Initial Evaluation, Diagnosis and Management of Patients with Suspected Multi-System Inflammatory Syndrome in Children (MIS-C)

Authors: Members of the Divisions of Pediatric Infectious Diseases, Pediatric Cardiology, Pediatric ED, General Pediatrics, Pediatric Hospital Medicine, Pediatric Intensive Care, Pediatric Hematology / Oncology, Pediatric Rheumatology and Pediatric Surgery

Approved by: Chairs of Pediatric Clinical Performance Committee, Clinical Vice Chairs of Departments of Pediatrics, and VCH President, Chief of Staff, and CNO

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Ambulatory and Inpatient Guidelines for evaluation of patients with suspected COVID-19 are detailed in separate documents.

Purpose:

To provide guidance for care of children with suspected Multi-system Inflammatory Syndrome in Children (MIS-C).

Background:

On May 14, 2020 the Centers for Disease Control and Prevention (CDC) released a case definition for Multisystem Inflammatory Syndrome in Children (MIS-C) and updated the definition on December 16, 2022 (https://www.cdc.gov/mmwr/volumes/71/rr/rr7104a1.htm?s_cid=rr7104a1_w#B1_down).

Case Definition for Multisystem Inflammatory Syndrome in Children (MIS-C):

1. An individual aged < 21 years presenting with fever[i], laboratory evidence of inflammation[ii], and evidence of clinically severe illness requiring hospitalization, with multisystem (> 2) organ involvement (cardiac involvement, hematologic, gastrointestinal, mucocutaneous or shock); AND
2. No alternative plausible diagnosis; AND
3. Detection of SARS-CoV-2 RNA by PCR or antigen up to 60 days before or during hospitalization OR detection of SARS-CoV-2 specific antibodies with current illness resulting in or during hospitalization OR close contact with a confirmed or probable case of COVID-19 in the 60 days before hospitalization

[i] Subjective or documented Fever ≥ 38 C
[ii] CRP ≥ 30 mg/L
[III] Organ system involvement may include

- Shock
- Cardiac (LVEF <55%, coronary artery dilatation, aneurysm or ectasia; or elevated troponin)
- Mucocutaneous (rash, inflammation of oral mucosa [e.g. mucosal erythema or swelling, drying or fissuring of the lips, strawberry tongue], conjunctivitis or conjunctival injection, or extremity findings such as erythema or edema of the hands or feet)
- Gastrointestinal involvement (indicated by abdominal pain, vomiting or diarrhea)
- Hematologic involvement (indicated by platelet count of <150,000 cells/μL or absolute lymphocyte count of <1,000 cells/μL

MIS-C Ambulatory & ED Pathway

Fever > 38C / Subjective fever + > 2 of the following and no alternative explanation:
- GI symptoms: Abdominal pain, vomiting diarrhea
- Mucocutaneous symptoms: Conjunctivitis, rash, oral mucosal changes, Swelling of hands and/or feet

Additional history / physical exam items to consider are in Box 1 below.

Toxic-appearing or abnormal vital signs (hypotension for age, elevated HR out of proportion to fever, hypoxia, altered mental status)?

- Yes → Refer patient to ED → **Suspected MIS-C with Shock**
  Fever/history of fever ≥ 38
  +
  Evidence of myocardial dysfunction or Hypotension/vasopressor requirement, elevated HR out of proportion to fever, hypoxia, altered mental status, confusion,+
  ≥ 2 clinical / historical features
  → **Sepsis CPG**
  Consult Cardiology
  Additional diagnostic laboratory studies (not included in sepsis CPG)
  - Troponin I, BNP
  - Ferritin
  - Red Top Tube to save in lab
  - SARS Co-V-2 antibody testing
  - SARS-CoV-2 PCR
  - Urinalysis (bag specimen)
  - ECG
  - Echocardiogram

  Gentle fluid resuscitation, vasopressors
  Antibiotics per sepsis CPG

  → Fluid responsive, no cardiac involvement?
  - Yes → **Admit to hospital medicine**
    Refer to inpatient pathway for further guidance.
  - No → **Admit to PICU**
    Consider CICU admission:
    - Severe valvular dysfunction, valvular insufficiency
    - Evidence of coronary artery involvement (ectasia, aneurysms)
    - Arrhythmias (ventricular ectopy, AV conduction abnormalities)
    - Elevated BNP or troponin with or without cardiac dysfunction

    Refer to ICU pathway for further guidance.

- No → Fever/history of fever ≥ 38.0 AND ≥ 2 characteristic features (Box 1)
  - No → Clinical workup as indicated
  - Yes → **Consider evaluation for possible MIS-C - Initial Lab Testing**
    Blood: CBC with diff, CMP, CRP, ESR, Blood culture
    NP Swab: SARS-CoV-2 PCR
    ECG
    Other testing as clinically indicated

    Consider ED referral if unable to obtain above labs or concern for time / space constraints.

    → Labs and physical exam reassuring?
    → **Discharge**
    Tolerates PO
    Reassuring PE
    PCP follow-up 24-48 hrs

    → CRP ≥ 30 mg/L AND
    - Lymphopenia < 1k or
    - Thrombocytopenia < 150k or
    - Abnormal imaging on abdominal ultrasound (enteritis, hydrops of gall bladder)

    → Concern for MIS-C

    Discuss with Cardiology re: timing of obtaining Echo (ED / ICU if unstable; inpatient if stable)

    Consider need for antibiotics.

    → **Admit to hospital medicine**
    Refer to inpatient pathway for further guidance.

Multisystem Inflammatory Syndrome in Children (MIS-C) Case Definition
- An individual aged <21 years presenting with fever[1], laboratory evidence of inflammation[2], and evidence of clinically severe illness requiring hospitalization, with multisystem (≥2) organ involvement (cardiac, hematologic, gastrointestinal, or mucocutaneous); **AND**
- No alternative plausible diagnoses; **AND**
- Detection of SARS-CoV-2 RNA by PCR or antigen up to 60 days before or during hospitalization OR detection of SARS-CoV-2 specific antibodies with current illness resulting in or during hospitalization OR close contact with a confirmed or probable case of COVID-19 in the 60 days before hospitalization

1. Subjective or documented fever ≥38.0°C
2. CRP ≥ 30 mg/L

Box 1. Clinical / Historical Features of MIS-C
- **Shock**
- **Cardiac** - LVEF <55%, coronary artery dilatation, aneurysm or ectasia; or elevated troponin
- **Mucucutaneous -** rash, inflammation of oral mucosa [e.g. mucosal erythema or swelling, drying or fissuring of the lips, strawberry tongue], conjunctivitis or conjunctival injection, or extermity findings such as erythema or edema of the hands or feet
- **GI symptoms** - diarrhea, abdominal pain, vomiting
- **Hematologic involvement** - platelet count <150,000 cells/uL or absolute lymphocyte count of <1,000 cells/uL

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MIS-C Inpatient Pathway

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Admit to Hospital Medicine for Suspected MIS-C

Precautions:
- If SARS-CoV-2 PCR positive: contact/droplet/eye protection
- If SARS-CoV-2 PCR negative: routine

Place patient on telemetry.

Consultants:
- Treatment decisions should be made in concert with consulting services
- All patients with concern for MIS-C:
  - Cardiology
  - ID
  - Rheumatology
- Optional consults based on clinical syndrome:
  - Hematology

Studies: Refer to table.

Treatment: Refer to algorithm. Patients presenting with "Classic Kawasaki Disease" should be treated according to 2017 AHA Guidelines.

Discharge Criteria:
- Afebrile ≥ 36 hours from end of IVIG, abnormal labs trending towards normal, hemodynamically stable without hypoxemia, otherwise meeting routine discharge criteria.
- Follow-up with Dr. Parra (Cardiology) and Dr. Patrick (Rheumatology) on a Thursday approximately 1 week after hospital discharge. (Appendix B)
- Patient should receive flu vaccine prior to discharge
- Specific instructions will be given to family for monitoring at home, including potential for deterioration after discharge. Contact information will be provided should the patients' clinical status worsen after discharge
- VUMC providers will contact PCP prior to patient discharge and send PCP eStar letter. We recommend that PCP follow up with patient by telephone within 1 week after discharge

Table. Diagnostic Studies

On admission (if not already obtained in ED)	Daily Labs
Additional Red and Purple Top tubes to save in lab	CBC/diff
COVID-19 antibody testing (if PCR negative; draw prior to IVIG administration)	CMP
IgG level (draw prior to IVIG administration)	CRP
Ferritin	Ferritin
PT/PTT/INR, Fibrinogen, antithrombin time	Troponin I / BNP if abnormal on admission, clinial changes or decrease in LV function on echo
Troponin I, BNP	
Urinalysis (bag sample)	
CXR	

Treatment Algorithm

Confirmed MIS-C
- Treatment to be determined by primary team and subspecialty consultants (e.g. infectious diseases/rheumatology).
  - IVIG 2g/kg (Max 80g; infusion duration to be determined by rheumatology)
  - IV Methylprednisolone: 1mg/kg q12h (max 30mg/dose) (unless contraindicated based on discussion with subspecialists). Conversion to PO and taper plan per rheumatology
  - Consider Cytokine Directed Therapy*
  - ASA 3-5mg/kg/day (avoid if bleeding or plt <30k; max dose 81mg)
  - Consider Enoxaparin:
    - Treatment dose if coronary artery aneurysms
    - Prophylaxis dose if additional baseline thrombosis risk**

Considerations for IVIG therapy
- Obtain red top tube prior to initial adminstration
- If evidence of circulatory failure, consider 1g/kg/day x 2 days
- Use with caution in patients with HLH-like features (increased thrombosis risk)

Anticoagulation considerations
- Platelet goal >30k (can transfuse to achieve goal) while on anticoagulation
- Avoid NSAIDs which counteract irreversible antiplatelet effects of ASA
- Consider risk of Reye syndrome associated with ASA use (see AHA 2017 KD guidelines)

Definitions

***Cytokine Directed Therapy:** Consideration for anti-cytokine therapy will be made for those patients with persistent fever or worsening hyperinflammatory features* despite initial treatment with IVIG +/- steroids. If given, Anakinra will be preferred anti-cytokine agent due to short half life and evidence for use in both Kawasaki disease and other hyperinflammation syndromes.

****Additional Baseline Thrombosis Risk:** Known inherited thrombophilia, history of thrombosis, low antithrombin levels, nephrotic syndrome, critical illness, age ≥ 12yr

Severe Hyperinflammation: Features may includehyperferritinemia, thrombocytopenia, hepatosplenomegaly, neurologic changes (AMS, seizure), hepatic dysfunction, vasodilatory shock
Treatment Failure: Defined as fever 36h after IVIG, worsening in 24h, ICU transfer, escalation of respiratory support, recrudescent fever within 7 days.

Suspected MIS-C[¥] (with Shock) Guidelines

- ❑ Fever/History of Fever ≥38C **AND**
- ❑ Evidence of Myocardial Dysfunction or Hypotension/Vasopressor Requirement **AND**
- ❑ ≥ 2 Clinical/Historical Features[¥¥]

Admit to CICU/PICU[§]

- ❑ **Antibiotics**
  - Broad spectrum Abx for patients presenting in shock with concerns for sepsis as per usual clinical care standards
  - Obtain cultures prior to treatment when able
- ❑ **GI Prophylaxis** with PPI

Treatment Algorithm

Confirmed MIS-C

- ❑ Treatment to be determined by primary team and subspecialty consultants (e.g. infectious diseases/rheumatology)
  - ❑ IVIg[¶] 2 g/kg (Max 80 g; infusion duration to be determined by rheumatology)
  - ❑ Methylpred 1mg/kg (max 30 mg/dose) IVq12h (unless contraindicated based on discussion with subspecialists). Conversion to PO and taper plan per rheumatology.
  - ❑ Consider cytokine directed therapy*
  - ❑ ASA 3-5 mg/kg/day[§§, ¶¶] (max 81mg)
  - ❑ Consider enoxaparin[¶¶]
    - ❑ Treatment dosing if evidence coronary artery aneurysms[§§]
    - ❑ Prophylaxis dosing if additional baseline thrombosis risk****

Consulting Services

ALL Patients meeting MIS-C Criteria

- ❑ ID
- ❑ Rheumatology
- ❑ Hematology
- ❑ Cardiology

Relevant End-Organ Considerations

- ❑ Gastroenterology (↑ Colitis)
- ❑ General surgery (↑ Acute abdomen)
- ❑ ECMO/CT Surgery

Diagnostic Studies in ICU[⊕]

- ➢ Antithrombin (once)
- ➢ CBC c diff (daily*)
- ➢ CMP (daily)
- ➢ CRP (daily)
- ➢ TG (daily if concern for MAS)
- ➢ Ferritin (daily)
- ➢ PT/PTT/INR (daily)
- ➢ D Dimer (daily)
- ➢ Fibrinogen (daily)
- ➢ LDH (daily)
- ➢ Troponin I (daily)
- ➢ BNP (daily)
- ➢ Blood gas (PRN)
- ➢ Echocardiography (on admit and PRN)
- ➢ Electrocardiography (on admit and PRN)
- ➢ Exploratory labs per consulting services

¶Considerations for IVIg Therapy

- ❑ Obtain red top (x2) prior to initial administration.
- ❑ If evidence of circulatory failure, consider 1g/kg/day x 2 days.
- ❑ Use with caution in patients with HLH-like features (increased thrombosis risk)

¶¶Anticoagulation considerations

- ❑ Platelet goal >30K (can transfuse to achieve goal) while on anticoagulation
- ❑ Avoid NSAIDs which counteract irreversible antiplatelet effects of ASA
- ❑ Consider risk of Reye syndrome associated with ASA use (see AHA 2017 KD guidelines[§§])

__Cytokine directed therapy:__ Consideration for anti-cytokine therapy will be made for those patients with persistent fever or worsening hyperinflammatory features despite initial treatment with IVIG +/- steroids. If given, Anakinra will be preferred anti-cytokine agent due to short half life and evidence for use in both Kawasaki disease and other hyperinflammation syndromes.

__Thrombosis risk factors:__ Thrombophilia, prior history of thrombosis, low AT levels, nephrotic syndrome, **critical illness, age ≥12yr)

Severe Hyperinflammation: Features may include hyperferritinemia, thrombocytopenia, hepatosplenomegaly, neurologic changes (AMS, seizure), hepatic dysfunction, vasodilatory shock

Treatment Failure: Defined as fever 36h after IVIG, worsening in 24h, ICU transfer, escalation of respiratory support, recrudescent fever within 7 days.

[§]Consider CICU Admission

- ❑ Severe ventricular dysfunction, valvar insufficiency
- ❑ Evidence coronary artery involvement (ectasia, aneurysms)
- ❑ Arrhythmias (e.g ventricular ectopy, AV conduction abnormalities)

[⊕]Daily laboratory studies may be scaled back with improvement, though decisions should be individualized and made in concert with consulting services where appropriate.

[§§]Kawasaki Disease Considerations

Refer to 2017 AHA Kawasaki Disease Guidelines (PMID 28356445) for case definitions of KD and "atypical" KD, as well as additional treatment guidelines.

Patients presenting with "Classical Kawasaki Disease" should be treated according to 2017 AHA Guidelines.

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[¥]Multisystem Inflammatory Syndrome in Children (MIS-C) Case Definition

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- ✓ No alternative plausible diagnoses; **AND**
- ✓ Detection of SARS-CoV-2 RNA by PCR or antigen up to 60 days before or during hospitalization OR detection of SARS-CoV-2 specific antibodies with current illness resulting in or during hospitalization OR close contact with a confirmed or probable case of COVID-19 in the 60 days before hospitalization

[i]Fever ≥38.0°C for ≥24 hours, or report of subjective fever lasting ≥24 hours

[ii]CRP ≥ 30 mg/L

[¥¥]Clinical/Historical Features of MIS-C

- ❑ **Mucocutaneous**
  Rash, inflammation of oral mucosa [e.g. mucosal erythema or swelling, drying or fissuring of the lips, strawberry tongue], conjunctivitis or conjunctival injection, or extremity findings such as erythema or edema of the hands or feet
- ❑ **GI Symptoms**
  Diarrhea, abdominal pain, vomiting
- ❑ **Cardiac**
  LVEF <55%, coronary artery dilatation, aneurysm or ectasia; or elevated troponin
- ❑ **Hematologic**
  Platelet count <150,000 cells/μL or absolute lymphocyte count <1,000 cells/μL

Appendix A. Pediatric cardiology INPATIENT management of patients with MIS-C

MCJCHAV Pediatric Cardiology

For patients with suspected MIS-C - clinically stable (likely under hospitalist service)

1. Suspected Kawasaki disease
    a. Follow routine KD (complete/incomplete) protocol with cardiology consult, echocardiogram and ECG
2. No signs of KD but with CRP ≥ 30, ESR ≥ 40, lymphopenia (<1k) or thrombocytopenia (<150K)
    a. Obtain ECG, troponin, and BNP
    b. Cardiology consulting team to determine timing of echo

For patients with suspected MIS-C – shock (ICU care)

1. Obtain ECG, echocardiogram, troponin, BNP and cardiology consult
2. Additional imaging for patients with ventricular dysfunction: cardiac MRI once patient is clinically stable

Imaging:

1. At diagnosis
2. For patients with normal function and normal coronary artery dimensions:
    a. f/u 1-2 weeks post diagnosis to recheck coronary siz

Appendix B. Ambulatory Management of Patients with MIS-C

1. Routine cardiology follow-up for patients with classic KD

2. Patients to be followed in multidisciplinary clinic:
    a. Those treated with "non KD symptoms" and CRP $\geq$ 3, ESR $\geq$ 40, lymphopenia (<1k) or thrombocytopenia (<150K)
    b. MISC-shock

Procedure for Ambulatory Follow Up for Patients with MIS-C:

1. Inpatient resident to ensure patient has follow-up with Dr. Parra (Cardiology) and Dr. Patrick (Rheumatology) scheduled for 1-week after discharge. Please ensure these appointments are scheduled / in the process of being scheduled prior to hospital discharge.

Text for Letter to PCPs:

Your patient was diagnosed with Multisystem Inflammatory Syndrome in Children (MIS-C), which is an inflammatory condition that is temporally associated with the SARS-CoV-2 virus. A multidisciplinary team will continue to follow your patient after discharge. Recurrence of symptoms such as fever, rash, abdominal pain, or altered mental status within the next 2-3 weeks should prompt medical evaluation.

MIS-C is thought to be a post-infectious inflammatory process; however, some patients will test positive for SARS-CoV-2 PCR. These patients should remain in home isolation until 24 hours after resolution of fever and other symptoms, and 10 days since first SARS-CoV-2 positive test.

Your patient will follow-up with our MIS-C multidisciplinary team within one week of discharge and will update you on any changes in clinical status or plan of care. We also recommend patients follow-up with their primary care providers by telephone within a few days of discharge.

We recommend that patients with MIS-C receive the COVID-19 vaccine once they meet the following two recovery criteria:

1. Clinical recovery has been achieved, including return to baseline cardiac function; and
2. It has been at least 90 days after the diagnosis of MIS-C or MIS-A.

Experts consider the benefits of COVID-19 vaccination for people with a history of MIS-C to outweigh the theoretical risk of an MIS-C like illness or the risk of myocarditis following COVID-19 vaccination. The timing of COVID-19 vaccination in people with a history of MIS-C or MIS-A should take into consideration current or planned immunomodulatory therapies for treatment MIS-C or MIS-A.

For patients with onset of MIS-C 60 days or fewer after their most recent COVID-19 vaccine dose who meet the recovery criteria above, the decision whether or not to administer subsequent COVID-19 vaccine dose(s) should be made on an individual basis by the MIS-C clinical care team and patient or parent or guardian. Subsequent COVID-19 vaccine dose(s) should especially be considered if there is strong evidence that the MIS-C was a complication of a recent SARS-CoV-2 infection.

With specific questions about the care of these patients, call 615-835-8088, which will connect you with the on-call provider for Pediatric Infectious Diseases.