A. MIS-C CRITERIA:
- History & Physical Exam
  - Fever ≥ 38.5°C for ≥ 2 days AND
  - Tachycardia for age AND
  - Presence of 2 or more Clinical/Historical Features (See Box B)
- Heightened Suspicion of MIS-C
  - Exposure history/prior SARS-CoV-2 positivity within 8 weeks
  - History of loss of smell & taste
  - Abdominal pain

B. CLINICAL/HISTORICAL FEATURES:
GI Symptoms
Abdominal pain (mild/severe), vomiting, and/or diarrhea

Rash
Polymorphic, maculopapular, petechial, NOT vesicular

Extremity changes
Erythema and edema of the hands and feet

Oral Mucosal changes
Erythema of oropharyngeal mucosa

Conjunctivitis
Bilateral bulbar conjunctival injection without exudate

Lymphadenopathy
Cervical > 1.5 cm

Neurologic Symptoms
Headache, irritability, lethargy, altered mental status

Epidemiologic Link to SARS-CoV-2
Patient with history of COVID-19 disease or close contact with known positive SARS-CoV-2 case in past 8 weeks, or person placed in quarantine

C. CONSIDER DIFFERENTIAL DIAGNOSIS FOR MIS-C:
- Acute SARS-CoV-2
- Kawasaki Disease
- Other viral or bacterial infection
- Toxic Shock Syndrome
- Systemic Onset Juvenile Idiopathic Arthritis (JIA)
- Macrophage Activation Syndrome (MAS)
- Hemophagocytic Lymphohistiocytosis (HLH)
- Myocarditis

Patient arrives with suspicion of MIS-C
Is this suspected MIS-C? (See Box A)

Evidence of shock? (Evidence: tachycardia AND myocardial dysfunction or hypotension/vasopressor requirement)

Testing to identify cause of Fever:
- CBC
- ESR
- CRP
- Any other testing as clinically indicated based on clinical features

Physical Exam
OR
- Labs = reassuring

Patients with abdominal pain, consider imaging and surgical consultation

Are additional labs abnormal and SARS-CoV-2 antibodies present?

Order additional labs:
- NTproBNP
- Troponin
- Ferritin
- SARS-CoV-2 Antibody
- Coag Panel 3

Immediate Actions:
- Notify provider
- Follow Sepsis Red Pathway: utilize order sets for fluid resuscitation and baseline labs including CMP, CBC, ESR, and CRP
- * High suspicion for myocardial dysfunction, 10-20/kg bolus and consult Cardiology
- Send blood cultures
- Start antibiotics

Consultation for Possible Multisystem Inflammatory Syndrome in Children (MIS-C)
Inpatient Care of Patient with Multisystem Inflammatory Syndrome in Children (MIS-C)

**CASE DEFINITION:**
- < 21 years of age
- Fever
- Lab evidence of inflammation
- Multi-system involvement
- Positive SARS-CoV-2 antibody

**INITIAL CONSIDERATIONS FOR ALL PATIENTS:**
- Appropriate antibiotic rule-out while cultures are pending (i.e., sepsis rule out or SBI rule out)
- General ID consult for treatment considerations based on clinical severity
- Use GI prophylaxis IV or PO while patient is receiving steroids
- Hematology consult to consider anti-thrombotic prophylaxis: Lovenox and/or low-dose aspirin
- Cardiology consult for abnormal echo, EKG, or troponin results
- Abdominal imaging and Pediatric Surgery consult for focal abdominal findings
- Head imaging and Neurology consult for focal neurologic findings, altered mental status, seizure, and/or severe headache with meningeval signs
- Supportive care per clinical scenario

**CLASSIFICATION OF CLINICAL SEVERITY:**

- MILD:
  - No vasoactive requirement
  - Minimal/no respiratory support

- MODERATE:
  - Single vasoactive requirement
  - Respiratory support required

- SEVERE:
  - High-dose or persistent vasoactive requirement
  - NIPPV or invasive respiratory support
  - Refractory to initial therapies

**IMPORTANT:** Patients may progress and need additional therapies; frequent reassessment of clinical severity is recommended

**THERAPEUTIC PLANNING**

**MILD**
- IVIG 2g/kg once
- Methylprednisolone 2mg/kg/day

**MODERATE**
- IVIG 2g/kg once
- Methylprednisolone 10mg/kg/day
  - If improved, 2mg/kg/day
- Patients with documented thrombosis or an EF < 35% should receive therapeutic anticoagulation with Lovenox
- Consider prophylactic LMWH for reduced cardiac function

**SEVERE**
- IVIG 2g/kg once
- Methylprednisolone 10mg/kg/day
- Consider Anakinra 4mg/kg/day

**LAB MONITORING**
- At least Every Other Day:
  - BMP
  - CRP
  - CBC
  - Troponin
  - One time & PRN: NT proBNP

**CARDIAC MONITORING**
- Echo twice weekly
- Baseline EKG
- Echo at least twice weekly
- EKG twice weekly
- Echo at least twice weekly
- EKG per Cardiology

**CONSULTING SERVICES**
- ID
- Cardiology
- Hematology
- PrilMe

**PREPARING FOR DISCHARGE**

- Discharge Readiness:
  - Hemodynamically stable
  - Afebrile
  - Steadily down-trending CRP

- Medications:
  - Transition to PO steroids and taper per ID
  - Expect discharge with prednisone taper based on CRP
  - Continue GI prophylaxis while on steroids
  - Discontinue Lovenox at discharge
  - Continue low-dose aspirin (if started) until seen by Cardiology at 6 week appointment or until instructed by Heme or Cardiology

- Outpatient Labs:
  - CRP will be trended on the 3rd day of each steroid dose to determine wean schedule
  - Other labs as needed

- Follow-up:
  - If ventilator dysfunction, consult Cardiology for follow-up plan
  - ID department will schedule appointment 2 weeks post-discharge along with echocardiogram
  - Cardiology will schedule 6 weeks post-discharge with echocardiogram
  - Consider outpatient laboratory follow-up if any significant neurologic symptoms while inpatient
Background & Problem:
The COVID-19 pandemic was declared in March 2020. Children were initially recognized as overall having mild disease compared to adults. In April and May of 2020, reports emerged from around the world describing a new multi-system inflammatory syndrome affecting children in the post-viral period after SARS-CoV-2 infection, some with very severe illness including cardiopulmonary failure, systemic inflammation, and varied involvement of multiple organ systems. This was later termed Multisystem Inflammatory Syndrome in Children (MIS-C) by the CDC, and was thought to be temporally related to SARS-CoV-2 infection and post-viral inflammatory reaction. MIS-C has significant overlap with other syndromes including sepsis, Toxic Shock Syndrome, Kawasaki Disease, and H1N1/MAS. Patient presentation and acuity is varied and subject to change rapidly. This affects resource use, time to diagnosis, and treatment planning. Given the recent development of this syndrome, data on MIS-C pathogenesis and management is limited. Little is known about clinical outcomes. This guideline is subject to change as evidence from this pandemic continues to grow.

Inclusion:
All patients in the Lurie ED or inpatient areas including intensive care units with suspected or known MIS-C.

Exclusion:
None

MIS-C Overview

Outcome Measure:
- Length of stay (Observed over Expected (O/E))

Process Measures:
- MIS-C order set utilization
- Cultures or RVP sent for febrile patients
- COVID PCR and COVID antibody testing sent
- Follow up appointments made with ID and cardiology

Balancing Measures:
- Readmitted within 30 days
- Return to ED within 72 hours of discharge
- Sepsis order set utilization

References
1. https://www.cdc.gov/mis-c/hcp/

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*See page 4 for literature review grading details

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Strength of recommendation</th>
<th>Quality of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients meeting criteria for MIS-C should be evaluated for common clinical/historical features and lab findings of MIS-C, especially if SARS-CoV-2 antibody positive which would be consistent with the timing of MIS-C occurring 4-6 weeks out from SARS-CoV-2 exposure.</td>
<td>Strong, consensus</td>
<td>Moderate</td>
</tr>
<tr>
<td>Other infectious or non-infectious etiologies that may explain the clinical presentation must be evaluated, including but not limited to sepsis, Kawasaki disease, or toxic shock syndrome.</td>
<td>Strong, consensus</td>
<td>Low to moderate</td>
</tr>
<tr>
<td>For patients presenting with concern for sepsis, even if also concerned for MIS-C, the sepsis guideline should be followed including drawing cultures and starting antibiotics.</td>
<td>Strong, consensus</td>
<td>N/A</td>
</tr>
<tr>
<td>Patients with MIS-C usually have multiple markers of inflammation and multiple organ involvement, recommend lab evaluation similar to sepsis work-up, plus inflammatory markers CRP, ESR, and cardiac markers troponin and NTproBNP. Lab markers should be repeated serially until normalized or no longer clinically applicable.</td>
<td>Strong, consensus</td>
<td>Moderate</td>
</tr>
<tr>
<td>For all patients with confirmed or strongly suspected MIS-C, give IVIG 2g/kg once and methylprednisolone dosing based on acuity.</td>
<td>Strong, consensus</td>
<td>Low to Moderate</td>
</tr>
<tr>
<td>Anticoagulation and anti-platelet therapy should be tailored to the patient’s platelet count and coronary artery z-score.</td>
<td>Strong, consensus</td>
<td>Low</td>
</tr>
<tr>
<td>Anakinra is an IL-1 receptor antagonist that has been used in children with severe infections and hyperinflammatory syndromes. Anakinra may be used for severe refractory MIS-C at a dose of 4mg/kg/day.</td>
<td>Strong, consensus</td>
<td>Low</td>
</tr>
</tbody>
</table>

Until more is known about the long-term sequelae of MIS-C, recommend following outpatient evaluation similar to Kawasaki disease protocol, including cardiology follow up with echocardiogram at 2 weeks and 6 weeks post-discharge, and ID follow up to monitor resolution of symptoms and inflammation.

This guideline is developed based on the best available evidence and local expert consensus for elements of which evidence are inconclusive. Please refer to recommendation table below for further details.
We are quite confident that the effect in the study is close to the true effect.

The true effect is likely to be substantially different from the estimated effect.

We are very confident that the effect in the study reflects the actual effect.

- The true effect may differ significantly from the estimate

This clinical care guideline is meant as a guide for the healthcare provider, does not establish a standard of care, and is not a substitute for medical judgment which should be applied based upon the individual circumstances and clinical condition of the patient.

References:

Ann-Marie Tantoco, Kelly Heyrman | Last edit: 10.07.2020

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