Multisystem Inflammatory Syndrome in Children (MIS-C) Associated with Coronavirus Disease (COVID-19) Diagnosis

Emergency Department

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***Symptoms of MIS-C**

- Rash (take pics in Epic)
- Bilateral conjunctivitis
- Mucositis/fissured lips/ strawberry tongue
- Hand/feet redness/swelling
- Abdominal pain, N/V/D
- Headache or confusion
- Respiratory symptoms/chest pain/shortness of breath
- Sore throat/adenopathy
- Hypotension/Shock
- Toxic-shock-like features
- Cytokine storm/MAS
- Thrombosis
- Poor cardiac function
- Acute Kidney Injury (AKI)

Initial Assessment
For patients < 21 years with concern for MIS-C

Definition & Diagnosis

Differential Diagnoses

Fever for ≥ 3 days AND
- Symptoms of MIS-C from > 2 systems* WITH
- Close contact (confirmed or probable) with COVID-19 in the past 60 days?

No → **OFF PATHWAY**
Consider alternate diagnoses. Arrange follow-up if necessary.

Yes

Is patient ill-appearing? — Yes →

ED MANAGEMENT & STABILIZATION
MIS-C patients can decompensate rapidly

- Sepsis protocol as indicated
- Monitor for volume overload
- Decreased cardiac function associated with MIS-C
- Cardiac monitor

INITIAL STUDIES
- BOX 1 – All patients
- BOX 2 – As indicated

Consider discussion with:
- Cardiology
- Infectious Diseases
- PICU/CTICU

Admit Patient
- Determine level of care in consultation with Cardiology/PICU/ CTICU teams
- PICU admission for hypotension or unexplained tachycardia

No

INITIAL STUDIES
- CBC with differential
- C-Reactive Protein (CRP) if available
- Sedimentation Rate (if CRP unavailable)
- Comprehensive Metabolic Panel (CMP)

CRP ≥ 3.0 mg/dL **OR** ESR ≥ 40 mm/hr
OR
Platelets < 150,000
OR
Abs. Lymphocyte count < 1000

No → **Off Pathway**
Consider alternate diagnoses. Discharge with close follow-up within 48 hours if fever persists

Yes

UC or LCED – Consider Direct Admit vs. Transfer to MCED
- BOX 1 – All patients
- BOX 2 – As indicated

One or more of the following?
- Elevated Troponin or BNP
- Elevated ANC
- Elevated Ferritin or LDH
- Hyponatremia
- Abnormal creatinine for age
- Abnormal CXR or EKG (if obtained)
- Other evidence of end-organ injury

AND NO ALTERNATIVE DIAGNOSIS

No → Off Pathway

Yes

Consider discussion with:
- Infectious Diseases
- Cardiology
- PICU/CTICU

Admit Patient
- Determine level of care in consultation with specialists
- Telemetry if cardiac abnormalities

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Treatment

Inpatient

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Patients admitted with suspicion for KD or MIS-C*

Obtain labs & imaging

Risk Factors for MIS-C?

No → Treat as conventional KD
- IVIG: Obtain pre/post **IVIG labs**
- High-dose Aspirin

Yes

Consult:
- Infectious Diseases
- Cardiology
- Rheumatology (if mod/severe disease)

D-dimer > 2?

Yes → Consult Hematology for possible anticoagulation with **Lovenox**

No

Start Methylprednisolone 2mg/kg/day and IVIG 2g/kg IV single dose
Obtain pre/post IVIG labs
- Consider divided IVIG dose for pts with cardiac dysfunction, weight > 50kg or concern for fluid overload
- Consider furosemide chaser if no AKI and discussed with cardiology

Severity of Disease?

MILD
- No respiratory distress
- No cardiac dysfunction
- No significant organ injury

→ Start **Aspirin** 3-5mg/kg/day (max 81mg) x 6 wks

MODERATE
- Oxygen requirement or respiratory distress
- Mild cardiac dysfunction/effusion
- Elevated creatinine
- Requiring fluid resuscitation for tachycardia/hypotension
- Coronary abnormalities (z ≥ 2.5)

SEVERE
- Vasoactive/inotropic support
- Ventilatory support (invasive or non-invasive)
- Moderate or severe single organ or multi-organ injury
- Moderate or severe cardiac dysfunction

Once severe bacterial infection is ruled out:
- Increase Methylprednisolone to 10mg/kg/day (1g max) for 1-3 days then 2mg/kg/day
- If fails to improve consider increasing steroid dose to 30mg/kg (1g max) and/or consider Anakinra (discuss with Rheum)
- Start Aspirin 3-5mg/kg/day (max 81mg) x 6 wks

Once convalescing plan steroid (and/or Anakinra) wean schedule

Post-Discharge Follow-Up

***During the first 24-48 hours, severe bacterial infection such as Toxic Shock Syndrome or Sepsis should be considered. Steroids should still be initiated in patients with high concern for MIS-C potentially with concurrent antibiotics.**

Return to Diagnosis Algorithm

Definition & Diagnosis

Any illness in a person < 21 years that meets:

- The clinical AND the laboratory criteria **OR**
- The clinical criteria AND close contact* with a confirmed or probable case of COVID-19 disease in the 60 days prior to hospitalization

Clinical Criteria	Laboratory Criteria
An illness characterized by <u>all of the following</u>, in the absence of a more likely alternative diagnosis • Subjective or documented fever ≥ 100.4ºF (38.0ºC) • Clinical severity requiring hospitalization or resulting in death • Evidence of systemic inflammation indicated by CRP ≥ 3.0 mg/dL • New onset manifestations in <u>at least two</u> of the following categories: 1. Cardiac involvement indicated by: ○ Left ventricular ejection fraction < 55% **OR** ○ Coronary artery dilatation, aneurysm, or ectasia, **OR** ○ Troponin elevated above laboratory normal range 2. Mucocutaneous involvement indicated by: ○ Rash **OR** conjunctivitis/conjunctival injection, **OR** ○ Inflammation of the oral mucosa (mucosal erythema or swelling, dry or fissured lips, strawberry tongue), **OR** ○ Extremity findings (erythema/edema of hands/feet) 3. Shock** 4. Gastrointestinal involvement indicated by: ○ Abdominal pain **OR** Vomiting **OR** Diarrhea 5. Hematologic involvement indicated by: ○ Platelet count < 150,000 cells/μL **OR** ○ Absolute lymphocyte count (ALC) < 1,000 cells/μL	Detection in a clinical specimen*** up to 60 days prior to or during hospitalization of: • SARS-CoV-2 RNA **OR** • SARS-CoV-2 specific antigen **OR** Detection of SARS-CoV-2 specific antibodies^ in serum, plasma, or whole blood associated with current illness resulting in or during hospitalization

*Close contact is generally defined as being within 6 feet for at least 15 minutes (cumulative over a 24-hour period). However, it depends on the exposure level and setting; for example, in the setting of an aerosol-generating procedure in healthcare settings without proper personal protective equipment (PPE), this may be defined as any duration.

** Clinician documentation of shock meets this criterion.

***Positive molecular or antigen results from self-administered testing using over-the-counter test kits meet laboratory criteria.

^Includes a positive serology test regardless of COVID-19 vaccination status. Detection of anti-nucleocapsid antibody is indicative of SARS-CoV-2 infection, while anti-spike protein antibody may be induced either by COVID-19 vaccination or by SARS-CoV-2 infection.

Adapted from **CDC Case Definition and Reporting**

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Return to Treatment Algorithm

Differential Diagnoses

- Kawasaki Disease
- Toxic Shock Syndrome
- Septic Shock
- Vasculitis
- Viral Myocarditis (e.g. Influenza, Enteroviruses)
- Other Viral illness (e.g. acute SARS-CoV-2, Influenza, Adenovirus)
- Pyelonephritis
- Rickettsial Disease
- Macrophage Activation Syndrome
- Appendicitis

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Initial Testing

BOX 1
Initial Screening Studies
(if concern for MIS-C)

- CBC with differential*
- CRP*
- CMP*
- Troponin I
- BNP (order stat)
- Urinalysis (microscopic)
- Fibrinogen
- Ferritin
- LDH
- Blood Culture

* if not already performed

BOX 2
Supplemental Studies
(Based on symptoms)

Labs

- Rapid Strep
- Urine Culture
- Procalcitonin
- ASO/Anti-Dnase B
- Neutrophil Gelatinase Associated Lipocalin (N-GAL)

Imaging

- EKG
- CXR
- Echocardiogram
- Abdominal US – if abdominal complaints
- Chest CT with contrast – if abnl CXR and resp distress
- Neck imaging – if concerned for phlegmon/deep neck infection

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Diagnostic Testing

- Obtain **initial testing** if not already done

Comprehensive Studies
(can be done upon admission)

- Quant D-Dimer
- Amylase/Lipase
- Triglycerides
- PT/PTT/INR
- CK
- IL-6
- SARS-CoV-2 Serologies
- SARS-CoV-2 dedicated PCR **and** FARVPP
- Save serum in red-top, EDTA and if available Tempus tubes (in case IVIG administered)

Daily Labs
(for mod/severely ill)

- CBC (initial with diff)
- CMP
- Coags
- CRP
- D-dimer
- BNP/Troponin

Imaging

Patients > 12yrs old with troponin leak should get Cardiac MRI before discharge (must have normal Creatinine and negative SARS-CoV-2-PCR)

- Consider **labs and imaging guidance**

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Labs & Imaging Guidance

- CRP is preferred inflammatory marker. If unavailable, may use ESR
- Consider drawing blood cultures if placing an IV so as to avoid a second procedure
- Consider urine analysis in initial work up, especially if able to provide clean catch urine or concern for urinary tract infection/pyelonephritis
- Consider FARVPP or other viral studies to assess for other etiologies
- Ferritin turnaround time is approximately one day, do not need this resulted for admission
- D-dimer is usually >2 ug/mL
- Consider discussion with hematology if concern for coagulopathy
- Consider chest XR for respiratory symptoms or distress
- Consider echocardiogram in ED if abnormal cardiac markers/EKG (discuss with cardiology)
- Cardiac monitor if ill-appearing and telemetry until cardiology can evaluate
- Consider ultrasound if abdominal complaints
- Consider chest CT with contrast if abnormal chest XR and respiratory distress or if pulmonary hypertension by echocardiogram or respiratory failure (discuss with cardiology i.e. for concerns of severe PE requiring possible interventional cath)

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Pre-Pathway Validation

Epidemiology

- 98% had a positive COVID-19 test
- 50% are between 5-13 years
- Median age is 9 years
- 60% male predominance
- 56% Hispanic/Latino or Black/Non-Hispanic

***Risk Factors for MIS-C**

- Respiratory symptoms
- Exposure to COVID-19
- Positive SARS-COV-2 Ab or PCR testing

Common Clinical Features	Common Lab Features
• Fever • Abdominal pain • Vomiting • Diarrhea • Rash • Mucocutaneous lesions • Hypotension • Shock • Neck pain • Altered mental status • Headache	• High CRP • Lymphopenia • Thrombocytopenia • Elevated ferritin • Neutrophilia • Elevated troponin • Acute kidney injury • Hyponatremia • Proteinuria • Coagulopathy • Elevated d-dimer >2 ug/ml

Imaging Findings		
Chest XR/Chest CT	EKG/Echocardiogram	Abdominal ultrasound
• Patchy asymmetric infiltrates • Pleural effusion • Coronary abnormalities (if contrast chest CT)	• Myocarditis • Valvulitis • Pericardial effusion • Coronary dilation/ aneurysm	• Colitis • Ileitis • Adenopathy • Ascites • HSM

Suspected cases should be reported to the CDC

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Medications & Pre/Post-IVIG Labs

Pre/Post -IVIG Labs		
Tests preferably done before IVIG or other immunosuppression *Please notify Dr. Roshini Abraham (email or 2-5329)* before sending samples Yellow research specimen cards available from Resident Workrooms or from Dr. Abraham		
Lab Name	**Ordering Process**	**Lab Schedule**
Box A • TBNK/Lymphocyte subset assay • T1A2MP [Type I/II Interferon assay]	• **LABTBNK** in Epic • LABT1A2MP • (1mL EDTA tube at room temp can be run on same tube)	Routine M-F, notify Dr. Abraham/Dr.Aluri 2-0809 by Friday noon if needed over weekend
Box B • (IL-6, TNF-alpha, IL-1 beta, Soluble IL-2 Receptor, IL-18) order individually or with DILCYT panel which includes all	• **LABDILCYTU** in Epic (if needed within 24 hrs) • **LABDILCYTN** in Epic (results within 48 hrs) • Send to lab within 2 hr of blood draw	Available M-F, weekends only by request to Dr. Abraham/Dr. Aluri 2-0809
Box C • IL-10 • SAA [SERUM AMYLOID A] • IL-8	• If ordering any **Box B** labs, collect in a red top tube and obtain: • 2 mL for ≤ 1-year-old • 3 mL ≥ 2 year-old - ≤ 12-year-old • 4 mL for > 12-year-old • B**ox C** labs can be added on and run on the same tube	Available M-F, weekends only by request to Dr. Abraham/Dr. Aluri 2-0809
• For serial monitoring of cytokines, use the same test for direct comparison. Cannot be compared across immunoassays (i.e. In-house testing is not comparable to send-out testing). • In certain patients, additional detailed T and B cell subset immunophenotyping (not TBNK) may be useful. Discuss with Dr. Abraham as these will be done offline. *Can obtain card by request from McKenzie Ludt 2-5713, Tyler Rogerson 2-5422, Dr. Abraham 2-5329. Also available with ID/HDP staff faculty, Hematology workroom H11A, and Dr. Guliz Erdem		

Medication	Precautions with Use
IVIG	Use with caution if fluid overloaded or renal dysfunction
Aspirin	• Use with caution in severe thrombocytopenia • Ensure flu negative before starting
Methylprednisolone (or other corticosteroids)	• Use with caution with positive PCR testing for SARS-CoV-2 suggesting active viral infection • Consider PPI with higher doses
Lovenox	Discuss with hematology if risk factors present: • Thrombocytopenia • Hypofibrinogenemia • Recent major bleeding • On Aspirin > 5mg/kg/day

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Follow-Ups

Follow-Up Indications	Clinic	Interval	Services
MIS-C diagnosis	COVID clinic (Infectious Diseases Clinic)	1-2 weeks	• ID • Cardiology • Rheum (if on biologic therapy)
On Anticoagulation	Anticoagulation Clinic	Per Hematology	Hematology

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Return to Pre-Pathway Validation

Patient & Caregiver Education

For more information: Search CDC, MIS-C signs and symptoms

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Metrics

Pathway Goal

- Increase recognition and prompt diagnosis of MIS-C.

Quality Measures

Outcome Metrics

- Average Inpatient LOS (goal = decrease)
- Decrease time to steroids and IVIG

Process Metrics

- Pathway Utilization/OrderSet usage

Balancing Metrics

- Percentage of Encounters with a Readmission within 7 Days (all cause)
- Percentage of Encounters with a Readmission within 30 Days (all cause)

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Clinical Pathway Development

This clinical pathway was developed using the process described in the NCH Clinical Pathway Development Manual Version 6, 2022. Clinical Pathways at Nationwide Children's Hospital (NCH) are standards which provide general guidance to clinicians. Patient choice, clinician judgment, and other relevant factors in diagnosing and treating patients remain central to the selection of diagnostic tests and therapy. The ordering provider assumes all risks associates with care decisions. NCH assumes no responsibility for any adverse consequences, errors, or omissions that may arise from the use or reliance on these guidelines. NCH's clinical pathways are reviewed periodically for consistency with new evidence; however, new developments may not be represented, and NCH makes no guarantees, representations, or warranties with respect to the information provided in this clinical pathway.

For more information about our pathways and program please contact:
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