Multisystem Inflammatory Syndrome in Children (MIS-C) Associated with Coronavirus Disease 2019 (COVID-19)

Clinician Outreach and Communication Activity (COCA) Webinar

Tuesday, May 19, 2020
Continuing Education

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- Using the Webinar System
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  - Type your question in the Q&A box.
  - Submit your question.

- If we are unable to get to your question during the call, you may also email your question to coca@cdc.gov.

- For media questions, please contact CDC Media Relations at 404-639-3286, or send an email to media@cdc.gov.
For More Clinical Care Information on COVID-19

- **Call** COVID-19 Clinical Call Center at 770-488-7100 (24 hours/day).
- **Refer** patients to state and local health departments for COVID-19 testing and test results.
  - Clinicians should NOT refer patients to CDC to find out where or how to get tested for COVID-19, OR to get test results.
- **Visit** CDC’s Coronavirus (COVID-19) website: [https://www.cdc.gov/coronavirus](https://www.cdc.gov/coronavirus)
- **Visit** [emergency.cdc.gov/coca](https://emergency.cdc.gov/coca) over the next several days to learn about future COCA Calls.
Today’s Presenters

- **Sapna Bamrah Morris, MD, MBA (no slides)**
  Clinical Team Lead
  COVID-19 Response
  Centers for Disease Control and Prevention

- **Ermias Belay, MD (no slides)**
  Special Investigations Team Lead
  COVID-19 Response
  Centers for Disease Control and Prevention

- **Michael Levin, MBE, PhD, FRCPCH, FMedSci**
  Professor of Pediatrics & International Child Health
  Imperial College
  London, United Kingdom

- **James Schneider, MD, FAAP, FCCP**
  Chief, Pediatric Critical Care Medicine
  Associate Professor of Pediatrics
  Cohen Children’s Medical Center

- **Vincent C. Marconi, MD**
  Professor of Medicine and Global Health
  Emory University School of Medicine
  Rollins School of Public Health
Paediatric Inflammatory Multisystem Syndrome - Temporally associated with SARS-CoV-2 – PIMS-TS
In March 2020 as COVID19 evolved in UK, Paediatricians noticed unusual illness

- Severe illness admitted to paediatric ward, or PICU
- Varied presentations - prolonged fever, sore throat, headache, abdominal pain and vomiting, rash, conjunctivitis
- Some developed shock, organ dysfunction
- In common - ↑ CRP, ↑ Neutrophil, ↓ lymphocytes, ↑ D-Dimers
- Some - typical Kawasaki disease features
- Majority SARS-CoV-2 PCR negative

We collected 37 cases from 8 hospitals in England and systematically reviewed their clinical features.
Development of a case definition

• All cases reviewed by panel of infectious diseases clinicians
• Case note review, data collated on a data base
• Initial report only Included children admitted to HDU/PICU
• Exclusion of any other microbial cause, including bacterial sepsis, staphylococcal or streptococcal shock syndromes; infections associated with myocarditis such as enterovirus and Macrophage activation syndromes
• NHS UK alerted on 24 April emerging new disorder
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
38 cases identified between March 25 and May 1

Demographic features

Age	1 – 16 years
(Median 11 years)

Sex	62% male (23 /37)

Co-morbidities	1 asthma, 1 epilepsy

Location of reported cases
## Demographic Features

<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>PIMS-TS</th>
<th>London</th>
<th>England and Wales</th>
</tr>
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<tbody>
<tr>
<td>Black / African / Caribbean / British</td>
<td>46% (17/37)</td>
<td>13%</td>
<td>3%</td>
</tr>
<tr>
<td>White</td>
<td>19% (7/37)</td>
<td>60%</td>
<td>86%</td>
</tr>
<tr>
<td>Asian / Asian British</td>
<td>11% (4/37)</td>
<td>19%</td>
<td>8%</td>
</tr>
<tr>
<td>Mixed</td>
<td>5% (2/37)</td>
<td>5%</td>
<td>2%</td>
</tr>
<tr>
<td>Unknown</td>
<td>11% (4/37)</td>
<td></td>
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</tr>
</tbody>
</table>
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

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Number</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shock</td>
<td>28</td>
<td>75.7</td>
</tr>
<tr>
<td>Rash</td>
<td>20</td>
<td>54.1</td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>12</td>
<td>32.4</td>
</tr>
<tr>
<td>Mucus membrane Involvement</td>
<td>7</td>
<td>18.9</td>
</tr>
<tr>
<td>Swollen hands/feet</td>
<td>3</td>
<td>8.1</td>
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<tr>
<td>Abdominal pain</td>
<td>21</td>
<td>56.8</td>
</tr>
<tr>
<td>Syncope</td>
<td>1</td>
<td>2.7</td>
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<tr>
<td>Lymphadenopathy</td>
<td>4</td>
<td>10.8</td>
</tr>
<tr>
<td>Sore Throat</td>
<td>5</td>
<td>13.5</td>
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<tr>
<td>Neck Swelling</td>
<td>3</td>
<td>8.1</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>22</td>
<td>59.5</td>
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<tr>
<td>Vomiting</td>
<td>16</td>
<td>43.2</td>
</tr>
<tr>
<td>Respiratory symptoms</td>
<td>12</td>
<td>32.4</td>
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<tr>
<td>Cough</td>
<td>7</td>
<td>18.9</td>
</tr>
<tr>
<td>Oxygen requirement</td>
<td>19</td>
<td>51.4</td>
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<tr>
<td>Neurological symptoms</td>
<td>7</td>
<td>18.9</td>
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<tr>
<td>Headache</td>
<td>12</td>
<td>32.4</td>
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<tr>
<td>Meningism</td>
<td>2</td>
<td>5.4</td>
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<tr>
<td>Confusion</td>
<td>5</td>
<td>13.5</td>
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<tr>
<td>Myocardial Involvement</td>
<td>19</td>
<td>51.4</td>
</tr>
<tr>
<td>Coronary Artery Involvement</td>
<td>6</td>
<td>16.2</td>
</tr>
<tr>
<td>Proven Vasculitis</td>
<td>1</td>
<td>2.7</td>
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<tr>
<td>Thrombosis</td>
<td>1</td>
<td>2.7</td>
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<tr>
<td>Acute Kidney Injury</td>
<td>14</td>
<td>37.8</td>
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<tr>
<td>Renal replacement therapy</td>
<td>1</td>
<td>2.7</td>
</tr>
<tr>
<td>Peripheral Oedema</td>
<td>4</td>
<td>10.8</td>
</tr>
<tr>
<td>Ascites</td>
<td>9</td>
<td>24.3</td>
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### Laboratory Features

- **Lymphopaenia**
- **Neutrophilia**
- **Anaemia**
- **Raised D-dimer**
- **Raised Troponin**
- **Raised CRP**

<table>
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<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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<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>
<td>72-96</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>
</tr>
<tr>
<td></td>
<td></td>
<td></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>9.0</td>
<td>0.1-2.9</td>
<td>0.4-0.8</td>
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<td></td>
<td></td>
<td></td>
<td>&lt;1</td>
<td>80.0</td>
<td>29</td>
<td></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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<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>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&gt;100</td>
<td>60.0</td>
<td>18</td>
<td></td>
<td></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>
<td>25-7391</td>
<td>98-729</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>
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<tr>
<td>30</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>55.0</td>
<td>14</td>
<td>810</td>
<td>265-6660</td>
<td>420-1088</td>
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<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>

...
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
Echocardiography

19/25 at least 1 echo performed
08/19 significantly impaired ventricular function (SF% <28 or equivalent)
05/19 dilated coronaries or aneurysms

<table>
<thead>
<tr>
<th>LMCA mm (z)</th>
<th>LAD mm (z)</th>
<th>RCA mm (z)</th>
<th>comment</th>
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<tbody>
<tr>
<td>4.6 (+4.6)</td>
<td>8.0 (+15)</td>
<td>4.0 (+3.7)</td>
<td>Early echo had normal coronaries</td>
</tr>
<tr>
<td>(&lt;2.0)</td>
<td>(&lt;2.0)</td>
<td>(&lt;2.0)</td>
<td>uniformly dilated LMS to LAD coronary arteries</td>
</tr>
<tr>
<td>3.5 (+0.7)</td>
<td>3.7 (+4.2)</td>
<td>3.7 (+1.8)</td>
<td>dilated left circumflex</td>
</tr>
<tr>
<td>4.4 (+1.8)</td>
<td>6.8 (+12.5)</td>
<td>5.4 (+4.5)</td>
<td>diffuse coronary ectasia:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Severe coronary ectasia involving both right &amp; left coronary artery</td>
</tr>
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</table>

Echocardiographic findings for the 5 children with dilated coronary arteries
Management

- All admitted to HDU/PICU for supportive care
- All required fluid resuscitation
- Inotropes required for 26 (70%)
- 38% of children did not receive IVIG, just supportive care

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<th>TREATMENT</th>
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<th>%</th>
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<tr>
<td>Intravenous immunoglobulin (IVIG)</td>
<td>23</td>
<td>62.2</td>
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<tr>
<td>Corticosteroid</td>
<td>19</td>
<td>51.4</td>
</tr>
<tr>
<td>Anakinra</td>
<td>3</td>
<td>8.1</td>
</tr>
<tr>
<td>Toculizimab</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Infliximab</td>
<td>2</td>
<td>5.4</td>
</tr>
<tr>
<td>Remdesivir</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Lopinavir/ritonavir</td>
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<td>0.0</td>
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<tr>
<td>Hydroxychloroquine</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Azithromycin</td>
<td>4</td>
<td>10.8</td>
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</table>
Outcomes

- Majority respond to treatment
- NB – 1 child has been noted to have coronary artery dilatation at follow up ECHO, did not receive immunosuppression

<table>
<thead>
<tr>
<th>OUTCOME</th>
<th>n</th>
<th>%</th>
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<tbody>
<tr>
<td>Ventilatory support</td>
<td>25</td>
<td>67.6</td>
</tr>
<tr>
<td>ECMO</td>
<td>2</td>
<td>5.4</td>
</tr>
<tr>
<td>Death</td>
<td>1</td>
<td>2.70</td>
</tr>
<tr>
<td>Remain in PICU</td>
<td>7</td>
<td>19.0</td>
</tr>
<tr>
<td>Discharged from PICU</td>
<td>16</td>
<td>43.0</td>
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</table>
SARS-CoV-2 Results

• SARS-CoV-2 PCR –
  – 12 positive
  – 24 negative
  – 1 refused
• SARS-CoV-2 IgG
  – 19 positive total
  – 11 IgG pos, PCR neg
  – 5 IgG pos, PCR pos
  – 3 IgG neg, PCR neg
  – 18 not done, 7 PCR pos
• Total SARS-CoV-2 pos (PCR & IgG) is 23
What do these children have?
Illness similar to several conditions

• Kawasaki disease / KD shock syndrome syndrome
• Staphylococcal or streptococcal toxic shock syndrome
• HLH / Macrophage activation syndromes
• Haemorrhagic shock and encephalopathy syndrome
• SLE/Vasculitic disease
Comparison with Kawasaki disease & Kawasaki Shock syndrome

• Rady Children’s Hospital, San Diego; 2002 Jan to 2019 March

• Pre-IVIG were available from 1164 KD pts.
  – Excluding KD shock

• Pre-IVIG data were available from 45 KD shock pts

• Thanks for sharing data - Jane Burns, Chisato Shimizu, Emelia Bainto, Elizabeth Moreno, Nipha Sivilay
Conclusion from our review

New and unusual childhood illness - emerging a month behind the COVID19 curve in UK

Distinctive features from other syndromes
Troponin elevated, D Dimers elevated, High CRP, BNP elevated Prominent cardiac injury

What is this due to?
PIMS-TS appear to be a month behind the COVID-19 peak in the population

Laboratory Confirmed COVID-19 cases, London
Very few children with severe disease prior to these cases
Mechanism??

- Timing a month after COVID19 curve
- Majority negative for SARS-Cov2 Virus but positive for Antibody

- This suggests the illness is mediated by the development of acquired immunity rather than by direct viral injury
An emerging new spectrum of SARS-CoV2 in children - not just COVID

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
Urgent Research Question

• Do patients progress from the less severe to more serious categories? i.e., FIS-TS to KD TIS or PIMS-TS; or KD -TS to PIMS TS.

• What is the risk of Coronary artery aneurysms in each group?

• What is the relationship between KD-TS and KD prior to the pandemic?

• Do anti-inflammatory and immuno-modulating treatment such as immunoglobulin, steroids, anti-TNF, anti-IL1, anti-IL6 or T cell inhibition, or anticoagulation or anti platelets agents improve outcome and reduce risk of coronary artery aneurysms?

• What are the mechanisms or pathogenesis?

• Are there biomarkers to distinguish each group and COVID from other conditions?
Two studies for addressing these questions

• DIAMONDS enrolling patients in 11 EU countries with COVID, and SARSov2 associated inflammatory disorders; RNA transcriptome; proteomic and genetic comparison of each disease with other infectious and inflammatory diseases

• **Best available Therapy Study (BATS)** anonymized, multi-country study of best treatment for PIMS-TS;KD-TS,FI-TS.

• **Principle is online data collection of all patients.** Each clinician gives their best “guess” treatment. Study compares rates of normalization of Inflammatory markers, development of coronary artery aneurysms, time on ventilator or inotropes in patients propensity matched for severity at enrollment.

• **BATS** is possible because we have good biomarkers of disease severity (CRP, Ferritin, Troponin) and clear endpoints for outcome (CAA, ICU). International enrollment commencing this week.
We have so much to learn

We can only understand this new threat with collaboration and placing research at the heart of clinical care.
Acknowledgements
PIMS-TS COVIDHGE Patients

World map by www.freeworldmaps.net
<table>
<thead>
<tr>
<th>Country</th>
<th>Investigator</th>
<th>Site</th>
<th>Number of patients</th>
</tr>
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<tbody>
<tr>
<td>Canada</td>
<td>Catherine Biggs</td>
<td>UBC</td>
<td>5</td>
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<tr>
<td>Croatia</td>
<td>Alenka Gagro</td>
<td>Children's Hospital Zagreb</td>
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<tr>
<td>Israel</td>
<td>Danny Eytan</td>
<td>Rambam Medicat Ctr</td>
<td>3</td>
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<tr>
<td></td>
<td>Hagit Baris Feldman</td>
<td>Telaviv Sourasky Medical ctr</td>
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<tr>
<td>France</td>
<td>Paul Bastard</td>
<td>Institut IMAGINE</td>
<td>At least 15</td>
</tr>
<tr>
<td></td>
<td>JL Casanova</td>
<td></td>
<td></td>
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<tr>
<td>Belgium</td>
<td>Filomeen Haerynk Isabell Metys</td>
<td>University Gent</td>
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<td>Saleh Musen</td>
<td>King Saud University</td>
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<td>Spain</td>
<td>Aurora Pujol Onofre</td>
<td>IDIBELL-Hospital Duran i Reynals</td>
<td>5</td>
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<tr>
<td></td>
<td>Sergio Auilera Albesa</td>
<td>Navarra Hospital</td>
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<td>Pere Soler Palacin</td>
<td>Univ Hospital Vall d’Hebron</td>
<td>At least 10</td>
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<td>Sweden</td>
<td>Petter Brodin</td>
<td>Karolinska Institute</td>
<td>4?</td>
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Multisystem Inflammatory Syndrome in Children Associated with COVID-19

James Schneider, MD, FAAP, FCCP
Chief, Division of Pediatric Critical Care Medicine
Associate Professor of Pediatrics
Multisystem Inflammatory Syndrome in Children Associated with COVID-19

CCMC Initial Case Definition

**Fever** (≥38.0) ≥ 4 days + ANY of
- GI symptoms
  - Severe pain, v/d
  - Enteritis on imaging
- Rash
- Conjunctivitis
- Oral changes
- Cough
- Headache/irritability

**Inflammation**
- CRP
- Ferritin
- Troponin
- Pro-BNP

**Any of**

**Classical Kawasaki symptoms** OR

**Incomplete Kawasaki symptoms** (i.e., at least 3/6 of anemia, WBC > 15,000, Platelets > 450 or <100, Albumin < 3 g/dL, Elevated ALT, Sterile pyuria >10 WBC/hpf OR + echo (↓LVEF, CA dilation, valvitis)

**Cardiogenic and/or distributive shock with evidence of single or multi organ dysfunction** (e.g., Fluid refractory hypotension with + echo and/or AKI and/or liver injury and/or oxygen requirement)
Case Definition for Multisystem Inflammatory Syndrome in Children (MIS-C)

- An individual aged <21 years presenting with fever\(^1\), laboratory evidence of inflammation\(^1\), 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

\(^1\)Fever ≥38.0°C for ≥24 hours, or report of subjective fever lasting ≥24 hours

\(^1\)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

Additional comments

- Some individuals may fulfill full or partial criteria for Kawasaki disease but should be reported if they meet the case definition for MIS-C

- Consider MIS-C in any pediatric death with evidence of SARS-CoV-2 infection

https://emergency.cdc.gov/han/2020/han00432.asp
Accessed 5/18/20
CCMC Experience - Demographics

- Patients included: April 17 - May 13, 2020

- Patients Included: 33 (43 currently reported to NYS DOH)
- Age: 8.6 yr (Range: 2.2-17 yr)
- Gender: 61% male
- Race: Black 24%, Asian 9%, White 9%
- Ethnicity: Hispanic 27%
CCMC Experience- Clinical Characteristics

• No underlying medical conditions (excluding obesity): 79%
• Normal weight: 45%; Obese: 39%
• Reactive airway disease: 15%
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%
CCMC Experience- Hospital Course

- PICU Admission: 79%
- LOS: 4 dy (IQR 3, 6.5)
CCMC Experience - Initial Laboratory Results

- **WBC**: 9.1 K/uL
- **Absolute lymphocyte count**: 0.80
- **Lymphopenia**: 80%
- **Hemoglobin**: 11.2 g/dL
- **Platelets**: 154 K/uL
- **C-reactive protein**: 206 mg/L
- **D-dimer**: 1700 ng/mL
- **Fibrinogen**: 736 mg/dL
- **Ferritin**: 736 ng/mL
- **Lactate dehydrogenase**: 320 U/L
- **INR**: 1.31
- **Pro-BNP**: 3325 pg/mL
- **Troponin T**: 31 ng/L
- **Procalcitonin**: 12.05 ng/mL
- **Na**: 133 mmol/L
- **ALT**: 38 U/L
- **AST**: 54 U/L
- **Total bilirubin**: 0.5 mg/dL
- **Albumin**: 3.4 mg/dL

---

*Image from Cohen Children's Medical Center Northwell Health*
CCMC Experience - SARS-CoV-2 testing

- IgG (+) and PCR (+): 18%
- IgG (+) and PCR (-): 73%
- PCR (+) and IgG unavailable: 9%
CCMC Experience- Organ Involvement

- Acute liver injury: 21%
- AKI: 70%
- O2 or Positive Pressure: 52%
- Mechanical ventilation: 18%
- Intubation days: 3
CCMC Experience- Cardiac involvement

• Any coronary artery abnormalities: 48%
• LAD/RCA findings: Z-score 2-2.49: 9%; Z-score >2.5: 15%; lack of tapering (Z-score <2): 24%
• Any myocardial dysfunction: 58%
  • Mild: 33%
  • Moderate: 24%
  • Severe: 0%
CCMC Experience- Medications Used

• IVIG: 100%
  • 2nd dose: 30%
• Methylprednisolone: 70%
• Aspirin: 88%
• Anakinra: 12%
• Tocilizumab: 9%
• Infliximab: 3%
• Enoxaparin: 42%
CCMC Experience- Disposition

• Mortalities: 0
• Discharged alive: 82% (18% still hospitalized)
• Cardiac function at discharge:
  • Always normal: 42%
  • Depressed then normalized: 18%
  • Mildly depressed: 27%
IMMUNE MODULATORS FOR COVID-19

VINCENT MARCONI, MD

PROFESSOR OF MEDICINE AND GLOBAL HEALTH

EMORY UNIVERSITY SCHOOL OF MEDICINE

ROLLINS SCHOOL OF PUBLIC HEALTH

EMORY VACCINE CENTER
At the time this presentation was given, I have received support from Lilly, ViiV, Gilead and Bayer.

Vincent Marconi
IMMUNE MODULATORS

Canakinumab
IL-6 receptor
Sarilumab
Siltuximab
Tocilizumab

Extracellular
Macrophage
Helper T Cell
Dupilumab
Rituximab
Ustekinumab (IL-12/IL-23)
Guselkumab (IL-23)

COVID-19
- SARS-CoV-2 infection
- IL-1β, IL-6, IL-10, IL-8, IFN-α, IFN-β, IFN-γ, IL-12, IL-23, IL-26

Type I IFN
Tα1
Tα17
Tα2

Plasma cell
B cell

Cytokine release/storm
Recruits and stimulates macrophages, neutrophils, and monocytes

DNA Replication
Glucocorticoids
Cyclosporine
Tacrolimus
Antigen presentation & T-cell activation

Antigen Presenting Cell (APC)
**Tocilizumab Case Series in COVID-19**

<table>
<thead>
<tr>
<th>Pub</th>
<th>Demographics</th>
<th>Clinical</th>
<th>Treatment</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Luo <em>J Med Vir</em> 2020 China</td>
<td>15 patients 73y 80% Male</td>
<td>47% critical 40% serious 13% moderate IL6 115 pg/mL</td>
<td>80-600 mg x1.47 doses (33% 2+) Methylpred 53%</td>
<td>67% decreased IL6 20% died 80% inpt</td>
</tr>
<tr>
<td>Xu <em>PNAS</em> 2020 China</td>
<td>21 patients 57y 86% Male</td>
<td>19% critical 81% serious IL6 132 pg/mL</td>
<td>400 mg x1 dose LPV/r Methylpred</td>
<td>0% died 90% discharged</td>
</tr>
<tr>
<td>Pereira <em>Am J Transp</em> 2020 U.S.</td>
<td>14 patients 57 y 59% Male 6.6 y post-tran</td>
<td>30% severe 15% moderate</td>
<td>400 mg or 8 mg/kg (max 800 mg) x1 (additional doses) Antivirals+Methyl</td>
<td>24% died (overall) 54% discharged 6% readmit</td>
</tr>
</tbody>
</table>

**IL-6/R BLOCKADE**

**Agents:** sarilumab, siltuximab, sirukumab, tocilizumab

**Pros:** MCD, CA, RA, SoJIA, CAR-T CRS, GCA

**Cons:** Hypersensitivity, lipids, infections (RTI), rash, edema, IV/SC, Liver

**IL-6/R BLOCKADE Agents:**

- sarilumab
- siltuximab
- sirukumab
- tocilizumab

**Pros:** MCD, CA, RA, SoJIA, CAR-T CRS, GCA

**Cons:** Hypersensitivity, lipids, infections (RTI), rash, edema, IV/SC, Liver
IL-1 BLOCKADE

Agents: anakinra, canakinumab

Pros: Periodic fever syndromes, SoJIA MAS, SC 26d

Cons: HA, inj rxn, lipids, infections, cytopenias, cancer?, IV QID-SC daily

Anakinra for COVID-19 Hemophagocytic Syndrome

Dimopoulos Cell Host Microbe 2020
GM-CSF BLOCKADE

Agents: TJ003234, gimsilumab, lenzilumab, mavrilimumab, otiligimab, namilumab

Pros: Ank Spon, CAR-T cytokine storm, RA, MS, CMML, GVHD, Eos Asthma, Th17, CNS, Gut

Cons: HTN, Hypersensitivity, Alveolar Proteinosis, SOB, IV
**JAK BLOCKADE**

Agents: baricitinib, ruxolitinib

Pros: RA, MF, PCV, oral, renal (bari), multiple cytokines, antiviral activity?

Cons: infections, thrombosis, cytopenias, liver (rux)

---

**Adaptive COVID-19 Treatment Trial (ACTT)**

NIAID is supporting a randomized, controlled clinical trial to evaluate the safety and efficacy of the investigational antiviral remdesivir in hospitalized adults diagnosed with coronavirus disease 2019 (COVID-19). It will take place in up to 75 locations globally.

Remdesivir, developed by Gilead Sciences Inc., is an investigational broad-spectrum antiviral treatment. It was previously tested in humans with Ebola virus disease and has shown promise in animal models for treating Middle East respiratory syndrome (MERS) and severe acute respiratory syndrome (SARS), which are caused by other coronaviruses.

What does the study involve?

All potential participants will undergo a baseline physical exam...
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Overall</th>
<th>Sulfasalazine/</th>
<th>Budesonide</th>
<th>Oral/parenteral</th>
<th>6MP/azathioprine monotherapy</th>
<th>Methotrexate monotherapy</th>
<th>Anti-TNF without 6MP/AZA/MTX</th>
<th>Anti-TNF + 6MP/AZA/MTX</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>877</td>
<td>233</td>
<td>24</td>
<td>66</td>
<td>87</td>
<td>6</td>
<td>263</td>
<td>89</td>
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<tr>
<td>Outpatient</td>
<td>590</td>
<td>124</td>
<td>13</td>
<td>20</td>
<td>52</td>
<td>3</td>
<td>218</td>
<td>54</td>
</tr>
<tr>
<td>Hospitalized</td>
<td>285</td>
<td>109</td>
<td>11</td>
<td>45</td>
<td>35</td>
<td>0</td>
<td>44</td>
<td>35</td>
</tr>
<tr>
<td>ICU</td>
<td>55</td>
<td>24</td>
<td>3</td>
<td>13</td>
<td>7</td>
<td>0</td>
<td>6</td>
<td>10</td>
</tr>
<tr>
<td>Ventilator</td>
<td>44</td>
<td>25</td>
<td>3</td>
<td>9</td>
<td>6</td>
<td>0</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Death</td>
<td>30</td>
<td>25</td>
<td>1</td>
<td>7</td>
<td>6</td>
<td>0</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>(n, %)</td>
<td>6%</td>
<td>11%</td>
<td>4%</td>
<td>14%</td>
<td>7%</td>
<td>0%</td>
<td>1%</td>
<td>2%</td>
</tr>
<tr>
<td>Death (n, %)</td>
<td>3%</td>
<td>7%</td>
<td>4%</td>
<td>11%</td>
<td>1%</td>
<td>0%</td>
<td>2%</td>
<td>2%</td>
</tr>
</tbody>
</table>

**Outcomes from Patients with Inflammatory Bowel Disease Treated Prior to COVID-19 Diagnosis**

Feldmann Lancet 2020

**TNF BLOCKADE**

Agents: adalimumab, certolizumab, etanercept, infliximab

Pros: RA, IBD, psoriasis, CRS, Ank Spon, Kawasaki, sepsis, SC

Cons: cytopenia, infections, anaphyl, demyelin, cancer, IV

**TNF BLOCKADE**

Agents: adalimumab, certolizumab, etanercept, infliximab

Pros: RA, IBD, psoriasis, CRS, Ank Spon, Kawasaki, sepsis, SC

Cons: cytopenia, infections, anaphyl, demyelin, cancer, IV
CONCLUSIONS

- First large scale test of anti-inflammatory for deadly viral disease, caution for off-label use outside study
- Appear to reduce fever and cytokine storm but time to recovery and mortality data are lacking
- Unclear impact of virus control, secondary infections, thromboses or cytopenias for short term use
- More classes than can fit in 15 min, trials underway
- Steroids not recommended unless in a trial*

*NIH COVID 19 Clinical Guidelines [https://www.covid19treatmentguidelines.nih.gov/critical-care/]
Special thanks to all patients, staff and my family!

- Gary Krishnan
- Tony Laracuente
- Aneesh Mehta
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- Raymond Schinazi
- David Stephens
- Boghuma Titanji

- John Beigel
- Sushma Cribbs
- Randi Connor-Schuler
- Stephanie De Bono
- Greg Deye
- Cameron Durrant
- Monica Farley
- Christina Gavegnano
- Jane Guidot
- Telisha Harrison
- Mike Hart
- Priscilla Hsue

CREDITS
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- **Using the Webinar System**
  - Click on the **Q&A** button in the Zoom webinar system.
  - Type your question in the **Q&A** box.
  - Submit your question.
  - You may also email your question to **coca@cdc.gov**.

- For media questions, please contact CDC Media Relations at 404-639-3286 or email **media@cdc.gov**.

- **For more Clinical Care information on COVID-19**
  - **Call** COVID-19 Clinical Call Center at 770-488-7100 (24 hours/day).
  - **Refer** patients to state and local health departments for COVID-19 testing and test results.
    - Clinicians should NOT refer patients to CDC to find out where or how to get tested for COVID-19 OR to get test results.
  - **Visit** CDC’s Coronavirus (COVID-19) website: **https://www.cdc.gov/coronavirus**.
Today’s COCA Call Will Be Available On-Demand

**When:** A few hours after the live call

**What:** Video recording

**Where:** On the COCA Call webpage at
[https://emergency.cdc.gov/coca/calls/2020/callinfo_051920.asp](https://emergency.cdc.gov/coca/calls/2020/callinfo_051920.asp)

On COCA’s Facebook Page *immediately* after the live call at
[https://www.facebook.com/CDCClinicianOutreachAndCommunicationActivity/](https://www.facebook.com/CDCClinicianOutreachAndCommunicationActivity/)
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