Background:
Over the past few weeks there have been numerous reports from Europe and the USA of previously healthy children presenting with an unexplained hyperinflammatory syndrome including shock (1–3). This syndrome has been defined in several case series as pediatric multiorgan syndrome or multisystem inflammatory syndrome in children (MIS-C). 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). Many (but not all) patients have tested positive for COVID-19 by PCR, have positive COVID-19 antibody, or have household exposure to COVID-19 patients. This association with COVID-19 has been increasingly featured in lay media after a national 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 patients who should be evaluated for MIS-C, the recommended initial evaluation for such patients, and management principles for patients who meet criteria for MIS-C.

Case definition

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

- An individual aged <21 years presenting with fever, laboratory evidence of inflammation, 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

Fever ≥38.0°C for ≥24 hours, or report of subjective fever lasting ≥24 hours

Including, 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 COVID MIS-C:
- Patients with unexplained fever for ≥5 days OR
- Patients with unexplained fever for ≥3 days AND diarrhea, vomiting, conjunctivitis, non-vesicular rash, swelling of hands/feet or altered mental status AND moderately ill-appearing OR
- Patients with any unexplained fever and shock

Initial evaluation for suspected MIS-C:
- Contact infectious diseases on-call for COVID PCR and serology
  - Patients with COVID-19+ PCR should be treated per COVID treatment algorithm
- EKG
- Echocardiogram if signs of shock, any concerns for cardiac dysfunction, or recommended per suspected Kawasaki algorithm (7).
- Labs if not already done: CBC, CMP, CRP, LDH, ferritin, procalcitonin, PT/PTT/fibrinogen, d-dimer, troponin, BNP, UA with urine protein and creatinine

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

Evaluation and management principles for patients meeting MIS-C Case Definition:
- All patients should be treated as suspected COVID-19+
- Consult COVID-Immunotherapy team
- Cardiology consult and echocardiogram if not already obtained; heart failure consult for any patient with coronary artery dilation or significant myocardial dysfunction (EF<40%)
- Inpatient disposition to be discussed with COVID-Immunotherapy team, cardiology, and critical care:
  - Patients with shock, coronary artery dilation, or myocardial dysfunction should be transferred to PICU or CVICU via MRT
  - Patients not needing ICU care should have frequent monitoring given reports of rapid deterioration until stable >24h (watcher status w/ frequent PEWS, MRT for any concerns)
- Above labs should be trended q24-48 until clinically improving
- Repeat echocardiogram with any clinical worsening or per cardiology recommendations

Treatment
Patients without shock, myocardial dysfunction, or coronary artery changes (non-critical care):
- Low dose aspirin
- IVIG 2gm/kg up to 100gm (note: consider monitoring patients with any myocardial dysfunction in CVICU during IVIG infusion)
- Steroids: 2mg/kg/d for 2 weeks followed by taper over 2-3 weeks; consider adding PPI
- Treatment refractory patients (continued fever >36h after IVIG, worsening clinical condition, new cardiac dysfunction or shock): discuss biologics with COVID-immunotherapy team
Patients with severe disease (Signs of shock, coronary artery dilation, or cardiac dysfunction):
- Inotropic support as needed; ECMO should be considered early in patients with refractory shock before signs of irreversible multi-organ damage.
- Low dose aspirin; discuss high-dose aspirin with cardiology for any coronary changes
- Anticoagulation as needed per cardiology and ICU team
- IVIG 2mg/kg up to 100gm
- Steroids: methylprednisolone 30mg/kg (up to 1000mg) daily for 1-3 days followed by 2mg/kg/d divided q8-q12. Continue high dose for 2 weeks (can consolidate to daily) then taper over 2-3 weeks; Consider adding PPI
- Discuss biologics with COVID-immunotherapy teams; consider anakinra, tocilizumab, infliximab

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<thead>
<tr>
<th>Medication</th>
<th>Dosing</th>
<th>Notes</th>
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<tbody>
<tr>
<td>Aspirin</td>
<td>Low dose (antiplatelet): 3-5 mg/kg/dose once daily</td>
<td>Round aspirin dose to nearest ½ 81 mg tablet size</td>
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<td>High dose (anti-inflammatory): 20-25 mg/kg/dose every 6 hours</td>
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<td>IVIG</td>
<td>2 gm/kg/dose IV (max 100 gm) for 1 dose</td>
<td>Retreatment may be considered if refractory (continued fever &gt;36h or worsening clinical condition)</td>
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<tr>
<td>Methylprednisolone</td>
<td>Low dose: 2mg/kg/day for 2 weeks followed by taper over 2-3 weeks</td>
<td>Consider adding a proton pump inhibitor for patients receiving steroids + aspirin to decrease risk for GI bleed</td>
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<td>High 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</td>
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**Biologic dosing recommendations:**

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<tr>
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<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>
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<td>Infliximab</td>
<td>10mg/kg/dose IV once</td>
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<td>Tocilizumab</td>
<td>&lt;30kg: 12mg/kg IV; &gt;30kg 8mg/kg IV, max 800mg</td>
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</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
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)