

Multi-System Inflammatory Syndrome in Children (MIS-C) Evaluation Pathway

Admit to PICU for 24 hour observation for new diagnosis of MIS-C with any of the following:

- Hypotension in last 12 hours despite a normal ECHO
- Poor perfusion despite a normal blood pressure
- Signs of shock

Inclusion Criteria

- Age <21 years with fever ≥ 38.0 for ≥ 24 hrs
- Lab evidence of inflammation
- Evidence of clinically severe illness requiring hospitalization, with multisystem (≥ 2) organ involvement AND no alternative plausible diagnoses AND positive for current or recent SARS-CoV-2 infection or exposure to SARS-CoV-2 in past 4 weeks

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)
 - Renal (8%)
 - Neurologic (6%)
 - See definitions of organ system involvement
- Recent COVID illness or exposure (note: Important to consider MIS-C with appropriate clinical symptoms even if COVID illness or exposure is not confirmed)

Lab Evidence of MIS-C

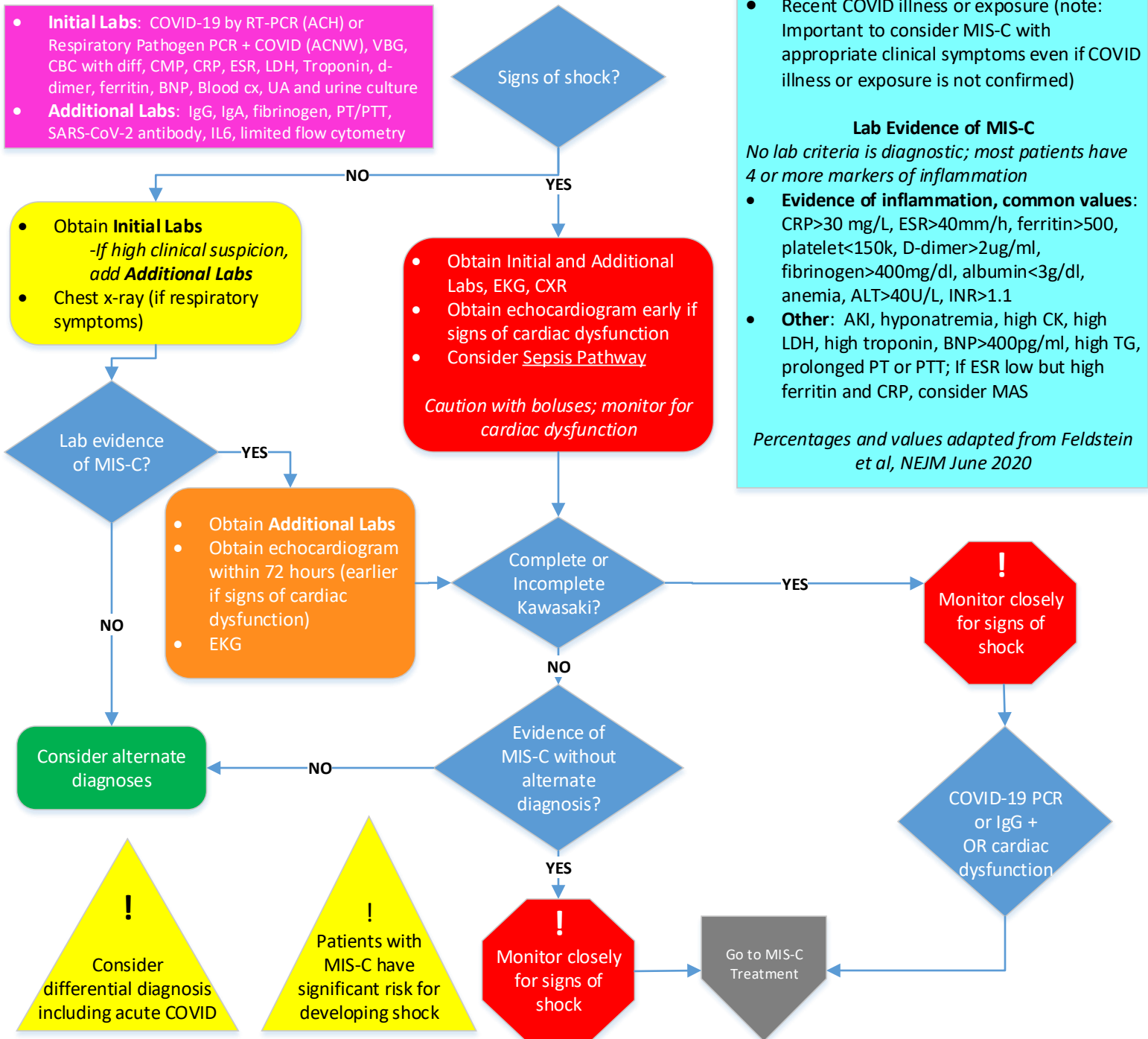
No lab criteria is diagnostic; most patients have 4 or more markers of inflammation

- **Evidence of inflammation, common values:** CRP>30 mg/L, ESR>40mm/h, ferritin>500, platelet<150k, D-dimer>2ug/ml, fibrinogen>400mg/dl, albumin<3g/dl, anemia, ALT>40U/L, INR>1.1
- **Other:** AKI, hyponatremia, high CK, high LDH, high troponin, BNP>400pg/ml, high TG, 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

Initial Labs: COVID-19 by RT-PCR (ACH) or Respiratory Pathogen PCR + COVID (ACNW), VBG, CBC with diff, CMP, CRP, ESR, LDH, Troponin, d-dimer, ferritin, BNP, Blood cx, UA and urine culture

Additional Labs: IgG, IgA, fibrinogen, PT/PTT, SARS-CoV-2 antibody, IL6, limited flow cytometry



Multi-system Inflammatory Syndrome in Children (MIS-C) Treatment Pathway

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)

- Echocardiogram if not already done; repeat as indicated
- Admit patients to ICU if any signs of shock, hypotension, or concern for cardiac dysfunction
- Consult Infectious Disease and Cardiology; goal for daily group discussion or rounds with primary team. If patient does not respond to first and second line therapies, consider Rheumatology consult.
- 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
- Methylprednisolone 2 mg/kg/day divided BID (max dose 60 mg per day), change to PO when tolerating diet
- Consider higher dose steroids (methylprednisolone 10 mg/kg/day) for patients with moderately or severely depressed cardiac function, in consultation with Cardiology
- 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 concerns for MAS
- Anticoagulation: Refer to anticoagulation guidelines

Second-line: Steroids if not improving ~12 hours post-IVIG

- Histamine (H2) blocker for GI ulcer prophylaxis while on both steroids and ASA
- Wean over minimum of 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, AL, Albumin, Ferritin, Creatinine, electrolytes, D-dimer, Fibrinogen, Troponin and B-type Natriuretic Peptide (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 intake, mild dehydration, or monitoring for worsening.*

**Serious: Definitively meets case definition and any of: ill-appearing, evidence of organ dysfunction/injury, require respiratory or cardiovascular support.*

Anticoagulation Guidelines for COVID-19 in Children at ACH

Guidelines are derived from adult guidelines and various adaptations from pediatric hospitals.

Pharmacologic thromboprophylaxis should be considered in all pediatric and adolescent patients admitted to Arkansas Children's Hospital unless contraindicated (active bleeding, thrombocytopenia, recent or upcoming surgical intervention, etc)

Target population to be considered for VTE prophylaxis:

- All hospitalized patients who have been diagnosed with COVID-19 who meet one or more of the following criteria of high-risk:
 - Any patient admitted to intensive care unit
 - Patients admitted with suspected MIS-C
 - Patients with active cancer, autoimmune disorders, decreased mobility, sickle cell disease, obesity, central line, personal or family history of thrombosis, inherited thrombophilia, estrogen therapy.
 - Elevated d-dimer that is >2 times the upper limit normal or with evidence of inflammation (elevated CRP, IL-6, etc)

Laboratory monitoring:

- Labs to be drawn at admission or upon consult:
 - CBC, PT/aPTT, d-dimer, fibrinogen, CRP, IL-6, BUN/Creatinine
 - Repeat CBC, D-dimer, fibrinogen, creatinine and inflammatory markers every 2-3 days as clinically indicated and prior to discharge.

Treatment considerations:

- If **d-dimer > 2x upper limit normal or other high-risk feature** present and no contraindication to anticoagulation:
 - **Start Lovenox 0.5mg/kg/dose SQ q12h (prophylaxis dose)**
 - No need to monitor anti-Xa unless renal insufficiency (follow ACH Anticoagulation guidelines)
- If **d-dimer >5 mcg/ml or respiratory failure, signs/symptoms of microvascular thrombosis, or very high risk of thrombosis** based on clinical impression
 - Consider **increase in enoxaparin (e.g. Lovenox) to 1mg/kg/dose SQ q12h (treatment dose)**
 - Target anti-Xa 0.5-1
- If contraindication to anticoagulation (bleeding, thrombocytopenia, surgery)
 - Mechanical thromboprophylaxis should be strongly considered (SCD)
- If CrCl <30 or very high risk of bleeding, utilize unfractionated heparin instead of Lovenox

Special considerations:

- MIS-C/Kawasaki patients – If cardiology recommends aspirin therapy, carefully review clinical indication for additional prophylactic lovenox. May not be required unless high risk for VTE based on above criteria.
- Direct Oral Anticoagulants (DOAC) are not preferred inpatient as they can interact with medications (antivirals) used to treat COVID-19.
- Daily assessment for signs/symptoms of DVT or PE with imaging (US or CTA chest) if VTE suspected.

Upon discharge:

- Assess patient for ongoing risk of thrombosis. If ready for discharge, it is likely patient no longer has risk factors for VTE.
- If high risk (active cancer, sickle cell disease, thrombophilia or history of thrombosis, d-dimer still >5 mcg/ml), consider discharge to home on thromboprophylaxis.
- Prophylaxis dosing of enoxaparin or DOAC for older adolescent x 2 weeks minimum. Can be seen in outpatient hematology clinic at that point to decide if further therapy needed.

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 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 Stevens Johnson Syndrome (SJS), Drug Reaction with Eosinophilia (DRESS), or serum sickness-like reaction
- History of recent or semi-recent exposure to drug; consider with arthralgias and diffuse mucositis

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 arrhythmia
- 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 above the upper limit of normal
- Receipt of vasopressor or vasoactive support
- Receipt of cardiopulmonary resuscitation (CPR)

Hematologic 76%

- Total white blood cell < 4k
- Anemia for age
- Platelet count <150,000/ μ L
- Deep vein thrombosis
- Pulmonary embolism
- Hemolysis
- Bleeding or prolonged PT/PTT
- Ischemia of an extremity

Mucocutaneous 74%

- Bilateral conjunctival injection
- Oral mucosal changes
- Rash or skin ulcers
- 'COVID' toes
- Swollen red cracked lips
- Erythema of palms or soles
- Edema of hands or feet
- Periungual (nails) desquamation

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
- Pulmonary infiltrates on chest radiograph
- Lower respiratory infection
- Pleural effusion
- 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

Myocarditis Follow-Up Information

Short to intermediate-term follow-up for patients identified to have myocarditis:

- There is a limited role for cardiac MRI in the acute phase of MIS-C. It may be helpful for patients in whom a tie-breaker test is needed to decide whether to give further immunomodulatory therapy (IVIg, steroids, IL-6, etc). Troponin trend can usually be a sensitive surrogate marker for whether the inflammatory process is under control. The decision for/against cardiac MRI in the acute phase of MIS-C should be considered on a case-by-case basis (risk vs benefit, monitoring if critically ill, MRI logistics, etc).
- Patients who have had evidence of myocardial injury (troponin / BNP elevation and/or cardiac dysfunction on echo) will need cardiology follow-up for sequelae of inflammatory myocarditis, within 2 weeks of hospital discharge.
- Patients who have had myocarditis should be restricted from sports for 3-6 months due to risk of sudden cardiac death; this is in line with recent expert analysis published by the American College of Cardiology⁴.
- Patients who have had myocarditis (troponin / BNP elevation and/or cardiac dysfunction on echo) should undergo cardiac MRI approximately 6 months after illness to determine myocardial viability and long-term follow-up plan⁵

Additional Note:

COVID antibodies should be sent in patients with unexplained troponin elevation but negative COVID PCR test, given that 1/3 of patients with MIS-C may be PCR negative but antibody positive².

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