MA/REGION 1 PARTNERSHIP *for*
Regional Disaster Health Response

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

May 29, 2020





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Timeline

- April 22: First MIS-C case at MGH*f*C
- April 26: Royal College of Paediatrics and Child Health advisory
- May 2: PCICS webinar
- May 6: UK Report published in Lancet
- May 13: Italian Report published in Lancet; NYS DOH advisory
- May 14: CDC, MA DPH advisory
- May 15: WHO case definition

Health

15 children in New York City have developed a puzzling and serious inflammatory syndrome possibly linked to covid-19

The condition is similar to what doctors have observed in Europe

15 Children Are Hospitalized With Mysterious Illness Possibly Tied to Covid-19

Children could be at risk of suffering heart attacks and aneurysms if Kawasaki disease is misdiagnosed as coronavirus, top medics fear

PMIS – PIMS – MIS-C

MassGeneral Hospital for Children

RCPCH Advisory 5/1/2020

Case definition:

1. A child presenting with persistent fever, inflammation (neutrophilia, elevated CRP and lymphopaenia) and evidence of single or multi-organ dysfunction (shock, cardiac, respiratory, renal, gastrointestinal or neurological disorder) with additional features (see listed in Appendix 1). This may include children fulfilling full or partial criteria for Kawasaki disease.

2. 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).

3. SARS-CoV-2 PCR testing may be positive or negative

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CDC Advisory 5/14/2020

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

WHO Case Definition 5/15/2020

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.

UK Report

- "Hyperinflammatory shock in children during COVID-19 pandemic" by Riphagen et al in Lancet on May 6, 2020
- Described 8 patients presenting with hyperinflammatory syndrome
  - Ages 6-14 years
  - 62.5% male
  - 75% Afro-Caribbean descent
  - 87.5% above 75%ile for weight
  - All initially PCR negative (2 later positive post-discharge)

Riphagen S, Gomez X, Gonzales-Martinez C, Wilkinson N, Theocharis P. Hyperinflammatory shock in children during COVID-19 pandemic. Lancet. 2020. Advance online publication, doi: 10.1016/S0140-6736(20)31094

	Age; weight; BMI; comorbidities	Clinical presentation		Organ support	Pharmacological treatment	Imaging results	Laboratory results	Microbiology results	PICU length of stay; outcome
		Initial	PICU referral						
Patient 1 (male, Afro-Caribbean)	14 years; 95 kg; BMI 33 kg/m²; no comorbidities	4 days >40°C; 3 days non-bloody diarrhoea; abdominal pain; headache	BP 80/40 mmHg; HR 120 beats/min; RR 40 breaths per min; work of breathing; SatO2 99% NCO2	MV, RRT, VA-ECMO	Dopamine, noradrenaline, argipressin, adrenaline milrinone, hydroxicortisone, IVIG, ceftriaxone, clindamycin	RV dysfunction/ elevate RVSP; ileitis, GB oedema and dilated biliary tree, ascites, bilateral basal lung consolidations and diffuse nodules	Ferritin 4220 µg/L; D-dimers 13·4 mg/L; troponin 675 ng/L; proBNP >35 000; CRP 556 mg/L; procalcitonin>100 µg/L; albumin 20 g/L; platelets 123×10⁹	SARS-CoV-2 positive (post mortem)	6 days; demise (right MCA and ACA ischaemic infarction)
Patient 2 (male, Afro-Caribbean)	8 years; 30 kg; BMI 18 kg/m²; no comorbidities	5 days >39°C; non-bloody diarrhoea; abdominal pain; conjunctivitis; rash	BP 81/37 mmHg; HR 165 beats/min; RR 40 breaths/ min; SVIA	MV	Noradrenaline, adrenaline, IVIG, infliximab, methylprednisolone, ceftriaxone, clindamycin	Mild biventricular dysfunction, severely dilated coronaries; ascites, pleural effusions	Ferritin 277 µg/L; D-dimers 4·8 mg/L; troponin 25 ng/L; CRP 295 mg/L; procalcitonin 8·4 µg/L; albumin 18 g/L; platelets 61×10⁹	SARS-CoV-2 negative; likely COVID-19 exposure from mother	4 days; alive
Patient 3 (male, Middle-Eastern)	4 years; 18 kg; BMI 17 kg/m²; no comorbidities	4 days >39°C; diarrhoea and vomiting; abdominal pain; rash; conjunctivitis	BP 90/30 mmHg; HR 170 beats/min; RR 35 breaths/ min; SVIA	MV	Noradrenaline, adrenaline, IVIG ceftriaxone, clindamycin	Ascites, pleural effusions	Ferritin 574 µg/L; D-dimers 11·7 mg/L; tropinin 45 ng/L; CRP 322 mg/L; procalcitonin 10·3 µg/L; albumin 22 g/L; platelets 103×10⁹	Adenovirus positive; HERV positive	4 days; alive
Patient 4 (female, Afro-Caribbean)	13 years; 64 kg; BMI 33 kg/m²; no comorbidities	5 days >39°C; non-bloody diarrhoea; abdominal pain; conjunctivitis	BP 77/41 mmHg; HR 127 beats/min; RR 24 breaths/ min; SVIA	HFNC	Noradrenaline, milrinone, IVIG, ceftriaxone, clindamycin	Moderate-severe LV dysfunction; ascites	Ferritin 631 µg/L; D-dimers 3·4 mg/L; troponin 250 ng/L; proBNP 13427 ng/L; CRP 307 mg/L; procalcitonin 12·1 µg/L; albumin 21 g/L; platelets 146×10⁹	SARS-CoV-2 negative	5 days; alive
Patient 5 (male, Asian)	6 years; 22 kg; BMI 14 kg/m²; autism, ADHD	4 days >39°C; odynophagia; rash; conjunctivitis	BP 85/43 mmHg; HR 150 beats/min; RR 50 breaths/ min; SVIA	NIV	Milrinone, IVIG, methylprednisolone, aspirin, ceftriaxone	Dilated LV, AVVR, pericoronary hyperechogenicity	Ferritin 550 µg/L; D-dimers 11·1 mg/L; troponin 47 ng/L; NT-proBNP 7004 ng/L; CRP 183 mg/L; albumin 24 g/L; platelets 165×10⁹	SARS-CoV-2 positive; likely COVID-19 exposure from father	4 days; alive
Patient 6 (female, Afro-Caribbean)	6 years; 26 kg; BMI 15 kg/m²; no comorbidities	5 days >39°C; myalgia; 3 days diarrhoea and vomiting; conjunctivitis	BP 77/46 mmHg; HR 120 beats/min; RR 40 breaths/ min; SVIA	NIV	Dopamine, noradrenaline, milrinone, IVIG, methylprednisolone, aspirin, ceftriaxone, clindamycin	Mild LV systolic impairment	Ferritin 1023 µg/L; D-dimers 9·9 mg/L; troponin 45 ng/L; NT-proBNP 9376 ng/L; CRP mg/L 169; procalcitonin 11·6 µg/L; albumin 25 g/L; platelets 158	SARS-CoV-2 negative; confirmed COVID-19 exposure from grandfather	3 days; alive
Patient 7 (male, Afro-Caribbean	12 years; 50kg; BMI 20 kg/m²; alopecia areata, hayfever	4 days >39°C; 2 days diarrhoea and vomiting; abdominal pain; rash; odynophagia; headache	BP 80/48 mmHg; HR 125 beats/min; RR 47 breaths/ min; SatO₂ 98%; HFNC FiO₂ 0.35	MV	Noradrenaline, adrenaline, milrinone, IVIG, methylprednisolone, heparin, ceftriaxone, clindamycin, metronidazole	Severe biventricular impairment; ileitis, ascites, pleural effusions	Ferritin 958 µg/L; D-dimer 24·5 mg/L; troponin 813 ng/L; NT-proBNP >35 000 ng/L; CRP 251 mg/L; procalcitonin 71·5 µg/L; albumin 24 g/L; platelets 273×10⁹	SARS-CoV-2 negative	4 days; alive
Patient 8 (female, Afro-Caribbean)	8 years; 50 kg; BMI 25 kg/m²; no comorbidities	4 days >39°C; odynophagia; 2 days diarrhoea and vomiting; abdominal pain	BP 82/41 mmHg; HR 130 beats/min; RR 35 breaths/ min; SatO₂ 97% NCO2	MV	Dopamine, noradrenaline, milrinone, IVIG, aspirin, ceftriaxone, clindamycin	Moderate LV dysfunction	Ferritin 460 µg/L; D-dimers 4·3 mg/L; troponin 120 ng/L; CRP 347 mg/L; procalcitonin 7·42 µg/L; albumin 22 g/L; platelets 296×10⁹	SARS-CoV-2 negative; likely COVID-19 exposure from parent	7 days; alive

UK Report

- Most without respiratory symptoms
- All progressed to vasoplegic shock requiring pressor support
- 1 patient escalated to ECMO – expired from large cerebrovascular infarct
- All received IVIG
- All discharged from ICU in 4-6 days

Riphagen S, Gomez X, Gonzales-Martinez C, Wilkinson N, Theocharis P. Hyperinflammatory shock in children during COVID-19 pandemic. Lancet. 2020. Advance online publication, doi: 10.1016/S0140-6736(20)31094

Italian Report

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

Summary

Background The Bergamo province, which is extensively affected by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) epidemic, is a natural observatory of virus manifestations in the general population. In the past month we recorded an outbreak of Kawasaki disease; we aimed to evaluate incidence and features of patients with Kawasaki-like disease diagnosed during the SARS-CoV-2 epidemic.

Methods All patients diagnosed with a Kawasaki-like disease at our centre in the past 5 years were divided according to symptomatic presentation before (group 1) or after (group 2) the beginning of the SARS-CoV-2 epidemic. Kawasaki-like presentations were managed as Kawasaki disease according to the American Heart Association indications. Kawasaki disease shock syndrome (KDSS) was defined by presence of circulatory dysfunction, and macrophage activation syndrome (MAS) by the Paediatric Rheumatology International Trials Organisation criteria. Current or previous infection was sought by reverse-transcriptase quantitative PCR in nasopharyngeal and oropharyngeal swabs, and by serological qualitative test detecting SARS-CoV-2 IgM and IgG, respectively.

Findings Group 1 comprised 19 patients (seven boys, 12 girls; aged 3·0 years [SD 2·5]) diagnosed between Jan 1, 2015, and Feb 17, 2020. Group 2 included ten patients (seven boys, three girls; aged 7·5 years [SD 3·5]) diagnosed between Feb 18 and April 20, 2020; eight of ten were positive for IgG or IgM, or both. The two groups differed in disease incidence (group 1 *vs* group 2, 0·3 *vs* ten per month), mean age (3·0 *vs* 7·5 years), cardiac involvement (two of 19 *vs* six of ten), KDSS (zero of 19 *vs* five of ten), MAS (zero of 19 *vs* five of ten), and need for adjunctive steroid treatment (three of 19 *vs* eight of ten; all $p<0·01$).

Interpretation In the past month we found a 30-fold increased incidence of Kawasaki-like disease. Children diagnosed after the SARS-CoV-2 epidemic began showed evidence of immune response to the virus, were older, had a higher rate of cardiac involvement, and features of MAS. The SARS-CoV-2 epidemic was associated with high incidence of a severe form of Kawasaki disease. A similar outbreak of Kawasaki-like disease is expected in countries involved in the SARS-CoV-2 epidemic.

Italian Report

	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
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

Verdoni L, Mazza A, Gervasoni A, Martelli L, Ruggeri M, Ciuffreda M, Bonanomi E, D'Anitga L. An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study. Lancet. 2020. Advance online publication, doi: 10.1016/ S0140-6736(20)31129-6

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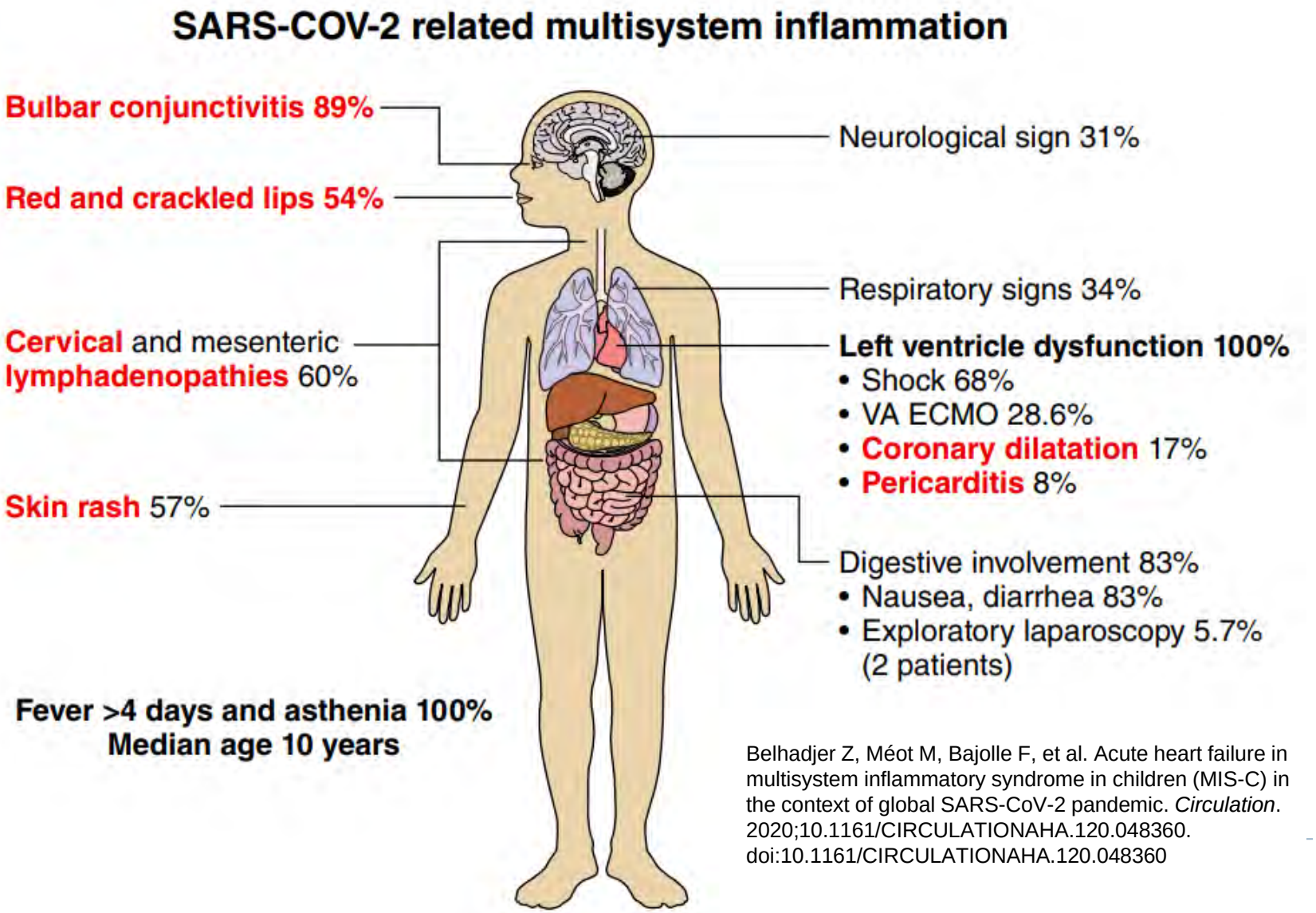
France/Switzerland Report

- "Acute heart failure in multisystem inflammatory syndrome in children (MIS-C) in the context of global SARS-CoV-2 pandemic" by Belhadjer et al. in Circulation on 5/17/2020
- Described 35 patients from 14 centers admitted to ICU for cardiogenic shock, LV dysfxn and severe inflammatory state
- Median Age: 10yo
- 88% positive by PCR or serology
- 28% with comorbidities including asthma and overweight
- All received IVIG, 1/3 +steroids
- 80% required inotropic support, 28% ECMO, no mortality

Belhadjer Z, Méot M, Bajolle F, et al. Acute heart failure in multisystem inflammatory syndrome in children (MIS-C) in the context of global SARS-CoV-2 pandemic. *Circulation*. 2020;10.1161/CIRCULATIONAHA.120.048360. doi:10.1161/CIRCULATIONAHA.120.048360

France/Switzerland Report



Belhadjer Z, Méot M, Bajolle F, et al. Acute heart failure in multisystem inflammatory syndrome in children (MIS-C) in the context of global SARS-CoV-2 pandemic. *Circulation*. 2020;10.1161/CIRCULATIONAHA.120.048360. doi:10.1161/CIRCULATIONAHA.120.048360

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SARS-CoV-2 Virus

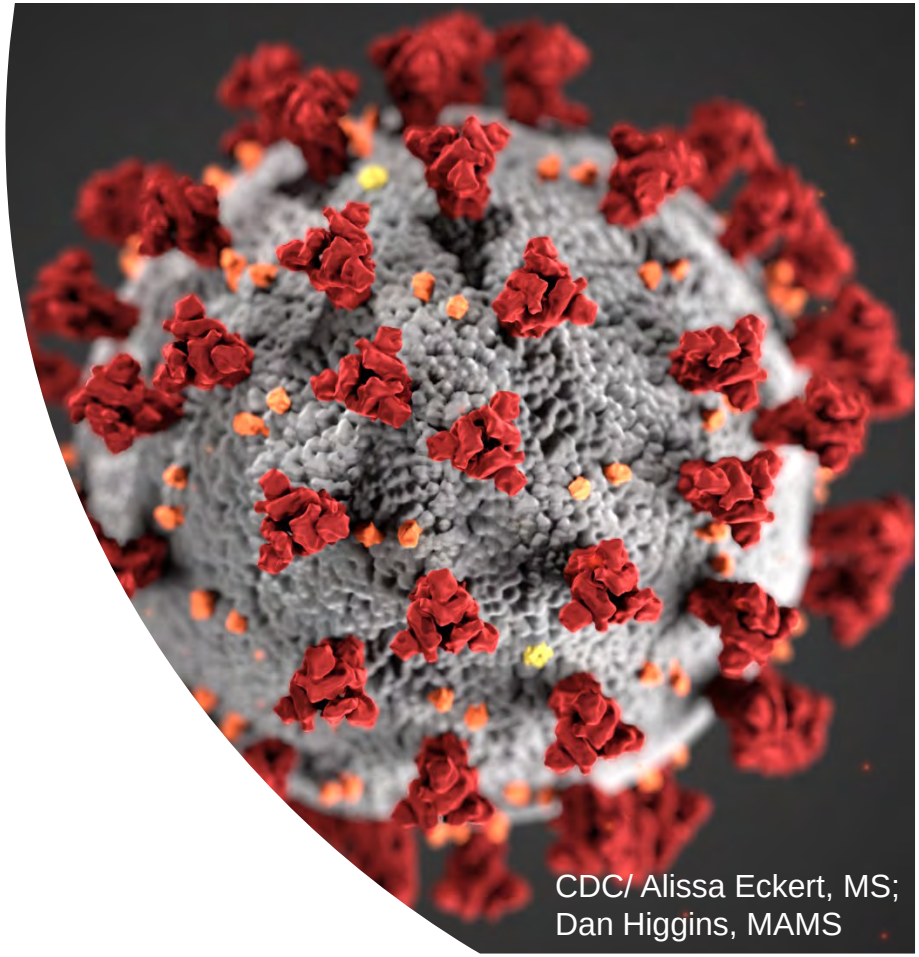
-An enveloped, non-segmented, positive sense RNA virus

-A novel beta-coronavirus in the same subgenus as the SARS-CoV-1 virus

-The spike protein mediates virus binding and uses ACE2 receptor for cell entry

-More transmissible person-to-person than SARS-CoV-1

-The mechanisms by which SARS-CoV-2 triggers MIS-C are currently unknown



CDC/ Alissa Eckert, MS; Dan Higgins, MAMS

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SARS-CoV-2 Virus Diagnostic Testing

-The diagnosis of COVID-19 infection is made by direct detection of SARS-CoV-2 RNA by nucleic acid amplification tests, most frequently reverse-transcription polymerase change reaction (RT-PCR)

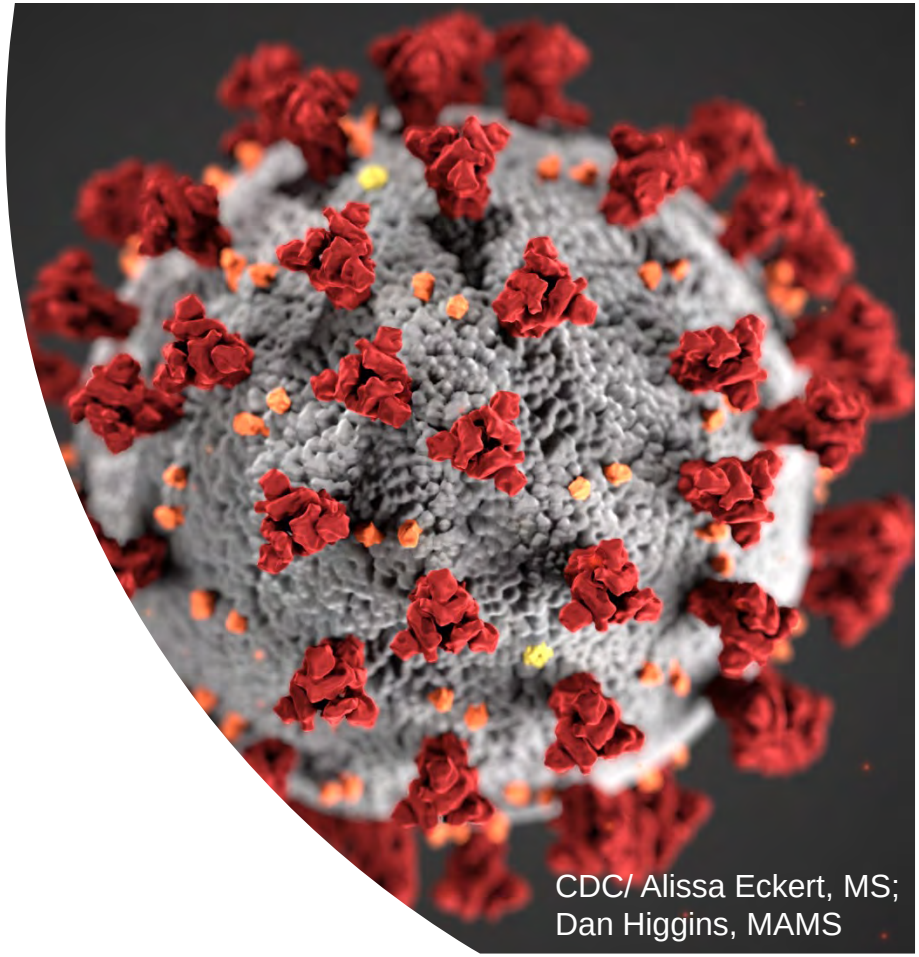
-Different RT-PCR assays amplify and detect different regions of the SARS-CoV-2 genome and most target at least two genes

-Nucleocapsid (N)

-Envelope (E)

-Spike (S)

-RNA-dependent RNA polymerase (RDRP)



CDC/ Alissa Eckert, MS; Dan Higgins, MAMS

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SARS-CoV-2 Virus Diagnostic Testing

All patients with suspected MIS-C should be tested for SARS-CoV-2

- RT-PCR from a nasopharyngeal (NP) swab, and if first swab is negative, send second separate NP swab at least 24 hours after the first test
- SARS-CoV-2 IgM and IgG blood serology

*Additional site specific SARS-CoV-2 testing may be available and could be considered if initial NP swabs RT-PCR and serology tests are negative. For example, we have sent out stool for RT-PCR testing and lower respiratory tract specimens can be sent for RT-PCR on intubated patients.

*For safety reasons, specimens should not be submitted for viral culture. Viral culture is reserved for research purposes.

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SARS-CoV-2 Virus Diagnostic Testing

-Detectable antibodies generally take several days to weeks to develop

-Zhao J et al. Antibody responses to SARS-CoV-2 in patients of novel coronavirus disease 2019. Clin Infect Dis. 2020;

The median time from symptom onset to antibody detection with ELISA that detects antibody to the receptor-binding domain of the spike protein in a study of 173 patients with COVID-19 was:

12 days for IgM

14 days for IgG

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SARS-CoV-2 Testing Results in MIS-C Patients

"Hyperinflammatory shock in children during COVID-19 pandemic" by Riphagen et al in Lancet on May 6, 2020 – Correspondence article from UK

-0/8 tested positive initially for SARS-CoV-2 virus on BAL or NP aspirates

-8/8 tested positive for antibody to SARS-CoV-2 either following discharge (7) or with post-mortem testing (1)

-Adenovirus and enterovirus were isolated in 1/8 children

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SARS-CoV-2 Testing Results in MIS-C Patients

Verdoni L, Mazza A, Gervasoni A, Martelli L, Ruggeri M, Ciuffreda M, Bonanomi E, D'Anitga L. An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study. Lancet. 2020.

-2/10 tested positive for SARS-CoV-2 virus on nasal swab

-0/10 had other respiratory pathogens isolated on nasal swab

-8/10 tested positive for antibody to SARS-CoV-2

-2/10 Both IgM/IgG negative

-5/10 IgM negative/IgG positive

-3/10 Both IgM/IgG positive

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SARS-CoV-2 Testing Results in MIS-C Patients

Belhadjer Z, Méot M, Bajolle F, et al. Acute heart failure in multisystem inflammatory syndrome in children (MIS-C) in the context of global SARS-CoV-2 pandemic. *Circulation*. - Case series in France and Switzerland published on 5/17/2020

- -12/35 (34%) tested positive for SARS-CoV-2 virus on nasal swab
- -0/10 had other respiratory pathogens isolated on nasal swab
- -2/35 (6%) tested positive for SARS-CoV-2 by fecal PCR
- -30/35 (86%) tested positive for antibody to SARS-CoV-2
  - -23/35 Both IgA and IgG positive
  - -3/35 Positive to IgG only
  - -2/35 Both IgM/IgG positive
  - -2/35 Positive for IgA only
- -Results were missing for 5 patients
- -History of recent contact with family members with viral illness in 13/35 patients

SARS-CoV-2 Testing Results in MIS-C Patients

-Unpublished data presented on CDC COCA call 5/19/2020

-UK 38 cases

-SARS-CoV-2 PCR testing

-12/38 positive (32%)

-24/38 negative (63%)

- 2/38 refused/not performed (5%)

-SARS-CoV-2 IgG

-19/38 positive (50%)

- 11 IgG +/ PCR neg

- 5 IgG - / PCR pos

- 3 IgG - / PCR neg

- 18 serology not done, 7 PCR pos

-Total SARS-CoV-2 pos by either method is 23/38 = 61%

SARS-CoV-2 Testing Results in MIS-C Patients

-Unpublished data presented on CDC COCA call 5/19/2020

-Cohen Children's Medical Center in NY

- IgG + and PCR + = 18%
- IgG + and PCR - = 73%
- PCR + and IgG unavailable = 9%

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SARS-CoV-2 Testing Results in MIS-C Patients

-Patients with MIS-C can have various testing results for SARS-CoV-2 virus

-Some test negative by PCR, antigen and antibody

-Some test positive by both PCR and antibody

-Some test positive by PCR and negative by antibody

-Some test negative by PCR and positive by antibody with various patterns of IgM/IgG positivity

-The majority of cases to date test positive by antibody

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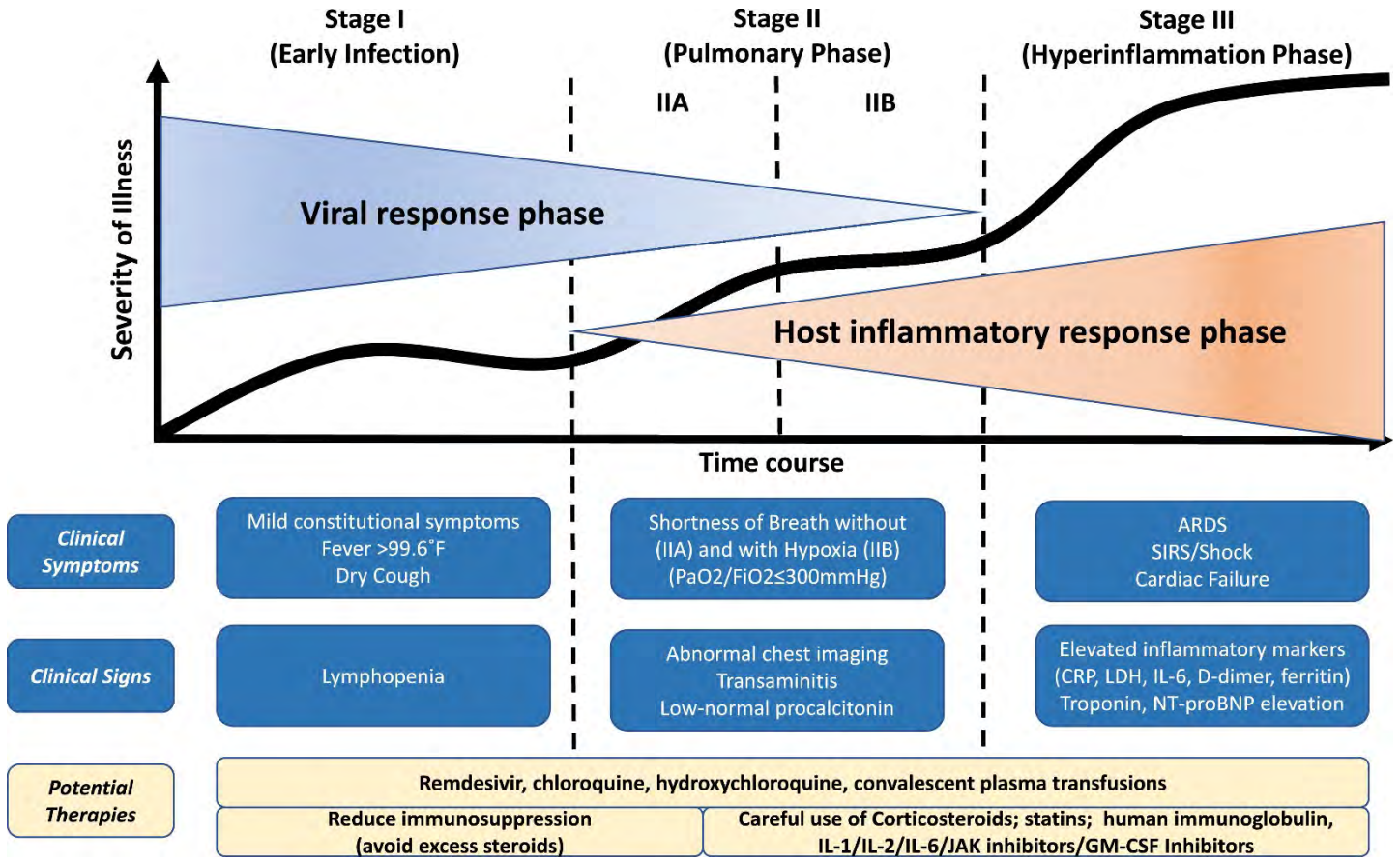

The Journal of Heart and Lung Transplantation 2020 39405-407DOI: (10.1016/j.healun.2020.03.012)

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Infectious differential diagnosis for febrile inflammatory shock:

- Streptococcal toxic shock syndrome
- Staphylococcal toxic shock syndrome
- Rocky Mountain Spotted fever septic shock
- Secondary Hemophagocytic Lymphohistiocytosis
  - Inciting viral agents: Adenovirus, enteroviruses, EBV, CMV, HHV-6, HHV-8, VZV, HIV, Influenza, measles, parvovirus B19, Dengue virus
  - Inciting bacterial agents: *Mycobacterium tuberculosis, Brucella, Coxiella*, Rickettsioses, gram-negative or gram-positive bacteremia
  - Inciting Parasitic agents: *Plasmodium* species, *Leishmania* species
  - Inciting Fungal agents: *Histoplasma capsulatum*, *Penicillium* species, *Fusarium* species

Infectious Diseases Considerations:

Given the differential diagnosis for patients with febrile shock:

- We send blood culture, urine culture +/- CSF culture and initiate broad spectrum empiric antibiotics while diagnostic evaluation is pending

  ceftriaxone

  + doxycycline (if concern for RMSF)

  + clindamycin (if concern for toxin mediated illness)

  + vancomycin (if concern for staphylococcal disease or meningitis)

- We send diagnostic testing for other viral, bacterial and tick-borne infections guided by clinical picture and epidemiologic risk/exposure history

- We save serum before IVIG is administered for possible future testing
- We add on Biofire Respiratory pathogen PCR panel for patients once admitted

Treatment Considerations:

- We do not yet know which treatments are beneficial or harmful for SARS-CoV-2 associated inflammatory conditions
- Several children do well with supportive care alone
- The role of antiviral therapy in the management of MIS-C is uncertain
- When decision is made to use antiviral therapy, Remdesivir is preferred

Treatment Considerations

- MIS-C may represent a post-infectious complication rather than active viral disease however some children with MIS-C do have positive PCR and negative serologic testing and may have current infection
- There is a potential concern for delay of viral clearance or even the risk of provoking viral replication with immunosuppression and therefore antiviral treatment could be potentially beneficial in patients with evidence of ongoing viral PCR positivity especially in the setting of severe or refractory/progressive MIS-C disease

Remdesivir

- A nucleoside analog prodrug which when activated binds to viral RNA-dependent RNA polymerase resulting in premature RNA chain termination. Maintains activity despite the unique 3'-to-5' exoribonuclease of coronaviruses that makes other nucleoside analogs like ribavirin ineffective
- Data in children is lacking, but randomized trials and case series in adults show benefits
- Data suggests it is well tolerated with lower known risks than other antiviral treatments. Reported adverse effects include transaminase elevations, nausea and vomiting.
- On Friday 5/1/2020, FDA issued emergency use authorization to treat hospitalized patients with severe COVID-19. Compassionate use portal remains available to pediatric patients.

https://cdn.arstechnica.net/wp-content/uploads/2020/05/GettyImages-1223960456-800x525.jpg

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Remdesivir

- No children in the published articles from UK or Italy received antiviral treatment
- Small numbers of children in New York and Massachusetts have received remdesivir as part of their treatment for severe MIS-C disease
- Consultation with an infectious disease specialist is advised to guide recommendations for antiviral treatment
- Dosing is 5mg/kg/dose (200mg max) IV on day 1 followed by 2.5mg/kg IV daily (100mg max) for 5-10 days

https://cdn.arstechnica.net/wp-content/uploads/2020/05/GettyImages-1223960456-800x525.jpg

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Jane W. Newburger, M.D., M.P.H.
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Multi-Inflammatory Syndrome in Children and Kawasaki Disease

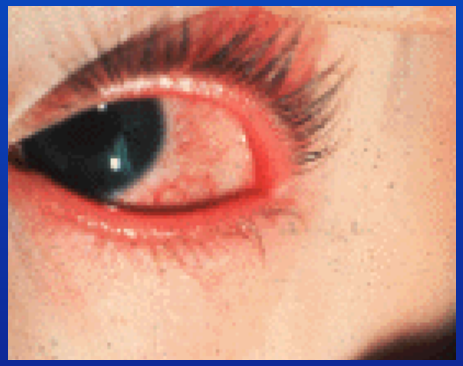
Are They The Same or Different?

Jane W. Newburger, M.D., M.P.H.

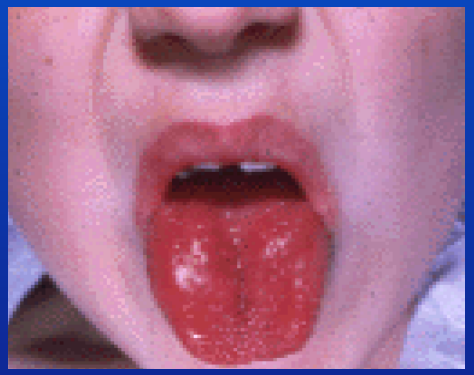
Department of Cardiology,
Children's Hospital Boston,
Harvard Medical School, Boston, MA

Diagnostic Criteria

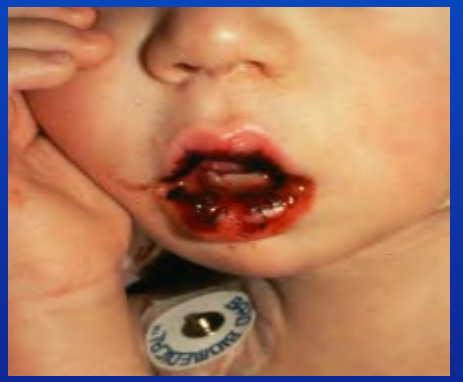
Fever > 101.3 °F persisting at least 5 days AND 4/5 following criteria:



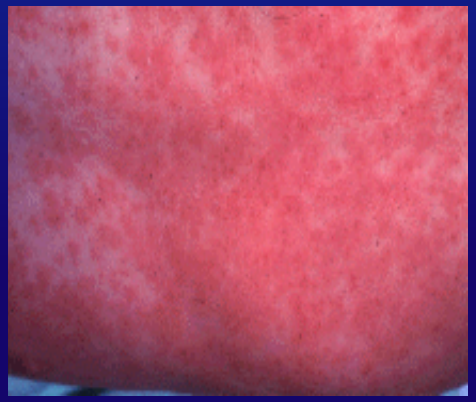
Conjunctival injection



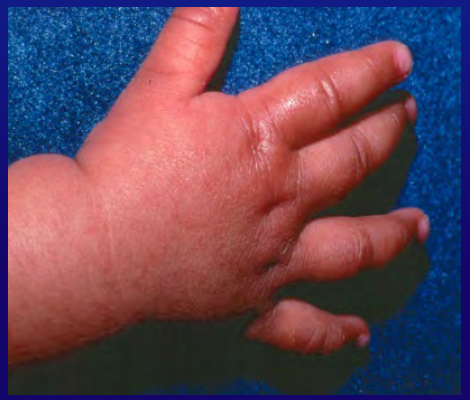
Strawberry tongue, pharyngeal erythema



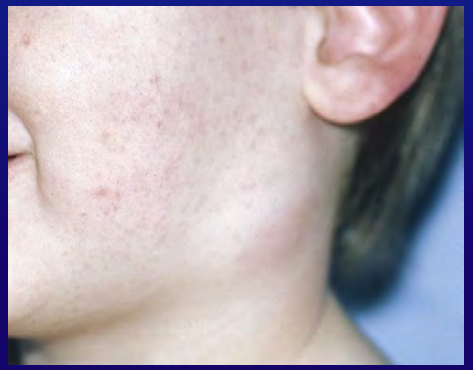
Erythema & cracking of lips



Polymorphous exanthem



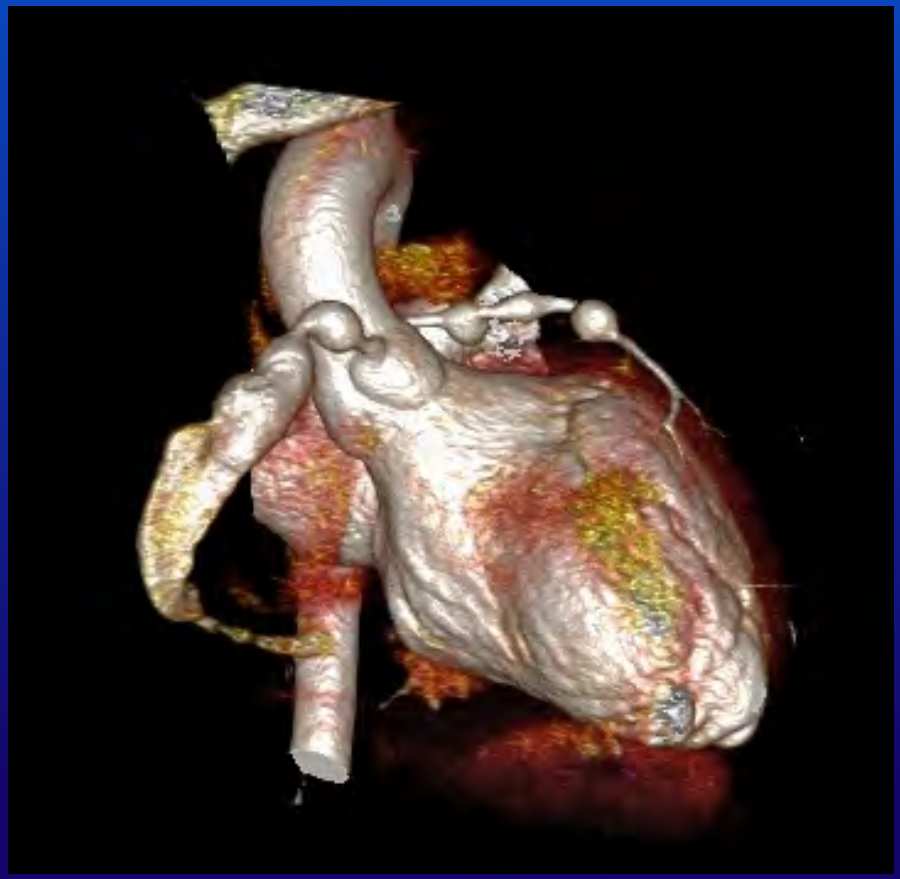
Hands and feet



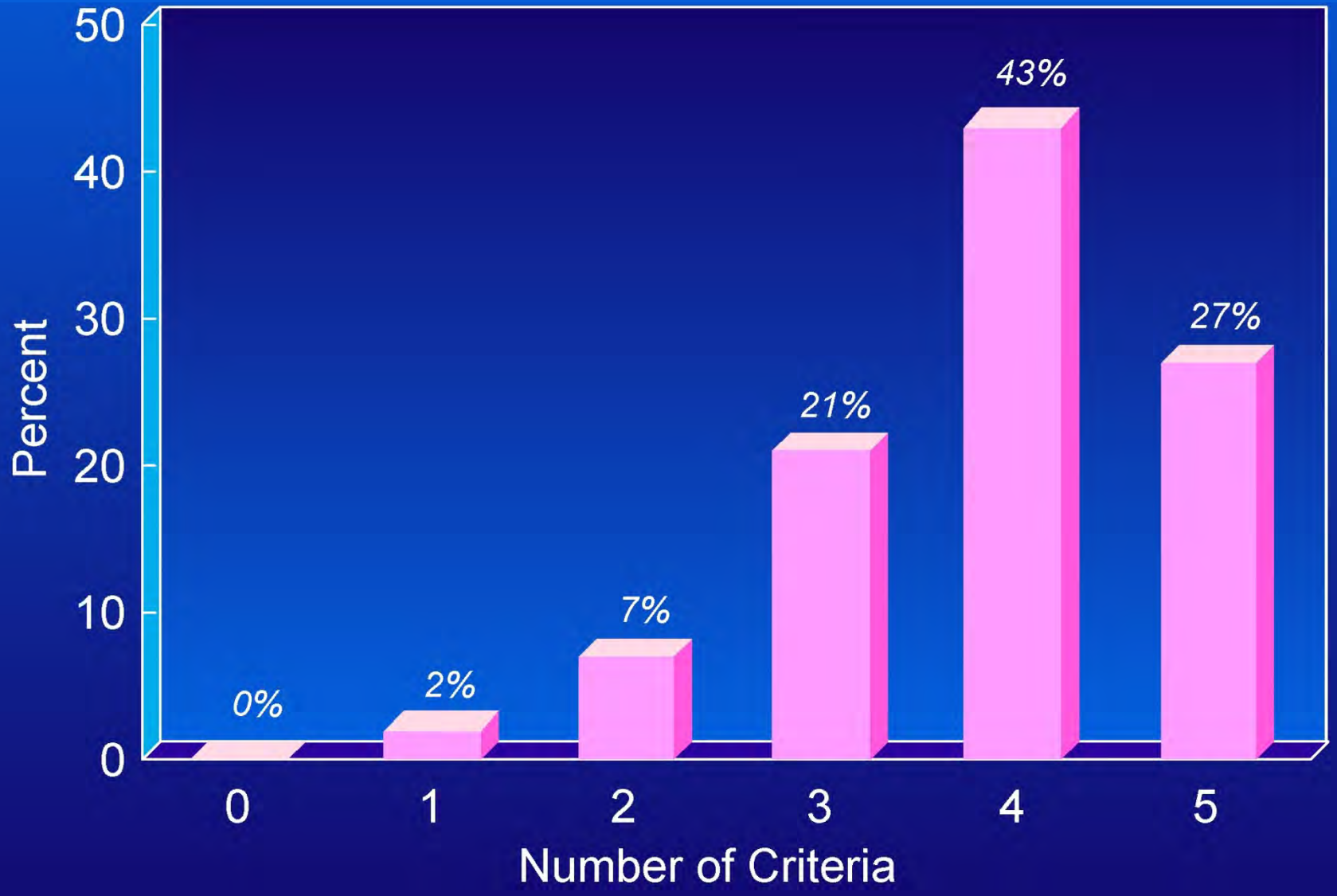
Unilateral cervical lymphadenopathy

Epidemiologic Case Definition

When coronary artery aneurysms detected by echocardiography or coronary angiography, KD can be diagnosed even in patients with fever and < 4 principal criteria



Number of Clinical Criteria Among Patients with Coronary Artery Aneurysms



Yellen et al, Pediatrics, 2010

How Is KD Different from MIS-C

- Age: KD occurs predominantly in early childhood (80% < 5 y.o), and MIS-C occurs predominantly in school age and adolescents.
- GI symptoms (diarrhea, vomiting, abdominal pain, even colitis) are strikingly prominent in MIS-C.
- MIS-C patients generally have a greater degree of “cytokine storm” and a lab profile with
  - Higher CRP, D-dimers, ferritin, troponin and BNP or NT-proBNP
  - Lower platelets and absolute lymphocyte count
- MIS-C patients are more likely to present with shock and with low left ventricular ejection fraction.

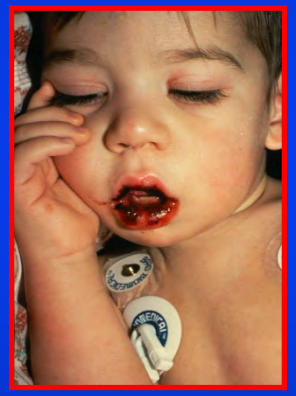
Kawasaki Shock Syndrome

(~5% of KD cases)

↑ severe GI symptoms

Often mistaken for septic shock or toxic shock syndrome

↑IVIG Resistance



↓Platelets, ↑D-dimer
↑CRP, ↓Na^+,
↑Hepatic enzymes, ↓Albumin
↑Lactic acid, +Coagulopathy

↑Troponin or CK-MB (80%)

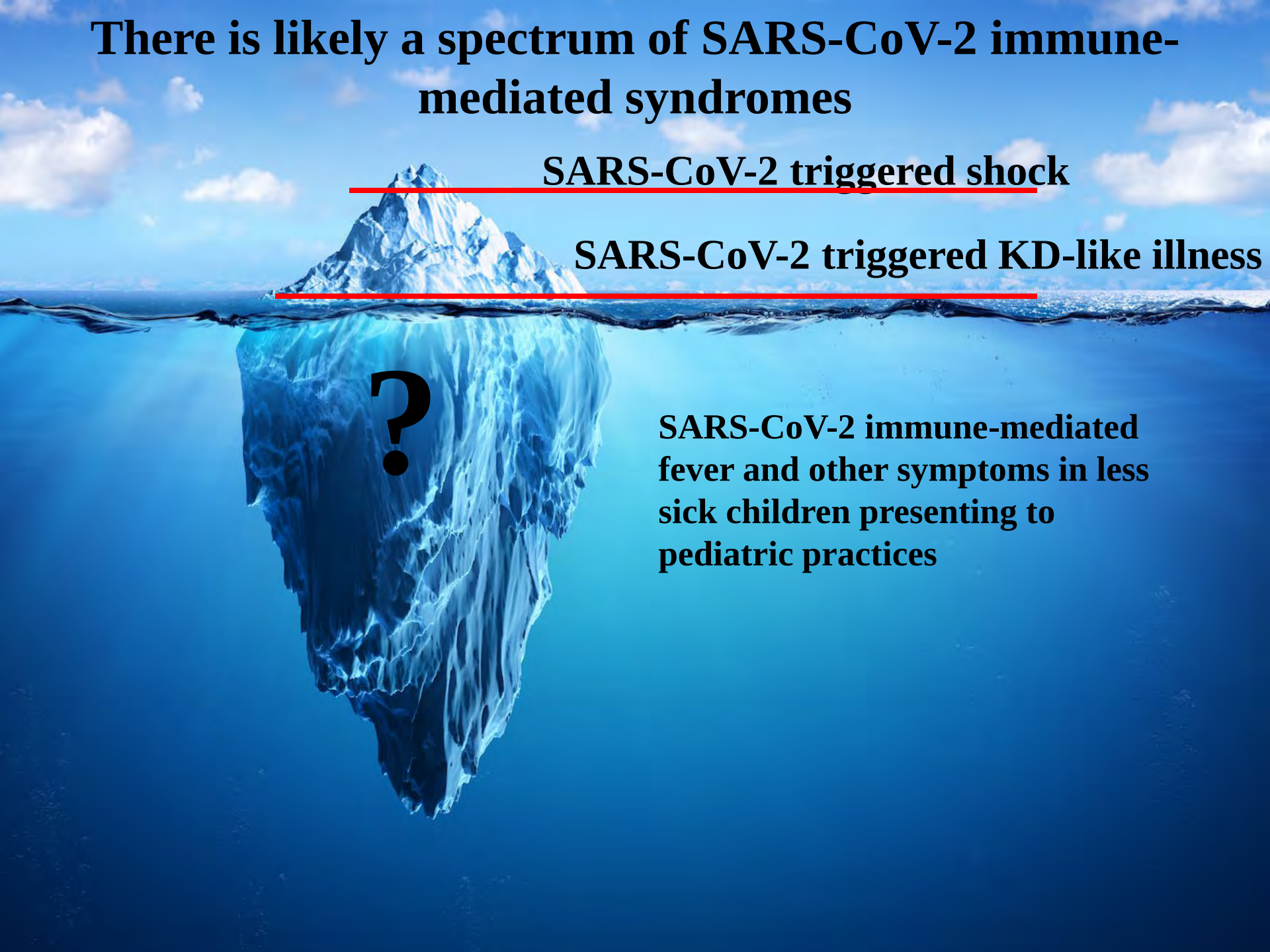
↑Risk of coronary artery aneurysms

>mild MR (40%)
↓LVEF (31%)
↓ SVR

What About Coronary Arteries in MIS-C?

- Children with MIS-C have been reported to have coronary artery dilation and more rarely aneurysms.
  - Coronary dimensions adjusted for BSA are based upon values in children without fever!
  - Febrile children have more dilated coronary arteries.
  - Coronary aneurysms occur in illnesses other than KD
- Series vary considerably in their reports of aneurysms.
  - 0/35 pts from France/Switzerand (Belhadger et al., Circ. 2020)
  - 2 of 10 pts from Bergemo (Verdoni et al, Lancet, 2020)
  - 1 of 8 patients from London (Riphagen et al, Lancet, 2020)
- No standardized definitions or Core Lab readings.

There is likely a spectrum of SARS-CoV-2 immune-mediated syndromes



SARS-CoV-2 immune-mediated fever and other symptoms in less sick children presenting to pediatric practices

Holly Rothermel MD
Clinical Director, Pediatric Rheumatology
Assistant Professor, Harvard Medical School
Pediatrician, MGH*f*C, Boston MA

Adult experience

- Critically ill adults developed signs of a 'cytokine storm' in response to infection with COVID 19
- Often associated with high fever, ARDS, confusion, coagulopathy. Often later in course after a more mild period
- Labs findings included:
  - Highly elevated CRP, ferritin, d-dimers
  - Cytopenias
  - Elevated cytokines IL1, IL6, IL12, soluble IL2 receptora, TNFγ

- Has led to therapeutic interventions aimed at modulating or suppressing the immune system in adults; tocilizumab and sarilumab in particular to inhibit IL6 mediated signal transduction

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Hemophagocytic lymphocytic histiocytosis(HLH)

Diagnostic Guidelines for HLH

- Persistent fever
- Splenomegaly
- Cytopenias (hgb, plt, neutrophils)
- Hypertriglyceridemia and/or hypofibrinogenemia
- Ferritin>500
- Increased soluble IL2receptor
- Low NK(natural killer) cell activity
- Marrow , spleen, lymph nodes with evidence of hemophagocytosis

Henter et al. HLH-2004,Diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. Pediatr Blood Cancer 2007;48:124-31.

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Macrophage Activation Syndrome (MAS)

- Life threatening complication of rheumatic disease, particularly So JIA
- Excessive activation and expansion of T cells and macrophages leading to overwhelming inflammatory reaction and release of pro-inflammatory cytokines
- Can happen early but also later in disease. Estimated to occur in more than 10% of patients in severe form; 30-40% in milder forms
- Manifestations similar to HLH—fever, hepatosplenomegaly, lymphadenopathy. Lab findings include pancytopenia, elevated ferritin, transaminitis, coagulopathy, elevated soluble IL-2 receptorα.
- Can be difficult to recognize because often occurs in setting of highly inflammatory conditions where ferritin, d-dimers , LFTS may already be abnormal

- Clues: Increasing d-dimers and ferritin, falling platelets or white cell counts, high CRP with a disproportionally low or falling ESR

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2016 Classification Criteria for Macrophage Activation Syndrome

Febrile patient with SoJIA

Ferritin >684 ng/ml **and** any 2 of following:

- AST >48
- Triglycerides >156
- Fibrinogen <360
- Platelets <181,000

Ravelli et al. 2016 Classification Criteria for Macrophage Activation Syndrome Complicating Systemic JIA. Ann Rheum Dis.2016 75(3) 481-9.

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MIS-C

- Different subgroups of patients
- Classic KD, atypical KD, shock-like syndromes, severe inflammatory syndromes. Pulmonary features not prominent.
- Some of these patients had findings suggestive of evolving cytokine storm, with MAS features
- Increased ferritin, CRP, LFTs, d-dimers
- Decreased platelets, lymphocytes, sodium,
- Not all patients have MAS type picture—clues would include:
  - Rapidly rising ferritin, CRP, d-dimer
  - Highly elevated CRP with discordant ESR
  - Falling platelets and lymphocytes
- Can have elevated IL2RA and IL6, but not always back soon enough

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Treatment

- Observation, fever control, close monitoring
- Clinical findings/criteria of KD lead to treatment as standard for KD or atypical KD
- More severe findings of KD may warrant intravenous steroids as well as repeated IVIg; possibly infliximab or cyclosporine
- Patients with features suggestive of MAS and cytokine storm, or severe illness requiring intensive support may warrant biologic therapy in addition to steroid therapy
- Targets: IL1 (anakinra canakinumab)IL6(tocilizumab, sarilumab) JAK(ruxolitinib, tofacitinib) TNF (infliximab)

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IL6 agents

- Tocilizumab (Actemra)—IL6 receptor inhibitor
  - Approved for treatment of polyarticular JIA, systemic JIA, RA, CAR-T cell-induced cytokine storm
  - Intravenous agent given monthly
  - Has shown promise in adult patients with ARDS and cytokine storm with COVID 19
  - Trials are ongoing
  - Sarilumab (Kevzara) has also been trialed in adults

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Anakinra(Kineret) IL1RA

Recombinant humanized Il1-receptor antagonist. Approved for treatment of RA, SoJIA, and cryopyrin-associated periodic fever syndromes

Has been used in treatment of MAS in rheumatology both SC/IV

Short acting, with 4-6 hour half-life

Licensed as subcutaneous administration in 100mg aliquots; can be safely given IV

Broad range of therapeutic doses, and in patients with highly elevated inflammatory conditions has been used in doses anywhere from 2-10mg/kg/day

Advantages: Short half-life, less myelosuppressive, less hepatotoxic, much shorter half-life

To consider…..

- Evolving information as to who needs escalated therapy
- Ongoing fevers and increasing CRP in setting of decreasing cell counts and normal ESR is concerning
- Ongoing elevation of D-dimers, elevations of triglycerides, LFTs, and falling fibrinogen can be helpful adjunctis
- Balancing act between risks of active infection and risks of hyperinflammation
- Interdisciplinary team to discuss each patient as there is clearly a wide variety of phenotypes

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Manuella Lahoud-Rahme, MD
Pediatric Cardiology/PCCM
Instructor, Harvard Medical School
Assistant Professor of Pediatrics MGH*f*C

Case I

Chief Complaint: fever, rash, conjunctivitis

HPI:

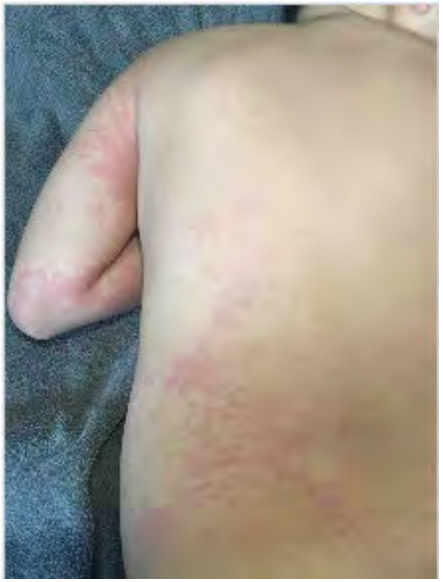
10 y healthy male presented with fever for 7 days, fatigue, diffuse abdominal pain, diarrhea, myalgias, poor po intake. T max 104.5 F.

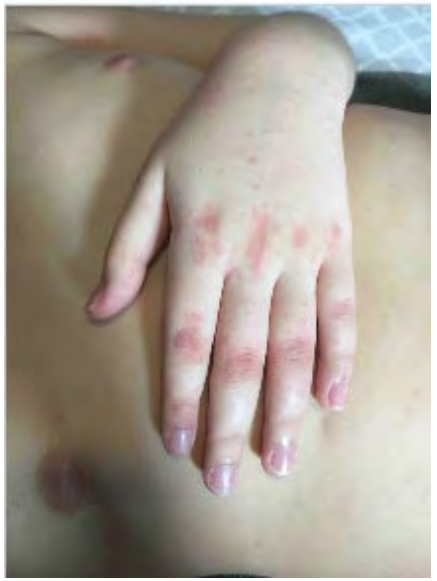
Evaluated 3 days prior at OSH with a nasal swab negative for SARS-COVID-2 and was sent home. Symptoms worsened and started having dry cough, and developed conjunctivitis with rash

Pertinent Exam Findings

VS: HR 160 b/min, T 40.2 , BP 96/52, RR 22, 97% on RA.

Fatigued, non toxic, talking in full sentences, minimally erythematous oropharynx, mildly cracked lips. No lymphadenopathy. No meningismus. Tachycardic, no murmur auscultated. Strong pulses with good cap refill. Clear lungs. Normal abdominal exam. No HSM. Made to march in place. HR increased to 180 b/min, no desaturations. He became lightheaded.





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VE RI TAS

Ancillary Testing

WBC 16.8 N86 L7, M5 E2

Hg 12.4, plt 207

Na 125

ESR 57, CRP 280

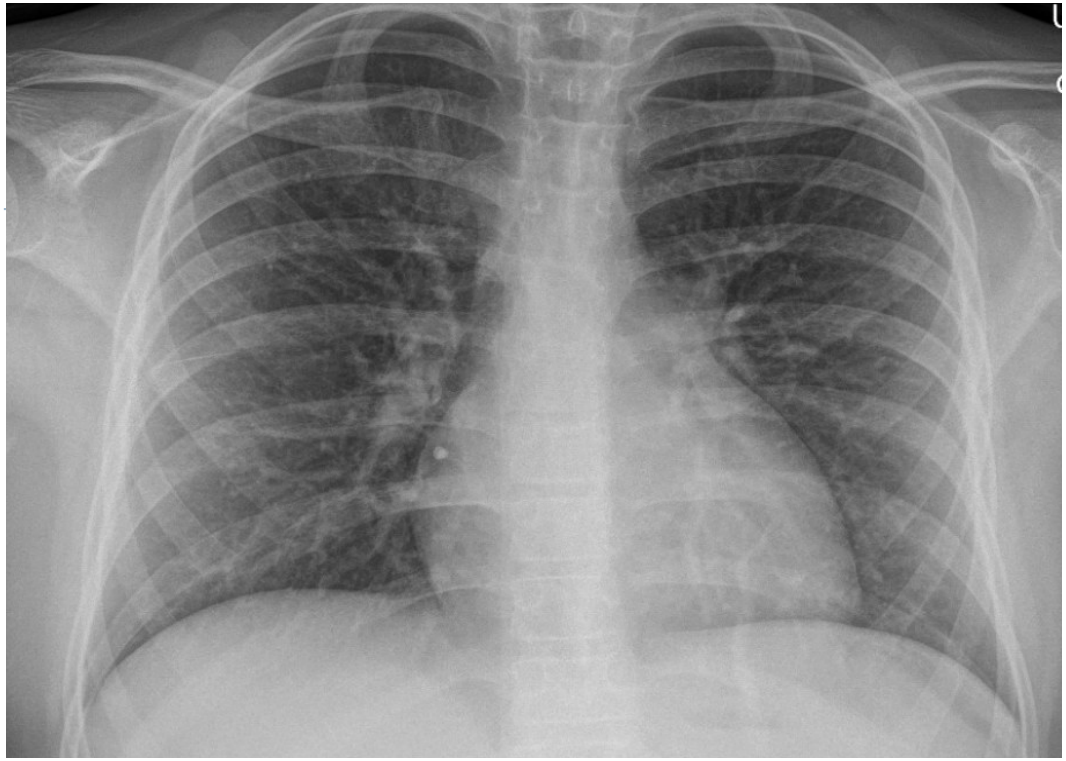
Troponin 84

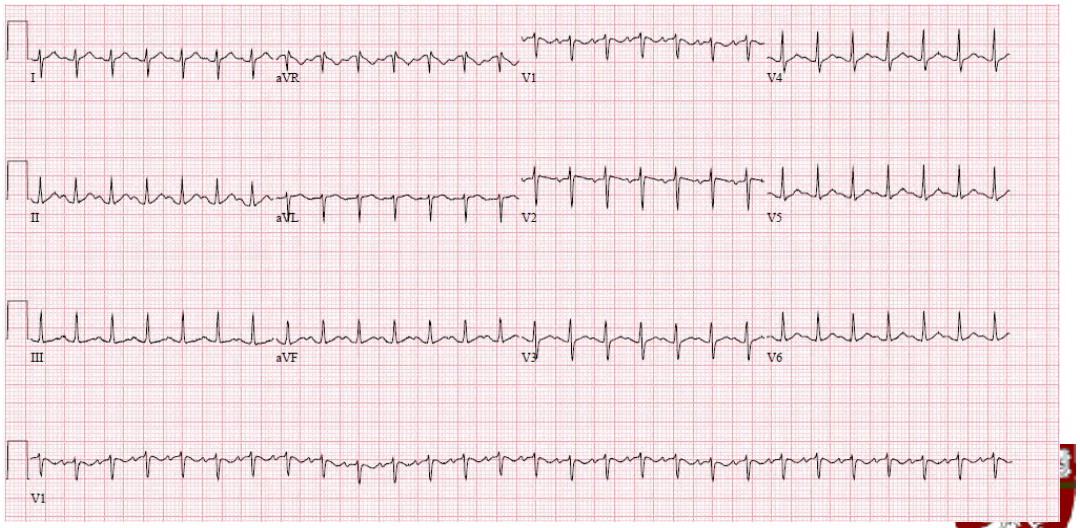
Ferritin 1089

LDH 360

Fibrinogen 748

D-Dimer 2727





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ED COURSE

12:13	Arrival
14:17	Ibuprofen, NS bolus
14:46	HR 160, RR 22, sat 97%
16:00	ID recommendations- start ceftriaxone and doxycycline – Biofire sent, Strep, EBV titers
16:45	Tp 100.3, HR 132, BP 84/45
16:58	COVID-19 PCR results positive.
18:00	Cardiology contacted. NT pro BNP requested – resulted at 9477 this prompted a POCUS

19:45 BP 71/42, HR 130-140 b/min, still asymptomatic. Gallop on exam, no HSM, clear lungs, decreased PP and cap refill. Started on dopamine. Transferred to OSH for a higher level of care

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CASE I

- Admitted to the ICU
- LVEF 30% on inotropic support (epinephrine and norepinephrine). Developed transient AV block, with good ventricular escape rhythm- no pacemaker was needed
- Never intubated.
- Given Remsidivir, Anakinra, steroids, IVIG and Aspirin
- Discharged home on weaning steroids, diuretics with improved function.

Case II

Chief Complaint: Fever, respiratory distress, shock

HPI:

8 y healthy male presented with fever for 6 days to OSH, increased WOB.

Evaluated on day of illness # 2, COVID PCR neg; On day 4 of illness he developed a polymorphic nonpruritic red rash. On day 5 of illness he developed NBNB emesis and watery nonbloody diarrhea as well as progressive increased work of breathing and fatigue. He had maintained UOP., URI symptoms. Rash, emesis and diarrhea with progressive fatigue, diffuse abdominal pain, diarrhea, myalgias, poor po intake. T max 104.5 F.

Pertinent Exam Findings at OSH

VS: HR 150 b/min, T 100.3 , BP 100/51 (in triage SBP 86) , RR 60, 94% on RA.

Looks unwell. Tachypneic with retractions developing as he became febrile, alert, conjunctival erythema, clear lungs, RRR with thread pulses, and cap refill of 5 seconds. Abdomen tender, maculopapular rash on trunk and lower extremities.

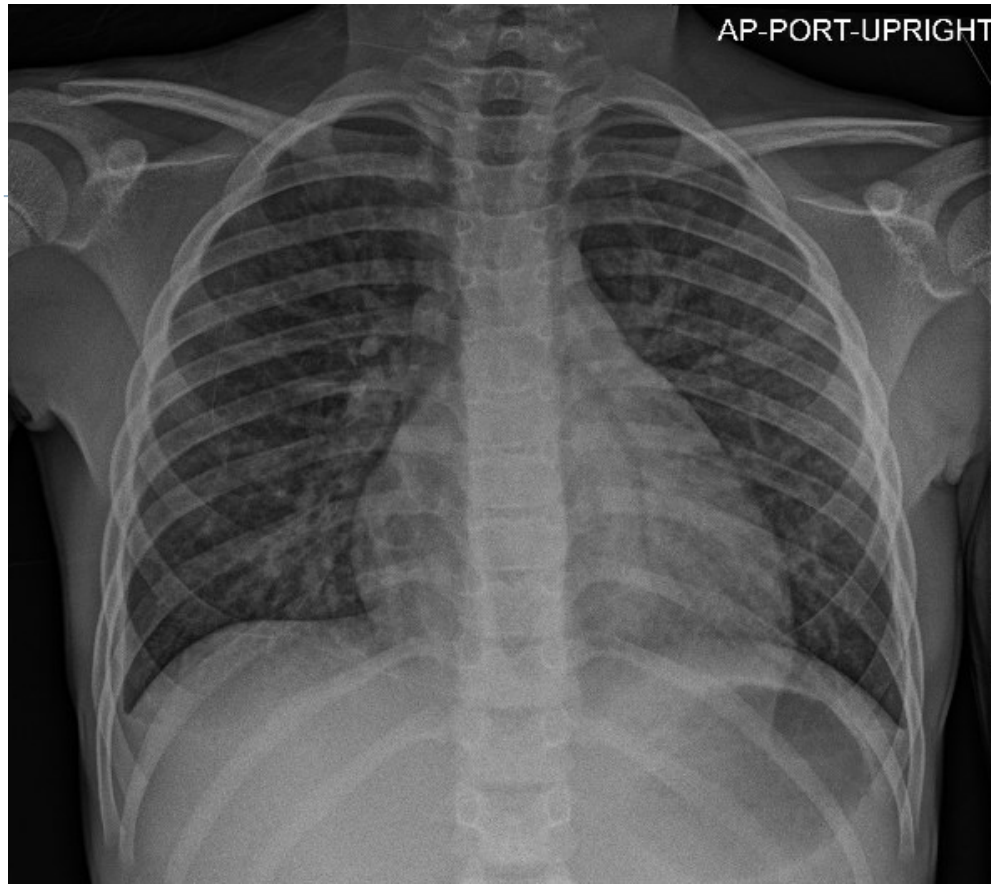
With fever, he became agitated, hypotensive and desaturated.

POCUS showed RV dilation with dysfunction, IVC plethora.

He was intubated

.

Ancillary Testing



WBC 27.38 N82 L8, M4 E2

Hg 12.4, plt 308

Na 127 Cl 88 BUN 45, Creatinine 1.04

Albumin 3 ALT 73

ESR 63, CRP 181.4

Initial VBG 7.42/35 HCO3 23

hsTroponin 201

Ferritin 1912

LDH 600 Fibrinogen 858

D-Dimer 5810

COVID-19 PCR positive

With worsening WOB and desaturation, repeat VBG 7.05/72 HCO3 19, he was intubated. Started on epinephrine and was airlifted to our institution.

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CASE II

- Cannulated on V-A ECMO upon arrival to the PICU.
- Decannulated 5 days later after his cardiac function recovered. Extubated the following day
- Received Remsidivir, IVIG, Anakinra, steroids and anticoagulation.
- Will be discharged to rehab center when a bed is available.

At MGH

- We have admitted many patients, 8 were reported to the DPH with symptoms compatible with MIS-C and few are still awaiting serology

- Clinical presentation ranges from
  - Fever and warm shock with normal cardiac function
  - Kawasaki like illness with features of MAS and normal echocardiograms.
  - Kawasaki like illness , with MAS and cardiogenic shock
  - Combinations of any

- Rise in patients with KD not related to COVID

MGH Outpatient Guidance

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INITIAL LABORATORY ASSESSMENT:

CBC with differential Complete metabolic panel CRP ESR	**If available,** SARS-CoV-2 PCR (from NP swab) Viral panel or respiratory pathogen panel (e.g. Biofire respiratory panel, rapid RSV/influenza) Ferritin D-Dimer Troponin or HS-Troponin NT-proBNP Urinalysis

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VE RI TAS

MGH Outpatient Guidance

REFERRAL:

- If the patient needs further evaluation and/or lab draw, please refer to the Respiratory Illness Clinic at MGHfC at Boston or other satellite locations.
- If the screening labs are abnormal, please refer to the nearest Pediatric Emergency Department for further evaluation.
- Patients with multi-system involvement, syncope, confusion or concern for clinical decompensation should be evaluated in the nearest Pediatric Emergency Department.

For questions about these recommendations or concerns about specific patient referral please contact either Pediatric Infectious Disease, Pediatric Cardiology, or Pediatric Rheumatology.

Final considerations:

- MIS-C is a rare condition
- MIS-C patients may be negative for SARS-CoV-2 with PCR**,** antigen and serologic testing
- Predominant symptoms are fever and gastro-Intestinal symptoms (abdominal pain/vomiting/diarrhea)
- Patients may appear well-appearing relative to concerning vital signs including tachycardia when afebrile and hypotension
- Patients may present critically ill but respond to treatment and supportive care and go on to do very well
- We need national and international collaboration to understand this disease treat it, develop guidelines

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Public Health Reporting

CDC recommends that Healthcare providers who have cared or are caring for patients younger than 21 years of age meeting MIS-C criteria should report suspected cases to their local, state, or territorial health department.

MA State Case Definition and Reporting

- Healthcare providers must immediately report cases of pediatric multi-system inflammatory syndrome, possibly associated with COVID-19, in patients who are under 21 years of age to DPH. For reporting purposes, the criteria which define a case are:
- An individual aged < 21 years presenting with fever (>38.0C for ≥24 hours), laboratory evidence of inflammation, and evidence of clinically severe hospitalized illness such as single or multi-organ dysfunction (shock, cardiac, renal, hematologic, gastrointestinal or neurological disorder); **AND**
- No evidence of alternative plausible diagnoses; **AND**
- SARS-CoV-2 PCR, serology, or antigen positive **OR** PCR negative with COVID-19 exposure in the past 4 weeks prior to onset of symptoms.
- Laboratory evidence of inflammation may include but is not limited to: neutrophilia, elevated CRP, lymphopenia, CRP, ESR, fibrinogen, procalcitonin, D-dimer, ferritin, LDH, IL-6, hypoalbuminemia. Additional recommended diagnostic testing includes a respiratory viral panel and blood culture. Isolated respiratory disease does not meet criteria.
- Please contact Katherine Hsu, MD, MPH at katherine.hsu@state.ma.us for further questions or to report a case in Massachusetts.

- **Providers in other states should contact their appropriate state department of health**

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