

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

**Patient with suspected MIS-C**

- Evaluate clinical features and lab evidence
- Assess Inclusion Criteria

**Labs to be collected:**

- VBG
- CBC with diff
- CMP
- CRP
- ESR
- LDH
- Troponin
- D-dimer
- Ferritin
- BNP
- COVID-19 by RT-PCR (ACH) or RPP + COVID PCR (ACH)
- Respiratory Pathogen PCR + COVID (ACNW)
- SARS-CoV-2 Spike (S) Protein Total (IgM/IgG) Antibody-Qualitative (LAB4595)
- IgG
- IgA
- Fibrinogen
- PT/PTT
- Blood culture
- UA and urine culture

**Inclusion Criteria for Pathway Below**

- Age <21 years with fever  $\geq 38.0$  for  $\geq 24$  hrs
- Lab evidence of inflammation
- Evidence of clinically severe illness requiring hospitalization, with multisystem ( $\geq 2$ ) 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**

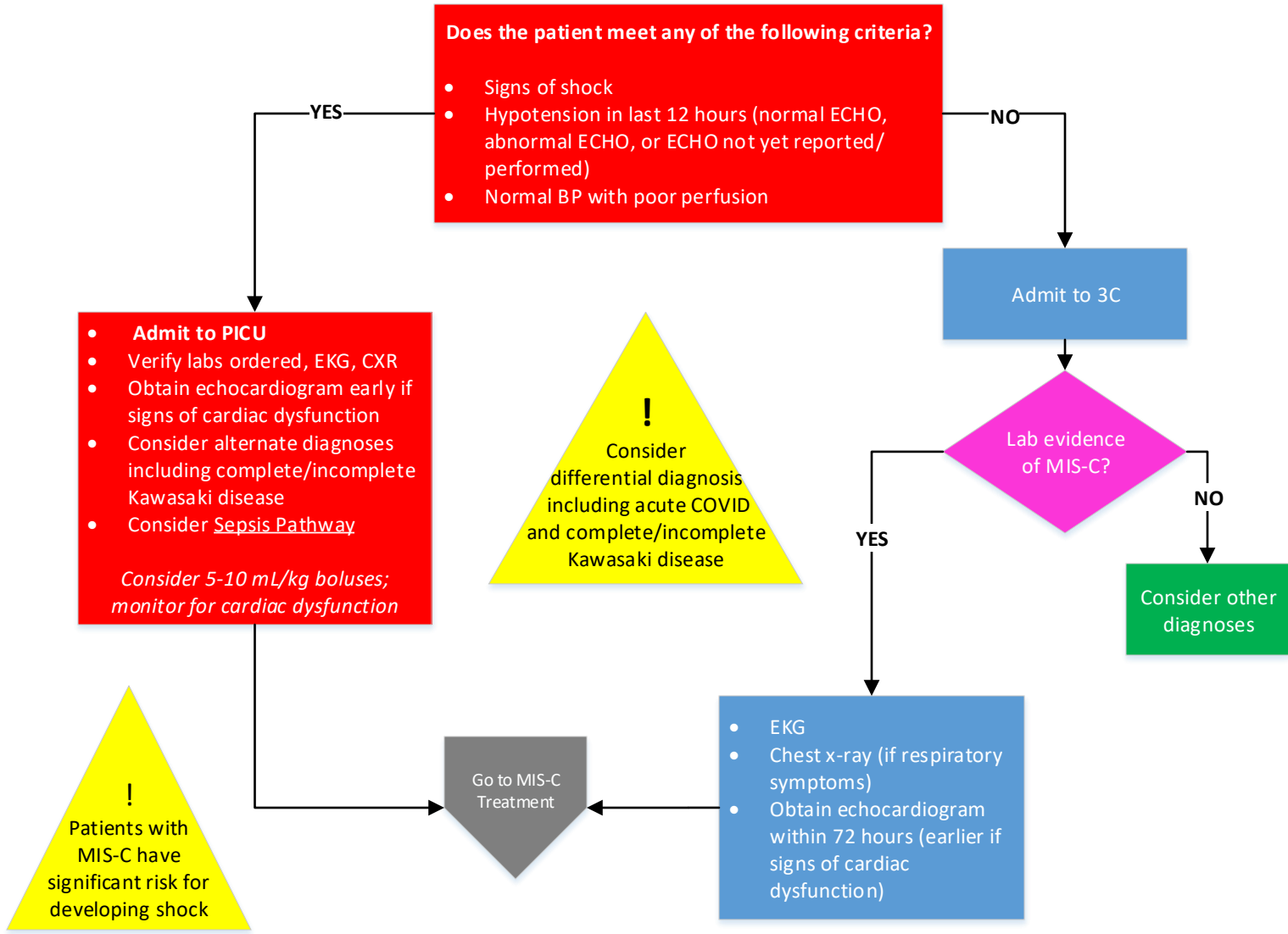
- Most patients have  $\geq 4$  organ system involvement;  $\geq 2$  required for diagnosis
- Involvement of following systems (percent of patients in case series):
  - Gastrointestinal (92%)
  - Cardiovascular (80%)
  - Hematologic (76%)
  - Mucocutaneous (74%, 59% had rash)
  - Renal (8%)
  - Neurologic (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  $> 40$  mm/h, ferritin  $> 500$  ng/ml, platelet  $< 150$  k, D-dimer  $> 2$  ug/ml, fibrinogen  $> 400$  mg/dl, albumin  $< 3$  g/dl, anemia, ALT  $> 40$  U/L, INR  $> 1.1$
- Other:** AKI, hyponatremia, high CK, high LDH, high troponin, BNP  $> 400$  pg/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*



# 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 Diseases 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:**

- Prior to initiation of IVIG or steroids, please draw lab to hold in 2 gold tops
- IVIG 2 g/kg (use ideal body weight) over 12 hours. If dose is higher than 100 g, consider dividing dose to 1 g/kg over 12 hours once daily for 2 days (if concerned for fluid status).
- Methylprednisolone 1 mg/kg/dose q12 hours (max dose 60 mg BID), change to PO when tolerating diet
- Famotidine 0.25 mg/kg q12h (use with methylprednisolone)
- 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:** If not improving post steroid initiation or if labs suggestive of MAS

- Obtain Rheumatology Consult
- Anakinra 1 mg/kg/dose Q12 hours, max dose 100 mg/dose
- Anakinra 4 mg/kg/dose Q12 hours (or frequency per Rheumatology), max dose 100 mg/dose

Trend CBC, CRP, LDH, ALK, Albumin, Ferritin, Creatinine, electrolytes, D-dimer, Fibrinogen, Troponin 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 intake, mild dehydration, or monitoring for worsening.*

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

# Anticoagulation Guidelines for Acute COVID-19/MIS-C

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, diabetes, personal or family history of thrombosis, inherited thrombophilia, estrogen therapy.
  - Elevated D-dimer that is  $\geq 5$  times the upper limit normal or with evidence of inflammation (elevated CRP, etc.).

## Laboratory monitoring:

- Labs to be drawn at admission or upon consult:
  - CBC, PT/PTT, D-dimer, fibrinogen, CRP, 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  $\geq 5$  times upper limit normal or other high-risk\* feature** present and no contraindication to anticoagulation:
  - **Start enoxaparin (e.g. Lovenox) 0.5mg/kg/dose SQ q12h (prophylaxis dose)**
  - At least weekly anti-Xa testing while critically ill with goal anti-Xa 0.2-0.5 (follow ACH Anticoagulation guidelines)
- If **signs/symptoms of microvascular thrombosis, or very high risk** of thrombosis based on clinical impression (e.g. active cancer, sickle cell disease, diabetes or history of thrombosis)
  - Consider **increase in enoxaparin (e.g. Lovenox) to 1mg/kg/dose SQ q12h (treatment dose)**
  - Target low molecular weight 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 enoxaparin (follow ACH Anticoagulation Guidelines)

## Special considerations:

- MIS-C/Kawasaki patients – If cardiology recommends aspirin therapy (due to concern for abnormal coronary arteries or persistently diminished systolic function), carefully review clinical indication for additional prophylactic Lovenox. May not be required unless high risk for VTE based on above criteria. Concomitant use of low dose aspirin ( $<5$  mg/kg/day) with prophylactic anticoagulation likely does not confer a high risk of bleeding in the absence of other bleeding risk factors.
- 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.

# 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

## **Staphylococcal 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

## **Autoimmune Disorders**

- Lupus, HLH, etc.

# 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  $\geq 2.5$
- Pericarditis or pericardial effusion or valvulitis
- 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/ $\mu$ 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
- Dizziness

*Adapted from Feldstein et al, NEJM June 2020*

# Discharge and Follow-Up Information

## Cardiology follow-up: Short to intermediate-term follow-up for patients with myocarditis

- No ongoing Cardiology treatment or follow-up is indicated for patients whose disease process never included abnormal systolic function on echocardiogram, serum troponin greater than 3x upper limit of normal or significant arrhythmia
- Patients with peak serum troponin level greater than 3x the upper limit of normal, mild systolic dysfunction (defined as ejection fraction >45%/fractional shortening 24-28%) and or moderate valve regurgitation with no significant arrhythmia require 2-week follow-up in Cardiology. No medication. Restriction from sports for 6-8 weeks
- Patients with moderate to severe myocardial dysfunction (ejection fraction <45% or fractional shortening less than 24%), persistent dysfunction at discharge or atrial or ventricular arrhythmia should have Cardiology follow-up in 2 weeks. Discharge on ACE inhibitor (lisinopril 0.1 mg/kg daily). Restrict from sports 4-6 months.

## Hematology follow-up:

- 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), discuss with Hematology the need for anticoagulation upon discharge
- No need to trend D-dimer or inflammatory markers after discharge
- If discharged home on Lovenox, follow up with Hematology within 2 weeks

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