# Multisystem Inflammatory Syndrome in Children (MIS-C)

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# Disclosures

- I have no financial disclosures to report
- NINDS Child Neurology Career Development Program-K12
- Site PI for Neurologic Manifestations of Covid-19 (Pediatric Arm)
- Co-PI on Maternal-Infant Covid Collaborative

# Outline

- Definition and clinical description
- Similarities to and differences from Kawasaki disease
- Diagnostic testing
- Proposed pathophysiology
- Treatments

# Timeline of MIS-C

| | |
|---|---|
| 11 March 2020 | • Covid-19 Pandemic declaration by World Health Organization |
| 27 April 2020 | • United Kingdom National Health Service issues an alert highlighting a multisystem inflammatory syndrome citing possible link to severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) |
| 5 May 2020 | • New York City Department of Health issues a health alert including 15 similar cases |
| 6 May 2020 | • London, England report of clinical and laboratory features of a cluster of 8 children with hyperinflammatory shock, all of whom tested positive for SARS-CoV-2 antibodies |
| 14 May 2020 | • Centers for Disease Control and Prevention issues a public health advisory and case definition for this hyperinflammatory syndrome, termed multisystem inflammatory syndrome in children (MIS-C) |

Chiotos, et al. Journal of the Pediatric Infectious Diseases Society 2020

# Definition of MIS-C

An individual aged <21 years presenting with:

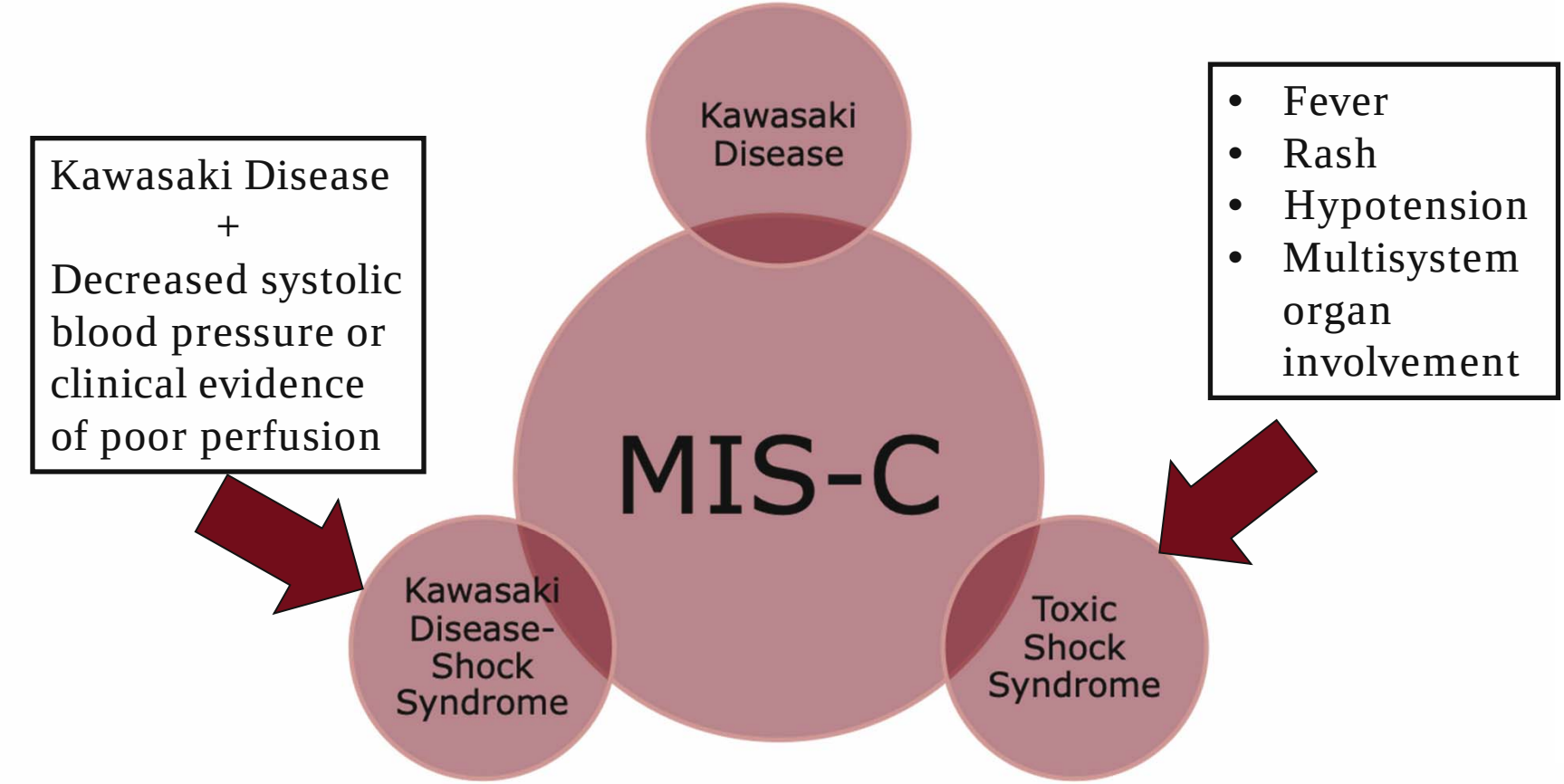
- Fever
- Laboratory evidence of inflammation
- Evidence of clinically severe illness requiring hospitalization
- Multisystem (≥2) organ involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic or neurological); **AND**

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

https://emergency.cdc.gov/han/2020/han00432.asp

# Overlap with Known Syndromes

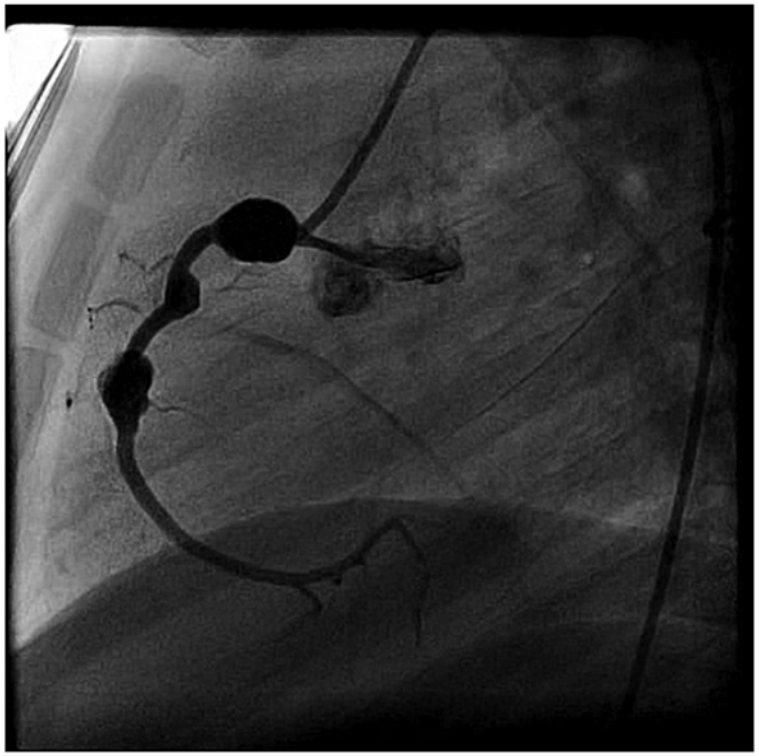



Kanegaye et al., Pediatrics May 2009, 123 (5) e783-e789

Ross A, Shoff HW. In: StatPearls [Internet]; 2020 Jan

# What is Kawasaki Disease?

- Vasculitis of medium-sized arteries with predilection for the coronary arteries.
- Remains a diagnosis based on clinical criteria
- All signs and symptoms resolve after the acute illness (even in the absence of treatment)
- Coronary artery lesions develop in 3% to 5% of children treated with intravenous immunoglobulin (IVIG) and in up to 25% of untreated children

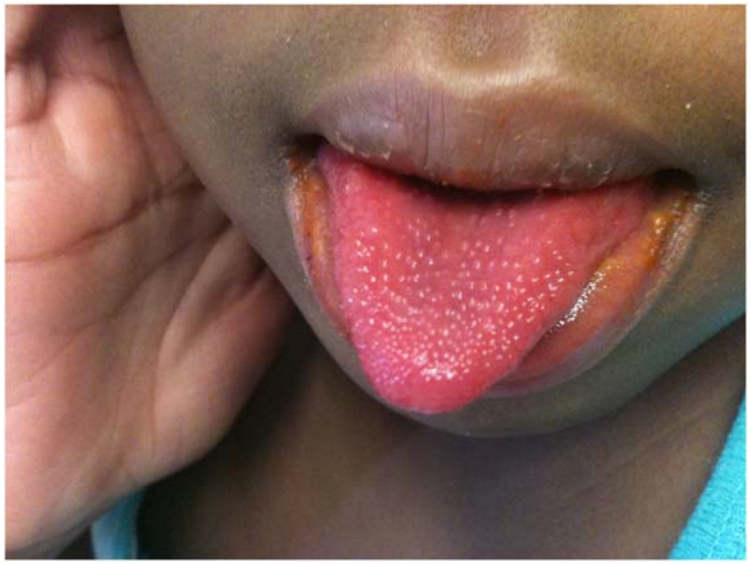


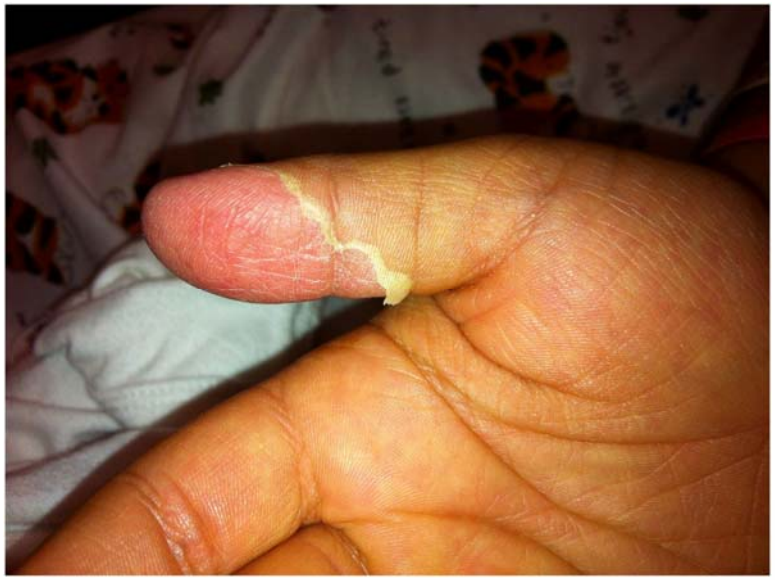
MBF Son and JW Newburger. *Peds in Review* 2018;39:78-90.

# Clinical Criteria for Kawasaki Disease

Presence of fever for at least 5 days together with ≥4 of the 5 following principal clinical features:

1. Erythema and cracking of lips, strawberry tongue, and/or erythema of the oral and pharyngeal mucosa
2. Bilateral bulbar conjunctival injection without exudate
3. Rash: maculopapular diffuse erythroderma or erythema multiforme-like
4. Erythema and edema of hands and feet in the acute phase and/or periungual desquamation in the subacute phase
5. Cervical lymphadenopathy (≥1.5 cm in diameter), usually unilateral





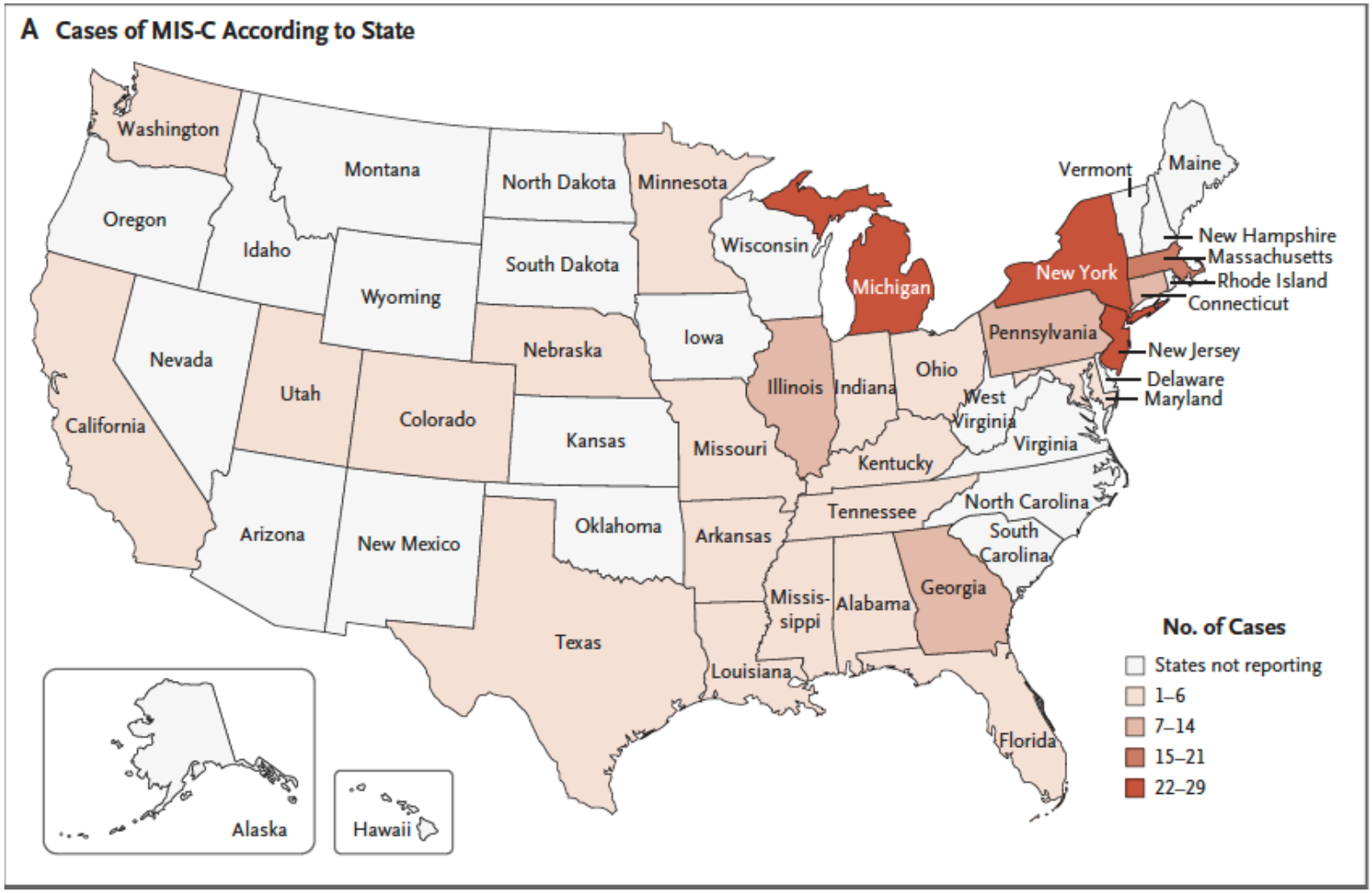
MBF Son and JW Newburger. *Peds in Review* 2018;39:78-90.

ORIGINAL ARTICLE

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

L.R. Feldstein, E.B. Rose, S.M. Horwitz, J.P. Collins, M.M. Newhams, M.B.F. Son, J.W. Newburger, L.C. Kleinman, S.M. Heidemann, A.A. Martin, A.R. Singh, S. Li, K.M. Tarquinio, P. Jaggi, M.E. Oster, S.P. Zackai, J. Gillen, A.J. Ratner, R.F. Walsh, J.C. Fitzgerald, M.A. Keenaghan, H. Alharash, S. Doymaz, K.N. Clouser, J.S. Giuliano, Jr., A. Gupta, R.M. Parker, A.B. Maddux, V. Havalad, S. Ramsingh, H. Bukulmez, T.T. Bradford, L.S. Smith, M.W. Tenforde, C.L. Carroll, B.J. Riggs, S.J. Gertz, A. Daube, A. Lansell, A. Coronado Munoz, C.V. Hobbs, K.L. Marohn, N.B. Halasa, M.M. Patel, and A.G. Randolph, for the Overcoming COVID-19 Investigators and the CDC COVID-19 Response Team*

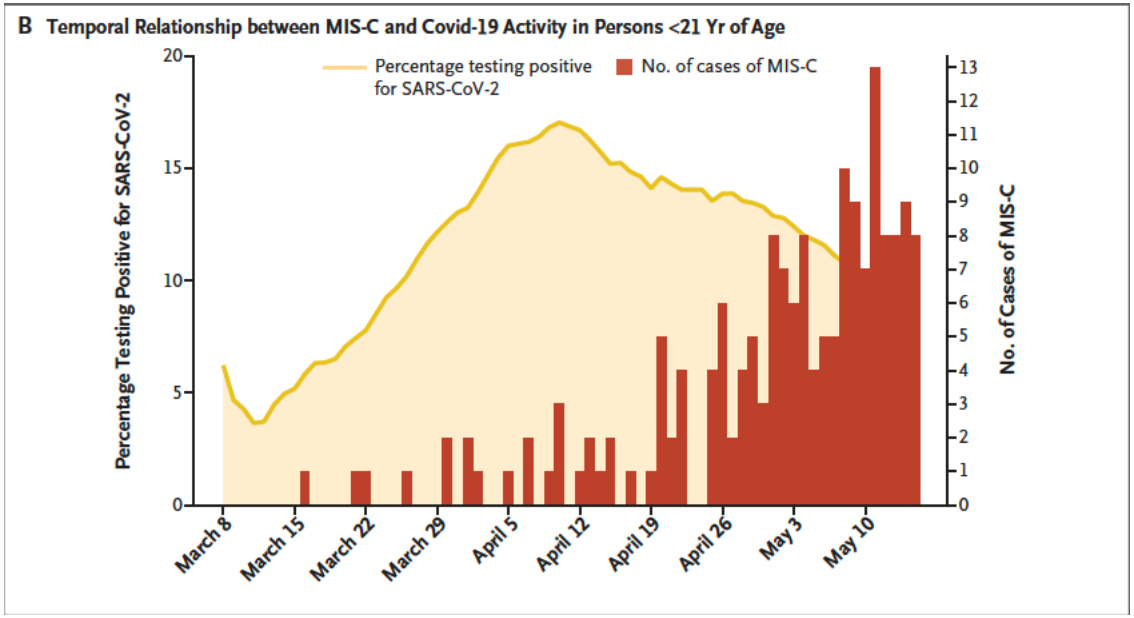
- 186 patients from 26 U.S. states
- Median age 8.3 years, 62% male, 73% previously healthy
- 70% positive by viral PCR or Ab testing
- 80% received intensive care
- 2% died
- Use of immunomodulating therapies common




Feldstein et al., *N Engl J Med* 2020; 383:334-346

# Timecourse

- Lag in presentation from infection
- Median interval between onset of Covid-19 symptoms and MIS-C was 25 days



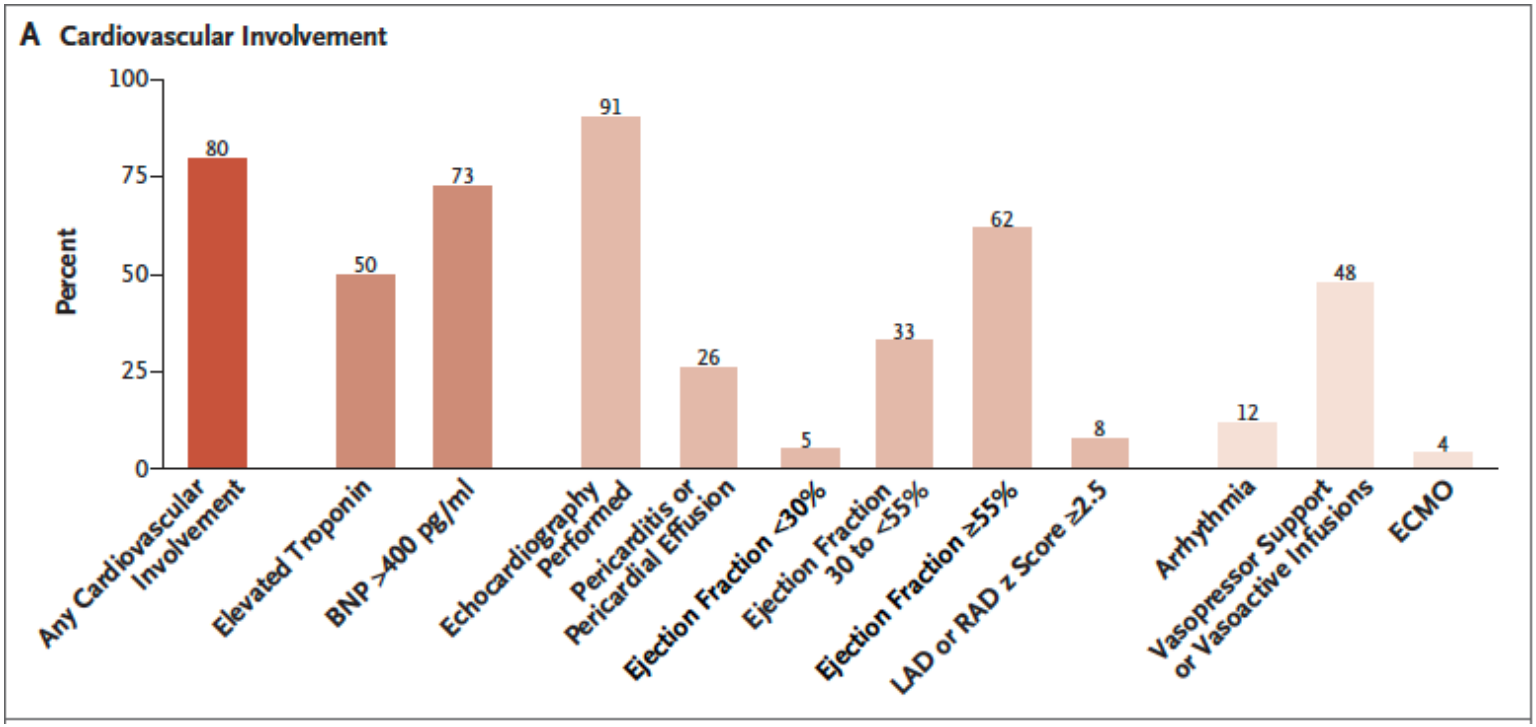

Feldstein et al., N Engl J Med 2020; 383:334-346

# Racial Disparity in Affected Children

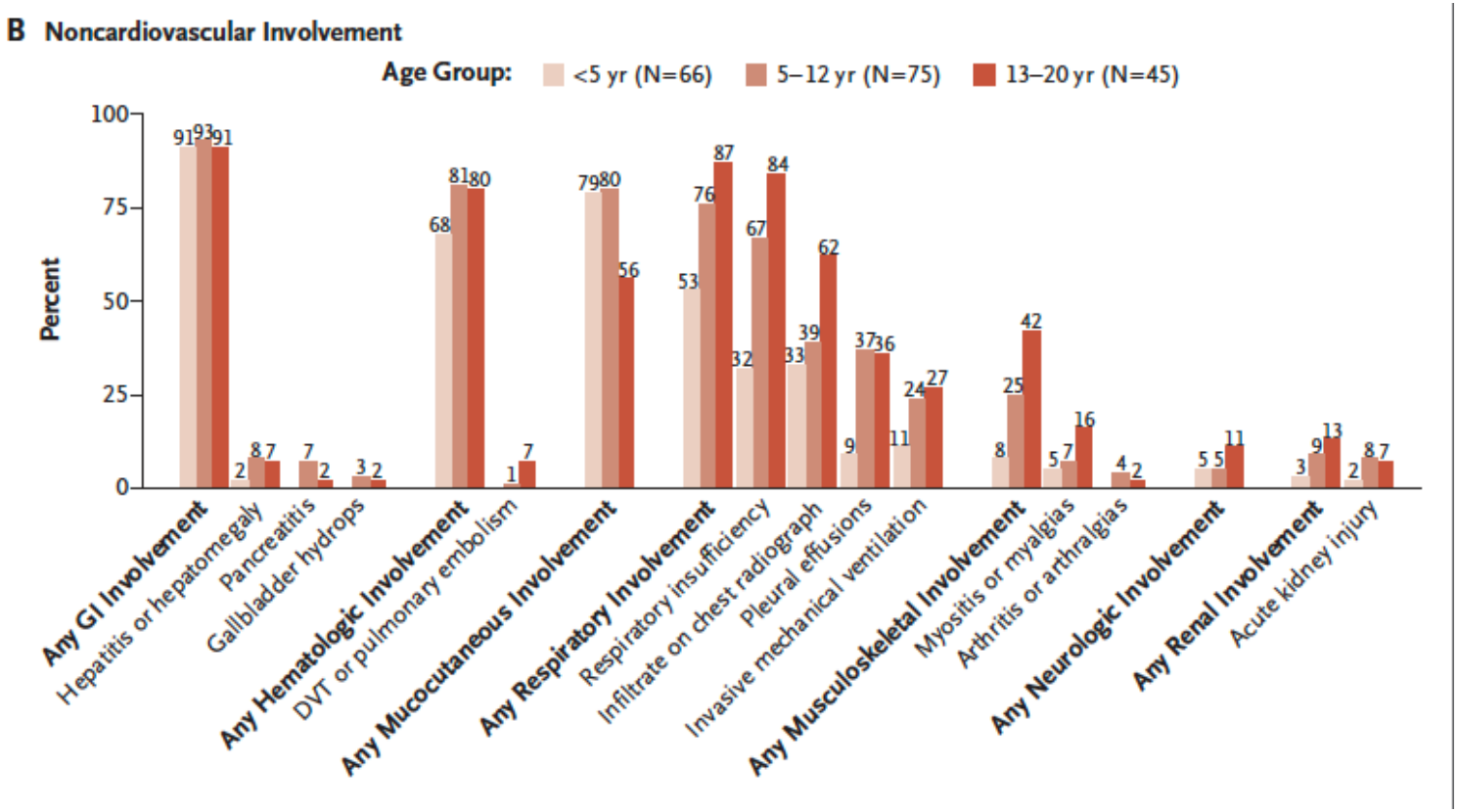
**Table 1. Demographic and Clinical Characteristics of the Patients According to SARS-CoV-2 Infection Status.**

| Characteristic | Laboratory Confirmation of SARS-CoV-2 Infection (N=131) | | Epidemiologic Link to Person with Covid-19 (N=55)* | All Patients (N=186) |
|---|---|---|---|---|
| | RT-PCR Positive (N=73)† | Antibody Test Positive, RT-PCR Negative or Unknown (N=58) | | |
| Male sex — no. (%) | 43 (59) | 36 (62) | 36 (65) | 115 (62) |
| Median age (interquartile range) — yr | 9.1 (4.8–14.2) | 9.1 (4.1–11.7) | 3.9 (1.4–11.6) | 8.3 (3.3–12.5) |
| Age group — no. (%) | | | | |
| <1 yr | 6 (8) | 0 | 7 (13) | 13 (7) |
| 1–4 yr | 13 (18) | 19 (33) | 21 (38) | 53 (28) |
| 5–9 yr | 21 (29) | 14 (24) | 11 (20) | 46 (25) |
| 10–14 yr | 17 (23) | 18 (31) | 10 (18) | 45 (24) |
| 15–20 yr | 16 (22) | 7 (12) | 6 (11) | 29 (16) |
| Race and ethnic group — no. (%)‡ | | | | |
| White, non-Hispanic | 13 (18) | 8 (14) | 14 (25) | 35 (19) |
| Black, non-Hispanic | 17 (23) | 18 (31) | 11 (20) | 46 (25) |
| Hispanic or Latino | 29 (40) | 12 (21) | 16 (29) | 57 (31) |
| Other race, non-Hispanic | 4 (5) | 1 (2) | 4 (7) | 9 (5) |
| Unknown | 11 (15) | 19 (33) | 11 (20) | 41 (22) |

Feldstein et al., N Engl J Med 2020; 383:334-346




Feldstein et al., N Engl J Med 2020; 383:334-346




Feldstein et al., N Engl J Med 2020; 383:334-346

**Table 2. Clinical Characteristics of the Patients According to the Number of Kawasaki's Disease–like Features Present.***

| Characteristic | Patients with 4 or 5 Features (N=38) | Patients with 2 or 3 Features plus Laboratory Findings (N=36) | Other (N=112)† | All Patients (N=186) |
|---|---|---|---|---|
| **Treatment** | | | | |
| Intravenous immune globulin — no. (%) | 38 (100) | 35 (97) | 71 (63) | 144 (77) |
| Median day of illness on which treatment was received (IQR) | 6 (6–8) | 7 (6–8) | 6 (5–8) | 6 (5–8) |
| Second dose received — no. (%) | 16 (42) | 9 (25) | 14 (12) | 39 (21) |
| Systemic glucocorticoid — no. (%) | 20 (53) | 18 (50) | 53 (47) | 91 (49) |
| Interleukin-6 inhibitor — no. (%)‖ | 1 (3) | 1 (3) | 12 (11) | 14 (8) |
| Interleukin-1Ra inhibitor — no. (%)** | 5 (13) | 6 (17) | 13 (12) | 24 (13) |
| Anticoagulation therapy — no. (%)†† | 14 (37) | 18 (50) | 55 (49) | 87 (47) |

Feldstein et al., N Engl J Med 2020; 383:334-346

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

- 58 children from 8 hospitals in England
- Meeting pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS) criteria
- Median age 9 years
- GI symptoms also common in this cohort
- Compared data to clinical characteristics of patients with KD, KD shock syndrome and toxic shock syndrome admitted to hospitals in Europe and the US

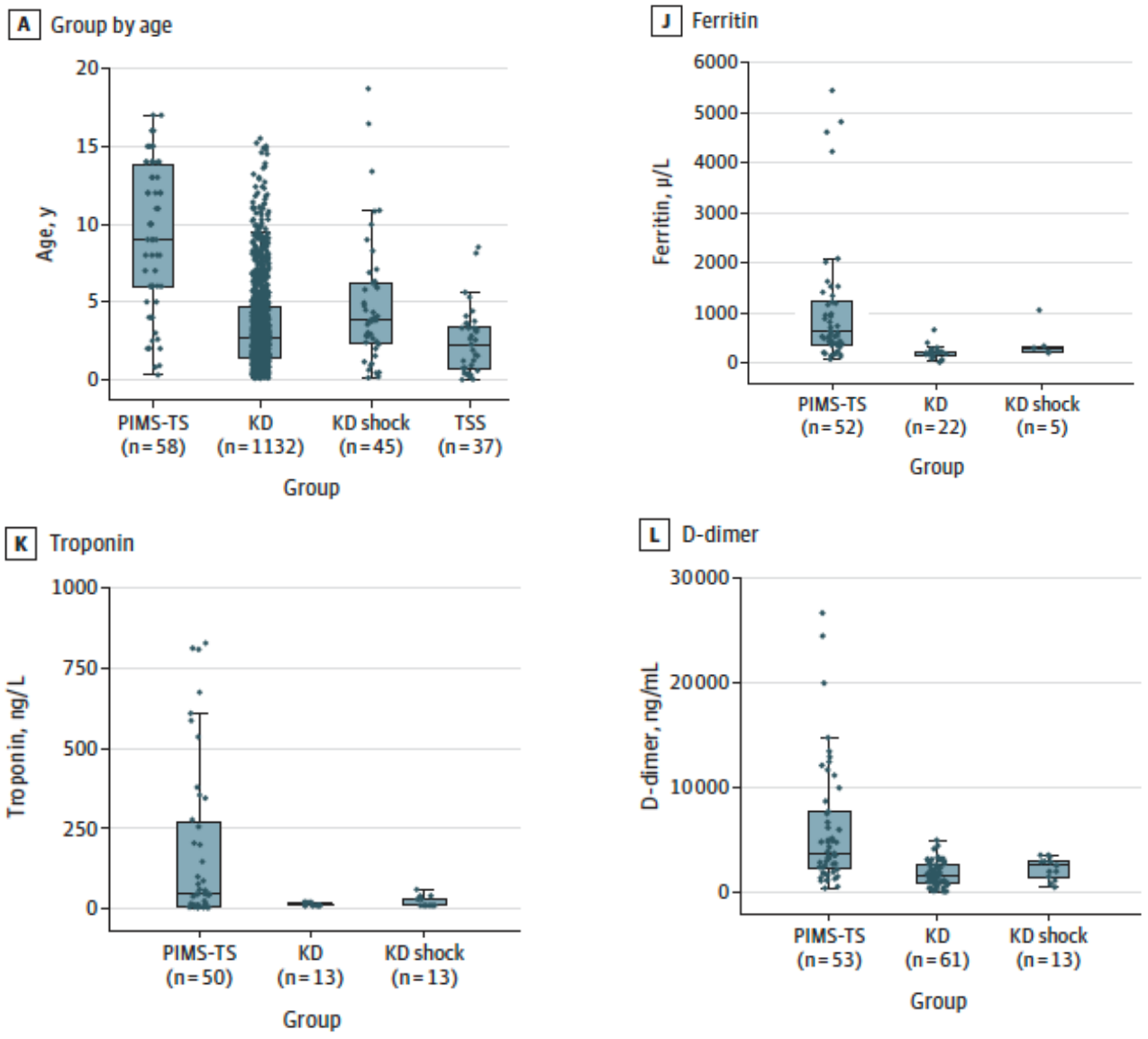
# PIMS-TS

- A child presenting with persistent fever, inflammation (neutrophilia, elevated CRP, and lymphopenia) and evidence of single or multiorgan dysfunction (shock, cardiac, respiratory, kidney, gastrointestinal, or neurological disorder) with additional features

- Exclusion of any other microbial cause, including bacterial sepsis, staphylococcal or streptococcal shock syndromes, infections associated with myocarditis such as enterovirus (waiting for results of these investigations should not delay seeking expert advice)

- SARS-CoV-2 PCR test results may be positive or negative

Whittaker et al., *JAMA*. 2020;324(3):259-269.




Whittaker et al., *JAMA*. 2020;324(3):259-269.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

# Multisystem Inflammatory Syndrome in Children in New York State

Elizabeth M. Dufort, M.D., Emilia H. Koumans, M.D., M.P.H., Eric J. Chow, M.D., M.P.H., Elizabeth M. Rosenthal, M.P.H., Alison Muse, M.P.H., Jemma Rowlands, M.P.H., Meredith A. Barranco, M.P.H., Angela M. Maxted, D.V.M., Ph.D., Eli S. Rosenberg, Ph.D., Delia Easton, Ph.D., Tomoko Udo, Ph.D., Jessica Kumar, D.O., Wendy Pulver, M.S., Lou Smith, M.D., Brad Hutton, M.P.H., Debra Blog, M.D., M.P.H., and Howard Zucker, M.D., for the New York State and Centers for Disease Control and Prevention Multisystem Inflammatory Syndrome in Children Investigation Team*

- 95 patients with confirmed and 4 with suspected MIS-C
- 54% male
- 40% black, 36% Hispanic
- 80% with GI symptoms
- 62% received vasopressor support, 53% with myocarditis
- 80% admitted to ICU
- 2 died

| Symptom Category | 0–5 Years (N=31) | 6–12 Years (N=42) | 13–20 Years (N=26) |
|---|---|---|---|
| Dermatologic or mucocutaneous | 87.1 | 78.6 | 61.5 |
| Gastrointestinal | 74.2 | 83.3 | 80.8 |
| KD or atypical KD | 48.4 | 42.9 | 11.5 |
| Myocarditis | 38.7 | 50.0 | 73.1 |
| Neurologic | 12.9 | 38.1 | 38.5 |


**Figure 1. Syndrome Clusters According to Age Group among Patients with Multisystem Inflammatory Syndrome in Children (MIS-C).**

Dufort et al, N Engl J Med 2020; 383:347-358

# Comparing Kawasaki's disease to MIS-C

Kawasaki's

- Age at presentation ~2-5 years
- Thrombocytosis
- Isolated coronary artery aneurysm pathology

MIS-C

- Age at presentation older
- Increased need for vasopressor/ inotropic support
- Prominent cardiac dysfunction with associated troponin leak, elevated BNPs
- Association with severe enteropathy
- Thrombocytopenia
- *Associated neurologic symptoms including headache, irritability (i.e., encephalopathy) and nuchal rigidity

Chiotos et al., *J. Ped. Infectious Diseases Society*. July 2020.

# Proposed pathophysiology

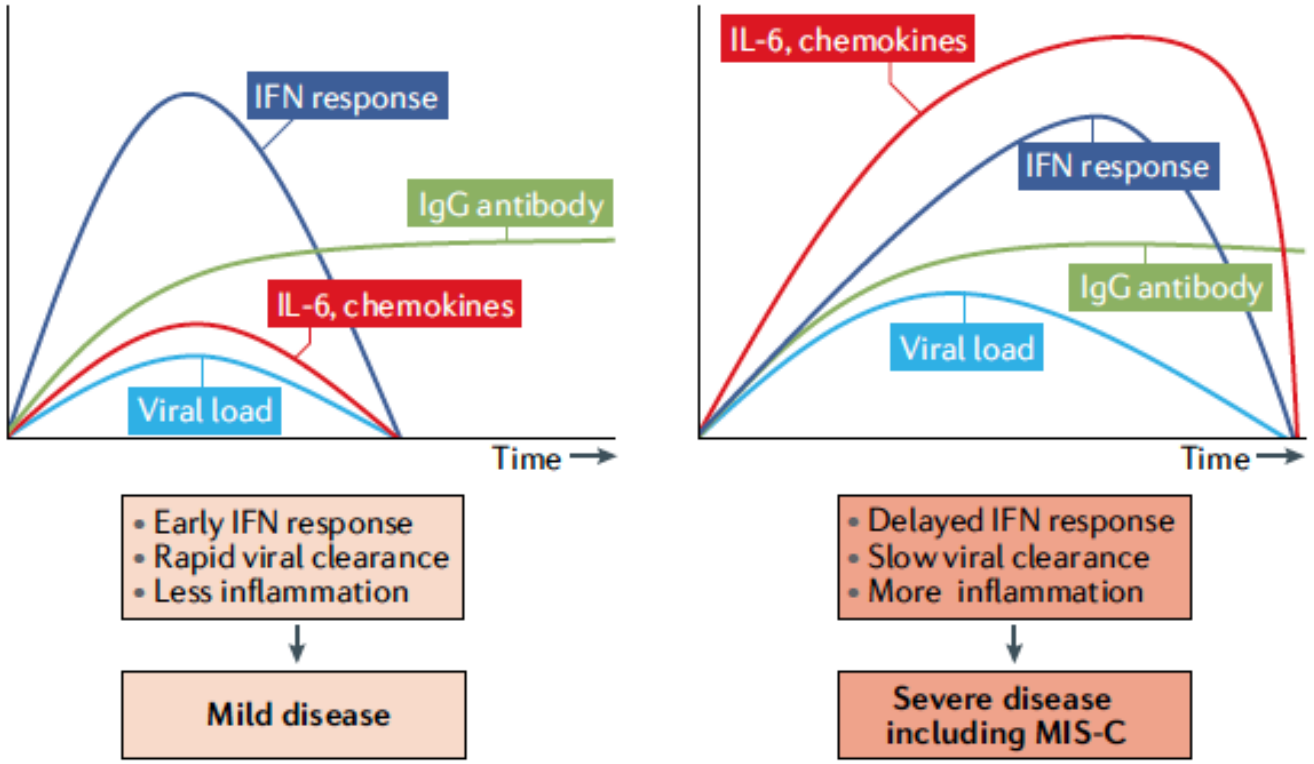



Fig. 1 | **Pathogenesis of multisystem inflammatory syndrome in children: a hypothesis.**

Rowley, Anne. *Nat. Rev. Immun.* (2020)

# Diagnostic workup

- Depending on time course, SARS-CoV-2 PCR and/or antibody testing

- Inflammatory markers
  - ESR/CRP
  - Fibrinogen, procalcitonin, d-dimer, ferritin, lactic acid dehydrogenase (LDH), or interleukin 6 (IL-6), elevated neutrophils, reduced lymphocytes and low albumin, low platelets

- Perform echocardiogram/EKG
  - Troponin, BNP

# Treatment

- 77% children in U.S. study treated with intravenous immunoglobulin, 49% treated with glucocorticoids
- 71% in UK study received IVIG; 64% received glucocorticoids
- Consider anti-interleukin (IL) 1b, possibly anti-IL 6 antibody treatments if no response to IVIG or glucocorticoids
- Patients meeting criteria for KD or with coronary artery changes should be considered for aspirin

*Remember to check cytokine panels and save serum prior to starting IVIG!

# Concluding Remarks

- Limited data available but similar hyperinflammatory spectrum disorders present in US and Europe
  - Of note, little data in Asia reported from early pandemic
- Little data on neurologic involvement
  - 1 case in CHOP case series
  - Kawasaki disease can be associated with cerebral vasculopathy
- Time course indicates a parainfectious/post-infectious phenomenon
  - Mechanisms still not understood (innate vs. adaptive)
  - Unclear how overlaps with adult cytokine release syndrome

# Questions?

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# Other Pediatric Stroke Cases during Covid-19

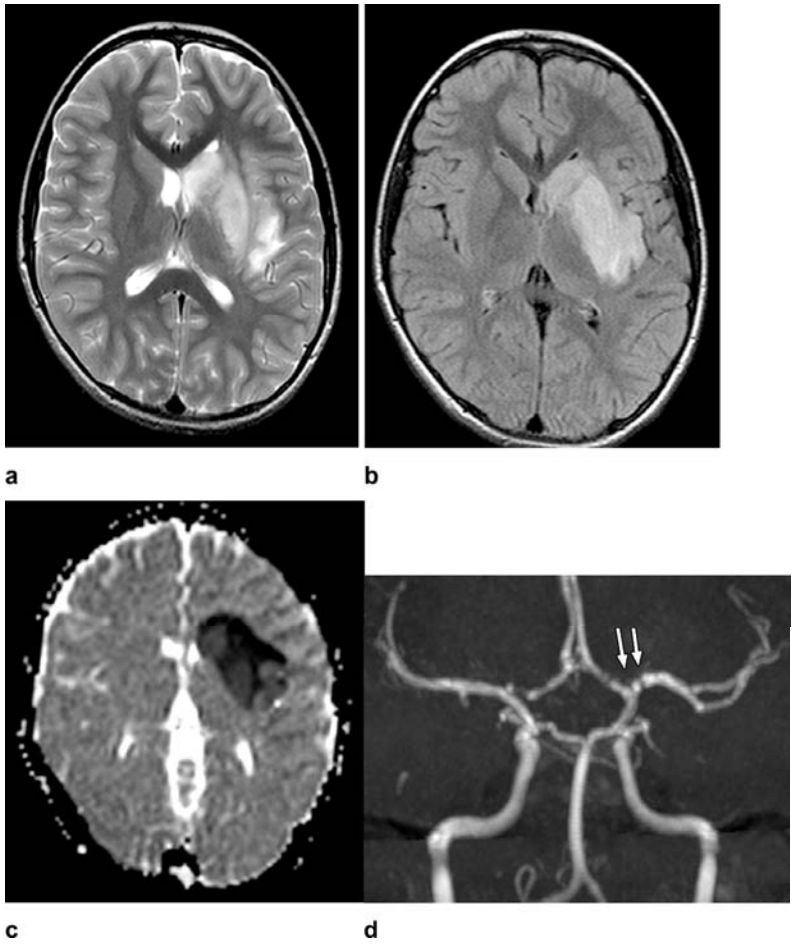


Figure 1: Axial T2-weighted (a) and FLAIR (b) Magnetic resonance imaging show diffuse hyperintense signal and edema of the caudate nucleus head, putamen, anterior limb of the internal capsule, and parts of external capsule and insula on the left side, with corresponding low values on the axial apparent diffusion coefficient map, in keeping with an acute infarct. Time-of-flight magnetic resonance angiography maximal intensity projection reformatted image demonstrates focal irregular narrowing and banding of the proximal left M1 segment of the middle cerebral artery with a slightly reduced distal flow in the middle cerebral artery.

**Mirzaee SMM. Published Online:** June 02, 2020
https://doi.org/10.1148/radiol.2020202197