MULTISYSTEM INFLAMMATORY SYNDROME in CHILDREN (MIS-C) ASSOCIATED with CORONAVIRUS DISEASE 2019 (COVID-19) CLINICAL PRACTICE GUIDELINE

This clinical guideline has been developed to ensure appropriate diagnosis, evaluation, and treatment for MIS-C. Please direct referrals to The Barbara Bush Children's Hospital (BBCH), Pediatric Hospital Medicine (PHM) service, via Maine Medical Center (MMC) One-Call at 866 662-6632.

MIS-C is an emerging syndrome. This Clinical Practice Guideline is based on current evidence. As more data and experience accumulates, this information will require revision; please refer back to this site for updates.

MIS-C presents days to weeks after COVID exposure; often, the initial COVID exposure results in no symptoms or minimal symptoms of COVID infection. Patients with MIS-C can have negative nasopharyngeal swabs for COVID-19 PCR RNA. Other lab evidence of COVID may be positive. Based on this experience, MIS-C is likely an immune-mediated response to COVID and is not due to direct viral injury.

CENTERS FOR DISEASE CONTROL AND PREVENTION (CDC) CASE DEFINITION

< 21 years of age with persistent fever (≥ 38°C or subjective fever, for at least 24 hours)

AND

Laboratory evidence of inflammation

AND

Multisystem (≥ 2) organ involvement (cardiac, renal, respiratory, hematology, GI, skin, neurologic)

AND

No alternative plausible diagnosis

AND

Positive for current or recent SARS-CoV-2 infection OR
COVID-19 exposure within 4 weeks prior to onset of symptoms

CLINICAL PRESENTATION/LABORATORY EVIDENCE, including any combination of the below

1. **Warm shock (similar to toxic shock syndrome), that is unresponsive to IVF boluses, and therefore, requiring inotropic and/or vasopressor support**
2. **Fever (≥38°C)**
3. **Abdominal pain, vomiting, diarrhea**
4. **Kawasaki Disease (KD)-like illness (both typical and atypical presentation), with fever, conjunctivitis, rash, swollen or red hands/feet, adenopathy (including non-cervical), mucus membrane changes, irritability. Kawasaki Disease will be classified as MIS-C if any COVID exposure, positive PCR, or positive antibody testing. (See Appendix for laboratory differences between Kawasaki Disease and MIS-C.)**
5. **Cardiac dysfunction, including secondary respiratory symptoms and tachycardia**
6. **Typically older children (9-11 years old) as opposed to KD (toddlers), with no underlying medical conditions, except for possibly obesity**
7. **Specific laboratory findings (See Appendix). Most patients need only Tier 1 Labs at initial presentation.**

REPORTING REQUIREMENTS: Report patients who meet the CDC MIS-C case definition or who are highly suspicious for MIS-C to the Maine CDC within 48 hours. Faxing (800 293-7534 or 207 287-8186) the completed Notifiable Disease Reporting Form (notifiable-form.pdf (maine.gov)) is preferred; alternatively, a verbal phone report (800 821-5821) is acceptable.

Algorithms are not intended to replace providers' clinical judgment or to establish a single protocol. Some clinical problems may not be adequately addressed in this guideline. As always, clinicians are urged to document management strategies.

Last revised February 2022 by Lorraine McElwain, MD.

The Barbara Bush Children's Hospital
At Maine Medical Center

OUTPATIENT/EMERGENCY DEPARTMENT GUIDANCE

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For pediatric patients with shock, typical or atypical Kawasaki Disease, or who are ill-appearing, consider consultation and/or referral to The BBCH, Pediatric Hospital Medicine (PHM) service. Call to MMC One-Call (866 662-6632) to discuss with the on-call PHM physician.

FOR WELL-APPEARING PATIENTS

With ≥ 4 days of fever (≥38°C) without a source

OR

With > 3 days of fever (≥ 38°C) PLUS features of Kawasaki Disease or GI symptoms

LABS

Collect and send Tier 1 Labs

- **CBC with differential**
- **CRP**
- **Any other labs that are clinically indicated, such as a Urinalysis (and Urine Culture, if the UA is concerning)**

AND

"Collect and hold" but DO NOT SEND Tier 2 Labs

D-dimer	**ESR**	**Troponin**
Ferritin	**CMP**	**2 ml of blood in a red top tube to hold**

DECISION-MAKING

If CRP < 50 mg/L: Consider home care with close outpatient follow-up within 48 hours and provide return precautions. If follow-up care cannot be secured, consider hospital admission.

If CRP 50-100 mg/L, send Tier 2 Labs. When the labs are resulted, consider discussion/consultation with on-call Pediatric Hospital Medicine physician. If home care is considered, ensure close outpatient follow-up within 24-48 hours (including repeat labs) and provide return precautions. If follow-up care cannot be secured, consider hospital admission.

If CRP > 100 mg/L, send Tier 2 Labs. Consult on-call Pediatric Hospital Medicine physician for admission.

INDICATIONS FOR ADMISSION

PICU

Ventilatory support (including CPAP/BiPAP)
Moderate-to-severe left ventricular dysfunction
Shock refractory to fluid boluses

INPATIENT PEDIATRIC UNIT

Mild illness requiring treatment with IVIG
Moderate-to-severe illness
Shock, responsive to fluid boluses
Unreliable follow-up care within 24-48 hours
Concern for Kawasaki or atypical Kawasaki Disease
Well-appearing patients with CRP > 100 mg/L

In well-appearing patients with CRP 50-100 mg/L, discussion with PHM physician is advised.

INPATIENT GUIDANCE at The BBCH

MULTISYSTEM INFLAMMATORY SYNDROME in CHILDREN (MIS-C) ASSOCIATED with CORONAVIRUS DISEASE 2019 (COVID-19) CLINICAL PRACTICE GUIDELINE (See Appendix for US Hospital Data)

LABS

Blood Culture	CBC with differential	ESR	CRP	Fibrinogen
LDH	Ferritin	d-dimer	CMP	Urinalysis, reflex culture
Troponin				

COVID PCR (nasopharyngeal swab) and consider SARS-CO-V-2 serology/antigen test, in consultation with ID
Extra red top tube to hold (2 cc blood prior to IVIG) for possible antibody testing, pending ID recommendations

Consider BNP, based on cardiology or critical care recommendations
Consider swabs and cultures for other infectious etiologies, depending time of year and clinical presentation

IMAGING/CARDIAC TESTING (See Appendix for the incidence/outcome of cardiovascular abnormalities)

CXR
ECHO to evaluate for myocarditis, left ventricular dysfunction, coronary artery size
ECG
Consider abdominal imaging (an appropriate work-up to rule out appendicitis or mesenteric adenitis with ultrasound vs CT scan w/ contrast) for patients with significant GI symptoms

TREATMENT

1. ABCs for initial stabilization. Consider antibiotics for bacterial sepsis.
2. Obtain a red top lab tube with 2 ml minimum of blood to hold PRIOR TO IVIG administration
3. For patients with Mild MIS-C
   a. IVIG 2 g/kg (maximum dose = 100 grams)
   b. Aspirin 3-5 mg/kg/day (maximum dose = 81 mg)
4. For patients with Moderate-to-Severe MIS-C
   a. IVIG 2 g/kg (maximum dose = 100 grams), consider 1 g/kg/day (maximum dose = 50 g/dose) x 2 days if there is significant myocardial dysfunction
   b. Aspirin 3-5 mg/kg/day (maximum dose = 81 mg)
   c. Methylprednisolone 2 mg/kg/day
5. For patients with Refractory MIS-C – already treated with IVIG, aspirin, and +/- methylprednisolone
   a. Methylprednisolone 10-30 mg/kg/day
   b. Consider H-2 blocker for GI prophylaxis
6. Symptom-focused treatment for severely ill patients (specifically shock, arrhythmia)
7. Consider risk of venous thrombosis and evaluate the risk:benefit ratio of anti-coagulation treatment. Strongly consider early ambulation, compression stockings, and/or pneumatic compression devices. Consider consultation with pediatric hematology.
8. Currently, there are no data for the following: IL-6 inhibitor (e.g. tocilizumab), IL-1 inhibitor (e.g. anakinra), and other immune-modulators. Use of these medications is discouraged without prior rheumatology consultation.

HIGHLY RECOMMENDED CONSULTATIONS: Pediatric Infectious Disease, Pediatric Cardiology

CONSIDERED CONSULTATIONS, depending on clinical presentation/course: Pediatric Critical Care, Pediatric Hematology, Pediatric Neurology, Pediatric Nephrology, Rheumatology

INFECTION CONTROL MEASURES for hospitalized patients with MIS-C should be determined in conjunction with MMC Infection Prevention

PATIENT/FAMILY EDUCATION

1. Get red top lab tube to hold prior to IVIG administration
2. If the patient gets IVIG: no live vaccines (MMR, Varicella) for 11 months
3. If the patient is diagnosed with MIS-C: no COVID vaccine for 90 days
4. If the patient is discharged on aspirin: strongly recommend seasonal influenza vaccine
5. If the patient is diagnosed with MIS-C: needs cardiology input and outpatient clearance to return to sports, gym class, etc,

REFERENCES

May 11, 2020: Maine CDC: Maine Health Alert Network (HAN) System, Public Health Advisory
May 14, 2020: CDC: https://emergency.cdc.gov/han/2020/han00432.asp
May 14, 2020: https://picsociety.uk/wp-content/uploads/2020/05/PIMS-TS-Critical-Care-Clinical-Guidance-v4.pdf
2020, Feldstein, Multisystem Inflammatory Syndrome in US Children and Adolescents; NEJM 383 (4), 334-346
2021, Feldstein, Characteristics and outcomes of US children and adolescents with multisystem inflammatory syndrome in children (MIS-C) compared with severe acute COVID-19; JAMA 325 (11), 1074-1087
2021, Ouldali, Association of intravenous immunoglobulins plus methyl prednisone vs immunoglobulins alone with course of fever in multisystem inflammatory syndrome in children; JAMA 325 (9), 855-864,
January 26, 2022: NIH Webinar: Update 2022: COVID-19, Multisystem Inflammatory Syndrome in Children, and the Heart; Presenters Jane Newburger, MD and Dongngan Truong, MD

APPENDIX

LABORATORY EVIDENCE of MIS-C

Tier 1 Labs: Elevated CRP, elevated neutrophils. Low platelets, lymphocytes, RBC (anemia).

Tier 2 Labs: Elevated ESR, d-dimer, ferritin, cardiac enzymes, LFTs, BNP, creatinine. Low albumin.

Other lab findings: Elevated procalcitonin, fibrinogen, LDH.

POSSIBLE LABORATORY DIFFERENCE BETWEEN Kawasaki Disease and MIS-C

	Troponin	Platelets	IL-6/Ferritin	Lymphocytes
Kawasaki Disease	normal	high	normal	normal
MIS-C	high	low	high	low

CARDIOVASCULAR ABNORMMALITIES and OUTCOMES in Patients with MIS-C

Findings in large case series: 80% of patients with some cardiovascular involvement (Feldstein, NEJM, 2020)
- **73% w/ elevated BNP >400**
- **50% w/ elevated troponin**
- **38% w/ LV ejection fraction <55%**
- **8% w/ coronary aneurysm**
- **7-60% w/ ECG changes: ST changes, prolonged QTc, atrial ectopy, AF, ventricular ectopy, NSVT/VT, AV block, PR prolongation**

Resolution of decreased LV EF by 3 months for most (Feldstein, JAMA 2021)

US DATA: Medications Utilized, Hospitalization/Level of Care Details, Length of Stay, and Recurrence Risk (186 cases reported to CDC March-May 2020, Feldstein, NEJM, 2020, unless otherwise indicated)

1. **Medications received: 77% IVIG, 21% 2nd dose IVIG, 49% steroids, 8% IL-6 inhibitor, 13% IL-1RA inhibitor, 47% systemic anticoagulation**
2. **Level of Care: 20% inpatient pediatric unit, 80% PICU. If in PICU: 48% vasoactive support, 20% mechanical ventilation, 4% ECMO**
3. **Median length of hospital stay: 7 days. Mortality rate: 2%**
4. **Recurrence of MIS-C: None yet reported (Newburger/Truong, Jan 2022)**