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

Delaware Communicable Diseases Summit 2020

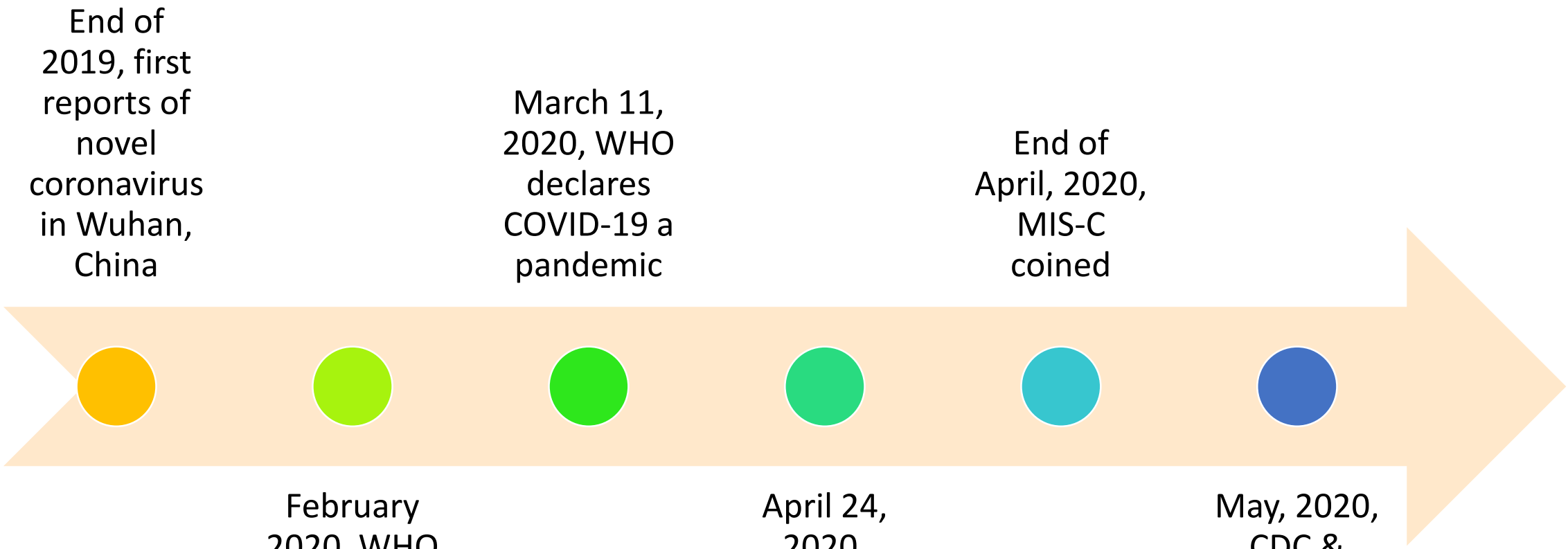
Monday, November 9, 2020

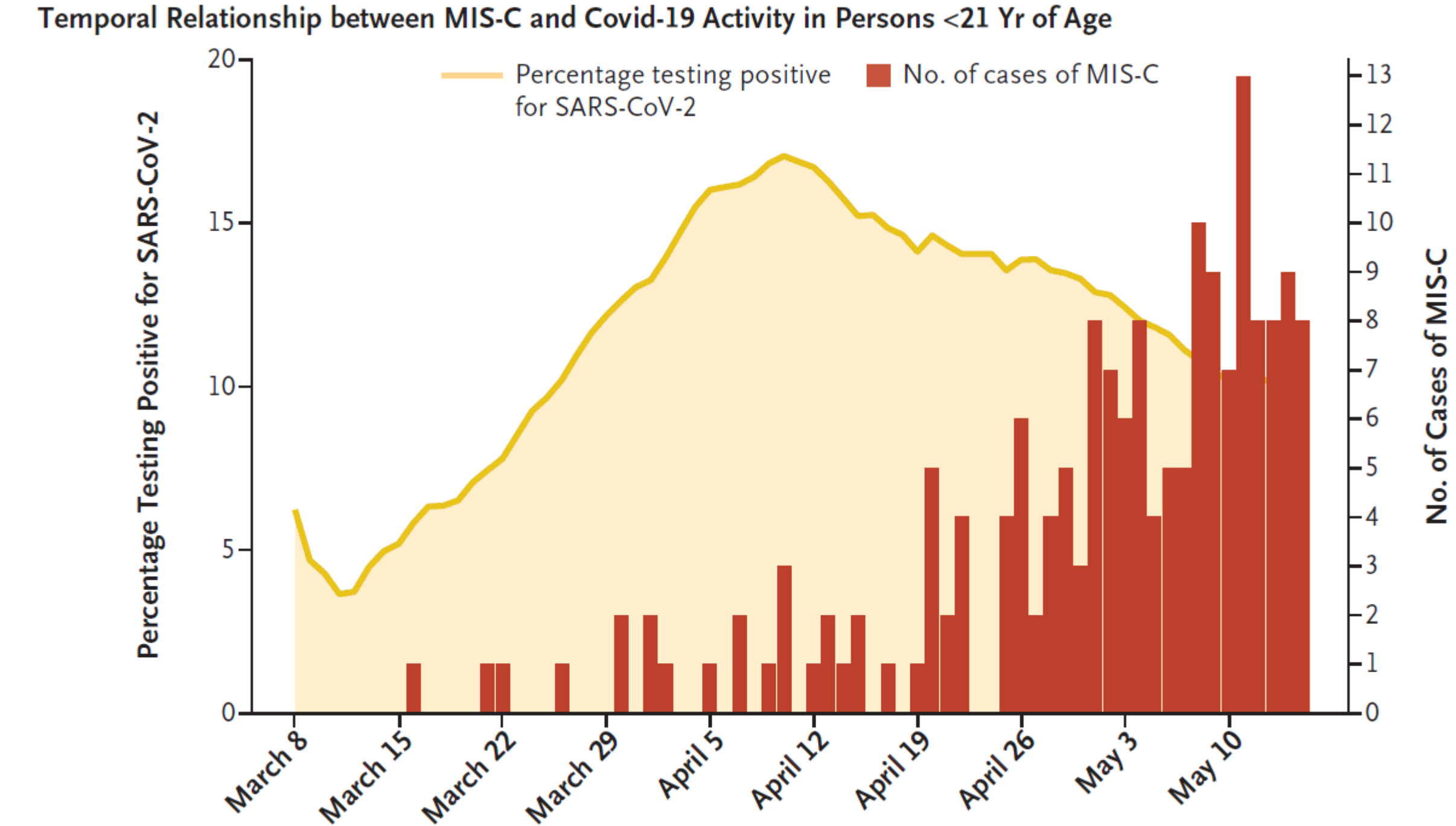
Neil Rellosa, MD

Nemours/Alfred I. duPont Hospital for Children

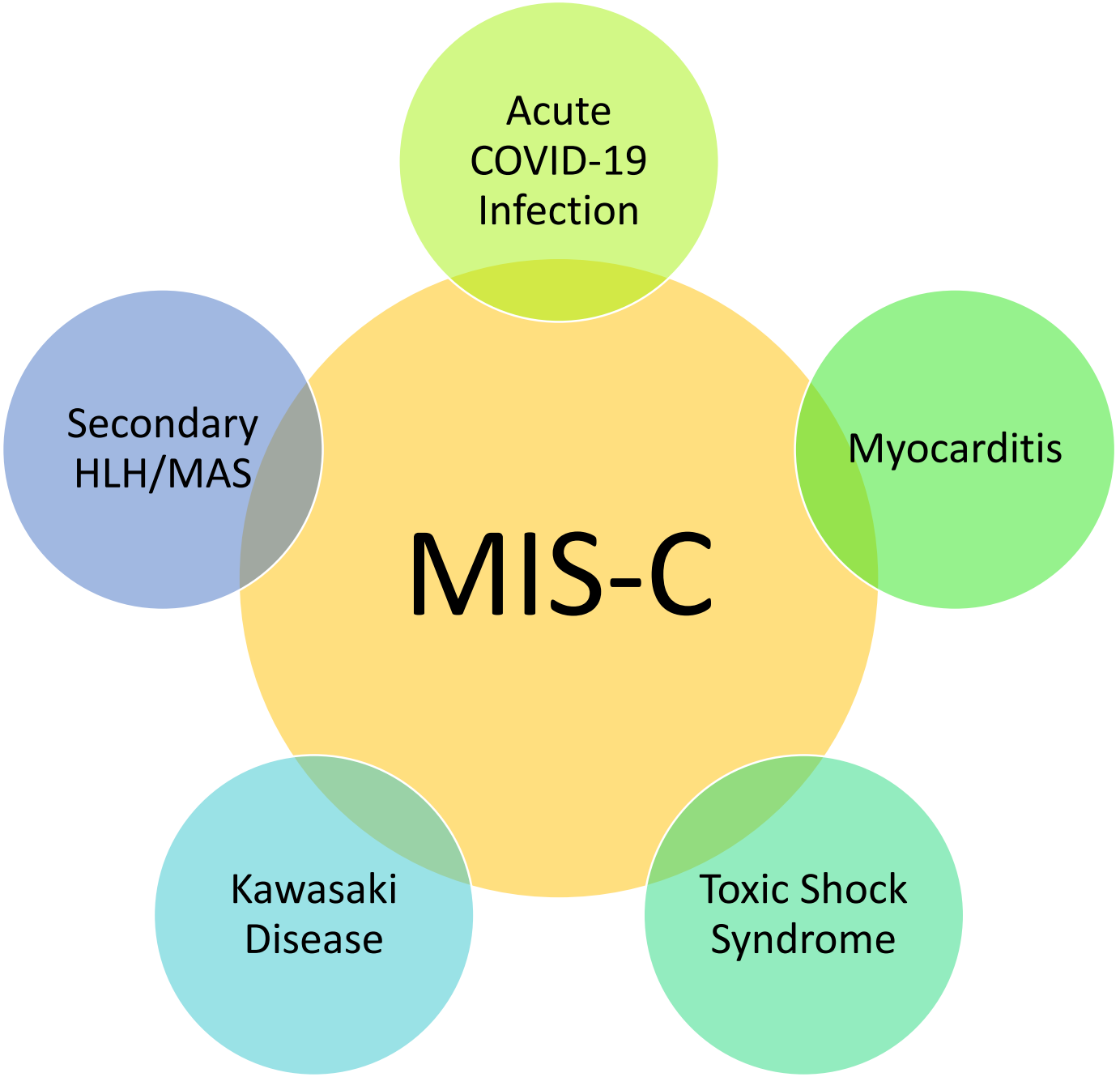
Division of Infectious Diseases

Time Line of Events for MIS-C

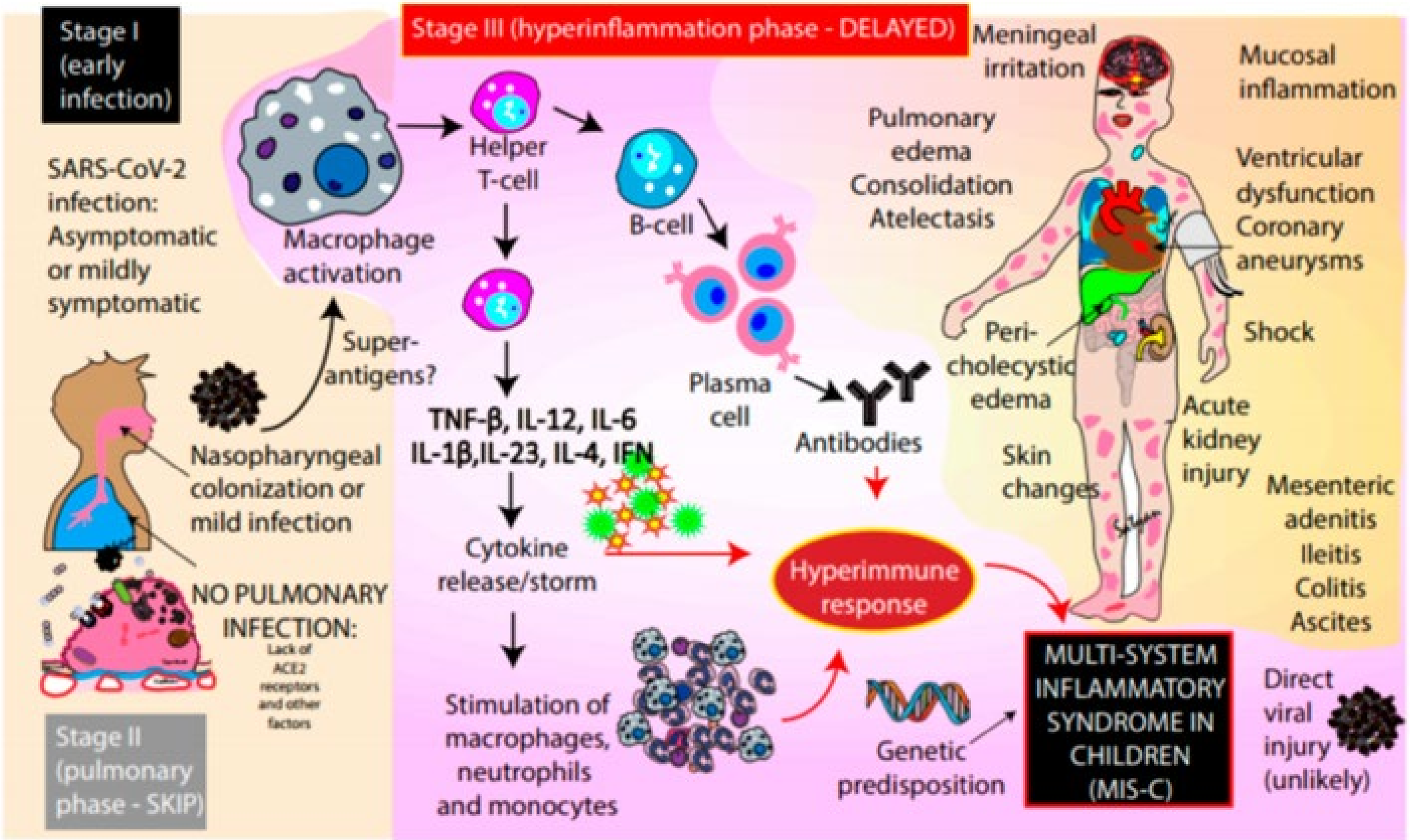




Feldstein LR, et al. *NJEM*, 2000.


Acute COVID-19 Infection
Secondary HLH/MAS
MIS-C
Myocarditis
Kawasaki Disease
Toxic Shock Syndrome

Pathogenesis of MIS-C



Nakra NA et al. *Children* 2020, 7,69

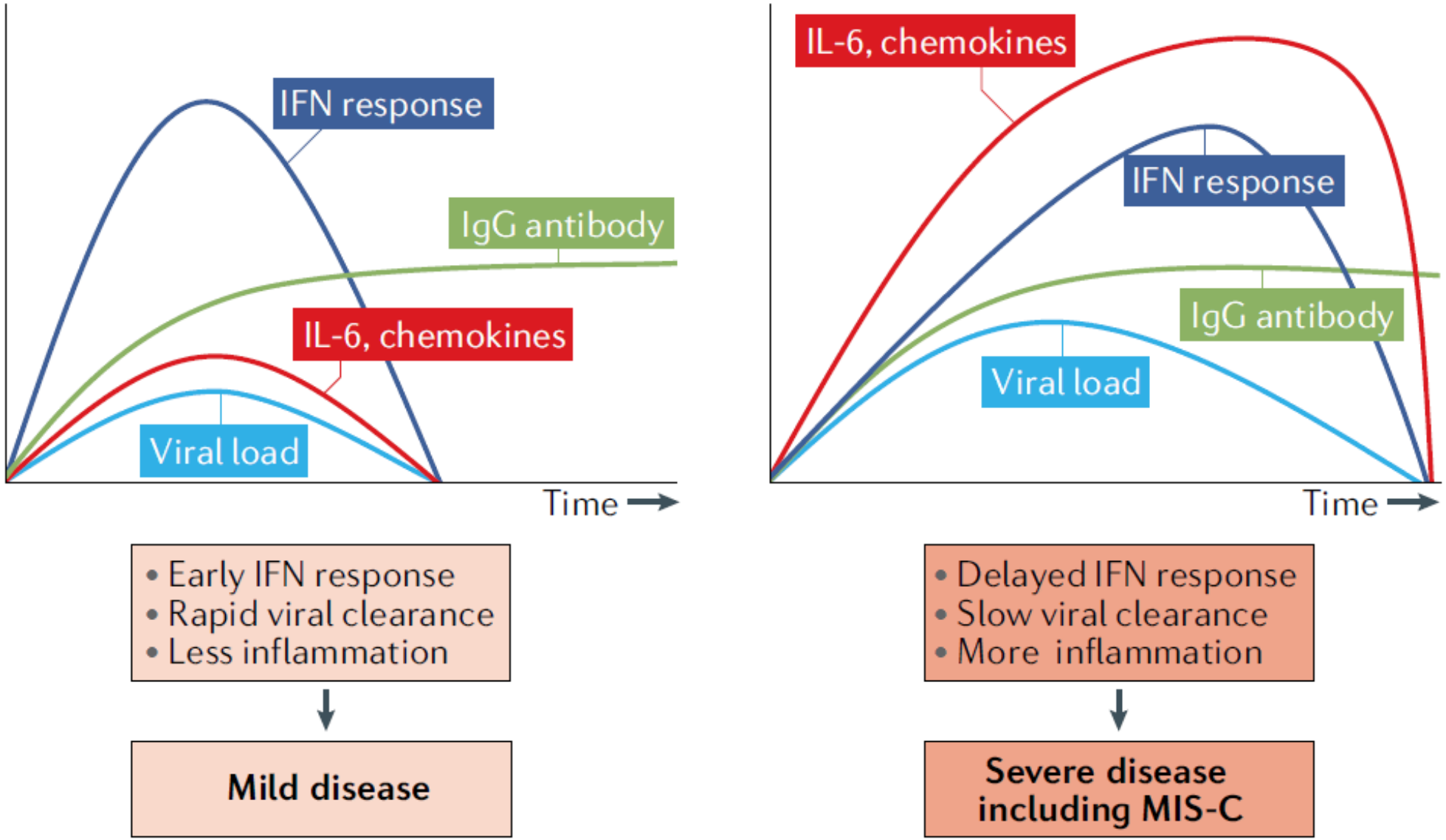
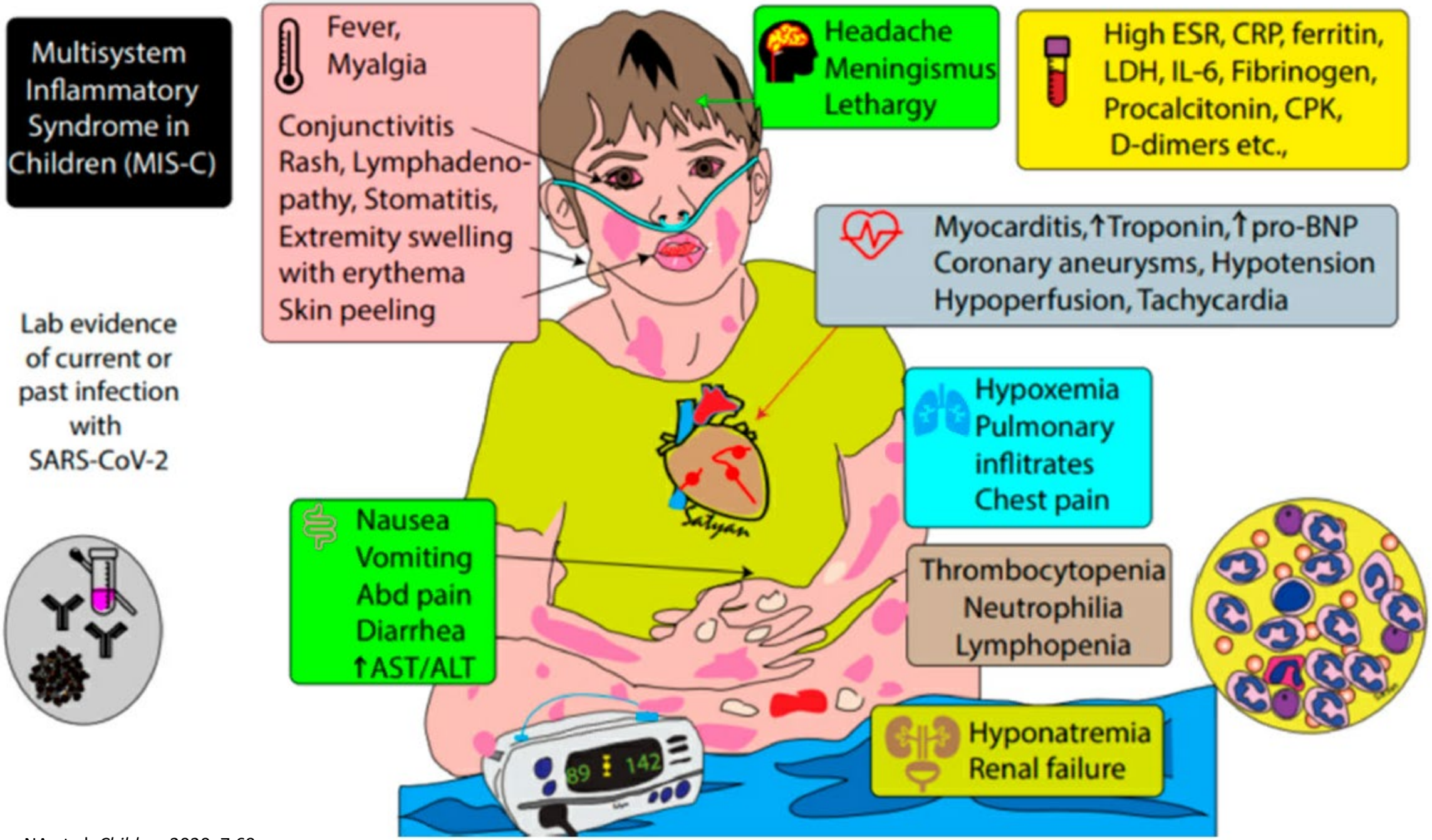


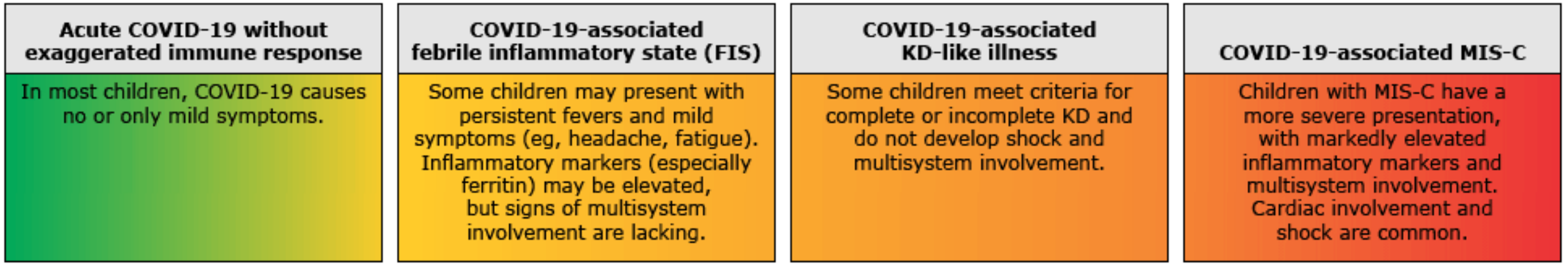
Fig. 1 | **Pathogenesis of multisystem inflammatory syndrome in children: a hypothesis.**

Rowley AH, *Nature Reviews,*2020



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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Centers for Disease Control and Prevention (CDC) Case Definition for MIS-C

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

- 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

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

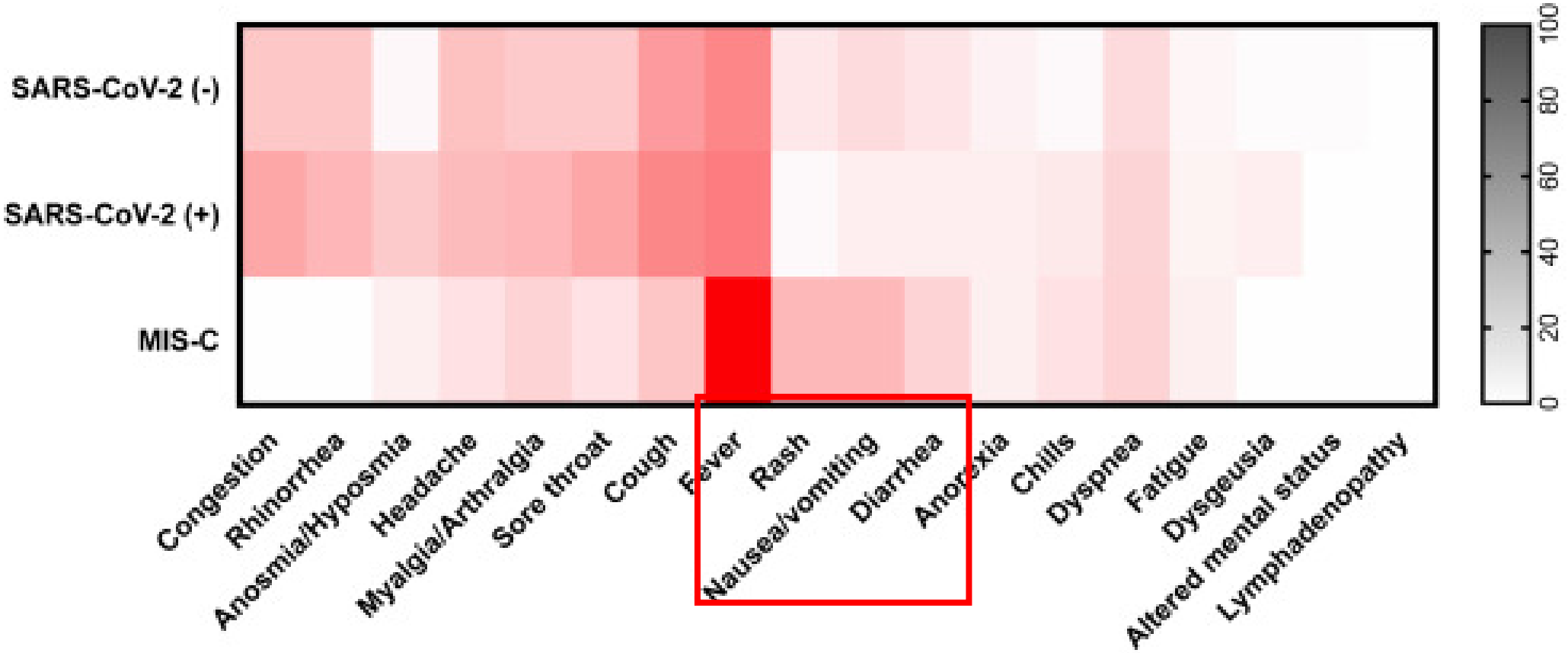
Elevated markers of inflammation such as ESR, C-reactive protein, or procalcitonin.

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.



Yonker et al. Journal of Peds, 2020

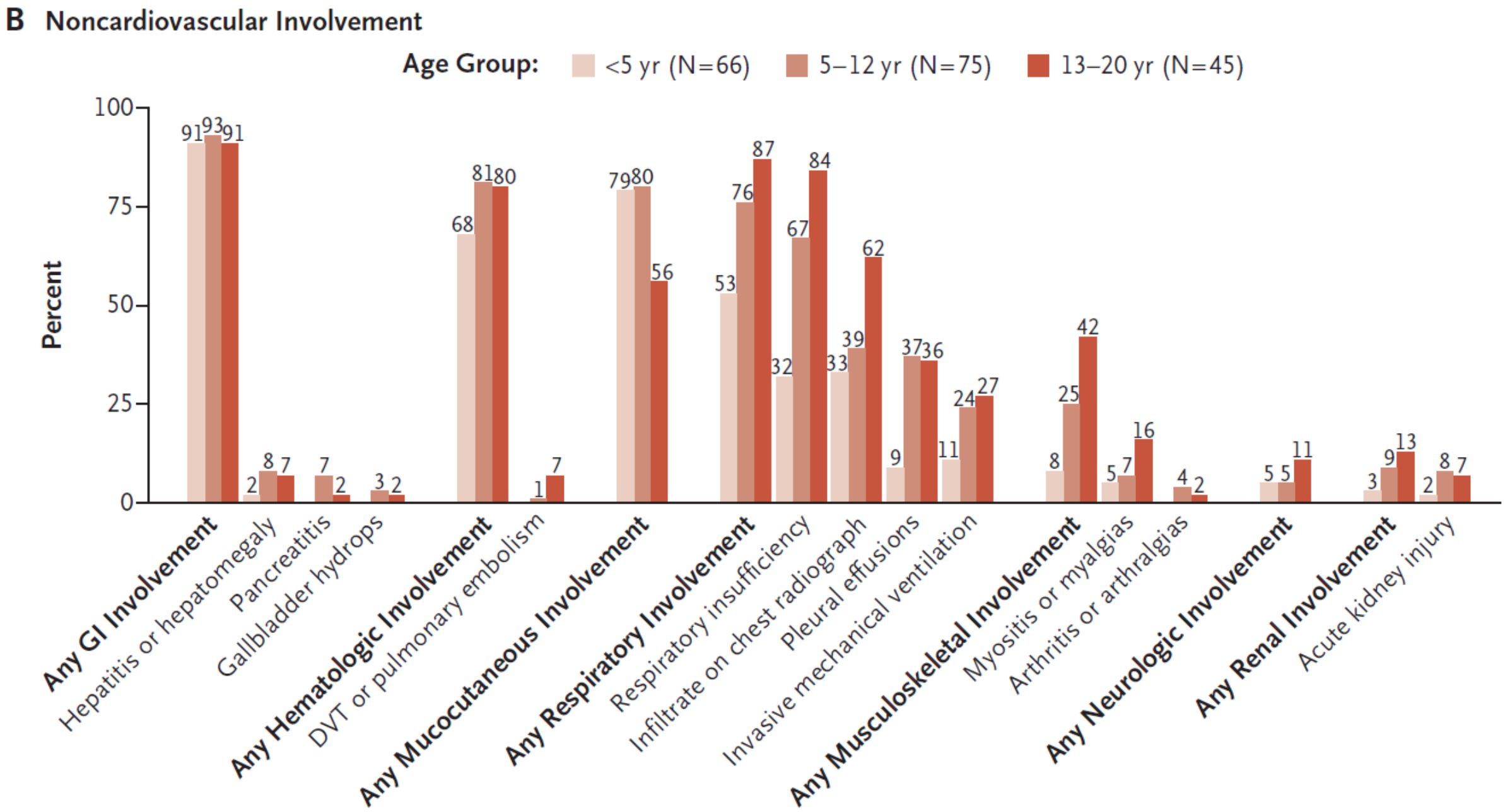
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

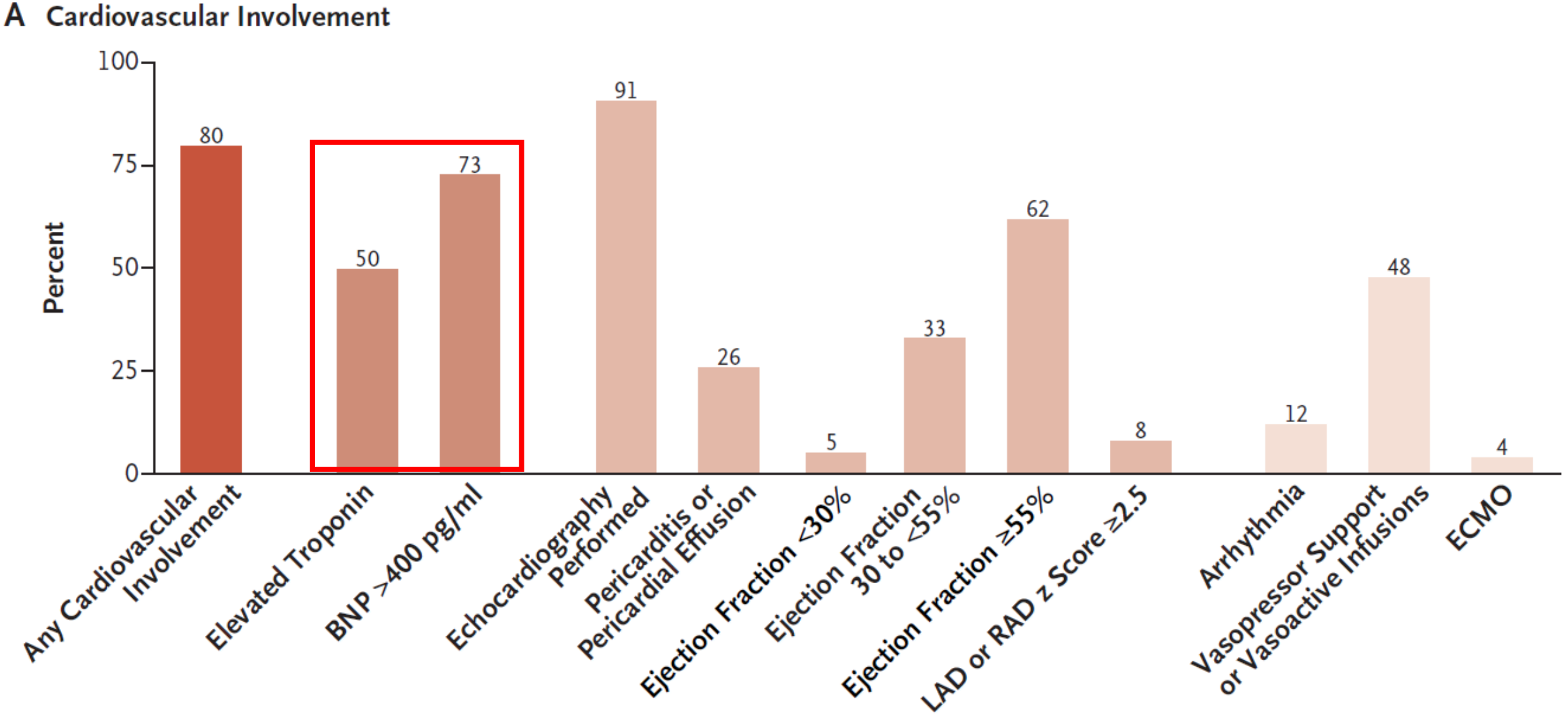
Multisystem Inflammatory Syndrome in U.S. Children and Adolescents

- 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

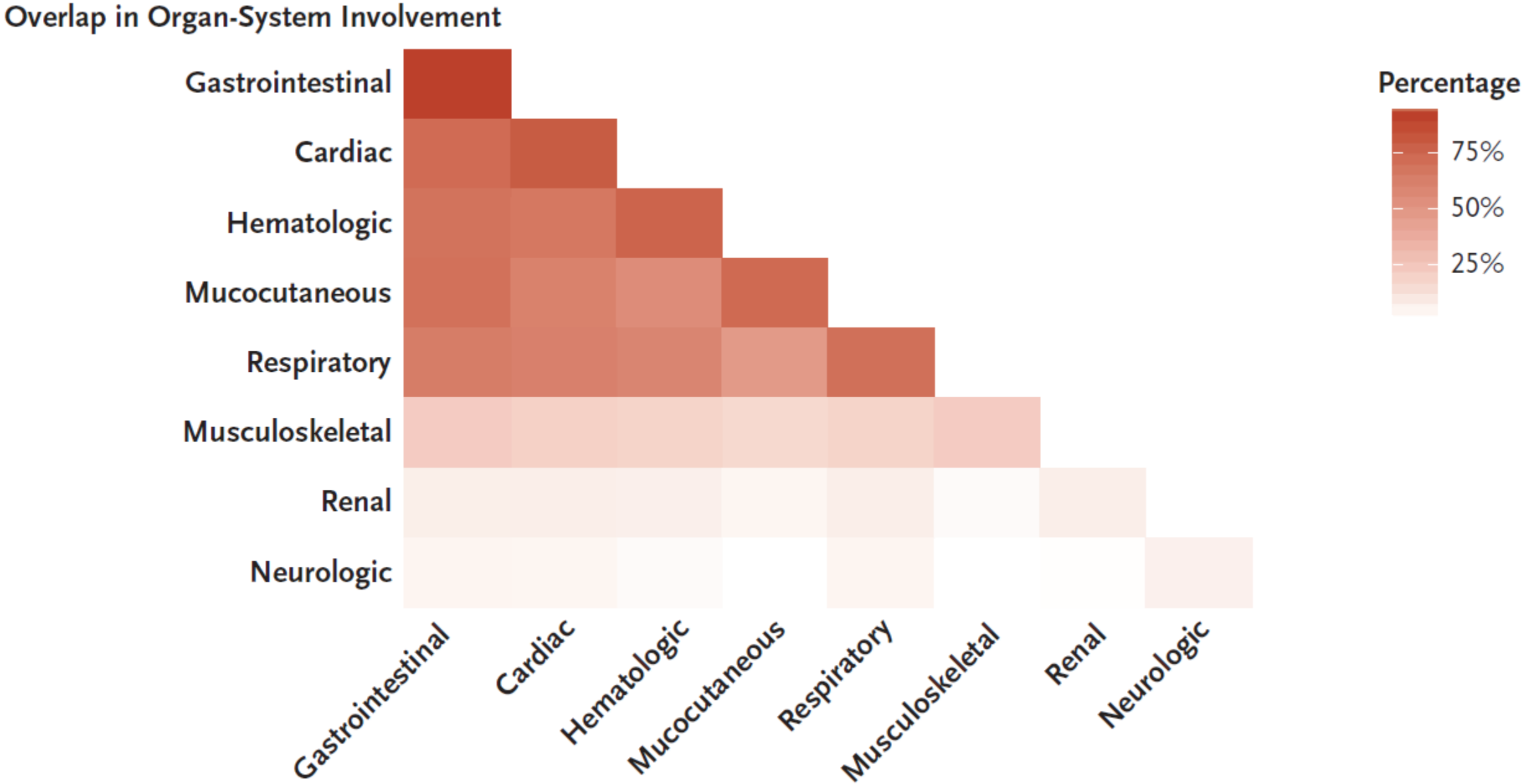
Feldstein LR, et al. *NJEM*, 2000.



Feldstein LR, et al. *NJEM*, 2000.



Feldstein LR, et al. *NJEM*, 2000.



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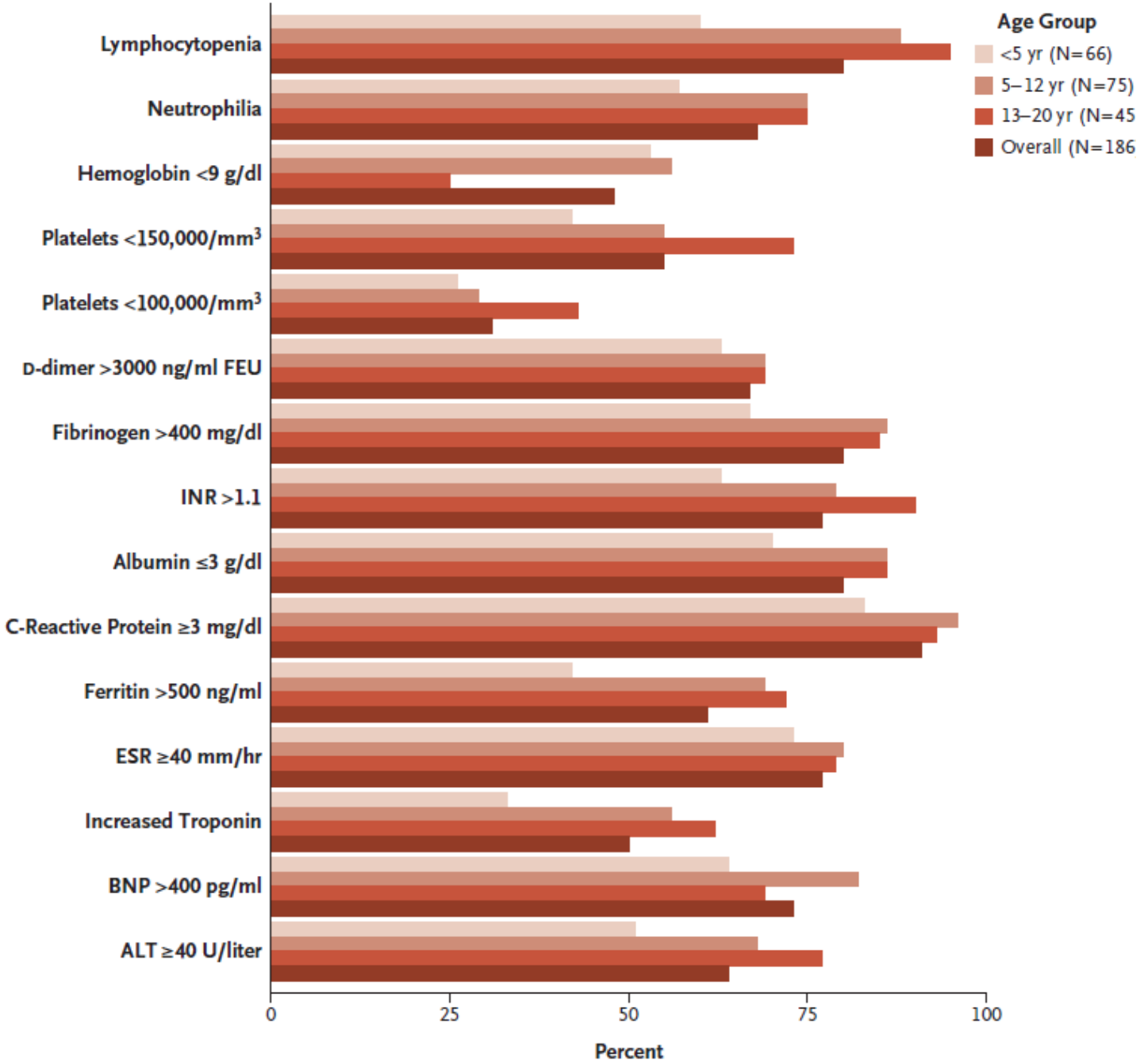


Feldstein LR, et al. *NJEM*, 2000.

Journal of the Pediatric Infectious Diseases Society

LITERATURE REVIEW

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 Vecchio[1,2]

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

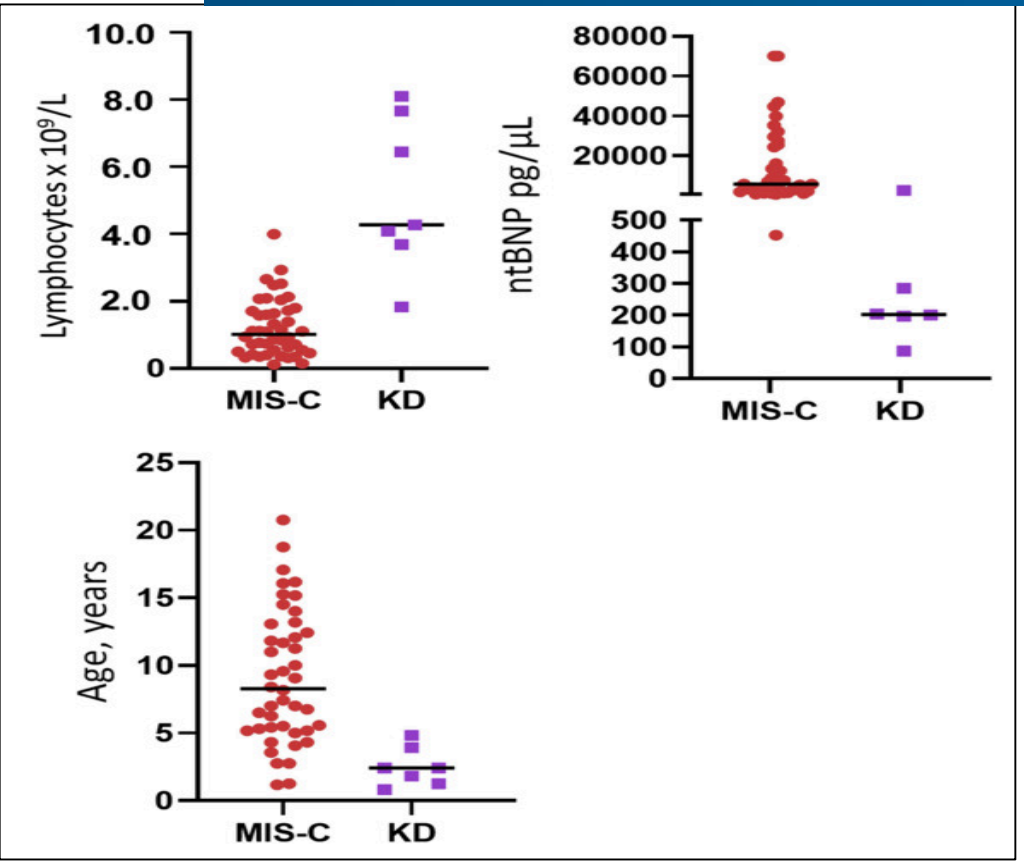
- Case reports & series recovered from MEDLINE searches performed between June 3 and July 23, 2020
- 10 articles; 16 reports describing 505 children with MIS-C
- Clinical findings: 100% fever (part of inclusion criteria), 88% gastrointestinal symptoms, 59.2 % rash, 50% conjunctivitis, 56% chelitis/strawberry 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

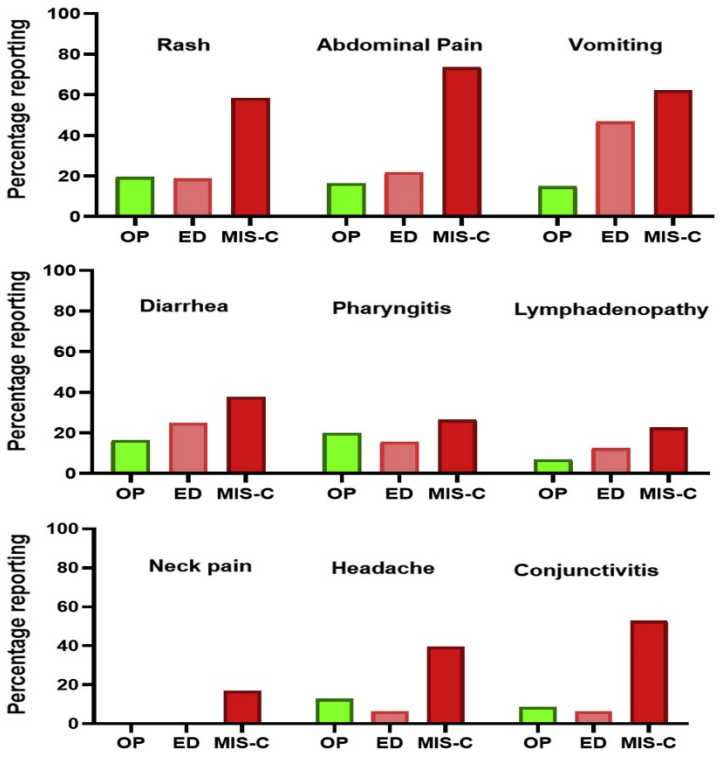
ORIGINAL ARTICLES | ARTICLES IN PRESS

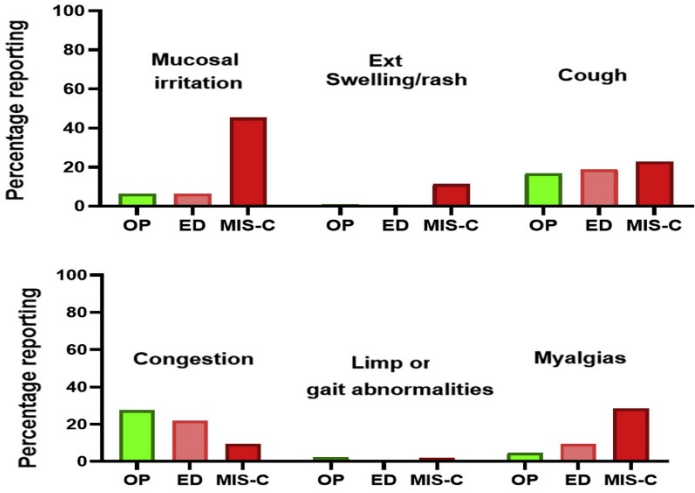
Discriminating MIS-C Requiring Treatment from Common Febrile Conditions in Outpatient Settings

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 • Show all authors • Show footnotes

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







Carlin et al. Journal of Peds, 2020

Latest CDC Data

Last updated October 30, 2020

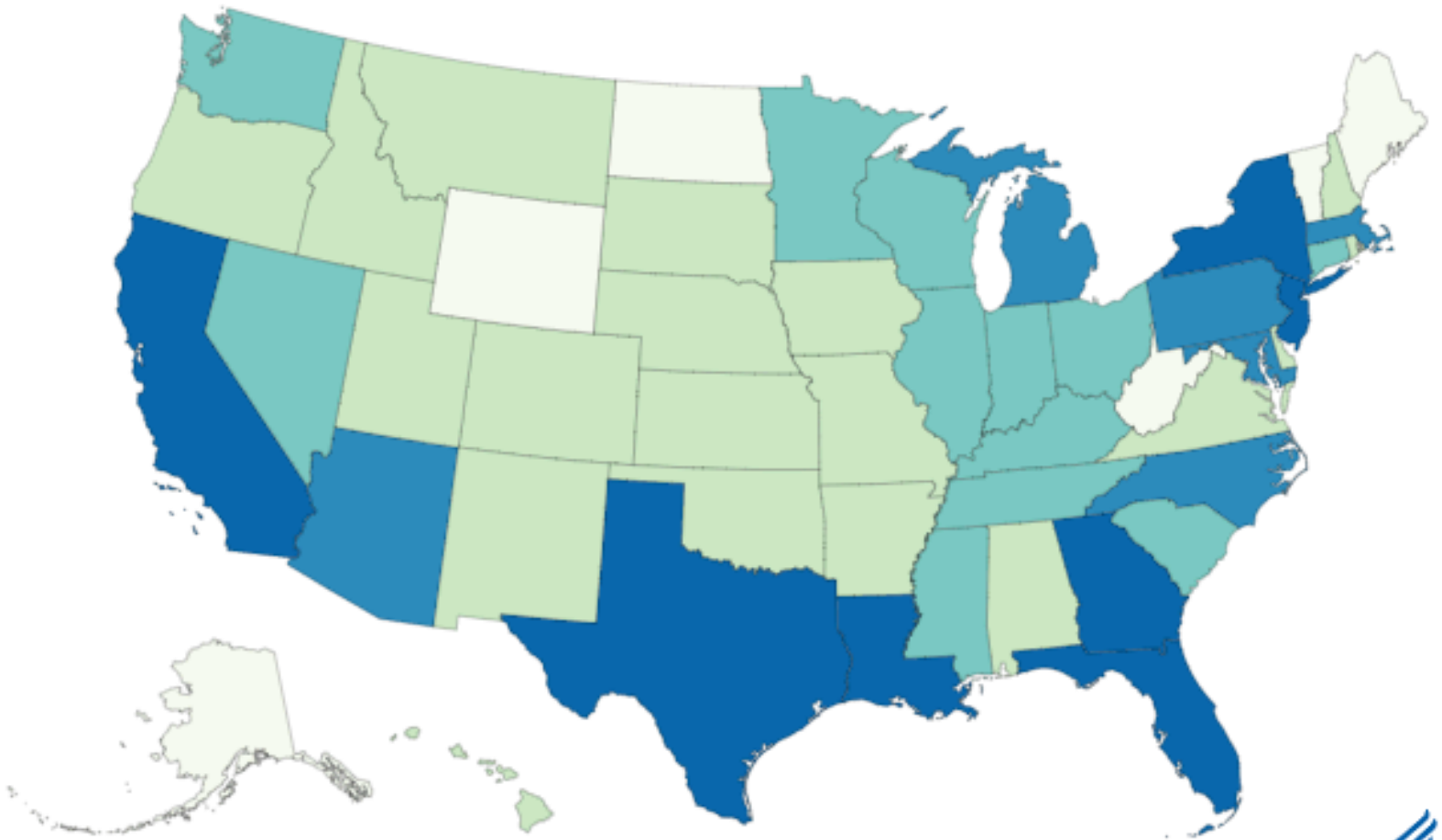
TOTAL CONFIRMED CASES*	TOTAL DEATHS
1,163	20

*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.

MIS-C Case Ranges by Territory, State, New York City, and Washington, DC*



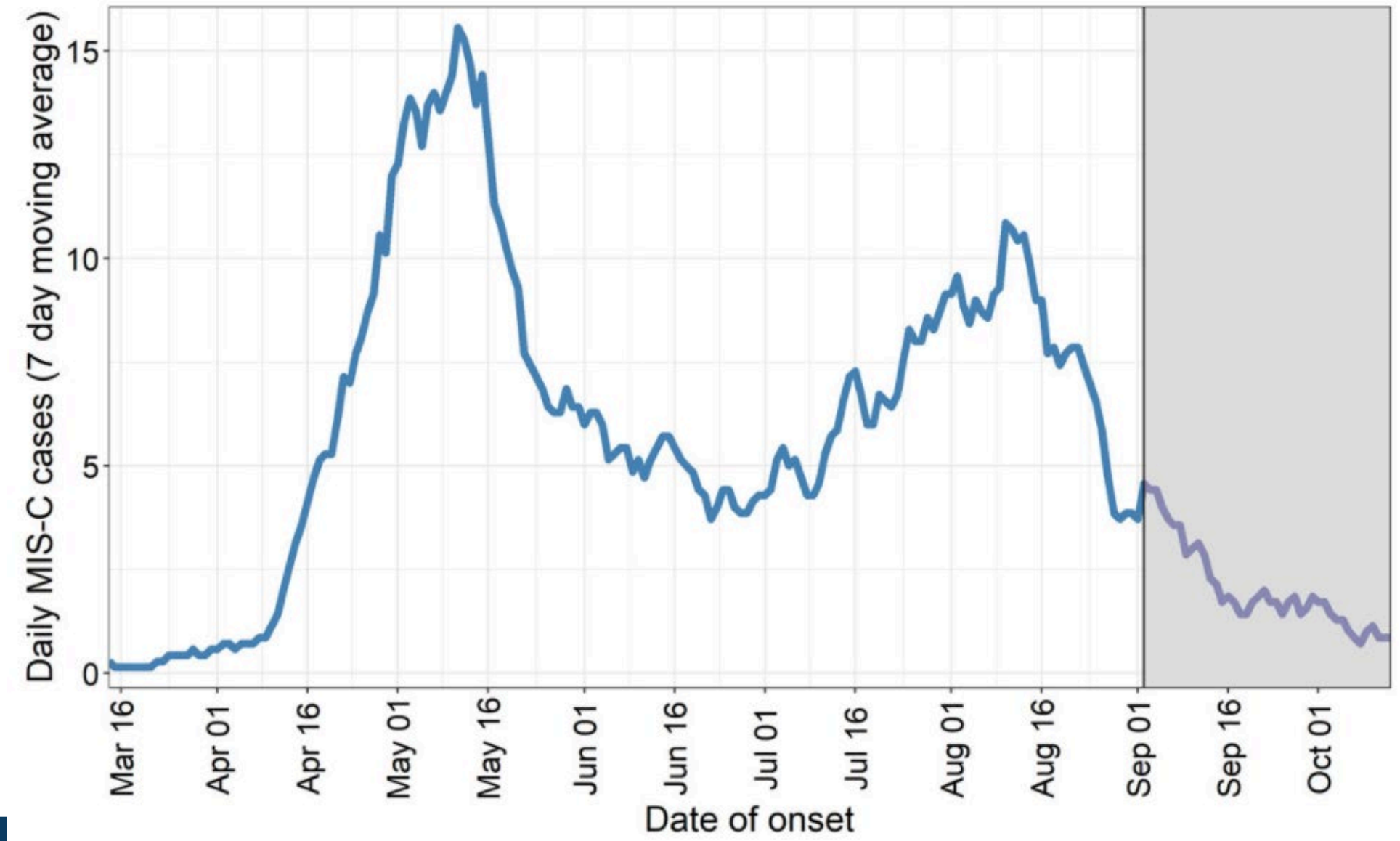
Reported MIS-C Cases

- No cases reported
- 1-10
- 11-30
- 31-50
- 51+

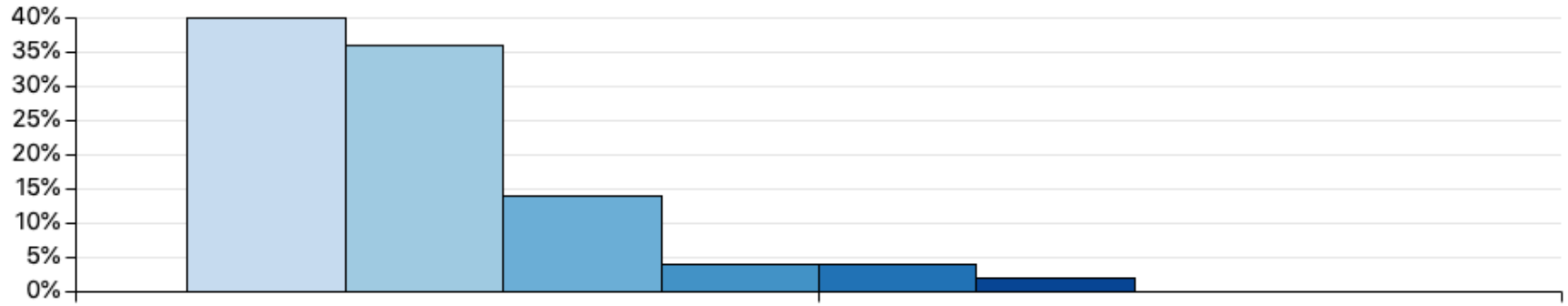
Territories AS FM GU MH MP PR PW VI

Nemours Children's Health System

Daily MIS-C Cases (Seven-Day Moving Average)



Cases by Race & Ethnicity



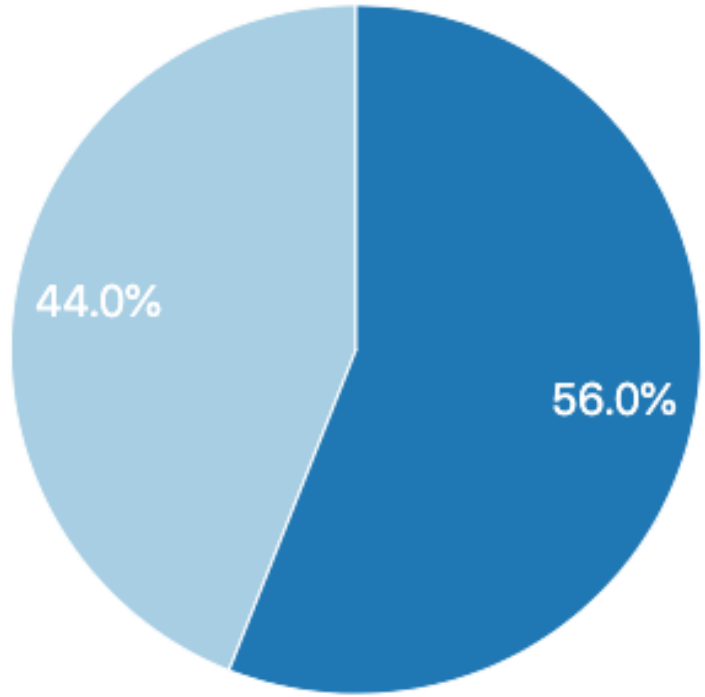
Race/Ethnicity

Hispanic/Latino | Black Non Hispanic | White Non Hispanic | Other | Multiple | Asian Non Hispanic

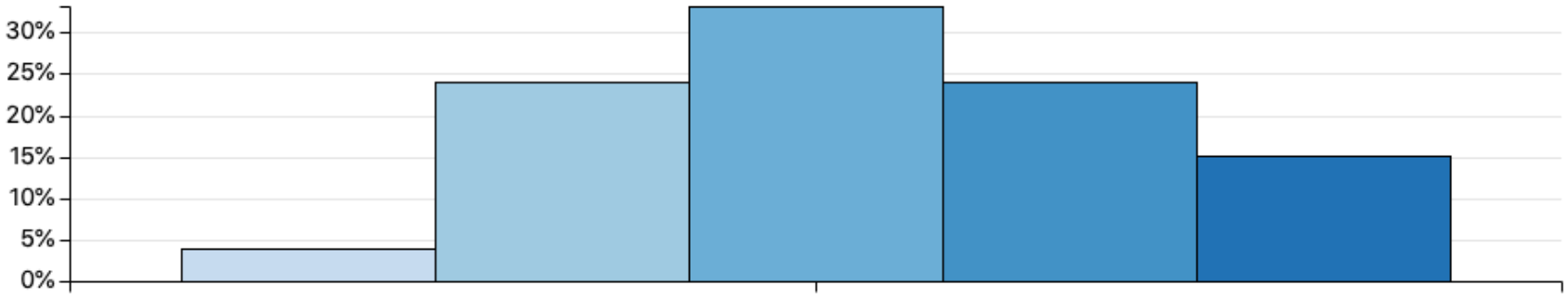
American Indian/Alaskan Native Non Hispanic | Native Hawaiian/Other Pacific Islander Non Hispanic | Reset

Cases by Gender

Female | Male | Reset



Cases by Age Group



Age (In Years)

Less than 1 | 1-4 | 5-9 | 10-14 | 15-20 | Reset

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)

Multisystem Inflammatory Syndrome in Children (MIS-C) Pathway

Nemours, Alfred I. duPont Hospital for Children

Emergency Department

INCLUSION CRITERIA

Patients <21 yo presenting with
- Fever >38°C AND no alternative dx AND ≥2 of the following:
  - GI (pain, vomiting, diarrhea, anorexia, loss of taste)
  - Rash
  - Conjunctivitis
  - Oral inflammation
  - Altered mental status
  - Extremity swelling
  - Lymphadenopathy

OR
- One or more of the following:
  - Hypotension or shock
  - Evidence of cardiac dysfunction
  - End organ involvement

EXCLUSION CRITERIA
- Alternative plausible diagnosis

[1]MIS-C Definition
- <21 yo presenting with fever >38C (or tactile) for ≥ 24 hrs AND
- Clinically severe illness requiring hospitalization AND
- Multisystem (≥2) organ involvement: cardiac, renal, pulm, heme, GI, derm, neuro AND
- Lab evidence of inflammation
  - (elevated CRP, ESR, fibrinogen, procalcitonin, d-dimer, ferritin, lactic acid, IL6, neutrophilia, lymphocytopenia, hypoalbuminemia) AND
- No alternative plausible dx AND
- Current or recent SARS-COV-2 infection by PCR or antigen test or serology; or COVID-19 exposure within 4 weeks of presentation

[2]ICU Admission Criteria
- Abnormal perfusion
- Hypotension
- Evidence of cardiac dysfunction or BNP>400 or Troponin > 0.04
- Sustained changed in mentation or perfusion
- Requiring ICU level respiratory support
- Lactate >2.5, Base deficit > -4

Initial Assessment
- Obtain and document vital signs and pulse ox
- Perform and document ED assessment
- Room to COVID screen positive zone or resuscitation bay
- Enhanced contact and droplet PPE with use of N95 for airborne generating procedures

Low Risk
- Mildly ill appearing pts presenting with ≥3 days of fever AND ≥2 symptoms from inclusion criteria

Moderate Risk
- Ill appearing pts presenting with ≥3 days of fever AND ≥2 symptoms from inclusion criteria

High Risk
- Toxic appearing OR evidence of shock OR evidence of cardiac dysfunction

Screening Evaluation
- CBC, CRP, CMP, BNP, troponin
- EKG if chest pain
- Further workup based on clinical indications

Diagnostics Normal[Pg 3]? No → Complete Evaluation; Yes → Treat other conditions as indicated

Complete Evaluation
- Screening evaluation AND
- VBG, lactic acid, ferritin, procalcitonin, UA, UCX, LDH, fibrinogen, PT/PTT, ESR, AND
- EKG
- CXR
- Consider blood culture
- Consider abdominal imaging if indicated
- Further workup based on clinical indications

Shock Management
- Fluid resuscitation with frequent re-evaluations (avoid fluid overload)
- Evaluate cardiac function
- Initiate Norepinephrine if refractory to fluids
- Send D-Dimer
- Initiate sepsis pathway (including antibiotics) if concern for septic shock

Meets MIS-C[1] Criteria? No → Off PW; Yes → Echo

Echo
- Does not need to be obtained in ED
- If BNP and troponin normal, can obtain within 24 h

Further Evaluation
- Echo (if BNP and troponin normal, can obtain within 24h)
- Further workup based on clinical indications

Treat other conditions as indicated

Discharge To Home
- Ensure f/u in 24 hours
- Anticipatory Guidance
- Return to ED for repeat labs if fevers last ≥ 5 days or if new symptoms from inclusion criteria develop

Admit to Hospital
- Send rapid SARS-COV-2 PCR when available otherwise send immunology SARS-COV-2 PCR
- Admit to ICU if meets ICU criteria, otherwise admit to general inpt unit
- Consult CICU if requires VA ECMO or known underlying complex cardiac condition

See page 2

Multisystem Inflammatory Syndrome in Children (MIS-C) Pathway

Nemours, Alfred I. duPont Hospital for Children

Inpatient

Page 1

Isolation
- If SARS-COV-2 PCR positive: Enhanced contact and droplet PPE with use of N95 for airborne generating procedures
- If SARS-COV-2 PCR negative: Standard precautions

Admission Diagnostic Evaluation
- SARS-COV-2 IGG if PCR is negative
- Labs listed on page 1 if not already completed
- To consider cytokine panel on a case by case basis
- Perform Echo if not completed in ED. If troponin and BNP normal, can obtain Echo within 24 hrs.

Ongoing Diagnostic Evaluation
- Send following labs every 24 hrs X2 then every 2-3 days as per care team's discretion
  - CBC/diff, ESR, CRP, procalcitonin, CMP, LDH, ferritin, PT/PTT, fibrinogen, D-dimer, BNP, troponin
- Troponin q6hrs if initially elevated
- EKG as needed per cardiology
- Echo
  - For pts with abnormal Echo, repeat every 1-2 days or as needed, and prior to discharge.
  - For pts with normal Echo, repeat prior to discharge. If they have prolonged fever or hemodynamic instability, obtain at discretion of cardiology

Consults
- Cardiology
- ID
- Rheumatology
- Hematology as needed

Meets diagnostic criteria from Pg 1? Yes → Therapies; No → Therapies

Therapies
- Steroids: start early for moderate or high risk
- IVIG: start early
- High dose aspirin if Kawasaki like presentation or not treating with steroids
- Enoxaparin: start early for high risk, consider for moderate risk (discuss with Heme)
- Antivirals: may consider remdesivir for significant respiratory distress (discuss with ID)
- Proton pump inhibitor for GI prophylaxis
- Pressors as indicated
- Continue broad spectrum antibiotics as per sepsis pathway until cultures result

See page 4

Therapies
- Consider other diagnoses
- Treat accordingly

COVID 19 Positive
- Consider Echo in 2 weeks if recurrence of fever or inflammatory symptoms

Reporting
- To department of health by infection prevention/control

Discharge Criteria
- Sats ≥ 95% on RA
- Tolerates PO
- Hemodynamically stable > 48 hrs
- Normal cardiac function
- Afebrile >48 hrs
- Inflammatory markers, troponin, BNP trending downwards

Discharge Instructions
- Continue low dose aspirin as per page 4
- Switch to low dose aspirin if on enoxaparin prophylaxis
- F/u cardiology and rheumatology in 2 weeks
- F/u hematology if anticoagulated

At Follow-up Visit
- CBC, CMP, CRP, BNP as needed
- EKG, Echo
- Consider cardiac MRI, holter if cardiac involvement was significant

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

Management by Clinical Severity			
Medication	**Mild Disease (Meets MIS-C definition and mildly ill appearing)**	**Moderate Disease (Meets MIS-C definition and Ill appearing without hemodynamic instability)**	**Severe Disease (Meets MIS-C definition and critically ill with hemodynamic instability)**
Methylprednisolone	Consider not treating with steroids and start high dose aspirin.	Start 1 mg/kg/dose BID (no max dose).	Start pulse dose regimen: 30 mg/kg/dose once daily for 3 days (max 1 g/day). Consult rheumatology for steroid taper.
Aspirin	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.	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.	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.
IVIG (Privigen 10%)	First dose: 2 g/kg (max 160 g). If second dose is approved, repeat 2 g/kg (max 100 g).	First dose: 2 g/kg (max 160 g). If second dose is approved, repeat 2 g/kg (max 100 g).	First dose: 2 g/kg (max 160 g). If second dose is approved, repeat 2 g/kg (max 100 g).
Enoxaparin	N/A	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.	Start prophylactic enoxaparin (dosed/monitored per AIDHC protocol) and consult hematology for further guidance.
Anakinra/Tocilizumab	Consider if resistant to initial treatment with IVIG/steroids. Consult rheumatology for dosing guidance.		
Remdesivir	To be used on a case-by-case basis. Consult ID for medication procurement and dosing guidance.		

Morbidity and Mortality Weekly Report

Case Series of Multisystem Inflammatory Syndrome in Adults Associated with SARS-CoV-2 Infection — United Kingdom and United States, March–August 2020

Sapna Bamrah Morris, MD[1]; Noah G. Schwartz, MD[1,2]; Pragna Patel, MD[1]; Lilian Abbo, MD[3]; Laura Beauchamps, MD[3]; Shuba Balan, MD[3]; Ellen H. Lee, MD[4]; Rachel Paneth-Pollak, MD[4]; Anita Geevarughese, MD[4]; Maura K. Lash, MPH[4]; Marie S. Dorsinville, MPH[4]; Vennus Ballen, MD[4]; Daniel P. Eiras, MD[4]; Christopher Newton-Cheh, MD[5,6]; Emer Smith, MPH[7,8]; Sara Robinson, MPH[7]; Patricia Stogsdill, MD[9]; Sarah Lim, MBBCh[10]; Sharon E. Fox, MD, PhD[11,12]; Gillian Richardson, MPH[13]; Julie Hand, MSPH[13]; Nora T. Oliver, MD[14]; Aaron Kofman, MD[15]; Bobbi Bryant, MPH[1,16]; Zachary Ende, PhD[1,16]; Deblina Datta, MD[1]; Ermias Belay, MD[1]; Shana Godfred-Cato, DO[1]