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

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ECHO Series

June 3, 2021

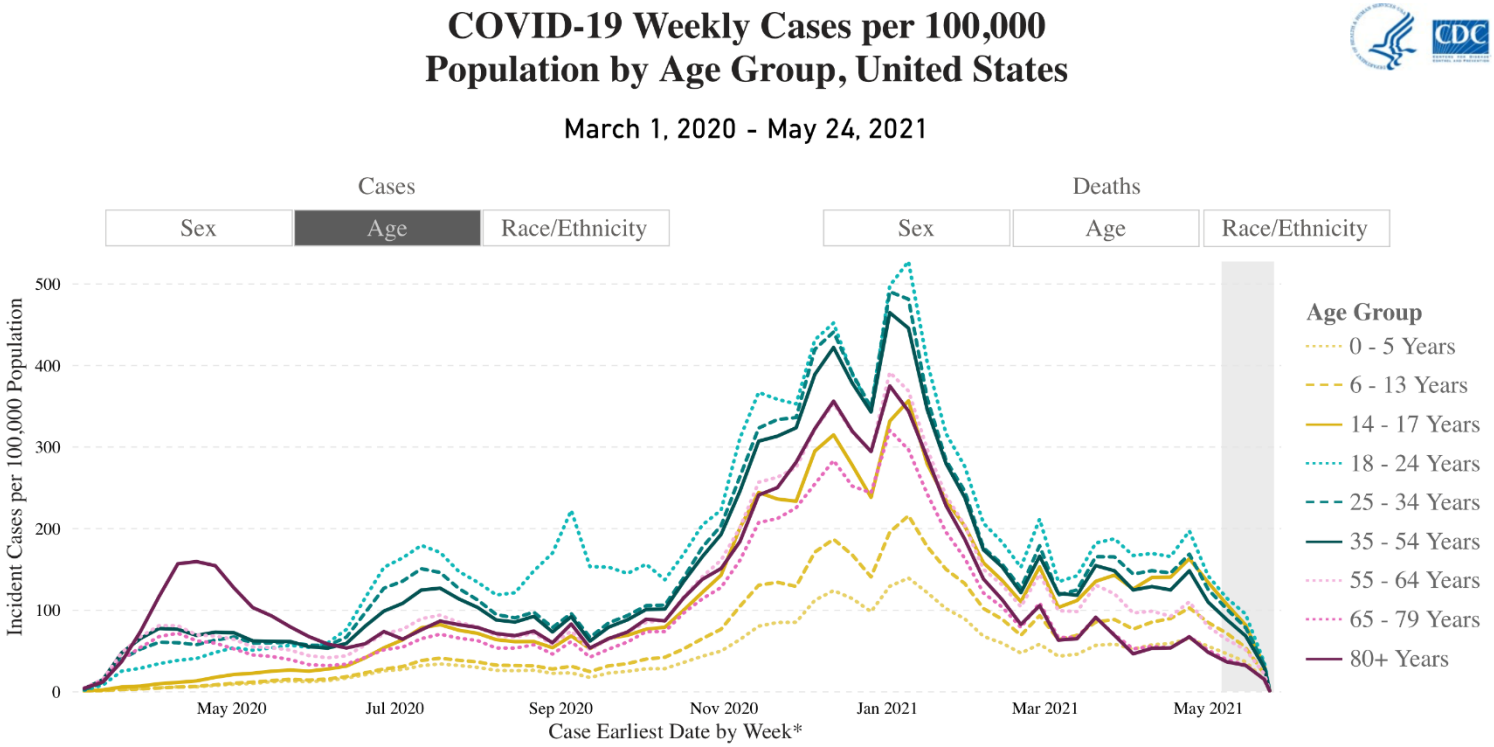
Disclosures

- 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.

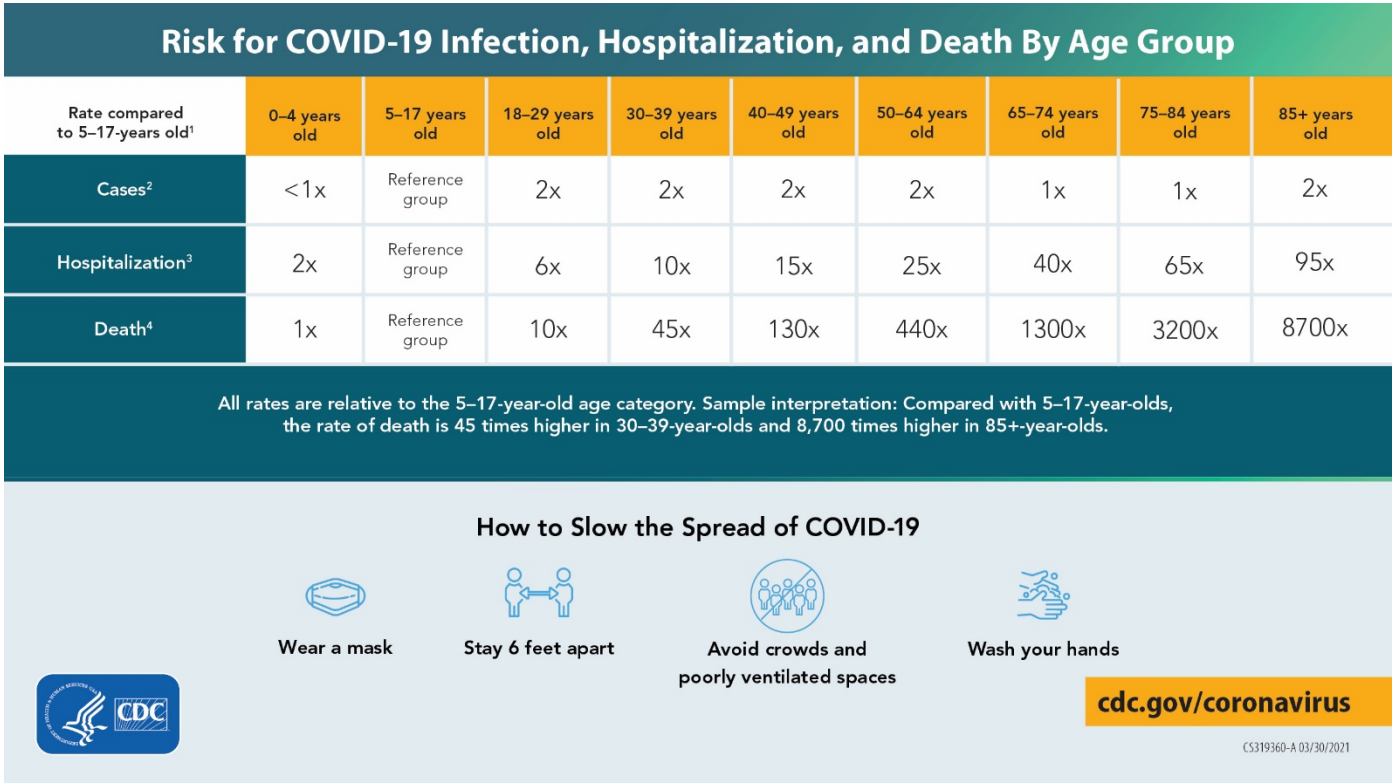
Overview

- 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 in children



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

Rate compared to 5–17-years old[1]	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[2]	<1x	Reference group	2x	2x	2x	2x	1x	1x	2x
Hospitalization[3]	2x	Reference group	6x	10x	15x	25x	40x	65x	95x
Death[4]	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

cdc.gov/coronavirus

CS319360-A 03/30/2021

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,[1] or toxic shock syndrome (typical n two children per week formed the basis of a r

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

Research

JAMA | Original Investigation

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

Elizabeth Whittaker, MD; Alasdair Bamford, MD; Julia Kenny, MD; Myrsini Kaforou, PhD; Christine E. Jones, MD; Priyen Shah, MD; Padmanabhan Ramnarayan, MD; Alain Fraisse, MD; Owen Miller, MD; Patrick Davies, MD; Filip Kucera, MD; Joe Brierley, MD; Marilyn McDougall, MD; Michael Carter, MD; Adriana Tremoulet, MD; Chisato Shimizu, MD; Jethro Herberg, MD; Jane C. Burns, MD; Hermione Lyall, MD; Michael Levin, MD; for the PIMS-TS Study Group and EUCLIDS and PERFORM Consortia

Journal of the Pediatric Infectious Diseases Society

CASE REPORT

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

Kathleen Chiotos,[1,2,3] Hamid Bassiri,[2,3] Edward M. Behrens,[4] Allison M. Blatz,[2] Joyce Chang,[3,4] Caroline Diorio,[5] Julie C. Fitzgerald,[1,3] Alexis Topjian,[1,3] and Audrey R. Odom John[2,3]

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Circulation
Volume 142, Issue 5, 4 August 2020, Pages 429-436
https://doi.org/10.1161/CIRCULATIONAHA.120.048360

ORIGINAL RESEARCH ARTICLE

Acute Heart Failure in Multisystem Inflam Syndrome in Children in the Context of G 2 Pandemic

Editorial, see p 437

Zahra Belhadjer, MD, Mathilde Méot, MD, Fanny Bajolle, MD, PhD, Diala Khraiche, MD, Antoine Legendre, MD, Samya Abakka, MD, Johanne Auriau, MD, PhD, Marion Grimaud, MD, Mehdi Oualha, MD, PhD, Maurice Beghetti, MD, PhD, Julie Wacker, MD, Caroline Ovaert, MD, PhD, Sebastien Hascoet, MD, Maëlle Selegny, MD, Sophie Malekzadeh-Milani, MD, Alice Maltret, MD, Gilles Bosser, MD, PhD, Nathan Giroux, MD, Laurent Bonnemains, MD, PhD, Jeanne Bordet, MD, PhD, Sylvie Di Filippo, MD, PhD, Pierre Mauran, MD, PhD, Sylvie Falcon-Eicher, MD, Jean-Benoît Thambo, MD, PhD, Bruno Lefort, MD, PhD, Pamela Moceri, MD, PhD, Lucile Houyel, MD, PhD, Sylvain Renolleau, MD, PhD, and Damien Bonnet, MD, PhD

e disease at the Italian nic: an observational cohort study

Lucio Verdoni, Angelo Mazza, Annalisa Gervasoni, Laura Martelli, Maurizio Ruggeri, Matteo Ciuffreda, Ezio Bonanomi, Lorenzo D'Antiga

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

HAN HEALTH ALERT NETWORK

This is an official CDC HEALTH ADVISORY

CDC MIS-C Case Definition

HAN HEALTH ALERT NETWORK

This is an official CDC HEALTH ADVISORY

- An individual aged <21 years presenting with fever[i], laboratory evidence of inflammation[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

  – [i]Fever ≥38.0° C for ≥24 hours, or report of subjective fever lasting ≥24 hours
  – [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

MIS-C Epidemiology

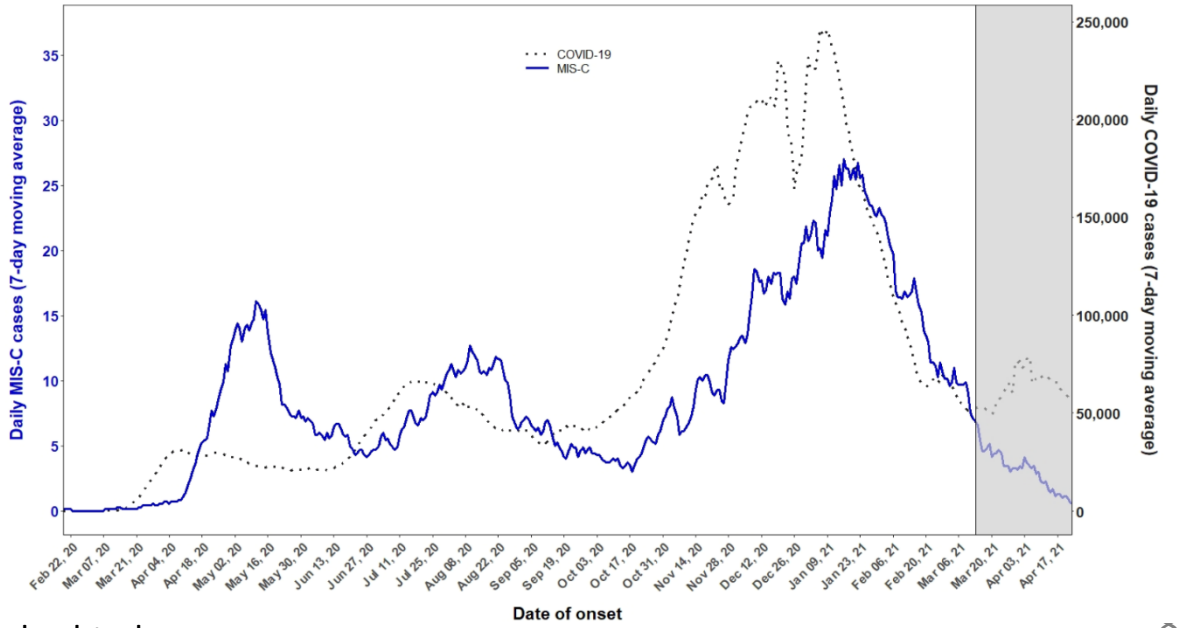
TOTAL MIS-C PATIENTS MEETING CASE DEFINITION*

3742

TOTAL MIS-C DEATHS MEETING CASE DEFINITION

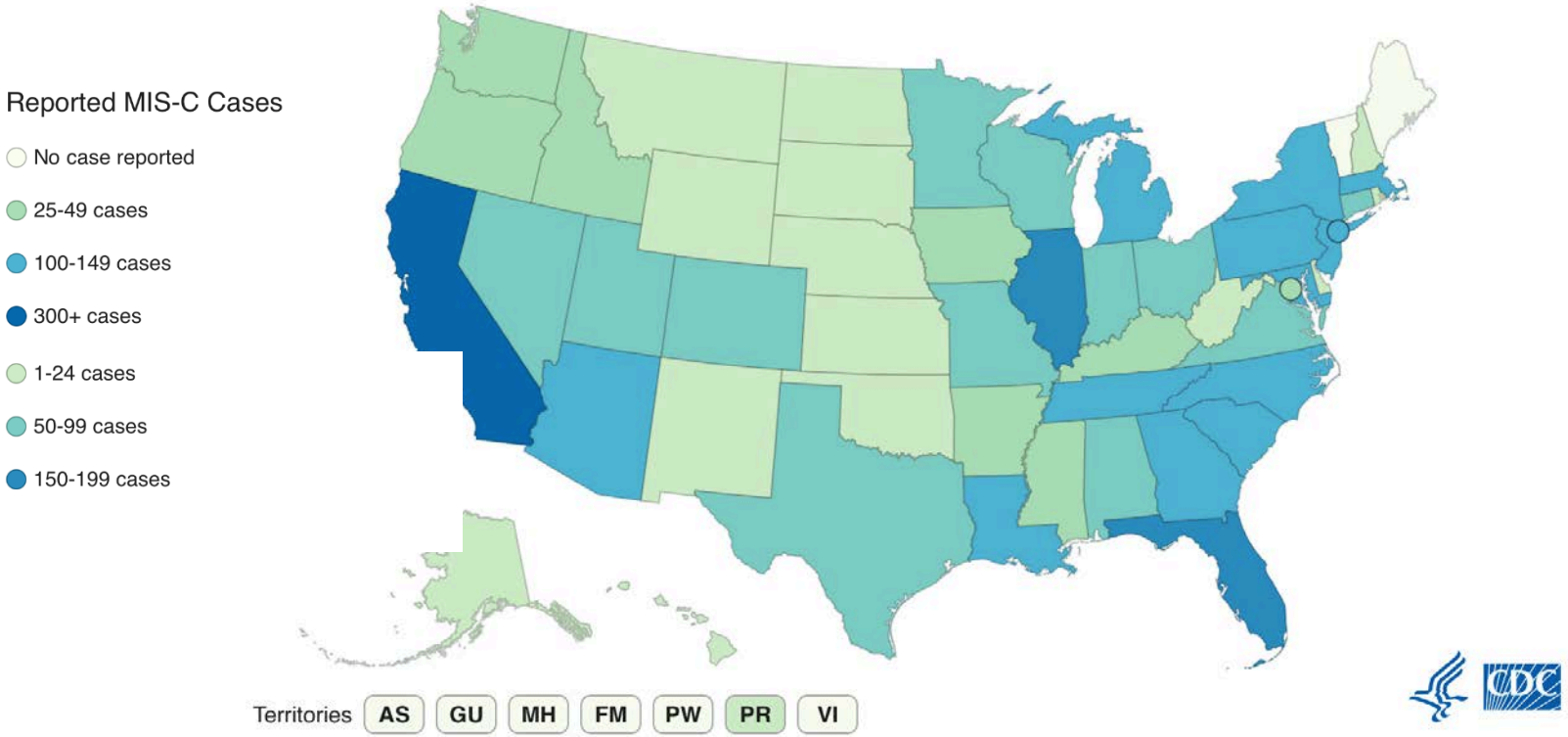
35

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



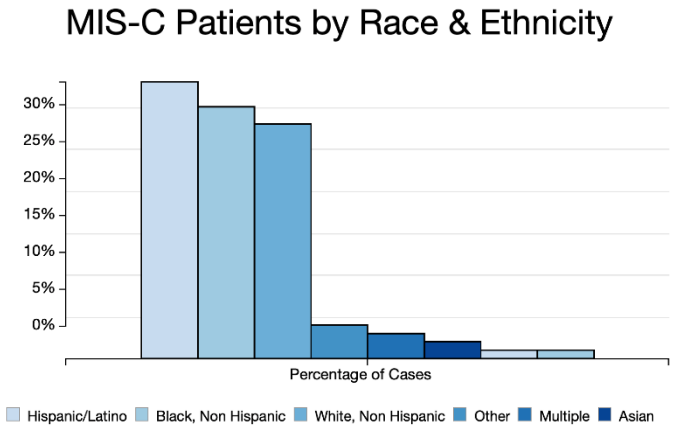
https://www.cdc.gov/mis-c/cases/index.html

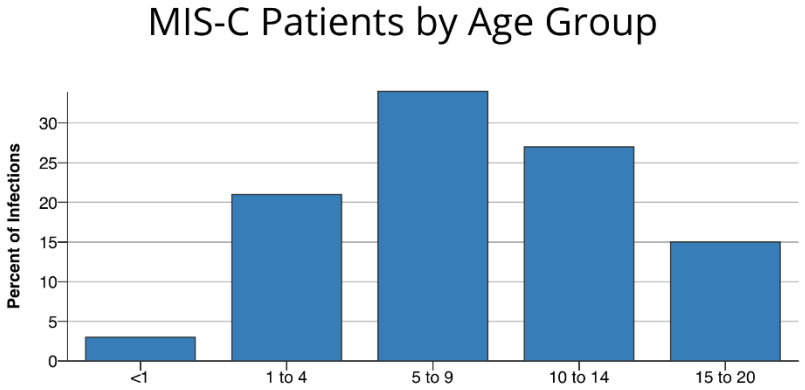
MIS-C Geographic Distribution

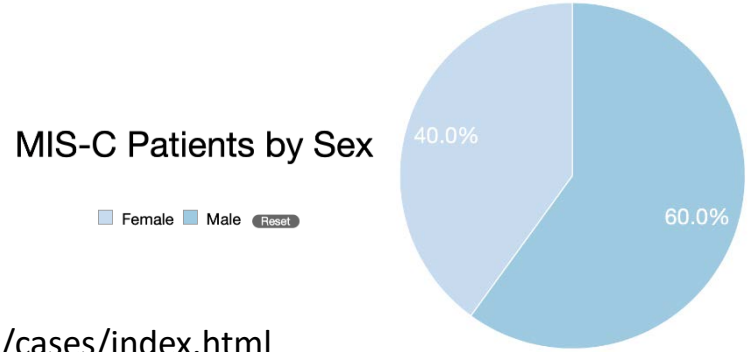


https://www.cdc.gov/mis-c/cases/index.html

MIS-C Epidemiology







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]

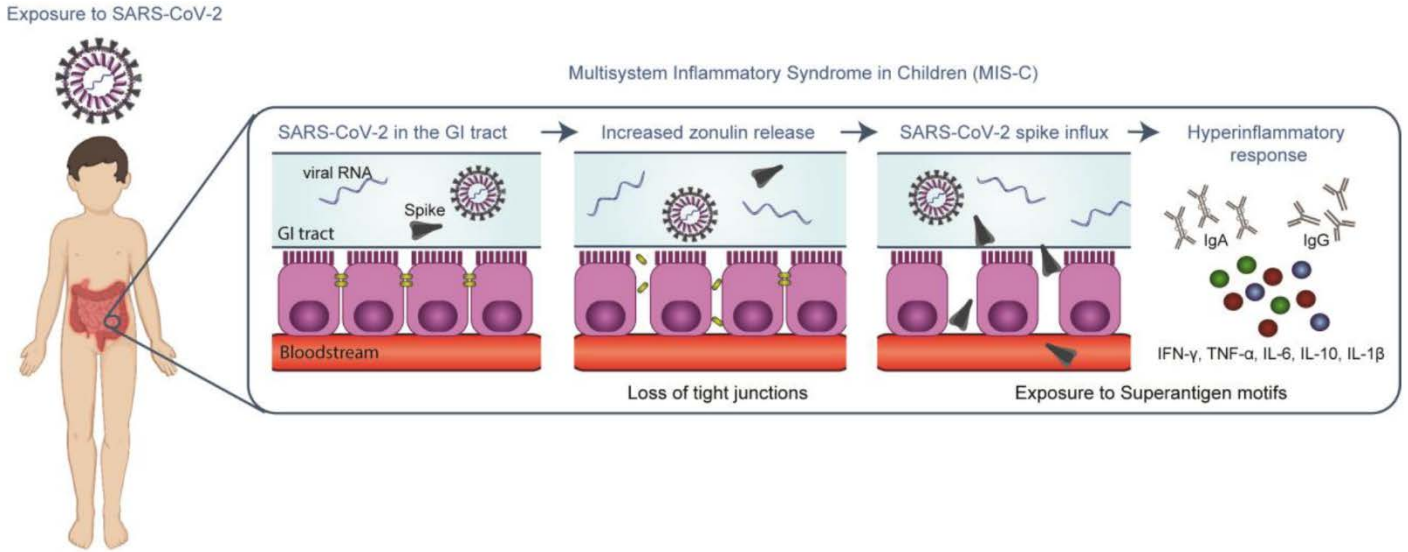
[1] Gruber, et. al. *Cell* 2020 Nov 12; 183(4): 982–995.e14. 10.1016/j.cell.2020.09.034.

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

[3] Yonker LM, et al. *JCI* 2021. https://doi.org/10.1172/JCI149633.

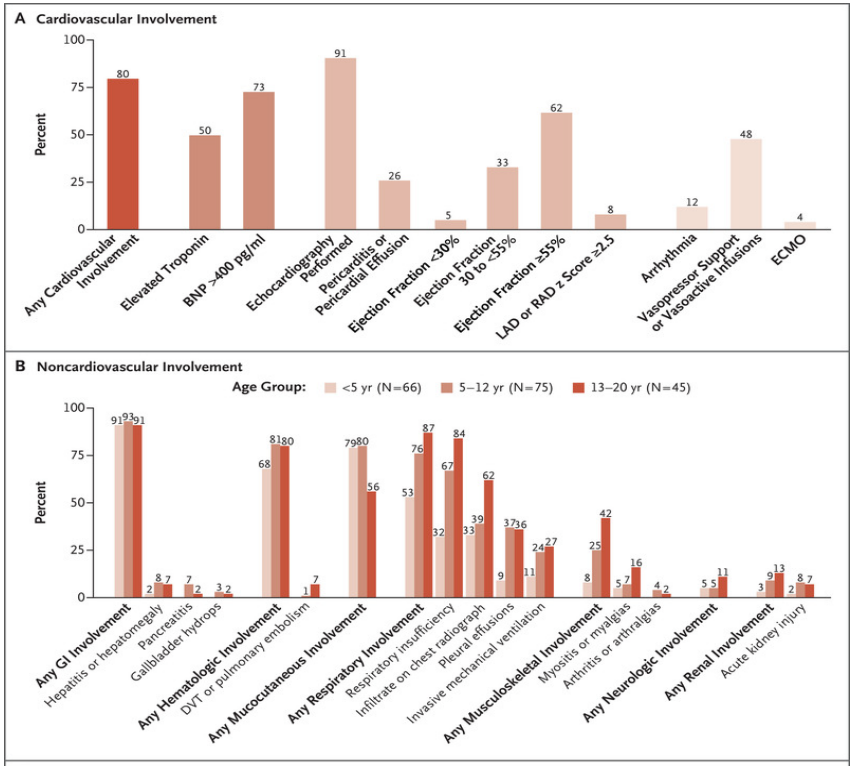
4 Cheng HY, et. al. *PNAS*. 2020 Oct; 117(41): 25254-25262. https://doi.org/10.1073/pnas.2010722117

MIS-C Pathophysiology: Plausible Mechanism?



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

MIS-C Clinical Features

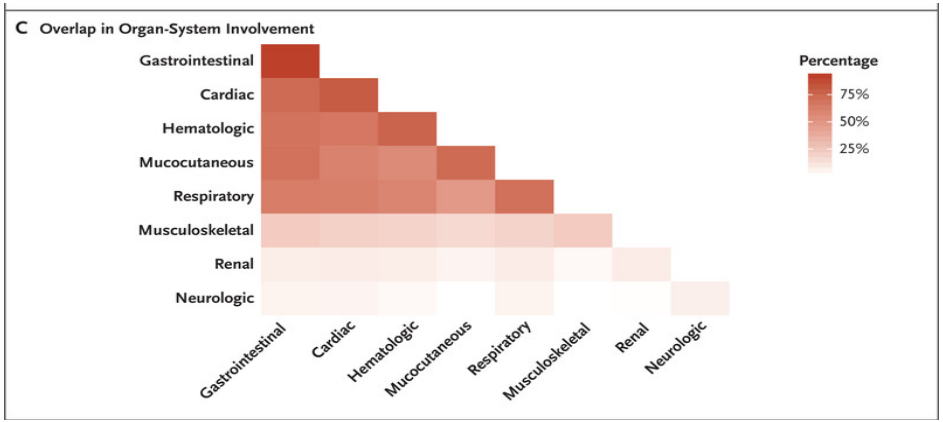


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

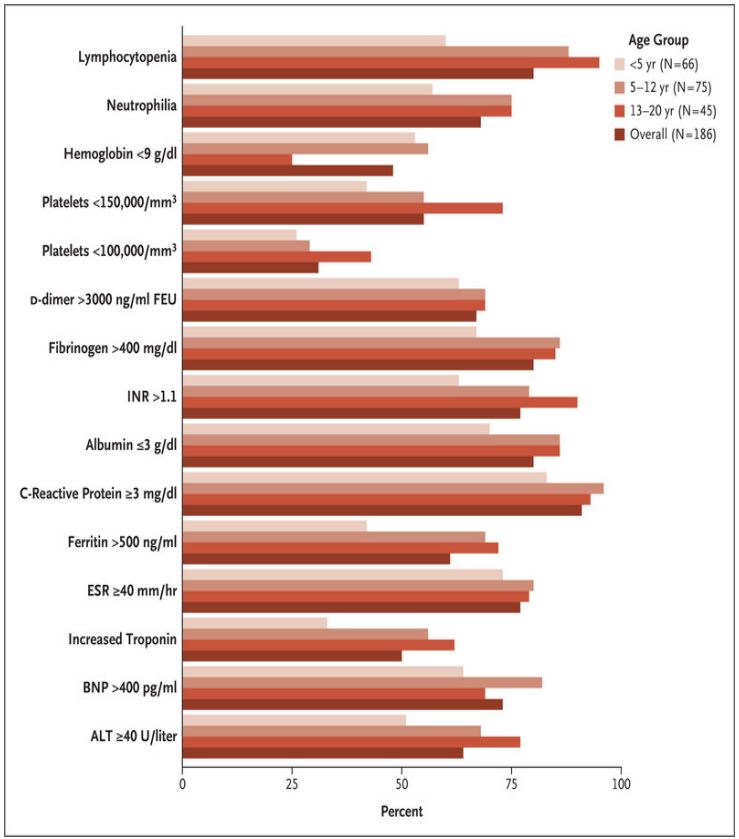
Multisystem Inflammatory Syndrome in U.S. Children and Adolescents

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



Feldstein LR, et. al. *NEJM*, June 29, 2020.

MIS-C Clinical Features



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Highest level of care — no. (%)				
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)

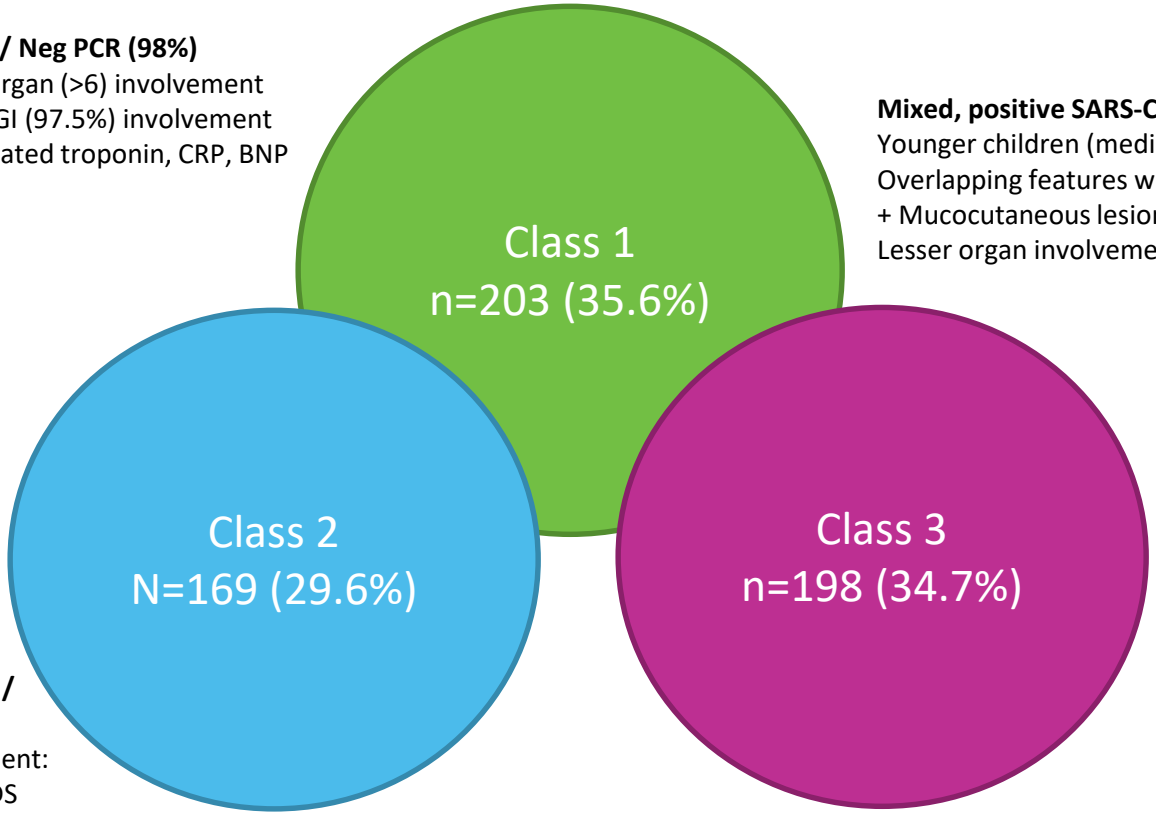
Feldstein LR, et. al. *NEJM*, June 29, 2020.

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



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

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

Godfred-Cato S, et al. *MMWR.* 69(32): 1074–1080. 2020 Aug.

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)

Corwin DJ, et al. *Pediatric Emergency Care.* 36(11):554-558, 2020 Nov.
Rostad CA, et. al. *Pediatrics.* 146(6) e2020018242; 2020 Dec.

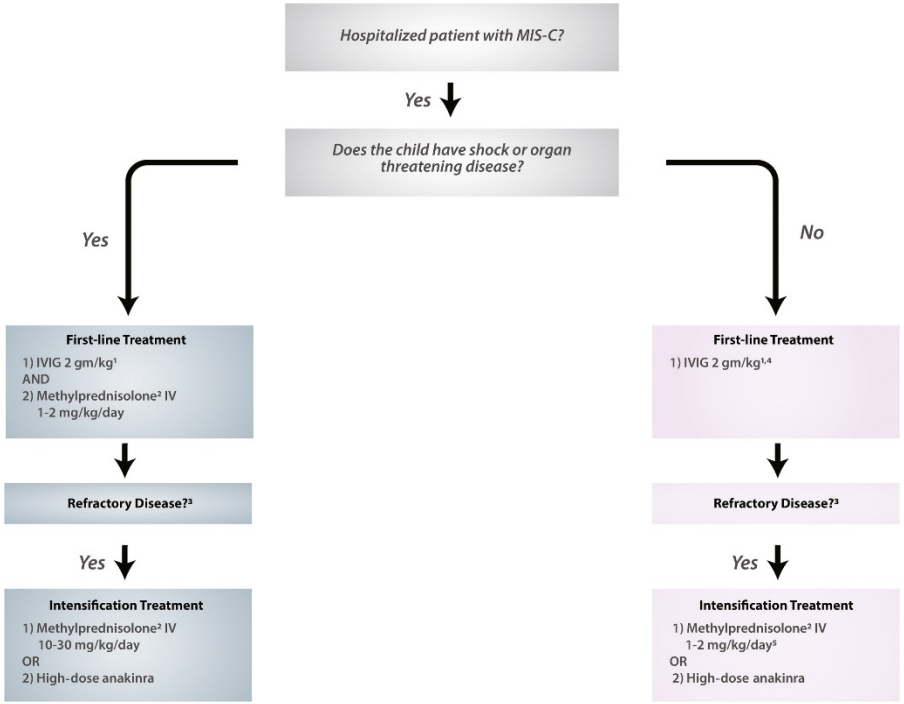
MIS-C Management: Diagnostic Testing

- 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

Henderson LA, et al. *Arthritis Rheumatol*. 2020; 73: e13-e29. https://doi.org/10.1002/art.41616
Ouldali N, et al. *JAMA*. 2021;325(9):855-864. doi:10.1001/jama.2021.0694

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

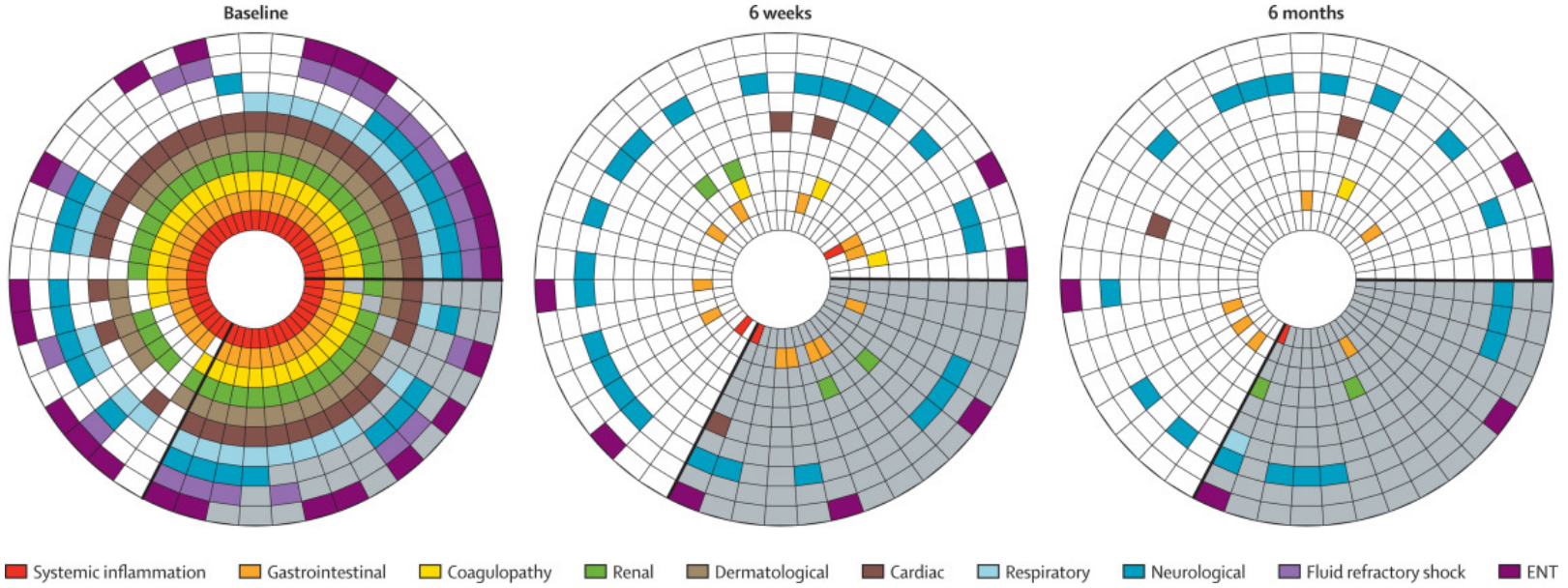
MIS-C Short-term outcomes

- 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

Godfred-Cato S, et al. *MMWR*. 69(32): 1074–1080. 2020 Aug.
Abrams JY, et al. *The Lancet Child & Adolescent Health*. 5(5): 323-331. 2021 May.

MIS-C Longitudinal Outcomes

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



Penner J, et. al. *The Lancet Child & Adolescent Health*. Published online May 24, 2021.

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

Penner J, et. al. *The Lancet Child & Adolescent Health*. Published online May 24, 2021.

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

- Abrams JY, et al. *The Lancet Child & Adol Health*. 5(5): 323-331. 2021 May.
- CDC Health Alert Network, May 14, 2020.
- Cheng HY, et. al. *PNAS*. 2020 Oct; 117(41): 25254-25262. https://doi.org/10.1073/pnas.2010722117
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Questions