Clinical Pathways Program

Guideline: Management of Multisystem Inflammatory Syndrome in Children, INPATIENT

Spectrum Health Contact: Rosey Olivero  Updated/reviewed: December 11, 2020

Clinical algorithm:

Fever >38.5 for > 3 days, AND no alternative source
Fever < 3 days, AND ill-appearing or previous COVID exposure/positivity

Proceed with workup for MIS-C if there is clinical evidence of multi-system inflammation defined by the presence of ≥2 of the following:
- Abdominal pain/vomiting/diarrhea
- Rash
- Conjunctivitis
- Extremity changes
- Lymphadenopathy

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

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

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

Admit to Hospitalists OR PICU Follow:

Consider Discharge if:
- Reassuring exam and vital signs
  AND
- Normal labs, isolated lab abnormality, or mil 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.

TREATMENT
Clinical guideline summary

CLINICAL GUIDELINE NAME: Management of Multisystem Inflammatory Syndrome 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 of 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

OTHER TEAM(S) IMPACTED (FOR EXAMPLE: CPCs, ANESTHESIA, NURSING, RADIOLOGY): Children’s health CPC, Nursing

IMPLEMENTATION DATE: 6/10/2020

LAST REVISED: 12/11/2020

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

TREATMENT AND MANAGEMENT:

- Admit to Hospitalists OR PICU
- Obtain Additional MIS-C labs/tests below

Additional MIS-C labs/tests to be ordered upon admission if not yet obtained:
- COVID PCR (NP swab x 2 total, 24 hrs apart)
- Blood Cx
- COVID-19 IgG Antibody if not sent*
- Urine Cx
- Film Array if COVID PCR negative
- ECHO, EKG
- VBG
- BNP
- Procalcitonin
- Peripheral Smear
- CK
- Cytokine Panel

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

Confirmed/High Likelihood MIS-C Diagnosis
- Consult ID on Admission. If ID agrees MIS-C is likely, consult rheumatology. ID reports the disease
- Place patient on continuous cardiac and respiratory monitors
- Place patient in Severe Respiratory Isolation until COVID PCR is negative x 2, 24 hrs apart. If pt had positive COVID 19 PCR > 20 days prior to admission, discuss need for continued Severe Respiratory Isolation with ID/Infection Prevention.
- Notify Nick Hartog for research study enrollment

Complete VTE Assessment in Epic
- If high risk based on VTE assessment, start appropriate pharmacologic prophylaxis
- If not high risk based on VTE assessment:
  - >12 yo consider pharmacologic prophylactic anticoagulation after discussion with Hem/Onc. Consider bleeding risks/coagulopathy/plt count. (MIS-C patients thought to have less thrombosis risk than patients with active COVID 19 infection)

Review:
- BNP
- Trop
- EKG
- Echo
- Continuous cardiac Monitoring

Consult Cardiology for:
- Dilated coronary arteries- cardiac dysfunction
- Otherwise abnormal Echo or ECG

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
- If any other diagnosis is considered more likely such as malignancy or HLH.

Start treatment with Low Dose ASA for all MIS-C patients
- Discuss steroids, IVIG and other treatments with ID/Rheumatology
- See further details on therapy options TABLE1

Daily Lab Monitoring:
- CBC with man diff
- CMP
- ESR, CRP
- BNP/trop
- D-dimer
- Ferritin
- Fibrinogen
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>
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<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>
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<tr>
<td>Steroids</td>
<td>Methylprednisone/Prednisone/Prednisolone 1-2 mg/kg/day divided BID, wean over 2-4 wks</td>
<td>IV/PO</td>
<td></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>Infuse over 45 minutes, give daily for 1-3 days.</td>
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<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>
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<tr>
<td>Remicade</td>
<td>5-7 mg/kg/day</td>
<td>IV</td>
<td>Discuss with Rheumatology</td>
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<tr>
<td><strong>Antiplatelet / Anticoagulation</strong></td>
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<tr>
<td>Aspirin (ASA)</td>
<td>3-5mg/kg/day, max=81mg</td>
<td>PO</td>
<td>Continue approximately 4-6 weeks.</td>
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<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>
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<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>
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<td></td>
<td>≥60kg: 40mg daily (40mg q12 hours in adolescent, and critically ill</td>
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<td></td>
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<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>
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<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>
</tbody>
</table>
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.

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 is 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>
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<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>
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</table>
**Cardiology**

- Continue aspirin for 4-6 weeks
- Cardiology Visit (new Consult or follow up) and Echo at 2 weeks and 4-6 weeks

**Hematology and Oncology**

- Follow up required only if patient has:
  - documented VTE
  - intracardiac thrombus
  - cardiac dysfunction
- 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

**Infectious Disease**

- Follow up at ~2 weeks and 4-6 weeks after discharge
- Echos to be 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).

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**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:

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
   - Elevated LDH
   - Elevated IL-6 level
   - Neutrophilia
   - Lymphocytopenia
   - Hypoalbuminemia
3. 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 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

**References:**

Multisystem Inflammatory Syndrome in U.S. Children

Lupus Anticoagulant in Patients with Covid-19 | NEJM

American College of Rheumatology Clinical Guidance for MISC