Multi-system Inflammatory Syndrome in Children associated with COVID-19 (MIS-C)

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ECHO Series
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Disclosures

• Clinical investigator in Emory Children’s Center Vaccine Research Center (ECC-VRC) and Vaccine Treatment and Evaluation Unit (VTEU)
  – Institution has received funds to conduct clinical research unrelated to this talk from BioFire Inc, GSK, Janssen, MedImmune, Micron, Merck, Moderna, Novavax, PaxVax, Pfizer, Regeneron, Sanofi-Pasteur

• Co-inventor of patented RSV vaccine technology unrelated to this talk, which has been licensed to Meissa Vaccines, Inc.
Overview

• Background: COVID-19 and emergence of MIS-C in children
• Epidemiology
• Pathogenesis
• Clinical & Laboratory features
  – Unusual associations/complications
• Distinguishing from other clinical entities
• Patient management
• Clinical outcomes
  – Short and Long-term
• Follow-up care
COVID-19 in children

COVID-19 Weekly Cases per 100,000 Population by Age Group, United States

March 1, 2020 - May 24, 2021

Age Group
- 0 - 5 Years
- 6 - 13 Years
- 14 - 17 Years
- 18 - 24 Years
- 25 - 34 Years
- 35 - 54 Years
- 55 - 64 Years
- 65 - 79 Years
- 80+ Years

Percentage of records reporting: Age = 99.31%

US territories are included in case and death counts but not in population counts. Potential two-week delay in case reporting to CDC denoted by gray box.

*Case Earliest Date is the earliest of the clinical date (related to illness or specimen collection) and the Date Received by CDC.

Source: CDC COVID-19 Case Line-Level Data, 2019 US Census, HHS Protect; Visualization: Data, Analytics & Visualization Task Force and CDC CPR DRO Situational Awareness Public
# COVID-19 in children

## Risk for COVID-19 Infection, Hospitalization, and Death By Age Group

| Rate compared to 5–17 years old | 0–4 years old | 5–17 years old | 18–29 years old | 30–39 years old | 40–49 years old | 50–64 years old | 65–74 years old | 75–84 years old | 85+ years old |
|---------------------------------|--------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|---------------|--------------|
| **Cases**<sup>2</sup>           | <1x          | Reference group | 2x             | 2x             | 2x             | 2x             | 1x             | 1x             | 2x            |
| **Hospitalization**<sup>3</sup> | 2x           | Reference group | 6x             | 10x            | 15x            | 25x            | 40x            | 65x            | 95x           |
| **Death**<sup>4</sup>           | 1x           | Reference group | 10x            | 45x            | 130x           | 440x           | 1300x          | 3200x          | 8700x         |

All rates are relative to the 5–17-year-old age category. Sample interpretation: Compared with 5–17 year-olds, the rate of death is 45 times higher in 30–39 year-olds and 8,700 times higher in 85+ year-olds.

## How to Slow the Spread of COVID-19

- Wear a mask
- Stay 6 feet apart
- Avoid crowds and poorly ventilated spaces
- Wash your hands

[cdc.gov/coronavirus](https://www.cdc.gov/coronavirus)
A Novel Hyperinflammatory Syndrome

Hyperinflammatory shock in children during COVID-19 pandemic

South Thames Retrieval Service in London, UK, provides paediatric intensive care support and retrieval to 2 million children in South East England. During a period of 10 days in mid-April, 2020, we noted an unprecedented cluster of eight children with hyperinflammatory shock, showing features similar to atypical Kawasaki disease, Kawasaki disease shock syndrome, or toxic shock syndrome (typical n two children per week formed the basis of a All children were p well. Six of the child Caribbean descent, children were boys. A one were well above

Journal of the Pediatric Infectious Diseases Society

Multisystem Inflammatory Syndrome in Children During the Coronavirus 2019 Pandemic: A Case Series

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ORIGINAL RESEARCH ARTICLE

Acute Heart Failure in Multisystem Inflammatory Syndrome in Children in the Context of COVID-19 Pandemic

Zahra Behzad, MD, Mathilde Mest, MD, Fanny Bajolle, MD, PhD, Diaa Khaire, MD, Antoine Lagendro, MD, Samya Aabak, MD, Johanne Arai, MD, PhD, Marion Grimaud, MD, Mehdi Ouaela, MD, PhD, Maurice Begehli, MD, PhD, Julie Wecker, MD, Caroline Ovaert, MD, PhD, Sebastien Haceo, MD, Mathieu Selegny, MD, Sophie Maszkadeh-Milani, MD, Alice Mallev, MD, Gilles Bossard, MD, PhD, Nathan Ginoux, MD, Laurent Bonnemains, MD, PhD, Jeannine Bocard, MD, PhD, Sylvie Di Capu, MD, PhD, Pierre Maurin, MD, PhD, Sylvie Falcon-Eichler, MD, Jean-Benoît Thambo, MD, PhD, Bruno Lefort, MD, PhD, Pamela Moceri, MD, PhD, Lucile Hougel, MD, PhD, Sylvain Renotteau, MD, PhD, and Damien Bonnet, MD, PhD

Journal of the Pediatric Infectious Diseases Society

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

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The disease at the Italian nic: an observational cohort study

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

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

\begin{itemize}
  \item \textsuperscript{i}Fever \(>38.0^\circ\text{C}\) for \(\geq 24\) hours, or report of subjective fever lasting \(\geq 24\) hours
  \item \textsuperscript{ii}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
\end{itemize}
MIS-C Epidemiology

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

TOTAL MIS-C PATIENTS MEETING CASE DEFINITION*

3742

TOTAL MIS-C DEATHS MEETING CASE DEFINITION

35

https://www.cdc.gov/mis-c/cases/index.html
MIS-C Geographic Distribution

Reported MIS-C Cases

- No case reported
- 25-49 cases
- 100-149 cases
- 300+ cases
- 1-24 cases
- 50-99 cases
- 150-199 cases

https://www.cdc.gov/mis-c/cases/index.html
MIS-C Epidemiology

MIS-C Patients by Race & Ethnicity

MIS-C Patients by Age Group

MIS-C Patients by Sex

https://www.cdc.gov/mis-c/cases/index.html
MIS-C Pathophysiology

- Systemic hyperinflammatory syndrome following SARS-CoV-2 infection by 2-6 weeks
  - Serology is consistent with early convalescence\(^1\)
  - Marked, transient hypercytokinemia characterized by pro-inflammatory cytokines, chemotaxis and activated immune cells\(^1\)
- Immune profile appears similar, but distinct from Kawasaki Disease\(^2\)
- Unclear trigger of hyperinflammation; hypotheses include:
  - Viral persistence in gastrointestinal or other sites\(^3\)
  - Superantigen potential of spike protein\(^4\)
  - Autoantibodies of pathogenic potential\(^2\)

MIS-C Pathophysiology: Plausible Mechanism?

MIS-C Clinical Features

A Cardiovascular Involvement

B Noncardiovascular Involvement

C Overlap in Organ-System Involvement

MIS-C Clinical Features


Multisystem Inflammatory Syndrome in U.S. Children and Adolescents

Other Clinical Features/Associations

• Neuro: Altered mental status, hallucinations, psychosis, aseptic meningitis, stroke
• Third spacing: Pleural effusions, pericardial effusions, free fluid in abdomen
• Acute abdomen, appendicitis, mesenteric adenitis
• Deep venous thrombosis
• Neck pain/meningismus
• Diabetes and DKA
• Acute pancreatitis
MIS-C Clinical Phenotypes

Positive SARS-CoV-2 Abs / Neg PCR (98%)
High prevalence of multiorgan (>6) involvement
   Cardiovascular (100%) & GI (97.5%) involvement
   + Shock, myocarditis, elevated troponin, CRP, BNP

Class 1
n=203 (35.6%)

Class 2
N=169 (29.6%)

Mixed, positive SARS-CoV-2 Abs and PCR
Younger children (median age 6 yrs)
   Overlapping features with Kawasaki Disease
   + Mucocutaneous lesions
   Lesser organ involvement and systemic inflammation

Class 3
n=198 (34.7%)

Positive SARS-CoV-2 PCR / Neg Abs (84%)
High respiratory involvement:
   + Cough, pneumonia, ARDS

# Distinguishing MIS-C from Kawasaki Disease

<table>
<thead>
<tr>
<th>Prominent Features</th>
<th>MIS-C</th>
<th>Kawasaki</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (median)</strong></td>
<td>9 years</td>
<td>3 years</td>
</tr>
<tr>
<td><strong>Recent COVID-19 illness/exposure</strong></td>
<td>+</td>
<td>+/-</td>
</tr>
<tr>
<td><strong>Positive SARS-CoV-2 IgG or PCR</strong></td>
<td>+</td>
<td>+/-</td>
</tr>
<tr>
<td><strong>Symptoms</strong></td>
<td>Prominent abdominal pain</td>
<td>Prominent mucocutaneous symptoms</td>
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<tr>
<td><strong>Cardiac involvement</strong></td>
<td>Myocardial dysfunction</td>
<td>Coronary artery aneurysms</td>
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<tr>
<td></td>
<td>Shock</td>
<td></td>
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<tr>
<td></td>
<td>Pericardial effusion</td>
<td></td>
</tr>
<tr>
<td><strong>Laboratory features</strong></td>
<td>Thrombocytopenia</td>
<td>Thrombocytosis (after day 7 of fever)</td>
</tr>
<tr>
<td></td>
<td>Lymphopenia</td>
<td></td>
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<tr>
<td></td>
<td>Hyponatremia</td>
<td></td>
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<tr>
<td></td>
<td>Elevated creatinine</td>
<td></td>
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<tr>
<td></td>
<td>Elevated troponin</td>
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</tr>
</tbody>
</table>

MIS-C Management: Diagnostic Testing

- EKG and echocardiogram
- SARS-CoV-2 RT-PCR and IgG
- CBCd, CMP
- ESR, CRP, DIC screen, ferritin
- Troponin, BNP
- Blood culture
- Urinalysis with reflex to culture
- Other infectious work-up*
MIS-C Management: Treatments & Interventions

• Isolation considerations
• Respiratory and circulatory support
• Antibiotics if concern for sepsis
• Anti-inflammatory
  – Systemic corticosteroids, IVIG, immunomodulators (IL-1β inhibitor anakinra, others)
• Anti-coagulation for VTE prophylaxis based on risk
• Anti-platelet: Aspirin 3-5 mg/kg (max 81 mg) daily
• Gastric protection: Famotidine
MIS-C Management: Stepwise treatment

- Substantial variability from center-to-center
- Limited evidence available
- Treatments can have risks/adverse effects
- Evidence that IVIG alone is inferior to IVIG + steroids
- Our approach:
  - Steroids for all
  - Add IVIG for severe disease or KD features
  - Consider pulse steroids vs. anakinra for refractory disease


MIS-C Follow-up & Care

• Aspirin 3-5 mg/kg (max 81 mg) daily x 4-6 weeks
  – Flu vaccine if during influenza season
• Repeat echocardiogram and Cardiology follow-up in 2 weeks and 4-6 weeks
  – Activity restriction until cleared by Cardiology
• Rheumatology follow-up if patient had refractory disease
MIS-C Short-term outcomes

- Median duration of hospitalization = 6 days
- ICU: 63.9%
- Vasopressor requirement: 41.9%
- Mechanical ventilation: 13.1%
- Any respiratory support: 38.1%
- Death: 1.8%
- Risk factors for ICU Admission: Age > 8 years, non-Hispanic Black patients, respiratory involvement, GI symptoms

MIS-C Longitudinal Outcomes

• Longitudinal outcomes are generally good with minimal end-organ involvement

MIS-C Outcomes at 6 months

• Neurological (of n=46)
  – Abnormal neurologic exams (n=18)
  – Dysmetria (n=12)
  – Hyperreflexia (n=9)
  – Proximal myopathy or lower limb weakness (n=8)
  – Abnormal eye movements or saccades (n=7)
  – Difficulty in tandem walking (n=4)
  – Abnormal posturing (n=3)
  – Hyporeflexia (n=2)
  – Upgoing plantars (n=2)
  – Sensory abnormalities (n=2)
  – Facial weakness (n=1)
  – Uper limb weakness (n=1)

• Renal:
  – 4 (10%) of 42 patients had raised blood pressure >95th %-ile

• Gastrointestinal:
  – 6 (13%) of 46 patients had persistent GI symptoms

• ENT:
  – 4 (9%) of 46 had dysphonia
  – 2 (4%) of 46 had anosmia or dysgeusia

• Aerobic capacity/endurance:
  – 18 (45%) of 40 children had 6-min walk test results <3rd %ile

• Health-related quality of life:
  – 7 (18%) of 38 had severe emotional difficulties by parental report in PedsQL
  – 8 (22%) of 38 by self-report in PedsQL
Conclusions

• MIS-C is a rare but severe inflammatory syndrome that typically follows SARS-CoV-2 infection by 2-6 weeks
• Characterized by marked systemic inflammation, GI and cardiac involvement
• Treated with corticosteroids, IVIG, and/or immunomodulatory medications, VTE prophylaxis and aspirin
• Short-term outcomes are generally good
• Long-term complications include subtle neurologic findings, de-conditioning, and emotional difficulties
• Future research is needed to better define distinguishing clinical features, prognostic variables, and optimal treatment regimens for short- and long-term outcomes
References

• CDC Health Alert Network, May 14, 2020.
• https://www.cdc.gov/mis-c/cases/index.html