Kavita Sharma, MD

Multisystem Inflammatory Syndrome in Children (MIS-C)

UT Southwestern
Medical Center

Background

- Acute myocardial injury/myocarditis associated with SARS-CoV-2 infection has been described in the adult population since the start of the pandemic
- SARS-CoV-2 infection in children has been thought to be relatively mild compared to adults
- In late April 2020, clinicians in the UK found a cluster of 8 previously healthy children presenting with cardiovascular shock, fever and hyperinflammation-Kawasaki Disease type symptoms

Background

- On May 14, 2020 the CDC issued a national health advisory to report on cases meeting the criteria for multisystemic inflammatory syndrome in children (MIS-C).

- MIS-C is a rare complication of SARS-CoV-2 infection that typically occurs 2-4 weeks after COVID-19 peaks within geographic regions.

- In a public health surveillance, the cardiovascular system was involved in 80% of patients.

CDC Case definition
Multisystem Inflammatory Syndrome in Children-associated with Covid 19 (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

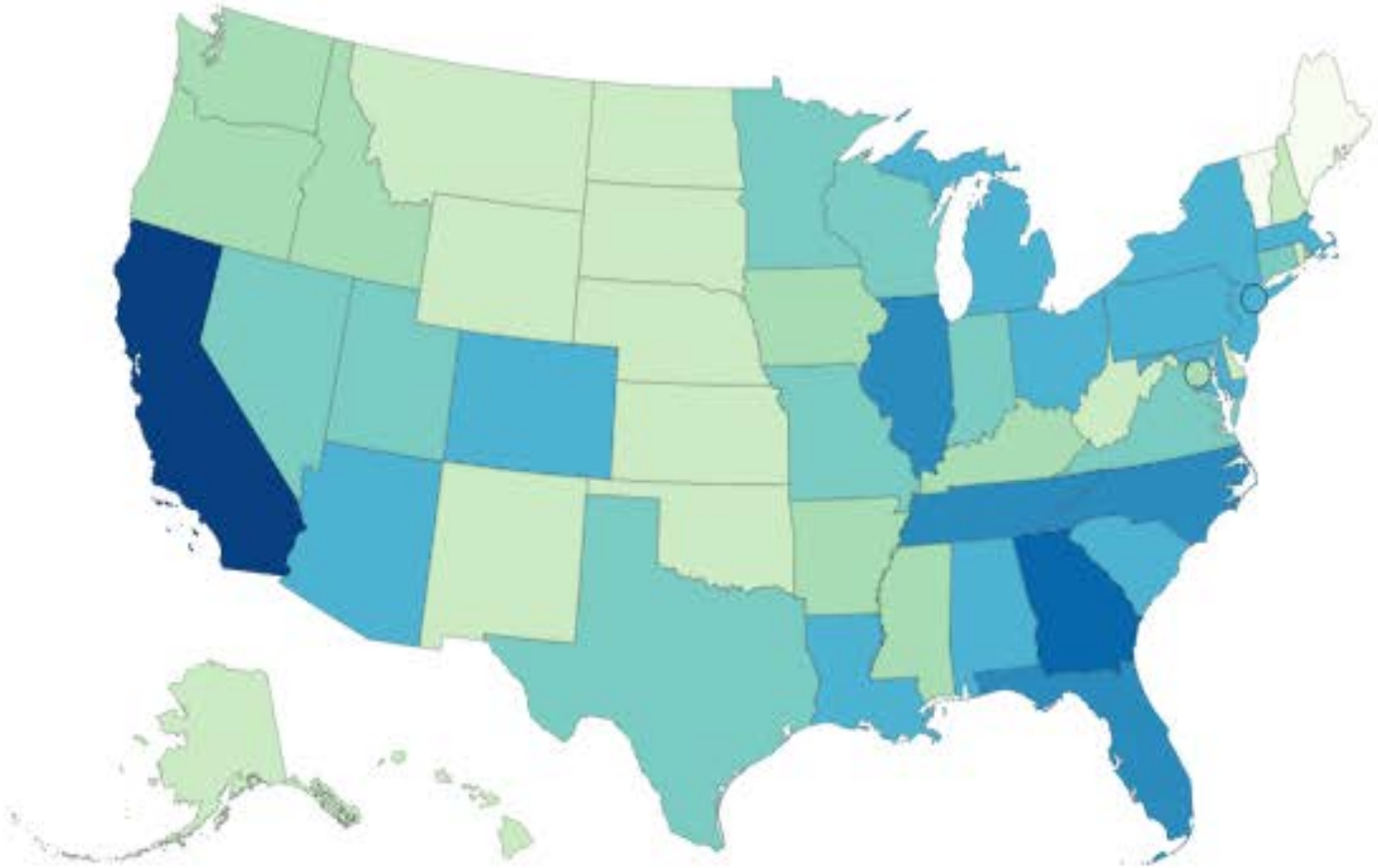
Additional comments

- 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

Reported MIS-C Case Ranges by Jurisdiction, on or before June 2, 2021*

TOTAL MIS-C PATIENTS MEETING CASE DEFINITION*	TOTAL MIS-C DEATHS MEETING CASE DEFINITION
4018	36

Reported MIS-C Case Ranges by Jurisdiction, on or before June 2, 2021*



Reported MIS-C Cases

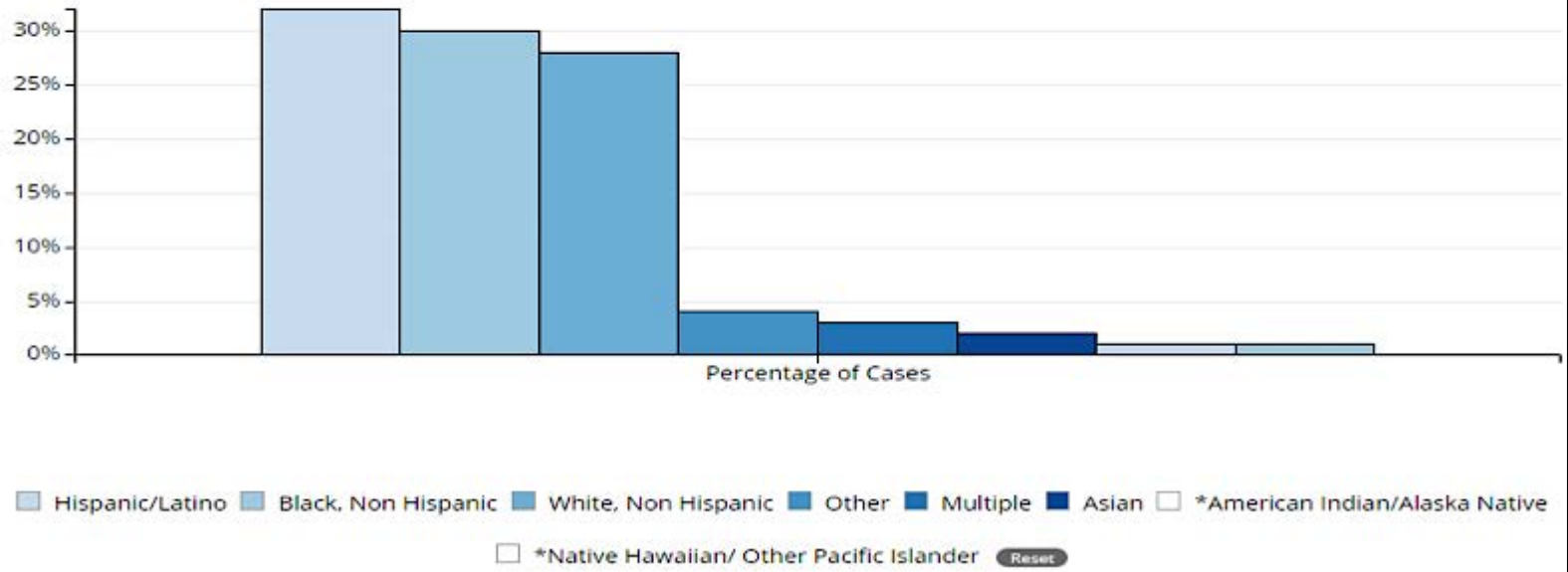
- No case reported
- 1-24 cases
- 25-49 cases
- 50-99 cases
- 100-149 cases
- 150-199 cases
- 200-249 cases
- 300+ cases

Territories AS GU MH FM PW PR VI

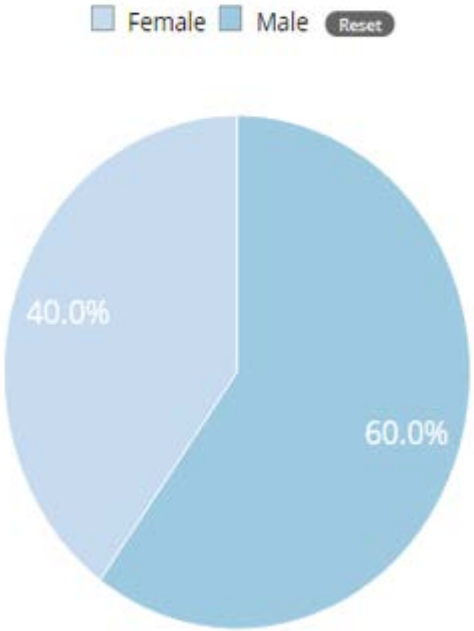
CDC

UT Southwestern Medical Center

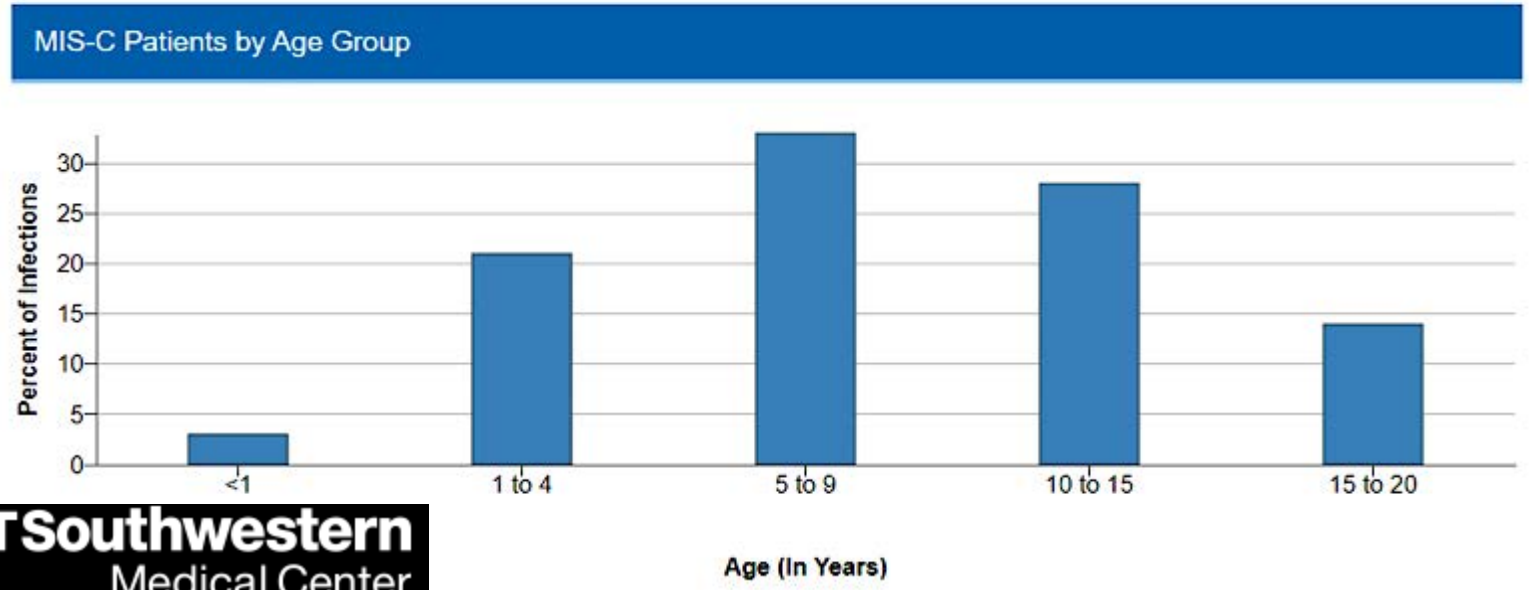
MIS-C Patients by Race & Ethnicity



MIS-C Patients by Sex

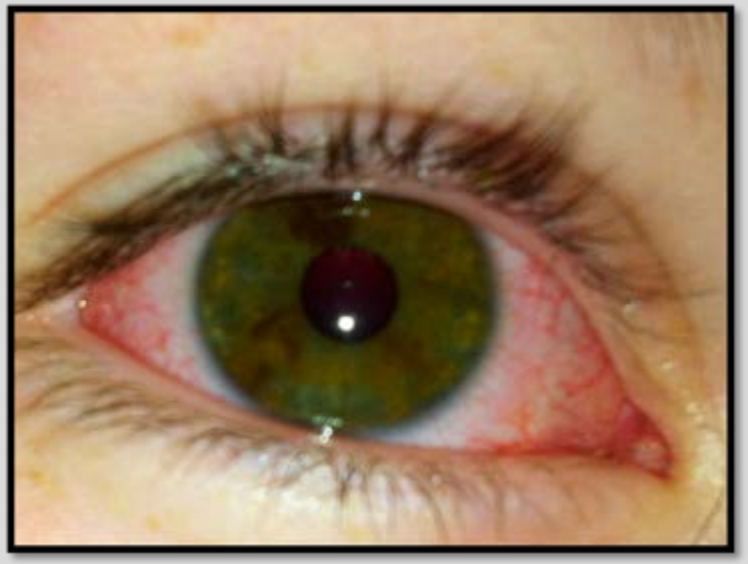


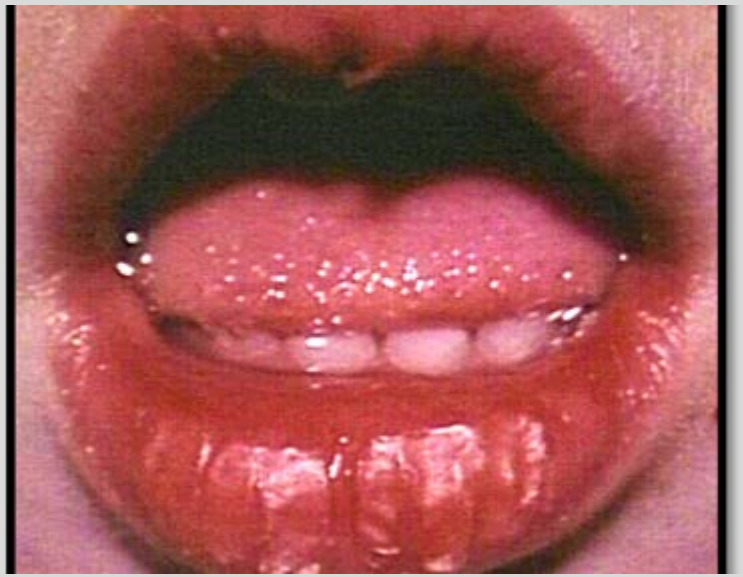
MIS-C Patients by Age Group



UT Southwestern Medical Center

Kawasaki Disease





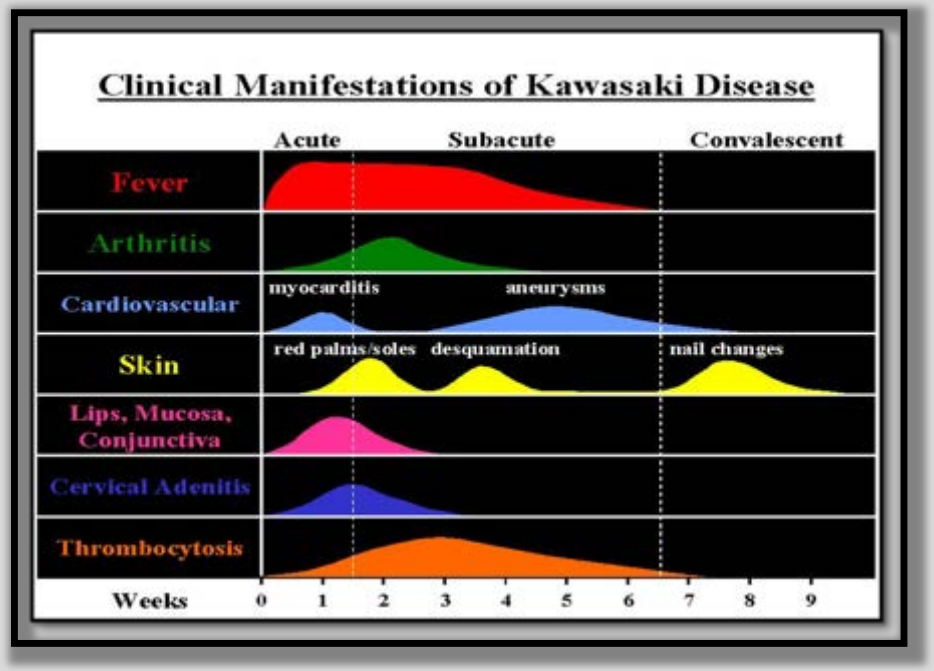
- Vasculitis of medium size blood vessels
- Fever for 5 days with 4 out of 5 features

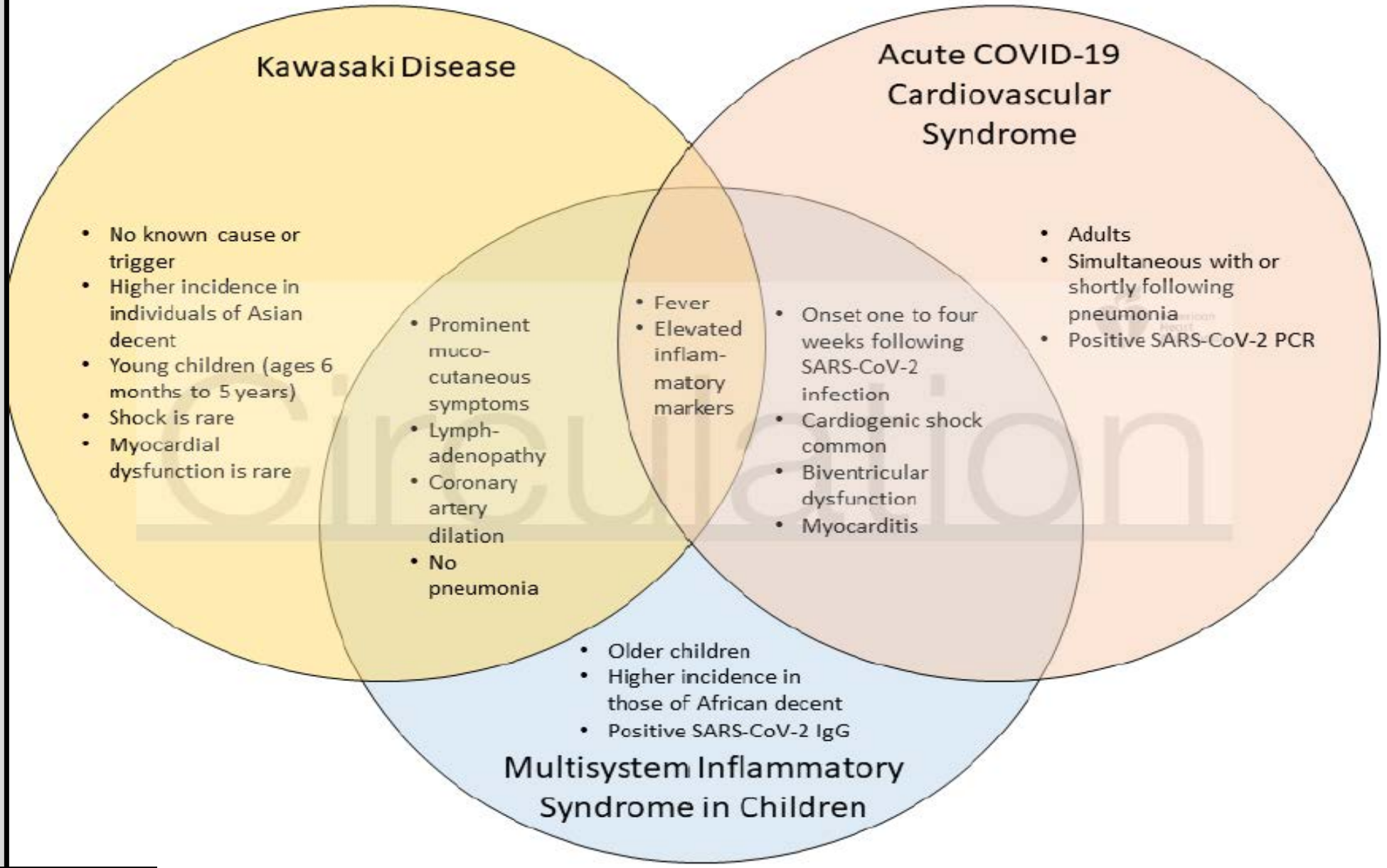
1. Erythema/cracking of lips, strawberry tongue
2. Bilateral bulbar conjunctival injection
3. Rash
4. Erythema & edema of the hands and feet in acute phase

   and/or periungual desquamation in subacute phase
5. Cervical lymphadenopathy (≥1.5 cm diameter)

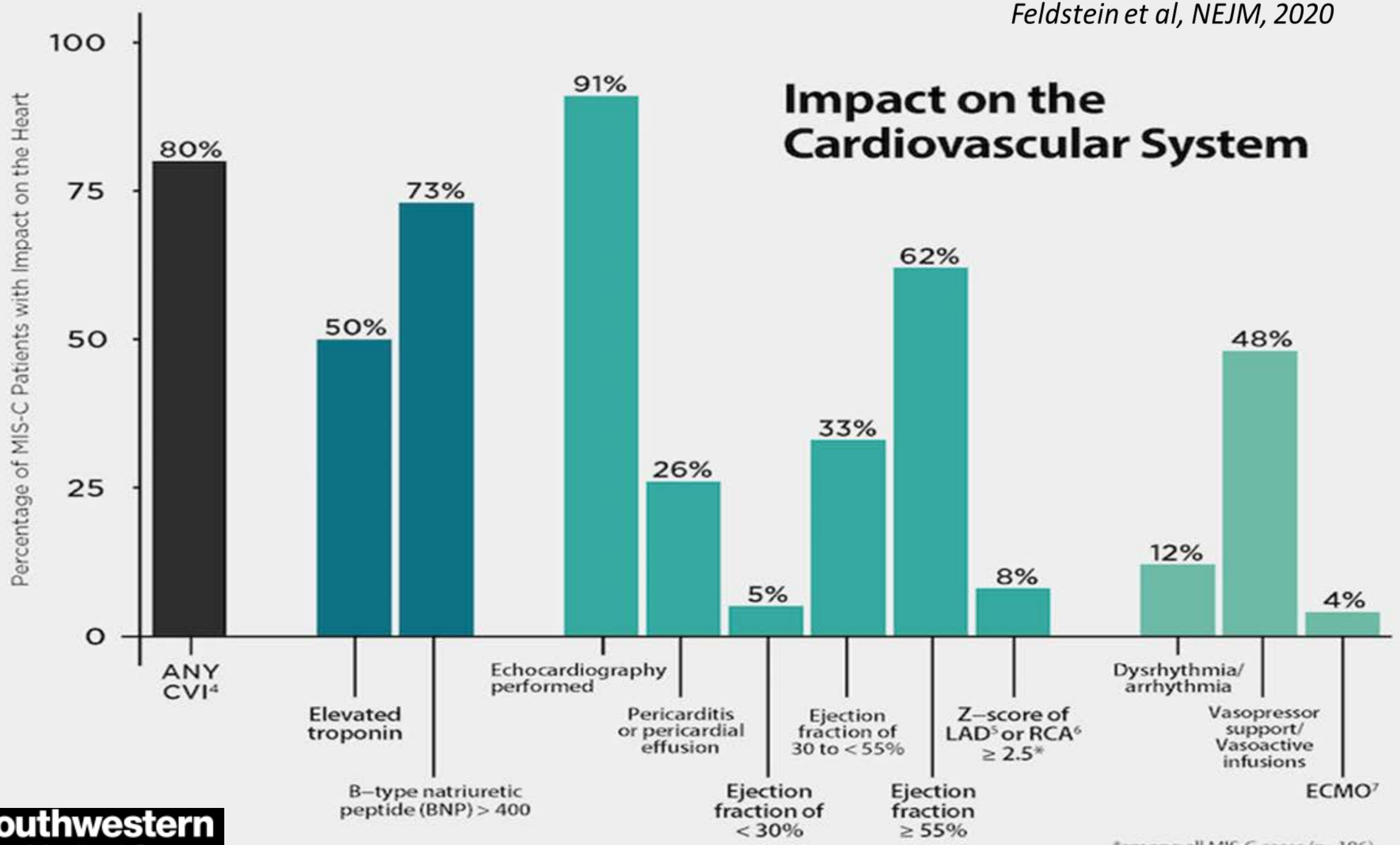
Kawasaki Disease- Cardiac

- Coronary aneurysm in 25% of patients
- Myocarditis 5% of patients
  - Acute left ventricular dysfunction is generally transient
  - Responds readily to anti-inflammatory treatment
  - KD myocarditis is caused from interstitial edema and inflammation



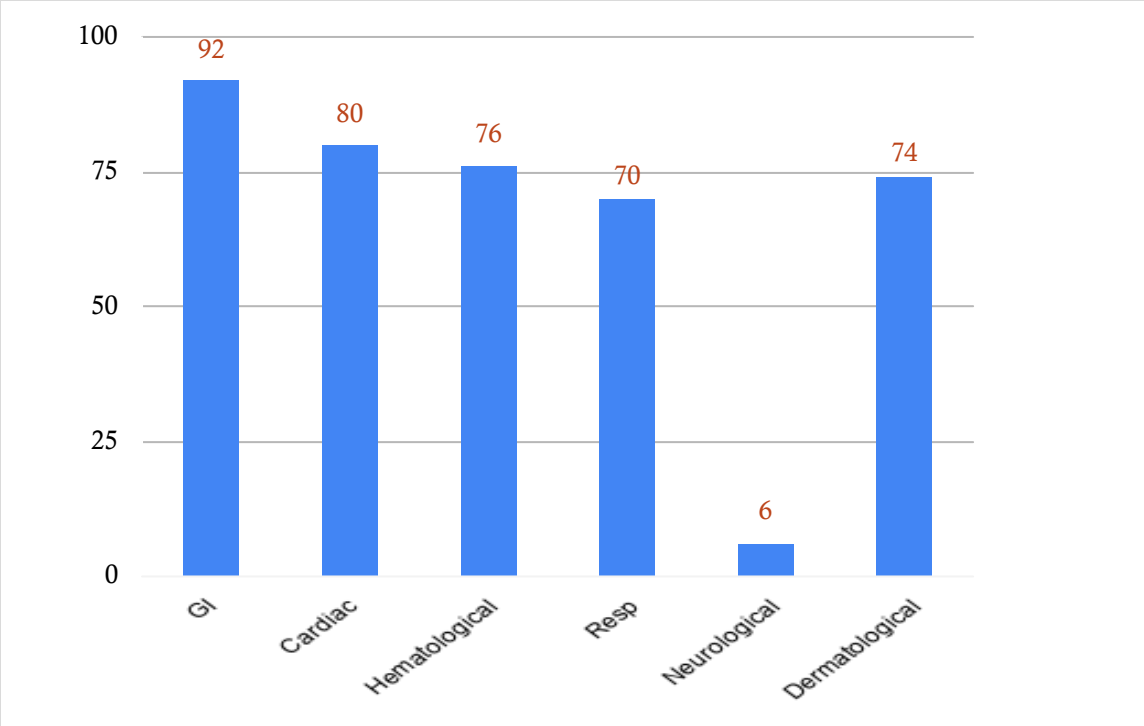


Feldstein et al, NEJM, 2020

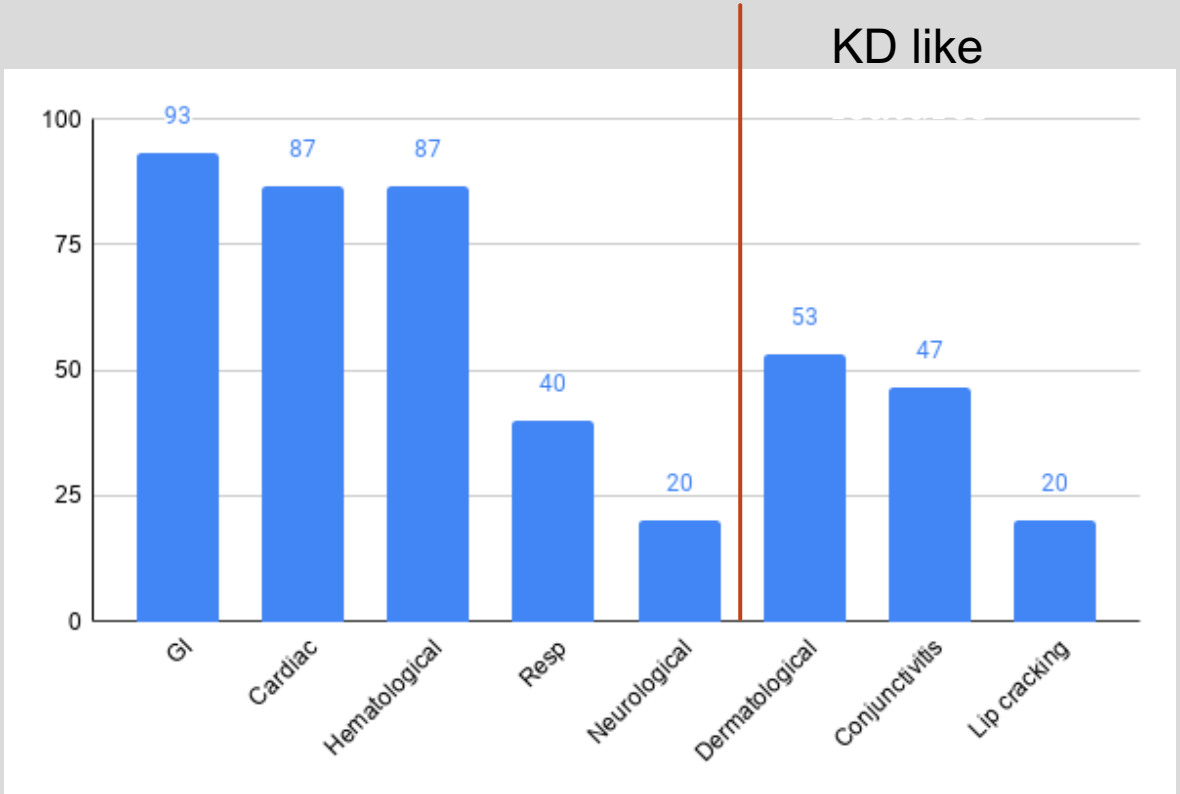


UT Southwestern Medical Center

Organ involvement in MIS-C patients in US (n=186)



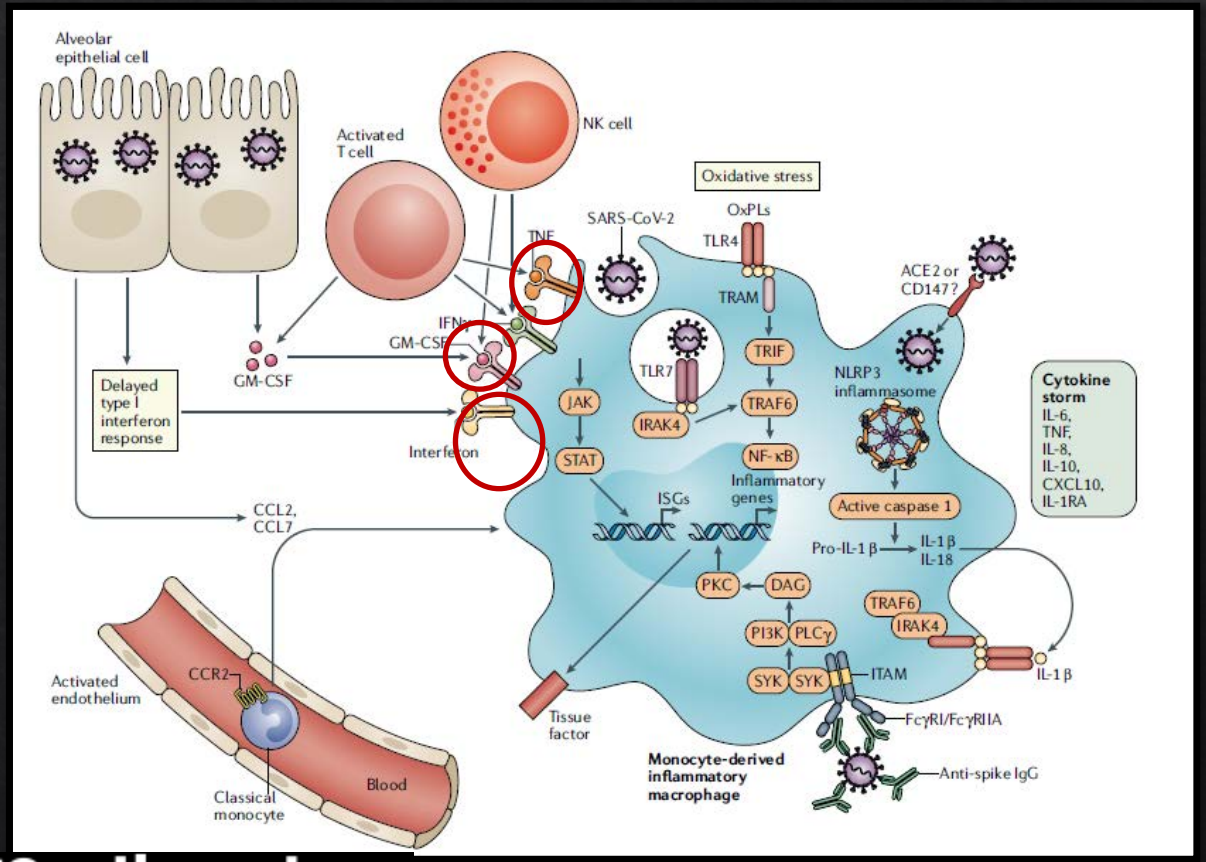
Organ involvement in MIS-C patients followed by ID at CMC (n=15)

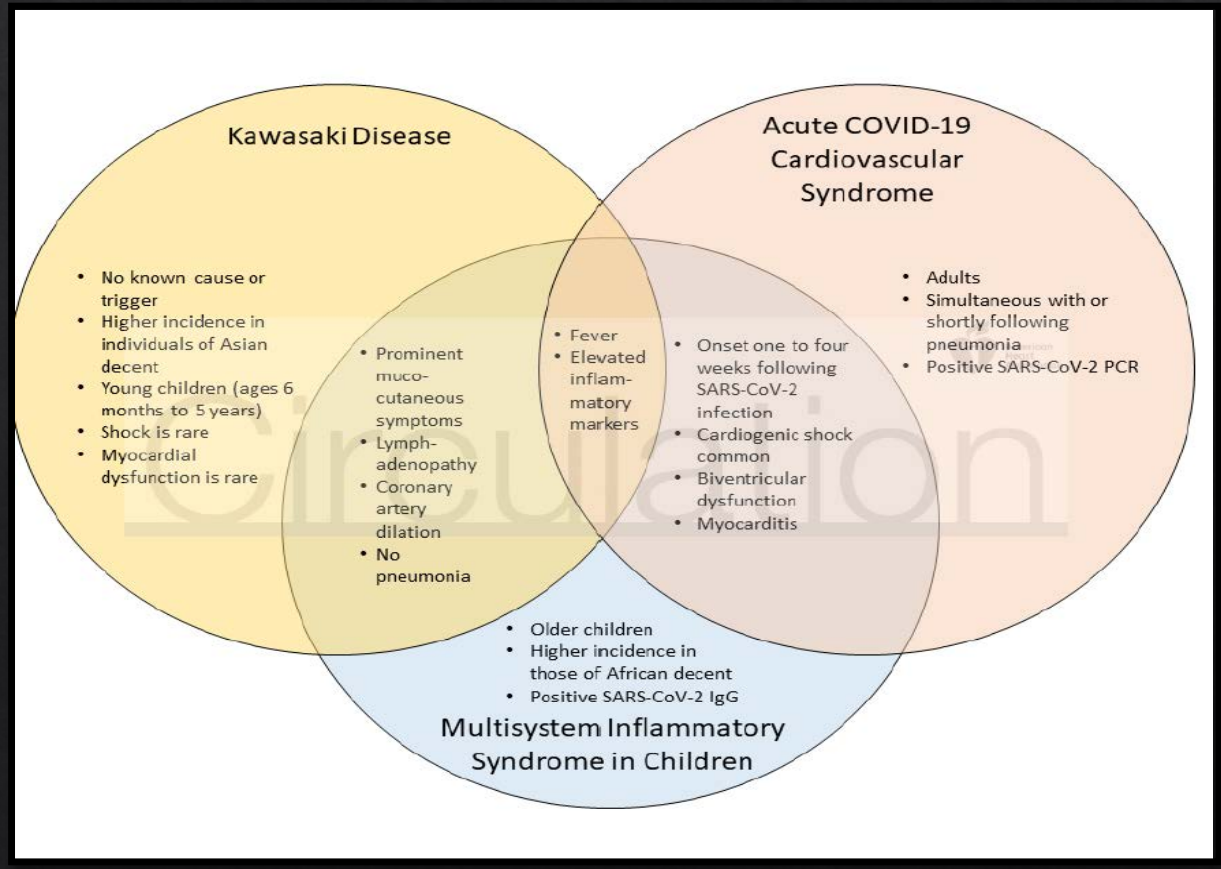


Feldstein, NEJM, 2020

Severe COVID-19 or Something Else?

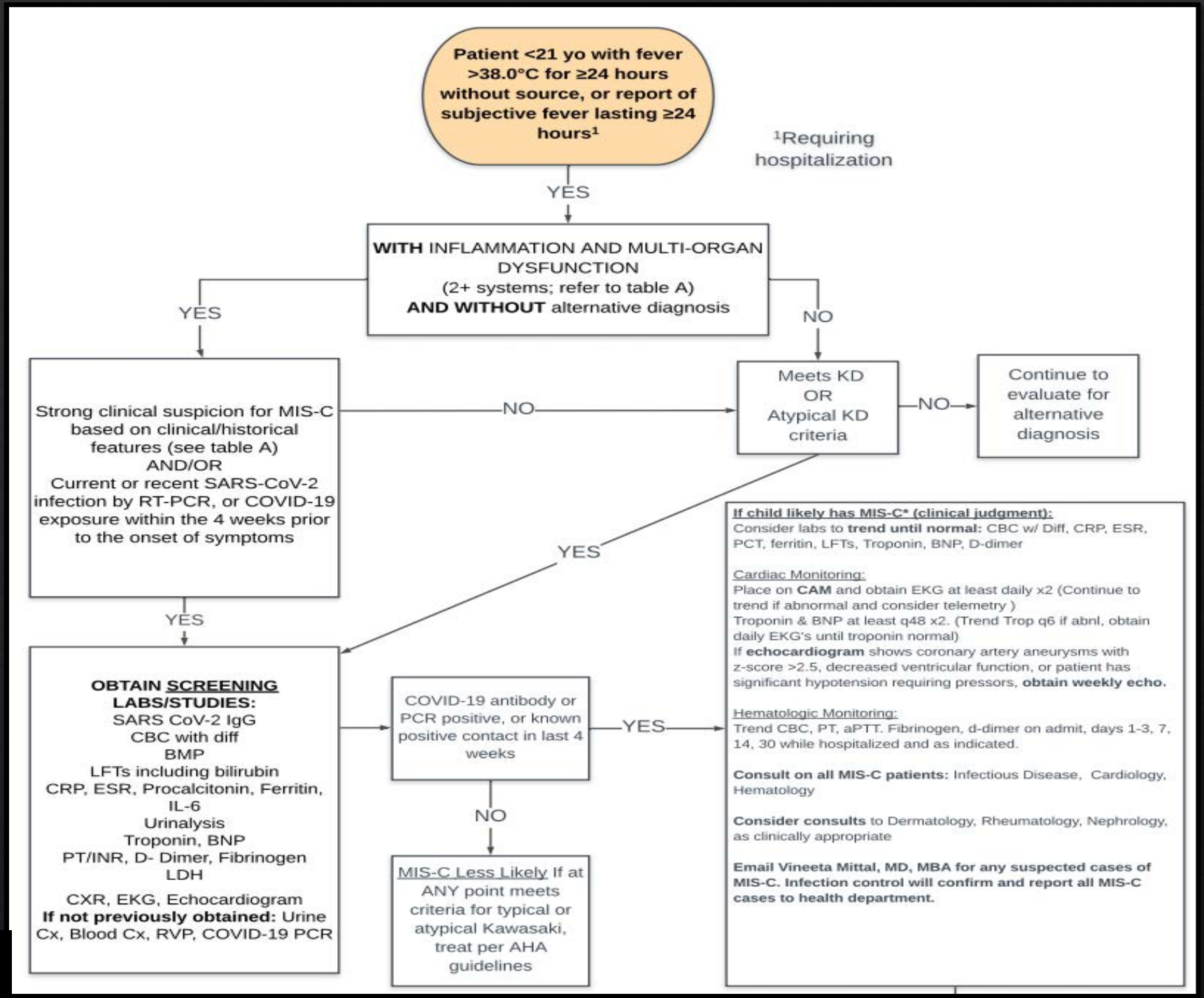
Mild COVID-19 → Moderate COVID-19 → Severe COVID-19 → Critical COVID → MIS-C?





UT Southwestern Medical Center

Most et al, Circulation, August 14, 2020 ; Merad et al, Nat Rev May 2020,



UT Southwestern Medical Center

Multidisciplinary Guidance for Treatment of MIS-C : A Work in Progress

- Collaborative effort between:

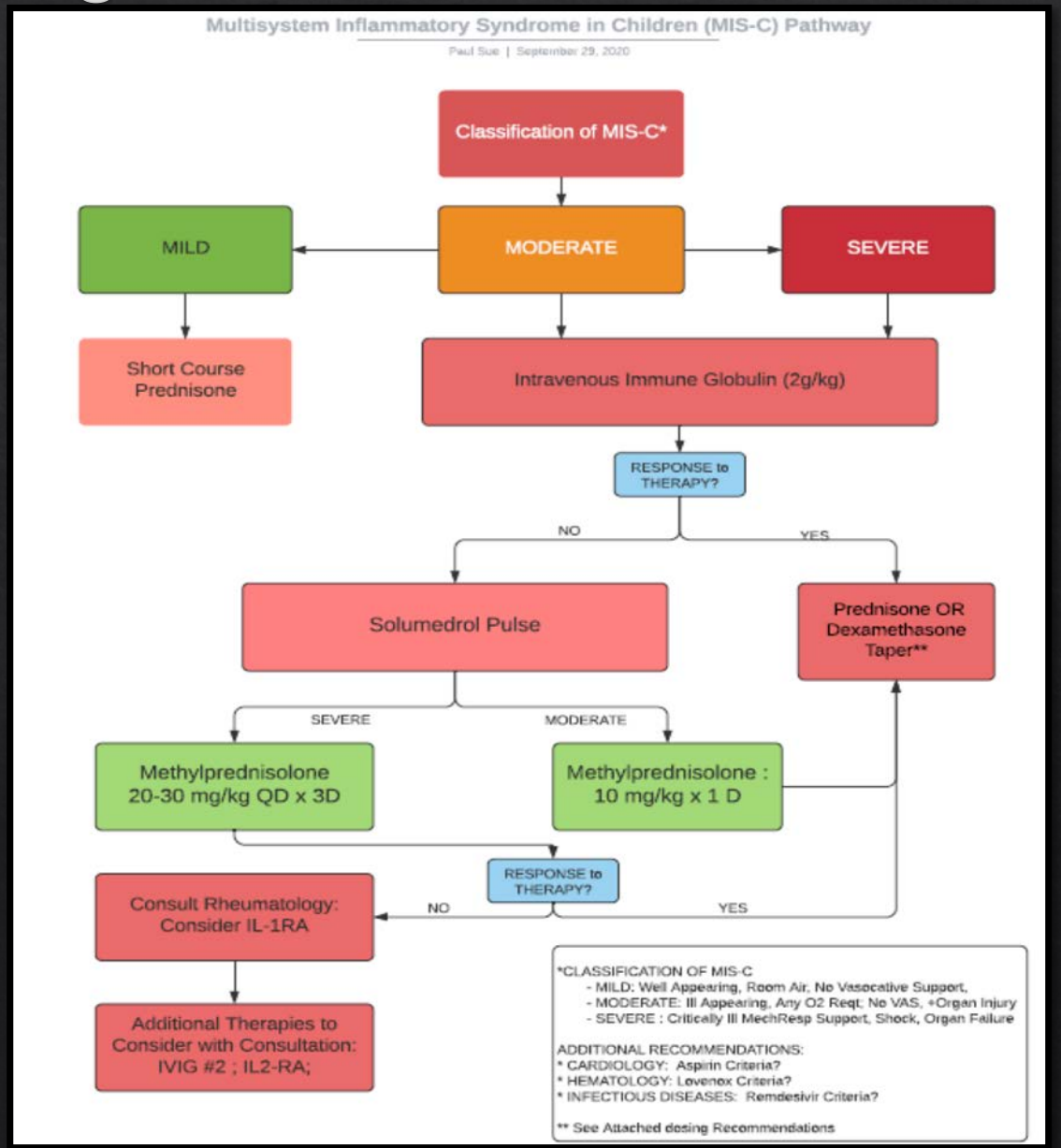
• PHM	• PICU	• Peds ID
• Cardiology	• Hematology	• Rheumatology

- Goal: Treatment support for section specific pathways

Stratification of disease severity

In addition to necessary supportive care measures, approach to MIS-C treatment will be guided by severity of disease presentation and clinical evolution. We recommend the following for the classification of MIS-C disease severity:

	Mild MIS-C	Moderate MIS-C	Severe MIS-C
Clinical Presentation	Well-appearing	Ill-appearing	Critically ill
Respiratory Support	Room air	Any supplemental oxygen requirement	Non-invasive respiratory support (i.e. HFNC, ETT)
Hemodynamic Stability	Stable; no vasoactive support	Stable; no vasoactive support	Shock; need for vasoactive support OR presence of any cardiac dysfunction
End Organ Disease: Hepatitis, acute kidney injury, myocarditis, rhabdomyolysis	None or minimal	Evidence of mild or isolated organ injury	End organ failure



UT Southwestern Medical Center

Vasoactive support

	Inotropy	Chronotropy	Lusitropy	Vasoactivity
Epinephrine	+	+	-	dilation/ constriction
Norepinephrine	+	-	-	constriction
Vasopressin	-	-	-	constriction
Milrinone	+	-	+	dilation

- *None of these treat the underlying condition!*

- Smith et al. Pediatric critical care. Shock states. 2017

MIS-C Discharge

DISCHARGE PLANNING

Afebrile for >48 hours without antipyretics, downtrending inflammatory markers, off oxygen/respiratory support for >24 to 48 hours.
Tolerating sufficient enteral intake

Cardiology Discharge Planning:
Echocardiogram and EKG at discharge
ESR, CRP, Ferritin, PCT, BNP, Troponin, AST at discharge (unless already normalized)
Cardiology follow-up within 2 weeks of discharge for repeat echocardiogram
Advise against vigorous activity until cleared by Cardiology
Low dose ASA 3-5 mg/kg/day for coronary thromboprophylaxis until discontinued by Cardiology
Avoid other NSAIDs while on ASA

Hematology Discharge Planning:
CBC w/ diff, PT, aPTT, Fibrinogen, d-dimer at discharge (unless already normalized)

If d-dimer remains >2.5 at discharge or other risk factors (see Table C), send home on SubQ LMWH BID prophylaxis x30 days.
(Pre-filled syringe only. aXa 0.2-0.5. No Hematology or lab f/up needed for routine cases)

If any thrombosis, or LVEF <35%, needs therapeutic LMWH, Heme follow-up, and lab monitoring

Advise against contact sports while on LMWH
(Note LMWH prophylaxis is not a contraindication to anti-platelet therapy)

PCP and/or Infectious Disease: Recommend physician to physician handoff prior to discharge and follow-up in 2-3 days with labs (CRP, BMP, and CBC). Labs should be trended until normalization. If followed by PCP alone, please provide Infectious Disease clinic/fellow-on-call information for any questions or concerns

NIH National Heart, Lung, and Blood Institute

Schedule of Measurements

Variable	Day 1	Discharge	2 wks (1<3wk)	6 wks (3-9wk)	3 mo (1-6m)	6 mo (9wk-1yr)	Years 1-5
Demographics	X						
Medical History	X	X	X	X		X	X
Echo	X	X	X	X		X*	X**
EKG	X	X	X	X		X	
Cardiac MRI and ETT					X***		
Clinical Labs	X	X	X	X		X*	
other research Labs	X	X	X	X		X	

* ≥6-mo echo and labs optional if all earlier echoes normal; ** if abnormal echo at 6 months, repeat ≥ annually until 2 consecutive normal echoes; *** All with history mod-severe LV dysfunction by protocol; Labs: to be checked until normal-cbc with diff, ESR, CRP, ferritin, D dimer, ALT, BNP and Troponin

PHN MUSIC Study

Long-Ter**M** O**U**tcomes after the Multisystem Inflammatory **S**yndrome **I**n **C**hildren

artery involvement, LV systolic function, and arrhythmias or conduction system disturbances within the first year from illness onset and to define associated clinical and laboratory factors.

- Design: Observational cohort study- use routinely clinical and cardiac data to assess the association between MIS-C and cardiac outcomes within the first year after hospital discharge
- Duration: 5 years

NIH National Heart, Lung, and Blood Institute

PEDIATRIC HEART NETWORK