LEB Guidelines for Management of Multisystem Inflammatory Syndrome in Children (MIS-C)

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MIS-C GENERAL INFORMATION

What is MIS-C?

Multisystem Inflammatory Syndrome in Children (MIS-C) is a novel inflammatory illness temporally associated with COVID-19. It is characterized by persistent fever, systemic inflammation, and multiorgan dysfunction manifesting weeks after SARS-CoV-2 infection.

What is the CDC surveillance case definition for MIS-C?

- An individual aged <21 years presenting with fever*, laboratory evidence of inflammation**, and evidence of clinically severe illness requiring hospitalization, with multisystem (≥2) organ involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic or neurological); AND
- No alternative plausible diagnoses; AND
- Positive for current or recent SARS-CoV-2 infection by RT-PCR, serology***, or antigen test; or exposure to a suspected or confirmed COVID-19 case within the 4 weeks prior to the onset of symptoms.

*Fever ≥38.0°C for ≥24 hours, or report of subjective fever lasting ≥24 hours
**Including, but not limited to, one or more of the following: an elevated C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), fibrinogen, procalcitonin, d-dimer, ferritin, lactic acid dehydrogenase (LDH), or interleukin 6 (IL-6), elevated neutrophils, reduced lymphocytes and low albumin
***Given the high prevalence of SARS-CoV-2 infection in many communities (including the Le Bonheur region), seropositivity to SARS-CoV-2 is common and has a limited role in the diagnosis of MIS-C. Negative SARS-CoV-2 serology does not rule out MIS-C; however, it should prompt investigation of alternative diagnoses.

What are some of the distinguishing features of MIS-C?

- Kawasaki disease features (rash, conjunctivitis, oropharyngeal changes, cervical lymphadenopathy, swelling/erythema of hands and feet
- Broad age range up to 21 years.
- Higher incidence in children of African, Afro-Caribbean, and Hispanic descent and lower incidence in children of Asian descent
- Prominent GI (abdominal pain, vomiting, and diarrhea) and neurologic symptoms (headache, somnolence, confusion)
- Shock and myocardial dysfunction
- Leukopenia (especially lymphopenia <1000) and thrombocytopenia
- Very high values for inflammatory markers (CRP, procalcitonin)

EVALUATION FOR MIS-C

Which patients should I evaluate for MIS-C?

Consider MIS-C in any patient presenting with either of the following syndromes (especially if the child has had COVID or has an epidemiologic link to a case of COVID):

- Persistent Fever
- Clinical signs of involvement of 2 or more organ systems (especially GI or neurologic)
    - Cardiac: hypertension, hypotension, chest pain, shortness of breath

- Dermatologic/mucocutaneous: polymorphous rash, erythema/swelling of hands and feet, conjunctivitis, erythema/cracking of lips, strawberry tongue, erythema of oropharyngeal mucosa
- Gastrointestinal: nausea, vomiting, abdominal pain, diarrhea
- Lymphadenitis (neck swelling causing significant pain and/or sore throat)
- Neurologic: headache, altered mental status/irritability, meningismus focal neurological findings
- Respiratory: cough, shortness of breath, pulmonary infiltrates

OR

- Any duration of fever with signs/symptoms of shock
- For in-patient admissions, consider MIS-C as a potential differential for patients with a positive severe sepsis alert (current LBCH SS alerts are active for patients between ages 1 – 21 years of age)

What should the initial evaluation for MIS-C be in a patient presented with 3 or more days of fever?

- History and physical exam
  - **Tier 1 testing:** CBC, CMP, CRP, ESR, SARS-CoV-2 PCR and/or serology (when available)

- **Tier 2 testing**:
  - **Should be done with Tier 1 testing in patients with shock of unclear etiology or if abnormalities on Tier 1 screening indicative of possible MIS-C are found: CRP≥30 or ESR≥40, and one of ALC<1000/µL, platelets<150,000/ µL, Na<135, neutrophilia, hypoalbuminemia**
    - BNP
    - Troponin
    - Procalcitonin
    - Ferritin
    - Lactate
    - PT/PTT
    - D-dimer
    - Fibrinogen
    - LDH
    - Urinalysis
    - Triglycerides
    - Consider Red top tube – hold in lab
    - SARS CoV-2 serology and RT-PCR if not already done
    - Blood smear
    - ECG and echo

What are the criteria for admission for suspected MIS-C?

- Outpatient evaluation for MIS-C *may* be appropriate for well appearing children with stable vital signs and reassuring physical exam provided close clinical follow-up can be assured and patient is admitted if diagnosis becomes more likely
- Patients under investigation for MIS-C should be considered for admission to the hospital for further observation while completing the diagnostic evaluation, especially if they display the

following

- Abnormal vital signs (tachycardia, tachypnea)
- Respiratory distress of any severity
- Neurologic deficits or change in mental status (including subtle manifestations)
- Evidence of even mild renal or hepatic injury
- Markedly elevated inflammatory markers (C-reactive protein ≥100 mg/dL)
- Abnormal EKG, BNP, or troponin

What additional evaluation should a child with suspected MIS-C undergo?

- Children under investigation for MIS-C should also be evaluated for other infectious and non-infectious etiologies
- Abnormalities on Tier 2 testing are not specific for MIS-C and can be seen in other infectious, inflammatory, or malignant conditions.
- Additional laboratory testing should be guided by presenting signs and symptoms and may include:
  - Blood culture
  - Culture of other sites e.g. wound culture, urine culture
  - Amylase/lipase
  - Chest radiograph
  - Abdominal ultrasound
  - CT scan of chest and/or abdomen
  - Respiratory virus PCR panel
- What is the cardiac evaluation for patients with suspected MIS-C?
- A baseline 12 lead EKG must be performed in all MIS-C patients. Repeat 12 lead EKG's need to be considered or performed based on the clinical acuity of the patient and after cardiology consultation. If conduction abnormalities are present, patients should be placed on continuous telemetry
- **Echocardiograms** should include evaluation of ventricular/valvar function, pericardial effusion, and coronary artery dimensions with measurements indexed to body surface area using z-scores
- Echocardiograms should be repeated at a minimum of 7-14 days and 4-6 weeks after presentation
- For those patients with cardiac abnormalities occurring in the acute phase of their illness, an echocardiogram 1 year after MIS-C diagnosis could be considered. Patients with left ventricular (LV) dysfunction and/or CAA will require more frequent echocardiograms

THERAPY OF MIS-C

Which services should be involved in the diagnosis and management of MIS-C?

Consider evaluation by Infectious Diseases, Rheumatology, and Cardiology in patients with suspected MIS-C. *Depending on patient-specific problems, consultation from Hematology, Neurology or Gastroenterology can be considered. There should be frequent, multidisciplinary discussions among the primary team (PICU or Hospital Medicine) and consultants about patients with suspected MIS-C and those receiving treatment for MIS-C.* ***Call ID and/or rheumatology early when diagnosis is uncertain or patient unstable.***

The decision to treat for MIS-C should be made by the primary team in discussion with Infectious Diseases and Rheumatology when additional support needed. Treating for MIS-C does not require

excluding all other diagnoses and it is possible that treatment for MIS-C may need to be provided while evaluation and empiric therapy (e.g. systemic antibiotics) for other etiologies is undertaken. ***All patients treated for MIS-C should have a cardiology consultation. Call rheumatology if patient is refractory to IVIG or if patient requires anakinra, high dose steroids, or other biologic medications.***

What is the treatment for MIS-C?

- Treatments have consisted primarily of supportive care and directed care against the underlying inflammatory process and multi-organ dysfunction syndrome. Supportive measures include but are not limited to:
  - fluid resuscitation
  - inotropic support
  - respiratory support including supplemental oxygen, non-invasive and invasive mechanical ventilation
  - dialysis
  - extracorporeal membranous oxygenation (ECMO)

I. Stable patients without cardiac involvement

- Children with mild manifestations may not require treatment should fever remit after admission
- IVIG 2 g/kg with a maximum dose of 100 grams
- If patient becomes unstable (persistent tachycardia, multiple fluid boluses/shock, altered mental status) call MRT for immediate support or consult PICU (PICU team member will be available within 1 hr) as required

II. Stable patients with elevated troponin or BNP or cardiac involvement on echocardiogram or ECG

- IVIG 2g/kg in divided doses q8h for 24 hours
- Low-moderate dose glucocorticoids (1-2 mg/kg/day IV methylprednisolone, typically max dose at 30 mg q12 hours)
  - observational studies report more rapid resolution of fever, shorter durations of hospital stay, and reduction in use of additional therapies in patients given initial IVIG plus steroids versus IVIG alone

III. Refractory fever or end organ dysfunction (after IVIG with or without moderate dose steroids)

- Call Rheumatology team to discuss next steps for immunomodulation which may include:
  - ♣ moderate dose glucocorticoids (1-2 mg/kg/day IV methylprednisolone)
  - ♣ "pulse dose" glucocorticoids (30 mg/kg/day IV methylprednisolone, max 1000 mg)
  - ♣ Anakinra (4 to 10 mg/kg/day, subcutaneously or intravenously, divided every 6 to 12 hours)

- **Consult rheumatology and Infectious disease for patients with refractory disease if not already involved**

IV. Unstable patients

- Transfer to PICU before IVIG initiation
- Call Rheumatology team to discuss immunomodulation which may include simultaneous use of medications such as:
    - IVIG
    - steroids
        - moderate dose glucocorticoids (1-2 mg/kg/day IV methylprednisolone)

        OR
        - "pulse dose" glucocorticoids (30 mg/kg/day IV methylprednisolone, max 1000 mg), especially if requiring vasopressor support
    - Anakinra (4 to 10 mg/kg/day, intravenously, divided every 6 to 12 hours)

General care

- Consider elective intubation / mechanical ventilation as dictated by critical clinical status
- Obtain stable vascular access: CVL / Arterial line
- ARDS Management – Per ICU guidelines, ECMO Watcher Status per guidelines
- Severe shock, requiring vasopressor support or not improving with lower dose steroids and IVIG
    - Discuss change in cardiovascular clinical status – with Cardiology
        - ♣ Repeat ECHO – Function and pericardial effusion assessment
        - ♣ General Cardiology to consult Cardiomyopathy team based on patient status
        - ♣ Arrhythmia management as required
    - Hemodynamic instability due to vasculopathy / shock:
        - ♣ Initiate Shock dose Vasopressin 0.2 – 0.5 mics/kg/min for warm shock
        - ♣ Initiate Epinephrine 0.03 – 0.05 mics/kg/min for cold shock, consider adding Milrinone once shock state improves
        - ♣ Transfuse PRBC for Hb < 7 gm/dl
        - ♣ ECMO Watcher Program notification
    - Hemodynamic instability due to Cardiomyopathy: Management details per discussions between Cardiomyopathy and PICU teams
    - Methylprednisolone 10-30 mg/kg/day for 1-3 days in discussion with Rheumatology

- Cardiac CT should be performed in patients with suspicion of distal CAAs that are not well seen on echocardiogram (M)
- In older patients, consider performing a trans-esophageal echo (TEE) if indicated.
- Cardiac MRI may be indicated 2-6 months after MIS-C diagnosis in patients who presented with significant transient LV dysfunction in the acute phase of illness (LV ejection fraction <50%) or persistent LV dysfunction. Cardiac MRI should focus on myocardial characterization including functional assessment, T1/T2 weighted imaging, T1 mapping and extracellular volume (ECV) quantification, and late gadolinium enhancement (H).

V. <u>Severe shock or unresponsive to IVIG, steroids, anakinra, and vasopressors</u>

- VA ECMO initiation pathway for shock unresponsive to escalation in medical management
- Monitor for Multi-Organ Dysfunction Syndrome (MODS) and consult appropriate services (e.g – Nephrology for CRRT)
- Biologics: Tocilizumab, infliximab, ruxolitinib in discussion with Rheumatology (if not initiated

already)

Anakinra taper

The timing and rate at which anakinra should be tapered is individualized for each patient in discussion with rheumatology team

General Principles:

- Begin taper once patient is stable and inflammatory markers decreasing
- Taper by extending the dosing interval to q8h followed by q12h, q24 h, and then discontinue
- Anakinra should be tapered off at least 24 hours before discharge

Steroid taper (typical 15 day plan)

- Some patients may be on steroids longer than 15 days if they start on pulse dose, but after pulse dose, begin on 15 steroid plan
  - Typically, steroids start as IV methylprednisolone and can later switch to PO prednisolone/prednisone when clinically stable and able to tolerate PO
  - Recommend GI protection while on steroids

- 1 mg/kg/dose q12h X 5 days (max 30 mg q12h)
- 0.5 mg/kg/dose BID (max 15 mg BID) X 5 days
- 0.5 mg/kg/dose QD (max 15 mg QD) X 5 days then discontinue

What adjuvant therapies should patients be given?

A. Antiplatelet therapy: Monitor TEG, Platelet and Coagulation profile

1. Antiplatelet therapy:
   - Low dose aspirin (3-5 mg/kg/day; max 81 mg/day) until confirmed normal coronary arteries at 4-6 weeks after diagnosis at cardiology follow up appointment
     - Avoid ASA in patients with a platelet count less than a platelet count of 20K
     - High dose Aspirin (80-100 mg/kg/day, div q6, max 4000mg/day, can be considered if there is a strong suspicion that patient has Kawasaki Disease and not MIS-C. However, continue to use low dose aspirin if patient has the KD phenotype of MIS-C.

2. Anticoagulation
   - Prophylactic anticoagulation with Enoxaparin:
     - Consider in all post-pubertal patients regardless of degree of mobility
     - Should be started in immobilized post-pubertal patients based on standard VTE prophylaxis
     - Consider increased doses for prophylaxis in pediatric patients with a BMI >40 kg/m^2
       - CrCl ≥ 30 mL/min = 0.5 mg/kg (maximum dose is 40 mg/dose q12h)
       - CrCl < 30 mL/min = 0.5 mg/kg (maximum dose is 30 mg/dose q24h)
   - Therapeutic anticoagulation with Heparin / Enoxaparin:
     - Documented thrombosis or an ejection fraction (EF) <35% in consultation with cardiology.

- Patients with coronary artery aneurysm with a z-score ≥10.0
- Anticoagulation (therapeutic dosing) should be continued in all cardiac cases until inflammatory markers have resolved, and EF demonstrates improvement. Discuss further with Peds Cardiology / Heart failure team.

- Long-term Anticoagulation management / discharge plan:
  - Enoxaparin prophylaxis may be discontinued for asymptomatic patients upon discharge at the discretion of the attending on service
  - For patients requiring long-term Enoxaparin administration – Hematology, Cardiology (if low EF / coronary aneurysm) should follow and Pharmacy (education) should be consulted, and appropriate follow-up required upon discharge.

Recommended platelet thresholds on enoxaparin:

- *If enoxaparin ppx is started, maintain platelet count >20,000.*
- *If enoxaparin treatment is started, maintain platelet count >30,000.*

Note: Combination therapy with enoxaparin and aspirin may be needed in some patients (i.e. patients with large or giant coronary aneurysms) per the AHA KD guidelines after discussion of risk and benefit with cardiology and hematology teams.

B. Antibiotics

Decisions regarding appropriate empiric antibiotic therapy should be made in discussion with Infectious Diseases

- MIS-C has a broad differential diagnosis all of which should be evaluated through history, physical exam, laboratory testing and diagnostic imaging
- Important differential diagnoses (for infections and other conditions) are in the appendix i
- Empiric antibiotics for most otherwise-healthy patients (after obtaining appropriate cultures) with vancomycin (with close monitoring of renal function) and ceftriaxone +/- doxycycline

C. COVID-19 directed therapies

- Patients presenting with suspected MIS-C may have respiratory tract involvement and/or have a positive RT-PCR for COVID 19.
- It may be difficult to difficult to distinguish COVID-19 infection from MIS-C with ARDS in these patients.
- Therapy for COVID-19 should be considered in these patients in discussion with Infectious Diseases

See document Pharmacologic management of COVID in pediatric inpatients *for indications and dosing*

How often should labs be followed in patients undergoing treatment for MIS-C?

Frequency of CBC, LFTs, coagulation profile, troponin, BNP should be followed based on patient status starting daily and then spacing out as the patient has clinical improvement.
Ferritin and CRP are used for trending severity of inflammation and improvement of inflammatory markers may lag behind clinical improvement. Ferritin and CRP should be followed a maximum of every other day ~~with recommended frequency of twice weekly~~.

Should I expect normalization of laboratory values prior to discharge home?

Laboratory findings may not complete normalize prior to discharge, including ferritin, platelet count, Hb, ALC, CRP, and D-dimer. If patient has been afebrile and clinically stable with these labs improving, it is reasonable to consider discharge with close follow-up with PCP with instructions to return if there is reoccurrence of fever or other symptoms.

What additional considerations should be made in a patient with suspected MIS-C with negative SARS-CoV2 PCR and serology?

Patients can have MIS-C *without* positive serology/PCR testing if they have a known COVID contact per the case definition. However, in these patients the differential diagnosis should remain broad and additional infectious disease, rheumatologic, and malignant etiologies should be considered, and further evaluation is warranted. Please see Appendix X for additional differential diagnoses.

What are the appropriate infection prevention precautions for patients with suspected MIS-C?

MIS-C occurs after COVID-19 infection 4-6 weeks after acute COVID-19. Some children will have prolonged convalescent shedding of virus and may test positive by RT-PCR for SARS-CoV-2 admitted with suspected MIS-C. The cycle threshold (CT) provides an approximation of the viral load. A low CT is associated with a higher viral load and a high CT (cutoff for positive test usually 40) associated with low viral load.

- SARS-CoV-2 PCR negative – no isolation
- SARS-CoV-2-positive:
    - If known COVID-19 prior to this admission more than 10 days before and complete resolution of symptoms (prior to onset of MIS-C) or asymptomatic infection more than 10 days prior – No isolation
    - If preceding COVID-19 was asymptomatic and unknown – must be in isolation for 10 days-

References

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3. MIS-C Sub-types using Latent Class Analysis (LCA): **********cdc.gov/mmwr/volumes/69/wr/pdfs/mm6932e2-H.pdf
4. Acute Heart Failure in Multisystem Inflammatory Syndrome in Children in the Context of Global SARS-CoV-2 Pandemic. Circulation. 2020; 142:429–436. DOI: 10.1161/CIRCULATIONAHA.120.048360
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Appendix. X Additional Differential Diagnoses to Consider

Infectious Disease:

1. Viral infections:
    - Respiratory viruses: COVID-19, influenza, adenoviruses
    - Systemic viruses (including viral myocarditis): EBV, CMV, HHV-6/7 (in under 2 year olds), parvovirus B19, adenoviruses, enteroviruses
2. Bacterial infections:
    - Toxic shock syndrome with or without clinical focus of infection such as pneumonia, skin/soft tissue infection, musculoskeletal infection, menstrual associated
    - Rickettsial infection: Rocky Mountain Spotted Fever/Ehrlichiosis
    - Severe bacterial infection (with or without focal disease) due to *S. aureus,* group A *Streptococcus*, *S. pneumoniae*, *N. meningitidis*; urosepsis, bacterial pneumonia, musculoskeletal infection, skin/soft tissue infection, meningitis, intra-abdominal infection, urosepsis, isolated bacteremia
    - Staphylococcal scalded skin syndrome

Rheumatological:

- Systemic JIA with or without associated macrophage activation syndrome (MAS)
- SLE with or without associated MAS
- DRESS/other drug hypersensitivity
- Thrombotic microangiopathy/thrombotic thrombocytopenic purpura/HUS/atypical HUS

Malignancy:

The most common malignancies that could present similarly to MIS-C include leukemia and lymphoma. Concern for possible leukemia and lymphoma should be increased if there is a *prolonged history of fever (i.e. > 7-10 days), fatigue, weight loss, night sweats, bone pain, lymphadenopathy, hepatosplenomegaly, mediastinal mass, abnormally high or low peripheral blood counts, coagulopathy, and/or evidence of high cell turn-over such as increased uric acid/LDH.* Cytopenias may not always be present at leukemia or lymphoma diagnosis; however, thrombocytopenia is extremely common.

If there are concerns for possible HLH, please call the on-call St Jude Oncology fellow (Pager 901-595-3578 2375) for an Oncology Consult.

HLH:

There have been reports of patients developing secondary HLH in the setting of MIS-C, which may require additional HLH-specific testing or therapy. Suspicion of HLH may be confounded by the common laboratory and physical exam findings seen in MIS-C. *Severity of hyperferritinemia alone is not specific for evolving HLH.*

Suspicion for HLH should be increased in patients with

- Persistent fever and bicytopenia, particularly after treatment has started with:
    - Fibrinogen < 150 **OR**
    - ANC < 1000 **OR**

- Presence of hepatosplenomegaly

If there are concerns for possible HLH, please call the on-call St Jude Oncology fellow (Pager 901-595-3578 2375) and request a Histiocytosis Treatment Team Consult.

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