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

**Patients with all of the following:**
- Fever > 38.0°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, see Note 1.

**History, exam + vital signs (VS) inc. BP**
- O2 to keep sat > 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).

**Do the labs show all of the following?**
1. CRP ≥ 5 mg/dL OR ESR ≥ 40 mm/hr
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
   **PLUS No alternate probable diagnostic explanation for symptoms and lab findings**

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

**Any instability including:**
- Low BP, tachycardia, or tachypnea for age
- Increased work of breathing or O2 sat < 90%
- Poor perfusion or altered mental status
- Ill-appearing
- Unable to maintain hydration by PO

**Transfer to ED for possible MIS-C**
Children’s Physician Access: 612-343-2121

Note 1. Link includes ANY of the following criteria: + COVID 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.
MIS-C: ED-Diagnostic/Dispos recs for Suspected Multisystem Inflammatory Syndrome in Children (MIS-C) Associated with COVID-19 (Age <21 years)

EXCLUSION GUIDELINES
Patients with alternate probable etiology of illness. Ddx includes: Bacterial sepsis, toxic shock syndrome, Kawasaki Disease (KD), appendicitis, ILH/MAS, ricketsia, viral syndrome (CMV, EBV, Adenovirus, Coxsackie, varicella, etc.), bacterial enteritis, lupus, vasculitis.

"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: blood culture, UA/UCx, lactate, blood gas, procalcitonin, serum to save, IgG, IgA, IgM, BNP, troponin, LDH, CPK, D Dim er, 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").

MIS-C Suspected, Complete additional workup:
- CXR, EKG. Get ECHO in ED on ly if h emodynamic instability.
- Call ID from ED.
- PICU if any signs of cardiac dysfn (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

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**ICU GUIDELINE**

**MIS-C: ICU Management: Patients meeting ICU criteria (any cardiac dysfunction or shock and/or sepsis)**

**(Age <21 years)**

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### Initial ICU Management

- **Echocardiography (Echo):** obtain after admission. Telemetry x 72 hours or until cardiology discontinues.

- **Empiric antibiotics as appropriate for clinical presentation** (e.g. vancomycin, ceftriaxone, and clindamycin for community-acquired shock) until cultures negative for 48 hour or as-directed by ID.

- **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 > 3 weeks.

- **IVIG:** Give 2 g/kg x 1 (use ideal body weight)- See Note 1 for repeat dose. In patients with cardiac dysfunction, IVIG may be given in divided doses (1 g/kg/day over 2 days).

- **Steroids:** Give methylprednisolone IV 2 mg/kg/day (max 60 mg/day), or bolus may be needed- See Note 1.

- **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 COVID 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 Q4 8 hr or sooner if clinical worsening**
- **Repeat other labs as indicated**
- **EKG Q4 8 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

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**Note 1. Refractory or rapidly progressive disease**

- “Refractory” is 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 most severely ill children, bolus methylprednisolone 10-30 mg/kg/day IV (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.
- Revist differential diagnosis.
**GUIDELINE**

**MIS-C: Med-Surg Management for patients identified as having MIS-C (Age <21 years)**

**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 euvoolemia.
- **Empiric antibiotics as appropriate for clinical presentation** (e.g. ceftriaxone and metronidazole for possible appendicitis; ceftriaxone for possible pyelonephritis) until cultures negative for 48 hour or as-directed by ID.
- **Consults**: ID: for all patients. Immunology: ID to contact Immunology as needed. 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 > 3 weeks. Goal is daily group rounding call with active consultants.
- **IVIG**: Give 2 g/kg x 1 (use ideal body weight) - See Note 1 and 2.
- **Steroids**: Methylprednisolone 2 mg/kg/day (max 60 mg/day) should be given to patients who are collaboratively determined with ID and Immunology to have moderate MIS-C. Discuss steroid use with ID (and Immunology if also consulted) in patients for whom the diagnosis of mild MIS-C is being considered. All patients with severe disease (ICU) should receive steroids. See Notes 1 and 2. See page 7 for weaning 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 Cardiology). Note, ok to use prophylactic enoxaparin with low-dose aspirin (which adds anti-platelet and coronary artery protection).
- **VTE prophylaxis** unless contraindication (see COVID 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 Med-Surg patients, by disease severity (see Note 1)**

- **Mild**: CBC w/ diff, CRP, BMP, d-dimer, 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 Q4 8 hr.
- **Moderate**: CBC w/ diff, CRP, BMP, d-dimer, ferritin Q day until afebrile and labs improving x 3 days then may do PRN for any clinical worsening. Repeat troponin in Q6 hr until normalized and BNP Q 48 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 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**

**Note 1. Disease Severity**

- **Not well defined in literature**
- **Mild**: Borderline or mild case. Normal VS a part 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 2. 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 consultants.
- Repeating IVIG is not recommended, though should also be discussed with consultants if presentation more similar to KD.
- For most severely ill children, bolus methylprednisolone 10-30 mg/kg/day IV (max 1,000 mg/day).
- In some cases anakinra 2-10 mg/kg/dose (max 1,000 mg/dose) SQ/IV Q6-24h may be needed.
- Revisit differential diagnosis.
- Consider PICU transfer.

**Discharge criteria:**

- 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

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**Initial Med-Surg Management: Change to full management page of guideline 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. ID attending will discuss case with Immunology if indicated.
- **VTE prophylaxis:** see COVID 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 1) who do not yet meet MIS-C case definition and without alternate diagnosis identified.**

- **Mild:** CBC w/diff, CRP, BMP, d-dimer, 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 > 5 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 > 38.0°C, 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.

**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

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

### 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 2 weeks after steroids started** (if anticipated duration ≥ 3 weeks), 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).
- If steroids were used, Immunology will advise on the duration of the acute wean (generally 2-3 weeks if milder, 4-8 weeks on a case-by-case basis with immunology involvement in more severe cases). Primary team will calculate and prescribe the wean doses and steps as part of discharge plan (see page 7). Endocrine will follow patients needing ≥ 3 weeks of steroids with a telehealth appointment 2 weeks after steroids were started 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 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/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 including: hemolytic anemia, 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)**
**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, v asculitis and other conditions.

**Orders sets:** ED-fever, ED-COVID, ED Suspected MIS-C, In patient Suspected MIS-C

**Steroid Dosing + Taper Suggestions (Discuss with consultants and pharmacist)**
- For moderate/severe cases consider methylprednisolone 2 mg/kg/day (max 60 mg per day) then taper over 2-3 weeks.
- For refractory or rapidly progressive cases (see criteria on pages 3 or 4) methylprednisolone 10-30 mg/kg/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).
- **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.

The purpose of the prolonged steroid taper in MIS-C is prevention of rebound inflammation.

**General guidance:**
- Initiate taper when patient has clinically improved (e.g. off pressors, off respiratory support, afebrile, downtrending CRP).
- Reduce steroid dose by 10-15% every 3 days while inpatient.
- Reduce steroid dose by 15-25% every 3-5 days while outpatient.
- Taper should be guided by clinical response and inflammatory markers (e.g. fever, CRP) and will be managed by primary provider.
- Patients receiving steroids for an anticipated duration of ≥3 weeks need to have an ACTH stim test.

Hospitalist/Intensivist to consult Endocrinology 2 days prior to discharge in these patients.

**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):
  - Gastrointestinal (92%)
  - Cardiovascular (80%)
  - Hematologic (76%)
  - Mucocutaneous (74%, 59% rash)
  - Respiratory (70%)
  - Musculoskeletal (23%)
  - Renal (8%)
  - Neurologic (6%)
- Recent COVID 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.
- **Evidence of inflammation, common values:**
  - CRP > 3 mg/dL, ESR > 40 mm/h, ferritin > 500 ng/mL, ANC > 7700, ALC < 1500, 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.


**Clinical Features by Organ System**
- **GI** (abdominal pain, vomiting/diarrhea)
- **CV** (Chest pain, tachycardia)
- **Heme** (cell line abnormalities, thrombosis)
- **Resp** (SOB, cough, tachypnea)
- **Mucocutaneous** (strawberry tongue, cracked lips, sore throat, polymorphic rash)
- **Extremity** (hand/foot redness or swelling)
- **Lymphadenopathy**
- **Neuro:** (headache, irritable, altered mental status, CN palsy)

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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
- CDC: Health Alert Network (HAN) No. 432 – Multisystem Inflammatory Syndrome in Children (MIS-C) Associated with Coronavirus Disease 2019 (COVID-19) 05/14/2020
- DeBiasiet al., "Severe COVID-19 in Children and Young Adults in the Washington, DC Metropolitan Region" JPeds May 12, 2020
- NY Presbyterian Kids Clinical Guideline
- Mayo Clinic Clinical Guideline
- https://www.ahajournals.org/doi/pdf/10.1161/CIRCULATIONAHA.120.050147

MIS-C Workgroup: Hester, Nowak, Garland, Pozos, Pomputius, Kalaskar, Koutsari, B. Chu, Bergmann, Wegmann, Sznewajs, Brunsberg, Lissick, Noble, Boman, Schultz, Wipflinger, Kuelbs, Derks, Singewald

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