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.

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
- Shock
Fever >38.5 for ≥3 days, no alternative source

**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

**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

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

**Order initial MIS-C**

Concerning exam and/or abnormal labs

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

Reassuring exam & labs

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)
- COVID serologies if not sent
- Film Array if COVID PCR negative
- VBG
- Procalcitonin
- Cytokine Panel

- PT/INR, PTT
- Blood Cx
- Fibrinogen
- UA/Urine Cx
- LDH
- ECHO, EKG
- Triglycerides
- BNP
- Peripheral Smear
- CK
**Inpatient Management**

Confirmed or High Likelihood MIS-C Diagnosis

If considering ECMO, consult CT surgery early

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

Consult Heme/Onc for patients with documented VTE

Review Echocardiogram, EKG results. Place patient on telemetry

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

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

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

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**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**

<table>
<thead>
<tr>
<th>CBC         with manual diff</th>
<th>CMP</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESR, CRP</td>
<td>Ferritin</td>
</tr>
<tr>
<td>BNP, and troponin if original values were elevated</td>
<td></td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>D-dimer</td>
</tr>
<tr>
<td>PT/INR/PTT</td>
<td></td>
</tr>
</tbody>
</table>

**ECHO Shows**
- EF < 30%
- Intracardiac Thrombus
- Severe coronary artery abnormalities
Consult Cardiology and Heme/Onc for Therapeutic Enoxaparin** IN ADDITION to ASA
<table>
<thead>
<tr>
<th>Medications</th>
<th>Dose</th>
<th>Route</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>IVIG</td>
<td>2g/kg/dose</td>
<td>IV</td>
<td>Infuse IVIG over 12-48 hours; consider fluid status</td>
</tr>
<tr>
<td>Steroids</td>
<td>Methlprednsione 1-2 mg/kg/day divided BID and wean over 2-4 weeks</td>
<td>IV/PO</td>
<td>Infuse over 45 minutes, give daily for 1-3 days.</td>
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<tr>
<td></td>
<td>Consider a pulse 30 mg/kg/day once, max 1000 mg in certain severe cases</td>
<td>IV</td>
<td></td>
</tr>
<tr>
<td>Anakinra</td>
<td>2-10 mg/kg once a day.</td>
<td>SC</td>
<td>Dose can be escalated pending the response.</td>
</tr>
<tr>
<td>Remicade</td>
<td>5-7 mg/kg/day</td>
<td>IV</td>
<td>Discuss with Rheumatology</td>
</tr>
<tr>
<td>Aspirin (ASA)</td>
<td>3-5mg/kg/day, max=81mg</td>
<td>PO</td>
<td>Continue approximately 4-6 weeks. Follow up with Cardiology</td>
</tr>
<tr>
<td>Enoxaparin (Prophylaxis dosing)</td>
<td>&lt; 2months: 0.75mg/kg/dose q12 hours</td>
<td>SQ</td>
<td>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.</td>
</tr>
<tr>
<td></td>
<td>≥ 2months: 0.5mg/kg/dose q12 hours</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enoxaparin (Therapeutic dosing)</td>
<td>&lt; 2months 1.5 mg/kg/dose q12 hours</td>
<td>SQ</td>
<td>Check LMWH level 4 hours after 3rd - 5th dose Target &gt;0.5-1.0 units/mL Dose adjustments by Heme/Onc</td>
</tr>
<tr>
<td></td>
<td>≥ 2months: 1 mg/kg/dose q12 hours</td>
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</table>
CDC case definition:
A. Age < 21 years
B. Clinical presentation including all of the following:
   1. Fever >38.0°C (100.4°F) 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
   3. Severe illness requiring hospitalization
   4. Multisystem (2 or more) involvement
      - Cardiovascular
      - Renal
      - Respiratory
      - Hematologic
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

Additional comments:
- 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