HDVCH Guidelines for Management of Pediatric Patient with Mutlisystem Inflammatory Syndrome in Children (MIS-C) – 10.1.2020 0934

An **emerging condition** associated with current or recent SARS-CoV-2 infection
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Multisystem Inflammatory Syndrome in Children (MIS-C) is a clinical entity believed to follow a SARS-CoV-2 infection or exposure. The clinical presentation is accompanied by significant hyper-inflammation similar to that of Kawasaki Disease or Toxic Shock Syndrome and can lead to organ dysfunction and shock. The pathogenesis is unclear, however it is thought to develop 4-6 weeks after an infection when macrophage activation and acquired immunity are occurring.

The CDC has since released a health advisory statement to alert health care providers and organize a case reporting system. Both the Centers for Disease Control and the World Health Organization have developed case definitions to guide the clinical diagnosis. See the links below and the full case definitions are copied on page 4 of this document for your reference as well.
CDC MIS-C definition
WHO MIS-C definition

Children with MIS-C will most consistently present with prolonged fever and GI complaints (abdominal pain, vomiting, and diarrhea). Additional features include rash, extremity swelling, conjunctivitis, lymphadenopathy and appear very similar to Kawasaki Disease. The most concerning feature of MIS-C is progression to cardiovascular abnormalities (myocarditis, coronary aneurysms, ventricular dysfunction), and potentially shock. Children with MIS-C rarely exhibit respiratory complaints and death is rare.

The recommendations provided in this document do not replace the importance of clinical judgment tailored to the unique circumstances of an individual patient. The below information is intended to be used as a tool to assist the multidisciplinary care team in determination of diagnosis, treatment, and discharge planning. The editors do not assume any liability with the use of any specific information provided herein.

Initial Workup/ED Evaluation

As MIS-C is an inflammatory syndrome, the initial laboratory workup is focused on uncovering signs of inflammation. Moreover, as the disease progresses, patients often develop end-organ dysfunction, in particular cardiac involvement and coagulopathies, and the recommended testing seeks to screen for those concerns as well.
Concerning presenting signs and symptoms:

- Persistent fever, not fully responsive to antipyretics
- GI complaints such as abdominal pain (may mimic appendicitis) and/or diarrhea
- Rash
- Conjunctivitis
- Headache
- Respiratory symptoms
- Sore throat
- Lymphadenopathy
- Schock

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Fever >38.5 for ≥ 3 days, no alternative source

Multi-system inflammation with ≥2 of the following:
- Abdominal pain/vomiting/diarrhea
- Rash
- Conjunctivitis
- Extremity changes
- Lymphadenopathy

Order initial MIS-C

Initial MIS-C Lab evaluation
CBC with manual diff
CMP
UA
ESR, CRP
D-Dimer
HS-troponin
EKG
Ferritin
COVID PCR (NP swab)
COVID serologies

Lab Thresholds of Concern
Absolute Lymphocyte Count < 0.5 k/uL
Albumin <2 g/dL
CRP > 10 mg/dL
D-dimer >1 mg/L
High Sensitivity Troponin >30 pg/mL
Ferritin >350 ng/mL

Concerning exam and/or abnormal labs

Reassuring exam & labs

Send Additional MIS-C labs/tests* and admit (general peds vs PICU)

Discharge home with PCP follow-up in 12-24 hours

***Additional MIS-C labs/tests to be collected and performed for admitted patients**

COVID PCR (NP swab x 2 total, 24 hrs apart)	PT/INR, PTT	Blood Cx
COVID serologies if not sent	Fibrinogen	UA/Urine Cx
Film Array if COVID PCR negative	LDH	**ECHO, EKG**
VBG	Triglycerides	BNP
Procalitonin	Peripheral Smear	CK
Cytokine Panel		

Inpatient Management

Confirmed or High Likelihood MIS-C Diagnosis

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If considering ECMO, consult CT surgery early

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Discuss or Consult Cardiology for EMPIRIC treatment of all MIS-C patients with low dose ASA.** Hold when platelets <80k

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Consult Heme/Onc for patients with documented VTE

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Review Echocardiogram, EKG results. Place patient on telemetry

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If ECHO is normal, refer to EPIC Admission VTE Risk Assessment. If patient is "High Risk" consider ADDING Prophylactic Enoxaparin** Consider bleeding risks.

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Repeat VTE Risk Assessment at least every 48 hours or with any clinical changes. Discontinue Prophylactic Enoxaparin when no longer "High Risk"

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Continue ASA for approximately 4-6 weeks. Follow up with Cardiology as outpatient. If patient is on Therapeutic Enoxaparin, follow up with Heme/Onc.

ECHO Shows
- EF < 30%
- Intracardiac Thrombus
- Severe coronary artery abnormalities

Consult Cardiology and Heme/Onc for Therapeutic Enoxaparin** IN ADDITION to ASA

Vital Sign Monitoring

Continuous cardiorespiratory monitoring and continuous pulse oximetry

Isolation

Place patient in severe respiratory isolation until COVID PCR is negative x 2 (24 hours apart)

Negative pressure not needed unless pt likely to undergo aerosolizing procedures.

Subspecialty Consultations

ID consult if MIS-C is being considered. ID team will be responsible for reporting the disease and for outpatient follow-up (labs, echo). If MIS-C is diagnosed, notify Nick Hartog to consider approaching patient for study enrollment.@ ID will recommend additional clinical consultations as indicated to rheumatology, cardiology, heme/onc, immunology.

@The **COVID Human Genome Effort** is an international effort to characterize genetic abnormalities that predispose otherwise healthy individuals to MIS-C and severe COVID-19 disease. Enrolled patients will have blood drawn at one time point and genetic sequencing completed and evaluated. Please contact Nick Hartog or see www.COVID-hge.com for more details on study.

Disease Reporting

ID team will be responsible for reporting if there is sufficient evidence to make the diagnosis

Treatment Considerations

Treatment approach will be individualized and may include supportive care, IVIG, steroids, immunomodulators as further evidence develops. ** Medication Table on next page*

Daily lab monitoring

CBC	with manual diff	CMP
ESR, CRP		Ferritin
BNP, and troponin if original values were elevated		
Fibrinogen		
D-dimer		PT/INR/PTT

***Mediations Table**

Medications	Dose	Route	Comments
IVIG	2g/kg/dose	IV	Infuse IVIG over 12-48 hours; consider fluid status
Steroids	Methlprednsione 1-2 mg/kg/day divided BID and wean over 2-4 weeks Consider a pulse 30 mg/kg/day once, max 1000 mg in certain severe cases	IV/PO IV	Infuse over 45 minutes, give daily for 1-3 days.
Anakinra	2-10 mg/kg once a day.	SC	Dose can be escalated pending the response.
Remicade	5-7 mg/kg/day	IV	Discuss with Rheumatology
Aspirin (ASA)	3-5mg/kg/day, max=81mg	PO	Continue approximately 4-6 weeks. Follow up with Cardiology
Enoxaparin (Prophylaxis dosing)	**< 2months:** 0.75mg/kg/dose q12 hours **≥ 2months:** 0.5mg/kg/dose q12 hours	SQ	Check LMWH level 4 hours after 3rd - 5th dose Target 0.3-0.5 units/mL Regular monitoring for prophylaxis dosing is optional. Obtain if there is new bleeding, change in liver or renal function, or in critically ill patients.
Enoxaparin (Therapeutic dosing)	**< 2months** 1.5 mg/kg/dose q12 hours **≥ 2months:** 1 mg/kg/dose q12 hours	SQ	Check LMWH level 4 hours after 3rd - 5th dose Target >0.5-1.0 units/mL Dose adjustments by Heme/Onc

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CDC case definition:

A. Age < 21 years
B. Clinical presentation including **all** of the following:
   1. Fever >38.0C (100.4F) for >/= 24 hours or subjective fever lasting >/= 24 hours
   2. Laboratory evidence of inflammation, including but not limited to:
      - Elevated CRP
      - Elevated ESR
      - Elevated fibrinogen
      - Elevated procalcitonin
      - Elevated D-dimer
      - Elevated ferritin
      - Elevated LDH
      - Elevated IL-6 level
      - Neutrophilia
      - Lymphcytopenia
      - Hypoalbuminemia
   3. Severe illness requiring hospitalization
   4. Multisystem (2 or more) involvement
      - Cardiovascular
      - Renal
      - Respiratory
      - Hematologic
      - Gastrointestinal
      - Dermatologic
      - Neurologic
C. No alternative plausible diagnosis
D. Recent or current SARS-CoV-2 infection or exposure, with **any** of the following:
   - Positive SARS-CoV-2 RT-PCR
   - Positive serology
   - Positive antigen test
   - COVID-19 exposure within the 4 weeks prior to the onset of symptoms

   <u>Additional comments</u>
   - Some individuals may fulfill full or partial criteria for Kawasaki disease but should be reported if they meet the case definition for MIS-C
   - Consider MIS-C in any pediatric death with evidence of SARS-CoV-2 infection

WHO case definition:

A. Age 0-19 years
B. Fever for >/= 3 days
C. **At least 2** of the following clinical signs:
   - Rash, bilateral nonpurulent conjunctivitis, or mucocutaneous inflammation signs (oral, hands, feet)
   - Hypotension or shock
   - Cardiac dysfunction, pericarditis, valvulitis, or coronary abnormalities (including echocardiographic findings or elevated troponin/BNP
   - Evidence of coagulopathy (prolonged PT or PTT; elevated D-dimer)
   - Acute gastrointestinal symptoms (diarrhea, vomiting, or abdominal pain)
D. Elevated markers of inflammation, such as ESR, CRP, procalcitonin
E. No other obvious microbial cause of inflammation, including bacterial sepsis and staphylococcal or streptococcal toxic shock syndromes
F. Evidence of COVID-19, with any of the following:
   - Positive SARS-CoV-2 RT-PCR
   - Positive serology
   - Positive antigen test
   - Likely contact with an individual with COVID-19