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

Clinician Outreach and Communication Activity (COCA) Webinar

Thursday, July 16, 2020
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- **Refer** patients to state and local health departments for COVID-19 testing and test results.
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- **Visit** emergency.cdc.gov/coca over the next several days to learn about future COCA Calls.
Today’s Presenters

▪ Ermias Belay, MD
  MIS-C Team Lead
  COVID-19 Response
  Centers for Disease Control and Prevention

▪ Eva Cheung, MD
  Assistant Professor of Pediatrics – Divisions of Pediatric Cardiology and Critical Care Medicine
  Columbia University Irving Medical Center/NewYork-Presbyterian Morgan Stanley Children’s Hospital

▪ Matthew Oster, MD, MPH
  CDC COVID-19 Response, MIS-C Team
  Associate Professor of Pediatrics
  Children’s Healthcare of Atlanta, Sibley Heart Center
  Emory University School of Medicine

▪ Adriana Tremoulet, MD
  Professor of Pediatrics and Associate Director of the Kawasaki Disease Research Center
  University of California, San Diego and Rady Children’s Hospital San Diego
Multisystem Inflammatory Syndrome in Children (MIS-C)
Introduction

- MIS-C first reported in late April in the United Kingdom in association with COVID-19\(^1,2\)

- MIS-C presentations may include persistent fever, gastrointestinal, mucocutaneous, and cardiac signs and symptoms, and elevated inflammatory markers\(^3\)

- Some overlap with Kawasaki disease, toxic shock syndrome, and acute COVID-19\(^3\)

- On May 14, CDC published a Health Advisory along with a case definition and requested reporting of suspected MIS-C cases from jurisdictions\(^2\)


\(^2\)https://emergency.cdc.gov/han/2020/han00432.asp

\(^3\)https://www.cdc.gov/mis-c/index.html
Sex Distribution of MIS-C Cases Reported to CDC (N=342), as of 7/15/20*

*Suspected MIS-C cases with complete MIS-C case report forms submitted to CDC that met all MIS-C case inclusion criteria
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)**

*Suspected MIS-C cases with complete MIS-C case report forms submitted to CDC that met all MIS-C case inclusion criteria*
Race and Ethnicity Distribution of MIS-C Cases Reported to CDC (N=342), as of 7/15/20*

*Suspected MIS-C cases with complete MIS-C case report forms submitted to CDC that met all MIS-C case inclusion criteria
Proportion of MIS-C Patients Receiving Different Types of Treatment: Summary of 8 Published Studies
Acknowledgments

- Local and State Health Departments for their valuable assistance in investigating suspected MIS-C cases and reporting to CDC

- CDC MIS-C Team
  - Ermias Belay (Lead)
  - Shana Godfred Cato (Deputy)
  - Bobbi Bryant
  - Matt Oster
  - Joseph Y. Abrams
  - Emily Koumans
  - Laura Conklin
  - Jessica Leung
  - Emily Prezzato
For More Information

Please visit the CDC webpage on Multisystem Inflammatory Syndrome in Children (MIS-C):

https://www.cdc.gov/mis-c/hcp/

The findings and conclusions of this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.
Multi-system Inflammatory Syndrome in Children Related to COVID-19: Clinical Cases and Lessons Learned

Eva Cheung, MD
Assistant Professor of Pediatrics
Divisions of Pediatric Cardiology and Critical Care Medicine
Medical Director, Pediatric ECMO
July 16, 2020
Multisystem Inflammatory Syndrome in Children in New York State

DISCLAIMER: SINGLE INSTITUTION APPROACH AND EXPERIENCE
MIS-C at NYP Morgan Stanley Children’s Hospital of Columbia Irving Medical Center

• First case in April 2020
• As of July 1, 2020, ~60 cases admitted
  • ~60% admitted to the PICU for shock and vasoactive support
  • Pediatric Intensive Care Unit (PICU) admission before 5/9/20 = 70%, after 5/9/20 = 40%
• Majority with no prior co-morbidities (~90%)
• Male 46%, median age 7 years (range 2 mos. - 20yrs)
• Caucasian 30%, Black 28%, Hispanic 30%, Unknown 12%
Fatigue and lethargy for 4 days, decreased oral intake

Vomiting and diarrhea

No respiratory symptoms, no rash

Physical Exam: Tachycardic, hypotensive, dry mucous membranes, normal conjunctiva, no rash, soft abdomen, delayed capillary refill

ED: Placed on high-flow nasal cannula, IVF resuscitation and antibiotics given, started on dopamine for BP 50/40’s ➔ Transfer to PICU
 Admission Laboratory Data 1

- Bands 24%
- ALC 1 x10^3/uL
- Procalcitonin: 126.9 (≤ 0.08 ng/mL)
- C-Reactive Protein: >300 (≤ 10 mg/L)
- D-dimer: 1.39 (≤ 0.80 ug/mL)
- Ferritin: 1195 (≤ 400.0 ng/mL)
- HS-Troponin-T: 85 (≤ 22 ng/L)
- NT-ProBNP 44677 (≤ 327 pg/mL)

Blood culture: pending
SARS-CoV-2 PCR Not Detected
COVID-19 Serology Positive
Inflammatory and cardiac biomarkers trended up

Echo with new LAD aneurysm (z-score 5).

- IVIG 2g/kg
- Anakinra 100mg subQ daily x 5 days
- Methylprednisolone 20mg/kg once – prednisone taper

PICU Course:
- High-dose vasopressors for 6 days
- Ceftriaxone x 10 days (BCx neg)
- Improved creatinine with IVF hydration
- Enoxaparin prophylaxis
- HFNC/NIPPV respiratory support

Admission Echo:
- Normal LV function
- Trivial pericardial effusion
- Normal coronary arteries
Lessons Learned from Experience with MIS-C in NYC

- Cases with clinical shock (+/- cardiac dysfunction) improved with early institution of methylprednisolone
  - Epidemiologic context of COVID-19 and likelihood of MIS-C needs to be balanced with the likelihood of other causes of shock (e.g., bacterial sepsis, HLH)

- Standardized echo protocols to thoroughly and efficiently evaluate myocardial function and coronary arteries are needed for suspected MIS-C cases
  - Cardiac evaluation is suggested early upon admission, serially throughout hospitalization and after discharge (2 weeks, 6 weeks, 6 months and 1-year post-discharge)

- Inflammatory (e.g., C-reactive protein) and cardiac (troponin and NT-ProBNP) biomarkers should be trended, even in the recovery phase
3 year-old Male with 4 days of Fever and New Onset Rash

- Fever and abdominal pain for 4 days
- SARS-CoV-2 PCR+ at local urgent care center with known exposure to symptomatic COVID-19 positive family members one month ago
- No respiratory symptoms
- Physical Exam: Tachycardia, non-toxic appearing, normal conjunctiva, +cervical lymphadenopathy, macular rash on chest, hands and feet, soft abdomen, normal perfusion
- Admitted to general floor
Admission Laboratory Data 2

- Neut 75%
- Lymph 18%
- Procalcitonin: 1.27 (< 0.08 ng/mL)
- Ferritin: 178 (< 400.0 ng/mL)
- C-Reactive Protein: 75.4 (< 10 mg/L)
- D-dimer: 4.1 (< 0.80 ug/mL)

- NT-ProBNP 773 (< 327 pg/mL)
- HS-Troponin-T: <6 (< =22 ng/L)

- Blood culture: pending
- SARS-CoV-2 PCR Detected
- COVID-19 Serology Positive
3 year-old Male with 4 days of Fever and New Onset Rash

- Continued fever and rash the next day
- Echo: LV EF 55%, trivial pericardial effusion, normal coronary arteries
- Trended laboratory data …
  - C-reactive protein 75.4 → 140.4
  - Troponin-T < 6 → 39
  - NT-ProBNP 773 → 12463
- Methylprednisolone 2 mg/kg/day and IVIG 2 g/kg
- Afebrile, resolved rash and abdominal pain
- Discharged home 2 days later on ASA 81mg and prednisone taper
**CLASSIFICATION OF CLINICAL SEVERITY**

- **Mild:** No vasoactive requirement, minimal/no respiratory support, minimal organ injury
- **Moderate:** Vasoactive-inotropic score** (VIS) ≤ 10, significant supplemental oxygen requirement, mild or isolated organ injury
- **Severe:** Vasoactive-inotropic score > 10, non-invasive or invasive ventilatory support, moderate or severe organ injury including moderate to severe ventricular dysfunction

**See supplement for instructions on VIS calculation.**

<table>
<thead>
<tr>
<th>Therapeutic Category</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Steroid Initial Dosing</strong></td>
<td>Methylprednisolone 2mg/kg/day</td>
<td>Methylprednisolone 10mg/kg x1, then 2mg/kg/day</td>
<td>Methylprednisolone 20-30mg/kg/day for 1-3 days, then 2mg/kg/day</td>
</tr>
<tr>
<td>For 2mg/kg/day dosing: max 60mg/day</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>For pulse dosing: max 1g/day</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Other Immunomodulation</strong></td>
<td>Consider pulse Methylprednisolone or Anakinra if refractory illness course</td>
<td>Consider 1-3 days pulse Methylprednisolone, consider Anakinra if refractory to steroids</td>
<td>Consider Anakinra if refractory to steroids</td>
</tr>
<tr>
<td>(see “Other Management Considerations” below for specific guidance)</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>For Anakinra dosing: 2-10mg/kg/dose (max 100mg/dose) up to q6h frequency</td>
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<tr>
<td><strong>Anticoagulation</strong></td>
<td>LMWH prophylaxis or low-dose ASA</td>
<td>LMWH prophylaxis or low-dose ASA</td>
<td>LMWH prophylaxis or low-dose ASA</td>
</tr>
<tr>
<td>Monitor for bleeding, thrombocytopenia, coagulopathy</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>LMWH = low molecular-weight heparin</td>
<td></td>
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<tr>
<td>ASA = aspirin</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td><strong>Gastric prophylaxis with proton pump inhibitor</strong></td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Broad-spectrum antibiotics</strong> (see “Other Management Considerations” below for specific guidance)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Steroid Taper</strong></td>
<td>2-3 weeks</td>
<td>6-8 weeks</td>
<td>Steroid taper with subspecialty consultation</td>
</tr>
</tbody>
</table>
Lessons Learned from Experience with MIS-C in NYC

• General pediatricians and emergency rooms faced challenges in evaluating and triaging patients with “mild” MIS-C symptoms:
  • No symptoms of shock and normal EKG/Echo
  • Close clinical observation and trending of laboratory data indicated
  • Consider full MIS-C work up and treatment if meets American College of Rheumatology Clinical Guidance Criteria*

• “A few days of abdominal pain and low-grade fever but is better and asymptomatic now” – What do you do? Is this MIS-C?
  • Do you refer into the ER? (only if currently symptomatic or ill-appearing)
  • Do you refer for laboratory evaluation? (probably yes)
  • Do you refer for cardiology evaluation? (it depends)

**MIS-C Treatment and Outcomes at NYP Morgan Stanley Children’s Hospital of Columbia Irving Medical Center**

<table>
<thead>
<tr>
<th>TREATMENT</th>
<th>ALL PATIENTS</th>
<th>ADMIITTED to PICU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methylprednisolone AND IVIG</td>
<td>67%</td>
<td>81%</td>
</tr>
<tr>
<td>Methylprednisolone only</td>
<td>9%</td>
<td>13%</td>
</tr>
<tr>
<td>IVIG only</td>
<td>17%</td>
<td>3%</td>
</tr>
<tr>
<td>Supportive Treatment only</td>
<td>7%</td>
<td>3%</td>
</tr>
</tbody>
</table>

- No mechanical ventilation, no mechanical circulatory support, no mortality
- Median Hospital Length of Stay = 4 days (1-19 days)
- Post-discharge follow-up in 76% of patients (avg 22 days, range 11-62 days):
  - 95% Echo with normal function (1 with mild and 1 with moderate dysfunction)
- All with normal coronary arteries
Summary of Lessons Learned

• Single institutional evaluation/treatment protocol and experience – more research is needed to understand treatment variations of MIS-C and how it may impact outcomes.

• Strongly encourage a multi-disciplinary team and protocol to uniformly screen, diagnose and treat MIS-C catered to institutional resources and expertise.

• Access to cardiology and intensive care (if shock or cardiac dysfunction present) is an important part of evaluation and management of MIS-C.

• Multi-disciplinary follow-up at discharge is essential to both understand and monitor disease progression.
Clinical Management of Multisystem Inflammatory Syndrome in Children (MIS-C)

Matt Oster, MD, MPH
Disclosure

• This presentation represents work performed as part of my non-CDC duties

• The findings and conclusions in this presentation are those of the presenter and do not necessarily represent the official position of the Centers for Disease Control and Prevention
Survey

- Protocols for managing MIS-C at US institutions

- June 16 – July 6, 2020

- **Elements:**
  - Hospital Characteristics
  - Definition
  - Evaluation
  - Treatment
  - Follow-up
Participants

- 41 centers across the United States
- 35 with established protocols
Participants: Pediatric Beds

Number of centers

Pediatric Beds

>350

200-350

<200
Participants: Experience with MIS-C

Experience with MIS-C

- >25 patients
- 11-25 patients
- 6-10 patients
- 1-5 patients
- 0

Number of centers
Participants: Has Protocol Changed?

- Yes: 17 centers
- No: 16 centers
- Not sure: 0 centers

Number of centers
Case Definition for Multisystem Inflammatory Syndrome in Children (MIS-C)

- An individual aged <21 years presenting with fever\(^1\), laboratory evidence of inflammation\(^2\), 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

\(^2\)Including, but not limited to one or more; 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
Case Definition: Days of Fever

Days of Fever Required

Number of centers

0  5  10  15  20  25

1  2  3  4

Number of centers
Case Definition: Labs

- Labs Required?
  - Yes
  - No

- Number of Abnormal Labs Required
  - >4
  - 4
  - 3
  - 2
  - 1

Number of centers:
- Labs Required?
  - Yes
  - No

Number of centers:
- Number of Abnormal Labs Required
Case Definition: Minimum Organ Systems

Number of centers

Minimum Organ Systems Involved

<table>
<thead>
<tr>
<th>Number of centers</th>
<th>System Involved</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
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<tr>
<td>1</td>
<td>1</td>
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<td>2</td>
<td>2</td>
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<tr>
<td>3</td>
<td>3</td>
</tr>
</tbody>
</table>
Case Definition: COVID Link

• Most require either:
  – SARS-CoV-2 PCR or
  – SARS-CoV-2 Antibody or
  – Known exposure to someone with COVID

BUT: In hotspot areas, some centers work under the assumption that all are exposed, so this requirement is not necessary
Evaluation: Bloodwork

Common bloodwork

- CRP, ESR
- Ferritin, D-dimer
- CMP
- CBC

- Troponin, BNP/pro-BNP
- Coagulation tests
- Blood culture
- Respiratory viral panel
Evaluation: Other Tests

- Chest CT
- Abdominal CT
- Abdominal Ultrasound
- Echocardiogram
- ECG
- CXR

Number of centers
Evaluation: Consultants

- Rheumatology
- Nephrology
- Infectious Disease
- Hematology
- Cardiology

Number of centers (All patients)
Of the 38 centers using IVIG, 22 recommend a 2nd dose if refractory to 1st dose.

Definition of severity varied widely.
Treatment: Common Drugs

Aspirin

- Regardless of Severity
- Severe Cases
- Moderate Cases
- Mild Cases

Corticosteroids

- Regardless of Severity
- Severe Cases
- Moderate Cases
- Mild Cases

Heparin

- Regardless of Severity
- Severe Cases
- Moderate Cases
- Mild Cases
Treatment: For Severe Cases

- **Anakinra**
  - Regardless of Severity
    - Severe Cases
      - Number of centers: 20
    - Moderate Cases
      - Number of centers: 10
    - Mild Cases
      - Number of centers: 0

- **Vasopressors**
  - Regardless of Severity
    - Severe Cases
      - Number of centers: 30
    - Moderate Cases
      - Number of centers: 10
    - Mild Cases
      - Number of centers: 0
Treatment: Rarely Used

Reported by <20 centers

- Tocilizumab (11)
- Remdesivir (11)
- Warfarin (6)
- Clopidogrel (5)
- Hydroxychloroquine (1)
Follow-Up: Per AHA Kawasaki Guidelines?

- Yes: 17 centers
- No: 16 centers
- Not sure: 1 center

Number of centers
Follow-Up: Clinic Visits

- Cardiology: 40
- Infectious Disease: 20
- Rheumatology: 20
- Hematology: 10
- Nephrology: 0
- Other: 0
Conclusions

• Much variability in the evaluation and management of patients

• Common themes:
  – It takes a team approach
  – IVIG and aspirin are common regardless of severity Steroids are common in severe cases
  – Follow-up currently similar to Kawasaki guidelines

• Protocols change often, and care is often individualized
Acknowledgments

• Children’s Healthcare of Atlanta/Emory
  – Matthew Dove, MD
  – Preeti Jaggi, MD
  – Mike Kelleman, MS

• Participants at collaborating centers
American College of Rheumatology: Clinical Guidance for Pediatric Patients with MIS-C Associated with SARS-CoV-2 and Hyperinflammation in COVID-19

Adriana Tremoulet, MD, MAS
Associate Director, Kawasaki Disease Research Center
Professor, Dept. of Pediatrics, UCSD
Disclosure

- ACR provided stipend to task force members for participation
Clinical Guidance for Pediatric Patients

COVID-19 Clinical Guidance Summary for Pediatric Patients with Rheumatic Disease

The recommendations for pediatric rheumatology patients address various treatment options and provide general guidance, as well as direction for when to start, stop or reduce medications. Peer reviewed journal publication in progress, will be posted here when available.

Clinical Guidance Summary for Pediatric Patients with MIS-C Associated with SARS-CoV-2 and Hyperinflammation in COVID-19

The recommendations for MIS-C focus on general guidance, diagnostic evaluation, and therapy options, as well as comparing and contrasting the features of MIS-C and Kawasaki Disease. For hyperinflammation in COVID-19, the recommendations also focus on general guidance, as well as immunomodulatory treatment. Peer reviewed journal publication in progress, will be posted here when available.
Purpose & Methods

- **Goals:** Identify the most appropriate
  1. diagnostic and therapeutic steps for MIS-C
  2. Recommendations for children with hyperinflammation due to COVID-19 respiratory illness

- **ACR Task Force**
  - 9 pediatric rheumatologists
  - 2 adult rheumatologists
  - 2 pediatric cardiologists
  - 2 pediatric infectious disease specialists
  - 1 pediatric critical care physician
Purpose & Methods (continued)

- Consensus built on 2 rounds of anonymous voting
- Used existing case definitions of MIS-C
- Guidance reflects available evidence through late May 2020
Diagnostic Evaluation of MIS-C

Does the child have ALL of the following?
1) Fever >38°C
2) Epidemiologic link to SARS-CoV-2
3) At least 2 suggestive clinical features
   - Rash
   - Gastrointestinal symptoms
   - Edema of hands/feet
   - Oral mucosal changes
   - Conjunctivitis
   - Lymphadenopathy
   - Neurologic symptoms

Yes  No

Does the child have shock of unclear etiology?

Yes  No

Consider child under investigation for MIS-C.

Complete full diagnostic evaluation (Tier 1 & 2) for MIS-C.

Have other causes that could explain the presentation been considered in the evaluation?

Yes  No

Send Tier 1 Screening Evaluation:
- CBC, CMP, ESR, CRP, 
- SARS-CoV-2 PCR and/or serology

Do the results show ALL of the following?
1) CRP >5 mg/dL or ESR >40 mm/hr
2) At least 1 suggestive laboratory feature
   - ALC <1,000/mL
   - Platelet count <150,000/mL
   - Na <135 mmol/L
   - Neutropenia
   - Hypoalbuminemia

Yes  No

Send Tier 2 Complete Evaluation:
- BNP, Troponin T, procalcitonin, ferritin, PT, PTT, D-dimer, fibrinogen, LDH, via cytokine panel, triacylglycerols, SARS-CoV-2 serology, EKG, echocardiogram

Continue standard of care and monitor for MIS-C features, particularly if there is an epidemiologic link to SARS-CoV-2.
Diagnostic Evaluation of MIS-C (continued)

- Outpatient eval may be appropriate if stable vitals, reassuring exam and close f/u
- Considerations for admission:
  - Abnormal vitals (tachycardia)
  - Neurological deficits, AMS; renal/hepatic injury
  - Markedly elevated inflammatory markers
  - Abnormal EKG, BNP or troponin
- Management of MIS-C requires a multi-disciplinary approach
Comparing and Contrasting Features of MIS-C and KD

- Patients with Kawasaki disease (KD) unrelated to SARS-CoV-2 illness continue to require eval and treatment

- Differences between KD and MIS-C
  - Ethnic/racial differences
  - MIS-C patients are older, have more prominent GI/neuro sx, more cardiac dysfunction
  - Patients with MIS-C have lower platelet counts, lower absolute lymphocyte count and higher CRP
Cardiac Management of MIS-C

- AbnI BNP/troponin on admission should be trended until normal
- EKG every 48h while hospitalized; f/u at outpatient visits (2 and 6 weeks); if abnl then telemetry in hospital and Holter at f/u
- Echo at admission that includes ventricular function and coronary artery Z scores
- Echo at 2 and 6 week f/u
- Cardiac MRI at 2-6 months if LVEF<50%
Immunomodulatory Treatment in MIS-C

- Stepwise progression of therapies- first tier include low-dose steroids and/or IVIG
  - Consider cardiac function and fluid status with IVIG
  - Steroid taper should be over 3 weeks
- Other immunomodulatories include anakinra and higher dose steroids

[Infliximab- not mentioned but has been used]
Antiplatelet & anticoagulation therapy in MIS-C

- Low dose aspirin (3-5 mg/kg/day; max 81mg)
  - Continue until normal platelets/coronaries (~4 wks)
  - Avoid if platelet count <80,000
- If coronary artery Z-score >10, add anticoagulation therapy
- If EF<35%, consider enoxaparin until 2 wks after discharge
Consider immunomodulatory therapy in children with ARDS, shock, or significant inflammation

» Steroids and anakinra

» Tocilizumab (though may increase risk of bacterial and fungal infections)
For more information, contact CDC
1-800-CDC-INFO (232-4636)

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To Ask a Question

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**What:** Video recording

**Where:** On the COCA Call webpage at
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Date: Tuesday, August 4, 2020
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