MULTISYSTEM INFLAMMATORY SYNDROME IN CHILDREN (MIS-C) ASSOCIATED W/ COVID-19

Patient < 21 YO presenting with signs and symptoms suspicious for Multisystem Inflammatory Syndrome in Children (MIS-C) Associated w/ COVID-19 w/ No Alternative Explanation for Clinical Presentation

Assure Rapid Assessment & Treatment of Signs of Sepsis/Shock Following PALS Algorithms (Click Here for More Info on Shock)

Initial Testing Based on General Appearance

Patient Requires Hospitalization | Consider transfer to YSC if require multidisciplinary assessments

Determine Unit for Admission Based on Disease Severity

- Severe Disease = PICU, Mild Disease = General Inpatient Unit
- Clinicians should have a relatively low threshold for admission to the PICU for patients with evidence of Moderate Disease

Patient Meets CDC Case Definition

Treatment Recommendations Based on Disease Severity

- Clinicians may pursue treatment for ill appearing patients while awaiting serology if suspicion for MIS-C is high

Inpatient Monitoring of Clinical Progression

- Inpatient Teams should have a low threshold for calling RRT/admission to PICU for concerning hemodynamics/clinical changes
- Discuss changes to treatment plan, trending of labwork, repeat echos and other diagnostic imaging in inpatient setting with the multidisciplinary team
- Patients should be on continuous telemetry and have daily EKGs - discuss discontinuation of daily EKGs with cardiology

Discharge Planning

- Discharge Criteria
- Discharge Medications
- Discharge Follow-Up Appointments

MIS-C is a Reportable Disease

Providers should contact YNHH Infection Prevention or Pediatric ID Team to assure proper reporting for patients meeting case definition

See Bed Algorithm for Patients w/ Suspected MIS-C

References & Authors
MIS-C* SHOULD BE SUSPECTED IN PATIENTS < 21 YEARS-OLD WITH:

- **Fever** (CDC criteria is ≥38.0 for ≥24 hours, but fevers are typically >38.5 and persistent for ≥3 days) AND
- Prior history of COVID or close contact with known positive COVID case in past 4 weeks AND
- No other plausible explanation for presentation (e.g., sepsis with UTI, patients without clinical features of MIS-C)

- **Evidence of ≥ 2 systems of involvement:**
  - **GI:** Severe abdominal pain w/ or without GI symptoms (vomiting/diarrhea)
  - **Neuro:** Neurologic symptoms such as changes in mental status/vision, headache, signs of meningismus
  - **Mucocutaneous** findings seen in Kawasaki Disease*** - (Each sign counts as a system to raise suspicion for MIS-C)
    - Rash - polymorphic
    - Oral Mucosal Changes - cracked lips, strawberry tongue
    - Conjunctivitis - non-purulent
    - Extremity changes - swelling, palmar/plantar erythema
  - **Lymphatic:** Cervical adenopathy > 1.5 cm
  - **Cardiac:** Signs of cardiogenic shock/dysfunction
  - **Hematologic:** Petechiae, bruising
  - **Respiratory:** Respiratory symptoms overall seem less likely to occur
  - **Renal:** Oliguria
  - **Other:** Reports of arthritis and severe pharyngitis/mimicking deep neck infections also reported

*The differential diagnosis for MIS-C is broad and clinicians may consider other clinical entities while pursuing workup and treatment

***Patients may meet criteria for KD and be diagnosed with MIS-C
Patient with Clinical Features Suspicious for MIS-C Without an Alternative Plausible Explanation

Recommended Initial Testing Based on General Appearance

Well Appearing
- SARS-CoV-2 RT-PCR
- COVID ELISA serology
- CBC w/ Differential
- CMP
- CRP & ESR
- Consider other testing as indicated by presentation and differential diagnosis

Notes on Initial Testing
- SARS-CoV-2 testing should be positive as per CDC case definition
- CBC may show neutrophilia, leukopenia and/or thrombocytopenia
- CMP may show hyponatremia, transaminitis, acute renal failure, and/or hypoalbuminemia
- CRP and/or ESR should be elevated

Ill Appearing w/ Evidence of Shock and/or Requiring PICU Admission
- SARS-CoV-2 RT-PCR
- COVID ELISA serology
- CBC w/ Differential
- CMP
- CRP & ESR
- Ferritin, D-dimer, IL-6, LDH, PT/PTT, Fibrinogen
- Pro-BNP, Troponin, EKG & Echocardiography
- Blood Culture & Procalcitonin
- Lactate
- CXR (if hypoxia, chest pain, resp distress)
- Abdominal Imaging (if concern for abdominal pathology)
- Other Workup in D/W Consultants on Case-By-Case Basis
- Consider other testing as indicated by presentation and differential diagnosis

If Results Reassuring
- Discharge to Home - Assure Appropriate Follow-up

If Lab Abnormalities or COVID + Testing
- Ferritin, D-dimer, IL-6, LDH, Fibrinogen
- Pro-BNP, Troponin, EKG & Echocardiography
- Blood Culture & Procalcitonin (if concern for sepsis)
- CXR (if hypoxia, chest pain, resp distress)
- Abdominal Imaging (if concern for abdominal pathology)
- Other Workup in D/W Consultants on Case-By-Case Basis

Consider Cardiology, Rheumatology & ID Consults for Patients Requiring Hospital Admission
<table>
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<tr>
<th><strong>FURTHER WORKUP TO CONSIDER ON A CASE-BY-CASE BASIS DEPENDING ON PRESENTATION, RESULTS OF INITIAL LABS, AND CLINICAL PROGRESSION</strong> (These tests may be completed in inpatient setting)</th>
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</table>
| **Rheumatology**  
- ANA, urinalysis w/ microscopy, urine Pr:Cr, C3/C4, Quantitative Immunoglobulins  
- If ANA >1:640, recommend antiphospholipid antibodies, ENA, dsDNA  
- PT/PTT, Von Willebrand Factor, TEG with Heparinase |
| **ID**  
- If COVID PCR and Serology testing negative, recommend considering:  
  - Full Respiratory PCR Panel  
  - CMV, EBV, Parvovirus, Adenovirus, HHV-6, Enterovirus PCR from Blood  
  - CMV, EBV, Parvovirus IgM/IgG (Prior to giving IVIG)  
  - ASO and anti-dnase B Abs |
| **GI**  
- Consider GI Pathogen PCR Panel, Calprotectin, C.Diff. abdominal imaging  
- Consider GI/Surgery Consults based on concern for abdominal findings |
| **Neurology**  
- Consider Neuro-imaging, LP (opening pressure, cell count, glucose, protein, lactate, culture, viral testing, other testing such as autoimmune/paraneoplastic) |
| **Dermatology**  
- Consider HSV and VZV PCR of blisters, Enterovirus PCR  
- Consider Dermatology consultation for rash |
| **Ophthalmology**  
- Consider ophthalmology consultation for fundoscopic exam to better understand ophthalmologic findings |
CDC’S CASE DEFINITION FOR MIS-C*

- An individual aged < 21 years presenting with:
  - Fever (≥ 38.0°C for ≥ 24 hours, or report of subjective fever lasting ≥ 24 hours)
  - Laboratory evidence of inflammation - including, but not limited to, one or more of the following:
    - Elevated CRP, ESR, Procalcitonin, D-dimer, Ferritin, Neutrophils, Fibrinogen, LDH and/or IL-6
    - Reduced Lymphocytes and/or Albumin
  - 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
  - Clinicians may consider diagnosis while awaiting serology or if all SARS-CoV-2 testing is negative but clinical suspicion for MIS-C still remains high

- 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

*MIS-C is a Reportable Disease and providers should contact YNHH Infection Prevention or Pediatric ID Team to assure proper reporting for patients meeting case definition

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<th>DISEASE SEVERITY</th>
<th>CRITERIA</th>
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| MILD             | • No vasoactive requirement - normal hemodynamics/responsive to minimal intervention (May be more similar to standard Kawasaki Disease cases)  
                      • No respiratory support  
                      • Minimal-No organ injury  
                      • Normal ventricular function on echo (if have results) |
| MODERATE         | • Concern for hemodynamics not responding to fluid administration and potential need for vasoactive therapy OR  
                      • Supplemental oxygen requirement OR  
                      • Mild-moderate end-organ injury OR  
                      • Mild ventricular dysfunction (if have results) |
| SEVERE           | • Requiring vasoactive therapy to maintain hemodynamics OR  
                      • Non-invasive or invasive ventilatory support OR  
                      • Moderate or severe organ injury OR  
                      • Moderate to severe ventricular dysfunction (if have results) |

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**Assure proper adjustments of dosing based on possible renal/hepatic injuries associated with MIS-C**
MIS-C DISCHARGE CRITERIA CONSIDERATIONS

- **General Discharge Criteria**
  - Afebrile x 24 hours, improved overall symptoms, normal mental status, tolerating PO to maintain adequate hydration, tolerating PO medications

- **Cardiac-Specific Discharge Criteria**
  - 48 hours off milrinone and/or pressor support
  - Troponin consistently down trending and less than 1.0
  - Heart failure symptoms, if any, controlled with oral medications
  - Echocardiogram
    - Stable or improved ventricular function
    - Stable or improved coronary artery abnormalities
    - Stable or improved valve function
  - No significant arrhythmia burden
MIS-C DISCHARGE MEDICATION CONSIDERATIONS

• **All patients should be discharged on 3-5mg/kg/day ASA (max 81 mg)**
  ◦ Avoid other NSAIDs while on ASA therapy

• **Avoid ASA if:**
  ◦ Patient being discharged to home on other anticoagulant (such as Lovenox)
  ◦ Concern for Reyes with altered mental status and liver injury
  ◦ Significant transaminitis not improving by time of discharge

• **All other medications should be tolerated orally**
  ◦ Including steroids, GI Prophylaxis, other treatments for heart failure, etc.

• **Recommended Steroid Taper Schedule**
  ◦ 2mg/kg/day (Max 60mg) x 1 week (including initial steroids)
  ◦ Then 1mg/kg/day x 1 week
  ◦ Then 0.5mg/kg/day x 1 week
  ◦ Then 0.25mg/kg/day x 3 days
  ◦ Then off
  ◦ May consider longer tapers in d/w rheum. based on severity of disease

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MIS-C DISCHARGE FOLLOW-UP CONSIDERATIONS

• General Follow-Up Recommendations
  ▪ Patients should have in-person f/u with Cardiology (check on availability of single multidisciplinary clinic appointment w/ ID/Rheum/Cards)
  ▪ 2-Week f/u is general rec. for repeat EKG/Echo (may change on case-by-case basis - see below)
  ▪ Other consultants and PMD should f/u by telemedicine - D/w rheumatology need for in-person f/u and repeat labwork schedule on case-by-case basis

• Cardiac-Specific Follow-Up Recommendations:
  ▪ If evidence of myocarditis during hospitalization:
    ▪ Repeat troponin and BNP as an outpatient if abnormal at discharge
    ▪ Repeat echocardiogram within 1-2 weeks if abnormal at discharge or at discretion of cardiology
    ▪ Requires exercise restrictions for 6 months until cleared by cardiology and stress testing
    ▪ Cardiac MRI at discretion of cardiology (1-2 months post acute illness to evaluate for edema, fibrosis, scarring, function)
  ▪ If evidence/concern for Kawasaki-like illness
    ▪ If coronary artery dimensions normal at discharge:
      ▪ Follow up echocardiogram 1-2 weeks after treatment (this may in hospital prior to discharge) and 6 weeks after treatment
    ▪ If coronary arteries dilated/aneurysmal (Z score > 2.5)
      ▪ Repeat echocardiogram every 3-4 days until coronary arteries stable and then at discretion of cardiologist
REFERENCES

- Jonat B, Cheung E. NY-Presbyterian KIDS Pediatric Guidelines for COVID-19 Multi-System Inflammatory Syndrome. 5/2020
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- PICU-COVID-19 International Collaborative
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