Multisystem Inflammatory Syndrome in Children (MIS-c)

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

<table>
<thead>
<tr>
<th>PCR +</th>
<th>Antibody +</th>
<th>Differentiating Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute COVID-19</td>
<td>Usually positive</td>
<td>May or may not be detected</td>
</tr>
<tr>
<td>Kawasaki disease</td>
<td>Incidental detection or overlapping features?</td>
<td>Incidental detection or overlapping features?</td>
</tr>
<tr>
<td>Other diseases (e.g., toxic shock, bacterial sepsis)</td>
<td>Incidental detection?</td>
<td>Incidental detection?</td>
</tr>
</tbody>
</table>

Meet MIS-C Case Definition

- Fever
- Evidence of inflammation
- 2 organ systems

"Severe" illness
- No other plausible diagnosis
- Evidence of histopathological evidence, imaging or NPS
Classes of MIS

- **Class I**: GI symptoms, shock, myocarditis, ≥ 98% by serology, 6 or more organ systems
- **Class 2**: Respiratory involvement, most similar to Acute COVID-19
- **Class 3**: Younger children, more overlap with acute KD, 63% serology positive only

Acute COVID or MIS-c?

- 12 y/o: Day 2 of illness: Came to ED with fevers, vomiting
- Day 3 of illness: Returned to ED with fevers, new cough,
- Day 5 of illness: Returned to ED with fevers, SOB
- 39.6°C HR 129 BP 108/63 RR 26-40 89% O2 sat.
- BiPAP ≥ high freq ventilation
- SARS CoV-2 PCR +

Mucocutaneous Manifestations of Multisystem Inflammatory Syndrome in Children During the COVID-19 Pandemic

Seroprevalence in Mississippi in Children

- Spike protein
- Convenience sample
- University of Mississippi
- May-Sept 2020
- Increased over time
- Seroprevalence higher in Black

Estimated Incidence of MIS-C, 7 Jurisdictions, April–June 2020

- Population-based incidence estimates (denominator was population of persons <21 years)
  - 1 to 8.5 MIS-C cases per million person-months
- Using denominator of estimated SARS-CoV-2 infections, incidence was higher among Black/African American and Hispanic/Latino children compared with White children

<table>
<thead>
<tr>
<th>Race and Ethnicity</th>
<th>Adjusted Incidence per Million SARS-CoV-2 Infections in Children (95% CI)</th>
<th>Adjusted Incidence Rate Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>White</td>
<td>120 (71–156)</td>
<td>Reference</td>
</tr>
<tr>
<td>Black/African American</td>
<td>616 (481–790)</td>
<td>6 (4–9)</td>
</tr>
<tr>
<td>Hispanic/Latino</td>
<td>467 (371–588)</td>
<td>4 (3–6)</td>
</tr>
<tr>
<td>Asian/Pacific Islander</td>
<td>315 (169–589)</td>
<td>3 (1–6)</td>
</tr>
</tbody>
</table>

A. Payne, et al, CDC COVID-19 Response Team, unpublished data


Trends in MIS-c During the COVID-19 Pandemic

- 1733 patients
- Excluded patients with respiratory symptoms but without other organ systems (except GI)
  - Respiratory symptoms and rash but no other symptoms
  - Negative test results for serology
- 33% Black, 37% Hispanic
- Median duration of fever was 5 days (IQR 4-7)
- Children <4 years of age were less likely to have lymphopenia and thrombocytopenia, but 40% overall had thrombocytopenia
- Only 24% had a preceding COVID like illness

Belay, IMAK Pediatrics April, 2021
Lee, IMAK Open Network, Oct, 2020
Definition of MIS-c

- An individual aged <21 years presenting with fever; laboratory evidence of inflammation; and 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
- Fever >38.0°C or subjective for ≥24 hours, 1 or more - an elevated CRP, ESR, fibrinogen, procalcitonin, d-dimer, ferritin, lactate dehydrogenase (LDH), or interleukin 6 (IL-6), elevated neutrophils, reduced lymphocytes and low albumin

<table>
<thead>
<tr>
<th>Laboratory test (units, normal range)</th>
<th>All MIS-c cases (n=1,733)</th>
<th>Most patients with CRP&gt;10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrinogen, peak (mg/dL, 200-400)</td>
<td>1534</td>
<td>I never used to order these tests unless clinically indicated for similar, pre-pandemic patients!</td>
</tr>
<tr>
<td>D-dimer, peak (mg/L, 0-4)</td>
<td>1222</td>
<td></td>
</tr>
<tr>
<td>Procalcitonin, peak (pg/mL, 0-25)</td>
<td>1264 (0.06-0.01-0.3)</td>
<td></td>
</tr>
<tr>
<td>ESR, peak (mm/hr, 1-20)</td>
<td>713</td>
<td></td>
</tr>
<tr>
<td>LDH, peak (IU/L, 25-210)</td>
<td>542</td>
<td></td>
</tr>
<tr>
<td>CRP, peak (mg/dL, 0-10)</td>
<td>1421</td>
<td></td>
</tr>
<tr>
<td>Ferritin, peak (ng/mL, 100-300)</td>
<td>2500</td>
<td></td>
</tr>
</tbody>
</table>

Most patients with CRP>10

https://emergency.cdc.gov/han/2020/han00432.asp
Clinical Characteristics of 58 Children With a Pediatric Inflammatory Multisystem Syndrome Temporally Associated With SARS-CoV-2


NS NA in most other conditions
ND in TSS NS but ND in TSS

Lower in those with shock

<table>
<thead>
<tr>
<th>Condition</th>
<th>RT-PCR +, antibody</th>
<th>RT-PCR +, antibody +</th>
<th>RT-PCR -, antibody +</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP &gt; 10.0 mg/dL</td>
<td>6 (35)</td>
<td>99 (66)</td>
<td>171 (76)</td>
</tr>
<tr>
<td>Neutrophil to lymphocyte ratio &gt; 5</td>
<td>5 (28)</td>
<td>101 (64)</td>
<td>149 (67)</td>
</tr>
<tr>
<td>BNP or pro-BNP ≥ 400 mg/mL</td>
<td>6 (50)</td>
<td>83 (63)</td>
<td>99 (55)</td>
</tr>
</tbody>
</table>

Discriminating MIS-c from Outpatient Febrile Conditions

- April 16 to June 10, 2020 in NY
- MIS-c (n=44) vs. other febrile conditions in ED or outpatient (n=181)
- Neck pain, vomiting, abdominal pain, extremity changes, conjunctivitis more in MIS-c
- Duration of fever longer in MIS-c
  - Lower absolute lymphocyte and platelet counts and greater CRP

Carlo et al. J Peds, Feb 2021
Some diagnoses we have seen in Atlanta:
- Systemic onset JIA
- Vaping injury
- Salmonella gastroenteritis
- Yersinia gastroenteritis
- Lemierre syndrome
- Appendicitis with abscess

BACTERIAL SEPSIS!

Definition of MIS-c... some areas to revise??

- Presenting with fever >38.0 for 3 days or more
- Evidence of inflammation - CRP could be defined
- Clinically severe illness with multisystem (>2) organ involvement
- Gastrointestinal involvement and cardiac high priority, neck pain??
- Renal, respiratory, hematologic, dermatologic or neurological
- Consideration for neutrophil to lymphocyte ratio
- Less sure of value of these unless clinically indicated: fibrinogen, procalcitonin, d-dimer, ferritin, lactic acid dehydrogenase (LDH), or interleukin 6 (IL-6), low albumin
- Should we consider race??

https://emergency.cdc.gov/han/2020/han00432.asp