UC DAVIS HEALTH | CHILDREN'S HOSPITAL

UC Davis Children's Hospital Guidelines for Treatment of Multisystem Inflammatory Syndrome in Children Following COVID-19 infection (MIS-C)

Consider the diagnosis of MIS-C in the following clinical situations:

A child 0-18 years of age presenting with fever >=3 days* and:

- Multisystem (>=2) involvement, including:
  - o Gastrointestinal (abdominal pain, vomiting, diarrhea)
  - o Cardiac (LV dysfunction, elevated troponin)
  - o Mucocutaneous (rash, conjunctivitis, extremity changes, oral mucosal changes)
  - o Shock
  - o Hematologic (lymphopenia, thrombocytopenia)
- Symptoms consistent with Kawasaki Disease
- Fever >=5 days with no alternative explanation

*A child who is ill-appearing with suspected MIS-C should be evaluated as per the diagnostic work-up below, even if fever is present <3 days

Recommended diagnostic evaluation (see algorithm on next page)

1. Initial laboratory evaluation (outpatient or ER)

   a. CBC with differential

   b. CMP

   c. ESR, CRP

d. Urinalysis

e. Blood culture

f. Procalcitonin (ER only)

g. VBG with lactate (ER only)

h. Imaging as clinically indicated (ER only):

i. Chest X-ray

ii. Abdominal ultrasound or CT scan if concerning symptoms/physical findings

2. If initial labs concerning for MIS-C without alternative explanation (ESR >=40 or CRP>=3mg/dL in addition to 1 of the following: lymphopenia with ALC <1000, platelets <150k, albumin <=3g/dL, hyponatremia Na<135), consider the following evaluation:

a. Cardiac markers: troponin T and BNP

b. Other markers of inflammation: ferritin

c. Coagulation panel: PT, PTT, fibrinogen, D-dimer

d. Serology for SARS-CoV-2 (please contact Peds ID and request that order be placed)

e. SARS-CoV-2 PCR from nasopharyngeal swab

f. Additional labs as clinically indicated: Resp pathogen panel, GI biofire panel, lumbar puncture

g. Twelve-lead electrocardiogram (EKG)

h. Echocardiogram (transthoracic) – may be done after admission

i. Chest X-ray if not done previously

j. Early consultation of specialists to assist in management (as needed), such as PICU, cardiology, rheumatology, infectious diseases, neurology, nephrology

See diagram for further guidance regarding disposition. Admission to PICU if any signs of impending shock (i.e. tachycardia unresponsive to fluid, etc.), need for non-invasive or invasive

respiratory support (i.e. CPAP, BIPAP, mechanical ventilation), or other concerning labs suggestive of significant organ disease (i.e. elevated troponin)

Diagnosis:

Diagnosis is made as per the CDC criteria below. If acute disease with cytokine storm is suspected, please refer to pediatric COVID guidelines.

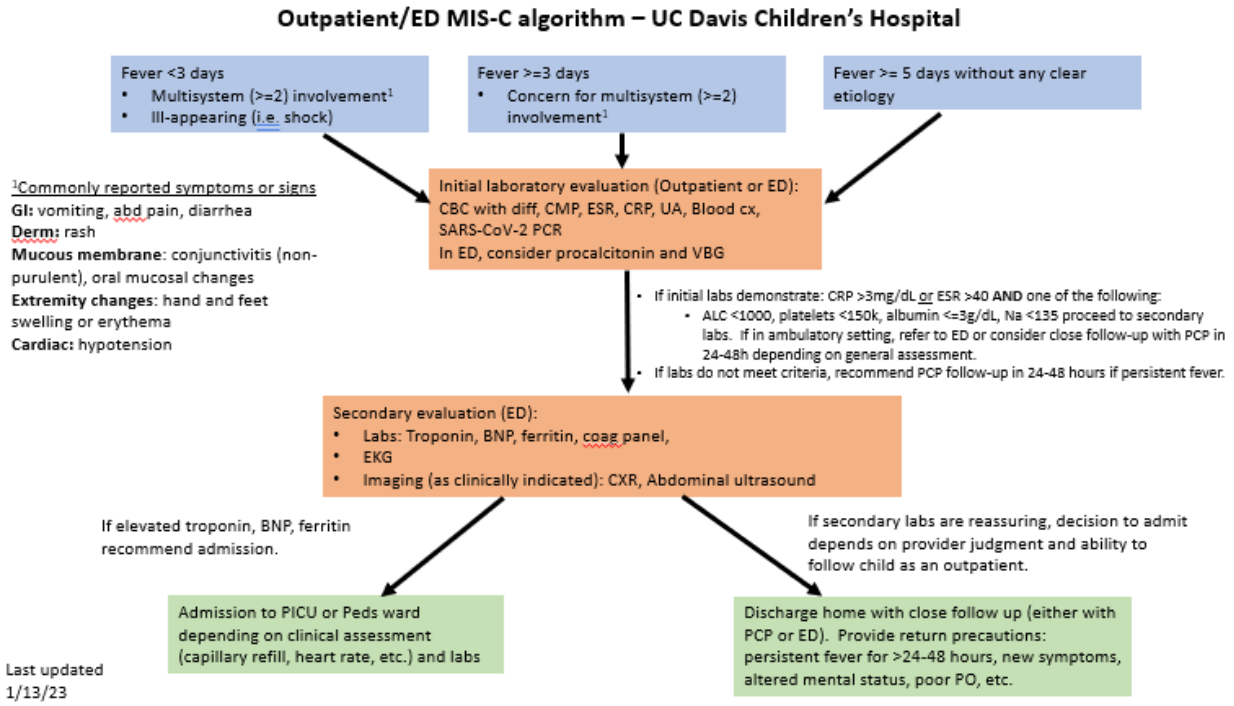


Table 1. Council of State and Territorial Epidemiologists/CDC surveillance case definition for multisystem inflammatory syndrome in children (MIS-C), updated December 2022.

Case definition classifications:

Confirmed case: Meets clinical and Laboratory criteria

Probable case: Meets clinical criteria and epidemiologic linkage criteria

Clinical criteria (all of the following must be met):

(1) Subjective or documented fever ≥ 38.0°C
(2) Clinical severity requiring hospitalization or resulting in death
(3) Evidence of systemic inflammation (indicated by CRP >3mg/dL)
(4) New onset manifestations in at least 2 of the following categories:
- Cardiac (EF <55%, coronary artery dilation or aneurysm, elevated troponin)
- Mucocutaneous involvement (rash, oral mucosal inflammation, conjunctival injection, extremity erythema or edema)
- Shock
- GI involvement (abdominal pain, vomiting, or diarrhea)

- Hematologic involvement (platelets <150,000 or absolute lymphocyte count <1000)

Laboratory criteria (any of the following):

(1) Detection of SARS-CoV-2 RNA in a clinical specimen up to 60 days before or during hospitalization
(2) Detection of SARS-CoV-2-specific antigen in a clinical specimen up to 60 days before or during hospitalization
(3) Detection of SARS-CoV-2-specific antibodies in blood associated with current illness

Epidemiologic linkage criteria

(1) Close contact with a confirmed or probable case of COVID-19 disease in the 60 days prior to hospitalization

Table 2. Treatment of MIS-C (dosages in table 4).

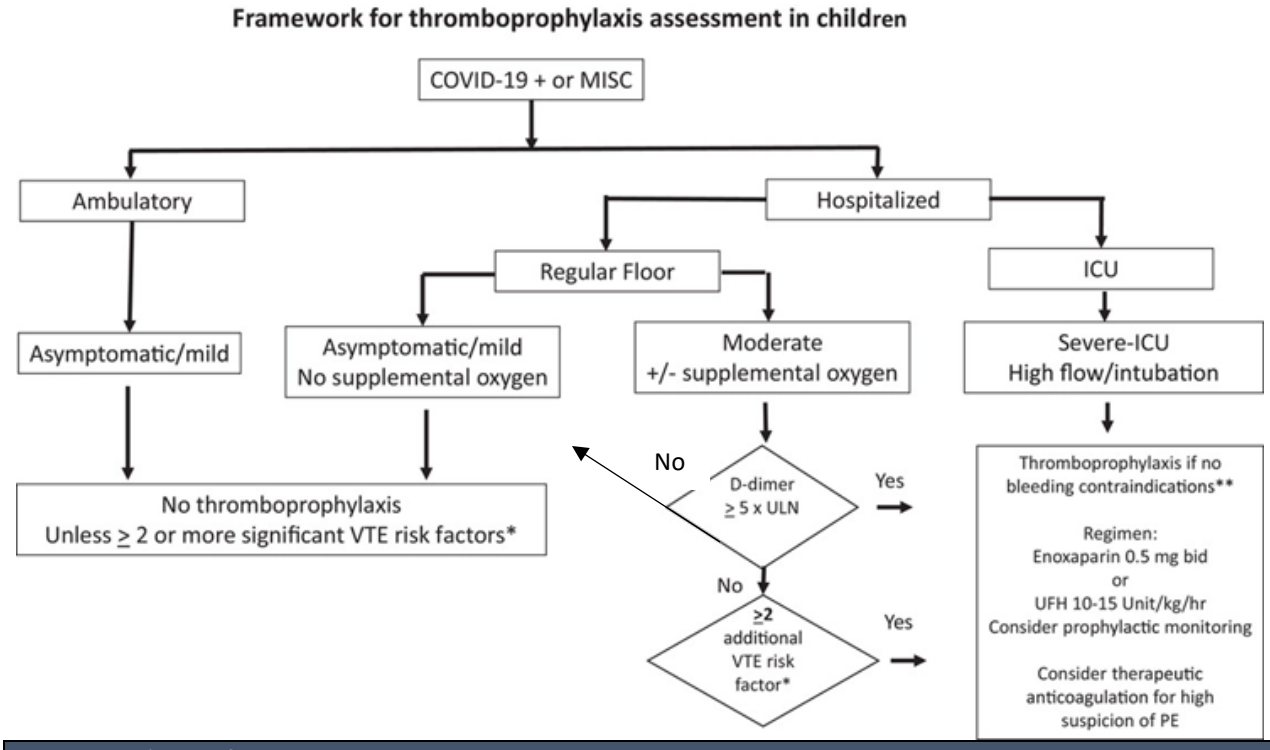
	Initial therapy	Refractory Disease
Steroids	Yes	Consider high dose pulsed steroids for severe, refractory cases
IVIG	See criteria below***	
Anakinra – requires CPCS approval	No	Consider for severe, refractory cases
Anticoagulation (see table below)	Low dose aspirin OR prophylactic enoxaparin as per Table 3. In some cases, aspirin may be added to enoxaparin as per cardiology discretion.	
GI protection	Yes	

CPCS = Clinical Pharmacology Consult Service

*** Criteria for IVIG*** (any of the following):

1) SARS-Co-V-2 positive test result by RT-PCR or serology **AND** ICU care **AND** Cardiovascular plus at least 1 other system involvement (cardiovascular involvement defined by: shock, LV dysfunction, coronary artery abnormality, significant troponin elevation, new valvular regurgitation)
2) Meets definition of Kawasaki Disease as per KD guideline
3) Meets criteria for hemophagocytic lymphohistiocytosis as per HLH-2004[11] or sJIA criteria[24]
4) Presence of coronary or peripheral aneurysms

Table 3. Anticoagulation guidelines for COVID-19 and MIS-C. Adapted from Sharathkumar et al. Pediatr Blood Cancer. 2021 Jul; 68(7).



Recommendations for use:	
Non-PICU admission	All patients with MIS-C should receive low-dose aspirin. Patients who are admitted to the pediatric ward do not need thromboprophylaxis with **enoxaparin** unless: 1. D dimer ≥ 5 times the upper limit of normal OR 2. ≥2 additional venous thromboembolism (VTE) risk factors: age ≥12 years, obesity, complete immobilization, central line, estrogen therapy, family history of VTE
PICU admission	Recommend **prophylactic** management with **enoxaparin or unfractionated heparin** for all COVID-19 patients unless otherwise contraindicated (platelet count <50,000, fibrinogen <100mg/dL, major bleeding). • Once patient is stable for transfer to ward, can usually be changed to aspirin unless they meet any of the criteria listed above (for non-PICU admission).
Hematology consult	• Rapidly increasing D-dimers • History of VTE • Patients with significant underlying medical conditions (i.e., malignancy, sickle cell disease or other hemoglobinopathy, cardiac disease, nephrotic syndrome, CF, autoimmune disease) • Patients with suspected or confirmed venous thrombo-embolism or pulmonary embolus
Discharge recommendations	• Consider stopping anticoagulation with enoxaparin at discharge unless patient has known thrombosis, central line, D dimer remains ≥ 5 times the upper limit of normal, or other medical conditions. In those situations, **please consult with pediatric hematology and arrange for outpatient follow up if they are discharged on enoxaparin.** All patients should continue low-dose aspirin until cardiology follow-up.
* For patients who do not meet requirements or are contraindicated for use with enoxaparin or UH, consider early ambulation and/or the use of sequential compression devices (SCDs). *If patients were previously on prophylactic dosing of enoxaparin or UH, they should be increased to treatment dosing *For initiation of heparin in COVID-19 patients, consult hematology and pharmacy to dose.	

In-hospital care

-Further tests to be considered depending on sub-specialty input: IL-6, anti-phospholipid antibody panel, quantiferon, hepatitis B panel
-Repeat CRP, CBC with diff, D dimer, ferritin, troponin T, BNP every 24-48 hours (do not repeat ESR as this will be affected by IVIG administration)
-If patient continues with fever or evidence of inflammation (i.e. persistently elevated CRP) 36-48 hours after administration of IVIG and/or steroids, please consult peds ID or peds rheumatology
-May consider use of anakinra or other immunomodulating drugs for severe or refractory cases
-Consider serial EKG or echocardiogram depending on initial studies, follow-up labs, and clinical status
-Consider discharge when patient has been afebrile for 36-48 hours with improving inflammatory markers and resolving multi-system organ involvement

Follow-up after hospital discharge (referrals should be placed prior to discharge):

-Follow up should be scheduled with pediatric cardiology 4 weeks after discharge

-Follow up should be scheduled with pediatric infectious diseases 1 week after the completion of steroid therapy

-Follow up to be scheduled with pediatric rheumatology if receiving anakinra at time of discharge.

-Follow up to be scheduled with pediatric hematology if patient is discharged home on enoxaparin

Discharge instructions for family (available as a smartphrase from Dr. Nakra .MISCDISCHARGE)

-Family should receive counseling about risk of adrenal insufficiency while on steroid wean. This should include directions about stress dose steroid use in the setting of fever, vomiting, or severe injury.

-If a child develops a fever within 7 days of discharge, they should be routed back to the UC Davis emergency room for evaluation.

-Please provide a flu shot for all children being discharged home on aspirin. Families should avoid any live vaccines for 11 months after receipt of high dose IVIG.

-Patients are eligible for COVID-19 vaccination once

(1) clinical recovery has been achieved (including return to baseline cardiac function) AND

(2) it has been >90 days from diagnosis of MIS-C. (*Caveat: If MIS-C occurred within 90 days of a prior COVID-19 vaccine, subsequent doses should be deferred at this time, except on a case-by-case basis, such as strong evidence that MIS-C occurred due to a recent SARS-CoV-2 infection*).

Table 4. Doses for immunomodulatory agents in the treatment of MIS-C.

Medication Class	Dose	Important Notes
IVIG	1–2 g/kg IV in a single dose or divided doses per attending discretion (Consider dividing dose or giving lower dose if cardiac dysfunction fluid overload, renal dysfunction.) Dosing based on ideal body weight.	IVIG may increase risk of hypercoagulability so initiate anticoagulation prior to administration of IVIG. Obtain blood for SARS-CoV-2 serology and other serologic tests (i.e.antiphospholipid antibodies) prior to administration. Side effects: anaphylaxis, infusion reaction, hemolysis, increased creatinine, aseptic meningitis, transaminitis No live viral vaccines for 11 months after IVIG.
Corticosteroids	Iniital treatment: Days 1-5: Methylprednisolone 1 mg/kg/dose IV q12h (max: 60 mg/day) – can switch to PO earlier as per peds ID recommendation Days 6-10: Prednisolone (or prednisone) 1 mg/kg/dose BID (max: 40 mg/day) Days 11-15: Prednisolone 0.5 mg/kg/dose BID (max: 20 mg/day) Days 16-20: Prednisolone 0.5mg/kg/dose once a day (max: 10 mg/day) Severe, refractory patients: In patients who are refractory to IVIG and steroids (ongoing hypotension, need for multiple pressors, worsening end organ disease), consider high-dose pulse steroids (below) followed by 20 day steroid wean as above Day 1: Methylprednisolone 10 mg/kg/dose q12h (max: 500mg/day) Days 2-5: Methylprednisolone 2 mg/kg/dose IV q12h (max: 60 mg/day; can switch to PO sooner if response is seen)	After completing steroid wean, early morning cortisol level should be obtained 1 week later (typically in peds ID clinic). If low, consider referral to pediatric endocrinology. Side effects: hypertension, hyperglycemia, electrolyte abnormalities, behavioral changes, dyspepsia, muscle weakness
Anakinra	Severe, refractory patients: • 4 mg/kg q12h IV/SQ (max 200mg/dose) – higher doses may be needed in recalcitrant cases • Can change to 4 mg/kg once daily (max 200mg/dose) if the following criteria are met: afebrile for >24 hours, weaned off vasoactives, significant reduction in CRP/other inflammatory markers • Recommend minimum 5-day course (but can be extended if slow response to treatment)	Please send quantiferon and Hepatitis B serology prior. Monitor LFTs while on anakinra. Side effects: anaphylaxis, neutropenia, eosinophilia, transaminitis, immunosuppression Avoid live viral vaccines

Aspirin	3–5 mg/kg/d (max 81mg/day) until follow up with cardiology	Precaution if platelets <80,000/µL Side effects: GI upset, allergic reaction, bleeding, tinnitus, interstitial nephritis. Reye's syndrome can occur in setting of active influenza or varicella infection. Consider influenza vaccine at time of discharge during flu season.
Enoxaparin	Prophylaxis: 1 to < 2 months: 0.75mg/kg SQ every 12 hours ≥ 2 months: 0.5mg/kg SQ every 12 hours Treatment: 1 to <3months: 1.8mg/kg/dose SQ q 12 hours 3-12 months: 1.5mg/kg/dose SQ q 12 hours 1-5 years: 1.2mg/kg/dose SQ q 12 hours 6-18 years: 1mg/kg/dose SQ q 12 hours	If thrombosis present or rapidly rising D-dimer, increase to treatment dosing. With treatment dosing, monitoring with anti-Xa levels is recommended. Side effects: Reactions at injection site, bleeding
Famotidine	0.5mg/kg IV or PO once a day (max 20mg)	

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