COVID-19’s Multisystem Inflammatory Syndrome in Children (MIS-C)

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COVID-19 in Children

• The good news: low rates of infection, hospitalization and complications in children and most children are asymptomatic or exhibit mild symptoms.

• Late April: clinicians in the UK recognized increased reports of previously healthy children presenting with a severe Pediatric Multisystem Inflammatory Syndrome (PMIS) with Kawasaki disease-like features: 38 cases from 8 hospitals with 1 death.

• From April 16 through May 4, 2020, 15 patients aged 2-15 years were hospitalized, many requiring ICU admission with similar clinical picture.

• As of May 12, 2020, the New York State Department of Health identified 102 patients with similar presentations, many of whom tested positive for COVID-19.

• Several cases of Multisystem Inflammatory Syndrome in Children are confirmed in Florida. (2 at Holtz’s Children’s hospital in Miami. 2 at WCH in Jacksonville (12 suspected), and 2 at Joe DiMaggio.)
UK Experience- 38 Cases (3/25-5/1)

Clinical presentations

- 75% shock, 51% Myocardial involvement
- 54% rash
  - 30% conjunctivitis, 20% mucus membrane
- 57% abdominal involvement
- 38% acute kidney injury, only 1 required renal replacement therapy
- Unlike adults - only 32% respiratory symptoms
Laboratory Features

<table>
<thead>
<tr>
<th>n=</th>
<th>Laboratory Test</th>
<th>units</th>
<th>Cut-off assigned</th>
<th>% at cut off</th>
<th>Number at cut off</th>
<th>Median</th>
<th>Range</th>
<th>IQR</th>
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<tbody>
<tr>
<td>30</td>
<td>Haemoglobin</td>
<td>g/L</td>
<td>&lt;90</td>
<td>70.0</td>
<td>21</td>
<td>84.5</td>
<td>60-110</td>
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<tr>
<td>37</td>
<td>Neutrophil</td>
<td>x10*9/l</td>
<td>&gt;8</td>
<td>89.2</td>
<td>33</td>
<td>16</td>
<td>3.4-65</td>
<td>11.9-26</td>
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<tr>
<td>37</td>
<td>Neutrophil</td>
<td>x10*9/l</td>
<td>&lt;2</td>
<td>3.0</td>
<td>1</td>
<td>6</td>
<td>1.0-39</td>
<td>3.9-10.6</td>
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<tr>
<td>37</td>
<td>Lymphocyte</td>
<td>x10*9/l</td>
<td>&lt;2</td>
<td>94.6</td>
<td>35</td>
<td>0.6</td>
<td>0.1-2.9</td>
<td>0.4-0.8</td>
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<tr>
<td>37</td>
<td>Lymphocyte</td>
<td>x10*9/l</td>
<td>&lt;1</td>
<td>80.0</td>
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<tr>
<td>36</td>
<td>Platelets</td>
<td>x10*9/l</td>
<td>&lt;100</td>
<td>30.6</td>
<td>11</td>
<td>146</td>
<td>22-457</td>
<td>68-200</td>
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<tr>
<td>33</td>
<td>D-Dimer</td>
<td>ug/L</td>
<td>&gt;2000</td>
<td>93.9</td>
<td>31</td>
<td>2563</td>
<td>1.2-26695</td>
<td>11.0-5085</td>
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<tr>
<td>33</td>
<td>Ferritin</td>
<td>ug/L</td>
<td>&gt;500</td>
<td>75.8</td>
<td>25</td>
<td>932</td>
<td>87-63626</td>
<td>506-1774</td>
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<tr>
<td>30</td>
<td>Troponin</td>
<td>ng/L</td>
<td>&gt;12</td>
<td>90.0</td>
<td>27</td>
<td>202</td>
<td>3.0-5113</td>
<td>45-549</td>
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<tr>
<td>21</td>
<td>Creatinine Kinase</td>
<td>U/L</td>
<td>&gt;250</td>
<td>42.9</td>
<td>9.00</td>
<td>222</td>
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<tr>
<td>36</td>
<td>Creatinine</td>
<td>umol/L</td>
<td>&gt;100</td>
<td>33.3</td>
<td>12</td>
<td>73.5</td>
<td>28-302</td>
<td>43-121</td>
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<tr>
<td>36</td>
<td>ALT</td>
<td>U/L</td>
<td>&gt;100</td>
<td>27.8</td>
<td>10</td>
<td>49</td>
<td>11-636</td>
<td>29-121</td>
</tr>
<tr>
<td>36</td>
<td>Albumin</td>
<td>g/L</td>
<td>&lt;25</td>
<td>73.3</td>
<td>22</td>
<td>22.5</td>
<td>12.0-39</td>
<td>20-25</td>
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<tr>
<td>25</td>
<td>Lactate dehydrogenase</td>
<td>U/L</td>
<td>&gt;750</td>
<td>56.0</td>
<td>14</td>
<td>810</td>
<td>265-6660</td>
<td>420-1088</td>
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<tr>
<td>29</td>
<td>Fibrinogen</td>
<td>g/L</td>
<td>&gt;4</td>
<td>89.7</td>
<td>26</td>
<td>6</td>
<td>1.8-10.8</td>
<td>2.4-7.8</td>
</tr>
<tr>
<td>37</td>
<td>C reactive protein</td>
<td>mg/L</td>
<td>&gt;100</td>
<td>91.9</td>
<td>34</td>
<td>301</td>
<td>16-556</td>
<td>193-359</td>
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<tr>
<td>10</td>
<td>pro-BNP</td>
<td>pg/ml</td>
<td>&gt;1000</td>
<td>90.0</td>
<td>9</td>
<td>23093</td>
<td>241-35000</td>
<td>8783-35000</td>
</tr>
</tbody>
</table>

- Lymphopaenia
- Neutrophilia
- Anaemia
- Raised D-dimer
- Raised Troponin
- Raised CRP
Radiology – summary of findings

- Chest X-ray:
  - Some normal
  - Small bilateral pleural effusions
  - Patchy consolidation
  - Focal consolidation
  - Atelectasis

- CT chest (on a subset):
  - Findings as for CXR
  - Nodular ground glass opacification

- Abdominal USS/CT
  - Some normal
    - Free fluid
    - Ascites
    - Bowel inflammation
      - ileum/ascending colon/RIF
    - Lymphadenopathy
    - Pericholecystic oedema
Acute Heart Failure in MIS-C in The Context of Global SARS-CoV-2 Pandemic
France-Switzerland Experience  Circulation May 2020

- Children from 14 PICUs with cardiogenic shock, LV dysfunction, and severe inflammation.
- Median age: 11yr. Comorbidities: asthma and overweight
- GI symptoms were prominent
- LV ejection fraction < 30%, 80% required inotropes, 28% required ECMO
- Positive inflammatory markers: D-Dimer median 5284
- 88% tested + for COVID (PCR or serology)
- All received IVIG and 1/3 received steroids
- LV function was restored in the 25/35 of patients who got D/C from PICU.
- All patients on ECMO were weaned and no death
CCMC Experience- Presenting Signs/Sx’s

- Fever duration prior to presentation: 4 dy (IQR: 3, 5)
- Neurocognitive sx’s: 58%
- GI sx’s: 97%
- Respiratory sx’s: 52%
- Shock: 76%
- Complete Kawasaki disease criteria: 64%
  - With shock: 76%
Case Definition: Multisystem Inflammatory Syndrome in Children (MIS-C)

- An individual aged <21 years presenting with
  - **Fever** (>38.0°C for ≥24 h)
  - **Laboratory evidence of inflammation**: one or more of the following: elevated CRP, ESR, fibrinogen, procalcitonin, d-dimer, ferritin, lactic acid dehydrogenase, or IL-6, elevated neutrophils, reduced lymphocytes and low albumin
  - **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
### Case Definition: Multisystem Inflammatory Syndrome in Children (MIS-C)

**PATIENT PRESENTATION WITH CLINICAL SUSPICION OF MIS-C**

Patients may have a preceding illness consistent with COVID-19 or had a COVID-19 sick contact

<table>
<thead>
<tr>
<th>Systemic Inflammation</th>
<th>Mucocutaneous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>Rash - reticular, morbilliform, purpuric</td>
</tr>
<tr>
<td>Myalgias</td>
<td>Lip swelling/cracking</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>Strawberry tongue</td>
</tr>
<tr>
<td>Hypotension</td>
<td>Extremity swelling/peeling</td>
</tr>
<tr>
<td>Hypoperfusion or hyperperfusion</td>
<td>Conjunctivitis</td>
</tr>
<tr>
<td>Lymphadenopathy/lymphadenitis</td>
<td>Blisters or erosions</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cardiopulmonary</th>
<th>Gastrointestinal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory distress</td>
<td>Nausea/Vomiting</td>
</tr>
<tr>
<td>Chest pain</td>
<td>Diarrhea</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Neurologic</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td></td>
</tr>
<tr>
<td>Altered mental status</td>
<td></td>
</tr>
<tr>
<td>Meningismus</td>
<td></td>
</tr>
<tr>
<td>Focal deficits</td>
<td></td>
</tr>
<tr>
<td>Seizure</td>
<td></td>
</tr>
</tbody>
</table>
COVID-19 Testing Timelines

Before symptom onset
- Detection unlikely

After symptom onset
- PCR - Likely positive
- PCR - Likely negative

Symptom onset
- Nasopharyngeal swab PCR
- Bronchoalveolar lavage/sputum PCR
- Virus isolation from respiratory tract
- Stool PCR
- IgM antibody
- IgG antibody
Hassenfeld Children’s Hospital
Pathway for Diagnosis and Management of Multisystem Inflammatory Syndrome in Children

Fever ≥ 3 days* and one or more of the following:
GI symptoms, Rash, Conjunctivitis, Oral changes, Cough, Headache/Irritability, Extremity Swelling, Lymphadenopathy
OR
Fever ≥ 4 days and no obvious source

Unstable with signs of shock
Initiate fluid resuscitation and sepsis protocol
Monitor for signs of cardiac dysfunction
Early PICU admission

Stable
Labs (MISC Order set)
CBC Urinalysis D-dimer Coag panel
BMP Blood culture Covid PCR Ferritin
LFTs Troponin Covid IgG Procalcitonin
CRP BNP VBG w/lactate Respiratory panel
ESR EKG LDH Chest x-ray

Please add pictures of rashes to Epic chart
Labs normal
Continue care as usual
Ensure follow-up with PMD within 24 hours
Labs abnormal and other sources of infection excluded
Maintain isolation precautions as per NYU protocol
Consult rheumatology (if patient has any elevated inflammatory markers)
Consult cardiology on all admitted patients
Consider hematology consult if significantly elevated D-dimer
Consider infectious diseases consult

Unstable
Admit to PICU
Stable
Admit to floor

*Strongly recommend follow-up within 24 hours (either with PMD or return to ER) for patients with 2 days of fever and any symptoms listed

Updated 5.18.20
Management: Multisystem Inflammatory Syndrome in Children

- Wear appropriate PPE
- Sepsis protocol: monitoring/labs/antibiotics
- Consider IVIG and aspirin early if meets criteria for KD
- Consider IVIG if meets criteria for toxic shock syndrome
- All cases with suspected myocardial involvement (elevated troponin/ECG change and/or ECHO abnormalities): Cardiology, ID Consults

**Be aware:** Deterioration can be rapid: Close F/U
Monitoring: Multisystem Inflammatory Syndrome in Children

- **Worsening clinical picture** including worsening fever, cardiorespiratory deterioration, worsening GI symptoms, increasing HSM or lymphadenopathy, rash extension or worsening neurological symptoms.

- **Laboratory signs of increasing inflammation**
  - Falling blood cell counts
  - Rising ferritin
  - Unexpectedly low or falling ESR
  - Rising fibrinogen or new onset low fibrinogen
  - Rising ALT, AST or LDH
  - Rising triglycerides
  - Rising D-dimers
  - Low serum sodium with worsening renal function

- **Be aware:** Deterioration can be rapid: Close F/U
Pediatric Multisystem Inflammatory Syndrome: The Spectrum of Disease

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Associate Professor of Clinical Pediatrics
Program Director, Pediatric Infectious Disease Fellowship
Department of Pediatrics
Division of Pediatric Infectious Diseases and Immunology
University of Miami Miller School of Medicine
2 cases to compare

- DR is a 20 mo male, previously healthy, full term infant who presented to the ED with 5 days of fever T max 102.5, runny nose and mild dry cough.
  - 1 day prior to presentation he developed bilateral conjunctivitis, increased lip swelling and erythema and decreased PO intake
  - Normal wet diapers and stooling pattern.
  - No rash, vomiting, diarrhea, hematuria, SOB.
  - 2 sick contacts at home (father and older brother) both with fever, cough and anosmia - not tested for COVID.

- NN is an 8yo male, previously healthy, who presented to the ED with 3 days of fever and periumbilical pain.
  - Mother reported she had previous positive COVID testing a month prior to ED visit.
  - Patient presented to multiple Emergency Departments prior to admission, with discharge diagnosis of constipation, acute gastro-enteritis, and at the time of transfer to our Institution with diagnosis of appendicitis.
  - No rash, vomiting, diarrhea, hematuria, SOB.
### Admission labs

<table>
<thead>
<tr>
<th>Case 1</th>
<th>CBC</th>
<th>Chemistry</th>
<th>Miscellaneous</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 month old male with persistent fever and fussiness</td>
<td>WBC 11.9</td>
<td>ESR 37</td>
<td>COVID NP PCR: <strong>positive</strong></td>
</tr>
<tr>
<td>Key Exam Findings:</td>
<td>Hb 12.6</td>
<td>CRP 4.0 mg/dl</td>
<td>UA: negative</td>
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<tr>
<td>- Bilateral conjunctivitis</td>
<td>HCT 35.9</td>
<td>Procalcitin 1.63</td>
<td>Kidney and Liver Function normal</td>
</tr>
<tr>
<td>- Mucositis</td>
<td><strong>Plt 352</strong></td>
<td>Fibrinogen 535</td>
<td>CXR normal</td>
</tr>
<tr>
<td>- Cervical lymphadenopathy</td>
<td>Neut 59%</td>
<td>Ferritin 121</td>
<td>Echocardiogram: normal coronary arteries</td>
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<tr>
<td></td>
<td>Lymphocytes 28.8</td>
<td>LDH 1032</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>proBNP 604</td>
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<table>
<thead>
<tr>
<th>Case 2</th>
<th>CBC</th>
<th>Chemistry</th>
<th>Miscellaneous</th>
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</thead>
<tbody>
<tr>
<td>8yo male with fever and abdominal pain</td>
<td>WBC: 6.2</td>
<td>AST/ALT: 54/19</td>
<td>D Dimer: 2.68</td>
</tr>
<tr>
<td>Key Exam Findings:</td>
<td>Hb: 12.6</td>
<td>CRP: <strong>15.8 mg/dl</strong></td>
<td>Troponin &lt;0.012</td>
</tr>
<tr>
<td>- No mucositis</td>
<td><strong>PLT: 110</strong></td>
<td>Procal: 14.5</td>
<td><strong>proBNP 264</strong></td>
</tr>
<tr>
<td>- No conjunctivitis</td>
<td>SN: 74%</td>
<td>PT: 16.2</td>
<td>LDH: 687</td>
</tr>
<tr>
<td>- No lymphadenopathy</td>
<td>B: 12%</td>
<td>INR: 1.29</td>
<td>RVP: negative</td>
</tr>
<tr>
<td>- Persistent tachycardia</td>
<td></td>
<td>APTT: 38</td>
<td>SARS CoV 2, PCR: negative</td>
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<tr>
<td></td>
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<td>Fib: 623</td>
<td>Serology: <strong>positive</strong></td>
</tr>
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COVID-19 in children: generally mild or asymptomatic

- PIMS-TS: Paediatric Inflammatory Multisystem Syndrome-Temporally associated with SARS-CoV-2
- KD-TS: Kawasaki Disease-Temporally associated with SARS-CoV2
- FIS-TS: Febrile Children with Inflammation-Temporally associated with SARS-CoV-2
Spectrum of Disease and Management

- Atypical KD a/w SARS-Cov-2
  - IV IG
  - High dose steroids
  - High dose ASA
  - 5 days LOS
  - No end organ damage

- PMIS a/w SARS Cov-2
  - IV IG
  - High dose steroids
  - ASA
  - Remdesivir
  - Anakinra for 2 weeks
  - Discharged with normal echocardiogram

Dx Spectrum