COVID-19 Pediatric Inflammatory Disease

June 17, 2020

Mark Daniel Hicar, MD, PhD

Declaration

- Nothing to declare

Reports

- “Kawashocky”,
- “Coronasacki”,
- hyperinflammatory shock in children with COVID-19,
- Pediatric COVID-19 Associated Inflammatory Disorder (PCAID)
- Pediatric Multisystem Inflammatory Syndrome (PMIS)
- Multisystem Inflammatory Syndrome in Children (MIS-C).

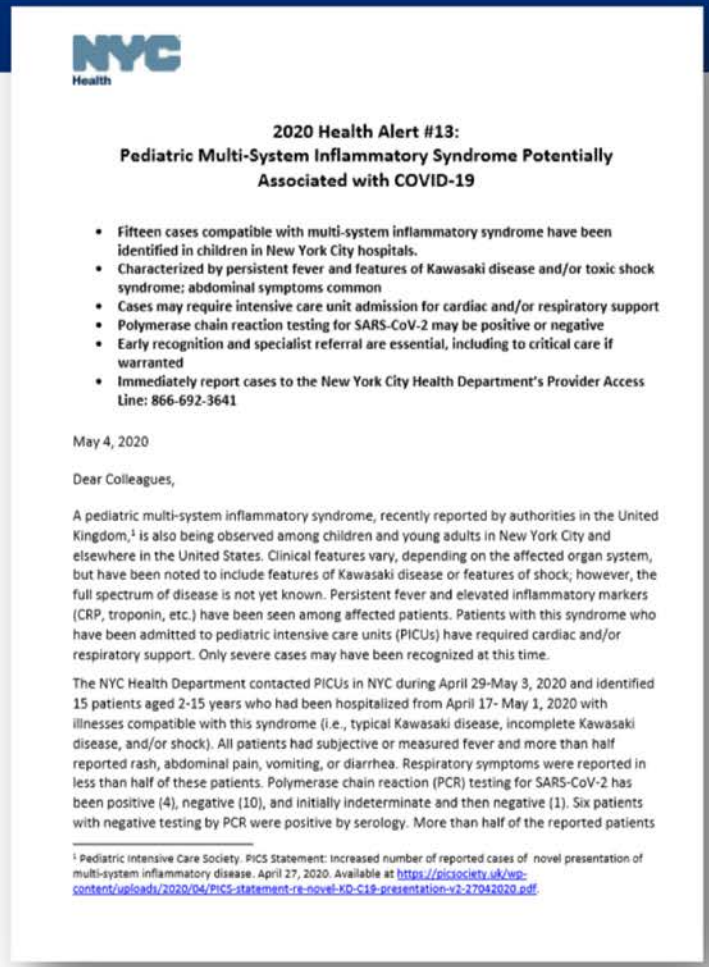
Noticed in Europe, clusters of inflamed cases

- UK National Health Service of the emergence of an unusual disorder, and an alert was issued on April 25.

- Strangely not really reported in Japan or China
  - Countries with higher incidence of Kawasaki disease

Pediatric Multisystem Inflammatory Syndrome

- NYC DOHMH Health Alert
- May 4th, 2020
  - **15 compatible cases identified in NYC pediatric intensive care units**
  - Fever, features of Kawasaki disease and/or toxic shock syndrome, abdominal symptoms were prominent
- Intensive care required for cardiovascular and respiratory support



NYC Health

2020 Health Alert #13:
Pediatric Multi-System Inflammatory Syndrome Potentially Associated with COVID-19

- **Fifteen cases compatible with multi-system inflammatory syndrome have been identified in children in New York City hospitals.**
- **Characterized by persistent fever and features of Kawasaki disease and/or toxic shock syndrome; abdominal symptoms common**
- **Cases may require intensive care unit admission for cardiac and/or respiratory support**
- **Polymerase chain reaction testing for SARS-CoV-2 may be positive or negative**
- **Early recognition and specialist referral are essential, including to critical care if warranted**
- **Immediately report cases to the New York City Health Department's Provider Access Line: 866-692-3641**

May 4, 2020

Dear Colleagues,

A pediatric multi-system inflammatory syndrome, recently reported by authorities in the United Kingdom,[1] is also being observed among children and young adults in New York City and elsewhere in the United States. Clinical features vary, depending on the affected organ system, but have been noted to include features of Kawasaki disease or features of shock; however, the full spectrum of disease is not yet known. Persistent fever and elevated inflammatory markers (CRP, troponin, etc.) have been seen among affected patients. Patients with this syndrome who have been admitted to pediatric intensive care units (PICUs) have required cardiac and/or respiratory support. Only severe cases may have been recognized at this time.

The NYC Health Department contacted PICUs in NYC during April 29-May 3, 2020 and identified 15 patients aged 2-15 years who had been hospitalized from April 17- May 1, 2020 with illnesses compatible with this syndrome (i.e., typical Kawasaki disease, incomplete Kawasaki disease, and/or shock). All patients had subjective or measured fever and more than half reported rash, abdominal pain, vomiting, or diarrhea. Respiratory symptoms were reported in less than half of these patients. Polymerase chain reaction (PCR) testing for SARS-CoV-2 has been positive (4), negative (10), and initially indeterminate and then negative (1). Six patients with negative testing by PCR were positive by serology. More than half of the reported patients

[1] Pediatric Intensive Care Society. PICS Statement: Increased number of reported cases of novel presentation of multi-system inflammatory disease. April 27, 2020. Available at https://picsociety.uk/wp-content/uploads/2020/04/PICS-statement-re-novel-KD-C19-presentation-v2-27042020.pdf.

NYSD DOHMH Peditric Multisystem Inflammatory Syndrome Potentially Associated with COVID-19

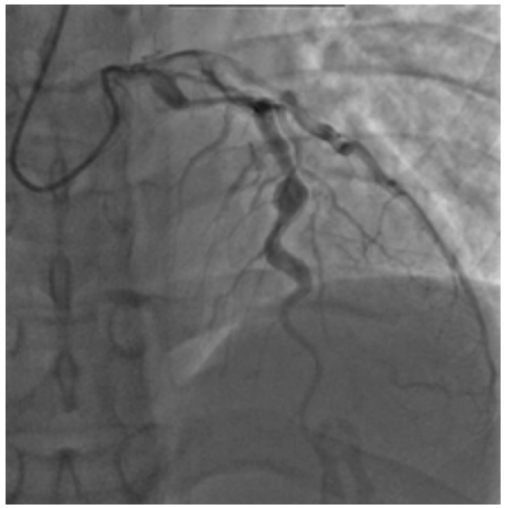
NEW YORK STATE | Department of Health

Appears like Kawasaki disease… kinda

- Kawasaki disease was originally described by Dr. Dr. Tomisaku Kawasaki (recently deceased, 1925-2020) as mucocutaneous lymph node syndrome”
- He initially put all cases in file, with the Japanese equivalent of “GOK.,” which stood for “God Only Knows.”
- Leading cause of pediatric acquired heart disease (25% untreated get coronary aneurysms)

Criteria

- Fever for ≥ 5 days
  - Generally high-grade (>102), irritability common
- 4 of 5 clinical findings for complete Kawasaki (2-3 and lab markers is termed incomplete Kawasaki)
  - Bilateral conjunctival injection
  - Mouth changes – mucosal erythema, fissured lips and/or “strawberry” tongue
  - Erythema/swelling of hands/feet, late desquamation
  - Polymorphous erythematous rash
  - Cervical lymph node enlargement > 1.5cm
- Illness not explained by other disease process



- IVIG is only treatment that has good evidence that reduces coronary aneurysms.
- Cause: still, GOK

MIS-C

- Currently, we have no firm criteria, a number of epidemiological definitions are being used (NYS, WHO, Royal College, CDC)

- Generally fever of some length (1-4 days)
- Signs of inflammation on laboratory work
- Multisystem involvement
- +/- history of COVID-19

Epidemiology: Italy saw spike in cases of KD like illness, compared to five previous years

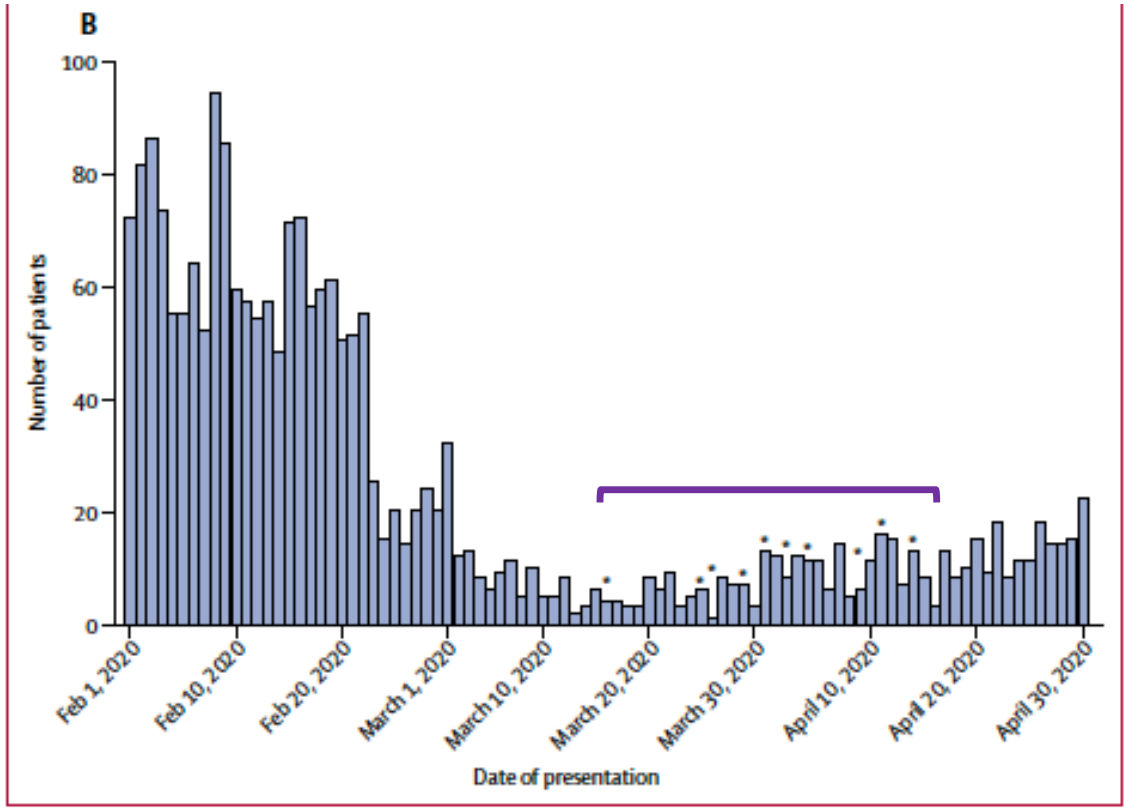
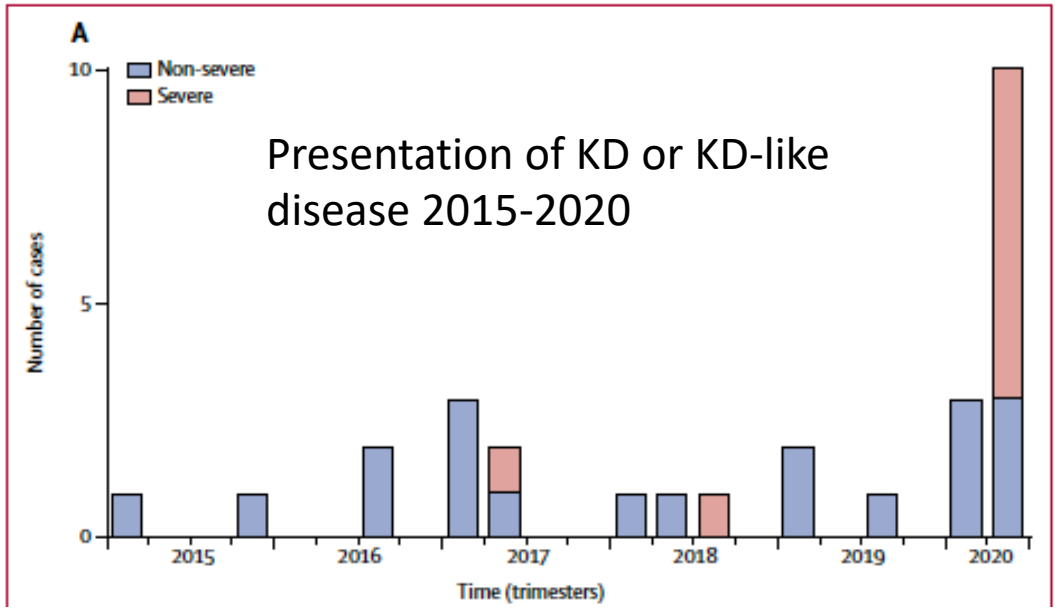


Figure: **Incidence of Kawasaki disease in the study period and in the past 5 years**
(A) Frequency of Kawasaki disease at the paediatric emergency department of Hospital Papa Giovanni XXIII of Bergamo, Italy, in the past 5 years, by case severity. (B) Number of patients presenting to the paediatric emergency department during the severe acute respiratory syndrome coronavirus 2 epidemic, and date of presentation of ten patients with Kawasaki-like disease (indicated by asterisks).



An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study

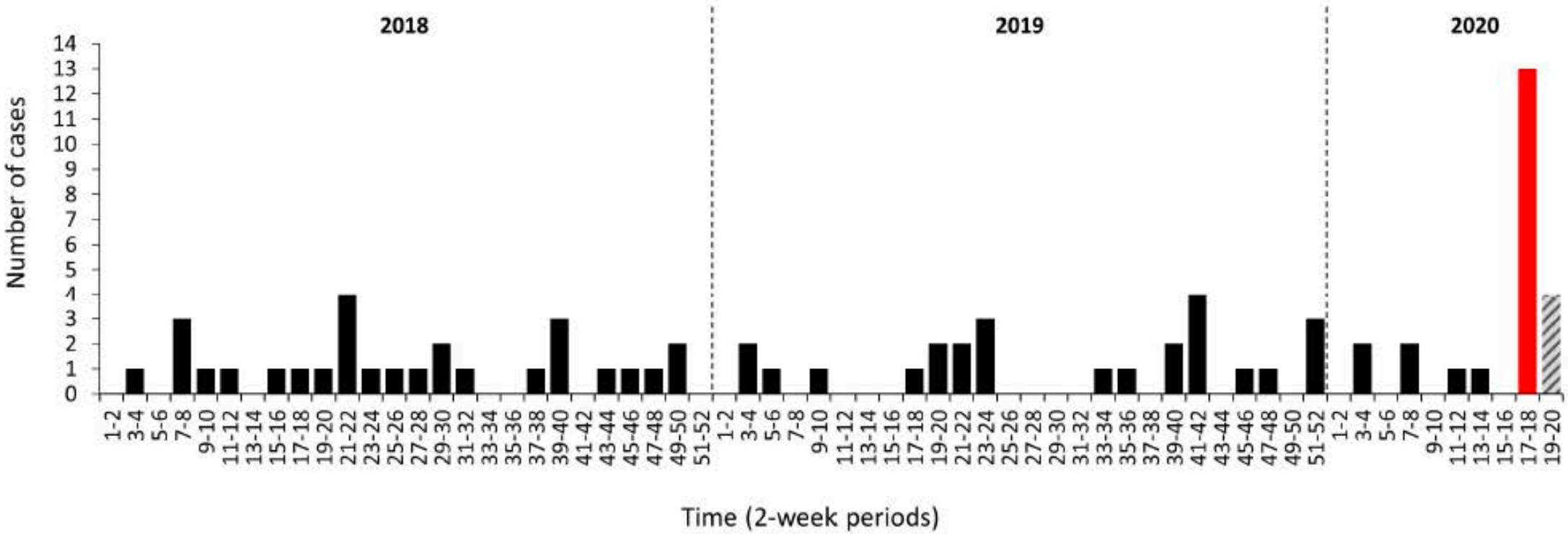
Lucio Verdoni, Angelo Mazza, Annalisa Gervasoni, Laura Martelli, Maurizio Ruggeri, Matteo Ciuffreda, Ezio Bonanomi, Lorenzo D'Antiga

Lancet, 2013

Outbreak of Kawasaki disease in children during COVID-19 pandemic: a prospective observational study in Paris, France

MedRxIV

Julie Toubiana[1,2*], Clément Poirault[1*], Alice Corsia[3], Fanny Bajolle[4], Jacques Fourgeaud[5], François Angoulvant[6], Agathe Debray[1], Romain Basmaci[7], Elodie Salvador[2], Sandra Biscardi[8], Pierre Frange[9], Martin Chalumeau[1,10], Jean-Laurent Casanova[11,12], Jérémie F. Cohen[1,10] and Slimane Allali[1]



COCA presentation-

Michael Levin, MBE, PhD, FRCPCH, FMedSci
Professor of Pediatrics & International Child Health
Imperial College
London, United Kingdom

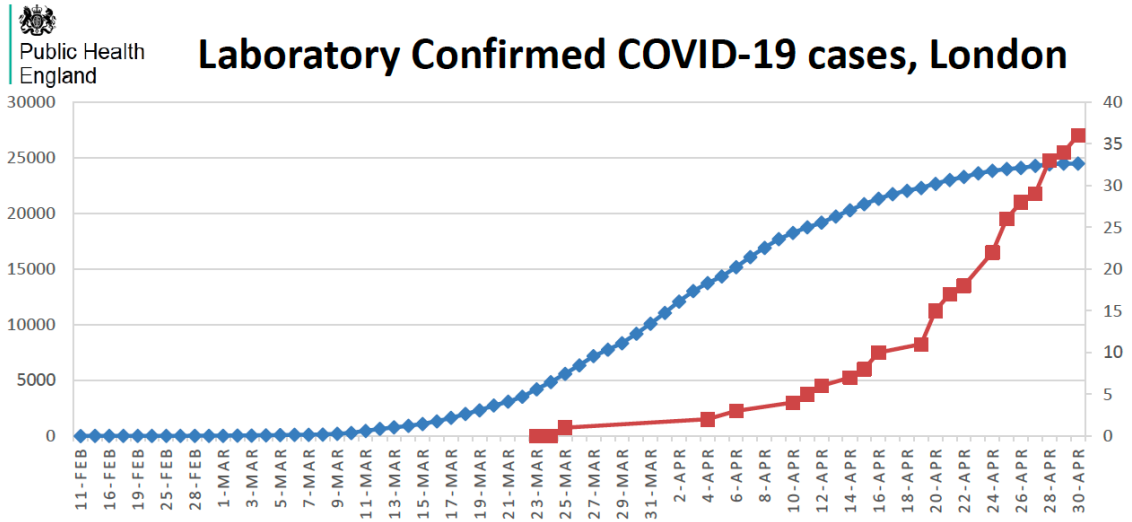
38 cases identified between March 25 and May 1

Demographic features

Age	1 – 16 years (Median 11 years)
Sex	62% male (23 /37)
Co-morbidities	1 asthma, 1 epilepsy

Location of reported cases

PIMS-TS appear to be a month behind the COVID19 peak in the population

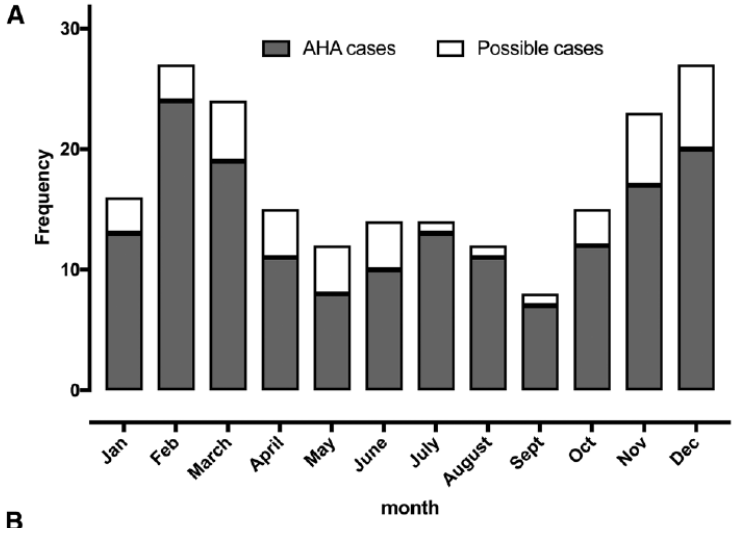


Local experience

- We have had five cases, six strong consideration
- 2 on ecmo, unconfirmed antibody responses
- 1 critically ill, overlap with Toxic shock
- 19yo with sickle cell, + PCR, + antibody, intubated, high ferritin, LFTs
- KD like, 6 month old, + PCR
- 15 month old with antibody responses, multiple pressors, high ferritin, high troponins, who is recovering

We have not seen a spike in Kawasaki cases above normal.

Cumulative of 16 years of cases



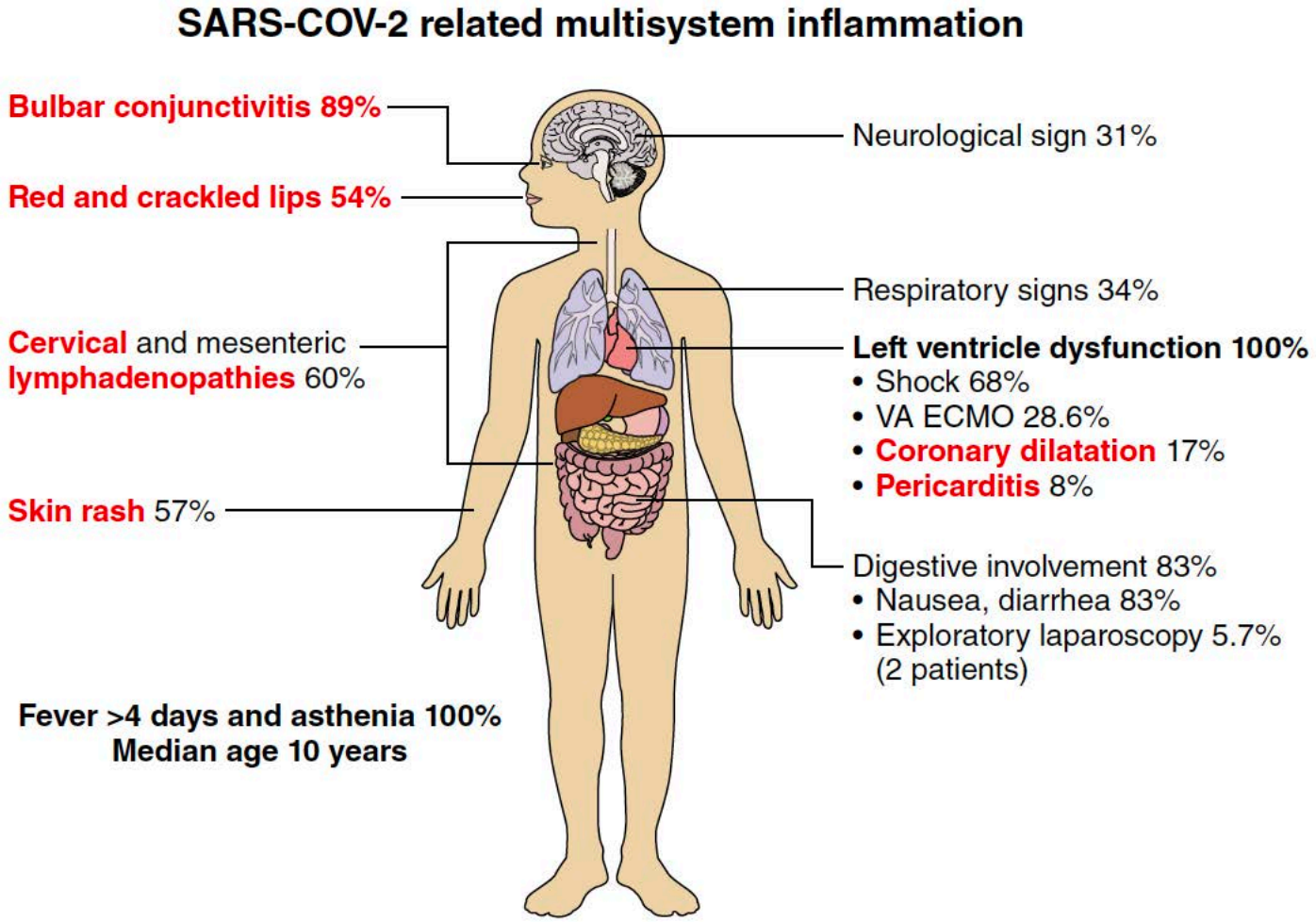
KD epidemiology of Western New York

From Chang, Delmerico, Hicar, PIDJ, 2019.

Clinical presentation

Acute heart failure in multisystem inflammatory syndrome in children (MIS-C) in the context of global SARS-CoV-2 pandemic

Zahra Belhadjer, MD[1,2]; Mathilde Méot, MD[1]; Fanny Bajolle, MD, PhD[1], Diala Khraiche, MD[1]; Antoine Legendre, MD[1]; Samya Abakka, MD[1]; Johanne Auriau, MD; PhD[1], Marion Grimaud, MD[1]; Mehdi Oualha, MD, PhD[1]; Maurice Beghetti, MD, PhD[3]; Julie Wacker, MD[3] Caroline Ovaert, MD, PhD[4,5]; Sebastien Hascoet, MD[6]; Maëlle Selegny, MD[7]; Sophie Malekzadeh-Milani, MD[1]; Alice Maltret, MD[1]; Gilles Bosser, MD, PhD[8]; Nathan Giroux, MD[8]; Laurent Bonnemains, MD, PhD[9]; Jeanne Bordet, MD, PhD[9]; Sylvie Di Filippo, MD, PhD[10]; Pierre Mauran, MD, PhD[11]; Sylvie Falcon-Eicher, MD[12]; Jean-Benoît Thambo, MD, PhD[13]; Bruno Lefort; MD, PhD[14], Pamela Moceri; MD, PhD[15]; Lucile Houyel, MD, PhD[1,2]; Sylvain Renolleau, MD, PhD[1,2]; Damien Bonnet, MD, PhD[1,2]



	Value
Age	
Median	10
Distribution, n	
<1yr	0
1-5 years	1
6-10 years	15
11-16 years	19
Sex, n (%)	
Male	18 (51)
Female	17 (49)
Comorbidity, n (%)	10 (28)
Asthma	3 (8.5)
Lupus	1 (3)
Overweight (BMI > 25)	6 (17)
Signs and symptoms, n (%)	
Asthenia	35 (100)
Fever	35 (100)
Gastrointestinal symptoms	29 (83)
Respiratory distress	23 (65)
Rhinorrhea	15 (43)
Adenopathy	21 (60)
Skin rash	20 (57)
Meningism	11 (31)

Data are median (IQR) or n (%), where n is the total number of patients with available data.

Table 2. Cardiac signs

	n (%)
Clinical signs	
Chest pain	6 (17)
Cardiogenic shock with collapse	28 (80)
Ventricular arrhythmia	1 (3)
Systolic blood pressure at admission (percentile (IQR))	1 (1-10)
Coronary artery dilatation Z-score > +2	6 (17)
Aneurysms at day 10 (echography only)	0 (0)
Left ventricular ejection fraction at baseline, n (%)	
<30%	10 (28)
30-50%	25 (72)
Evolution of LVEF (median±SD)	
Baseline (35 patients)	32±9
Day 3 (23 patients)	52±10
Day 7 (34 patients)	60±6
Recovery left ventricular ejection fraction	
LVEF > 60% at day 7 n (%)	25 (71)
Time to full recovery, days (median and range)	2 (2-5)

Data are median (IQR) or n (%), where n is the total number of patients with available data.

Table 3. Laboratory findings

	Baseline	Peak value (Day) (n patients)	Nadir value (Day) (n patients)	Normal values
High sensitive troponin I (ng/L) (n=35)	347 (186-1267)	408 (258-679) Day 1 (n=16)	28 (18-53) Day 10 (n=16)	<26 ng/ml
Creatinine kinase (U/L) (n=19)	174 (110-510)	-	-	<180 U/L
NT-proBNP (n=5)	41484 (35811 - 52475)	-	-	< 300 pg/mL
BNP (pg/mL) (n=28)	5743 (2648 - 11909)	4256 (2340-6503) Day 1 (n=11)	72 (56-140) Day 7 (n=12)	< 100 pg/mL
D-Dimer (ng/ml) (n=20)	5284 (4069-9095)	-	-	< 500 ng/mL
C-reactive protein, (mg/mL) (n=35)	241 (150-311)	-	-	< 6 mg/mL
Procalcitonin (ng/ml) (n=26)	36 (8-99)	-	-	< 2 ng/mL
White blood cell count, $x10^3$/L (n=35)	16 (12-23)	-	-	< $12x10^3$/L
Neutrophil count, x 10^3/L (n=34)	13 (8-19)	-	-	< $8.5x10^3$/L
Interleukin 6 (pg/mL) (n=13)	135 (87-175)	-	-	< 8.5 pg/mL

BNP Brain natriuretic peptide

Data are median (IQR) or n (%), where n is the total number of patients with available data.

Table 4. Treatment and responses

Treatment, n (%)	
Inotropic support	28 (80)
Immunoglobulin infusion	25 (71)
Intravenous corticosteroids	12 (34)
Interleukin 1 receptor antagonist	3 (8)
Anticoagulation with heparin	23 (65)
Respiratory support, n (%)	33 (94)
Invasive	22 (62)
Non invasive	11 (32)
VA-ECMO, n (%)	10 (28)
ECMO duration in days (range)	4.5 (3-6)
Recovery left ventricular ejection fraction	
LVEF > 60% at day 7 n (%)	25 (71)
Death, n (%)	0 (0)

VA ECMO: veno-arterial Extracorporeal membrane oxygenation.
Data are median (IQR) or n (%), where n is the total number of patients with available data.

Lancet- May 13 Italy Verdoni et al

	Group 1	Group 2	p value
Time of presentation	Until February, 2020	March–April, 2020	NA
Number of patients	19	10	NA
Age at onset, years	3·0 (2·5)	7·5 (3·5)	0·00035
Incidence	0·3 per month	10 per month	<0·00001
Sex	NA	NA	0·13
Female	12	3	NA
Male	7	7	NA
Incomplete Kawasaki disease	6/19 (31%)	5/10 (50%)	0·43
CRP, mg/dL	16·3 (8·0)	25 (15·3)	0·05
ESR, mm/h	82 (29)	72 (24)	0·38
White cell count, ×10⁹ per L	19·4 (6·4)	10·8 (6·1)	0·0017
Neutrophils	71·9% (17·2)	84·5% (5·7)	0·034
Lymphocytes, ×10⁹ per L	3·0 (1·8)	0·86 (0·4)	0·0012
Haemoglobin, g/dL	10·8 (2·0)	11 (1·2)	0·79
Platelets, ×10⁹ per L	457 (96)	130 (32)	<0·00001
Albumin, g/dL	3·3 (0·5)	3·2 (0·3)	0·55
Sodium, mEq/L	134·7 (1·6)	130·8 (3·9)	0·0011

CRP 73-525 (only 1 <100)

AST, U/L	120 (218)	87 (70)	0·64
ALT, U/L	92 (122)	119 (217)	0·67
Ferritin, ng/mL	187 (89)	1176 (1032)	0·011
Triglycerides, mg/dL	..	239 (108)	..
Fibrinogen, mg/dL	543 (300)	621 (182)	0·51
D-dimer, ng/mL	3244 (943)	3798 (1318)	0·52
CPK, IU/L	61 (28)	85 (64)	0·19
Troponin I, ng/L	..	1004 (1862)	..
proBNP, ng/L	..	1255 (929)	..
Kobayashi score ≥5	2/19 (10%)	7/10 (70%)	0·0021
MAS[18]	0/10 (0%)	5/10 (50%)	0·021
KDSS[14]	0/10 (0%)	5/10 (50%)	0·021
Abnormal echocardiography	2/19 (10%)	6/10 (60%)	0·0089
Adjunctive steroid treatment	4/19 (16%)	8/10 (80%)	0·0045
Inotropes treatment	0/19 (0%)	2/10 (20%)	0·11
Response to treatment	19/19 (100%)	10/10 (100%)	1

Data are mean (SD) or n/N (%), unless otherwise stated. SARS-CoV-2=severe acute respiratory syndrome coronavirus 2. NA=not applicable. CRP=C-reactive protein. ESR=erythrocyte sedimentation rate. AST=aspartate aminotransferase. ALT=alanine aminotransferase. CPK=creatine phosphokinase. BNP=B-type natriuretic peptide. MAS=Macrophage Activation Syndrome. KDSS=Kawasaki disease shock syndrome.

Table 2: **Comparison between patients with Kawasaki-like disease**

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

They took any child who met WHO, Royal College or CDC definition

Table 1. Case Definitions for Emerging Inflammatory Condition During COVID-19 Pandemic From the World Health Organization, Royal College of Paediatrics and Child Health, and Centers for Disease Control and Prevention

World Health Organization[8]	Royal College of Paediatrics and Child Health (United Kingdom)[7]	Centers for Disease Control and Prevention (United States)[9]
Children and adolescents 0-19 y of age with fever >3 d AND 2 of the following: 1. Rash or bilateral nonpurulent conjunctivitis or mucocutaneous 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, APTT, elevated D-dimers) 5. Acute gastrointestinal problems (diarrhea, vomiting, or abdominal pain) AND Elevated markers of inflammation such as ESR, CRP, 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 Consider this syndrome in children with features of typical or atypical Kawasaki disease or toxic shock syndrome	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 (see listed in eAppendix in Supplement 2). This may include children fulfilling full or partial criteria for Kawasaki disease[a] 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	An individual aged <21 y presenting with fever, laboratory evidence of inflammation, and evidence of clinically severe illness requiring hospitalization, with multisystem (>2) organ involvement (cardiac, kidney, respiratory, hematologic, gastrointestinal, dermatologic, or neurological) Fever >38.0 °C for ≥24 h or report of subjective fever lasting ≥24 h Laboratory evidence including, but not limited to, ≥1 of the following: an elevated CRP level, ESR, fibrinogen, procalcitonin, D-dimer, ferritin, lactic acid dehydrogenase, or IL-6; elevated neutrophils; reduced lymphocytes; and low albumin 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 wk prior to the onset of symptoms 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

Abbreviations: APTT, activated partial thromboplastin time; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; ECHO, echocardiography; ESR, erythrocyte sedimentation rate; MIS-C, multisystem inflammatory syndrome in children; NT-proBNP, N-terminal pro–B-type natriuretic peptide; PT, prothrombin time; RT-PCR, reverse transcriptase–polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

[a] Criteria for Kawasaki disease include persistent fever and 4 of 5 principal clinical features: erythema and cracking of lips, strawberry tongue, and/or erythema of oral and pharyngeal mucosa; bilateral bulbar conjunctival injection without exudate; rash (maculopapular, diffuse erythroderma); erythema and edema of the hands and feet and/or periungual desquamation; and cervical lymphadenopathy.

New York State

INTERIM CASE DEFINITION: PEDIATRIC MULTISYSTEM INFLAMMATORY SYNDROME TEMPORALLY ASSOCIATED WITH SARS-CoV-2

Clinical Criteria: An individual aged < 21 years with:

- A minimum one-day history of subjective **OR** objective fever (≥ 100.4° F/38° C); **AND**
- Hospitalization; **AND**
- **Either:**
  - **One or more** of the following:
    - Hypotension or shock (cardiogenic or vasogenic)
    - Features of severe cardiac illness including but not limited to myocarditis, pericarditis, or valvulitis, significantly elevated troponin/pro-BNP, or coronary artery abnormalities
    - Other severe end-organ involvement including but not limited to neurological or renal disease (excluding severe respiratory disease alone)

    OR
  - **Two or more** of the following:
    - Maculopapular rash
    - Bilateral non-purulent conjunctivitis
    - Mucocutaneous inflammatory signs (mouth, hands, or feet)
    - Acute gastrointestinal symptoms (diarrhea, vomiting, or abdominal pain); **AND**
- The absence of a more likely diagnosis of the illness, e.g., bacterial sepsis or other viral infection.

Laboratory Criteria:

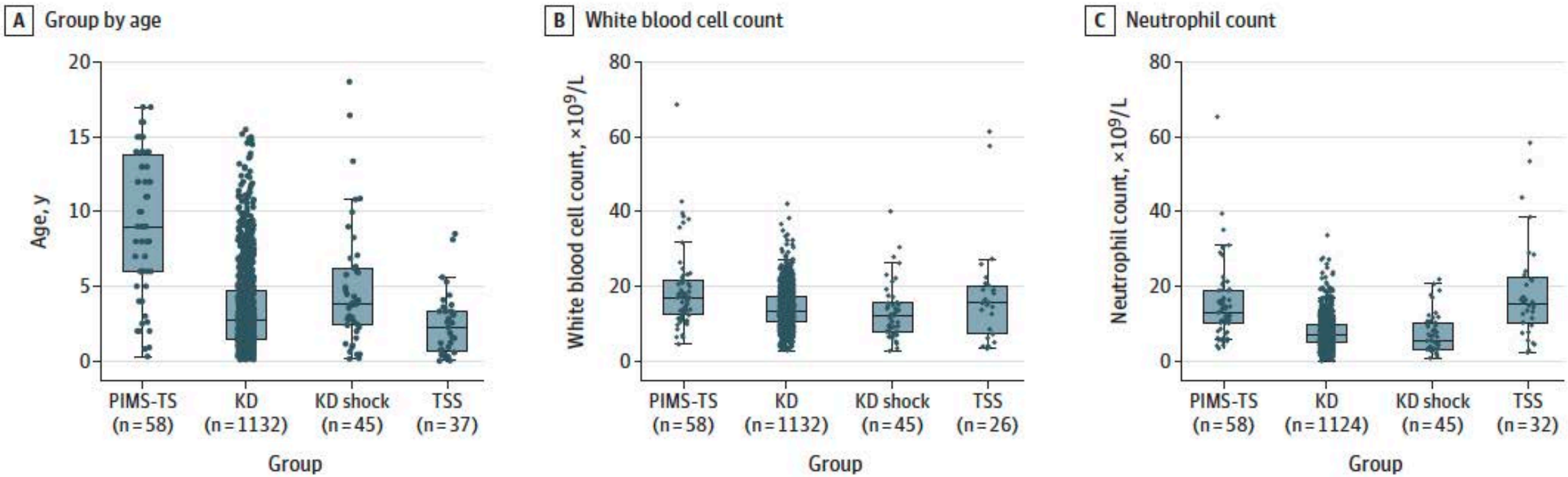
- ***General Laboratory Criteria*: Two** or more of the following markers of inflammation:
  - Neutrophilia, lymphopenia, thrombocytopenia, hypoalbuminemia, elevated C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), fibrinogen, D-Dimer, ferritin, lactic acid dehydrogenase (LDH), interleukin 6 (IL-6), OR elevated procalcitonin
- ***Virologic Laboratory Criteria*:** One of the following SARS-CoV-2 laboratory results[1]
  - Detection of SARS-CoV-2 RNA in a clinical specimen using a molecular amplification detection test (e.g., RT-PCR) (or detection of SARS-CoV-2 antigen in a clinical specimen), at the time of presentation with this clinical picture or within the prior 4 weeks.
  - Detection of SARS-CoV-2 antibody in serum, plasma, or whole blood indicative of a new or recent infection.

Epidemiologic Criteria:

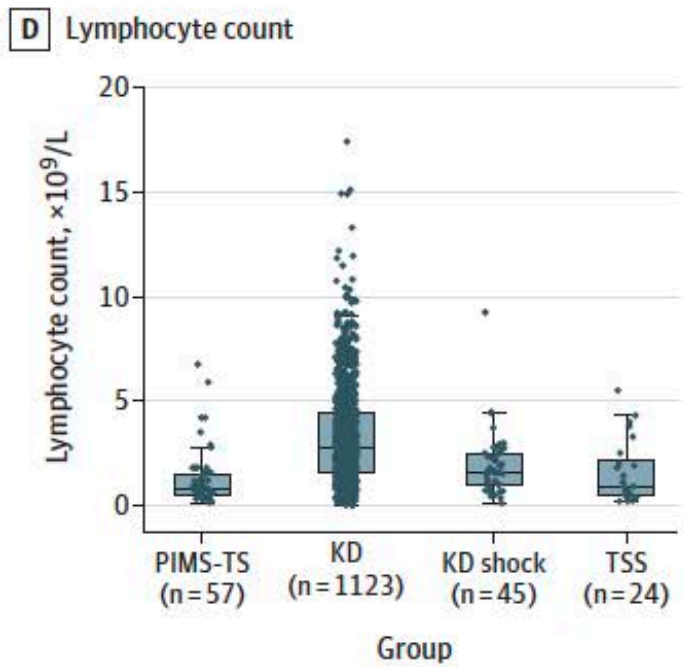
One or more of the following exposures in the 6 weeks prior to the onset of symptoms:

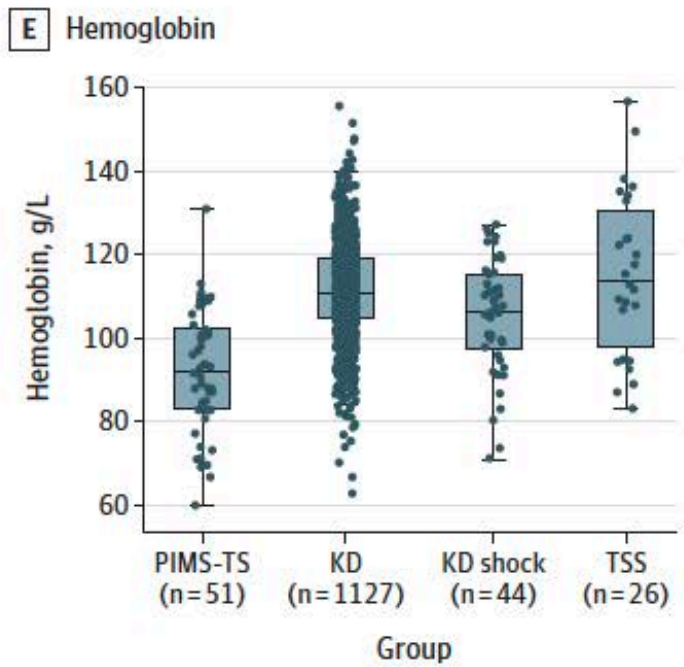
- Close contact with an individual with laboratory-confirmed SARS-CoV-2 infection.[1]
- Close contact with an individual with illness clinically compatible with COVID-19 disease who had close contact with an individual with laboratory-confirmed SARS-CoV-2 infection.[1]
- Travel to or residence in an area with sustained, ongoing community transmission of SARS-CoV-2.

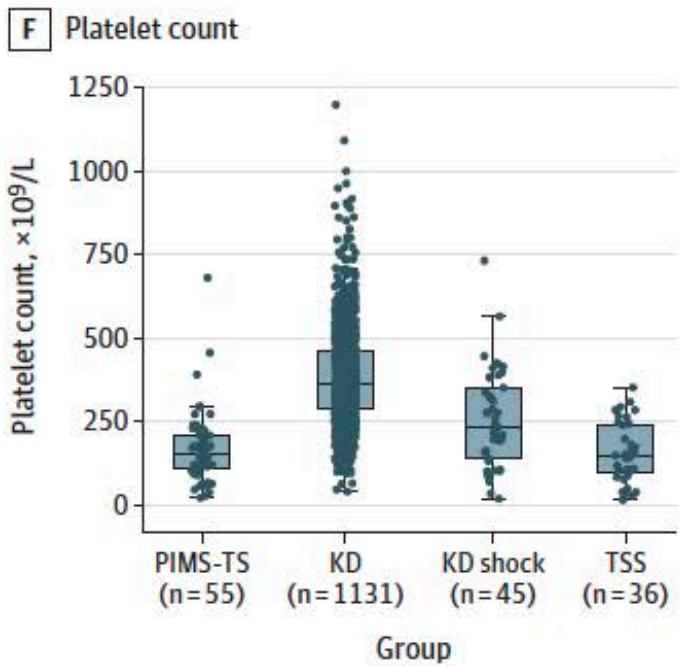
Comparison to KD, KDSS, and TSS



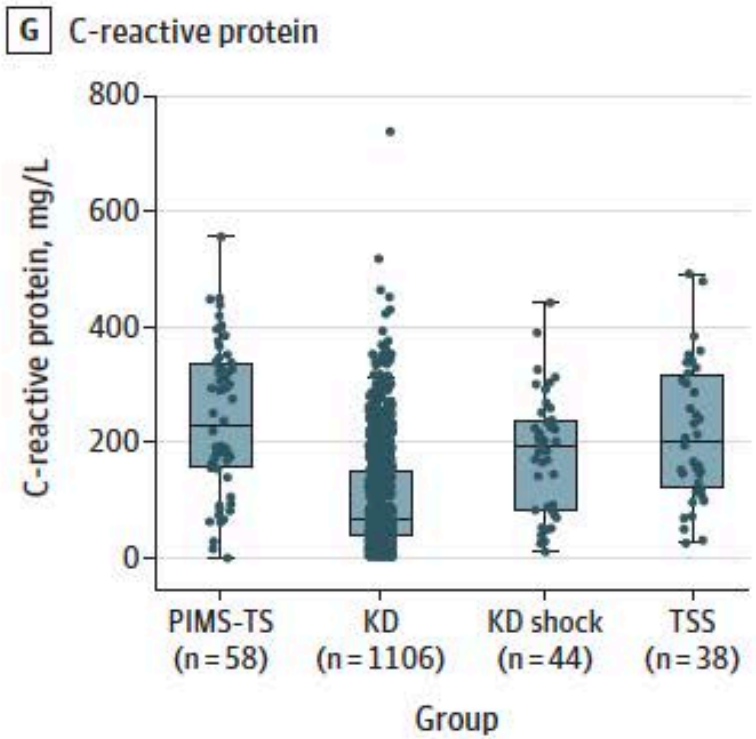
Comparison to KD, KDSS, and TSS

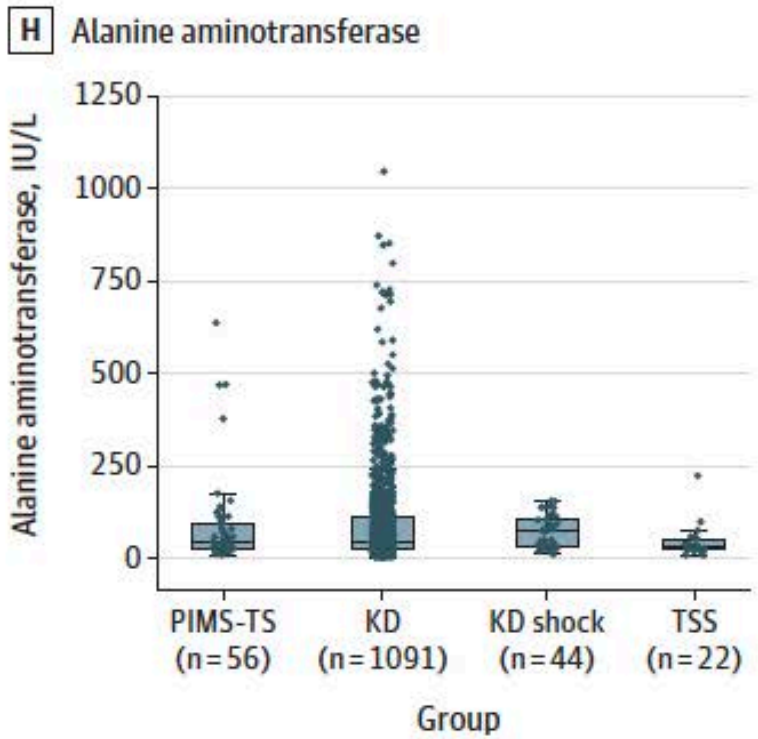


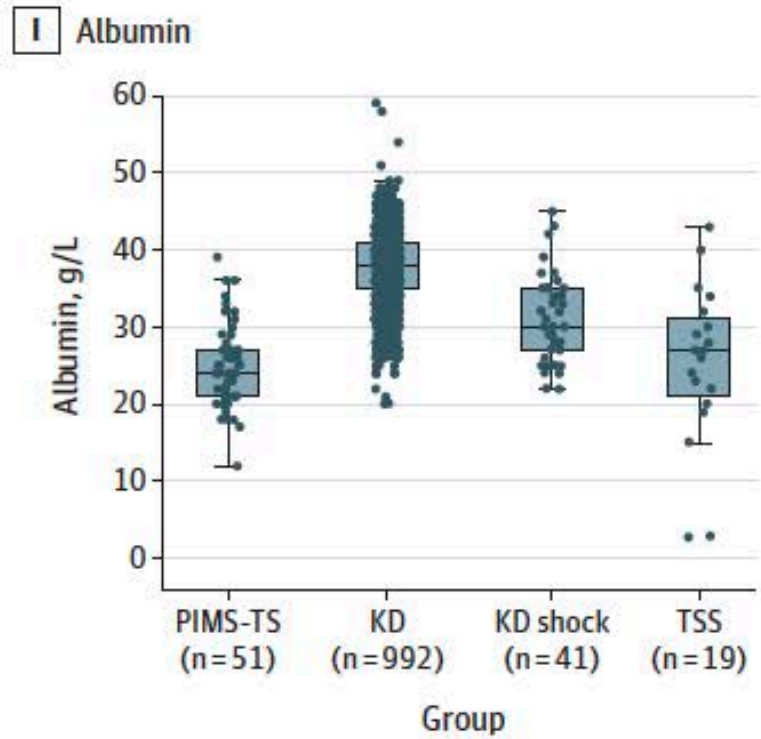


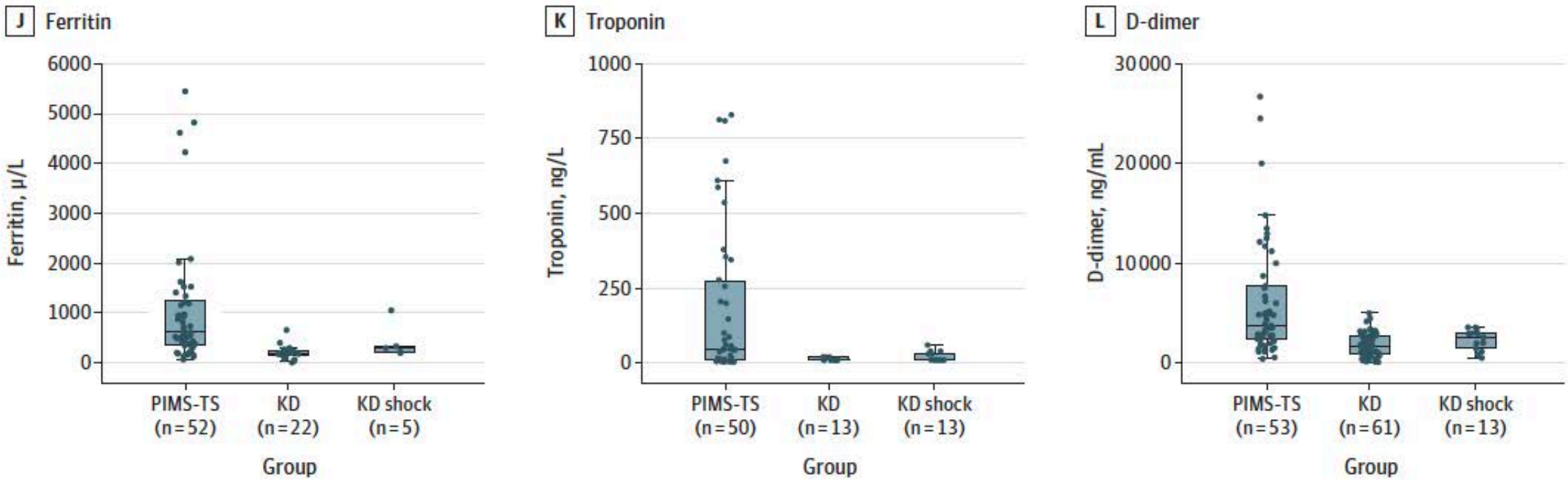


Comparison to KD, KDSS, and TSS








J
Ferritin
Ferritin, µ/L
6000
5000
4000
3000
2000
1000
0
PIMS-TS (n = 52)
KD (n = 22)
KD shock (n = 5)
Group
K
Troponin
Troponin, ng/L
1000
750
500
250
0
PIMS-TS (n = 50)
KD (n = 13)
KD shock (n = 13)
Group
L
D-dimer
D-dimer, ng/mL
30 000
20 000
10 000
0
PIMS-TS (n = 53)
KD (n = 61)
KD shock (n = 13)
Group

Highlights of Published Reports of MIS-C

First Author	Geography	# cases	Myocardial inotropes	Aneurysms	Echo findings	CRP range	Other notable	Age median
Verdoni	Italy	10	20%	2	Mitral regurge 4 Effusions 3	73-525	2 pcr +	7.5
Riphagen	UK	8	100%	1	All were “bright”	169-556	1 ecmo All PCR neg	9
Belhadjer	France	35	All had failure , 80% on inotropes	None	6 - Z score >2	150-311	7 ecmo	10
Cheung	US, NY Columbia	17	61%	None	7/16 ‘bright’ 8/16 effusions	17-300	8/17 PCR +	8
Toubiana	France	21	76%	None	3 ‘bright’ 5- z score 2-2.5	89-363	8/21 PCR + 8/18 CT	7.9
Whitaker	UK	58	47%	8	2 giant aneurysms	156-338	45/58 PCR + AKI 22%	9

Treatments

- Cardiopulmonary support is most crucial
  - Ventilation
  - Inotrope support is common
  - ECMO use not uncommon

- Specific treatment- unclear if any of this works
  - Antivirals (remdesivir) used sparingly in reports as most kids seem post acute infectious
  - Immunomodulators
    - Lots of centers using low dose steroids
    - IVIG in most but not all
    - Anakinra (IL-1 blockade)
    - Toculizamab (IL-6 blockade) used in some
    - TNF blockade less common

Progress in Pediatric Cardiology 57 (2020) 101232

Contents lists available at ScienceDirect

Progress in Pediatric Cardiology

journal homepage: www.elsevier.com/locate/ppedcard

Editorial

COVID-19 associated Multisystem Inflammatory Syndrome in Children (MIS-C) guidelines; a Western New York approach

Teresa R. Hennon, Michelle D. Penque, Rabheh Abdul-Aziz, Omar S. Alibrahim, Megan B. McGreevy, Andrew J. Prout, Beverly A. Schaefer, Steven J. Ambrusko, John V. Pastore, Stephen J. Turkovich, Oscar G. Gomez-Duarte, Mark D. Hicar*

- **MIS-C CDC Case Definition-**
- Fever (>24 hours reported or documented ≥38.0°C) **AND** Laboratory evidence# of inflammation **AND**
- Illness requiring hospitalization **AND**
- Multisystem (≥2) organ involvement *(i.e.* cardiac, renal, resp, gi, heme, derm or neuro)

- **AND** No alternative plausible diagnoses
- **AND COVID 19 positivity/exposure (PCR, AB or exposure)**

May include one or more of the following laboratory value abnormalities: reduced lymphocytes , low albumin, or elevations in any of the following (Neutrophil count, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), fibrinogen, procalcitonin, d-dimer, ferritin, lactic acid dehydrogenase (LDH), or interleukin 6 (IL-6)).

Evaluation for COVID 19 Associated Multisystem Inflammatory Syndrome in Children (MIS-C)

Consider this condition in children presenting with fevers without an explanatory alternative diagnosis and any of the following: after initial resolution of known/highly suspected COVID-19 infection or recent COVID-19 exposure, symptoms of Kawasaki Disease (rash, conjunctivitis, oral/mucosal inflammation), or systemic illness with signs of shock or significant vomiting/diarrhea/abdominal pain. *see below CDC case definition

Overlap with MIS-C definition, but mild illness, mild lab abnormalities on screening labs, and lacking alternative diagnosis

Perform ***Set 1 studies*** not already performed
Additional studies to consider
- chest x-ray
- abdominal imaging as indicated

If concerning labs or clinical decline perform ***Set 2 studies and admit***

Consider discharge if clinically well appearing, stable vital signs, reassuring labs (such as low levels of inflammation, *i.e.* CRP <30, ESR <30), normal imaging if done, and other other workup not concerning.

PMD should follow up in 24 - 48 hours, review symptoms, consider repeating labs and evaluations on ongoing basis.

Sick child / cardiogenic shock / overlap with Kawasaki disease (KD) / toxic-shock like
- Admit and….

- Establish good IV access and start fluids: judicious use with frequent reevaluation
- Perform ***Set 1 and 2 studies if not already done***
- Notify local Department of Health
- Consults:
  - PICU (all patients)
  - Infectious Diseases (all patients)
  - Consider: Hematology, Rheumatology
- Urgent Echo and Cardiology consult for any of the following:
  - Hemodynamically compromised (hypotension, tachycardia out of proportion of fever)
  - Troponin or BNP elevated
  - EKG suggestive of myocardial injury/inflammation
  - If considering KD and on day 9 or longer of fevers
- Empiric Antibiotics (will vary, guided by ID) consider:
  - Ceftriaxone + Metronidazole for abdominal concern
  - Vancomycin, Clindamycin, Cefepime for Toxic Shock

PCR + or more consistent with acute COVID inflammation
-Remdesivir if available
- IVIG 2g /kg, particularly if KD overlap

Daily Labs [A]

Remote infection and predominant KD features
-IVIG 2g /kg
-Aspirin
-Consider corticosteroid

Daily Labs [A]

Reassess, may deteriorate quickly

Myocarditis/Cardiogenic and/or distributive shock (KD predominant or non-KD predominant)
-Critical care
-IVIG 2g /kg and 3 day pulse methylprednisolone with taper
-Enoxaparin prophylaxis
-Rheumatology and Hematology consults
-Consider disease modifying agents

Daily Labs [A B]

Set 1- Studies
COVID-19 PCR (if not performed within 48 hours)
COVID IgG (unless known +)
Respiratory viral panel
EKG
Procalcitonin
ESR
Urinalysis with microscopic (clean catch to assess urethritis)
Blood culture
Urine culture
[A] CBC with differential
[A] CMP (albumin and LFTs)
[A] CRP
[A] Ferritin
[A] D-dimer
[A] Troponin
[A] BNP
[A] LDH
[B] VBG
[B] Lactate
[B] PT/PTT
[B] Fibrinogen
[B] CK
[B] LDH

Set 2- Studies
Chest X-ray
Echocardiogram
Triglycerides
Anti-thrombin III
ADAMTS13
Consider:
Blood type and Screen
Additional blood cultures
Rapid strep and throat culture and Antistreptolysin O (ASO)
Specific viral titers or collecting large volume (5-10mLs) serum to store for future studies
Cytokine panel
Von Willebrand Panel
Immunoglobulins , including IgA (particularly if your center uses IVIG known to have significant IgA contamination)

So, febrile kid in the community. When do you worry?

The kids reported are sick with high CRPs and significant fever at the time of decompensation

Kids with- >24 hours of fever, lack explanatory alternative diagnosis AND one or more of the following categories:

- Sick with symptoms of Kawasaki Disease (rash, conjunctivitis, oral/mucosal inflammation)
- Systemic illness with signs of shock or multisystem involvement
- Significant vomiting/diarrhea/abdominal pain

= referral to a tertiary care center

Milder illness or those with other explanation

- consider screening labs: CRP is fairly universally elevated in almost all cases, normal lymphocytes level and normal platelet level would be reassuring (both low in MIS-C)
  - Most centers have adopted the Kawasaki criteria of <30 mg/L or <3 mg/dL as reassuring cutoffs
- Good anticipatory guidance for kids with overalp early in their course
  - (some reports kids are sick for 3-4 days prior to presentation)

- Peds ID is available to discuss consults and can see children quickly in our clinic any day of the week (Tue/Wed/Fri)

Ongoing studies on these patients

- Our lab, collecting PBMCs and plasma from COVID-19 related cases, including MIS-C
  - Biobanking for other groups
    - Antibody sequences, creation of antibodies
- Helping with consortium analysis of cases
- Helping with group focused on myocarditis
- Revisiting epidemiology of Kawasaki - ongoing (Arthur Chang and Jasdip Singh)

MIS-C –take home points

- Generally post-infectious
  - Studies suggest mostly weeks to months later
  - As we will continue to have low number (hopefully) of SARS-CoV-2, future MIS-C cases in our area will appear sporadic

- Be cautious with mildly ill febrile children without a solid alternative diagnosis
  - a child looking well on day 1 or 2 of fever should be followed and given anticipatory guidance

MIS-C –take home points

- Referral to a tertiary children's hospital is crucial early in course
  - Moderately inflamed children can become sick quickly
- Significant mortality but long-term outcomes seem good
- Many unknowns- true rate, are there "mild" MIS-C cases, etc.
- Long-term follow-up unknown

acknowledgements

- University at Buffalo
  - Hakimuddin Sojar, PhD
  - Sarah Baron
  - Arthur Chang, MD
  - Michael Croix, MD
  - Patrick Kenney, MD

  - UB/Kaleida MIS-C group

  - Steven Lipshultz
  - Theresa Quattrin, MD
  - Stanley Schwartz, MD, PhD
  - James Jarvis, MD
  - Oscar Gomez, MD, PhD
  - Howard Faden, MD
  - Shamim Islam, MD
  - Karl Yu, MD, PhD

  - Jonathon Lovell, PhD
  - Jessica Reynolds, MD
  - Haiping Qiao, MD
  - Brian Wrotniak, PhD
  - Stephen Spence

  - Josh Milner, Mark Gorelik (Columbia)

  - Carl Allen (Baylor)
  - Mary Beth Son, Jane Newburger (Boston)

- UB Genomics core
  - Norma J. Nowak, Ph.D.
  - Donald A. Yergeau, Ph.D.

- Funding
  - KD: Wildermuth foundation
  - COVID-19 SUNY Research Seed Grant Program #20-03-COVIDComparing the COVID-19 antibody response of adults and children

Kate
Willful
Caboose
-Katebits

Tedx2012

COLIN **MAGGIE**

Don’t forget your mask!

New York State Department of Health COVID-19 Tracker

Testing data as of: 6/14/2020 Midnight
Testing data last updated on: 6/15/2020
(Updated daily before 2 PM)

Statewide

Total Persons Tested
2,991,210

Total Tested 6/14
56,611

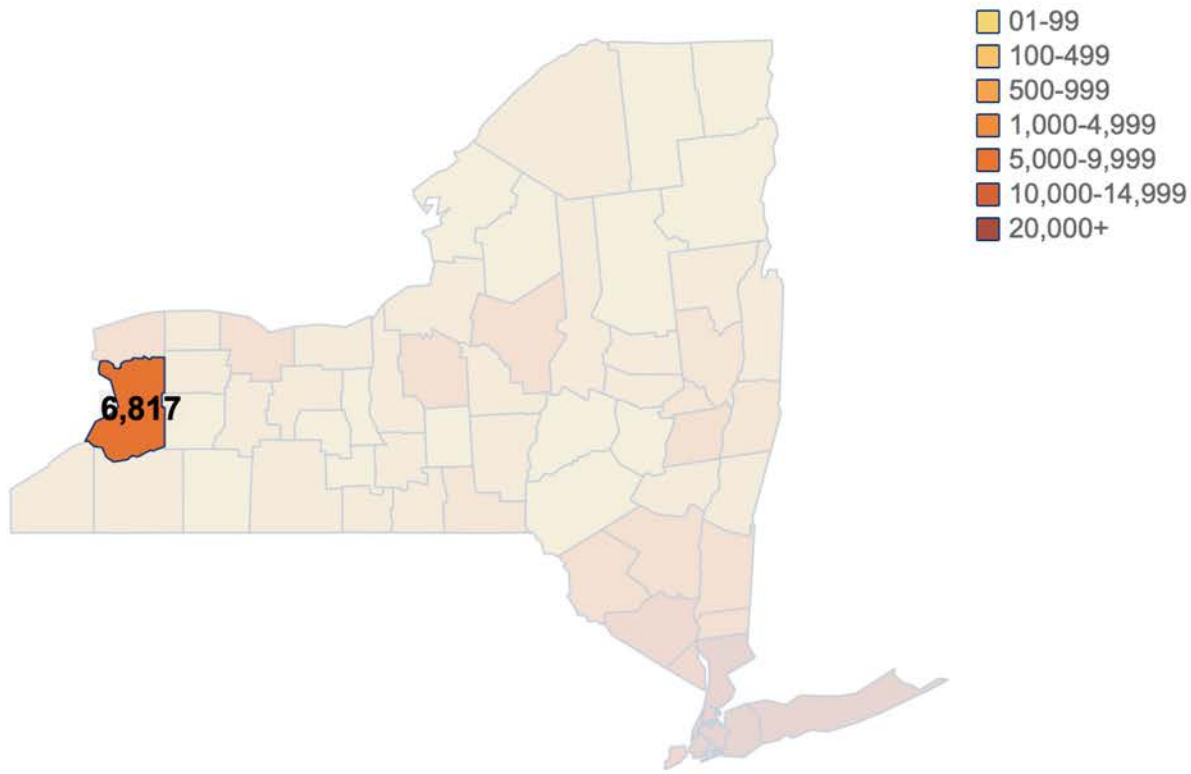
Total Tested Positive
383,944

Sex Distribution of Positive Cases

Female	Male	Unknown
48.5%	50.9%	0.6%

New Positives 6/14
620

Persons Tested Positive by County



Click County to See Detail
Click Again for Statewide

Albany	2,022
Allegany	55
Bronx	46,645
Broome	655
Cattaraugus	106
Cayuga	106
Chautauqua	107
Chemung	138
Chenango	138
Clinton	98
Columbia	439
Cortland	42
Delaware	88
Dutchess	4,068
Erie	6,817
Essex	40
Franklin	25
Fulton	235
Genesee	213
Greene	251

Click for Daily Trends

Click for Table View

Click for Fatality Data

FAQs & Helpful Links

County Stats

County Name	Number of Persons Tested	Tested Positive	% Positive Results	Persons Tested Today	New Positives Today
Erie	102,181	6,817	6.7%	1,796	32

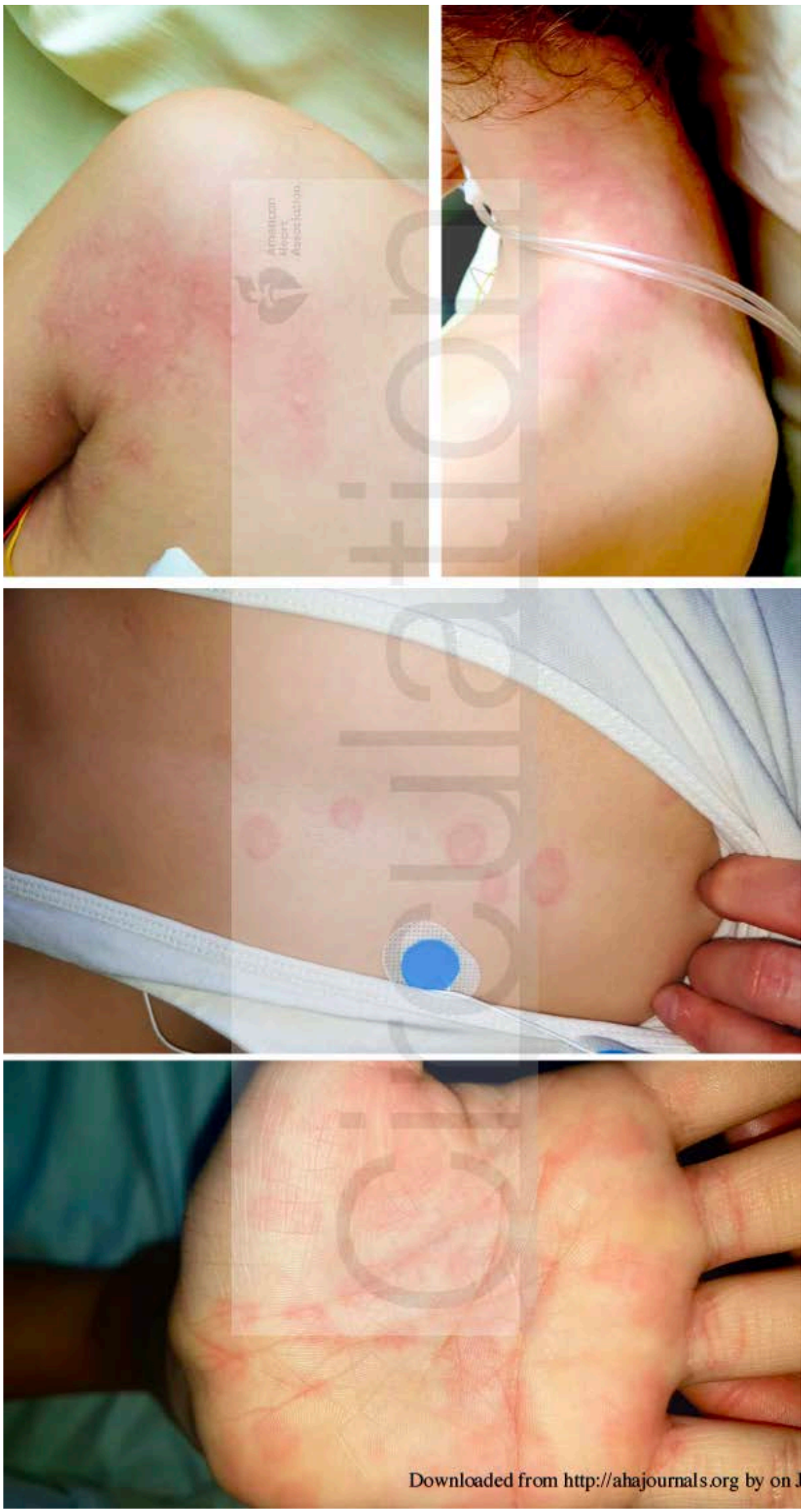


Table 2. Demographics and Clinical Features of the PIMS-TS Cohort

Characteristic	No. (%)[a]											
			Stratification by shock[d]		Stratification by Kawasaki disease[e]		Stratification by Kawasaki clinical criteria[e]		Stratification by coronary artery aneurysm[f]		Stratification by evidence of SARS-CoV-2 infection[g]	
	All PIMS-TS cases (n = 58)[b]	Febrile and inflammatory (n = 23)[c]	Shock present (n = 29)	Shock absent (n = 29)	Kawasaki disease (n = 13)	Not Kawasaki disease (n = 45)	Criteria met (n = 7)	Criteria not met (n = 51)	Present (n = 8)	Absent (n = 50)	Positive (n = 45)	Negative (n = 13)
Age, median (IQR), y	9 (5.7-14)	10 (5.5-14)	10.5 (7-14)	10 (3-14)	8 (5-11)	10.5 (5.7-14)	6 (2-8)	10 (6-14)	9.5 (8-12.3)	9 (5-11)	10 (6-14)	7 (2.5-14)
Sex												
Male	25 (43)	17 (74)	16 (55)	22 (76)	10 (77)	28 (62)	6 (86)	32 (63)	6 (75)	32 (64)	19 (43)	8 (61)
Female	33 (57)	6 (26)	13 (45)	7 (24)	3 (23)	17 (38)	1 (14)	18 (37)	2 (25)	19 (36)	26 (57)	5 (39)
Race/ethnicity												
Black	22 (38)	7 (30)	14 (48)	8 (28)	8 (62)	14 (31)	2 (29)	20 (39)	7 (87.5)	15 (30)	18 (40)	4 (31)
Asian	18 (31)	6 (26)	6 (21)	6 (21)	0	12 (27)	0	12 (24)	0	12 (24)	11 (24)	1 (8)
White	12 (21)	8 (35)	6 (21)	12 (42)	4 (31)	14 (31)	4 (57)	14 (27)	1 (12.5)	17 (34)	13 (29)	5 (38)
Other[h]	6 (10)	2 (9)	3 (10)	3 (10)	1 (8)	5 (11)	1 (14)	5 (10)	0	6 (12)	3 (7)	3 (23)
Clinical features at presentation[i]												
Abdominal pain	31 (53)	13 (57)	18 (62)	13 (45)	2 (15)	29 (64)	1 (14)	30 (59)	2 (33)	29 (58)	24 (55)	7 (50)
Diarrhea	30 (52)	10 (44)	19 (66)	11 (38)	7 (54)	23 (51)	2 (29)	28 (55)	6 (75)	24 (48)	25 (75)	5 (36)
Rash	30 (52)	9 (39)	15 (52)	15 (50)	10 (77)	20 (44)	7 (100)	23 (45)	4 (63)	25 (50)	21 (48)	9 (64)
Shock[d]	29 (50)	0	29 (100)	0	6 (46)	23 (51)	1 (14)	28 (55)	6 (75)	23 (46)	25 (56)	4 (31)
Vomiting	26 (45)	10 (44)	15 (52)	11 (38)	5 (38)	21 (47)	2 (29)	23 (45)	5 (63)	21 (42)	20 (45)	6 (43)
Conjunctival injection	26 (45)	9 (39)	11 (38)	15 (52)	11 (85)	15 (33)	7 (100)	19 (37)	5 (63)	21 (42)	20 (45)	6 (43)
Mucous membrane changes	17 (29)	5 (22)	6 (21)	11 (38)	6 (46)	11 (24)	6 (86)	11 (22)	1 (17)	11 (22)	11 (25)	6 (43)
Headache	15 (26)	4 (17)	11 (38)	4 (14)	4 (31)	11 (24)	1 (14)	14 (27)	4 (50)	11 (22)	13 (30)	2 (14)
Respiratory symptoms	12 (21)	2 (13)	9 (31)	3 (10)	3 (23)	9 (20)	1 (14)	11 (22)	3 (38)	9 (18)	9 (20)	3 (21)
Lymphadenopathy	9 (16)	3 (13)	2 (7)	7 (24)	5 (38)	4 (9)	4 (57)	5 (10)	2 (33)	7 (14)	8 (18)	1 (7)
Swollen hands and feet	9 (16)	2 (13)	4 (14)	5 (17)	4 (31)	5 (11)	4 (57)	5 (10)	1 (17)	7 (14)	7 (16)	2 (14)
Sore throat	6 (10)	1 (4)	5 (17)	1 (3)	0	6 (13)	0	6 (12)	1 (17)	5 (10)	6 (14)	0
Confusion	5 (9)	0	5 (17)	0	1 (8)	4 (9)	0	5 (10)	1 (17)	4 (8)	5 (11)	0

Abbreviations: IQR, interquartile range; PIMS-TS, pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

[a] Clinical features are listed in order of frequency. In addition, pairwise comparison is included dividing the cohort by febrile and inflammatory, shock, Kawasaki disease, clinical diagnostic criteria of Kawasaki, presence of coronary artery aneurysm, and laboratory evidence for SARS-CoV-2 infection.

[b] Fever >38 °C for >72 hours was an entry point to the study.

[c] Febrile and inflammatory only: this cohort of children were those who did not meet the criteria for shock (footnote d) or the clinical diagnostic criteria for Kawasaki disease (footnote e).

[d] Shock was defined as needing inotrope support or fluid resuscitation >20 mL/kg.

[e] American Heart Association criteria for the definition of Kawasaki disease is to have persistent fever and 4 of the following 5 mucocutaneous features: erythema and cracking of lips, strawberry tongue, and/or erythema of oral and pharyngeal mucosa; bilateral bulbar conjunctival injection without exudate; rash (maculopapular, diffuse erythroderma); erythema and edema of the hands and feet in acute phase and/or periungual desquamation in subacute phase; and cervical lymphadenopathy (>1.5 cm diameter). Patients with fewer than 4 features were stratified as having Kawasaki disease if coronary artery aneurysms were present. In the absence of coronary artery changes, stratification by Kawasaki clinical criteria required 4 of 5 features to be present.

[f] Coronary artery aneurysm is dilatation of any coronary artery seen on echocardiogram with a *z* score of >2.0 in the acute phase.

[g] SARS-CoV-2 infection includes positive SARS-CoV-2 polymerase chain reaction or positive SARS-CoV-2 IgG serology results.

[h] Other includes those of mixed race/ethnicity, Middle Eastern, or other ethnicity (https://www.ethnicity-facts-figures.service.gov.uk/ethnic-groups).

[i] Presentation refers to the admission clerking to hospital, for example, the point at which the patient was considered to have a potential diagnosis of PIMS-TS.

Table 3. Clinical Outcomes and Management

Characteristic	No. (%)[a]											
			Stratification by shock[d]		Stratification by Kawasaki disease[e]		Stratification by Kawasaki clinical criteria[e]		Stratification by coronary artery aneurysm[f]		Stratification by evidence of SARS-CoV-2 infection[g]	
	All PIMS-TS cases (n = 58)[b]	Febrile and inflammatory (n = 23)[c]	Shock present (n = 29)	Shock absent (n = 29)	Kawasaki disease (n = 13)	Not Kawasaki disease (n = 45)	Criteria met (n = 7)	Criteria not met (n = 51)	Present (n = 8)	Absent (n = 50)	Positive (n = 45)	Negative (n = 13)
Cardiac/circulatory/kidney												
Acute kidney injury[h]	13 (22)	2 (9)	11 (38)	2 (7)	3 (23)	10 (22)	0	13 (25)	3 (38)	10 (20)	11 (24)	2 (67)
Inotropic support	27 (47)	0	27 (93)	0	6 (46)	21 (47)	1 (14)	26 (51)	6 (75)	21 (42)	23 (52)	4 (29)
Extracorporeal membrane oxygenation	3 (5)	0	3 (10.3)	0	0	3 (7)	0	3 (60)	0	3 (6)	3 (7)	0
Respiratory												
Intubation	25 (43)	2 (9)	23 (79)	2 (7)	5 (38)	20 (44)	1 (14)	24 (47)	5 (63)	20 (40)	20 (45)	5 (36)
Pharmacotherapy												
Intravenous immunoglobulin	41 (71)	14 (61)	21 (72)	20 (69)	13 (100)	28 (62)	7 (100)	34 (68)	8 (100)	33 (66)	33 (75)	8 (57)
Corticosteroids	37 (64)	12 (52)	19 (66)	18 (62)	12 (92)	25 (56)	7 (100)	30 (59)	7 (88)	30 (60)	33 (75)	4 (29)
Anakinra (IL-1 receptor antagonist)	3 (5)	1 (4)	2 (7)	1 (3.4)	0	3 (7)	0	3 (6)	0	3 (6)	2 (5)	1 (8)
Infliximab (TNF-α antagonist)	8 (14)	4 (17)	2 (7)	6 (21)	4 (31)	4 (9)	3 (43)	5 (19)	3 (38)	5 (10)	7 (16)	1 (8)
No. of immunomodulatory agents												
2[i]	35 (60)	11 (48)	18 (62)	17 (59)	12 (92)	23 (51)	7 (100)	28 (55)	7 (88)	28 (56)	32 (71)	3 (23)
3[j]	9 (16)	4 (17)	3 (10)	6 (21)	4 (31)	5 (11)	3 (43)	6 (12)	3 (38)	6 (12)	8 (18)	1 (8)
Outcomes												
Coronary artery aneurysm (*z* score >2)	8 (14)	1 (4)	5 (17)	3 (10)	8 (62)	0	1 (14)	7 (14)	8 (100)	0	6 (13)	2 (15)
Death	1 (2)	0	1 (3)	0	0	1 (2)	0	1 (2)	0	1 (2)	1 (2)	0

Abbreviations: PIMS-TS, pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TNF, tumor necrosis factor.

[a] A pairwise comparison is included dividing the cohort by febrile and inflammatory, shock, Kawasaki disease, clinical diagnostic criteria of Kawasaki, presence of coronary artery aneurysm, and laboratory evidence for SARS-CoV-2 infection.

[b] Fever >38 °C for >72 hours was an entry point to the study.

[c] Febrile and inflammatory only: this cohort of children were those who did not meet the criteria for shock (footnote d) or the clinical diagnostic criteria for Kawasaki disease (footnote e).

[d] Shock was defined as needing inotrope support or fluid resuscitation >20 mL/kg.

[e] American Heart Association criteria for the definition of Kawasaki disease is to have persistent fever and 4 of the following 5 mucocutaneous features: erythema and cracking of lips, strawberry tongue, and/or erythema of oral and pharyngeal mucosa; bilateral bulbar conjunctival injection without exudate; rash (maculopapular, diffuse erythroderma); erythema and edema of the hands and feet in acute phase and/or periungual desquamation in subacute phase; and cervical lymphadenopathy (>1.5 cm diameter). Patients with fewer than 4 features were stratified as having Kawasaki disease if coronary artery aneurysms were present. In the absence of coronary artery changes, stratification by Kawasaki clinical criteria required 4 of 5 features to be present.

[f] Coronary artery aneurysm is dilatation of any coronary artery seen on echocardiogram with a *z* score of >2.0 in the acute phase.

[g] SARS-CoV-2 infection includes positive SARS-CoV-2 polymerase chain reaction or positive SARS-CoV-2 IgG serology results.

[h] Acute kidney injury defined by creatinine level greater than the upper limit for age.

[i] Two agents of intravenous immunoglobulin, corticosteroids, anakinra, or infliximab were given to manage inflammation.

[j] Three agents of intravenous immunoglobulin, corticosteroids, anakinra, or infliximab were given to manage inflammation.

Table 4. Laboratory Results

	Reference range	Median (IQR)[a]											
				Stratification by shock[d]		Stratification by Kawasaki disease[e]		Stratification by Kawasaki clinical criteria[e]		Stratification by coronary artery aneurysm[f]		Stratification by evidence of SARS-CoV-2 infection[g]	
		All PIMS-TS cases (n = 58)[b]	Febrile and inflammatory (n = 23)[c]	Shock present (n = 29)	Shock absent (n = 29)	Kawasaki disease (n = 13)	Not Kawasaki disease (n = 45)	Criteria met (n = 7)	Kawasaki criteria not met (n = 51)	Present (n = 8)	Absent (n = 50)	Positive (n = 45)	Negative (n = 13)
Virology, No. (%)													
SARS-CoV-2 respiratory PCR positive		15 (26)	5/23 (22)	10 (35)	5 (17)	0	15 (33)	0	15 (29)	0	15 (30)	15 (33)	
SARS-CoV-2 IgG antibody		40/46 (83)	15/18 (83)	22/25 (88)	18/23 (78)	8/12 (67)	32/36 (89)	4/6 (67)	36/42 (86)	6 (75)	34/40 (75)	40/42 (95)	
Any SARS-CoV-2 PCR or IgG positive		45/58 (78)	17 (74)	25 (86)	20 (69)	8 (62)	37 (82)	4 (57)	41 (80)	6 (75)	39 (78)	45 (100)	
No positive test result		13 (22)	6 (26)	4 (14)	9 (31)	5 (39)	8 (18)	3 (43)	10 (20)	2 (25)	11 (22)	0	13/13 (100)
Laboratory values													
Hematology													
Total white blood cell count, $\times 10^9$/L	4-13.5	17 (12-22) [n = 58]	16 (11.2-19) [n = 23]	18 (14-28) [n = 29]	17 (11.3-18.8) [n = 29]	17 (13.5-26.4) [n = 13]	17 (12.15-22.6) [n = 45]	17 (11-17) [n = 7]	17.4 (12.5-22.4) [n = 51]	20 (15-29) [n = 8]	17 (11.6-21.7 [n = 50]	17 (12-23) [n = 45]	17 (13-21) [n = 13]
Neutrophil count, $\times 10^9$/L	1.5-7	13 (10-19) [n = 58]	10.7 (7.4-16) [n = 23]	16 (11-25) [n = 29]	10.8 (6.8-16) [n = 29]	13.2 (10.2-16.4) [n = 13]	12.5 (8.5-19.5) [n = 45]	12.5 (6-14) [n = 7]	14 (10.1-19.2) [n = 51]	16 (13-26) [n = 8]	12 (7.9-18.9) [n = 50]	14 (9-20) [n = 45]	13 (8-18) [n = 13]
Lymphocyte count, $\times 10^9$/L	1.5-4	0.8 (0.5-1.5) [n = 58]	1.2 (0.7-2.9) [n = 23]	0.7 (0.4-0.9) [n = 29]	1.3 (0.7-2.8) [n = 29]	1.2 (0.5-1.6) [n = 13]	0.8 (0.6-1.5) [n = 45]	1.3 (0.5-1.8) [n = 7]	0.8 (0.5-1.4) [n = 51]	0.6 (0.4-1.3) [n = 8]	0.8 (0.6-1.6) [n = 50]	0.8 (0.4-1.4) [n = 45]	0.8 (0.5-2.9) [n = 13]
Hemoglobin, g/L	111-147	92 (83-103) [n = 51]	97 (87-108) [n = 19]	85 (74-100) [n = 27]	99.5 (88-109) [n = 24]	88.5 (72-109) [n = 12]	92.5 (83-102) [n = 39]	109 (84-110) [n = 6]	91 (83-101.5) [n = 45]	80 (70-95) [n = 8]	93 (83-106) [n = 43]	93 (83-103) [n = 42]	88 (79-106) [n = 9]
Platelet count, $\times 10^9$/L	200-450	151 (104-210) [n = 55]	175.5 (101-209) [n = 22]	136 (75-214) [n = 28]	176 (118-210) [n = 27]	176 (125-262) [n = 12]	147.5 (93-195) [n = 43]	176 (106-302) [n = 6]	150 (101-210) [n = 49]	173 (123-230) [n = 8]	151 (97-209) [n = 47]	142 (91-201) [n = 42]	180 (129-332) [n = 13]
Inflammatory markers													
C-reactive protein, mg/L	0-5	229 (156-338) [n = 58]	176 (82-192) [n = 23]	321 (223-371) [n = 29]	176 (83-229) [n = 29]	295 (173-357) [n = 13]	206 (151-331) [n = 45]	238 (106-339) [n = 7]	220 (156-338) [n = 51]	301 (205-361) [n = 8]	191 (132-330.5) [n = 50]	251 (158-342) [n = 45]	220 (131-323) [n = 13]
Ferritin, µg/L	7-140	610 (359-1280) [n = 52]	379.5 (195-831) [n = 20]	888 (556-1530) [n = 28]	378 (180-907) [n = 25]	620 (306.3-1254) [n = 12]	592 (373-1443) [n = 41]	357 (146-1078) [n = 6]	631 (381-1342) [n = 47]	637 (376-1076) [n = 8]	574 (355-1378) [n = 45]	679 (374-1249) [n = 42]	495 (190-1627) [n = 11]

(continued)

Table 4. Laboratory Results (continued)

		Median (IQR)[a]											
				Stratification by shock[d]		Stratification by Kawasaki disease[e]		Stratification by Kawasaki clinical criteria[e]		Stratification by coronary artery aneurysm[f]		Stratification by evidence of SARS-CoV-2 infection[g]	
	Reference range	All PIMS-TS cases (n = 58)[b]	Febrile and inflammatory (n = 23)[c]	Shock present (n = 29)	Shock absent (n = 29)	Kawasaki disease (n = 13)	Not Kawasaki disease (n = 45)	Criteria met (n = 7)	Kawasaki criteria not met (n = 51)	Present (n = 8)	Absent (n = 50)	Positive (n = 45)	Negative (n = 13)
Biochemistry													
Lactate dehydrogenase, U/L	125-243	419 (319-887) [n = 41]	327 (274-463) [n = 15]	764 (291-989) [n = 23]	327 (273.5-451.8) [n = 18]	373 (309-828) [n = 9]	448 (319-912.5) [n = 32]	359 (246-373) [n = 3]	434 (323-906) [n = 38]	615 (371-905) [n = 6]	408 (311-900) [n = 35]	414 (310-915) [n = 34]	1104 (327-1209) [n = 7]
ALT, U/L	0-34	42 (26-95) [n = 56]	40 (21-79) [n = 23]	47 (30-107) [n = 28]	31.5 (20-77) [n = 28]	36.5 (18.75-117.8) [n = 12]	42 (27-97) [n = 44]	26 (12-141) [n = 6]	43 (28-96) [n = 50]	86 (34-129) [n = 8]	40 (25-77) [n = 48]	42 (30-95) [n = 43]	28 (22-273) [n = 13]
Albumin, g/L	35-54	24 (21-27) [n = 51]	27 (24-33) [n = 19]	22 (20-24) [n = 27]	27 (25-32) [n = 24]	24 (20-27) [n = 12]	24 (21-29) [n = 39]	27 (23-28) [n = 6]	24 (21-28) [n = 45]	21 (18-26) [n = 8]	25 (21-29) [n = 43]	24 (21-27) [n = 41]	27 (21-31) [n = 10]
Creatinine, µmol/L	30-80 (varies with age)	71 (43-108) [n = 48]	62 (42-93) [n = 19]	78 (42-104) [n = 32]	61 (45-92) [n = 20]	72 (46-123) [n = 8]	71 (41-102) [n = 33]	42 (40-46) [n = 3]	76 (40-118) [n = 25]	72 (46-122) [n = 8]	71 (40-101) [n = 33]	67 (44-116) [n = 30]	76 (40-96) [n = 11]
Cardiac markers													
Troponin, ng/L	0-15	45 (8-294) [n = 56]	8 (5-45) [n = 17]	124 (45-497) [n = 26]	8 (5-45) [n = 22]	19.3 (7-153) [n = 12]	45.1 (8-355) [n = 38]	10 (5-38) [n = 6]	47.5 (11-353) [n = 44]	100 (25-379) [n = 7]	45 (7-278) [n = 43]	45 (8-202) [n = 41]	256 (9-598) [n = 9]
NT-proBNP, pg/mL	<100	788 (174-10 548) [n = 29]	310.5 (106-1354) [n = 17]	14 017 (7004-35 000) [n = 11]	212.5 (70-876) [n = 18]	788 (56-32 169) [n = 7]	921.5 (180-9962) [n = 22]	118 (23-636) [n = 4]	1833 (213-12 868) [n = 25]	32 169 (1994-35 000) [n = 3]	629 (155-7597) [n = 26]	1140 (184-11 719) [n = 27]	11 (10-12) [n = 2]
Coagulation													
Fibrinogen, g/L	1.99-4.09	5.7 (4.4-7) [n = 51]	4.8 (3.5-5.8) [n = 18]	6.1 (5-7.3) [n = 27]	4.9 (3.9-6.7) [n = 24]	7.1 (4.8-7.6) [n = 13]	5.7 (4.3-6.8) [n = 38]	6 (4.7-7.4) [n = 7]	5.7 (4.3-6.9) [n = 44]	6.9 (5.7-7.8) [n = 8]	5.5 (4.3-6.8) [n = 43]	5.8 (4.4-7.1) [n = 42]	5.5 (3.8-7.6) [n = 9]
D-dimer, ng/mL	100-560	3578 (2085-8235) [n = 53]	2402 (1336-4248) [n = 20]	5935 (3548-12 842) [n = 28]	2383 (1357-4360) [n = 25]	3238 (969-6262) [n = 11]	3578 (2205-10 000) [n = 42]	3494 (1733-6650) [n = 6]	3578 (2205-8729) [n = 47]	4375 (2662-6906) [n = 6]	3564 (1964-10 000) [n = 47]	3910 (2563-10 000) [n = 27]	2094 (1379-5815) [n = 10]

Abbreviations: ALT, alanine aminotransferase; IQR, interquartile range; NT-proBNP, N-terminal pro–B-type natriuretic peptide; PIMS-TS, pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2; PCR, polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

SI conversion factors: To convert ALT and lactate dehydrogenase to µkat/L, multiply by 0.0167; to convert creatinine to mg/dL, divide by 88.4.

[a] A pairwise comparison is included dividing the cohort by febrile and inflammatory, shock, Kawasaki disease, clinical diagnostic criteria of Kawasaki, presence of coronary artery aneurysm, and laboratory evidence for SARS-CoV-2 infection.

[b] Fever >38 °C for >72 hours was an entry point to the study.

[c] Febrile and inflammatory only: this cohort of children were those who did not meet the criteria for shock (footnote d) or the clinical diagnostic criteria for Kawasaki disease (footnote e).

[d] Shock was defined as needing inotrope support or fluid resuscitation >20 mL/kg.

[e] American Heart Association criteria for the definition of Kawasaki disease is to have persistent fever and 4 of the following 5 mucocutaneous features: erythema and cracking of lips, strawberry tongue, and/or erythema of oral and pharyngeal mucosa; bilateral bulbar conjunctival injection without exudate; rash (maculopapular, diffuse erythroderma); erythema and edema of the hands and feet in acute phase and/or periungual desquamation in subacute phase; and cervical lymphadenopathy (>1.5 cm diameter). Patients with fewer than 4 features were stratified as having Kawasaki disease if coronary artery aneurysms were present. In the absence of coronary artery changes, stratification by Kawasaki clinical criteria required 4 of 5 features to be present.

[f] Coronary artery aneurysm is dilatation of any coronary artery seen on echocardiogram with a *z* score of >2.0 in the acute phase.

[g] SARS-CoV-2 infection includes positive SARS-CoV-2 polymerase chain reaction or positive SARS-CoV-2 IgG serology results.