Pediatric Management of Multisystem Inflammatory Syndrome in Children (MIS-C), Inpatient

Updated: February 22, 2022

Clinical algorithm:

JUMP TO TREATMENT AND MANAGEMENT:

Fever >38.5 for ≥ 3 days, AND no alternative source

Obtain Initial MIS-C Labs
- CBC with manual diff
- CMP
- UA
- ESR, CRP
- D-Dimer
- Extra gold top tube
- Ferritin
- Troponin
- EKG
- Ferritin
- COVID PCR (NP swab)
- COVID-19 IgG Antibody
- Fibrinogen

Consider admission if:
- Multiple lab values are outside of normal reference ranges
- Single lab value that is extremely outside of the normal reference range
- D Dimer > 3000 ng/mL

Admit to Hospitalists OR PICU
Initial treatment with IVIG and steroids per Peds ID on-call

Consider Discharge if:
- Reassuring exam and vital signs AND
- Normal labs, isolated lab abnormality, or mild deviation from normal

Consider phone consult with ID to discuss borderline cases

Discharge home with PCP follow-up in 12-24 hours and repeat labs in 24-48 hours.

Lab Thresholds for Concern
- Absolute Lymphocyte Count < 0.5 k/uL
- Albumin <2 g/dL
- CRP > 100 mg/L
- D-dimer > 3000 ng/mL
- High Sensitivity Troponin >30 ng/L
- Ferritin >350 ng/mL
Clinical guideline summary

CLINICAL GUIDELINE NAME: Management of Multisystem Inflammatory Syndrom in Children

PATIENT POPULATION AND DIAGNOSIS: Age <21 years Multisystem Inflammatory Syndrome in Children (MIS-C)

APPLICABLE TO: All Spectrum Health Sites

BRIEF DESCRIPTION: Multisystem Inflammatory Syndrome in Children (MIS-C) is a syndrome that follows a SARS-CoV-2 infection or exposure. The clinical presentation is accompanied by significant hyper-inflammation that can have some similarities to Kawasaki Disease and Toxic Shock Syndrome and can lead to organ dysfunction and shock. The pathogenesis is unclear, but in most cases develops 2-8 weeks after a COVID-19 infection or exposure. In most cases, MIS-C is post-infectious, but occasionally occurs during acute respiratory COVID-19

OVERSIGHT TEAM LEADER(S): Andrea Hadley MD, Rosemary Olivero

OWNING EXPERT IMPROVEMENT TEAM (EIT): N/A

MANAGING CLINICAL PRACTICE COUNCIL (CPC): COVID-19 CPC

CPC APPROVAL DATE: 12/10/2020

OTHER TEAM(S) IMPACTED: Children’s Health CPC & Nursing

IMPLEMENTATION DATE: 6/10/2020

LAST REVISED: 2/22/2022

FOR MORE INFORMATION, CONTACT: Andrea Hadley or Rosemary Olivero
Clinical pathways clinical approach

TREATMENT AND MANAGEMENT:

**Additional MISC labs/tests to be ordered upon admission if not yet obtained:**

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>PT/INR, PTT</td>
<td>Fibrinogen</td>
</tr>
<tr>
<td>Blood Cx</td>
<td>LDH</td>
</tr>
<tr>
<td>ECHO, EKG</td>
<td>CK</td>
</tr>
<tr>
<td>VBG</td>
<td>COVID-19 IgG, Antibody if not sent*</td>
</tr>
<tr>
<td>COVID PCR (NP swab x 2 total, 24 hrs apart)</td>
<td>Film Array if COVID PCR negative</td>
</tr>
<tr>
<td>BNP</td>
<td>Triglycerides</td>
</tr>
<tr>
<td>Procalcitonin</td>
<td>Peripheral Smear</td>
</tr>
<tr>
<td>UV Urine Cx</td>
<td></td>
</tr>
</tbody>
</table>

*If COVID IgG is reported as negative, Peds ID will request anti-spike protein result to be released.

**Confirmed/High Likelihood MISC Diagnosis**

- Consult ID on Admission. If ID agrees MISC is likely, consult rheumatology. ID reports the disease.
- Place patient on continuous cardiac and respiratory monitors.
- Keep patient in Severe Respiratory Isolation until COVID 19 PCR is negative x1. If PCR positive COVID-19 PCR >20 days prior to admission, discuss need for continued Severe Respiratory Isolation with ID/Infection Prevention.

**Daily Lab Monitoring:**

- CBC with manual diff
- CMP
- ESR, CRP
- BNP, Crp
- D-dimer
- Ferritin
- Fibrinogen

**Consult Hematology/Oncology for:**

- Imaging confirmed VTE
- Intracardiac thrombus - heart dysfunction (EF < 30%) that will require higher dose of anticoagulation to prevent intracardiac thrombus, determined by Cardiology
- Severe coronary artery abnormalities that warrant higher dose of anticoagulation, determined by Cardiology
- INR >1.4 OR PTT 35 OR platelet count <100K
- If any other diagnosis is considered more likely such as malignancy or HLH.
- Concerns for risk of bleeding - active bleeding with VTE algorithm
- Anticoagulation with Apixaban or Citepar

**Complete VTE Assessment in Epic**

- If high risk based on VTE assessment, start appropriate pharmacologic prophylaxis.
- If not high risk based on VTE assessment, consider pharmacologic prophylactic anticoagulation after discussion with Hem/Onc. Consider bleeding risks/coagulopathy/plt count.

**Repeat VTE Assessment every 48 hours**

**Consult Cardiology for:**

- Dilated coronary arteries (Z-score > 2.5)
- Cardiac dysfunction
- ECMO
- Anticoagulation concerns
- Otherwise abnormal Echo or ECG

**Start treatment with Low Dose ASA for all MISC patients:**

- Discuss steroids, IVIG and other treatments with ID/Rheumatology
- See further details on therapy options in

**TABLE1**
Treatment and Management:

The CDC has 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 this document for your reference as well.

[CDC MIS-C definition](#)
[WHO MIS-C definition](#)

<table>
<thead>
<tr>
<th>Medications</th>
<th>Dose</th>
<th>Route</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Immunosuppressive Agents</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IVIG</td>
<td>2g/kg/dose (max = 100 grams)</td>
<td>IV</td>
<td>Infuse IVIG over 12-48 hours; consider fluid status</td>
</tr>
<tr>
<td>Steroids</td>
<td>IV Methylprednisolone 1 mg/kg BID (max 30mg BID) for three days, followed by oral taper over 2 weeks</td>
<td>IV/PO IV</td>
<td>Consider a &quot;pulse&quot; in certain severe/refractory cases with rheumatology input</td>
</tr>
<tr>
<td>Anakinra</td>
<td>2-10 mg/kg once a day</td>
<td>SC</td>
<td>Discuss with Rheumatology for severe/refractory cases</td>
</tr>
<tr>
<td>Remicade</td>
<td>5-7 mg/kg/day</td>
<td>IV</td>
<td>Discuss with Rheumatology for severe/refractory cases</td>
</tr>
<tr>
<td><strong>Antiplatelet / Anticoagulation</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin (ASA)</td>
<td>3-5mg/kg/day, max=81mg</td>
<td>PO</td>
<td>Continue approximately 6 weeks.</td>
</tr>
<tr>
<td>Enoxaparin (aka LMWH) (Prophylaxis dosing)</td>
<td>&lt; 2months: 0.75mg/kg/dose q12 hours</td>
<td>SQ</td>
<td>Not to be used if acute kidney injury and CrCl &lt;30 mL/min</td>
</tr>
<tr>
<td></td>
<td>≥ 2months and &lt; 60kg: 0.5mg/kg/dose q12 hrs</td>
<td></td>
<td>Monitoring for prophylaxis dosing is optional. Obtain if there is new bleeding, change in liver or renal function, or in critically ill pts. If monitoring, check LMWH level 4 hours after 3rd-5th dose. Target 0.2-0.4 units/mL</td>
</tr>
<tr>
<td></td>
<td>≥60kg: 40mg daily (40mg q12 hours in adolescent, and critically ill</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enoxaparin (aka LMWH) (Therapeutic dosing)</td>
<td>&lt; 2months 1.5 mg/kg/dose q12 hours</td>
<td>SQ</td>
<td>Not to be used in patient with acute kidney injury and CrCl &lt;30 mL/minute</td>
</tr>
<tr>
<td></td>
<td>≥ 2months: 1 mg/kg/dose q12 hours</td>
<td></td>
<td>Check LMWH level 4 hours after 3rd - 5th dose Target &gt; 0.5-1.0 units/mL, Dose adjustment by Heme/Onc</td>
</tr>
<tr>
<td>Unfractionated Heparin (UFH) (Prophylaxis dosing)</td>
<td>Any dose ≤ 10 units/kg/hr</td>
<td>IV</td>
<td>No monitoring required unless signs or symptoms of bleeding, or patient was coagulopathic to begin with.</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>Significant number of patients who are critically ill or with COVID have antiphospholipid antibodies. aPTT may be unreliable. If aPTT is prolonged at baseline, use Unfractionated Heparin assay (anti-Xa for UFH).</td>
</tr>
<tr>
<td>Unfractionated Heparin (UFH) (Therapeutic dosing)</td>
<td>Any dose &gt; 10 units/kg/hr</td>
<td>IV</td>
<td>Baseline labs prior to initiation of heparin: aPTT, PT/INR, CBC.</td>
</tr>
</tbody>
</table>
| | | | Significant number of patients who are critically ill or with COVID + on PCR have antiphospholipid antibodies. aPTT may be unreliable lab. If aPTT is prolonged at baseline,
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 remarkably 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.

If MIS-C is diagnosed, notify Nick Hartog to consent patient for the COVID Human Genome Effort study. This study 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.

**Treatment**

If MIS-C suspected based on the above workup, treatment approach will be individualized and multidisciplinary in nature and should involve discussion between ID, rheumatology, hematology and cardiology when indicated, and hospitalist/PICU teams.

<table>
<thead>
<tr>
<th>Specialty</th>
<th>Instructions</th>
<th>Orders/ Instructions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Care Physician</td>
<td>Hospitalist team to contact PCP prior to discharge to provide verbal handoff and summary of hospital course.</td>
<td>Hospital follow-up with PCP recommended within 1 week Patient/PCP to contact ID clinic with any clinical change/ fevers PCP to also monitor for side effects related to medications Annual influenza vaccination is recommended Reminder: no live vaccines for 11 months if pt received IVIG Return to School instructions per ID/rheum Return to Sports instructions per Cardiology</td>
</tr>
<tr>
<td>Cardiology</td>
<td>Continue aspirin for 6 weeks</td>
<td>Cardiology Visit (new Consult or follow up) and Echo at 2 weeks and 4-6 weeks</td>
</tr>
<tr>
<td>Hematology and Oncology</td>
<td>Follow up required only if patient has: - documented VTE - intracardiac thrombus - cardiac dysfunction</td>
<td>Discuss with Chi Braunreiter or Ali Mastin via PerfectServe - LMWH level in approximately 2-4 weeks if on lovenox - Repeat imaging of confirmed VTE in approximately 4-6 weeks</td>
</tr>
</tbody>
</table>

### Table 2. Discharge Coordination and Follow-up

Use Unfractionated Heparin assay (anti-Xa for UFH).

Utilize age-specific UFH titration nomogram for dosing and monitoring using aPTT or Unfractionated Heparin Level Anti-Xa Assay to monitor.

Unfractionated Heparin (UFH) (Prophylaxis ONLY)

| < 60kg: 75 units/kg/dose SQ every 12 hours | ≥60kg: 5000 units every 12 hours | >18 yrs or >125 kg: 5000 units SQ every 8 hrs | SQ UFH is used for prophylaxis only if number of lines/lumens are limited AND patient can’t have LMWH. |

**Unfractionated Heparin (UFH) (Prophylaxis ONLY)**

Unfractionated Heparin (UFH) (Prophylaxis ONLY)
Infectious Disease | Follow up at ~2 weeks and 4-6 weeks after discharge | Echos ordered by ID RN ID RN to report to state (if not already done) ID to coordinate labs if KD only (not MIS-C) Rheum to coordinate labs if MIS-C
---|---|---
Rheumatology | Follow up at about 1 week after discharge | Follow up may occur in person or via telemedicine depending on patient. Patient will have labs done (ordered by Rheum for prior to or on day of follow up).

### Follow-up Details based on Patient Characteristics

**MIS-C with aneurysms:**
- Rheum does telemed visit and labs ~1 week out and defines the lab plan for the rest of the course
- ID does follow-up visit (in person) ~2 weeks out and carries out lab plan and Echo
- Rheum, ID and Cards does follow-up visit (in person) ~4-6 weeks out, carries out lab plan and Echo
- Long term follow-up with Cards

**MIS-C without aneurysms:**
- Rheum does telemed visit and labs ~1 week out and defines the lab plan for the rest of the course
- Rheum does follow-up visit (in person) ~2 weeks out and carries out lab plan and Echo
- Rheum, ID and Cards does follow-up visit (in person) ~4-6 weeks out, carries out lab plan and Echo
- Long term follow-up with Cards

**KD (with or without aneurysms) but NOT diagnosed with MIS-C:**
- ID does follow-up visit (in person) ~2 weeks out, carries out lab plan and Echo
- ID and Cards does follow-up visit (in person) ~6 weeks out, carries out lab plan and Echo
- Long term follow-up with Cards

### CDC Case Definition:

- **A.** Age < 21 years
- **B.** Clinical Presentation including all of the following:
  - Fever >38.0°C (100.4°F) for >/= 24 hours or subjective fever lasting >/= 24 hours
  - 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
    - Severe illness requiring hospitalization
      - 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-week 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

References:

1. Multisystem Inflammatory Syndrome in U.S. Children
2. Lupus Anticoagulant in Patients with Covid-19 | NEJM
3. American College of Rheumatology Clinical Guidance for MISC