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 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 often have negative nasopharyngeal swabs for COVID PCR RNA. Other lab evidence of COVID (serum antibodies) 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 (as of May 14, 2020)

< 21 years of age with persistent fever (≥38.5°C or subjective fever, for at least 24 hours)
AND
Laboratory evidence of inflammation (1 or more: elevated CRP, ESR, fibrinogen, procalcitonin, d-dimer, ferritin, LDH, IL-6, neutrophils; or low lymphocytes, albumin)
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 (by RT-PCR, serology, or antigen test) 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 (≥38.5°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**
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. **Elevated CRP, ESR, fibrinogen, procalcitonin, d-dimer, ferritin, LDH, cardiac enzymes, IL-6, ferritin, neutrophils, LFTs, BNP, creatinine. Low platelets, lymphocytes, albumin, RBC (anemia).**

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

INDICATIONS FOR ADMISSION: See OUTPATIENT GUIDANCE (on the following page) for lab recommendations

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

INPATIENT PEDIATRIC UNIT
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 pediatrician is advised.

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 service. Call to MMC One-Call (866 662-6632) to discuss with on-call PHM pediatrician.

FOR WELL-APPEARING PATIENTS

With ≥ 4 days of fever (≥38.5°C) without a source

OR

With > 3 days of fever (≥38.5°C) PLUS features of Kawasaki Disease or GI symptoms

LABS

Send: CBC with differential, CRP, and any other labs indicated by the clinical scenario

AND

"Collect and hold" the following: d-dimer, ferritin, ESR, CMP, troponin, 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 "collect and hold" labs. When the labs are resulted, consider discussion/consultation with on-call Pediatric Hospital Medicine pediatrician. 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 "collect and hold" labs. Consult on-call Pediatric Hospital Medicine pediatrician for admission.

REPORTING REQUIREMENTS: Report patients who meet the CDC MIS-C case definition (see page 1) or who are highly suspicious for MIS-C to the Maine CDC within 48 hours. Faxing the completed Notifiable Disease Reporting Form (https://www.maine.gov/dhhs/dlc/licensing/children/documents/Notifiable-Conditions-Reporting-Form.pdf) is preferred; alternatively, a verbal phone report (800 821-5821) is acceptable.

INPATIENT GUIDANCE at The BBCH

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LABS

Blood Culture	CBC with differential	ESR	CRP	CMP
LDH	Ferritin	IL-6	d-dimer	Fibrinogen
Troponin				

COVID PCR (nasopharyngeal swab)
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 soluble IL-2
Consider swabs and cultures for other infectious etiologies depending time of year and clinical presentation

IMAGING/CARDIAC TESTING

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 versus CT scan with contrast) to exclude abdominal pathology for patients presenting with significant GI symptoms

TREATMENT

1. ABCs for initial stabilization
2. Consider antibiotics for bacterial sepsis
3. For patients with Kawasaki Disease or Kawasaki-like Disease, manage based on usual Kawasaki Disease care.
   - IVIG 2 g/kg (maximum dose = 100 grams)
   - Medium-to-high dose aspirin (transition to low dose aspirin once afebrile)
   - Consult pediatric cardiology to consider prednisone if early coronary artery involvement or age < 6 months
4. Symptom focused treatment for severely ill patients (specifically shock, arrhythmia). (This advice is based on early case series):
   - Expect PICU stay to be short (3-4 days)
   - Most patients survive (UK data)
   - 60% of patients require mechanical ventilation (UK data)
   - 50% of patients presenting with shock are refractory to fluid boluses, requiring inotropic and/or vasopressor support
5. For patients with myocarditis-like presentations: Consider IVIG 1g/kg/day (maximum dose = 50 grams/day) x 2 days and consultation with pediatric cardiology
6. Consider risk of venous thrombosis and evaluate the risk:benefit ratio of anti-coagulation treatment. Consider consultation with pediatric hematology.
7. 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 consultation from rheumatology.

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

REPORTING REQUIREMENTS: See bottom of "Outpatient/Emergency Department Guidance" (page 2) for details.

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

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 May 2020 by Lorraine McElwain, MD.

The Barbara Bush Children's Hospital
At Maine Medical Center