COVID-19 v3.0: MIS-C

Approval & Citation

Summary of Version Changes

Explanation of Evidence Ratings

MIS-C Case Definitions
- CDC
- WHO

Consider differential diagnosis including acute COVID

Inclusion Criteria
- Fever AND critically ill OR
- Persistent fever ≥3d AND evidence of MIS-C (see box) AND ill-appearing OR
- Persistent unexplained fever ≥5 days

Clinical Features/Evidence of MIS-C
- Most patients have ≥4 organ system involvement; ≥2 required for diagnosis
- Involvement of following systems (percent of patients in case series):
  - Gastrointestinal (92%)
  - Cardiovascular (80%)
  - Hematologic (76%)
  - Mucocutaneous (74%, 59% had rash)
  - Respiratory (70%)
  - Musculoskeletal (23%)
  - Renal (8%)
  - Neurologic (6%)
- See definitions of organ system involvement
- 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 >5000 ng/mL, ANC >7700, ALC <1500, platelet <150K, D-dimer >2 mg/mL, fibrinogen >400 mg/dL, albumin <3 g/dL, anemia, ALT >40 U/L, INR >1.1
- Other: AKI, hyponatremia, high LDH, high troponin, BNP >400 pg/mL, prolonged PT or PTT; if ESR low but high ferritin and CRP, consider MAS

Percentages and values adapted from Feldstein et al, NEJM June 2020

Overview:

Lab Evidence of MIS-C?
- Yes: Obtain Initial and Additional Labs, EKG, CXR
- Yes: Consider Sepsis Pathway Caution with boluses; monitor for cardiac dysfunction

Complete or Incomplete Kawasaki?
- Yes: Follow Kawasaki Disease Pathway if COVID testing negative or while pending
- Yes: Monitor closely for signs of shock

Evidence of MIS-C without alternate diagnosis?
- Yes: Go to MIS-C Treatment
- No: Consider alternate diagnoses
- Consider discharge with close follow-up

Signs of shock?
- Yes: Follow Kawasaki Disease Pathway if COVID testing negative or while pending

Lab Evidence of MIS-C?
- Yes: Obtain Initial Labs
- Yes: If high clinical suspicion, add Additional Labs
- Yes: CXR (if resp sx)

Initial Labs: CBCd, CRP, ESR, BMP, ALT, albumin, UA, COVID PCR, COVID IgG, RVP

Obtain Initial and Additional Labs.
- EKG
- CXR
- Consider Sepsis Pathway Caution with boluses; monitor for cardiac dysfunction

Obtain Initial Labs
- If high clinical suspicion, add Additional Labs

Obtain Additional Labs
- EKG
- Contact Cardiologist to discuss necessity/timing of Echo

Additional Labs:
- BNP, troponin, ferritin, D-dimer, coags, fibrinogen, LDH, blood culture if indicated, red top to hold prior to IVIG (freeze), further labs on consultant advice

PATIENTS WITH MIS-C HAVE SIGNIFICANT RISK FOR DEVELOPING SHOCK
Suspected MIS-C: Ongoing fever, lab evidence of inflammation (most patients have 4 or more markers), multi-system involvement, and clinically seriously ill, without alternative diagnosis (review differential diagnosis).

MIS-C: Above plus confirmed SARS-CoV-2 or known exposure (see case definition links)
- Admit patients to ICU if any signs of shock, hypotension, or concern for cardiac dysfunction
- Consult Infectious Disease, Rheumatology, and Cardiology; goal for daily group discussion or rounds with primary team
- Antibiotics per Sepsis Pathway only if and while bacterial infection suspected
- Consider supportive care only for patients who have mild illness; monitor for increasing severity until clearly improving

First-line treatment for all seriously ill patients with MIS-C:
- IVIG 2 g/kg (use ideal body weight) over 12 hours
- Anti-platelet: ASA 3-5 mg/kg max of 81 mg
- Anticoagulation: SQ enoxaparin prophylaxis until discharge (barring contraindications or indications for treatment dosing)
- Early initiation of steroids and/or higher dose of steroids may be indicated for critically ill patients, such as those with persistent shock/inotropic requirement, respiratory or heart failure, or concern for MAS

Second-line: Steroids if not improving ~12 h post-IVIG
- Methylprednisolone 2 mg/kg/day divided BID, change to PO when tolerating diet
- Consider higher dose steroids (methylprednisolone 10mg/kg/day) for patients with moderately or severely depressed cardiac function, in consultation with heart failure team
- Consider H2 blocker for GI ulcer prophylaxis while on both steroids and ASA
- Wean over minimum 3 weeks due to risk of rebound with short course

Third-line: Anakinra if not improving post steroid initiation or if labs suggestive of MAS
- 4 mg/kg/dose q6 hours (or frequency per Rheumatology), max dose 100 mg/dose

Trend CBC, CRP, LDH, ALT, Albumin, Ferritin, Creatinine, Lytes, D-Dimer, Fibrinogen and BNP (frequency dependent on clinical status and medication weaning; post-discharge labs per consultants)

Classification of illness severity is not well defined. Consider:
*Mild: Normal vital signs apart from fever, does not meet inpatient criteria other than poor PO, mild dehydration, or monitoring for worsening.
*Serious: Definitively meets case definition and any of: ill-appearing, evidence of organ dysfunction/injury, require for respiratory or cardiovascular support.

Indications for therapeutic dosing of anticoagulation (heparin or enoxaparin):
- Documented thrombosis (also consult Hematology)
- Moderate to severe ventricular dysfunction per Cardiology
- Coronary aneurysm Z score >10
- More than one of the following:
  - Personal history of thrombosis
  - History of acquired or inherited thrombophilia
  - Sedated and muscle-relaxed
  - D-dimer >3 mcg/mL and up-trending
  - Any rhythm abnormalities: heart block, etc.
  - Inotropic infusion
  - Central venous catheter
  - Age >13 years
- Contraindication to anticoagulation: Active major bleeding
- Discontinue prophylactic LMWH at discharge or earlier if patients are ambulatory with near-normal inflammatory markers
- Continue therapeutic dosing while indicated and formulate outpatient plan with consultants
**Labs**

- **Tier 1 Labs**
  - COVID PCR, RVP, CBC/d, CRP, ESR, LDH, UA, AST, BMP, D-dimer, Albumin, Ferritin
  - Testing guidance documents (for SCH only)
  - Antibody Testing Indications
  - Guidance on Who to Test

- **Tier 2 Labs**
  - BNP, Troponin, Fibrinogen, INR/PT/PTT, specimen storage (red, freeze), COVID IgG

  Consider **Sepsis Pathway** labs

**Illness Severity Definitions**

- **Mild**
  - Symptoms of viral illness or upper respiratory tract infection (such as fever, cough, diarrhea, myalgias, rhinorrhea, sore throat, etc.)

- **Moderate**
  - Signs or symptoms of pneumonia (such as tachypnea, retractions, abnormal chest xray, etc.) AND
  - No sustained hypoxia

- **Severe**
  - Signs or symptoms of pneumonia AND
  - New or increased oxygen requirement

**Critical**

- Pneumonia AND
- Requiring positive pressure ventilation OR
- Signs of sepsis or multi-organ failure

**Asymptomatic, Mild, or Moderate Illness**

- No hypoxia

- No labs indicated
- Review admission criteria
- Inpatient or outpatient supportive care and monitoring for increasing severity
- **Home Quarantine Handout**

**Severe Illness**

New or increased oxygen requirement

- Tier 1 labs
- EKG, CXR
- Consult Infectious Disease
- Trend labs if symptoms persist/worsen to monitor for complications such as hyperinflammation or multi-system inflammatory syndrome

**Critical Illness**

Requires positive pressure ventilation, sepsis, or multi-organ failure

- Tier 1 and 2 labs
- Consider **Sepsis Pathway**
- ED Guidance: Resuscitation for High-Risk COVID Patient (for SCH only)
- EKG, CXR, consider ECHO
- Consult PICU and Infectious Disease
- Consult Rheumatology for hyperinflammation

**Clinically worse OR lab evidence of hyperinflammation?**

- Yes
- **Go To Acute COVID Treatment**

**Inpatient Admit Criteria**

Admit to Special Isolation Unit (SIU)

- Hypoxia
- Inability to tolerate PO
- Increased work of breathing (grunting, retracting, tachypnea)

**PICU Admit Criteria**

- Altered mental status
- Concern for respiratory failure, sepsis
- Need for positive pressure ventilation
- Hypotension requiring inotropic support

**Explanation of Evidence Ratings**

- **Inclusion Criteria**
  - Suspected COVID-19 acute infection

**Contribution**

- **PCR+ or high clinical suspicion for COVID**

- **Review illness severity**

**Lab Evidence of Hyperinflammation**

No lab criteria is diagnostic; consider if multiple markers 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 ug/mL
  - fibrinogen >400 mg/dL
  - albumin <3 g/dL, anemia, ALT >40 U/L, INR >1.1

**Immune suppressed/deficient or chronic illness:**

- Consult primary outpatient team/medical home

**In adults, these factors are associated with poor prognosis:**

- ↑ BNP, Troponin
- ↑ CRP, D-dimer, ferritin
- ↑ Neutrophil: Lymphocyte ratio

**Last Updated:** September 2020

**Next Expected Review:** October 2020

For questions concerning this pathway, contact: COVID19Pathway@seattlechildrens.org

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Acute COVID Treatment

- Review MIS-C algorithm if indicated
- Plan for daily multi-disciplinary consultants and primary team discussion, and more often if escalation of care
- Consider if clinical trials are applicable

**Pathogen-directed:** Use only in consultation with Infectious Disease
- Remdesivir: To be obtained by ID team (emergency IND [https://rdvcu.gilead.com](https://rdvcu.gilead.com) or state allotment)
- Convalescent plasma: (In rare circumstances) Contact transfusion services to obtain

**Immunomodulatory:**
- Dexamethasone: Consider for patients, especially adolescents, requiring positive pressure ventilation or with rapidly progressive severe illness
  - 0.15 mg/kg/dose (6 mg max) once daily for up to 10 days or until discharge
- Other corticosteroids: Consider for ARDS or in consultation with Rheumatology for hyperinflammation
- Biologic immunomodulatory medications
  - Anakinra: In consultation with Rheumatology for hyperinflammation

**Adjunctive:**
- Prophylactic anticoagulation with heparin or enoxaparin if critically ill with risk factors (see box below); continue until risks resolve or discharge
- Mechanical prophylaxis with SCDs if possible
- Stress dose hydrocortisone: For patients on chronic glucocorticoids if febrile, requiring O2, hypotensive, or unexplained vomiting

**Indications for therapeutic dosing of anticoagulation (heparin or enoxaparin):**
- Documented thrombosis (also consult Hematology)

**Indications for prophylactic dosing of anticoagulation (heparin or enoxaparin):**
- Critical illness AND
- One or more of the following:
  - Personal history of thrombosis
  - History of acquired or inherited thrombophilia
  - Sedated and muscle-relaxed
  - D-dimer >3 mcg/mL and up-trending
  - Any rhythm abnormalities: heart block, etc.
  - Inotropic infusion
  - Central venous catheter
  - Age >13 years

- Contraindication to anticoagulation: Active major bleeding
- Discontinue prophylactic LMWH at discharge or earlier if patients are ambulatory and improving
Differential Diagnoses

Kawasaki Disease
- More common in younger children, if COVID testing negative, and without shock/cardiac dysfunction

Bacterial Infections/Sepsis
- Obtain cultures and evaluate for source
- Consider meningitis

Staphylococcal and streptococcal toxin-mediated diseases
- Diffuse rash and hypotension
- Obtain cultures and evaluate for source including gynecologic or scarlet fever

Staph Scalded Skin Syndrome (SSSS)
- Increasing erythema and bullae
- Younger children
- Obtain cultures

Tick-Borne Illnesses
- With epidemiologic risk factors
- Rocky Mountain Spotted Fever or Leptospirosis

Viral Infections
- Measles, adenovirus, enterovirus, active COVID infection

Myocarditis
- May overlap with MIS-C or have alternate cause

Drug Hypersensitivity Reactions
- Consider SJS, DRESS, or serum sickness like reaction
- History of recent or semi-recent exposure to drug; consider with arthralgias and diffuse mucositis

Labs to Consider with Consultants

- Quantitative immunoglobulins (IgG, IgA, IgM, red tube)
- Specimen storage, red and lavender (freeze)
- Lymphocyte subset – Full Panel with TCR
- Antiphospholipid Ab (anticardiolipin, β2 glycoprotein, lupus anticoagulant)
- Cytokine panel
- IL-1β (ARUP test code 0051536, collect 2-3mL in gold/red top, spin and freeze within 2h)
- sIL-2R (AKA sCD25)
# Definitions of Organ System Involvement

## Gastrointestinal 92%
- Nausea/vomiting
- Diarrhea
- Abdominal pain
- Appendicitis
- Pancreatitis
- Hepatitis
- Gallbladder hydrops or edema

## Cardiovascular 80%
- Hypotension or shock
- Cardiac dysrhythmia or arrythmia
- Ejection fraction <55%
- Pulmonary edema due to left heart failure
- Coronary artery z score ≥ 2.5
- Pericarditis or pericardial effusion or valvulitis
- B-type natriuretic peptide (BNP) >400 pg/mL
- Elevated troponin
- Receipt of vasopressor or vasoactive support
- Receipt of cardiopulmonary resuscitation (CPR)

## Respiratory 70% (more frequent in teens)
- Receipt of mechanical ventilation or any type of supplemental oxygen (or increased support for patients receiving respiratory support at baseline)
- Severe bronchospasm requiring continuous bronchodilators or
- Pulmonary infiltrates on chest radiograph
- Lower respiratory infection
- Pleural effusion
- Pneumothorax or other signs of barotrauma
- Pulmonary hemorrhage
- Chest-tube or drainage required

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- Pneumothorax or other signs of barotrauma
- Pulmonary hemorrhage
- Chest-tube or drainage required

## Musculoskeletal 23% (more frequent in teens)
- Arthritis or arthralgia
- Myositis or myalgia

## Renal 8%
- Acute kidney injury with or without dialysis

## Neurologic 6%
- Stroke or acute intracranial hemorrhage
- Seizures
- Encephalitis, aseptic meningitis, or demyelinating disorder
- Altered mental status
- Suspected meningitis with negative culture

Adapted from Feldstein et al, *NEJM* June 2020

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**Seattle Children's**

**Hospital * Research * Foundation**
Approved by the CSW COVID-19 Pathway team for July 9, 2020, go-live

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Please cite as:
This pathway was developed through local consensus based on published evidence and expert opinion as part of Clinical Standard Work at Seattle Children’s. Pathway teams include representatives from Medical, Subspecialty, and/or Surgical Services, Nursing, Pharmacy, Clinical Effectiveness, and other services as appropriate.

When possible, we used the GRADE method of rating evidence quality. Evidence is first assessed as to whether it is from randomized trial or cohort studies. The rating is then adjusted in the following manner (from: Guyatt G et al. J Clin Epidemiol. 2011;4:383-94, Hultcrantz M et al. J Clin Epidemiol. 2017;87:4-13.):

Quality ratings are downgraded if studies:
- Have serious limitations
- Have inconsistent results
- If evidence does not directly address clinical questions
- If estimates are imprecise OR
- If it is felt that there is substantial publication bias

Quality ratings are upgraded if it is felt that:
- The effect size is large
- If studies are designed in a way that confounding would likely underreport the magnitude of the effect OR
- If a dose-response gradient is evident

Certainty of Evidence:
- 🌟🌟🌟🌟 High: The authors have a lot of confidence that the true effect is similar to the estimated effect
- 🌟🌟🌟 Moderate: The authors believe that the true effect is probably close to the estimated effect
- 🌟🌟 Low: The true effect might be markedly different from the estimated effect
- 🌟🌟🌟🌟 Very low: The true effect is probably markedly different from the estimated effect

Guideline: Recommendation is from a published guideline that used methodology deemed acceptable by the team

Expert Opinion: Based on available evidence that does not meet GRADE criteria (for example, case-control studies).
Summary of Version Changes

- **Version 1.0 (7/9/2020):** Go live.
- **Version 2.0 (8/13/2020):** Removed CK and triglycerides from Labs. Added consult with Cardiology with Echo and added Indications for therapeutic dosing of anticoagulation to Treatment page.
- **Version 3.0 (9/17/2020):** Added Acute COVID algorithm and treatment pages.
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Medicine is an ever-changing science. As new research and clinical experience broaden our knowledge, changes in treatment and drug therapy are required.

The authors have checked with sources believed to be reliable in their efforts to provide information that is complete and generally in accord with the standards accepted at the time of publication.

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Readers should confirm the information contained herein with other sources and are encouraged to consult with their health care provider before making any health care decision.

Return to Home
Methods
Both CDC and WHO case definitions were utilized in the development of this pathway. The articles cited are a representation of local and international experts’ and national societies' resources that were being shared widely, some pre-publication and many that were published by the centers that were diagnosing and treating this new syndrome as the pandemic swept across the globe.

A systematic literature review is in process and may inform future versions of this document. Due to the rapidly evolving literature and the need for urgent guidance, a non-systematic review was used to guide the development of the initial version of this algorithm.
References


References (continued)

