CLINICAL GUIDELINE | SUSPECTED MULTISYSTEM INFLAMMATORY SYNDROME IN CHILDREN (MIS-C), POSSIBLY ASSOCIATED WITH COVID-19 (Age < 21 years)

Children's MINNESOTA

Aim: To standardize MIS-C management based upon best available evidence.

Patients with all of the following:
- Fever ≥ 38º C
- At least 2 suggestive clinical features (rash, GI symptoms, hand/foot edema, conjunctivitis, mucosal changes, lymphadenopathy, neurological changes) (See page 7)
- May also have link to COVID-19 (See Note 1)

→

- History, exam + vital signs (VS) inc. BP
- O_2 to keep sats > 90%
- Consider and investigate alternate etiologies as indicated

Categorize patient

Patient stable:
- Reassuring VS for age
- Tolerating PO
- Well-appearing

↓

- **Obtain Tier 1 labs:** SARS CoV-2 PCR and serology, CBC w/ diff, CRP, ESR, CMP
- Additional tests if indicated per symptoms (e.g., strep swab)

↓

Assess for following:
1. CRP ≥ 3 mg/dL OR ESR ≥ 40 mm/hr AND
2. At least 1 additional suggestive lab abnormality
   - ALC < 1000/ul
   - Platelets < 150,000/ul
   - Na < 135 mmol/L
   - Neutrophilia (ANC > 7,700)
   - Albumin < 3

3. AND No alternate probable diagnostic explanation for symptoms and lab findings.

OR

Labs or exam concerning but not clearly consistent with MIS-C

No ←

MIS-C not suspected
Manage off-guideline, re-evaluate if symptoms do not improve in 1–2 days

Yes →

Any instability including:
- Low BP, tachycardia or tachypnea for age
- Increased work of breathing or O_2 sat < 90%
- Poor perfusion or altered mental status
- Ill-appearing
- Unable to maintain hydration by PO

↓

Transfer to ED for possible MIS-C or other diagnosis
Children's Minnesota Physician Access: 612-343-2121

NOTE 1
Link includes ANY of the following criteria: + COVID-19 PCR or serology, preceding illness resembling COVID-19 or close contact with confirmed or suspected COVID-19 cases in the past 4–6 weeks. Link is not required for MIS-C diagnosis.

EXCLUSION GUIDELINES:
Patients **excluded** from this guideline: **Patients with alternate probable etiology of illness.** DDx includes: Bacterial sepsis, toxic shock syndrome, Kawasaki Disease (KD), appendicitis, Hemophagocytic Lymphohistiocytosis (HLH) or Macrophage Activation Syndrome (MAS), rickettsia, viral syndrome (CMV, EBV, Adenovirus, Coxsackie, varicella, etc.), bacterial enteritis, lupus, vasculitis.

ED GUIDELINE | SUSPECTED MULTISYSTEM INFLAMMATORY SYNDROME IN CHILDREN (MIS-C), POSSIBLY ASSOCIATED WITH COVID-19 (Age < 21 years)

Children's MINNESOTA

Aim: To standardize MIS-C management based upon best available evidence.

Patients with all of the following:
- Fever ≥ 38º C
- At least 2 suggestive clinical features: rash, GI symptoms, hand/foot edema, conjunctivitis, mucosal changes, lymphadenopathy, neurological changes (see page 7)
- May also have link to COVID-19. (see Note 1)

- History, exam + vital signs (VS) including BP
- O_2 to keep sats > 90%
- Consider and investigate alternate etiologies as indicated

Categorize patient

EXCLUSION GUIDELINES:
Patients **excluded** from this guideline: **Patients with alternate probable etiology of illness.** DDx includes: Bacterial sepsis, toxic shock syndrome, Kawasaki Disease (KD), appendicitis, HLH/MAS, rickettsia, viral syndrome (CMV, EBV, Adenovirus, Coxsackie, varicella, etc.), bacterial enteritis, lupus, vasculitis.

Patient well-appearing
w/ normal VS aside from fever

- Obtain Tier 1 labs* (ED suspected MIS-C order set)
- Add Tier 2 Floor labs if high clinical suspicion for MIS-C
- Add CXR if resp symptoms

Do Tier 1 labs show all of the following?
1. CRP ≥ 3 mg/dL OR ESR ≥ 40 mm/hr
2. At least 1 of the following
   - ALC < 1000/ul
   - Platelets < 150,000/ul
   - Na < 135 mmol/L
   - Neutrophilia (ANC > 7,700)
   - Albumin < 3

PLUS No alternate probable diagnosis

No

MIS-C not suspected. Manage off-guideline, re-evaluate if symptoms do not improve in 1–2 days.

Yes

Add Tier 2 Floor labs* if not yet obtained

Patient ill-appearing; hypotension, poor perfusion, signs of sepsis, toxidrome/ toxic shock **or with Kawasaki Disease (KD) criteria**

- Stabilize patient: PIV, fluid resuscitate (caution with boluses)
- Add CXR if resp symptoms. Consider adding limited abdominal US based on location of pain.
- Obtain Tier 1 and Tier 2 PICU labs. Add Tier 3 if toxin-mediated suspected
- Consult ID
- Consider other guidelines/order-sets (e.g., sepsis)
- If meets KD criteria, discuss with ID and utilize KD guideline

Labs suggestive of MIS-C?
Most patients have ≥ 4 abnl markers of inflammation
- **Evidence of inflammation:** CRP ≥ 3 mg/dL, ESR > 40 mm/h, ferritin > 500 ng/mL, ANC > 7700, ALC < 1000, platelet < 150k, D-Dimer > 2 mg/L, fibrinogen > 400 mg/dL, albumin < 3 g/dL, anemia, ALT > 40 U/L, INR > 1.2
- **Other:** AKI, hyponatremia, high LDH, high troponin, BNP > 400 pg/mL, prolonged PT or PTT, elevated procalcitonin, low albumin

No

Yes

MIS-C suspected, complete additional workup:
- CXR, EKG. Get ECHO in ED only if hemodynamic instability.
- Call ID from ED.
- Give methylprednisolone IV 2 mg/kg (max 60 mg) if MIS-C felt likely.
- PICU if any signs of cardiac dysfxn (abnl EKG or troponin-obtain result before transfer), shock/hypotension, high resp support, or concern for rapid progression.
- Med-Surg if not meeting PICU criteria.

***Laboratory tiers.**
Workup other etiologies as indicated.
- **Tier 1:** SARS CoV-2 PCR and serology, CBC w/ diff, CRP, ESR, CMP. Additional tests if indicated per symptoms (e.g., strep swab).
- **Tier 2 Floor:** blood culture, UA/UCx, procalcitonin, serum to save, IgG, IgA, IgM, BNP, troponin, CPK, D Dimer, PT, PTT, Fibrinogen, ferritin, type and cross, MRSA nasal swab.
- **Tier 2 PICU:** blood culture, UA/UCx, lactate, blood gas, procalcitonin, serum to save, IgG, IgA, IgM, BNP, troponin, LDH, CPK, D Dimer, PT, PTT, Fibrinogen, ferritin, TG, type and cross, cytokine storm and cytokine inflammation panels, MRSA nasal swab.
- **Tier 3:** Vaginal swab for Group A Strep and Staph aureus (order "Genital culture").

NOTE 1
Link includes ANY of the following criteria: + COVID-19 PCR or serology, preceding illness resembling COVID-19 or close contact with confirmed or suspected COVID-19 cases in the past 4–6 weeks. Link is not required for MIS-C diagnosis.

SUSPECTED MULTISYSTEM INFLAMMATORY SYNDROME IN CHILDREN (MIS-C), POSSIBLY ASSOCIATED WITH COVID-19 (Age < 21 years)

Aim: To standardize MIS-C management based upon best available evidence.

Initial ICU management

- **Echo:** Obtain after admission. Telemetry x 72 hours or until cardiology discontinues.
- **Use empiric antibiotics** in all patients with severe MIS-C until cultures negative for 48 hour or as directed by ID. Ceftriaxone should be used, in addition to therapy targeted to the clinical presentation (e.g., ceftriaxone PLUS metronidazole for possible appendicitis; ceftriaxone PLUS vancomycin and clindamycin for possible toxic shock).
- **Consults:** ID, Immunology and Cardiology for all ICU patients. Hematology if questions not addressed on guideline. Endocrine 2 days prior to discharge for patients on steroids anticipated 2 weeks or more. Additional consultants if indicated by co-morbid conditions (e.g., surgery if concern for appendicitis).
- **IVIG:** Give 2 g/kg x 1 (use ideal body weight, max dose 100 g). See Note 2 for repeat dose. In patients with cardiac dysfunction, IVIG may be given in divided doses (1 g/kg/day over 2 days)
- **Steroids:** All patients should receive methylprednisolone 2 mg/kg at minimum. For patients who have hypotension, diminished cardiac function, or require inotropic/vasopressor support, bolus methylprednisolone 10 mg/kg/day (max 1,000 mg/day). For patients with ongoing requirement for moderate to high dose vasopressor (i.e. norepinephrine or epinephrine > 0.25 mcg/kg/min), strongly consider methylprednisolone 20–30 mg/kg/day (max 1,000 mg/day).
- **Aspirin:** Use low-dose (3–5 mg/kg/day with max dose of 81 mg/day) in MIS-C (including if KD features) unless platelet count is < 80,000 (as guided Cardiology). Note: ok to use prophylactic enoxaparin with low- dose aspirin (which adds anti platelet and coronary artery protection).
- **VTE prophylaxis** unless contraindication (see VTE guideline) until hospital discharge
- **Therapeutic anticoagulation:**
  - Patients with CAA z-score of ≥ 5 should be treated with low-dose aspirin and therapeutic anticoagulation with enoxaparin (factor Xa level 0.5–1.0) or warfarin
  - Patients with EF < 35% or documented thrombosis should be treated with therapeutic anticoagulation alone (no aspirin needed)
- **GI prophylaxis** until off steroids

Trending of labs and EKGs in ICU patients

- CBC w/ diff, CRP, BMP, d-dimer, ferritin Q day until afebrile and labs improving x 3 days
- Troponin Q6 hr, decrease as indicated
- BNP Q48 hr or sooner if clinical worsening
- Repeat other labs as indicated
- EKG Q48 hrs to monitor QT interval or sooner if clinical worsening

Repeat inpatient Echo frequency

- **Initial normal:** 1–2 weeks and 4–6 weeks
- **Initial abnormal** with CA z-score > 2.5: repeat Q 2–3 days until CA aneurysm stable, then weekly until discharge.
- Repeat echo earlier if clinical worsening

Transfer to Med-Surg unit once meeting criteria

- No ongoing cardiac dysfunction or shock
- Normalized troponin
- Respiratory support at levels allowed on med-surg unit

NOTE 2

Refractory or rapidly progressive disease

- Defined in ACR guidelines as persistent fevers and/or ongoing and significant end organ involvement. Timing of fever in relation to IVIG is not defined. For Kawasaki Disease this has been 36 hours *after* completion of IVIG.
- Discuss treatment options with consultants.
- Repeating IVIG is **not** recommended, though should also be discussed with consultants if presentation more similar to KD.
- For patients with ongoing requirement for moderate to high dose vasopressor (i.e., norepinephrine or epinephrine > 0.25 mcg/kg/min), strongly consider methylprednisolone 20–30 mg/kg/day (max 1,000 mg/day).
- *In some cases anakinra* 2–10 mg/kg/dose (max 100 mg/dose) SQ/IV q6–12h *may be needed. Tocilizumab has also been used for refractory MIS-C per RECOVERY 2024*
- Revisit differential diagnosis.

MED-SURG GUIDELINE | SUSPECTED MULTISYSTEM INFLAMMATORY SYNDROME IN CHILDREN (MIS-C), POSSIBLY ASSOCIATED WITH COVID-19 (Age < 21 years)

Children's MINNESOTA

Aim: To standardize MIS-C management based upon best available evidence.

Initial Med-Surg management: Change to full management on page 5 if case definition is met

- **Echo:** Obtain non-urgently after admission.
- **Neuroimaging:** Consider if neurological changes concerning for clot/stroke.
- **Fluids:** Resuscitate in 10 ml/kg aliquots with re-evaluation after each bolus. Maintain euvolemia.
- **Consults:** ID for all patients. Consider immunology consult.
- **VTE prophylaxis:** See COVID-19 VTE guideline to determine if patient meets criteria.
- **Investigate alternate potential etiologies.** Differential diagnosis for MIS-C is broad and includes bacterial sepsis, toxic shock syndrome, Kawasaki Disease, appendicitis, HLH/MAS, rickettsia, viral syndrome (CMV, EBV, Adenovirus, Coxsackie, varicella, etc.), bacterial enteritis, SLE, vasculitis and other diseases.

Trending of labs and EKGs in Med-Surg patients with mild disease (See Note 3) **who do not yet meet MIS-C case definition and without alternate diagnosis identified**

- **Mild:** CBC w/ diff, CRP, BMP, ferritin Q day until afebrile and labs improving x 1 day then may do PRN for any clinical worsening. Repeat troponin and BNP if clinical worsening or persistent fever. EKG Q48 hours. Repeat Echo if clinical worsening or cardiac markers become abnormal (change to full management page).

Repeat labs or evolution of symptoms suggestive of MIS-C without other likely cause?

Most patients have ≥ 4 abnl markers of inflammation

- **Evidence of inflammation:** CRP ≥ 3 mg/dL, ESR > 40 mm/h, ferritin > 500 ng/mL, ANC > 7700, ALC < 1000, platelet < 150k, D-Dimer > 2 mg/L, fibrinogen > 400 mg/dL, albumin < 3 g/dL, anemia, ALT > 40 U/L, INR > 1.2
- **Other:** AKI, hyponatremia, high LDH, high troponin, BNP > 400 pg/mL, prolonged PT or PTT
- **Symptoms:** Fever ≥ 38.0C, epidemiologic link to SARS-CoV-2 infection (not required) and at least 2 suggestive clinical features (rash, GI symptoms, hand/foot edema, conjunctivitis, mucosal changes, lymphadenopathy, neuro changes) (See page 7)

No →

Discharge criteria:

- CRP, ferritin and d-dimer improving or not meeting MIS-C thresholds
- Afebrile
- Blood cultures without growth x 24 hr, if applicable
- EKG without arrhythmia
- Tolerating enteral diet
- Not requiring oxygen
- Follow-up with PCP

Yes ↓

MIS-C Suspected

- CXR, EKG
- Refer to page 5 for full management

NOTE 3

Disease Severity

- *Not well defined in literature.*
- **Mild:** Borderline or mild case. Normal VS apart from fever, no inpt criteria other than poor PO, mild dehydration or monitoring for worsening.
- **Moderate:** Meets case definition without shock or other ICU criteria.
- **Severe:** Meets case definition and any ICU criteria: ill-appearing, evidence of organ dysfunction/injury, require for respiratory or cardiovascular support.

MED-SURG GUIDELINE

SUSPECTED MULTISYSTEM INFLAMMATORY SYNDROME IN CHILDREN (MIS-C), POSSIBLY ASSOCIATED WITH COVID-19 (Age < 21 years)

Children's MINNESOTA

Aim: To standardize MIS-C management based upon best available evidence.

Initial Med-Surg management:
Patients **not** meeting ICU criteria (any cardiac dysfunction or shock and/or sepsis). Note, if patient meets classic Kawasaki Disease criteria, consider KD guideline if no other MIS-C features.

- **Echo:** Obtain after admission. Telemetry x 24 hours or until cardiology discontinues.
- **Fluids:** Resuscitate in 10 ml/kg aliquots with re-evaluation after each bolus. Maintain euvolemia.
- **Use empiric antibiotics** in all patients with moderate MIS-C until cultures negative for 48 hour or as directed by ID. Ceftriaxone should be used, in addition to therapy targeted to the clinical presentation (e.g., ceftriaxone PLUS metronidazole for possible appendicitis; ceftriaxone PLUS vancomycin and clindamycin for possible toxic shock). For patients with mild disease and normal vital signs discuss antibiotic need with ID.
- **Consults:** ID: for all patients. For patients with MIS-C who are worsening clinically or who are critically ill, please consult immunology urgently. Cardiology: for all patients with cardiac abnormalities or refractory disease. Hematology: if questions not addressed on guideline. Endocrine: 2 days prior to discharge for patients on steroids anticipated total 2 weeks or more. Additional consultants if indicated by co-morbid conditions (e.g., surgery if concern for appendicitis).
- **IVIG:** Give 2 g/kg x 1 (use ideal body weight, max dose 100 g). (See Note 3 and 4)
- **Steroids:** Give Methylprednisolone 2 mg/kg/day (max 60 mg/day). Timing of weaning and duration of steroids depends on clinical severity (note 3). See page 7 for weaning inpatient/outpatient and follow-up.
- **Aspirin:** Use low-dose (3–5 mg/kg/day with max dose of 81 mg/day) in MIS-C (including if KD features) unless platelet count is < 80,000 (as guided by cardiology). Note: ok to use prophylactic enoxaparin with low-dose aspirin (which adds anti-platelet and coronary artery protection).
- **VTE prophylaxis** unless contraindication (see VTE guideline) until hospital discharge
- **Therapeutic anticoagulation:**
  - Patients with CAA z-score of ≥ 5 should be treated with low-dose aspirin and therapeutic anticoagulation with enoxaparin (factor Xalevel 0.5–1.0) or warfarin.
  - Patients with EF < 35% or documented thrombosis should be treated with therapeutic anticoagulation alone (no aspirin needed).
- **GI prophylaxis** until off steroids

Trending of labs and EKGs in Med-Surg patients, by disease severity (See Note 3)

- **Mild:** CBC w/ diff, CRP, BMP, ferritin Q day until afebrile and labs improving x 1 day then may do PRN for clinical worsening. Repeat troponin and BNP if clinical worsening/persistent fever. EKG Q48 hr.
- **Moderate:** CBC w/ diff, CRP, BMP, ferritin Q day until afebrile and labs improving, then may do PRN for any clinical worsening. Repeat troponin Q6 hr until normalized and BNP and d-dimer Q48 hr — repeat cardiac markers sooner if clinical worsening or persistent fever. Non-urgent cardiology consult if increasing cardiac markers. EKG Q48 hours to monitor QT. Immunology service to advise on timing of repeat cytokine panels if indicated.

Repeat inpatient Echo frequency

- **Initial normal:** 1–2 wks and 4–6 wks
- **Initial abnormal** with CA z-score > 2.5: repeat Q 2–3 days until CA aneurysm stable, then weekly until discharge
- Repeat echo earlier if clinical worsening

NOTE 3

Disease severity

- *Not well defined in literature.*
- **Mild**: Borderline or mild case. Normal VS apart from fever, no inpt criteria other than poor PO, mild dehydration or monitoring for worsening.
- **Moderate:** Meets case definition without shock or other ICU criteria.
- **Severe:** Meets case definition and any ICU criteria: ill-appearing, evidence of organ dysfunction/injury, require for respiratory or cardiovascular support.

NOTE 4

Refractory disease

- Defined in ACR guidelines as persistent fevers and/or ongoing and significant end organ involvement. Timing of fever in relation to IVIG is not defined. For Kawasaki Disease, this has been 36 hours *after* completion of IVIG.
- Discuss treatment options with immunology.
- Repeating IVIG is **not** recommended, though should also be discussed with consultants if presenting similar to KD
- Revisit differential diagnosis.
- Consider PICU transfer.
- All patients with severe illness (ICU) should receive methylprednisolone 10–30 mg/kg/day IV (max 1,000 mg/day).

DISCHARGE CRITERIA (see page 6-7):

- CRP, ferritin and d-dimer improving
- Afebrile x 48 hours
- Blood cultures without growth x 48 hours
- EKG without arrhythmia
- Latest echo stable/improved
- Tolerating enteral diet
- Not requiring oxygen
- Follow-up coordinated

Aim: To standardize MIS-C management based upon best available evidence.

POST-HOSPITAL CARE

INITIAL FOLLOW-UP PLAN

- Follow up with PCP in 2–3 days. Only repeat labs if they had not normalized prior to discharge. Labs include CRP, CBC w/ differential, BNP, Troponin, D-Dimer. Labs can then be repeated if the patient develops any recurrence of fever/rash/GI symptoms during the steroid wean. For patients who stay asymptomatic, labs should be repeated again prior to transition to hydrocortisone (if applicable).
- Follow-up with cardiology 1–2 weeks after discharge with repeat EKG and Echo.
- Follow-up with endocrinology via telehealth if anticipated duration of steroids is 2 weeks or more, see below.
- Follow-up 4–6 weeks with cardiology with Echo, consider cardiac MRI 1–3 months.
- Discharge medications: low-dose aspirin until cardiology discontinues and gastritis prophylaxis until off steroids. Patients will not routinely be discharged on anticoagulation (aside from aspirin) regardless of d-dimer unless there is clinical diagnosis of VTE or a need based on significantly abnormal CAA z-score or ejection fraction.
- See page 7 for steroid wean information. Primary team will calculate and prescribe the wean doses and steps as part of discharge plan (see page 7). Endocrine will follow patients needing 2 weeks or more of steroids with a telehealth appointment in order to plan the stress wean and ACTH stim test. Endocrinology will not be responsible for adjusting steroids in response to recurrence of MIS-C clinical symptoms or lab changes.

WHEN TO CONSIDER READMISSION

- Any recurrent fever or other recurrence of symptoms (rash, mucositis, conjunctivitis, vomiting/diarrhea, neurological changes, chest pain, etc.) should prompt urgent evaluation by primary provider. If patient is stable and can be assessed by outpatient provider within 6–12 hours, that may be considered. Otherwise refer patient to local ED (if > 60 minutes away) or to Children's Minnesota emergency department (ED).
- If seen in primary clinic with recurrence of symptoms, obtain full exam + VS including BP. If unstable transfer to Children's Minnesota ED. If stable and no alternate source of illness is suspected, may obtain labs: CBC w/ diff, CRP, ESR, ferritin, procalcitonin, CMP. Consider troponin, d-dimer, UA, urine culture, blood culture, rapid strep. Outpatient providers should contact ID or immunology to discuss whether re-evaluation at Children's Minnesota is needed. Worsening laboratory markers (e.g., increasing CRP) in absence of clinical signs should prompt outpatient discussion with specialists (ID, immunology, cardiology, hematology depending on the laboratory study).
- Call Children's Minnesota Physician's Access 866-755-2121 to be connected with specialists on-call and/or ED

EDUCATION FOR FAMILY

- Avoid NSAIDs while on aspirin.
- No live-virus vaccines x 11 months if IVIG was given *(pts at high risk of exposure may receive sooner and be reimmunized after 11 months if they have an inadequate serological response*).
- Risks of IVIG include hemolytic anemia and aseptic meningitis.
- Discuss plan for recurrent fever or other KD symptoms (rash, mucositis) with family — recommend any symptoms be evaluated by PCP or ED ASAP.
- Families should receive teaching on stress-dose steroids.
- Limit exercise and strenuous activity until cleared by cardiology, *anticipate several months.*
- COVID-19 vaccination may be considered in patients who are at least 90 days out from their MIS-C diagnosis and have fully recovered (including normal cardiac function). Given limited data in this patient population, recommend using a shared decision-making approach to weigh the risks vs. benefits of COVID-19 vaccination for each patient.
- Seasonal influenza vaccine is recommended in patients with MIS-C. Timing considerations should include local circulating influenza and dose of steroid medicine (e.g., may wait until on lower steroid dose if low circulating influenza).

SUSPECTED MULTISYSTEM INFLAMMATORY SYNDROME IN CHILDREN (MIS-C), POSSIBLY ASSOCIATED WITH COVID-19 (Age < 21 years)

Children's MINNESOTA

Aim: To standardize MIS-C management based upon best available evidence.

ADDITIONAL NOTES

Differential diagnosis for MIS-C includes bacterial sepsis, toxic shock syndrome, Kawasaki Disease (KD), appendicitis, hemophagocytic lymphohistiocytosis (HLH) or macrophage activation syndrome (MAS), rickettsia, viral syndrome (CMV, EBV, Adenovirus, Coxsackie, varicella, etc.), bacterial enteritis, lupus, vasculitis and other conditions.

STEROID DOSING + TAPER SUGGESTIONS (DISCUSS WITH CONSULTANTS AND PHARMACIST):

- Initial doses based on severity of case per MIS-C management on page 3 or 5.
  - *Mild cases may only need steroids for a few days with no taper required.*
  - *Typical duration for steroids (including tapers) are 2-3 weeks for moderate-severe cases.*
  - *See last bullet for information on refractory or rapidly progressive cases.*
- **Transition to oral steroid therapy:** Transition from IV methylprednisolone to oral prednisolone (liquid) or oral prednisone (tablet) using the following conversion: 4 mg methylprednisolone = 5 mg prednisolone or prednisone. If a mild or moderate case is being treated with IV steroids and there is very rapid improvement, consider transitioning to oral steroids when patient has been afebrile for 24-48 hours and down-trending inflammatory markers. Decision to transition to oral steroids for moderate and severe cases should be made in conjunction with multidisciplinary teams.
- **Tapers**:
  - If a taper is needed for moderate-severe cases, initiate taper when patient has clinically improved (e.g., off pressors, off respiratory support, afebrile, down-trending CRP) and then reduce steroid dose by 10–15% every 3 days while inpatient. The speed of the taper while inpatient (e.g., 15% vs. 20% decreases) should be guided by clinical response and inflammatory markers (e.g., fever, CRP.
  - For refractory or rapidly progressive cases (see criteria on page 3 note 2), methylprednisolone 10–30 mg/kg/day (max 1,000 mg/day) for 1–3 days, then 2 mg/kg/day (max 60 mg/day) and taper over 4–8 weeks on a case-by-case basis with immunology involvement (re: acute wean) and endocrinology (re: stress wean).
- **Outpatient steroid plan:**
  - Reduce steroid dose by 15–25% every 3–5 days while outpatient (taper over 2 weeks if inpatient steroid duration was >1 week)
  - Extended duration of steroid taper for severe cases should be determined by immunology in discussion with the primary team (e.g., hospitalist/intensivist). *The purpose of a prolonged steroid taper in severe MIS-C is prevention of rebound inflammation.*
  - At the time of discharge, the full taper for the outpatient stage will be prescribed by the hospitalist team. Subsequently, the outpatient primary provider may consider changes to intended taper if needed based upon clinical response and inflammatory markers. PCP can contact Immunology if concerns regarding steroids/clinical response/relapse.
  - Patients receiving steroids for an anticipated duration of 2 weeks or more need to have an ACTH stim test. Hospitalist/intensivist to consult endocrinology 2 days prior to discharge for these cases.

OUTCOMES

- Limited data suggests good short-term outcomes in patients with MIS-C, with most patients achieving recovery to normal cardiac function by 6 months .
- In one study of 50 patients with MIS-C, they found that at 2 weeks, there was persistent mild LV systolic dysfunction in 1 patient, coronary aneurysms in 2, and dilated coronary artery in 1. By 8 weeks through 6 months, all patients returned to functional baseline with normal LV systolic function and resolution of coronary abnormalities. Cardiac MRI performed during recovery in select patients revealed no myocardial edema or fibrosis. Some patients demonstrated persistent diastolic dysfunction at 2 weeks (5, 11%), 8 weeks (4, 9%), and 6 months (1, 4%).

Clinical features/evidence of MIS-C

- Most patients have ≥ 4 organ system involvement; ≥ 2 required for diagnosis.
- Involvement of the following systems (percent of patients in case series):
  - Gastrointestional (92%) - abdominal pain, vomiting/diarrhea, some patients with MIS-C may also have appendicitis
  - Cardiovascular (80%) - Chest pain, tachycardia
  - Hematologic (76%) - cell line abnormalities, thrombosis
  - Mucocutaneous (74%, 59% rash) - strawberry tongue, cracked lips, sore throat, polymorphic rash
  - Respiratory (70%) - SOB, cough, tachypnea
  - Musculoskeletal (23%) - hand/foot redness or swelling
  - Renal (8%)
  - Neurologic (6%) - headache, irritable, altered mental status, CN palsy
  - Lymphadenopathy
- Recent COVID-19 illness ***or*** exposure (note: not necessary to suspect MIS-C)

Lab evidence of MIS-C

No lab criteria is diagnostic; most patients have 4 or more markers of inflammation (see page 2)

Adapted from Feldstein LR, Rose EB, Horwitz SM, Collins JP, Newhams MM, Son MBF, et al. Multisystem Inflammatory Syndrome in U.S. Children and Adolescents. *N Engl J Med* [internet]. 2020; Available from: http://www.ncbi.nlm.nih.gov/pubmed/32598831

Aim: To standardize MIS-C management based upon best available evidence.

REFERENCES/RESOURCES

- CDC's 24-hour Emergency Operations Center: 770-488-7100
- American College of Rheumatology Guideline
- Evelina London Clinical Guideline https://pubmed.ncbi.nlm.nih.gov/33277976/
- Royal College of Paediatrics and Child Health: https://www.rcpch.ac.uk/sites/default/files/2020-05/COVID-19-Paediatric-multisystem-%20inflammatory%20syndrome-20200501.pdf
- CDC: Health Alert Network (HAN) No. 432 — Multisystem Inflammatory Syndrome in Children (MIS-C) Associated with Coronavirus Disease 2019 (COVID-19) 05/14/2020
- https://www.who.int/publications-detail/multisystem-inflammatory-syndrome-in-children-and-adolescents-with-COVID-19
- Viner and Whittaker. "Kawasaki-like disease: emerging complication during the COVID-19 pandemic." *Lancet* May13, 2020
- Verdonietal. "An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic" May 13, 2020 Lancet
- Toubiana et al., "Outbreak of Kawasaki disease in children during COVID-19 pandemic: a prospective observational study in Paris, France." medrix
- Riphagen et al., "Hyperinflammatory shock in children during COVID-19 pandemic." *Lancet* May7, 2020
- DeBiasi et al., "Severe COVID-19 in Children and Young Adults in the Washington, DC Metropolitan Region" *JPeds* May12, 2020
- CHOP Pathway CDC COCA webinar 5-19-2020: https://emergency.cdc.gov/coca/calls/2020/callinfo_051920.asp
- NY Presbyterian Kids Clinical Guideline
- Mayo Clinic Clinical Guideline
- Feldstein LR, Rose EB, Horwitz SM, Collins JP, Newhams MM, Son MBF, et al. Multisystem Inflammatory Syndrome in U.S. Children and Adolescents. *N Engl J Med* [internet]. 2020; Available from: http://www.ncbi.nlm.nih.gov/pubmed/32598831
- Whittaker E, Bamford A, Kenny J, Kaforou M, Jones CE, Shah P, et al. Clinical Characteristics of 58 Children With a Pediatric Inflammatory Multisystem Syndrome Temporally Associated With SARS-CoV-2. *JAMA* [internet]. 2020 Jun 8 [cited 2020 Jun 15]; Available from: https://jamanetwork.com/journals/jama/fullarticle/2767209
- Cheung EW, Zachariah P, Gorelik M, Boneparth A, Kernie SG, Orange JS, et al. Multisystem Inflammatory Syndrome Related to COVID-19 in Previously Healthy Children and Adolescents in New York City. *JAMA* [internet]. 2020 Jun 8 [cited 2020 Jun 15]; Available from: https://jamanetwork.com/journals/jama/fullarticle/2767207
- https://pubmed.ncbi.nlm.nih.gov/33003176/https://jamanetwork.com/journals/jama/fullarticle/2767207
- https://www.ahajournals.org/doi/pdf/10.1161/CIRCULATIONAHA.120.050147
- Jonat B, Gorelik M, Boneparth A, Geneslaw AS, Zachariah P, Shah A, et al. Multisystem Inflammatory Syndrome in Children Associated With Coronavirus Disease 2019 in a Children's Hospital in New York City. *Pediatr Crit Care Med*. 2020;
- Henderson LA, Canna SW, Friedman KG, Gorelik M, Lapidus SK, Bassiri H, et al. American College of Rheumatology Clinical Guidance for Pediatric Patients with Multisystem Inflammatory Syndrome in Children (MIS-C) Associated with SARS-CoV-2 and Hyperinflammationin COVID-19. Version 3. *Arthritis & Rheumatol* Vol. 74, No. 4, April 2022, pp e1–e20
- Ouldali N, Toubiana J, Antona D, Javouhey E, Madhi F, Lorrot M, et al. Association of Intravenous Immunoglobulins Plus Methylprednisolone vs Immunoglobulins Alone With Course of Fever in Multisystem
  Inflammatory Syndrome in Children. *JAMA*. 2021;
- Capone CA, Subramony A, Sweberg T, Schneider J, Shah S, Rubin L, et al. Characteristics, Cardiac Involvement and Outcomes of Multisystem Inflammatory Syndrome of Childhood Associated with severe acute respiratory syndrome coronavirus 2 Infection. *J Pediatr* [internet]. 2020 [cited 2021 Jan 27];224:141 5. Available from: http://www.ncbi.nlm.nih.gov/pubmed/32553873
- Carlin RF, Fischer AM, Pitkowsky Z, Abel D, Sewell TB, Landau EG, et al. Discriminating Multisystem Inflammatory Syndrome in Children Requiring Treatment fromCommon Febrile Conditions in Outpatient Settings. *J Pediatr* [internet]. 2021 Feb [cited 2021 Jan 27];229:26-32.e2. Available from: http://www.ncbi.nlm.nih.gov/pubmed/33065115
- Choi NH, Fremed M, Starc T, Weller R, Cheung E, Ferris A, et al. MIS-C and Cardiac Conduction Abnormalities. *Pediatrics* [internet]. 2020 [cited 2021 Jan27];146(6). Available from: http://www.ncbi.nlm.nih.gov/pubmed/33184170
- Matsubara D, Kauffman HL, Wang Y, Calderon-Anyosa R, Nadaraj S, Elias MD, et al. Echocardiographic Findings in Pediatric Multisystem Inflammatory Syndrome Associated With COVID-19 in the United States. *J Am Coll Cardiol* [internet]. 2020 [cited 2021 Jan 27];76(17):1947 61. Available from: http://www.ncbi.nlm.nih.gov/pubmed/32890666

Aim: To standardize MIS-C management based upon best available evidence.

REFERENCES/RESOURCES *(continued)*

- https://www.cdc.gov/vaccines/covid-19/clinical-considerations/covid-19-vaccines-us.html#CoV-19-vaccination"Interim Clinical Considerations for Use of COVID-19 Vaccines | CDC
- https://www.aap.org/en/pages/2019-novel-coronavirus-covid-19-infections/clinical-guidance/multisystem-inflammatory-syndrome-in-children-mis-c-interim-guidance/" Multisystem Inflammatory Syndrome in Children (MIS-C) Interim Guidance (aap.org)
- Capone CA, Misra N, Ganigara M, et al. Six Month Follow-up of Patients With Multi-System Inflammatory Syndrome in Children. Pediatrics. 2021;148(4):e2021050973
- Son MBF, et. al. Overcoming COVID-19 Investigators. Multisystem Inflammatory Syndrome in Children - Initial Therapy and Outcomes. *N Engl J Med.* 2021 Jul 1;385(1):23-34. doi: 10.1056/NEJMoa2102605. Epub 2021 Jun 16. PMID: 34133855
- Menon NM, Srivaths LV. Thromboembolism in children with multisystem inflammatory syndrome: a literature review. Pediatr Res. 2022 Jan 14:1–5. doi: 10.1038/s41390-021-01873-0.
- He M, Leone DM, Frye R, Ferdman DJ, Shabanova V, Kosiv KA, Sugeng L, Faherty E, Karnik R. Longitudinal Assessment of Global and Regional Left Ventricular Strain in Patients with Multisystem Inflammatory Syndrome in Children (MIS-C). Pediatr Cardiol. 2022 Jan 7:1–11. doi: 10.1007/s00246-021-02796-7.
- Yuksel S, Demirkan NC, Comut E, Yilmaz M, Gurses D. Histopathological and Clinical Analysis of Skin Rashes in Children With Multisystem Inflammatory Syndrome Associated With COVID-19. Am J Dermatopathol. 2022 Jan 5. doi: 10.1097/DAD.0000000000002091.
- Aeschlimann FA, Misra N, Hussein T, Panaioli E, Soslow JH, Crum K, Steele JM, Huber S, Marcora S, Brambilla P, Jain S, Navallas M, Giuli V, Rücker B, Angst F, Patel MD, Azarine A, Caro-Domínguez P, Cavaliere A, Di Salvo G, Ferroni F, Agnoletti G, Bonnemains L, Martins D, Boddaert N, Wong J, Pushparajah K, Raimondi F. Myocardial involvement in children with post-COVID multisystem inflammatory syndrome: a cardiovascular magnetic resonance based multicenter international study-the CARDOVID registry. J Cardiovasc Magn Reson. 2021 Dec 30;23(1):140. doi: 10.1186/s12968-021-00841-1. PMID: 34969397; PMCID: PMC8717054.
- Levy M, Recher M, Hubert H, Javouhey E, Fléchelles O, Leteurtre S, Angoulvant F. Multisystem Inflammatory Syndrome in Children by COVID-19 Vaccination Status of Adolescents in France. JAMA. 2022 Jan 18;327(3):281-283. doi: 10.1001/jama.2021.23262. PMID: 34928295; PMCID: PMC8689418.

MIS-C Workgroup: Nowak, Garland, Pozos, Pomputius, Kalaskar, B. Chu, Bergmann, Wegmann, Sznewajs, Brunsberg, Lissick, Noble, Schultz, Wiplinger, Kuelbs, Derks, Singewald. Previous members contributing to original content: Koutsari, Hester, Boman