

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

Version: 12/04/2020

What is MIS-C?

Multisystem Inflammatory Syndrome in Children (MIS-C) appears to be an inflammatory response to a prior SARS-CoV-2 infection. It is a condition characterized by fever, inflammation, and multiorgan dysfunction manifesting late in the course or after a SARS-CoV-2 infection, generally two to four weeks after.

Preliminary CDC data reported on 570 case of MIS-C in the U.S. Latent class analysis revealed 3 classes of patients:

- **Class 1** (35.6%, median age 9 yr) – highest number of organ systems involved (*cardiovascular and gastrointestinal most common*); markedly elevated inflammatory markers (CRP, ferritin) and markers of cardiac involvement (troponin, BNP); little clinical overlap with acute COVID-19 or Kawasaki disease, SARS-CoV-2 serology positive in 98%.
- **Class 2** (29.6%, median age 10 yr)- most had respiratory involvement with cough, shortness of breath, *pneumonia, ARDS* indicating overlap with acute COVID-19; high rate of SARS-CoV-2 RT-PCR positivity (84%). This overlap might result from the development of MIS-C soon after symptomatic acute COVID-19 illness. *Highest case-fatality rate.*
- **Class 3** (34.7%, median age 6 yr) - generally less severe MIS-C illness with *clinical manifestations overlapping with Kawasaki disease*, more likely to have rash, mucocutaneous findings, less inflammation and cardiac involvement (except coronary abnormalities); 63.1% had positive SARS-CoV-2 serology and 33.8% had positive serology and RT-PCR. In this group it may be difficult to distinguish MIS-C from Kawasaki disease.

Kawasaki Vs. MIS-C differentiation – Patients with MIS-C:

- Are from a broader age range (including many children over 5 years)
- Have more prominent GI and neurologic symptoms
- Are more likely to present with shock
- Are more likely to have cardiac dysfunction including myocardial dysfunction, arrhythmias
- Have lower platelet, and absolute lymphocyte counts, higher CRP levels

What is the 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 COVID-19 exposure 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

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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 \geq 3 days
- Clinical signs of involvement of 2 or more organ systems
 - 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
- If patient has shock, proceed to **Tier 2 testing:**
 - 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 ECG and echo
- If CRP \geq 50 mg/L or ESR \geq 40 mm/hr and one of the following is present proceed to **Tier 2 testing**

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- Absolute lymphocyte count < 1000 / μ L
- Platelets < 150,000/ μ L
- Neutrophilia
- Hypoalbuminemia

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 \geq 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
- 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 chest and/or abdomen
 - Respiratory virus PCR panel
- Consult Infectious Diseases, Rheumatology, and Cardiology. Other subspecialists may be needed based on clinical presentation

What is the cardiac evaluation for patients with suspected MIS-C?

- EKGs should be performed at a minimum of every 48 hours
- 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

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What is the suggested therapy for MIS-C?

The decision to treat for MIS-C should be made in discussion with the primary team, Infectious Diseases and Rheumatology. Treating for MIS-C does not require ruling-out all other diagnoses and it is likely that treatment for MIS-C need to be provided while evaluation and empiric therapy (e.g. systemic antibiotics) for other etiologies is undertaken.

All patients with suspected MIS-C should be evaluated by Infectious Diseases, Rheumatology, and Cardiology. 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-

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
 - dialysis
 - extracorporeal membranous oxygenation (ECMO)

FIRST TIER: Stable patients (managed on the floor service but should be listed as Watcher Status*)

- IVIG 2 g/kg
 - Consider maximum dose of 100 grams OR
 - Use adjusted body weight for dosing and divide dose to be given q8h for 24 hours
- If patient becomes unstable* – call MRT for immediate support or consult PICU (PICU team member will be available within 1 hr) as required

*Signs or symptoms of instability include persistent tachycardia, need for multiple fluid boluses, shock, altered mental status

SECOND TIER: Unstable patients

- Transfer to PICU before IVIG initiation if on regular ward
- Consider Anakinra (10 mg/kg/day divided Q6H) before IVIG in discussion with rheumatology, especially in patients requiring vasopressor support (see below)
- IVIG 2 g/kg
 - Consider maximum dose of 100 grams OR
 - Use adjusted body weight for dosing and divide dose to be given q8h for 24 hours
- Methylprednisolone 1-2 mg/kg/day divided divide q12h X 5 days dosed on adjusted body weight
 - Taper steroids every 5 days for 10-15 days depending on starting dose
 - Methylprednisolone may be started after IVIG / Anakinra if patient becomes unstable
- Consider elective intubation / mechanical ventilation as dictated by critical clinical status

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- 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).

THIRD TIER: Severe shock or unresponsive to IVIG, steroids and vasopressors

- 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: Anakinra or Tocilizumab in discussion with Rheumatology (if not initiated already)

Adjuvant therapies

- A. Antiplatelet therapy: Monitor TEG, Platelet and Coagulation profile
1. Antiplatelet therapy:
 - High dose ASA (80-100 mg/kg/day) until afebrile for patients meeting criteria for complete or incomplete Kawasaki Disease
 - Transition to 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 $\leq 20,000/ L$
 - Continue high dose ASA and therapeutic anticoagulation

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- Coronary artery aneurysm and z-score ≥ 10.0

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
- Therapeutic anticoagulation with Heparin / Enoxaparin:
 - Documented thrombosis or an ejection fraction (EF) $< 35\%$ in consultation with cardiology.
 - 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 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

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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 completely 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 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 COVID precautions
- SARS-CoV-2-positive with IgG positive and CT of PCR ≥ 35 – no COVID precautions
- SARS-CoV-2-positive and IgG negative or CT < 35 , needs COVID precautions

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References

1. Children’s Hospital of Philadelphia Emergency Department, ICU and Inpatient Clinical Pathway for Evaluation of Possible Multisystem Inflammatory Syndrome (MIS-C)
[*****.chop.edu/clinical-pathway/multisystem-inflammatory-syndrome-mis-c-clinical-pathway](https://www.chop.edu/clinical-pathway/multisystem-inflammatory-syndrome-mis-c-clinical-pathway)
2. American College of Rheumatology Clinical Guidance for Pediatric Patients with Multisystem Inflammatory Syndrome in Children (MIS-C) Associated with SARS-CoV-2 and Hyperinflammation in COVID-19 [*****.rheumatology.org/Portals/0/Files/ACR-COVID-19-Clinical-Guidance-Summary-MIS-C-Hyperinflammation.pdf](https://www.rheumatology.org/Portals/0/Files/ACR-COVID-19-Clinical-Guidance-Summary-MIS-C-Hyperinflammation.pdf)
3. MIS-C Sub-types using Latent Class Analysis (LCA):
[*****.cdc.gov/mmwr/volumes/69/wr/pdfs/mm6932e2-H.pdf](https://www.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

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**

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- 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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Le Bonheur MIS-C Guidelines Committee Contributing Members (Alphabetical – Last name):

1. Dr. Sandra Arnold, Chief, Pediatric Infectious Diseases
2. Dr. Bindya Bagga, Attending Physician, Pediatric infectious Diseases
3. Ms. Kelli Bobo, Pharmacy
4. Dr. Katie Collins, Attending Physician, Pediatric Rheumatology
5. Dr. Cynthia Cross, Chief, Pediatric Hospitalist Program
6. Dr. Terri Finkel, Chief, Pediatric Rheumatology
7. Ms. Kim Giles, Director – Clinical Decision Support
8. Dr. Barry Gilmore, Chief Medical Officer, Le Bonheur
9. Dr. Rick Hanna, Chief, Pediatric Emergency Medicine
10. Dr. Melissa Hines, Assistant member, Pediatric Critical Care, St. Jude Children’s Research Hospital
11. Dr. Nick Hysmith, Director, Infection Prevention
12. Dr. Jonathan Jacobs, Attending, Pediatric Emergency Medicine
13. Dr. Jason Johnson, Associate Chief, Pediatric Cardiology
14. Mr. William Mabry, Pharmacy
15. Ms. Andrea Orman, Clinical Director, PICU & Neuro ICU
16. Dr. Steve Pishko, Attending, General Pediatrics
17. Dr. Nadeem Shafi, Medical Director, PICU
18. Dr. Samir Shah, Chief, Pediatric Critical Care Medicine
19. Ms. Barbie Stewart, Clinical Director, Emergency Medicine
20. Dr. Brittany Wagner, Fellow, Pediatric Emergency Medicine