Cardiac involvement in multisystem inflammatory syndrome in children (MIS-C): The TCH Experience

8th Annual TCHAPP Conference
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Medical Director of Preventive Cardiology, MIS-C, KD
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Outline

• What is MIS-C?

• How do kids present?

• What have we seen?

• How do we do follow-up?
Initial UK cohort

- 33 cases
- At presentation:
  - ~75% shock
  - ~33% AKI

- Presenting symptoms
  - 60% GI symptoms
  - 32% respiratory symptoms
  - 50% cardiac symptoms or echo changes (only ½ had echos)

- Outcomes
  - 2 ECMO
  - 1 death
Guidance: Paediatric multisystem inflammatory syndrome temporally associated with COVID-19

Case definition:

1. A child presenting with persistent fever, inflammation (neutrophilia, elevated CRP and lymphopaenia) and evidence of single or multi-organ dysfunction (shock, cardiac, respiratory, renal, gastrointestinal or neurological disorder) with additional features (see listed in Appendix 1). This may include children fulfilling full or partial criteria for Kawasaki disease.

2. Exclusion of any other microbial cause, including bacterial sepsis, staphylococcal or streptococcal shock syndromes, infections associated with myocarditis such as enterovirus (waiting for results of these investigations should not delay seeking expert advice).

3. SARS-CoV-2 PCR testing may be positive or negative
**Guidance: Paediatric multisystem inflammatory syndrome temporally associated with COVID-19**

### Clinical

<table>
<thead>
<tr>
<th>All:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Persistent fever &gt;38.5°C</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Most:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxygen requirement</td>
</tr>
<tr>
<td>Hypotension</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Some:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal pain</td>
</tr>
<tr>
<td>Confusion</td>
</tr>
<tr>
<td>Conjunctivitis</td>
</tr>
<tr>
<td>Cough</td>
</tr>
<tr>
<td>Diarrhoea</td>
</tr>
<tr>
<td>Headache</td>
</tr>
<tr>
<td>Lymphadenopathy</td>
</tr>
<tr>
<td>Mucus membrane changes</td>
</tr>
<tr>
<td>Neck swelling</td>
</tr>
<tr>
<td>Rash</td>
</tr>
<tr>
<td>Resp symptoms</td>
</tr>
<tr>
<td>Sore throat</td>
</tr>
<tr>
<td>Swollen hands and feet</td>
</tr>
<tr>
<td>Syncope</td>
</tr>
<tr>
<td>Vomiting</td>
</tr>
</tbody>
</table>

### Laboratory

<table>
<thead>
<tr>
<th>All:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abnormal Fibrinogen</td>
</tr>
<tr>
<td>Absence of potential causative organisms (other than SARS-CoV-2)</td>
</tr>
<tr>
<td>High CRP</td>
</tr>
<tr>
<td>High D-Dimers</td>
</tr>
<tr>
<td>High ferritin</td>
</tr>
<tr>
<td>Hypoalbuminaemia</td>
</tr>
<tr>
<td>Lymphopenia</td>
</tr>
<tr>
<td>Neutrophilia in most – normal neutrophils in some</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Some:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute kidney injury</td>
</tr>
<tr>
<td>Anaemia</td>
</tr>
<tr>
<td>Coagulopathy</td>
</tr>
<tr>
<td>High IL-10 (if available)*</td>
</tr>
<tr>
<td>High IL-6 (if available)*</td>
</tr>
<tr>
<td>Neutrophilia</td>
</tr>
<tr>
<td>Proteinuria</td>
</tr>
<tr>
<td>Raised CK</td>
</tr>
<tr>
<td>Raised LDH</td>
</tr>
<tr>
<td>Raised triglycerides</td>
</tr>
<tr>
<td>Raised troponin</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
</tr>
<tr>
<td>Transaminitis</td>
</tr>
</tbody>
</table>

### Imaging and ECG

- Echo and ECG – myocarditis, valvulitis, pericardial effusion, coronary artery dilatation
- CXR – patchy symmetrical infiltrates, pleural effusion
- Abdo USS – colitis, ileitis, lymphadenopathy, ascites, hepatosplenomegaly
- CT chest – as for CXR – may demonstrate coronary artery abnormalities if with contrast
Case Definition for Multisystem Inflammatory Syndrome in Children (MIS-C)

- An individual aged <21 years presenting with fever\textsuperscript{i}, laboratory evidence of inflammation\textsuperscript{i}, 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

\textsuperscript{i}Fever \geq 38.0°C for \geq 24 hours, or report of subjective fever lasting \geq 24 hours

\textsuperscript{i}Including, but not limited to, one or more of the following: an elevated C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), fibrinogen, procalcitonin, d-dimer, ferritin, lactic acid dehydrogenase (LDH), or interleukin 6 (IL-6), elevated neutrophils, reduced lymphocytes and low albumin
*based on healthy adult data
Updated UK PIMS cohort

- 78 cases
- 14 admissions per week
- Median age 11 years (IQR 8–14)
- 67% male
- 78% from ethnic minority

• Presenting Symptoms
  - 100% fever
  - 87% shock
  - 62% abdominal pain, 63% vomiting, 64% diarrhea

- Initially inflammatory markers improve however troponin increase

• Treatments
  - 46% ventilated
  - 83% vasoactive infusions
  - 73% received steroids
  - 76% received IVIg
  - 22% received biologics

• 36% coronary artery abnormalities
  - 18 aneurysms and 10 echogenic

• 3 ECMO (2 deaths)
CDC MMWR

• July 29 - 570 reported MIS-C patients
• 203 (35.6%) - shock, cardiac dysfunction, abdominal pain, and markedly elevated inflammatory markers, and almost all had positive SARS-CoV-2 test
• 367 (64.4%) - acute COVID-19, had a less severe clinical course, or Kawasaki disease features
• Median duration of hospitalization was 6 days
• 364 patients (63.9%) required care in an intensive care
CDC MMWR – MIS-C in the US

Sex Distribution of MIS-C Cases Reported to CDC (N=342), as of 7/15/20*

- Male, 55%
- Female, 45%

Age Distribution of MIS-C Cases Reported to CDC (N=342), as of 7/15/20*

81% Cases Aged 1-14 y
Median (range): 8 (0-20)

https://www.cdc.gov/mmwr/preview/mmwrhtml/mm6923a2.htm
FIGURE. Geographic distribution of 570 reported cases of multisystem inflammatory syndrome in children — United States, March–July 2020

MIS-C Cases by Jurisdiction

Since reporting began in mid-May, 44 states, New York City, and Washington, DC, have reported at least one case of MIS-C to CDC. Most of those jurisdictions have 10 or fewer reported cases. Because of the small number of cases in most states and to protect the privacy of patients and their families, CDC is not reporting individual states' case counts.

MIS-C Case Ranges by Territory, State, New York City, and Washington, DC*

Reported MIS-C Cases

- No cases reported
- 1-10
- 11-30
- 31-50
- 51+

Abbreviations: DC = District of Columbia; NYC = New York City.
All are not created equally in MIS-C

Race and Ethnicity Distribution of MIS-C Cases Reported to CDC (N=342), as of 7/15/20*
Treatment

- 424 (80.5%) received intravenous immunoglobulin (IVIG)
- 331 (62.8%) received steroids
- 309 (58.6%) received antiplatelet medication
- 233 (44.2%) received anticoagulation
- 221 (41.9%) received vasoactive medication

- 10 (1.8%) died
Research Paper

Multisystem inflammatory syndrome in children: A systematic review

Mubbasheer Ahmed, Shailesh Advani, Axel Moreira, Sarah Zoretic, John Martinez, Kevin Chorath, Sebastian Acosta, Rija Naqvi, Finn Burmeister-Morton, Fiona Burmeister, Aina Tarriela, Matthew Petershack, Mary Evans, Ansel Hoang, Karthik Rajasekaran, Sunil Ahuja, Álvaro Moreira

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‡Department of Otolaryngology, The University of Pennsylvania, Philadelphia, PA, USA
662 patients

### Table 2

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th># Patients with available data</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender</td>
<td>662</td>
<td>346 (52.3)</td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>528</td>
<td>9.3 ± 0.5</td>
</tr>
<tr>
<td>Race/Ethnicity</td>
<td>471</td>
<td></td>
</tr>
<tr>
<td>African American/Afro-Caribbean/African</td>
<td>164 (34.8)</td>
<td></td>
</tr>
<tr>
<td>White/European/Caucasian</td>
<td>130 (27.6)</td>
<td></td>
</tr>
<tr>
<td><strong>Hispanic/Latino</strong></td>
<td>91 (19.3)</td>
<td></td>
</tr>
<tr>
<td>Asian/Indian/Middle Eastern</td>
<td>38 (8.1)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>48 (10.2)</td>
<td></td>
</tr>
<tr>
<td>Co-morbidities*</td>
<td>558</td>
<td>268 (48.0)</td>
</tr>
<tr>
<td>Overweight/Obese</td>
<td></td>
<td>136 (50.8)</td>
</tr>
<tr>
<td>Respiratory</td>
<td></td>
<td>71 (26.5)</td>
</tr>
<tr>
<td>Immunologic/Allergic</td>
<td></td>
<td>17 (6.3)</td>
</tr>
<tr>
<td>Cardiac</td>
<td></td>
<td>8 (2.9)</td>
</tr>
<tr>
<td>Hematologic</td>
<td></td>
<td>4 (1.5)</td>
</tr>
<tr>
<td>Endocrine/Gastrointestinal</td>
<td>5 (1.9)</td>
<td></td>
</tr>
<tr>
<td>Neurologic/Behavioral</td>
<td>3 (1.1)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>24 (9.0)</td>
<td></td>
</tr>
<tr>
<td>SARS-CoV-2 positive (RT-PCR/antibody)</td>
<td>628</td>
<td>532 (84.7)</td>
</tr>
<tr>
<td>Number of days symptomatic before presenting to hospital</td>
<td>294</td>
<td>4.8 ± 0.3</td>
</tr>
<tr>
<td>Hospital length of stay (days)</td>
<td>422</td>
<td>7.9 ± 0.6</td>
</tr>
<tr>
<td>Admission to intensive care unit</td>
<td>662</td>
<td>470 (71.0)</td>
</tr>
</tbody>
</table>

Continuous data presented as Mean ± SD. Multiple co-morbidities in a subset of patients *. RT-PCR-reverse transcriptase polymerase chain reaction; SARS-CoV-2-severe acute respiratory syndrome coronavirus 2.
# Multisystem inflammatory syndrome in children: A systematic review

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Clinical signs and symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td># Patients with available data</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>CONSTITUTIONAL</strong></td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td>662</td>
</tr>
<tr>
<td>Myalgia, fatigue</td>
<td>662</td>
</tr>
<tr>
<td>Lymphadenopathy</td>
<td>662</td>
</tr>
<tr>
<td><strong>GASTROINTESTINAL</strong></td>
<td></td>
</tr>
<tr>
<td>Abdominal pain, diarrhea</td>
<td>662</td>
</tr>
<tr>
<td>Vomiting</td>
<td>662</td>
</tr>
<tr>
<td>Loss of appetite</td>
<td>662</td>
</tr>
<tr>
<td><strong>HEAD, EYES, EARS, NOSE, THROAT</strong></td>
<td></td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>662</td>
</tr>
<tr>
<td>Cheilitis</td>
<td>662</td>
</tr>
<tr>
<td>Tongue swelling</td>
<td>662</td>
</tr>
<tr>
<td>Sore throat</td>
<td>662</td>
</tr>
<tr>
<td><strong>RESPIRATORY</strong></td>
<td></td>
</tr>
<tr>
<td>Dyspnea, shortness of breath</td>
<td>662</td>
</tr>
<tr>
<td>Cough</td>
<td>662</td>
</tr>
<tr>
<td>Rhinorrhea, nasal congestion</td>
<td>662</td>
</tr>
<tr>
<td><strong>NEUROLOGIC</strong></td>
<td></td>
</tr>
<tr>
<td>Headache, dizziness</td>
<td>662</td>
</tr>
<tr>
<td>Somnolence, altered mental status, lethargy, fussy</td>
<td>662</td>
</tr>
<tr>
<td><strong>DERMATOLOGIC</strong></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>662</td>
</tr>
<tr>
<td>Edema to extremities</td>
<td>662</td>
</tr>
</tbody>
</table>
Fig. 4. Comparison of the signs and symptoms of individuals with MIS-C versus COVID-19. Pediatric cases of MIS-C are depicted in gold, while children with COVID-19 are the solid blue bars. All 662 MIS-C patients were included in this analysis. The sample size for COVID-19 patients was 2445 patients for all the signs/symptoms, except for symptomatic (n = 2367).
### Table 4
Laboratory measures.

<table>
<thead>
<tr>
<th>HEMATOLOGY</th>
<th># Patients</th>
<th>Mean ± SD</th>
<th>Ref. range</th>
</tr>
</thead>
<tbody>
<tr>
<td>White blood cell count (10^3/µL)</td>
<td>395</td>
<td>13.2 ± 0.8</td>
<td>4.0–12.0</td>
</tr>
<tr>
<td>Neutrophil (%)</td>
<td>276</td>
<td>80.7 ± 7.8</td>
<td>54–62</td>
</tr>
<tr>
<td>Lymphocyte (%)</td>
<td>306</td>
<td>9.8 ± 0.8</td>
<td>25–33</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>211</td>
<td>10.2 ± 0.8</td>
<td>11.5–14.5</td>
</tr>
<tr>
<td>Platelets (10^3/µL)</td>
<td>394</td>
<td>215 ± 11.4</td>
<td>150–450</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>LIVER and RENAL FUNCTION</th>
<th># Patients</th>
<th>Mean ± SD</th>
<th>Ref. range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumin (g/dL)</td>
<td>337</td>
<td>2.8 ± 0.2</td>
<td>4.0–5.3</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>158</td>
<td>0.9 ± 0.1</td>
<td>0.22–0.59</td>
</tr>
<tr>
<td>Alanine transaminase (U/L)</td>
<td>226</td>
<td>59.8 ± 4.1</td>
<td>5–45</td>
</tr>
<tr>
<td>Aspartate aminotransferase (U/L)</td>
<td>145</td>
<td>57.3 ± 5.8</td>
<td>15–50</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>INFLAMMATORY MARKERS</th>
<th># Patients</th>
<th>Mean ± SD</th>
<th>Ref. range</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-reactive protein (mg/L)</td>
<td>439</td>
<td>160 ± 7.0</td>
<td>Male 0.6–7.9 Female 0.5–10.0</td>
</tr>
<tr>
<td>Ferritin (ng/mL)</td>
<td>303</td>
<td>977 ± 55.8</td>
<td>10–60</td>
</tr>
<tr>
<td>Procalcitonin (ng/mL)</td>
<td>312</td>
<td>30.5 ± 2.1</td>
<td>&lt;0.15</td>
</tr>
<tr>
<td>Lactate dehydrogenase (U/L)</td>
<td>980</td>
<td>4.0 ± 4.4</td>
<td>150–500</td>
</tr>
<tr>
<td>Interleukin-6 (pg/mL)</td>
<td>257</td>
<td>184 ± 15.6</td>
<td>≤1.8</td>
</tr>
<tr>
<td>Creatine kinase (U/L)</td>
<td>49</td>
<td>135 ± 46.0</td>
<td>5–130</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>COAGULATION</th>
<th># Patients</th>
<th>Mean ± SD</th>
<th>Ref. range</th>
</tr>
</thead>
<tbody>
<tr>
<td>D-dimer (mg/L)</td>
<td>349</td>
<td>3.5 ± 0.4</td>
<td>&lt;0.4</td>
</tr>
<tr>
<td>Fibrinogen (mg/dL)</td>
<td>267</td>
<td>499 ± 58.3</td>
<td>220–440</td>
</tr>
<tr>
<td>Erythrocyte sedimentation rate</td>
<td>191</td>
<td>59.4 ± 9.1</td>
<td>0–20</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CARDIAC</th>
<th># Patients</th>
<th>Mean ± SD</th>
<th>Ref. range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Troponin (ng/L)</td>
<td>281</td>
<td>494 ± 38.3</td>
<td>&lt;10</td>
</tr>
<tr>
<td>Brain natriuretic peptide (pg/mL)</td>
<td>147</td>
<td>3904 ± 352</td>
<td>0–100</td>
</tr>
<tr>
<td>Prohormone of brain natriuretic peptide (ng/L)</td>
<td>164</td>
<td>5854 ± 743</td>
<td>0–450</td>
</tr>
</tbody>
</table>

Reference (Ref) ranges were obtained from Nelson Textbook of Pediatrics (we chose eight years as the age category provided the overall mean of included patients). *Data from Kaushik et al. was used for the normal cardiac values.


Multisystem inflammatory syndrome in children: A systematic review

• Cardiac findings
  • 88% had an echo
  • 54% had an abnormal echo
  • 45% had decreased function
  • 15% had coronary dilation or aneurysms

• 71% admitted to ICU
  • 60% in shock
  • 40% required respiratory support (22% mechanical ventilation)
  • 52% required vasoactive agents
  • 4.6% ECMO
  • 1.2% died
Multisystem inflammatory syndrome in children: A systematic review

Table 5
Medications.

<table>
<thead>
<tr>
<th>Medication</th>
<th>N</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total n = 662</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intravenous immunoglobulin</td>
<td>506</td>
<td>76.4</td>
</tr>
<tr>
<td>Vasoactive support</td>
<td>347</td>
<td>52.3</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>347</td>
<td>52.3</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>108</td>
<td>16.3</td>
</tr>
<tr>
<td>Anticoagulants</td>
<td>172</td>
<td>25.9</td>
</tr>
<tr>
<td>Aspirin</td>
<td>111</td>
<td>16.8</td>
</tr>
<tr>
<td>Interleukin-1ra inhibitor</td>
<td>56</td>
<td>8.5</td>
</tr>
<tr>
<td>Interleukin-6 inhibitor</td>
<td>40</td>
<td>6.0</td>
</tr>
<tr>
<td>Remdesivir</td>
<td>6</td>
<td>0.9</td>
</tr>
<tr>
<td>Hydroxychloroquine</td>
<td>5</td>
<td>0.8</td>
</tr>
</tbody>
</table>
Illness Classes – Class 1

• Class 1 – Multisystem organ involvement (35.7%)
  • Abdominal pain, Shock, Myocarditis – chest pain
  • >6 systems in 50% of cases
  • Median age 9 years

• Class 2 – Respiratory (29.5%)
  • Coronary artery aneurysms (16%), median age 10 years
  • Mortality 5.6%

• Class 3 – Kawasaki like (34.8%)
  • Younger kids (median age 6 years) and they do better
There's No Place Like Home
TCH experience

All TCH SARS CoV-2 RNA Positive Patient Counts by Day and 7-Day Averages by Location
(1): Signs and Symptoms MIS-C:
Consider most likely causes first. If a cause for the symptoms is suspected clinically, off algorithm and manage appropriately. Lower threshold for MIS-C in those with past COVID positive, exposure to COVID positive, or those who are ill appearing or in shock. MIS-C symptoms can include:
• Fever ≥ 3 days in well appearing patient or ≥ 1 day in ill appearing patient
• Epidemiologic contact with COVID positive person
• Physiologic shock; tachycardia, tachypnea, +/-hypotension, signs of poor perfusion
• Cardiac symptoms/heart failure: gallop, arrhythmia, rales, hepatosplenomegaly
• GI symptoms: diarrhea, abdominal pain, vomiting
• Neurologic symptoms: headache, irritability, lethargy, AMS
• Signs and symptoms of Kawasaki’s disease: Kawasaki Disease: Diagnosis & Management Guidelines
TENAS CHILDREN’S HOSPITAL: EVIDENCE BASED OUTCOMES CENTER
Evaluation and Treatment of Suspected Multi-System Inflammatory Syndrome in Children
Potentially Associated with COVID-19 Algorithm (MIS-C)
Clinical Pathway

Patient suspected signs and symptoms of Multi-System Inflammatory Syndrome in Children
Initiate Appropriate PPE per TCH recommendations and Treat as PUI

Cardiac monitoring and pulse ox
Resuscitate and start supportive management as indicated

MIS-C Labs (IP Gen MIS-C or EC Quick Orders)
- SARS-CoV-2 RNA PCR
- SARS-CoV-2 antibodies
- CBC
- Chem 10
- Ferritin
- Troponin
- Albumin
- Fibrinogen
- BNP
- LDH
- D-Dimer
- Procalcitonin
- UA
- ALT
- AST
- CRP

Order EKG
POCUS if available
Order Echo at time of initial evaluation if high suspicion (does NOT need to be done in the EC)

Order blood cultures if febrile, unstable, or in shock
Order Blood gas with lactate and DIC panel if unstable, in shock

Consider following based on differential:
- Additional bacterial cultures: urine, throat, or wound culture
- Viral studies based on season: Flu/RSV, summer or winter respiratory panel
- Murine typhus: Murine typhus antibodies
- Kawasaki disease: Children meeting KD criteria warrant Sars-Cov-2 testing
Texas Children's Hospital: Evidence Based Outcomes Center

Evaluation and Treatment of Suspected Multi-System Inflammatory Syndrome in Children Potentially Associated with COVID-19 Algorithm (MIS-C)

Clinical Pathway

(4): Laboratory signs of inflammation:
- Elevated CRP
- Elevated D-dimers
- Elevated BNP and troponin
- Elevated ferritin
- Elevated fibrinogen or new onset low fibrinogen
- Elevated ALT, AST or LDH
- Elevated procalcitonin
- Decreased hemoglobin
- Decreased lymphocytes
- Elevated PMN or bandemia

(7): Based on experience at TCH, consider lower threshold for transfer to MC or escalate to ICU for following characteristics:
- >9yo
- Persistent tachycardia, borderline normal blood pressure
- Fever > 5 days
- Elevated BMI
- Elevated troponin or BNP
- Escalating care (i.e., repeated boluses)
TExAS CHILdren’S HoSpITAL: EVIDENCE bASED OUTCOMES CENTER
Evaluation and Treatment of Suspected Multi-System Inflammatory Syndrome in Children Potentially Associated with COVID-19 Algorithm (MIS-C)

Clinical Pathway

- If POCUS positive, refer to POCUS MISC Pathway (POCUS MIS-C Workflow). If severe dysfunction, follow EC critical cardiac patient pathway also: consult CICU via 3-CICU (all campuses) and cardiology.
- Order ECHO ASAP if not already ordered (can be performed inpatient).
- Early consultation of rheumatology and cardiology, especially if MIS-C is high on differential. Consider ID consult as appropriate. Consults can be performed inpatient unless significant delay to inpatient.
- Admit to PHM vs CCM as appropriate based on clinical status of patient.
  - Do NOT need to wait in the EC for PCR nor Antibody result for admission.
  - Do NOT need to wait for echo/cards consult in the EC prior to transfer to inpatient at any campus. For community campuses, do NOT wait for echo/cards consult in the EC prior to transfer to MC if out of scope for campus or if echo/consult cannot be done in timely manner (<1 hour).
  - Consider lower threshold for escalation to ICU or transfer to MC from community for factors listed in box 7.
  - High risk for cardiac concern:
    - Clinical evidence of cardiac dysfunction
    - EKG, Echo, and Lab parameters: ventricular dysfunction, significant tricuspid or mitral regurgitation, significant coronary artery dilation, arrhythmia, increasing BNP or troponin
  - WC/WL PHM admits: transfer to acute care MC if community PHM feels better served at MC, concern regarding timely consultation and/or diagnostic testing, or out of scope for campus.
  - For CCM: Determine PICU vs CICU based on severity of shock and EKG (and available results from labs/echo). Can admit to any campus PICU if PCR pending/negative. If PCR+, do not admit to WL PICU (can go to any other ICU area). Lower threshold for transfer to MC if concern of inability to provide services at community campus.

- Acute care recommendations:
  - Place on continuous CV monitoring, consider telemetry in discussion with cardiology
  - Close monitoring & place on Watcher List for initial 12 hrs as patients can deteriorate quickly
  - Keep as PUI per current recommendations (click here for TCH COVID Resources)
  - If PCR neg, antibody negative: Repeat testing based on consultation with infection control and MIS-C team if MIS-C still in differential
  - Some MIS-C patients will remain PCR positive: manage as MIS-C, not per primary COVID algorithms
  - Utilize IP Gen MIS-C order set as appropriate
  - Additional labs based on discussion and evaluation by primary team and consultants
Rx just like KD → IVIG

2nd dose IVIG if fevers >36 hrs after first ends

Just like regular KD, could be “KD-shock”, if so add steroids if worsening or if also cardiac dysfxn → generally 2mg/kg

anakinra as “next line” but some are so sick that we are adding it right away (multiple of 100mg up to 400mg/day)

* sending home on 2-3 weeks of outpatient steroids

Not c/iKD (red eyes alone does not count), no coronary dilation but shock/cardiac dysfunction

does not meet iKD criteria but coronary dilated or other cardiac sign of KD (ie valvulitis)

start steroids and anakinra ASAP*

*cardiac indications for IVIG (do not delay hyperinflammatory treatment)

troponin >1 ng/ml
OR
any TWO:
- EF < 50%
- troponin ≥ 0.1 ng/ml
- classic ECG changes

classic ECG changes = abnormal ST segments and/or low voltage QRS and/or AV conduction delay and/or ventricular arrhythmia
Cardiology Recommendations:

• Critically ill or worsening patients:
  • Daily troponin and NT-ProBNP
  • ECG and echo on admission
  • Daily echo and ECG (occasionally more frequently if clinically indicated)

• Non-ICU patients:
  • Daily troponin and NT-ProBNP
  • Ecg and echo on admission
  • ECG and echo every 2 days until improving
Cardiology Recommendations:

• In patients with coronary artery dilation or aneurysms consider CT angiogram for cross-sectional evaluation of distal coronary artery sizes.

• Treatment (in conjunction with consulting COVID cardiologist):
  • If coronary involvement, consider anticoagulation:
    • Aspirin
    • Lovenox
    • Plavix if large aneurysms
  • Consider cardiac support (ACE-I, etc) if there is poor function
Rx @ TCH

• Best supportive care
  • ER, PICU, rheumatology, cardiology, ID, hematology, hospitalists

• Immune modulation = careful infusions to inflamed hearts!
  • IVIG
  • Steroids
  • Biologics
    • Anakinra (injection)
    • Infliximab?

• Anti-platelet/anti-coagulation case by case basis

• *PCR positive patients may qualify for ID trials using anti-virals/plasma
Case 1

- 17 yo F, previously healthy (obese)
- 10 days of fever
  - Tmax reportedly 105.9
- Associated with
  - Abdominal pain
  - Red eyes
  - Fatigue/myalgias/headache
  - Abnormal hand coordination
- No respiratory symptoms
- +COVID-19 contact
- Transferred to PICU
- Started on pressors in route
- Intubated on arrival (AMS, not respiratory)
- Treated with best supportive care and immune modulation
- Off pressors HD#3
- Extubated HD#4
- Doing well overall
Case 1 – Echo findings

- **HD1-0516**
  - No coronary artery changes.
  - Normal right ventricular systolic function.
  - Hyperdynamic left ventricular systolic function

- **HD1-1223**
  - Normal appearance of the coronary arteries. Normal biventricular systolic function

- **HD1-1808**
  - Mild "buckling" of the anterior mitral valve leaflet with upper mild mitral regurgitation.
  - Normal biventricular systolic function

- **HD3-1311**
  - The right coronary artery appears prominent, similar to the previous echocardiogram.
  - Qualitatively normal biventricular systolic function
02-AUG-2002 (17 yr) 
Female Black 
Room: LT10- 
Loc: 552

Technician: Felicita Cavazos
Test ind: EVAL TRO PonIN

Confirmed By: Tam Dan Pham

- Vent. rate: 48 BPM
- PR interval: 168 ms
- QT/QTc: 532/476 ms
- P-R-T axes: -40 47 52
- Low right atrial bradycardia
- ST elevation in inferior and anterolateral leads
- Prolonged QT

Confirmed by Pham, Tam Dan (4147) on 5/22/2020 3:51:10 PM
Case 1: Exercise test

• Bruce protocol:
  • 07:13 min:s (<10th %), METS: 10.1.
  • Heart rate: 59 bpm of 176 bpm (86 % of the maximal, age-predicted heart rate).

• Interpretation
  • HR Response to Exercise: appropriate.
  • BP Response to Exercise: normal resting BP - appropriate response.
  • Chest Pain: none.

• Conclusions
  • Appropriate HR response to exercise. Blunted BP response to exercise
  • Baseline rhythm was low right atrial rhythm. Frequent ventricular ectopy seen in exercise and recovery. Multiple 3-6 beat runs of slow VT seen in stage 2 of exercise. Ectopy subsided by end of recovery.
  • Nonspecific ST-T wave changes seen. (T-wave inversions)
Electrical Activity Changes

- ECG – persistent asymptomatic bradycardia
- Holter –
  - average HR 51bpm (37-104bpm)
  - two episodes of non-conducted beats - One following a PVC likely due to retrograde invasion and a second dropped beat without PR prolongation and could not rule out second degree heart block, Mobitz type 2.
- EST – accelerated ventricular rhythm/slow VT
Case 2

- 9 y.o. Hispanic female
- Symptoms:
  - abdominal pain
  - 6 days of fever
  - Conjunctivitis
- Initially concern for shock and appendicitis
- Initial labs
  - Lymphopenic
  - Neutrophilic
  - Coagulopathic
  - Thrombocytopenic
  - elevated troponin
  - Sars-CoV-2 antibodies and PCR were positive
- Treatment
  - multiple fluid boluses
  - Pressors- epinephrine and dobutamine
  - Inflammation - steroids and anakinra
- Labs showed mild improvements in inflammatory parameters
Cardiac Findings

• Initial echo - normal coronary arteries and no evidence of myocardial dysfunction.
• ECG - sinus tachycardia, diffuse t-wave flattening.
• Troponin I and BNP trended up
And 24 hours later

- Developed ventricular ectopy and ST elevation which deteriorated into ventricular tachycardia
- Increased epinephrine, vasopressin, calcium
- ECG - normal QTc and sinus tachycardia
- Echocardiogram – lack of tapering of her distal right coronary artery
  - severely depressed left ventricular systolic function with severe hypokinesis
  - moderately depressed right ventricular systolic function
- Labs worsened
- Cannulated on ECMO -> severe mitral regurgitation -> 2.5 Impella
- 48 hours after Impella placement on ECMO the biventricular function was low normal
The TCH experience

• 80+ cases thus far
• Average age is 8 years
• 62% male
• Average days of fever
  • at admission – 5 days
  • after admission – 2 days
The TCH Experience

Insurance Type:
- No insurance: 63%
- Medicaid/CHIP: 23%
- Private: 12%

Race/Ethnicity:
- Hispanic: 63%
- Black: 23%
- White: 12%
- Other/Unknown: 2%
The TCH Experience

• Abnormal Cardiac Enzymes
  • 79% abnormal troponin I
  • 87% abnormal BNP

• 73% lymphopenic
• 75% neutropenic

• Sars-CoV-2 Testing
  • 73% PCR positive
  • 95% IgG positive
  • 16% IgM positive
<table>
<thead>
<tr>
<th></th>
<th>Initial echocardiogram</th>
<th>Follow up echocardiogram</th>
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</thead>
<tbody>
<tr>
<td><strong>Function Change</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>23%</td>
<td>30%</td>
</tr>
<tr>
<td>Moderate</td>
<td>2%</td>
<td>2%</td>
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<tr>
<td>Severe</td>
<td></td>
<td>8%</td>
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<tr>
<td>Hypokinesis</td>
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<td>11%</td>
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<tr>
<td><strong>Coronary changes</strong></td>
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<td></td>
</tr>
<tr>
<td>Lack of tapering</td>
<td>47%</td>
<td>36%</td>
</tr>
<tr>
<td>Mild dilation</td>
<td>32%</td>
<td>26%</td>
</tr>
<tr>
<td>Moderate dilation</td>
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<td>6%</td>
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<tr>
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<td>8%</td>
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<tr>
<td><strong>AV valve regurgitation</strong></td>
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<td></td>
</tr>
<tr>
<td>Mitral</td>
<td>11%</td>
<td>23%</td>
</tr>
<tr>
<td>Tricuspid</td>
<td>8%</td>
<td>15%</td>
</tr>
<tr>
<td><strong>Pericardial effusion</strong></td>
<td></td>
<td>13%</td>
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</tbody>
</table>
The TCH experience

• ECG changes:
  • Early noted 1st degree AV block
    • Occasionally resulted in bradycardia
    • More common in teenagers
  • Borderline/long Qt interval
  • Ventricular arrhythmias

• Holter changes:
  • Bradycardia
  • Frequent PVCs
TCH experience - treatment

• Inotropes – 34%

• Anti-inflammatory treatment
  • Steroids- 94%
  • IVIg – 70%
  • Second IVIG – 15%
  • Anakinra – 38%

• Anticoagulation – 49%

• Anti-platelet – 42%
The TCH experience

• Invasive cardiac support:
  • ECMO
  • Impella

• Respiratory support (26%):
  • CPAP
  • BiPAP
  • Intubated

• Overall Los – 8 days

• ICU LOS – 7 days (earlier 9 days)

• Deaths - 0
### Discharge echocardiogram

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<table>
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<td><strong>Coronary changes</strong></td>
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<tr>
<td>Lack of tapering</td>
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<td>23%</td>
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</tbody>
</table>

35 echos were normal at discharge.
TCH experience- discharge treatment

• Steroid taper
• Anticoagulation
  • If ICU – lovenox
  • If KD like – aspirin
• Home oxygen
Cardiac Management Following Discharge

• Frequency depends on hospital course
  • Echo
  • ECG
  • Consider cardiac MRI
  • Consider repeat CT angiogram of the coronary
  • Ensure normalization of labs: troponin, BNP, CRP, d-dimer, ferritin, CBC with diff, hepatic panel, cholesterol panel until normalized
  • Measure COVID-19 IgG ~4-6 weeks after initial presentation
In Conclusion

• MIS-C is here (and likely here to stay)
• Increasing number of patients
• This is a team sport – Cardiology, EM, Hematology, Intensive Care, PHM, Rheumatology
• Cardiac involvement is primarily myocarditis
• Coronary arteries can be dilated
• Electrical activity of the heart is involved
• All patients need follow up