Update on Pediatric Multisystem Inflammatory Syndrome (MIS-C)

Midwest Winter Symposium January 27-30, 2022

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The authors declare that they have no relevant or material financial interests that relate to the content of this presentation.

Define/describe Multisystem Inflammatory Syndrome in Children (MIS-C)
Recognize the clinical findings, especially cardiac and GI manifestations
Evaluate laboratory findings in the ED
Provide anticipatory guidance for patients admitted for clinical monitoring or treatment for MIS-C

Case Presentation

CC: Fever
HPI: 10-year-old boy who presents with fever and myalgia for 6 days. Diagnosed with strep throat 1 day prior to arrival at urgent care and started on amoxicillin. He also has headache, fatigue, generalized abdominal pain, emesis, and joint pain in bilateral knees. Denies nasal congestion, cough, shortness of breath, chest pain.

PMs: Previously healthy.
Imm: Not up to date. Did not receive COVID-19 vaccine.
FHx: Mom reports she is healthy.

Temp 39.0 °C, HR 117 bpm, RR 36 bpm, BP 73/59, SpO2 96% on room air
Exam (highlights):
- General: Ill-appearing male, appears tired, uncomfortable
- CV: Tachycardia, nl S1 & S2 without murmurs, cap refill 3 sec.
- Pulm: Clear to auscultation bilaterally
- Abd: Diffuse pain, no guarding, non-distended
- Integumentary: No rash

Laboratory Results

<table>
<thead>
<tr>
<th>Test</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBC</td>
<td></td>
</tr>
<tr>
<td>WBC</td>
<td>17.6 k/μL (78% N, 7% L)</td>
</tr>
<tr>
<td>Hgb</td>
<td>11.6 g/dL</td>
</tr>
<tr>
<td>Hct</td>
<td>31.7 g/dL</td>
</tr>
<tr>
<td>RBC</td>
<td>5.12 M/μL</td>
</tr>
<tr>
<td>Hct</td>
<td></td>
</tr>
<tr>
<td>BE</td>
<td></td>
</tr>
<tr>
<td>HCO3</td>
<td></td>
</tr>
<tr>
<td>S/Cr</td>
<td></td>
</tr>
<tr>
<td>BUN</td>
<td>76 mg/dL</td>
</tr>
<tr>
<td>Creat</td>
<td>2.2 mg/dL</td>
</tr>
<tr>
<td>Glu</td>
<td>91 mg/dL</td>
</tr>
<tr>
<td>Ca</td>
<td>7.9 mg/dL</td>
</tr>
<tr>
<td>Albumin</td>
<td>3.0 g/dL</td>
</tr>
<tr>
<td>GFR</td>
<td>64.4 mL/min/1.73 m²</td>
</tr>
<tr>
<td>TP</td>
<td>6.6 mg/dL</td>
</tr>
<tr>
<td>ESR</td>
<td>6 mm/hr</td>
</tr>
<tr>
<td>Platelet</td>
<td>86 K/μL</td>
</tr>
<tr>
<td>Ferritin</td>
<td>599 ng/mL</td>
</tr>
<tr>
<td>ANA</td>
<td></td>
</tr>
<tr>
<td>RF</td>
<td></td>
</tr>
<tr>
<td>ASD</td>
<td></td>
</tr>
<tr>
<td>S/D</td>
<td></td>
</tr>
<tr>
<td>W/D</td>
<td></td>
</tr>
<tr>
<td>Eosinophils</td>
<td>7.0%</td>
</tr>
<tr>
<td>Neutrophils</td>
<td>80.0%</td>
</tr>
<tr>
<td>Monocytes</td>
<td>12.0%</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>9.0%</td>
</tr>
<tr>
<td>Basophils</td>
<td>0.0%</td>
</tr>
</tbody>
</table>

Microbiology

<table>
<thead>
<tr>
<th>Test</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>SARS-COV-2 Antibodies</td>
<td>Positive</td>
</tr>
<tr>
<td>RSV/A/FluA/B</td>
<td>Negative</td>
</tr>
<tr>
<td>Monospot</td>
<td>Negative</td>
</tr>
<tr>
<td>Rapid COVID-19</td>
<td>Negative</td>
</tr>
<tr>
<td>Blood Culture</td>
<td>Pending</td>
</tr>
</tbody>
</table>

Cardiac

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Troponin</td>
<td>29 ng/mL (Upper limit 0.03 ng/mL)</td>
</tr>
<tr>
<td>EKG</td>
<td>NSR, 112 bpm</td>
</tr>
</tbody>
</table>

Physical Exam

- Temp 39.0 °C, HR 117 bpm, RR 36 bpm, BP 73/59, SpO2 96% on room air
- Exam (highlights):
  - General: Ill-appearing male, appears tired, uncomfortable
  - CV: Tachycardia, nl S1 & S2 without murmurs, cap refill 3 sec.
  - Pulm: Clear to auscultation bilaterally
  - Abd: Diffuse pain, no guarding, non-distended
  - Integumentary: No rash
ED/Hospital Course

- **ED**
  - Patient given Zofran, 40cc/kg NS, IV KCl, Cefepime, Vancomycin
  - Vital signs improved.
  - Patient admitted to PICU for AKI, possible MIS-C.
- **PICU**
  - US and MR Abdomen did not reveal appendicitis.
  - MAPS remained above 60 mmHg without vasopressors.
  - Treated with 2g/kg IVIG. Patient defervesced on HD1. Troponin decreased to 65 pg/mL.
  - Low-dose aspirin started. Antibiotics stopped after 48 hours.
- **Floor**
  - Transferred to floor on HD3. Discharged on HD5 with daily aspirin.

What is MIS-C?

- First reported in the UK in association with COVID-19 in April 2020 about one month after the big surge in COVID disease.¹
- Novel, severe hyperinflammatory illness in small subset of children and adolescents usually up to 4–6 weeks after SARS-CoV-2 infection.²
  - Thought to be related to immune dysregulation that appears after an acute infection
  - Initially thought to be Kawasaki Disease and/or Toxic Shock Syndrome, quickly determined to have overlap
  - In May 2020, the European and US CDC published a Health Advisory with case criteria and requested reporting of suspected cases of MIS-C
  - Mortality rate less than 1%

Incidence of MIS-C

Daily MIS-C Cases and COVID-19 Cases Reported to CDC (7-Day Moving Average)

National Distribution of MIS-C Case Ranges by Territory, State

Reported MIS-C Case Ranges by Jurisdiction, on or before January 3, 2022*
1/29/2022

**US Reported Cases and Deaths**

Last updated with cases reported to CDC on or before January 3, 2022*

<table>
<thead>
<tr>
<th>TOTAL MIS-C PATIENTS MEETING CASE DEFINITION*</th>
<th>TOTAL MIS-C DEATHS MEETING CASE DEFINITION</th>
</tr>
</thead>
<tbody>
<tr>
<td>6,431</td>
<td>55</td>
</tr>
</tbody>
</table>

*Additional patients are under investigation. After review of additional clinical data, patients may be excluded if there are alternative diagnoses that explained their illness.

**Comparison between CDC/WHO Definition**

<table>
<thead>
<tr>
<th>Feature</th>
<th>CDC</th>
<th>WHO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>&lt;21 years</td>
<td>0-19 years</td>
</tr>
<tr>
<td>Fever</td>
<td>&gt;38°C for 24 or more hrs</td>
<td>3 or more days</td>
</tr>
<tr>
<td>Organ system involvement</td>
<td>2 or more + hospitalization</td>
<td>2 or more</td>
</tr>
<tr>
<td>Laboratory findings</td>
<td>Elevated CRP, ESR, fibrinogen, procalcitonin, D-dimer, liver enzymes, leukocytes</td>
<td>Elevated CRP, ESR, procalcitonin</td>
</tr>
<tr>
<td>COVID-19 infection</td>
<td>PCR, serology, or antigen positive</td>
<td>Exposure within 4 weeks prior to symptom onset</td>
</tr>
</tbody>
</table>

**Outpatient Evaluation for Suspected MIS-C**

Spectrum & Subtypes of MIS-C

- **A spectrum of severity for diagnosis of MIS-C has been created to aid in identification and treatment.**
- **“Febrile MIS-C”** Persistent fevers, mild symptoms (i.e. headache, fatigue) elevated inflammatory markers without severe multisystem involvement
- **“KD-Like” MIS-C** Meets criteria for complete or incomplete KD but does not have signs of severe multisystem involvement or shock
- **“Severe MIS-C”** Severe multisystem involvement including cardiac involvement


**KD vs. MIS-C**

<table>
<thead>
<tr>
<th>Feature</th>
<th>KD</th>
<th>MIS-C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>eGFR</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>Decreased</td>
<td>Decreased</td>
</tr>
<tr>
<td>Erythrocytes</td>
<td>Increased</td>
<td>Increased</td>
</tr>
<tr>
<td>ESR</td>
<td>Increased</td>
<td>Increased</td>
</tr>
<tr>
<td>CRP</td>
<td>Increased</td>
<td>Increased</td>
</tr>
<tr>
<td>Ferritin</td>
<td>Increased</td>
<td>Increased</td>
</tr>
<tr>
<td>Procalcitonin</td>
<td>Increased</td>
<td>Increased</td>
</tr>
<tr>
<td>D-dimer</td>
<td>Increased</td>
<td>Increased</td>
</tr>
<tr>
<td>Cardiac enzymes</td>
<td>Increased</td>
<td>Increased</td>
</tr>
<tr>
<td>C-reactive protein</td>
<td>Increased</td>
<td>Increased</td>
</tr>
</tbody>
</table>

**ED Presentation**

- Out of 114 total patients screened for MIS-C in ED, 47 (41%) patients were evaluated and treated as MIS-C.
- 32 (89%) had laboratory-confirmed MIS-C (defined as MIS-C or MIS-C confirmed) and 15 (37%) were admitted with severe respiratory condition and lacked confirmation of SARS-CoV-2 infection (MIS-C suspected)

**Spectrum and Subtypes of MIS-C**

- Abdominal Inflammatory State
  - KD-like Illness
  - Severe MIS-C

**Outpatient Evaluation for Suspected MIS-C**

- **Out of 314 total patients screened for MIS-C in ED, 47 (15%) patients were evaluated and treated as MIS-C.**
- 32 (68%) had laboratory-confirmed MIS-C (defined as MIS-C or MIS-C confirmed) and 15 (32%) were admitted with severe inflammatory condition and lacked confirmation of SARS-CoV-2 infection (MIS-C suspected).
American College of Rheumatology Clinical Guidance for Multisystem Inflammatory Syndrome in Children Associated with SARS-CoV-2 and Hyperinflammation in Pediatric COVID-19: Version 2

**Initial Labs**
- CBC, CMP, ESR, CRP, Ferritin, high sensitivity troponin
- SARS-CoV-2 PCR test nasal or NP swab, SARS-CoV-2 serologies before IVIg

**Additional Labs/Testing**
- D-dimer, fibrinogen, PT/PTT, ABG/VBG with lactate, CK, NT-proBNP, blood/urine/throat cultures, UA, immunoglobulins
- EKG, ECHO, CXR

**Organ-specific based on patient symptoms**
- GI-SARS-CoV-2 stool PCR (if available), GI pathogen PCR panel, calprotectin, C. diff toxin PCR

**Consultation**
- Pediatric infectious disease
- Pediatric cardiology
- Pediatric rheumatology
- Pediatric hematology
- Disease is reported to the CDC

**Fluid Resuscitation**
- Caution with boluses due to cardiac compromise
- Continuous cardiorespiratory monitor
- Vital signs q2h if increased concern for instability
- Continuous pulse oximetry

**Empiric Antibiotics**
- Ceftriaxone PLUS metronidazole for possible appendicitis
- Ceftriaxone PLUS vancomycin and clindamycin for possible toxic shock

**Inotropes**
- Vasopressors per Surviving Sepsis Campaign and the American College of Critical Care Medicine guidelines.
  - May use epinephrine or dopamine as first-line vasopressors, norepinephrine as second-line.
  - Norepinephrine and epinephrine can be given through peripheral IV. Risk of extravasation injury 2-3% in 1st 12 hours

**Mechanical Ventilation**

**Classify Clinical Severity**

- **Mild**: No vasoactive requirement, minimal/no respiratory support, and/or minimal organ injury
- **Moderate**: Significant supplemental oxygen requirement, and/or mild or isolated organ injury
- **Severe**: Non-invasive or invasive ventilatory support, and/or moderate or severe organ injury including moderate to severe ventilatory dysfunction

**Steroid Initial Dosing**
- For 2mg/kg/day dosing: max 60mg/day
- For pulse dosing: max 1g/day

**Other Immunomodulation**
- For Anakinra dosing: 2-10mg/kg
  - Consider pulse Methylprednisolone or Anakinra if refractory illness
- Consider 1-3 days pulse Methylprednisolone, consider Anakinra if refractory to steroids
  - Consider Anakinra 10mg/kg/dose q6h if refractory to steroids, consider other biologics if refractory to Anakinra

**Anticoagulation Monitoring**
- LMWH prophylaxis or low-dose ASA

**Broad-spectrum antibiotics**
- Yes

**Steroid Taper**
- 2-3 weeks

**MIS-C Treatment**
- 63% received IVIg (7% required 2nd dose for ongoing fever)
- 49% received corticosteroids
- 8% received anakinra
- 6.5% received tocilizumab
- 1.2% received infliximab

**Critical Care Therapies**
- 40% received inotropes
- 15% received mechanical ventilation (often as result of CV collapse)
- 2.7% were on ECMO

**Other Therapies**
- 34% received therapeutic anticoagulation
- Antiplatelet agents for KD-like features
Complications

- High prevalence of cardiac involvement
  - In a small observational study in Italy, there is an increase rate of cardiac involvement from KD-like disease after outbreak of COVID-19; the rate was 6/10 cases post-pandemic compared to 2/33 cases pre-pandemic.\(^9\)
  - Shock is seen in 35-50% of patients.\(^10\)
  - Coronary dilation/anomalies (35-50%), cardiac dysfunction (28-62%), myocarditis (17-22%), retnal vein occlusion or pericardial effusion
  - Pleural, pericardial, ascitic effusions (24-57%)
  - Acute kidney injury (18-52%)
  - Most patients (71-90%) present with involvement of at least four organ systems, and over half of patients require admission to ICU during hospital stay.\(^11,13\)

Summary

- MIS-C, a SARS-CoV-2 related condition, is characterized by presence of fever, elevated inflammatory markers, multi-organ involvement
- Fever, abdominal pain, diarrhea, vomiting are most common symptoms in MIS-C
- Clinical characteristics are shared to some extent with KD
- Investigations into a variety of treatment/supportive care domains are ongoing
- Further research is required to create diagnostic criteria consensus, optimize treatment protocols, and assess short- and long-term outcomes

Prognosis & Follow-up

- Approximately 75% of children with MIS-C require critical care during admission\(^6\)
- Majority of MIS-C patients, even with severe cardiovascular involvement, recover without sequelae (70-95%)\(^1,4\)
- ECHO follow-up is needed, even in patients with no cardiac involvement in the acute phase of illness\(^13\)
- It is reasonable to use KD guidelines to guide outpatient follow-up, as long-term monitoring has not been standardized to date\(^13\)

Questions?

Thank you for your attention