Background:
The COVID-19 pandemic has resulted in previously healthy children presenting with an unexplained hyperinflammatory syndrome defined in several case series as pediatric multiorgan syndrome or multisystem inflammatory syndrome in children (1–3) (See Appendix I). These children have some similarity to incomplete/atypical Kawasaki disease (KD), but also have other clinical features including gastrointestinal involvement, and a high incidence of myocardial dysfunction and shock (4) (See Appendix II). Many (but not all) patients have tested positive for SARS-CoV-2 by PCR, have positive SARS-CoV-2 antibody, or have household exposure to individuals with COVID-19. This association with COVID-19 has been increasingly featured in lay media after a alert was issued by the Royal College of Paediatrics and Child Health on May 1 (5), followed by a Health Advisory from the CDC on May 14 (6). The purpose of this document is to provide guidance regarding which patients should be evaluated for MIS-C, the initial evaluation of suspected MIS-C, and the management of patients who meet the MIS-C case definition.

Case definition (note: this is a purposely broad definition for reporting purposes and NOT designed as a clinical pathway)¹

**Case Definition for Multisystem Inflammatory Syndrome in Children (MIS-C)**

- An individual aged <21 years presenting with fever¹, laboratory evidence of inflammation²⁶, and evidence of clinically severe illness requiring hospitalization, with multisystem (≥2) organ involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic or neurological); **AND**
- No alternative plausible diagnoses; **AND**
- Positive for current or recent SARS-CoV-2 infection by RT-PCR, serology, or antigen test; or COVID-19 exposure within the 4 weeks prior to the onset of symptoms

¹Fever ≥38.0°C for ≥24 hours, or report of subjective fever lasting ≥24 hours
²Including, but not limited to, one or more of the following: an elevated C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), fibrinogen, procalcitonin, d-dimer, ferritin, lactic acid dehydrogenase (LDH), or interleukin 6 (IL-6), elevated neutrophils, reduced lymphocytes and low albumin
Patients to be evaluated for suspected MIS-C:
- Patients with unexplained fever for ≥3 days AND diarrhea, vomiting, conjunctivitis, non-vesicular rash, swelling of hands/feet or altered mental status
- Patients with any unexplained fever and shock
  - Note: even if there is an apparent explanation for fever, persistent fever should prompt further evaluation particularly if there is a suspected COVID exposure

Tiered approach for initial evaluation for suspected MIS-C:

![Evaluation flowchart diagram]

**Patients with suspected Kawasaki disease (complete or incomplete) but negative SARS-CoV-2 testing and no documented COVID exposure should be evaluated and managed per AHA guidelines** (7)

Evaluation and management principles for patients who meet the MIS-C Case Definition:
- Other diagnostic possibilities should be considered and potentially treated even in patients meeting the MIS-C case definition
- An evaluation for sepsis should be completed for all patients with signs of shock. A sepsis huddle should be performed per protocol with timely initiation of antibiotics.
- Treat all patients as SARS-CoV-2 PCR positive until documented negative PCR testing; this includes placing patients in contact and strict droplet precautions.
- Consult ID and rheumatology if not already involved
- Consult Cardiology and order echocardiogram if not already obtained. Obtain echocardiography prior to the initiation of IVIG whenever possible, including in patients without signs of shock, to assess myocardial function. Consult heart failure for any patient with significant myocardial dysfunction (EF<40%)
- Repeat echocardiogram with any clinical worsening or per cardiology recommendations
Management decisions should be made by primary team (hospital medicine or critical care) in consultation with general ID, rheumatology, and cardiology.

Inpatient unit assignment should be discussed between primary team (hospital medicine or critical care) and cardiology:
  - Patients not needing ICU care should have frequent monitoring until stable >24h (watcher status w/ frequent PEWS, MRT for any concerns)
  - Patients who develop shock, coronary artery dilation, or myocardial dysfunction should be transferred to PICU or CVICU via MRT

When possible draw serum sample pre-IVIG to hold in lab for future diagnostic studies
- Trend above labs q24-48 h until clinically improving
- Infection Prevention & Control will report patients to the CDC

Treatment

Patients with MILD DISEASE (no signs of shock, no myocardial dysfunction, and no coronary artery changes):
- Admit to hospital medicine
- Low dose aspirin
- IVIG
- Methylprednisolone/Prednisone for 2 weeks followed by taper over 2-3 weeks; consider adding PPI

Patients with MILD DISEASE with PROGRESSIVE DISEASE or who are REFRACTORY TO TREATMENT (continued fever >36h after IVIG, worsening clinical condition, new cardiac dysfunction or shock):
- Transfer to ICU for shock and/or new cardiac dysfunction
- Continue low dose aspirin and methylprednisolone/prednisone
- Consider repeating IVIG and/or pulse dose methylprednisolone
- Consider biologics in consultation with rheumatology

Patients with MODERATE/SEVERE disease (shock, cardiac dysfunction, or coronary artery dilation):
- Admit or Transfer to ICU for monitoring and care
- Inotropic support as needed; ECMO should be considered early in patients with refractory shock
- Low dose aspirin; discuss high-dose aspirin with cardiology for any coronary changes
- Anticoagulation as needed per cardiology and ICU team
- IVIG
- Methylprednisolone/Prednisone for 2 weeks followed by taper over 2-3 weeks. Consider pulse methylprednisolone for 1-3 days in severely ill patients after discussions between primary and consulting teams. Consider adding PPI
- Consider biologics (anakinra, tocilizumab, infliximab) in consultation with rheumatology

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dosing</th>
<th>Notes</th>
</tr>
</thead>
</table>


Aspirin

**Low dose (antiplatelet):** 3-5 mg/kg/dose once daily  
**High dose (anti-inflammatory):** 20-25 mg/kg/dose every 6 hours  
Round aspirin dose to nearest ½ 81 mg tablet size

IVIG

2 gm/kg/dose IV (max 100 gm) for 1 dose  
Retreatment may be considered if refractory (continued fever >36h or worsening clinical condition)

Methyprednisolone

2mg/kg/day for 2 weeks followed by taper over 2-3 weeks  
**Pulse dose:** 30mg/kg/day (max 1000mg/day) for 1-3 days followed by 2mg/kg/day divided q8-q12. Continue high dose for 2 weeks (can consolidate to daily) then taper over 2-3 weeks  
Consider adding a proton pump inhibitor for patients receiving steroids + aspirin to decrease risk for GI bleed

**Biologic dosing recommendations:**

<table>
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<tr>
<th>Medication</th>
<th>Dosing</th>
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<tbody>
<tr>
<td>Anakinra</td>
<td>2-4 mg/kg/dose (max 100mg/dose) SQ twice daily (may increase to 3 times daily) for 3 days</td>
</tr>
<tr>
<td>Infliximab</td>
<td>10mg/kg/dose IV once</td>
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<tr>
<td>Tocilizumab</td>
<td>&lt;30kg: 12mg/kg IV; &gt;30kg 8mg/kg IV, max 800mg</td>
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</tbody>
</table>

References:
2. Belhadjer Z et al. Acute heart failure in multisystem inflammatory syndrome in children (MIS-C) in the context of global SARS-CoV-2 pandemic. [Internet]. *Circulation* [published online ahead of print: May 17, 2020]; doi:10.1161/CIRCULATIONAHA.120.048360
7. BW M et al. Diagnosis, Treatment, and Long-Term Management of Kawasaki Disease: A Scientific Statement for Health Professionals From the American Heart Association [Internet]. *Circulation* 2017;135(17). doi:10.1161/CIR.0000000000000484
Appendix I: Notes on cases and above definition:

- From *Lancet* UK series (8 patients) (1):
  - All cases had fever >39 for at least 4 days at presentation
  - 7/8 had GI symptoms of non-bloody diarrhea +/- vomiting, 5/8 had conjunctivitis
  - All COVID-19 negative by nasal swab and/or BAL; one COVID-19+ at autopsy (and 50% with positive caregivers)
- Further UK data (N=38)
  - 23/38 PCR or antibody +
  - Shock 76%, diarrhea 60%, rash 54%, vomiting 43%, conjunctivitis 32%
- From Italian series in *Lancet* (3):
  - 2/10 COVID-19+ PCR, 8/10 serology +.
  - 6/10 with diarrhea
  - 5/10 met KD criteria; remaining met incomplete KD criteria. 50% presented with shock
  - 30-fold increased incidence than historical KD in this period (10 in <2 months vs 19 in 5 years) – started about 30 days after peak of COVID outbreak
  - Vs historical KD more likely to have shock/MAS features: cytopenias, hyperferritinemia
  - All received IVIG, 80% steroids
- *Circulation* paper of French/Swiss hospitals (2):
  - 35 patients with acute heart failure; 10/30 with EF<30%, 25/35 30-50%; 10/35 required VA-ECMO (all survived)
  - 31/35 with positive COVID-19 PCR or IgG
  - 83% with GI symptoms including 2 who received emergency exploratory laparotomy prior to MIS-C diagnosis
  - 6 had coronary dilation but no aneurysms. None met classic KD criteria
  - All had elevations of troponin I (mild-moderate) and BNP (1000s pg/mL)
- Italians note referral bias – rheumatologists vs intensivists
Appendix II: (2)

SARS-COV-2 related multisystem inflammation

- Bulbar conjunctivitis 89%
- Red and crackled lips 54%
- Cervical and mesenteric lymphadenopathies 60%
- Skin rash 57%
- Fever >4 days and asthenia 100%
  Median age 10 years

- Neurological sign 31%
- Respiratory signs 34%
- Left ventricle dysfunction 100%
  - Shock 68%
  - VA ECMO 28.6%
  - Coronary dilatation 17%
  - Pericarditis 8%
- Digestive involvement 83%
  - Nausea, diarrhea 83%
  - Exploratory laparoscopy 5.7%
  (2 patients)