Multisystem Inflammatory Syndrome in Children (MIS-C)

June 2, 2020
This document stemming from Trinity Health was created in collaboration with IHA and University of Michigan C.S. Mott Children’s Hospital. We thank you!

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Purpose
To provide guidance on Multisystem Inflammatory Syndrome in Children (MIS-C) evaluation and pediatric patients presenting with symptoms.

Overview
Areas hard hit by COVID-19 around the world have described a new pediatric illness that appears to follow a SARS-CoV-2 infection or exposure. Multisystem Inflammatory Syndrome in Children (MIS-C) is a clinical entity of uncertain etiology that involves significant hyper-inflammation, potentially leading to organ dysfunction and shock. Presentation features may overlap Kawasaki Disease or Toxic Shock Syndrome. It is postulated that MIS-C is a post-infectious hyper-inflammatory process, rather than a manifestation of an acute infection. In case series in NYC and the UK, patients had antibodies for the virus despite negative nasopharyngeal SARS-CoV-2 PCR swabs.

As we gain experience with this new illness, it appears that MIS-C (sometimes also called Pediatric Inflammatory Multisystem Syndrome or PIMS) is on a spectrum of febrile, inflammatory illnesses associated with COVID-19. We do not know yet if they represent a single, continuous process or separate clinical entities with overlapping features, and it is unclear if that distinction is important in determining health outcomes in children with MIS-C.

While we know that these patients are at high risk for developing cardiovascular collapse, resulting in the need for high levels of critical care support, what is less clear at this time is how these patients can be differentiated from those with more common pediatric febrile illnesses such as viral gastroenteritis or a urinary tract infection.

This document and the associated algorithms are intended to help physicians understand the clinical presentation of MIS-C, providing a systematic framework for the evaluation and early diagnosis of patients.
with suspected MIS-C, when they are hopefully at lower risk of cardiovascular collapse. The algorithms are designed to be used in addition to your typical approach to the febrile pediatric patient.

**Important Considerations**

MIS-C is a very new syndrome, and little information exists in the literature regarding signs, symptoms, laboratory data, or best practices, such as basic care guidelines and treatment options. The medical community is still in the early stages of investigating this condition, and our understanding of MIS-C will surely evolve and change in the next few weeks to months.

The recommendations found here are based on the expert opinions of pediatric specialists at C.S. Mott Children’s Hospital. We have taken into account published case reports of patients with MIS-C, as well as information from webinars presented by clinicians treating MIS-C patients around the world. Our goal is to identify patients who are at risk for further clinical deterioration at a point prior to cardiovascular collapse, without including every child with a common febrile illness.

Keeping in mind our goal of differentiating patients with MIS-C from patients with more typical febrile childhood illnesses, we have recommended clinical criteria for initiating a laboratory workup, and then laboratory thresholds that warrant further observation and/or investigation. The clinician’s judgment is an important factor as well and should be taken into consideration.

As MIS-C becomes better understood and more data become available, we anticipate that these guidelines will be frequently updated to reflect new information.

**Presentation**

Children with MIS-C exhibit signs and symptoms that significantly overlap with typical pediatric febrile illnesses. It is therefore important to consider the fever curve carefully. Patients universally present with prolonged or persistent fever and often complain of fever that is resistant to antipyretics. Most patients experience gastrointestinal symptoms, including abdominal pain, diarrhea, nausea, and vomiting. Additional features include rash, conjunctivitis, headache, and sore throat.

A subset of patients’ present with shock and require high levels of supportive care in addition to coverage for sepsis and consideration for MIS-C.

**Concerning Presenting Signs and Symptoms**

- Persistent fever, not fully responsive to antipyretics
- GI complaints such as abdominal pain (may mimic appendicitis) and/or diarrhea
- Rash
- Conjunctivitis
- Headache
- Respiratory symptoms
- Sore throat
- Lymphadenopathy
- Shock
Initial Workup
As MIS-C is an inflammatory syndrome, the initial laboratory workup is focused on uncovering signs of inflammation. Moreover, as the disease progresses, patients often develop end-organ dysfunction, in particular cardiac involvement and coagulopathies, and the recommended testing seeks to screen for those concerns as well.

**Initial laboratory testing:**
- CBCPD
- Comprehensive Panel
- CRP
- D-Dimer
- High Sensitivity Troponin
- Ferritin

**Laboratory thresholds of concern:**
- Absolute Lymphocyte Count < 0.5 k/uL
- Albumin < 2 g/dL
- CRP > 10mg/dL
- D-Dimer > 1mg/L
- High Sensitivity Troponin > 30pg/mL
- Ferritin > 350 ng/mL

Please refer to the ED/Outpatient Algorithm for further decision-making guidance.

Inpatient Considerations
Once a patient suspected of having MIS-C is admitted, further workup to look for specific areas of inflammation will be initiated. Given the high risk of cardiovascular collapse, patients admitted with a diagnosis of presumed MIS-C also warrant very close monitoring and a multidisciplinary approach to care.

**Additional Workup at Admission**

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<thead>
<tr>
<th>Test</th>
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<td>UA w/ reflex urine</td>
<td>Fibrinogen</td>
<td>LDH</td>
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<td>SARS-CoV2 serologies</td>
<td>culture</td>
<td>ESR</td>
<td>Cytokine Panel</td>
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<td>Procalcitonin</td>
<td>Triglycerides</td>
<td>Echocardiogram</td>
</tr>
<tr>
<td></td>
<td>PT/PTT</td>
<td>BNP</td>
<td>Peripheral smear</td>
</tr>
</tbody>
</table>

- If ALC <0.5, order a Primary Immunodeficiency Flow Panel
- Consider obtaining IgG levels
- To order the peripheral smear:
  - Order “Peripheral Smear Morphology Review Request”
  - Type in “for Cellavision Review” in the additional comments box

**Daily Labs to Trend**

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</table>

Special Pathogen Isolation
Patients with MIS-C are presumed to have current or recent SARS-CoV2 infection and should be placed in special pathogen precautions.
• To clear the patient and discontinue special pathogen precautions, patients will need to have two negative SARS-CoV2 PCR swab, at least 24 hours apart. They should remain in special pathogen isolation until the 2nd swab has returned as negative.
• Once cleared for COVID-19, patients will require isolation precautions appropriate to their clinical presentation and diagnosis.
• Please refer to the Infection Prevention and Epidemiology (IPE) website for the most up-to-date recommendations regarding special pathogen precautions: http://www.med.umich.edu/ice/resources/clinical_guidance.html

Disease Reporting
MIS-C is currently a reportable disease process, but should only be reported after there is sufficient evidence to make a diagnosis of presumed MIS-C.
• Notify IPE at pager 30032 or by email at UM-ICE@med.umich.edu to report the case. IPE will enter the case into the state database.
• Please document in the chart once IPE has been notified.

Vital Sign Monitoring
All patients admitted for presumed MIS-C require close and continuous monitoring to ensure hemodynamic stability.
• Continuous cardiorespiratory monitor (+/- telemetry)
• Continuous pulse oximetry
• Consider checking vital signs every 2 hours initially if there is increased concern for instability.

Subspecialty Calculations
The management of MIS-C requires a multidisciplinary team approach as it is a complex, multi-organ disease. Consultations should be ordered whenever there are clinical concerns, but the following services are frequently involved in the care of MIS-C patients.
• ID – Consult at the time of admission
• Hematology – Consult at the time of admission
• Rheumatology – Consult if there are clinical concerns
• Cardiology – Consult for criteria listed below

Antibiotic Coverage
As MIS-C is not a bacterial process, patients do not require coverage with antibiotics unless there is concern for concomitant bacterial infection or sepsis. Empiric antibiotic coverage should be determined according the institutional sepsis guidelines and should be tailored if a bacterial process is identified.
• http://www.med.umich.edu/asp/pdf/pediatric_guidelines/Sepsis_PEDS.pdf

Anticoagulation
Although patients with MIS-C often have evidence of hypercoagulability, not all patients develop thromboses or require anticoagulation. Hematology should be consulted at the time of admission to help determine the need for anticoagulation and the appropriate medication choices. Before starting anticoagulation, please check platelet count and kidney function.
Cardiac Workup

MIS-C was first recognized due to the unexpected incidence of atypical Kawasaki Disease in pediatric COVID-19 patients. It is now recognized as a separate clinical entity, but similar to KD, patients have an increased risk of cardiovascular abnormality, ranging from myocarditis to coronary aneurysms to ventricular dysfunction.

- A cardiac workup should be initiated at the time of admission, including high-sensitivity troponin, BNP, EKG, and transthoracic echocardiogram.
- Consult cardiology for all patients with abnormal screening cardiac labs, EKG, echocardiogram or other clinical concerns for cardiac involvement.
- Initial echocardiogram can be a routine study, performed without sedation, unless the clinical situation warrants a more expedited evaluation.
- Note that the coronary arteries may be difficult to visualize in non-sedated patients, but the risk/benefit analysis does not currently justify sedating all patients. We suggest beginning with a non-sedated echocardiogram, and if views are suboptimal or there is a suspicion for important findings, a discussion between the inpatient and cardiology attendings should take place to decide if sedation is warranted.
- Follow-up recommendations below:

<table>
<thead>
<tr>
<th>Initial cardiac workup</th>
<th>Clinical condition</th>
<th>Recommendations</th>
</tr>
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<tbody>
<tr>
<td>Normal labs AND Normal echo</td>
<td>• Inflammatory markers improving &lt;72hrs</td>
<td>• Repeat echo 2 weeks after discharge</td>
</tr>
<tr>
<td></td>
<td>• Inflammatory markers improving &gt;72hrs</td>
<td>• Repeat echo prior to discharge</td>
</tr>
<tr>
<td>Abnormal labs OR Abnormal echo</td>
<td>• Inflammatory markers significantly abnormal or worsening</td>
<td>• Repeat echo and cardiac screening labs prior to discharge</td>
</tr>
<tr>
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<td>• Clinical deterioration</td>
<td>• Follow-up 2 weeks after discharge with clinic visit and repeat echo</td>
</tr>
<tr>
<td></td>
<td>• Meets criteria for Kawasaki Disease or atypical KD</td>
<td>• Cardiology consult</td>
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<td>• Management for KD as per AHA algorithm</td>
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Outpatient and ED Workflows

- [Outpatient MIC-C Evaluation Algorithm](#)
- [ED MIS-C Evaluation Algorithm](#)
Additional Considerations
Consider undertaking genetic testing to help identify underlying susceptibilities in patients with MIS-C. They may share genetic predispositions with other inflammatory syndromes. The recommended genetic test is the Blueprint Genetics Comprehensive Immune and Cytopenias panel. It is a very new test, and only certain providers (Rheumatology and Hematology) have access to order it, and they will often already be consulted.

Discharge Criteria
Patients can be considered for discharge once they have been afebrile for at least 24 hours and their lab work is returning to baseline. Naturally, discharge decisions will be dependent on the patient's condition and the provider's clinical judgment.

Inpatient Quick Reference - PICU
Multisystem Inflammatory Syndrome in Children (MIS-C) is a newly recognized inflammatory syndrome presenting in pediatric patients, associated with current or recent SARS-CoV-2 infection. The pathogenesis is unclear, and the manifestations are still being clarified. At present, we know that children present with prolonged or persistent fever and a constellation of variable symptoms. They exhibit many markers of significant inflammation and are at high risk for cardiovascular collapse. This document accompanies the MIS-C protocol and is designed to be a quick reference guide when admitting these patients.

Initial evaluation criteria
- \( T > 38.5 \)C for at least 3 days
- No specific etiology identified

### Concerning signs and symptoms
- Persistent fever, not fully responsive to antipyretics
- GI complaints such as abdominal pain (may mimic appendicitis) and/or diarrhea
- Rash
- Conjunctivitis
- Headache
- Respiratory symptoms
- Sore throat
- Lymphadenopathy

### Initial Lab testing and thresholds of concern
- Absolute lymphocyte count < 0.5 k/uL
- Albumin <2 g/dL
- CRP > 10 mg/dL
- D-Dimer > 1 mg/L
- High Sensitivity Troponin > 30 pg/mL
- Ferritin > 350 ng/mL

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  Order “Peripheral Smear Morphology Review Request”
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### Vital Signs Monitoring
- Continuous cardiorespiratory monitor (+/- telemetry)
- Continuous pulse oximetry
- Consider checking vital signs every 2-4 hours initially if there is any concern for instability.

### Subspecialty Consultations
- Place patients in special pathogen precautions.
- May discontinue precautions after 2 negative SARS-CoV2 PCR swabs, at least 24 hours apart.
- Most up-to-date recommendations regarding special pathogen precautions:
  [http://www.med.umich.edu/i/ice/resources/clinical_guidance.html](http://www.med.umich.edu/i/ice/resources/clinical_guidance.html)

### Disease Reporting
- Must report disease if there is sufficient evidence to make diagnosis of presumed MIS-C
- Enter the case into the state database.
- Please document in the chart once IPE has been notified

### Subspecialty Consultations
- ID – Consult at the time of admission
- Hematology – Consult at the time of admission
- Rheumatology – Consult if there are clinical concerns
- Cardiology – Consult if abnormal cardiac screening labs, abnormal EKG, or abnormal echo, or if there is clinical concern for cardiac involvement

### Antibiotic Coverage
- Only if concerned about concomitant bacterial infection or sepsis
- Empiric antibiotic coverage for sepsis per the institutional sepsis guidelines and should be tailored if a bacterial process is identified

### Increasing Level of Care
• Please have a lower threshold for calling an RRT on these patients; the PICU is aware this will occur.