



EMORY  
UNIVERSITY

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

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**ECHO Series**

**June 3, 2021**



# Disclosures

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- 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

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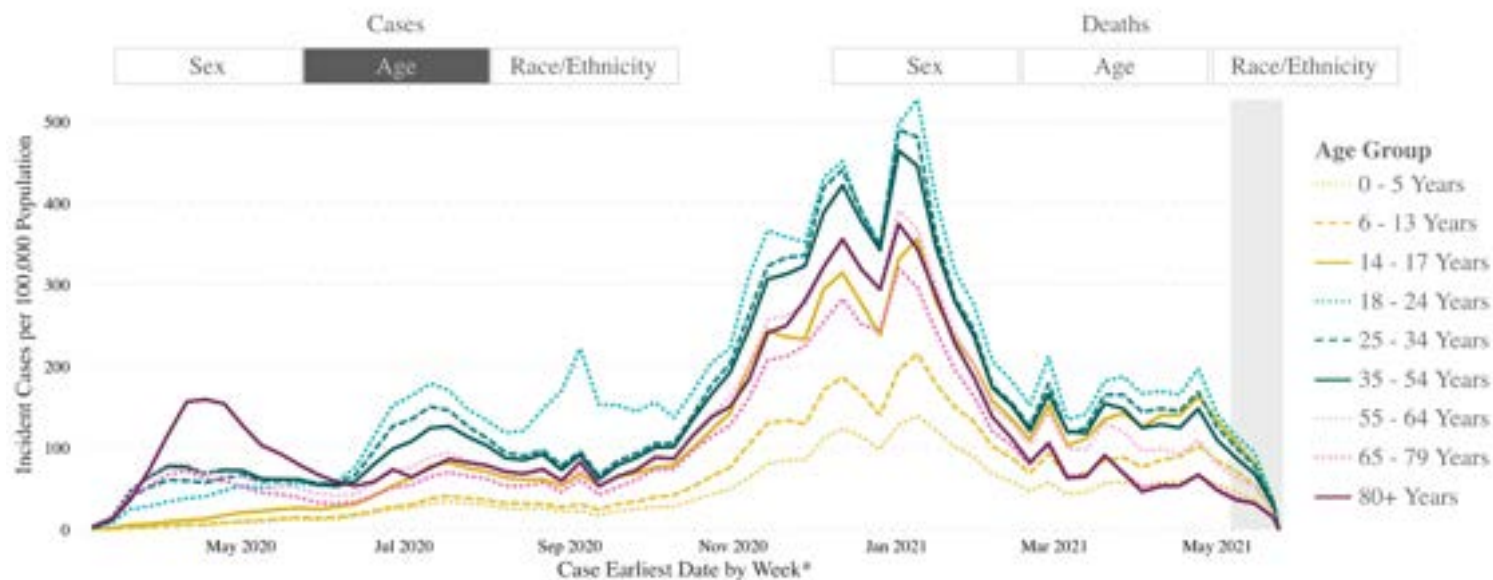
- Background: COVID-19 and emergence of MIS-C in children
- Epidemiology
- Pathogenesis
- Clinical & Laboratory features
  - Unusual associations/complications
- Distinguishing from other clinical entities
- Patient management
- Clinical outcomes
  - Short and Long-term
- Follow-up care

# COVID-19 in children

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



March 1, 2020 - May 24, 2021



Percentage of records reporting: Age = 99.31%

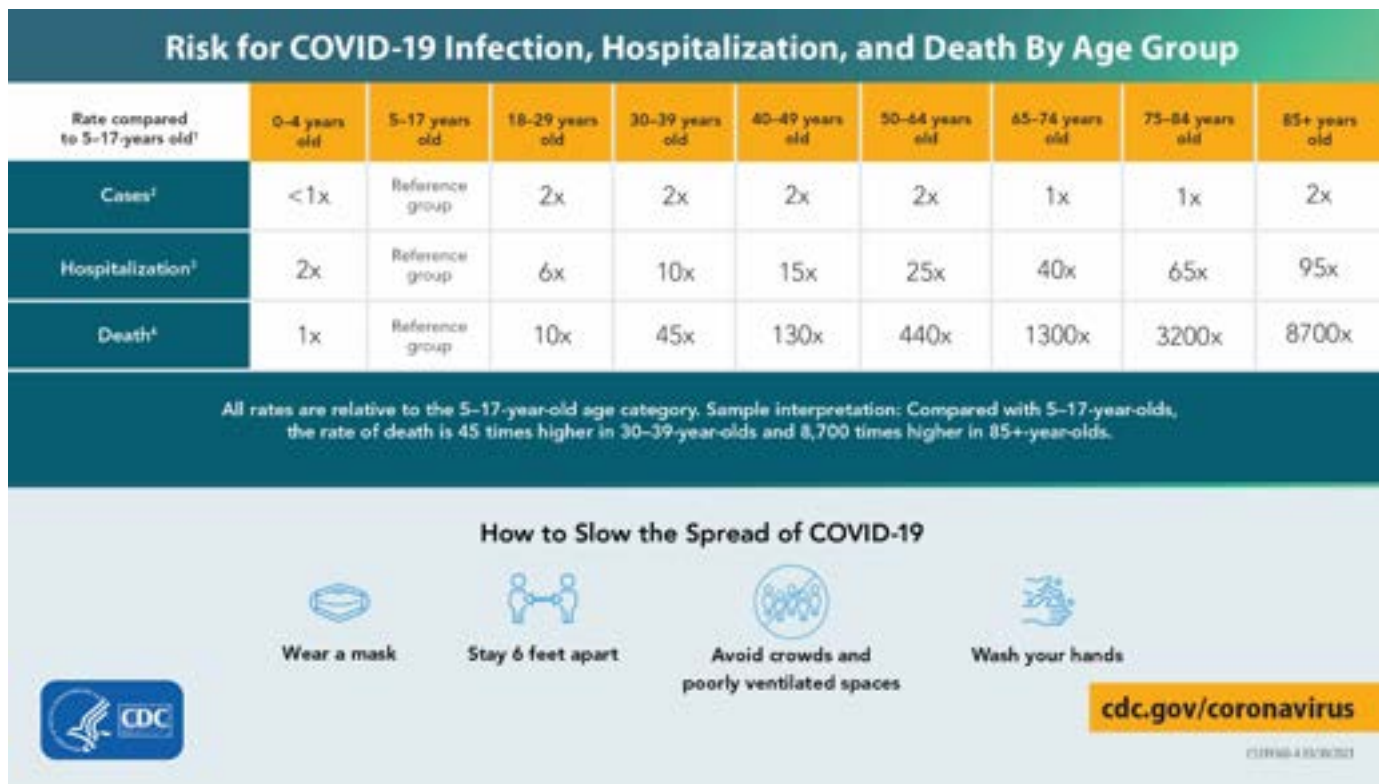
US territories are included in case and death counts but not in population counts. Potential two-week delay in case reporting to CDC denoted by grey bar.

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

Last updated: May 26, 2021

Source: CDC COVID-19 Case Line-Level Data, 2019 US Census, AWE Press; Visualization: Data, Analytics & Visualization Tool Force and CDC COVID Situation Awareness Public

# COVID-19 in children



# 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,<sup>1</sup> or toxic shock syndrome (typical in two children per week formed the basis of a

All children were p well. Six of the childr Caribbean descent, children were boys. A one were well above

Journal of the Pediatric Infectious Diseases Society

### CASE REPORT

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

Kathleen DiLillo,<sup>1,2</sup> Ramil Bessir,<sup>1,2</sup> Edward M. Beltram,<sup>1</sup> Allison M. Eble,<sup>1</sup> Joyce Chang,<sup>1,2</sup> Caroline Diorio,<sup>1</sup> Julie E. Fitzgerald,<sup>1,2</sup> Alexis Tappin,<sup>1,2</sup> and Audrey R. Odian Jaha<sup>1,2</sup>

<sup>1</sup>Division of Critical Care Medicine, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania, USA; <sup>2</sup>Division of Infectious Diseases, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania, USA; <sup>3</sup>Paradise School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, USA; <sup>4</sup>Division of Rheumatology, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania, USA; and <sup>5</sup>Division of Hematology and Oncology, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania, USA

Editorial, see p 437

### Circulation

Volume 142, Issue 4, August 2020, Pages 429–438  
<https://doi.org/10.1161/CIRCULATION.120.473828>

### ORIGINAL RESEARCH ARTICLE

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

Zehra Belhadjer, MD, Mathilde Méot, MD, Fanny Bojolle, MD, PhD, Diala Khraiche, MD, Antoine Legendre, MD, Sampa Abekka, MD, Johanne Aurias, MD, PhD, Martin Grimaud, MD, Mehdi Ouahia, MD, PhD, Maurice Beghetti, MD, PhD, Julie Wacker, MD, Caroline Owaer, MD, PhD, Sébastien Pascoet, MD, Maëlle Selegny, MD, Sophie Malekzadeh-Milani, MD, Alice Mathvat, MD, Gilles Besser, MD, PhD, Nathan Giroux, MD, Laurent Bonnemains, MD, PhD, Jeanne Bordet, MD, PhD, Sylvie Di Filippo, MD, PhD, Pierre Mauran, MD, PhD, Sylvie Falcou-Eicher, MD, Jean-Benoît Thambo, MD, PhD, Bruno Lefort, MD, PhD, Pamela Mocco, MD, PhD, Lucile Houyel, MD, PhD, Sylvain Renolleau, MD, PhD, and Damien Bonnet, MD, PhD

Research

JAMA | Original Investigation

## Clinical Characteristics of 58 Children With a Pediatric Inflammatory Multisystem Syndrome Temporally Associated With SARS-CoV-2

Elizabeth Whittaker, MD, Alexander Bamford, MD, Julia Kewey, MD, Myrini Kafrou, PhD, Christine E. Jones, MD, Priyen Shah, MD, Padmanabhan Ramnarayan, MD, Alan Franks, MD, Owen Miller, MD, Patrick Davies, MD, Filip Kucera, MD, Joe Stanley, MD, Marilyn McDougall, MD, Michael Carter, MD, Adriana Tremoulet, MD, Chisato Shimizu, MD, Jeffery Herberg, MD, Jane C. Burns, MD, Hermione Lyall, MD, Michael Levin, MD, for the PIMS-TS Study Group and EUCLIDS and PERFORM Consortia

## COVID-19 disease at the Italian epicenter: an observational cohort study

Lucia Verdari, Angiola Mazza, Annalisa Geronzi, Laura Menetti, Maurizio Roggeri, Matteo Cui, Fabio, Edo Bonasoni, Lorenzo D'Arzuffi

## 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<sup>i</sup>, laboratory evidence of inflammation<sup>ii</sup>, and evidence of clinically severe illness requiring hospitalization, with multisystem ( $\geq 2$ ) 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
  - <sup>i</sup>Fever  $\geq 38.0^{\circ}$  C for  $\geq 24$  hours, or report of subjective fever lasting  $\geq 24$  hours
  - <sup>ii</sup>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

# MIS-C Epidemiology

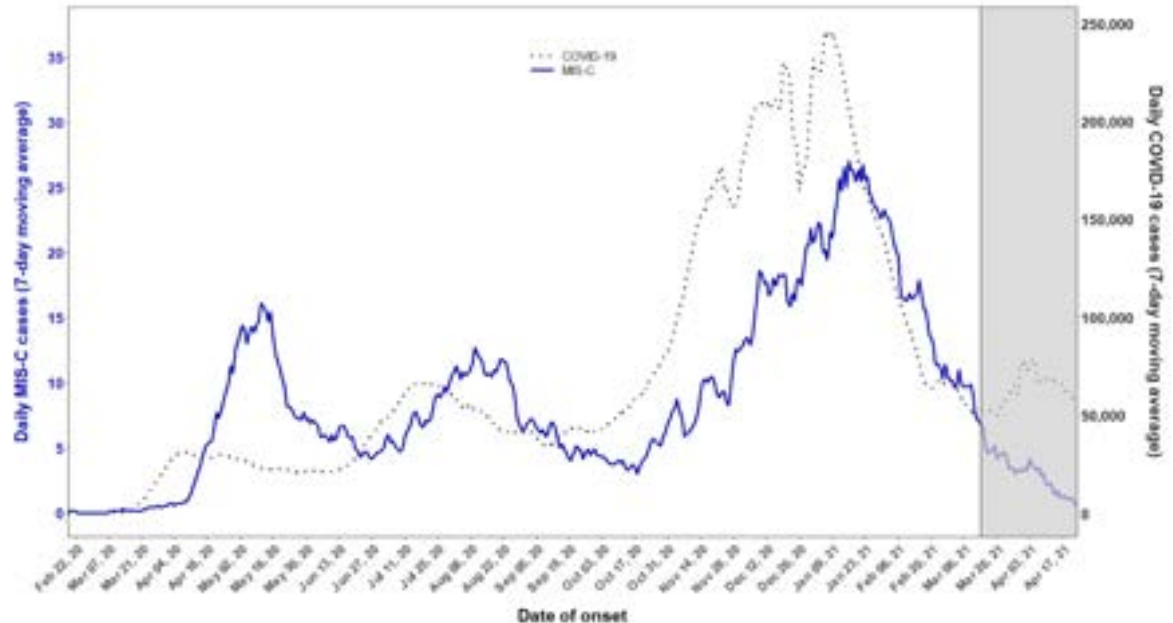
TOTAL MIS-C PATIENTS  
MEETING CASE  
DEFINITION\*

3742

TOTAL MIS-C DEATHS  
MEETING CASE  
DEFINITION

35

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



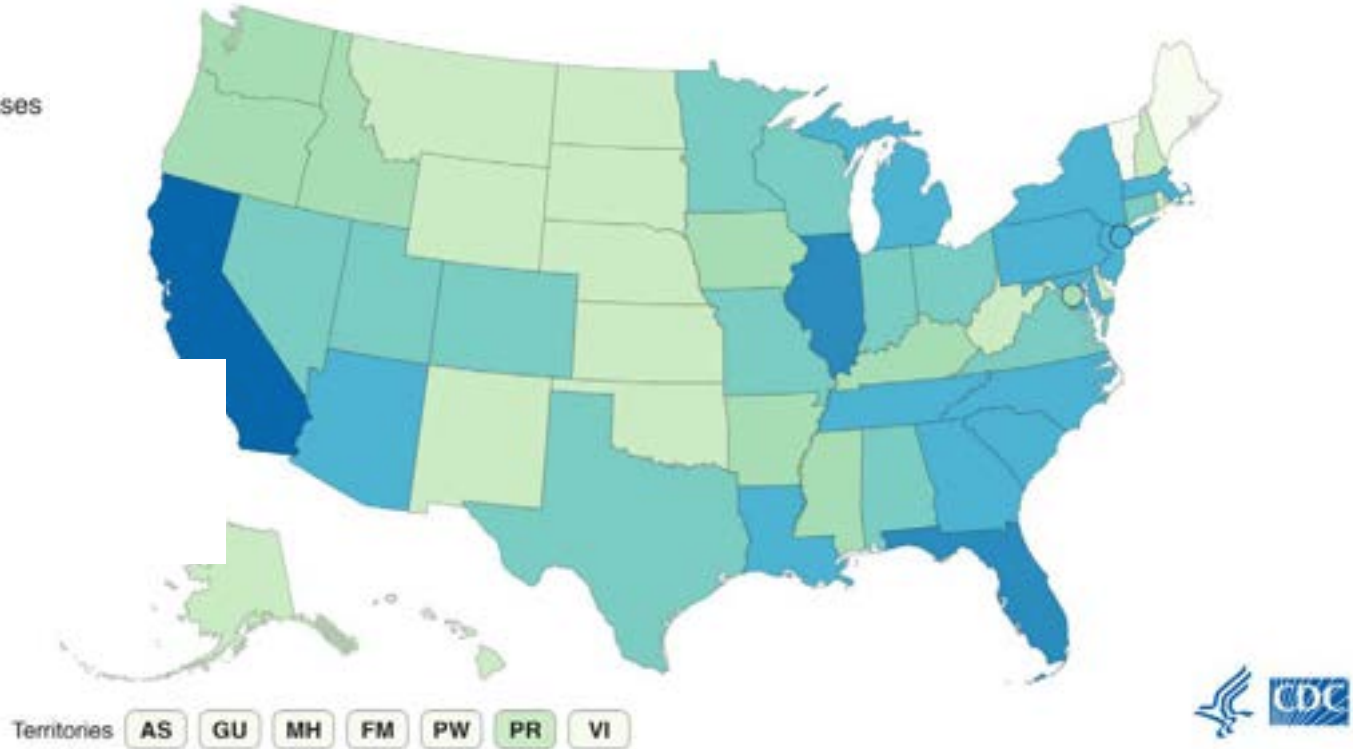


# MIS-C Geographic Distribution

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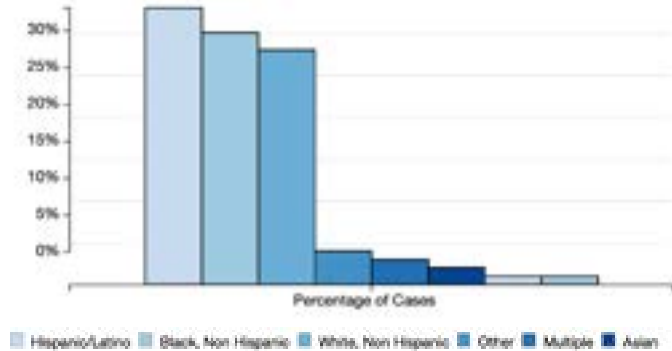
## Reported MIS-C Cases

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

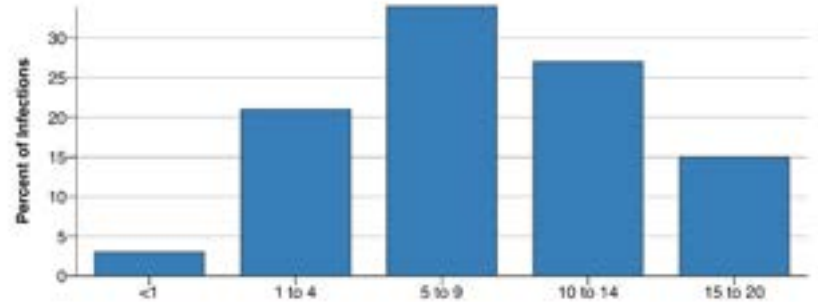


# MIS-C Epidemiology

## MIS-C Patients by Race & Ethnicity

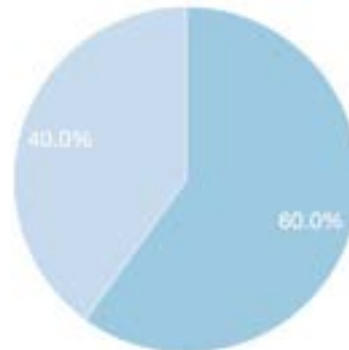


## MIS-C Patients by Age Group



## MIS-C Patients by Sex

Female Male



# MIS-C Pathophysiology

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

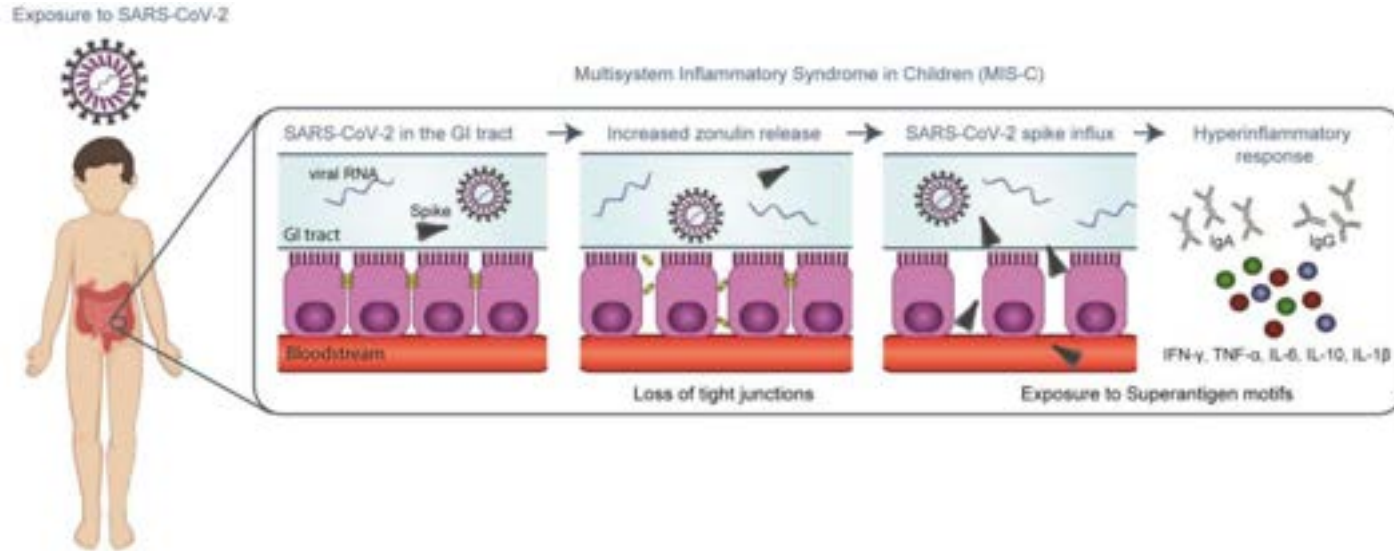
<sup>1</sup> Gruber, et. al. *Cell* 2020 Nov 12; 183(4): 982–995.e14. [10.1016/j.cell.2020.09.034](https://doi.org/10.1016/j.cell.2020.09.034).

<sup>2</sup> Consiglio, et. al. *Cell* 2020 Nov 12; 183(4): 968-981.e7. <https://doi.org/10.1016/j.cell.2020.09.016>

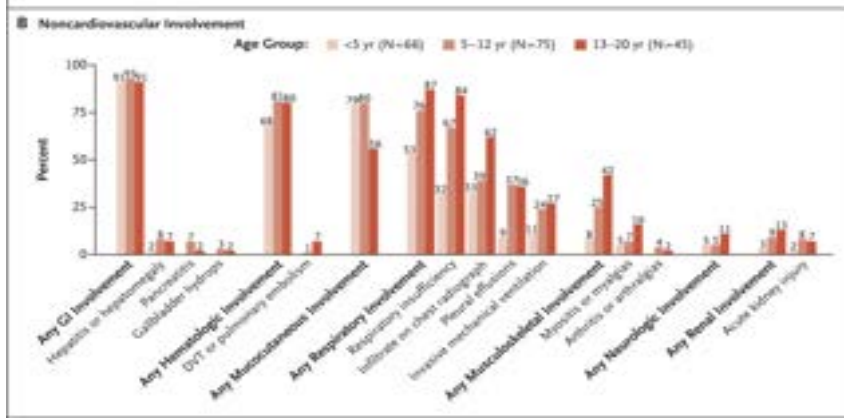
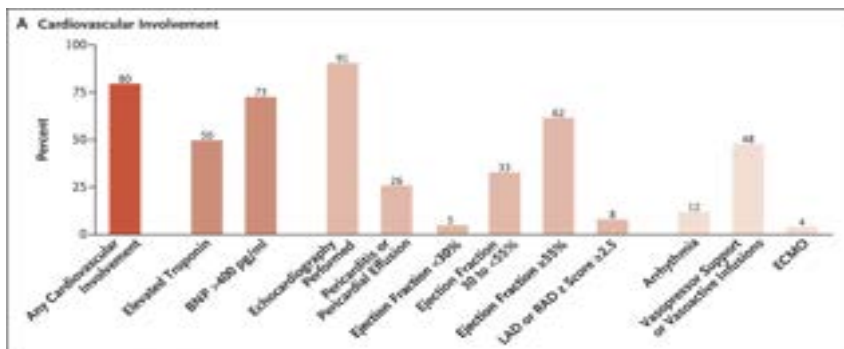
<sup>3</sup> Yonker LM, et al. *JCI* 2021. <https://doi.org/10.1172/JCI149633>.

<sup>4</sup> Cheng HY, et. al. *PNAS*. 2020 Oct; 117(41): 25254-25262. <https://doi.org/10.1073/pnas.2010722117>

# MIS-C Pathophysiology: Plausible Mechanism?



# MIS-C Clinical Features

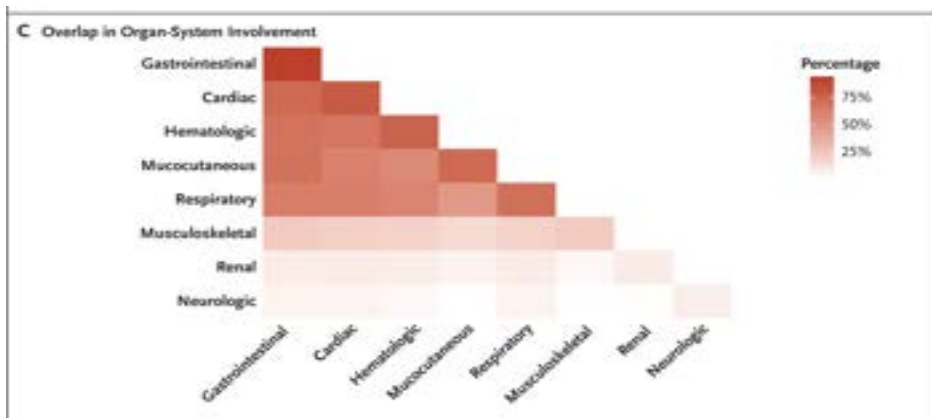


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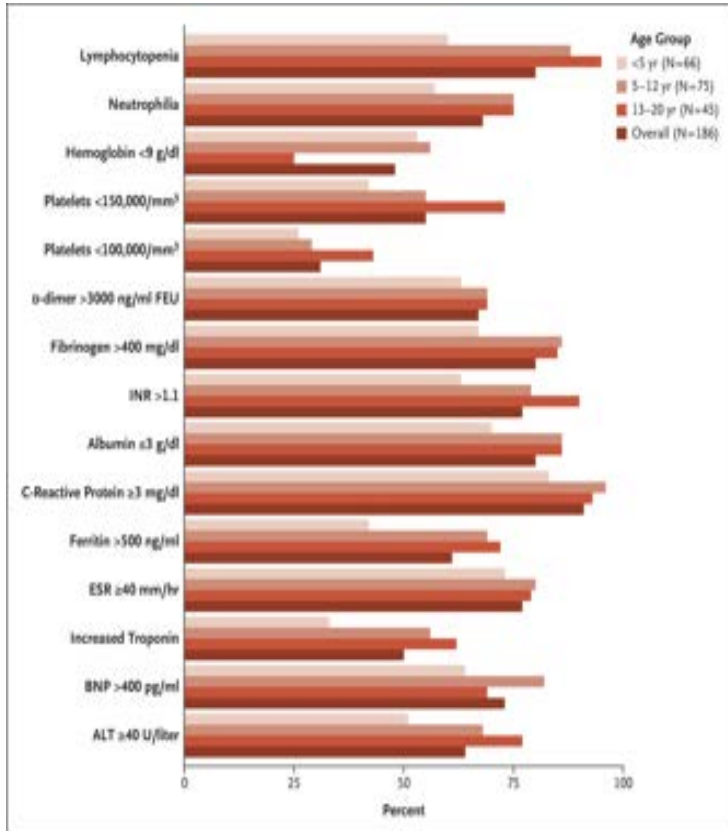
ORIGINAL ARTICLE

## Multisystem Inflammatory Syndrome in U.S. Children and Adolescents

Feldstein LR et al. *N Engl J Med* 2020;383:334-46. DOI: 10.1056/NEJMoa2021680



# MIS-C Clinical Features



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ORIGINAL ARTICLE

## Multisystem Inflammatory Syndrome in U.S. Children and Adolescents

Feldstein LR et al. *N Engl J Med* 2020;383:334-46. DOI: 10.1056/NEJMoa2021680

Highest level of care — no. (%)	<5 yr (N=66)	5-12 yr (N=73)	13-20 yr (N=43)	Overall (N=186)
Ward	11 (15)	5 (9)	22 (40)	38 (20)
Intensive care unit	62 (85)	53 (91)	33 (60)	148 (80)
Extracorporeal membrane oxygenation	6 (8)	1 (2)	1 (2)	8 (4)
Mechanical ventilation	23 (32)	8 (14)	6 (11)	37 (20)

# Other Clinical Features/Associations

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- 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

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## 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%)

## 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 2  
N=169 (29.6%)

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

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

# MIS-C Management: Diagnostic Testing

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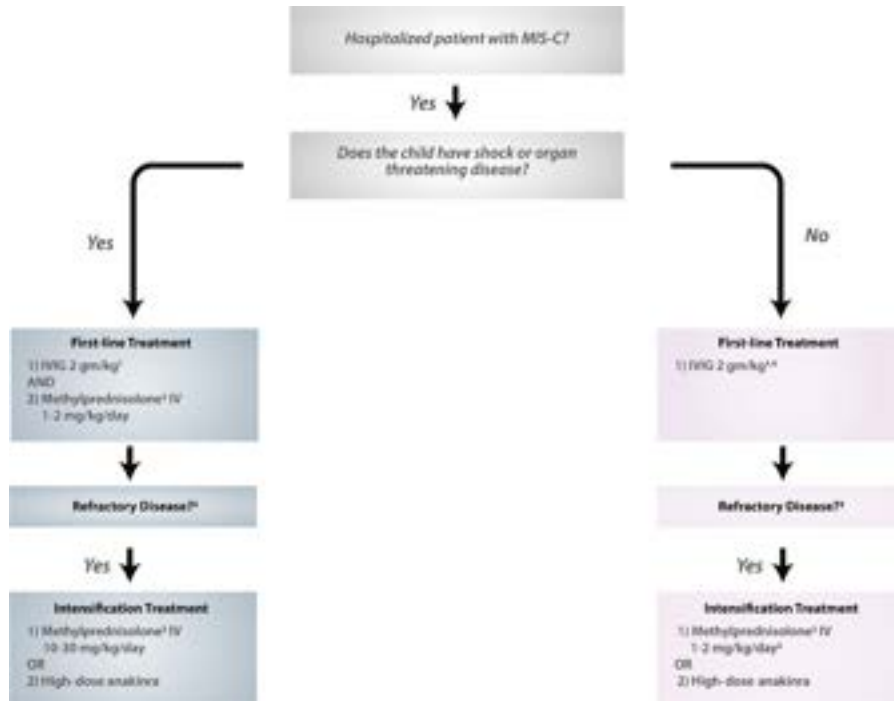
- EKG and echocardiogram
- SARS-CoV-2 RT-PCR and IgG
- CBCd, CMP
- ESR, CRP, DIC screen, ferritin
- Troponin, BNP
- Blood culture
- Urinalysis with reflex to culture
- Other infectious work-up\*

# MIS-C Management: Treatments & Interventions

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- Isolation considerations
- Respiratory and circulatory support
- Antibiotics if concern for sepsis
- Anti-inflammatory
  - Systemic corticosteroids, IVIG, immunomodulators (IL-1 $\beta$  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

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- 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

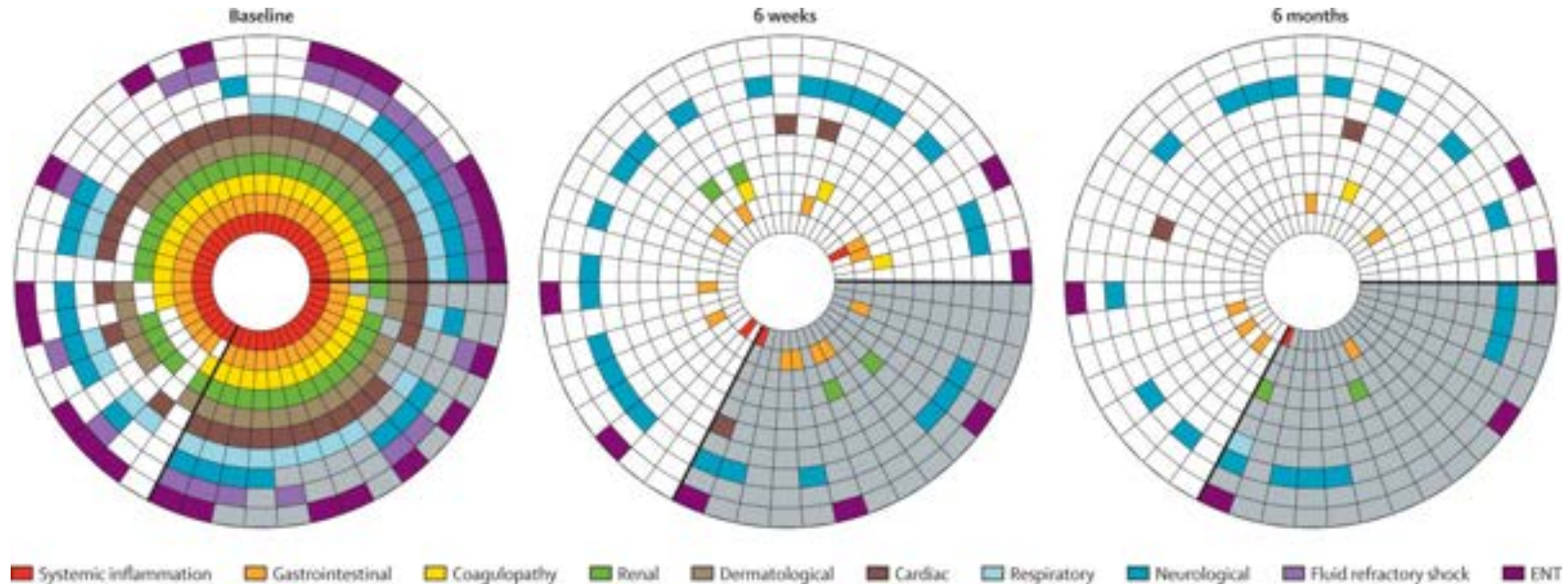
# MIS-C Short-term outcomes

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- 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

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- 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 >95<sup>th</sup> %-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 <3<sup>rd</sup> %-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

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- 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, deconditioning, 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

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- Abrams JY, et al. *The Lancet Child & Adol Health*. 5(5): 323-331. 2021 May.
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- Feldstein LR, et. al. *NEJM*, June 29, 2020.
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- Yonker LM, et al. *JCI* 2021. <https://doi.org/10.1172/JCI149633>.

# Questions

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