COVID-19 Associated Multisystem Inflammatory Syndrome (MIS-C) in Children: Overview & the Nemours/AIDHC Experience

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End of 2019, first reports of novel coronavirus in Wuhan, China

February 2020, WHO designated disease as COVID-19

March 11, 2020, WHO declares COVID-19 a pandemic

April 24, 2020, Reports out of UK of increase of KD-like illness in children

End of April, 2020, MIS-C coined

May, 2020, CDC & WHO issue health advisory with case definitions
MIS-C Acute COVID-19 Infection Myocarditis Toxie Shock Syndrome Kawasaki Disease Secondary HLH/MAS
Pathogenesis of MIS-C

Nakra NA et al. Children 2020, 7,69
Fig. 1 | Pathogenesis of multisystem inflammatory syndrome in children: a hypothesis.

Rowley AH, Nature Reviews, 2020
Multisystem Inflammatory Syndrome in Children (MIS-C)

- Fever
- Myalgia
- Conjunctivitis
- Rash, Lymphadenopathy, Stomatitis
- Extremity swelling with erythema
- Skin peeling

Lab evidence of current or past infection with SARS-CoV-2

- Nausea
- Vomiting
- Abd pain
- Diarrhea
- ↑AST/ALT

- Headache
- Meningismus
- Lethargy

- High ESR, CRP, ferritin, LDH, IL-6, Fibrinogen, Procalcitonin, CPK, D-dimers etc.

- Myocarditis, ↑Troponin, ↑pro-BNP
- Coronary aneurysms, Hypotension
- Hypoperfusion, Tachycardia

- Hypoxemia
- Pulmonary infiltrates
- Chest pain

- Thrombocytopenia
- Neutrophilia
- Lymphopenia

- Hyponatremia
- Renal failure

Nakra NA et al. *Children* 2020, 7,69
Clinical Spectrum of Disease of Acute COVID-19 & COVID-19 Associated Multisystem Inflammatory Syndrome in Children (MIS-C)

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<td>In most children, COVID-19 causes no or only mild symptoms.</td>
<td>Some children may present with persistent fevers and mild symptoms (eg, headache, fatigue). Inflammatory markers (especially ferritin) may be elevated, but signs of multisystem involvement are lacking.</td>
<td>Some children meet criteria for complete or incomplete KD and do not develop shock and multisystem involvement.</td>
<td>Children with MIS-C have a more severe presentation, with markedly elevated inflammatory markers and multisystem involvement. Cardiac involvement and shock are common.</td>
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Adapted from Son MBF & Friedman K, © 2020 UpToDate, Inc. and/or its affiliates
Case Definition for Multisystem Inflammatory Syndrome in Children (MIS-C)

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

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

\(^i\)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

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
World Health Organization (WHO) Case Definition for MIS-C

**Preliminary case definition[a]**

Children and adolescents 0–19 years of age with fever >3 days

**AND** two of the following:

1. Rash or bilateral non-purulent conjunctivitis or muco-cutaneous inflammation signs (oral, hands or feet).
2. Hypotension or shock.
3. Features of myocardial dysfunction, pericarditis, valvulitis, or coronary abnormalities (including ECHO findings or elevated Troponin/NT-proBNP),
4. Evidence of coagulopathy (by PT, PTT, elevated d-Dimers).
5. Acute gastrointestinal problems (diarrhoea, vomiting, or abdominal pain).

**AND**

Elevated markers of inflammation such as ESR, C-reactive protein, or procalcitonin.

**AND**

No other obvious microbial cause of inflammation, including bacterial sepsis, staphylococcal or streptococcal shock syndromes.

**AND**

Evidence of COVID-19 (RT-PCR, antigen test or serology positive), or likely contact with patients with COVID-19.
SARS-CoV-2 (-)
SARS-CoV-2 (+)
MIS-C

Yonker et al. Journal of Peds, 2020
186 patients with MIS-C
62% male, median age 8.3 years; <1 yr (13%), 1-4 yrs (28%), 5-9 yrs (25%), 10-14 yrs (24%), 15-20 (16%)
Black, non-Hispanic :25%, Hispanic or Latino: 31%
73% previously healthy, 27% w/at least one underlying condition-> 29% with obesity
71% with 4 or more organ systems involved
70% had positive SARS-CoV-2 testing; PCR=56%, IgG Ab=44%
29% with epidemiologic link to person with COVID-19
4 patients (2%) died
A Cardiovascular Involvement

The Natural History of Severe Acute Respiratory Syndrome Coronavirus 2–Related Multisystem Inflammatory Syndrome in Children: A Systematic Review

Stephen C. Aronoff,1,2 Ashleigh Hall,1 and Michael T. Del Vecchio1

1Department of Pediatrics, Lewis Katz School of Medicine, Temple University, Philadelphia, Pennsylvania, USA; and 2St Christopher’s Hospital for Children, Philadelphia, Pennsylvania, USA

• Case reports & series recovered from MEDLINE searches performed between June 3 and July 23, 2020
• 10 articles; 16 reports describing 505 children with MIS-C
• Clinical findings: 100% fever (part of inclusion criteria), 88% gastrointestinal symptoms, 59.2% rash, 50% conjunctivitis, 56% chelitis/strawberry tongue, 47.5% extremity edema/erythema
• Major complications: 57% myocardial dysfunction, 5.3% plus ECMO, 26% mechanical ventilation, 12% acute kidney injury, 1.4% died
Discriminating MIS-C Requiring Treatment from Common Febrile Conditions in Outpatient Settings

Rebecca F. Carlin, MD • Avital M. Fischer, MD • Zachary Pitkowsky, BA • ... Melissa S. Stockwell, MD, MPH • Brett R. Anderson, MD, MBA, MS • Mark Gorelik, MD

Published: October 13, 2020 • DOI: https://doi.org/10.1016/j.jpeds.2020.10.013
Latest CDC Data

Last updated October 30, 2020

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<th>TOTAL CONFIRMED CASES*</th>
<th>TOTAL DEATHS</th>
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<td>1,163</td>
<td>20</td>
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*Confirmed cases were reported in 44 states, New York City, and Washington, DC. Additional cases are under investigation.

Summary

- Most cases are in children and adolescents between the ages of 1 and 14 years, with an average age of 8 years.
- Cases have occurred in children and adolescents from <1 year old to 20 years old.
- More than 75% of reported cases have occurred in children who are Hispanic or Latino (412 cases) or Black, Non-Hispanic (369 cases).
- 98% of cases (1,145) tested positive for SARS CoV-2, the virus that causes COVID-19. The remaining 2% were around someone with COVID-19.
- Most children developed MIS-C 2-4 weeks after infection with SARS-CoV-2.
- Slightly more than half (56%) of reported cases were male.
Multisystem Inflammatory Syndrome in Children (MIS-C) & The Nemours/AIDHC Experience

- April 12, 2020: First patient treated at AIDHC; initially diagnosed with rheumatic fever vs. Kawasaki Disease (KD)
- April 24, 2020: First reports KD-like inflammatory syndrome from the United Kingdom; our patient diagnosis changed to MIS-C & confirmed based on antibody testing
- Since April, between nearly 100 patients “evaluated” for MIS-C; total of 20 patients diagnosed & treated with MIS-C; one outpatient
- Presentation of patients varied: 5 mos-16 yrs of age, majority older children or adolescents; mostly males, African American or Latinx/Hispanic; ranged from mild to critically ill; Good outcomes with no deaths or serious morbidities
- Multidisciplinary approach (Infectious Diseases, Cardiology, Rheumatology, Critical Care, Hospitalist Medicine, Emergency Medicine, Hematology, Pharmacy); formation of clinical pathway & multiple research studies
Diagnoses that have been mistaken for MIS-C

- Sepsis
- Shock
- Focal bacterial infections
  - Musculoskeletal Infections
  - Community acquired pneumonia
  - Urinary tract infections
- Lyme Disease
- Acute viral infections
- Inflammatory bowel disease (Crohn’s disease)
Cardiac Manifestation

- **Myocardial Dysfunction/Ventricular Dysfunction**
  - 35-100% in reported case series
  - Pancarditis
  - Left ventricular systolic dysfunction
  - Low ejection fraction
  - Mitral regurgitation
  - Pericardial effusion
  - Heart failure

- **Coronary Involvement**
  - 6-24% in reported case series
  - Mild ectasia/dilation
  - Aneurysms

- **Arrhythmia**
  - 7-60% in reported cases series
  - ST segment changes
  - QTc prolongation
  - Premature atrial or ventricular beats
  - First- and second-degree AV blocks
  - Atrial fibrillation
  - Sustained arrhythmias leading to hemodynamic collapse & ECMO

Sperotto at. European Journal of Peds, 2020
Long-Term Cardiac Effects

- Longitudinal study showed significant improvement in patient with left ventricular dysfunction within 30-day follow-up period
- However, some had residual low-normal function at 4-6 weeks follow-up
- Medium and long-term follow likely needed
- May need multiple modalities to evaluate
  - Echocardiography
  - Cardiac CT and MRI
- Considerations for return to sports

Jhaveri et al. Journal of Peds, 2020
Treatment

- Immunomodulation
  - Intravenous Immunoglobulin
  - Corticosteroids
  - Biologics: anakinra, tocilizumab
- Antiplatelet and anticoagulation
  - Aspirin
  - Enoxaparin
- Antiviral therapy?
  - Remdesivir
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<tr>
<th>Medication</th>
<th>Mild Disease (Meets MIS-C definition and mildly ill appearing)</th>
<th>Moderate Disease (Meets MIS-C definition and ill appearing without hemodynamic instability)</th>
<th>Severe Disease (Meets MIS-C definition and critically ill with hemodynamic instability)</th>
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<td>Methylprednisolone</td>
<td>Consider not treating with steroids and start high dose aspirin.</td>
<td>Start 1 mg/kg/dose BID (no max dose).</td>
<td>Start pulse dose regimen: 30 mg/kg/dose once daily for 3 days (max 1 g/day). Consult rheumatology for steroid taper.</td>
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<td>Aspirin</td>
<td>Consider high dose aspirin (80 mg/kg/day divided three times daily) if not using steroids. Switch to low dose (3-5 mg/kg/day once daily) 48 hours after afebrile and continue at discharge.</td>
<td>Start low dose aspirin (3-5 mg/kg/day once daily) -OR- prophylactic enoxaparin (dosed/monitored per AIDHC protocol). If on prophylactic enoxaparin, switch to low dose aspirin at discharge.</td>
<td>Initiate low dose aspirin (3-5 mg/kg/day once daily) 2-3 days prior to stopping enoxaparin (refer to enoxaparin section below) and continue at discharge.</td>
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<td>IVIG (Privigen 10%)</td>
<td>First dose: 2 g/kg (max 150 g). If second dose is approved, repeat 2 g/kg (max 100 g).</td>
<td>First dose: 2 g/kg (max 160 g). If second dose is approved, repeat 2 g/kg (max 100 g).</td>
<td>First dose: 2 g/kg (max 160 g). If second dose is approved, repeat 2 g/kg (max 100 g).</td>
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<tr>
<td>Enoxaparin</td>
<td>N/A</td>
<td>Start prophylactic enoxaparin (dosed/monitored per AIDHC protocol) -OR- low dose aspirin (3-5 mg/kg/day once daily). If on prophylactic enoxaparin, switch to low dose aspirin at discharge.</td>
<td>Start prophylactic enoxaparin (dosed/monitored per AIDHC protocol) and consult hematology for further guidance.</td>
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<td>Anakinra/Tocilizumab</td>
<td>Consider if resistant to initial treatment with IVIG/steroids. Consult rheumatology for dosing guidance.</td>
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<td>Remdesivir</td>
<td>To be used on a case-by-case basis. Consult ID for medication procurement and dosing guidance.</td>
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Case Series of Multisystem Inflammatory Syndrome in Adults Associated with SARS-CoV-2 Infection — United Kingdom and United States, March–August 2020

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