pro-BNP, troponin, ECG, Echo; Ferritin, PT/PTT, D-dimer, fibrinogen

[4] Multi-disciplinary consult: Infectious Diseases, Rheumatology, Cardiology, Hematology

IV. Management

Probable MIS-C

- The following subspecialty teams should be consulted for **all** patients with probable MIS-C: Infectious Diseases, Rheumatology, Cardiology, Hematology. Other subspecialty consultations to be guided by presenting symptoms. Consultation should occur prior to initiation of targeted therapies for MIS-C, but may occur either from the emergency department or after admission at the discretion of the treating providers.
- Data regarding outcomes of specific therapies in MIS-C are limited**.** Suggestions in Table 1 are based on expert opinion. All treatment decisions should be considered in coordination with consulting teams and may sometimes deviate from this protocol, especially in patients with underlying medical problems.
- Shock should be managed using existing protocols. Therapies below are not directed at the management of shock and should await input from consulting team.
- Please obtain an IgG level prior to administration of intravenous immunoglobulins.
- The following labs should be repeated every 48 hours, or more frequently depending on guidance from consulting teams: CBC w/diff, CRP, ferritin, troponin, pro-BNP

Possible MIS-C

- Patients suspected to have MIS-C who do not meet criteria may merit admission and observation depending on the clinical judgement of treating providers.
- Repeat Tier 1 evaluation at 24h. Echo and Tier 2 evaluation recommended for patients strongly suspected of having MIS-C. Those who meet criteria for MIS-C should be managed according to guidance in Table 1.
- Consider subspecialist consultation based on presenting symptoms to evaluate for alternative etiologies and re-evaluate diagnosis and management for MIS-C.

Table 1. Recommendations for the management of patients with probable MIS-C

	Mild	Moderate	Severe
Definition	No SIRS, or SIRS without end organ injury[1] And: • No vasoactive infusion or vasoactive infusion <4 hours • No need for new or increase in baseline non-invasive/invasive ventilation[2]	SIRS with or without end organ injury[1] And/or: • Single low-dose vasoactive infusion[3] • New or increase in baseline non-invasive ventilation[2] without need for intubation	SIRS with end organ injury[1] And/or: • Single vasoactive infusion <u>above</u> low dose or more than one vasoactive infusion[3] • Invasive mechanical ventilation • Moderate to severe cardiac dysfunction by echo
Intravenous immunoglobulin (IVIG)[4]	IVIG 2 g/kg (by ideal body weight) once (max 100 grams) In patients who meet Kawasaki disease (KD) or incomplete KD criteria, consider 2nd dose if febrile 36h after initial IVIG	IVIG 2 g/kg (by ideal body weight) once (max 100 grams)	
Steroids[5]	None initially, **except:** If patient lacks KD features, or if febrile >36h after initiation of IVIG, consider methylprednisolone 1-2 mg/kg/day IV divided q12h (max 60 mg/dose q12h) Duration: 1-3 days Taper over 1-2 weeks	Methylprednisolone 1-2 mg/kg/day IV divided q12h (max 60 mg/dose q12h) Duration: 1-5 days Taper over 2-3 weeks	Methylprednisolone 1-2 mg/kg/day IV divided q12h (max 60 mg/dose q12h) Refractory: high-dose methylprednisolone 10-30 mg/kg/day IV divided q12h (max 500 mg/dose q12h) Duration: 1-5 days Taper over 2-3 weeks
Anakinra[5]	Not recommended	Consider for patients who do not respond to IVIG and steroids (10). Anakinra initial dose 4 mg/kg/day (max 100 mg/dose, 200 mg/day) SQ daily or divided q12h	
Aspirin[6]	For patients meeting KD criteria or with coronary artery changes, dosing per AHA KD guideline: initial high-dose aspirin 80-100 mg/kg/day divided q6h, max dose 975 mg q6h (max 4g/day). Transition to low-dose aspirin (3-5 mg/kg/day, max 81 mg) once afebrile for 48h (11) For patients with ejection fraction <35%: low-dose aspirin (3-5 mg/kg/day, max 81 mg)		
Anticoagulation[8,9]	<12 years: early ambulation & SCDs if tolerated	<12 years: Consider prophylactic enoxaparin per VTE order set in patients with **2** or more additional VTE risk factors[7] and for patients with CAAs[8,9]	Prophylactic anticoagulation per VTE order set, in the absence of increased risk of bleeding[8,9]
	≥12 years: Consider prophylactic enoxaparin per VTE order set for patients with **2** or more additional VTE risk factors[7] and for patients with coronary artery aneurysms (CAAs)[8,9]	≥12 years: Consider prophylactic enoxaparin per VTE orderset for patients with **1** or more additional VTE risk factors[7] and for patients with CAAs[8,9]	
Antibiotics	Not routinely indicated	Empiric antibiotics recommended for 48h while blood cultures are pending: ceftriaxone +/- clindamycin (concern for toxic shock) +/- vancomycin (history/concern for MRSA)	
Antivirals	Antivirals are **not** routinely indicated, but may be considered for patients with positive PCR for SARS-CoV-2 and severe disease, particularly respiratory failure		

[1]Systemic inflammatory response syndrome (SIRS): 2 or more of hyper/hypothermia, tachycardia for age, tachypnea for age. End organ injury: at least 1 of hypotension for age, new non-invasive/invasive ventilation, creatinine >1.5x ULN for age, Bilirubin >2 mg/dL, lactate >2 mmol/L, INR > 1.5, aPTT >60 sec, platelets <100 k/mm^3

[2]Non-invasive ventilation includes high-flow nasal cannula, continuous positive airway pressure (CPAP), or bilevel positive airway pressure (BiPAP)

[3]Low-dose vasoactive infusion: Epinephrine <0.05 mcg/kg/min, Norepinephrine <0.05 mcg/kg/min, Vasopressin <0.5 mUnits/kg/min, Dopamine <5 mcg/kg/min, Dobutamine <5 mcg/kg/min

[4]IVIG will lead to increase in ESR, which should not be repeated after administration of IVIG

[5]Rheumatology consultation required for patients who are refractory to IVIG and prior to consideration of anakinra. Rheumatologist may adjust steroid and anakinra dosing based on evaluation

[6]Due to risk of Reye Syndrome, all patients administered aspirin should receive an influenza immunization

[7]VTE risk factors: obesity, presence of central venous catheter, chronic inflammatory illness, use of estrogen-containing contraception, personal history of VTE or thrombophilia trait, family history of VTE in 1st-degree relative, altered mobility 30 days prior to admission (major surgery, significant trauma), d-dimer >5x the upper limit of normal

[8]May consider withholding VTE prophylaxis in the presence of bleeding risk factors: platelets <50 k/mm^3, fibrinogen <100 mg/dL, elevated PT/aPTT, hepatic or renal failure, recent or ongoing bleeding, recent surgery. May consider low-dose unfractionated heparin (10 units/kg/hr) for high risk of bleeding and thrombosis. Anti-Xa goal 0.1-0.3 units/mL. PTT goal 60-75 sec.

[9]Patients with CAAs with a Z-score ≥10 and those with VTE may require therapeutic anticoagulation, which should be managed in coordination with cardiology and hematology

V. Isolation Precautions & Reporting

- Full COVID-19 precautions are recommended at the time of presentation for patients with suspected MIS-C. Please contact infection prevention (IP) through the SLCH operator (314-454-6000) to discuss duration of isolation precautions, which will be determined based on the patient's clinical course and SARS-CoV-2 testing results.
- The IP team must report MIS-C patients to the health department. The infectious diseases team is responsible for notifying IP of probable MIS-C patients at the number above or SLCH-Infection.Prevention@bjc.org

VI. Discharge and Outpatient Follow Up

Probable MIS-C

Discharge preparation and criteria:

- If more than 2 days since last echocardiogram, obtain echocardiogram prior to discharge
- Discharge readiness should be discussed with all consulting teams. Minimum discharge criteria:
    - 48 hours without fever, vasoactive medications, and supplemental oxygen
    - Minimum of 48 hours downtrending CRP
    - Troponin downtrending (if previously elevated)
    - ECG without arrhythmia
    - Latest echocardiogram improved/stable
    - QT interval improved (if previously prolonged)

Follow-up:

- All patients should follow up with primary care clinician 48-72 hours and 2 weeks after discharge.
- All patients should follow up with cardiology and rheumatology 2 weeks after discharge, and cardiology 6 weeks after discharge.
    - 2 week follow up to include ECG, Echo, labs
- Children should not participate in sports until evaluated by primary care clinician and cardiology.
    - Children with concerns for myocarditis may be excluded from sports for 3-6 months.
- Follow-up with other subspecialists to be determined on a case-by-case basis per consultants.

Unlikely MIS-C

- Patients discharged from the ED or inpatient setting deemed unlikely to have MIS-C should receive anticipatory guidance regarding progression of symptoms that would merit re-evaluation for MIS-C and should follow up with PMD within 24-48 hours.

VII. COVID-19 Vaccination following MIS-C(12)

The mechanisms of MIS-C are not well understood but likely include a dysregulated immune response to SARS-CoV-2 infection. It is not clear whether people with a history of MIS-C are at risk of recurrence of MIS-C if they are reinfected with SARS-CoV-2 or for a MIS-C-like illness after COVID-19 vaccination, though initial studies did not report serious adverse events after vaccination (13). Clinicians should carefully discuss the risks and benefits of vaccination with patients and families. Due to the widespread transmission of SARS-CoV-2 and increased hospitalizations in unvaccinated people, many experts consider the benefits of COVID-19 vaccination to outweigh the theoretical risks for people with a history of MIS-C who meet all of the following criteria:

- Clinical recovery has been achieved, including return to normal cardiac function;
- It has been ≥90 days since their diagnosis of MIS-C;
- They are in an area of high or substantial community transmission of SARS-CoV-2 or otherwise have an increased risk for SARS-CoV-2 exposure and transmission; and
- Onset of MIS-C occurred before any COVID-19 vaccination.

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