Multi-system Inflammatory Syndrome in Children (MIS-C) Guidelines
Updated 8.20.20

Purpose: These guidelines are intended to serve as a reference to initiate and
guide diagnosis and comprehensive clinical management associated with MIS-C
in pediatric COVID-19 patients. Pediatric patients with suspected MIS-C who are
moderately to severely ill should be transferred to a center with pediatric sub-
specialty capability to appropriately manage this condition.

Consider the diagnosis of MIS-C in the following clinical situations:

A child 0-18 years of age presenting with fever >=3 days* and:

- Multisystem (>=2) involvement, including
  - Gastrointestinal (abdominal pain, vomiting, diarrhea)
  - Cardiac (cardiogenic shock, LV dysfunction)
  - Neurologic (confusion, headache, altered mental status, irritability)
  - Renal (acute kidney injury)
  - Respiratory (respiratory distress or pulmonary infiltrates)
  - Hematologic (lymphopenia, neutrophilia, anemia, thrombocytopenia)
- Symptoms consistent with Kawasaki Disease (KD), including: rash, conjunctivitis, cervical
  lymphadenopathy, and extremity swelling
- Fever >=5 days with no alternative explanation

*A child who is ill-appearing with suspected MIS-C should be evaluated as per the diagnostic work-up
below, even if fever is present <3 days.

Recommended diagnostic evaluation:

1. Initial laboratory evaluation
   a. CBC with differential
   b. CMP
   c. ESR, CRP (inflammatory)
   d. Urinalysis
   e. Blood culture
   f. Procalcitonin
   g. Additional labs as clinically indicated:
      i. Resp pathogen panel
      ii. VBG with lactate
      iii. GI biofire panel: consider send-out for patients with diarrhea
      iv. Lumbar puncture
   h. Imaging:
      i. Chest X-ray
      ii. Abdominal ultrasound or CT scan if concerning symptoms/physical findings
2. If initial labs concerning for MIS-C without alternative explanation (including lymphopenia with
ALC <1000, platelets <150k, albumin <=3g/dL, hyponatremia <135, ESR >=40, CRP (inflammatory
> 3), consider the following evaluation:
   a. Cardiac markers: troponin T and BNP
   b. Other markers of inflammation: ferritin, triglycerides, LDH, CK
   c. Coagulation panel: PT, PTT, fibrinogen, D-dimer
   d. Serology for SARS-CoV-2
   e. SARS-CoV-2 PCR from nasopharyngeal swab
   f. Twelve-lead electrocardiogram (EKG)
   g. Echocardiogram (transthoracic)
   h. Early consultation of pediatric specialists to assist in management as needed, such as:
      PICU, cardiology, rheumatology, infectious disease, neurology, nephrology
3. Admission to PICU if any concern for moderate to severe MIS-C, including: signs of impending
   shock (i.e. tachycardia unresponsive to fluid, etc.), need for non-invasive or invasive respiratory
   support (i.e. CPAP, BIPAP, mechanical ventilation), or other concerning labs suggestive of
   significant organ disease (i.e. elevated troponin)

Diagnosis:

Diagnosis is made as per the CDC criteria below. Even if SARS-CoV-2 testing is negative, treatment
may be considered for patients with high suspicion of MIS-C, if recommended by pediatric
infectious disease consultants.

CDC case definition for multisystem inflammatory syndrome in children (MIS-C).

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<tr>
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<tbody>
<tr>
<td>(1)</td>
<td>An individual aged &lt; 21 years with:</td>
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<td>Clinical criteria:</td>
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<tr>
<td></td>
<td>• A minimum 24-hour history of subjective or objective fever ≥ 38.0°C AND</td>
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<td>• Severe illness necessitating hospitalization AND</td>
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<td>• Two or more organ systems affected (i.e., cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic, neurological)</td>
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<td>Laboratory evidence of inflammation</td>
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<td>• One or more of the following: an elevated CRP, ESR, fibrinogen, procalcitonin, D-dimer, ferritin, LDH, or IL-6; elevated neutrophils or reduced lymphocytes; low albumin</td>
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<td>Laboratory or epidemiologic evidence of SARS-CoV-2 infection</td>
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<td>• Positive SARS-CoV-2 testing by RT-PCR, serology, or antigen OR</td>
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<td>• COVID-19 exposure within 4 weeks prior to onset of symptoms</td>
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<td>No alternative diagnosis</td>
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Infection Prevention:
- No isolation needed if SARS-CoV PCR testing negative
- COVID isolation if SARS-CoV PCR testing positive
Treatment of MIS-C (see doses in table on page 4):

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Mild disease</th>
<th>Moderate-severe disease**</th>
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<tbody>
<tr>
<td>IVIG (consider ID consult)</td>
<td>Yes</td>
<td>Yes</td>
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<td>Steroids</td>
<td>Yes, see table for dosing</td>
<td>Yes, see table for dosing</td>
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<tr>
<td>Anakinra OR tocilizumab (ID or rheumatology consult required)</td>
<td>No</td>
<td>May be considered per ID consult; preference for Anakinra in pediatric population</td>
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<tr>
<td>Anticoagulation</td>
<td>Low dose aspirin</td>
<td>Prophylactic enoxaparin</td>
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<td>GI protection</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>Empiric antibiotics</td>
<td>As per discretion of provider</td>
<td>Yes (see sepsis guidelines)</td>
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**Moderate-severe disease defined as: Need for vasoactives or inotropes, mechanical ventilation, presence of significant coronary dilation or aneurysm, significantly decreased LV function

In-hospital care

- Further tests to be considered depending on sub-specialty input: IL-6, anti-phospholipid antibody panel, quantiferon, hepatitis B panel
- Repeat CRP, CBC with diff, coagulation panel, ferritin, troponin T, BNP every 24-48 hours (do not repeat ESR, as this will be affected by IVIG administration)
- If patient continues with fever or evidence of inflammation 36 hours after administration of IVIG and/or steroids, please consult infectious disease
- May consider use of anakinra OR tocilizumab for severe or refractory cases, per recommendation from infectious disease consult
- Consider serial EKG or echocardiogram depending on initial studies, advanced imaging, follow-up labs, and clinical status.

Follow-up after hospital discharge:

- Follow up should be scheduled with pediatric cardiology for repeat echocardiography at 2 and 4-6 weeks (similar to KD follow-up)
- Follow up to be scheduled with pediatric rheumatology if receiving anakinra at time of discharge
- Follow up to be scheduled with pediatric hematology if patient is discharged home on enoxaparin or other anticoagulation
- If child is sent home on steroid wean, he/she should have early morning cortisol and ACTH after steroids are weaned off. If low, would consider referral to pediatric endocrinology.
### Doses for immunomodulatory agents in the treatment of MIS-C

<table>
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<tr>
<th>Medication Class</th>
<th>Drug</th>
<th>Dose</th>
<th>Important Notes</th>
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<tbody>
<tr>
<td><strong>IVIG</strong></td>
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<td>1–2 g/kg IV in a single dose or divided doses per attending discretion</td>
<td>Consider dividing dose or giving lower dose if fluid overload, renal dysfunction. Obtain blood for SARS-CoV-2 serology and other serologic tests (i.e. antiphospholipid antibodies) prior to administration</td>
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<td><strong>Corticosteroids</strong></td>
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<td><strong>Mild disease:</strong> Methylprednisone 1 mg/kg/dose q12h IV for 5–7 d or until CRP normalizes followed by 14 day course of prednisolone detailed below: Days 1-5: Prednisolone (or prednisone) 1mg/kg/dose BID Days 6-10: Prednisolone 0.5mg/kg/dose BID Days 11-14: Prednisolone 0.5mg/kg/dose once a day</td>
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<td><strong>Moderate to severe disease:</strong> Day 1: Methylprednisolone 10 mg/kg/dose q12h (maximum 500 mg) Day 2-5: Methylprednisolone 2 mg/kg/dose IV q 12h (max:50mg/day; can switch to PO sooner if response is seen) Day 6-10: Prednisolone (or prednisone) 1 mg/kg/dose BID PO (max:40mg/day)</td>
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<td>Day 11-15: Prednisolone 0.8 mg/kg/dose BID (max:40mg/day) Day 16-20: Prednisolone 0.6 mg/kg/dose BID (max:35mg/day) Day 21-25: Prednisolone 1 mg/kg/dose once a day (max:25mg/day) Day 26-29: Prednisolone 0.9 mg/kg/dose once a day (max:20mg/day) Day 30-32: Prednisolone 0.7 mg/kg/dose once a day (max:15mg/day) Day 33-35: Prednisolone 0.5 mg/kg/dose once a day (max:15mg/day) Day 36-38: Prednisolone 0.4 mg/kg/dose once a day (max:10mg/day) Day 39-41: Prednisolone 0.2 mg/kg/dose once a day (max:7.5mg/day) Day 42-44 Prednisolone 0.1 mg/kg/dose once a day (max:5mg/day) Day 45-48 Prednisolone 0.05 mg/kg/dose once a day (max:2.5mg/day) Day 49-51 Prednisolone 0.05 mg/kg/dose once every other day and then stop (max:2.5mg/day)</td>
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<td><strong>Anakinra</strong></td>
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<td>2-6 mg/kg/day IV/SQ, length of therapy to be decided with input from pediatric infectious disease</td>
<td>Safe in setting of sepsis, please send quantiferon and Hepatitis B serology prior</td>
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<td><strong>Tocilizumab</strong></td>
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<td>&lt; 30 Kg: 12 mg/kg IV in a single dose &gt; 30 Kg: 8 mg/kg IV in a single dose (max 800mg)</td>
<td>Trials ongoing for safety and efficacy in the setting of active coronavirus infection</td>
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<td><strong>Aspirin</strong></td>
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<td>3–5 mg/kg/d (max 81mg/day) until follow up with cardiology</td>
<td>Precaution if platelets &lt;80,000/µL</td>
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<td><strong>Enoxaparin</strong></td>
<td><strong>Prophylaxis:</strong> 0.5 mg/kg/dose q 12 hours (max dosing 30mg IV q12h)</td>
<td><strong>Treatment:</strong> 1 to &lt;3months: 1.8mg/kg/dose q 12 hours 3-12 months: 1.5mg/kg/dose q 12 hours 1-5 years: 1.2mg/kg/dose q 12 hours 6-18 years: 1mg/kg/dose q 12 hours</td>
<td>If thrombosis present or rapidly rising D-dimer, increase to treatment dosing. With treatment dosing, monitoring with anti-Xa levels is recommended.</td>
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References


