Pediatric Multisystem Inflammatory Syndrome (PMIS) versus Multisystem inflammatory syndrome in Children (MIS-C): a Kawasaki-like syndrome

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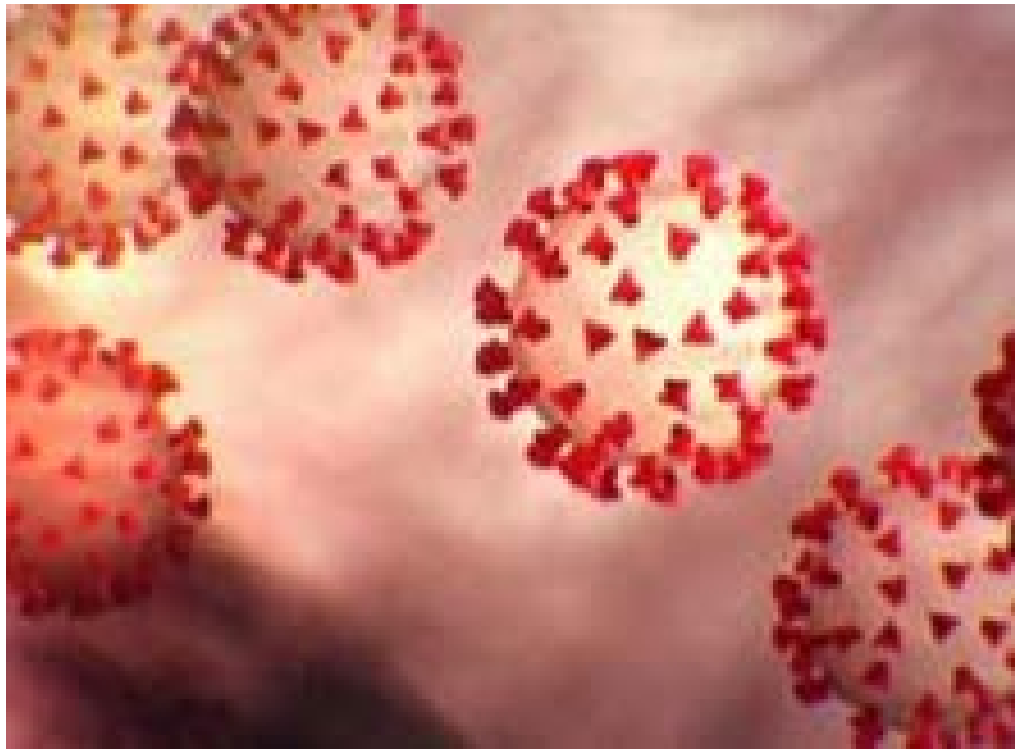
By next week, this presentation will be out of date

Names

- **MIS-C**: Multi system inflammatory syndrome in children
- **PMIS / PIMS**: Pediatric multisystem inflammatory syndrome
- **PIMS:** Pediatric multisystem inflammatory syndrome, temporarily associated with SARS



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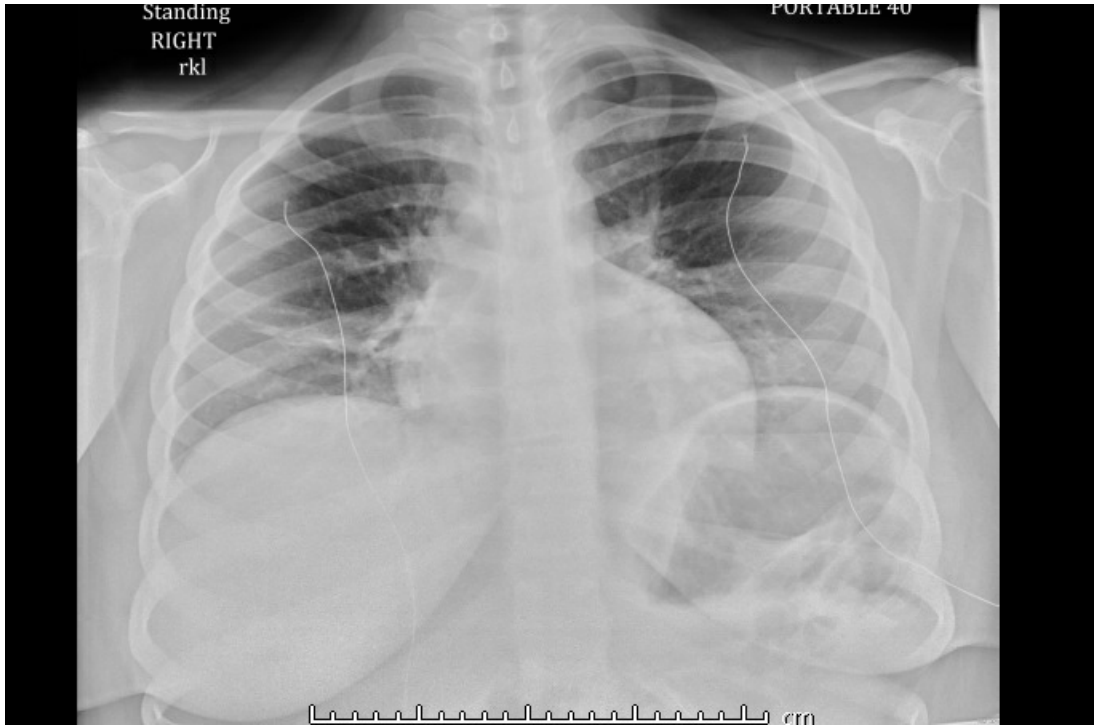
List of topics

- Case presentation
- Definition
- Epidemiology
- Presentation
- Evaluation
- Differential diagnosis
- Treatment
- Follow up
- Summary

CASE PRESENTATION CCMC

- 14 yo F obese and single right kidney
- 4 day history fever 103 F
  - Erythematous macular rash
  - Cough
  - Diarrhea
  - Body aches
  - **WADAO**
- **Multiple family members COVID +**
- Brought to CCMC ER Sepsis Alert



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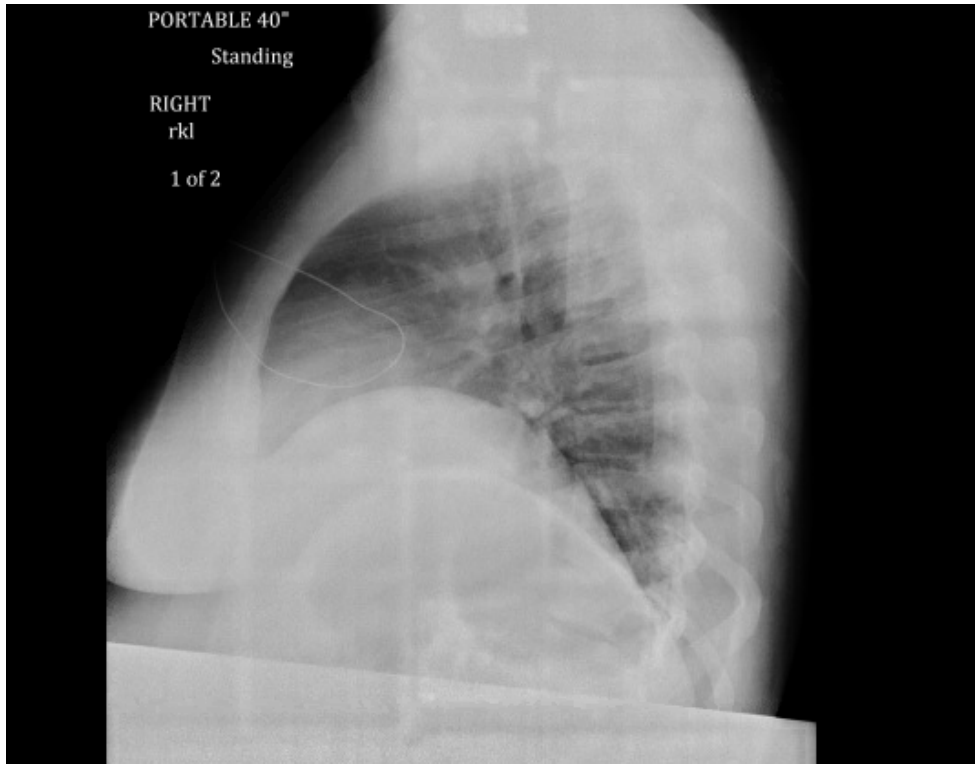
CASE CCMC

- CBC WBC 15k with bandemia rest wnl
- CMP wnl
- CRP 30 mg/dl
- CK nl
- Resp panel nl
- GI panel nl



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CASE CCMC Cardiac Work up

ECHO 5/12

- Coronary arteries are prominent measuring at the upper limits of normal. No evidence of aneurysms.
- On subcostal images there is suggested to be a secundum ASD
- Normal biventricular size, wall thickness and function.
- Trace pericardial effusion with thickened and **echobright pericardium.**
- **Troponin 0.727**
- **BNP 2766**

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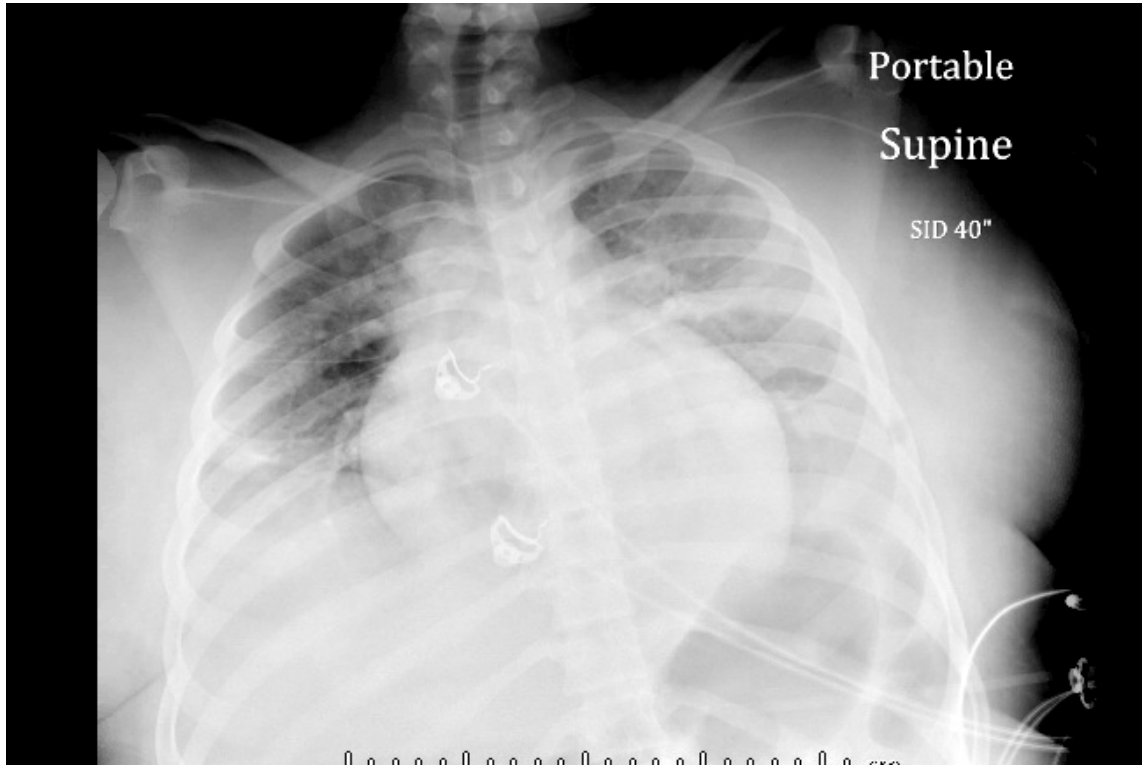
CASE 2 CCMC Rheumatology Labs

- Ferritin 207.55
- D dimer 3.66
- Cytokines
  - **IL-6 40**
  - **Soluble IL-2 2850**
- CRP 30
- TG WNL



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CASE 2 CCMC

- Transferred to COVID floor on 2 l O2
- Transferred to PICU after increased 02 and low BP
- Intubated on 5/12 in pm
- Required milrinone and epinephrine for support
- Started on Remdesivir 5/13

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CASE CCMC Treatment

- IVIG 110 g x 1 dose
- Anakinra 100 SQ 3 times daily
- Solumedrol 50mg IV every 8 hrs
- Remdesivir 100mg every 24hr IV
- Enoxaparin 60mg every 12 hrs AntiXA 0.3-0.5

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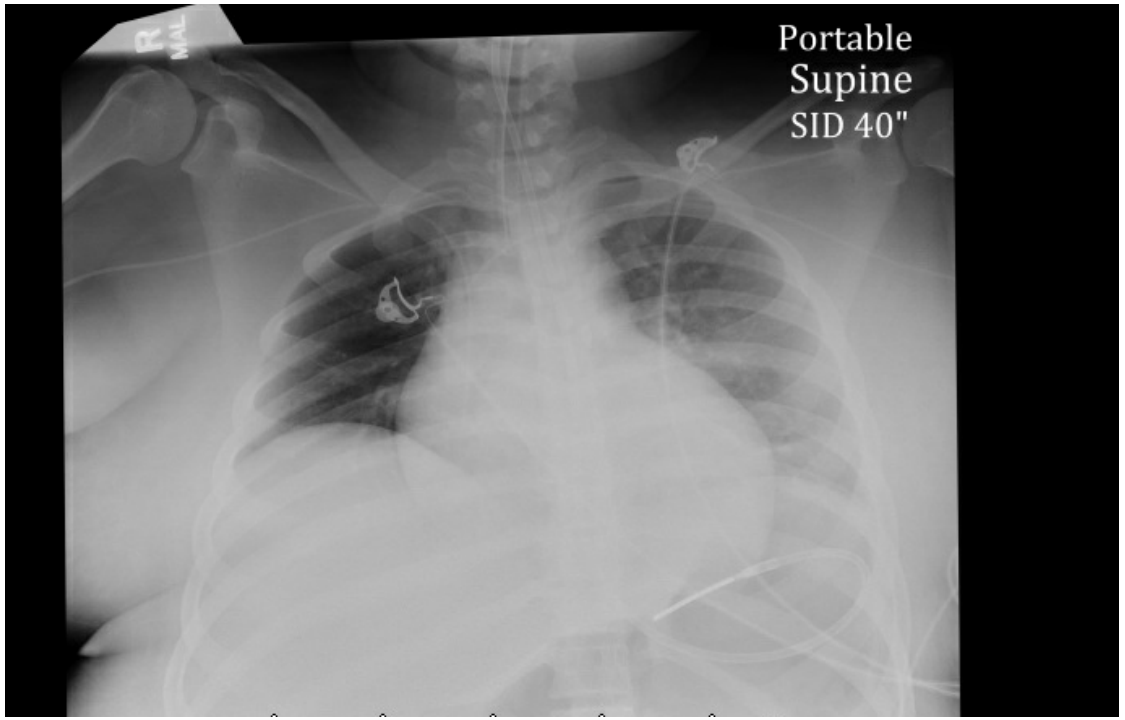
CASE CCMC

- Extubated 5/17 on 3L O2
- Milrinone decreased
- D dimer 1.6
- Ferritin 411
- CRP 20
- CBC WBC 29.27
- CMP wnl



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CASE CCMC Cardiac Labs Current

ECHO 5/15

- Normal left ventricle structure, size and function
- Normal LVEF= 61% by bullet method
- Normal right ventricular size and systolic function
- Atrial septum was not assessed on repeat echo
- Small pericardial effusion noted posterior to the LV.
- **BNP 254** ↓
- **Troponin 0.598** ↓

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Questions and Observations?

- Rapid clinical deterioration!!
- Ferritin not terribly high?
  - Soluble IL-2 high
  - IL -6 high
  - No Cytopenias/Lymphopenia
- **Definite Cardiac Dysfunction(Carditis)**
  - No aneurysms so far? Did not meet criteria for KD?
- Coagulopathy
- Role of Concomitant Antiviral treatment?
- When to Stop?

Hyper inflammatory shock in children during Covid-19 pandemic, London, UK

	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

ACA=anterior cerebral artery. ADHD=attention deficit hyperactivity disorder. AVR=atrioventricular valve regurgitation. BMI=body mass index. BP=blood pressure. COVID-19=coronavirus disease 2019. CRP=C-reactive protein. FiO_2=fraction of inspired oxygen. HERV=human endogenous retrovirus. HFNC=high-flow nasal canula. HR=heart rate. IVIG=human intravenous immunoglobulin. LV=left ventricle. MCA=middle cerebral artery. MV=mechanical ventilation via endotracheal tube. NIV=non-invasive ventilation. PICU=paediatric intensive care unit. RA=room air. RR=respiratory rate. RRT=renal replacement therapy. RV=right ventricle. RVSP=right ventricular systolic pressure. SARS-CoV-2=severe acute respiratory syndrome coronavirus 2. $SatO_2$=oxygen saturation. SVIA=self-ventilating in air. VA-ECMO=veno-arterial extracorporeal membrane oxygenation.

Table: **Demographics, clinical findings, imaging findings, treatment, and outcome from PICU**

www.thelancet.com **Published online May 6, 2020 https://doi.org/10.1016/S0140-6736(20)31094-1**

10-patient series of PMIS from Italy

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9	Patient 10
Age, years	8·2	7·0	2·9	7·7	7·5	16·0	5·0	9·2	5·5	5·5
Sex	Male	Male	Female	Female	Female	Male	Male	Male	Male	Male
Type of Kawasaki disease	Incomplete	Incomplete	Classic	Incomplete	Incomplete	Classic	Classic	Incomplete	Classic	Classic
Other symptom	..	Diarrhoea, meningeal signs	..	Diarrhoea, meningeal signs	Diarrhoea	Diarrhoea	Meningeal signs	Diarrhoea	Meningeal signs	Diarrhoea, drowsiness
MAS[18]	..	Yes	Yes	Yes	Yes	Yes	No	No	No	No
Ferritin >684 ng/mL	..	Yes (1183)	Yes (893)	Yes (1972)	Yes (3213)	Yes (2027)	No (199)	No (449)	No (307)	No (341)
Nasal swab for SARS-CoV-2	Negative	Positive	Negative	Negative	Positive	Negative	Negative	Negative	Negative	Negative
Serology for SARS-CoV-2 (IgG, IgM)	Negative, negative	Positive, negative	Positive, negative	Positive, positive	Positive, positive	Negative, negative*	Positive, negative	Positive, negative	Positive, positive	Positive, negative
Serology (days from onset)	30	18	16	11	11	10	8	7	4	6
Contact with suspected or confirmed case	No	Yes	No	No	Yes	No	Yes	No	Yes	Yes
Caregiver nasal swab for SARS-CoV-2	..	Positive	Negative	Negative	Negative	Negative	Positive	Negative	Negative	Positive
Treatment	IVIG plus aspirin	IVIG plus mPDN	IVIG plus mPDN	IVIG plus mPDN	IVIG plus mPDN	IVIG plus mPDN	IVIG plus aspirin	IVIG plus mPDN	IVIG plus mPDN	IVIG plus mPDN
Inotropes	No	No	No	Yes	Yes	No	No	No	No	No
Response	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

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Jones Hospital Peds 2020 https://doi.org/10.1542/hpeds.2020-0123
Verdoni Lancet 2020 https://doi.org/10.1016/S0140-6736(20)31103-X

Multisystem inflammatory syndrome in Children in New York State

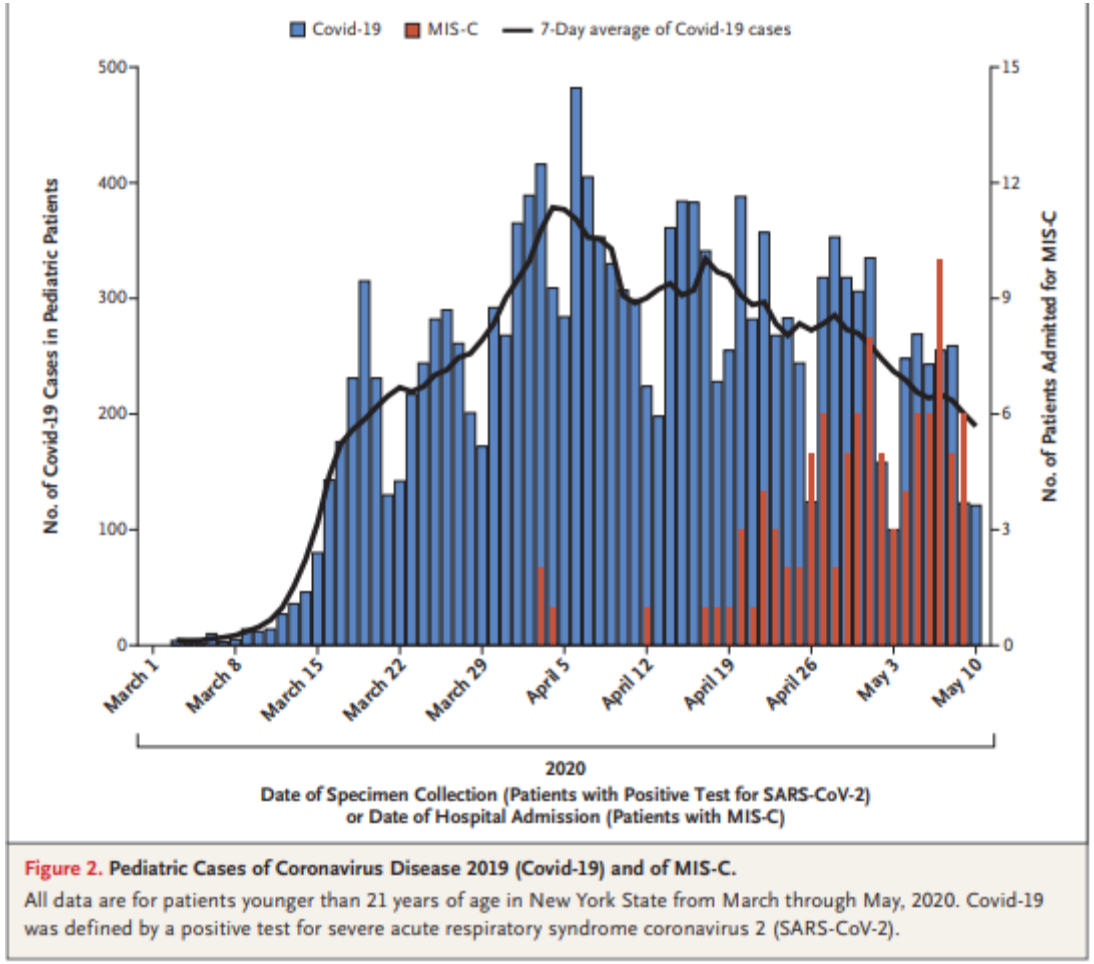

Figure 2. Pediatric Cases of Coronavirus Disease 2019 (Covid-19) and of MIS-C.

All data are for patients younger than 21 years of age in New York State from March through May, 2020. Covid-19 was defined by a positive test for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

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Dufort EM et al. N engl j med 383;4 nejm.org July 23, 2020

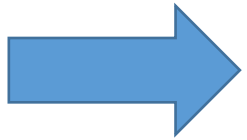

Table 2. Demographic and Clinical Characteristics of the Patients at Hospital Admission, According to Age Group.*

Characteristic	Overall (N=99)	0–5 Years (N=31)	6–12 Years (N=42)	13–20 Years (N=26)
Positivity for SARS-CoV-2 — no./total no. (%)				
On RT-PCR assay	50/98 (51)	15/31 (48)	19/41 (46)	16/26 (62)
On serologic assay for IgG antibodies	76/77 (99)	24/25 (96)	33/33 (100)	19/19 (100)
Male sex — no. (%)	53 (54)	20 (65)	18 (43)	15 (58)
Race — no./total no. (%)†				
White	29/78 (37)	10/27 (37)	13/34 (38)	6/17 (35)
Black	31/78 (40)	13/27 (48)	12/34 (35)	6/17 (35)
Asian	4/78 (5)	0/27	2/34 (6)	2/17 (12)
Other‡	14/78 (18)	4/27 (15)	7/34 (21)	3/17 (18)
Ethnic group — no./total no. (%)†				
Hispanic	31/85 (36)	12/28 (43)	11/35 (31)	8/22 (36)
Not Hispanic	54/85 (64)	16/28 (57)	24/35 (69)	14/22 (64)
Coexisting conditions — no. (%)§				
Any	36 (36)	10 (32)	14 (33)	12 (46)
Chronic lung disease¶	14 (14)	2 (6)	5 (12)	7 (27)
Obesity	29 (29)	10 (32)	11 (26)	8 (31)
Symptoms at admission — no. (%)				
Constitutional: fever or chills	99 (100)	31 (100)	42 (100)	26 (100)
Cardiovascular: chest pain	11 (11)	1 (3)	3 (7)	7 (27)
Any gastrointestinal	79 (80)	23 (74)	35 (83)	21 (81)
Abdominal pain	60 (61)	18 (58)	29 (69)	13 (50)
Nausea or vomiting	57 (58)	16 (52)	25 (60)	16 (62)
Diarrhea	49 (49)	13 (42)	23 (55)	13 (50)
Any dermatologic	61 (62)	24 (77)	25 (60)	12 (46)
Rash	59 (60)	23 (74)	25 (60)	11 (42)
Swollen hands or feet	9 (9)	6 (19)	1 (2)	2 (8)
Any gastrointestinal and any dermatologic	48 (48)	17 (55)	21 (50)	10 (38)
Any mucocutaneous	60 (61)	22 (71)	25 (60)	13 (50)
Conjunctivitis	55 (56)	21 (68)	23 (55)	11 (42)
Mucosal changes	27 (27)	15 (48)	8 (19)	4 (15)
Any gastrointestinal and any muco-cutaneous	48 (48)	16 (52)	21 (50)	11 (42)
Any neurologic	30 (30)	4 (13)	16 (38)	10 (38)
Headache	29 (29)	4 (13)	15 (36)	10 (38)
Altered mental status or confusion	2 (2)	0	1 (2)	1 (4)
Lymphadenopathy	6 (6)	4 (13)	2 (5)	0
Any musculoskeletal	20 (20)	2 (6)	9 (21)	9 (35)
Muscle aches or myalgias	17 (17)	1 (3)	8 (19)	8 (31)
Joint pain	4 (4)	1 (3)	1 (2)	2 (8)
Upper respiratory	27 (27)	12 (39)	9 (21)	6 (23)
Congestion	13 (13)	8 (26)	2 (5)	3 (12)

Table 2. (Continued.)

Characteristic	Overall (N=99)	0–5 Years (N=31)	6–12 Years (N=42)	13–20 Years (N=26)
Sore throat	16 (16)	5 (16)	8 (19)	3 (12)
Lower respiratory	40 (40)	13 (42)	14 (33)	13 (50)
Cough	31 (31)	11 (35)	11 (26)	9 (35)
Shortness of breath	19 (19)	5 (16)	6 (14)	8 (31)
Wheezing	1 (1)	1 (3)	0	0

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Multisystem inflammatory syndrome in Children in New York State

Table 4. Clinical Course and Outcomes, According to Age Group.*

Variable	Overall (N=99)	0–5 Years (N=31)	6–12 Years (N=42)	13–20 Years (N=26)
Median time from symptom onset to hospital admission (IQR) — days	4 (3–6)	4 (3–6)	5 (4–5)	4 (3–6)
ICU admission — no. (%)	79 (80)	19 (61)	38 (90)	22 (85)
Median time to ICU entry (IQR) — days	0 (0–1)	0 (0–2)	0 (0–1)	0 (0–1)
Median length of stay (IQR) — days				
Overall	6.0 (4.0–9.0)	6.0 (3.0–8.0)	6.0 (4.0–10.0)	6.5 (6.0–10.0)
Among those discharged	6.0 (4.0–8.0)	5.0 (3.0–7.0)	4.0 (4.0–8.0)	6.0 (5.0–10.0)
Therapy — no. (%)				
BiPAP or CPAP†	7 (7)	1 (3)	3 (7)	3 (12)
High-flow nasal cannula†	16 (16)	1 (3)	10 (24)	5 (19)
Mechanical ventilation†	10 (10)	3 (10)	3 (7)	4 (15)
ECMO	4 (4)	1 (3)	2 (5)	1 (4)
Vasopressor support	61 (62)	15 (48)	29 (69)	17 (65)
Systemic glucocorticoids	63 (64)	16 (52)	30 (71)	17 (65)
IVIG	69 (70)	26 (84)	30 (71)	13 (50)
Systemic glucocorticoids and IVIG	48 (48)	15 (48)	25 (60)	8 (31)
Diagnoses — no. (%)‡				
Kawasaki's disease or atypical Kawasaki's disease	36 (36)	15 (48)	18 (43)	3 (12)
Myocarditis	52 (53)	12 (39)	21 (50)	19 (73)
Shock	10 (10)	4 (13)	5 (12)	1 (4)
Coronary-artery aneurysm	9 (9)	4 (13)	4 (10)	1 (4)
Acute kidney injury	10 (10)	3 (10)	4 (10)	3 (12)
Death — no. (%)	2 (2)	1 (3)	1 (2)	0

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

Distributed via the CDC Health Alert Network
May 14, 2020, 4:45 PM ET
CDCHAN-00432

Multisystem inflammatory Syndrome in Children

- Newly recognized , potentially serious illness in children that seems to be related to COVID19.
- Seems to be a delayed complication of coronavirus infection.
- Variety of symptoms that affect different organs.
  - Many children present with symptoms resembling TSS or KD
    - GI symptoms
    - Kidney injury
    - Neurological symptoms
    - Heart inflammation
    - Coagulopathy
- Most children recover well with careful observation and treatment

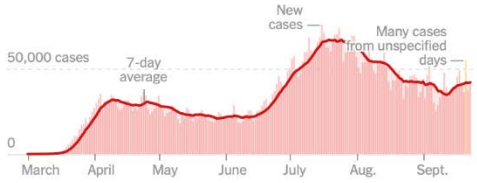
Epidemiology

- Rare
- Incidence of SARS CoV2 in < 21 year old: 322 per 100.000
- Incidence of MIS-C: 2 per 100.000
- Older children and adolescent
- >>> Black and Hispanics
- Lag of several weeks between the peak of COVID cases in the community and the rise of MIS-C
- MIS-c collection of data across the country

MIS-C cases (7 day moving Average)

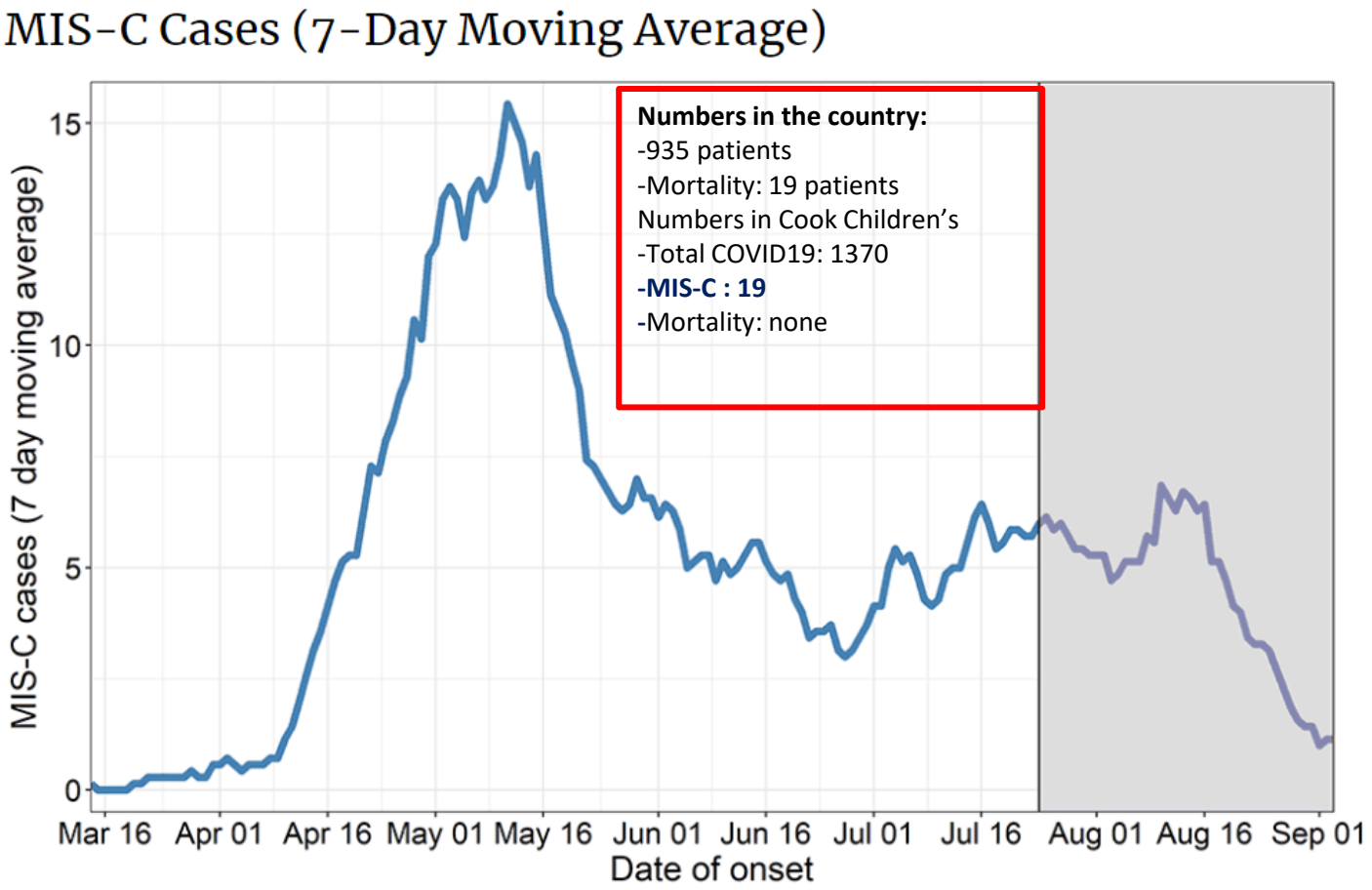
Covid in the U.S.: Latest Map and Case Count

By The New York Times Updated September 24, 2020, 9:39 P.M. E.T.



	TOTAL REPORTED	ON SEPT. 23	14-DAY CHANGE
Cases	7.0 million+	41,566	+14%
Deaths	202,704	1,091	+1%

Day with data reporting anomaly.
Includes confirmed and probable cases where available. 14-day change trends use 7-day averages.



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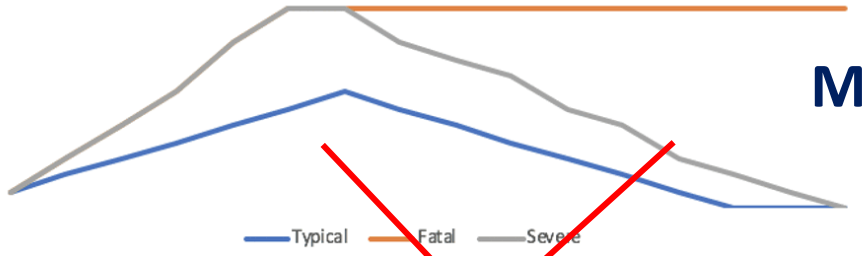
https://www.cdc.gov/mis-c/cases/index.html

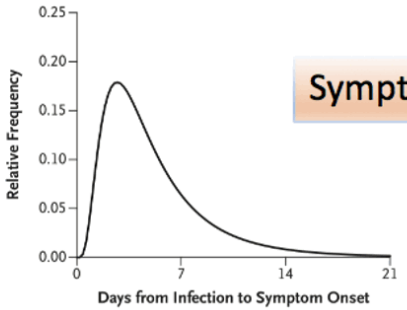
COVID-19 Disease Course

SARS-CoV-2 Respiratory Tract Viral Load



MIS-C presentation

5.1 days (median)	5-10 days	Days - weeks	
Incubation Period	**Acute Mild Phase ***	**ARDS/Pro-inflammatory Phase**	**Recovery**



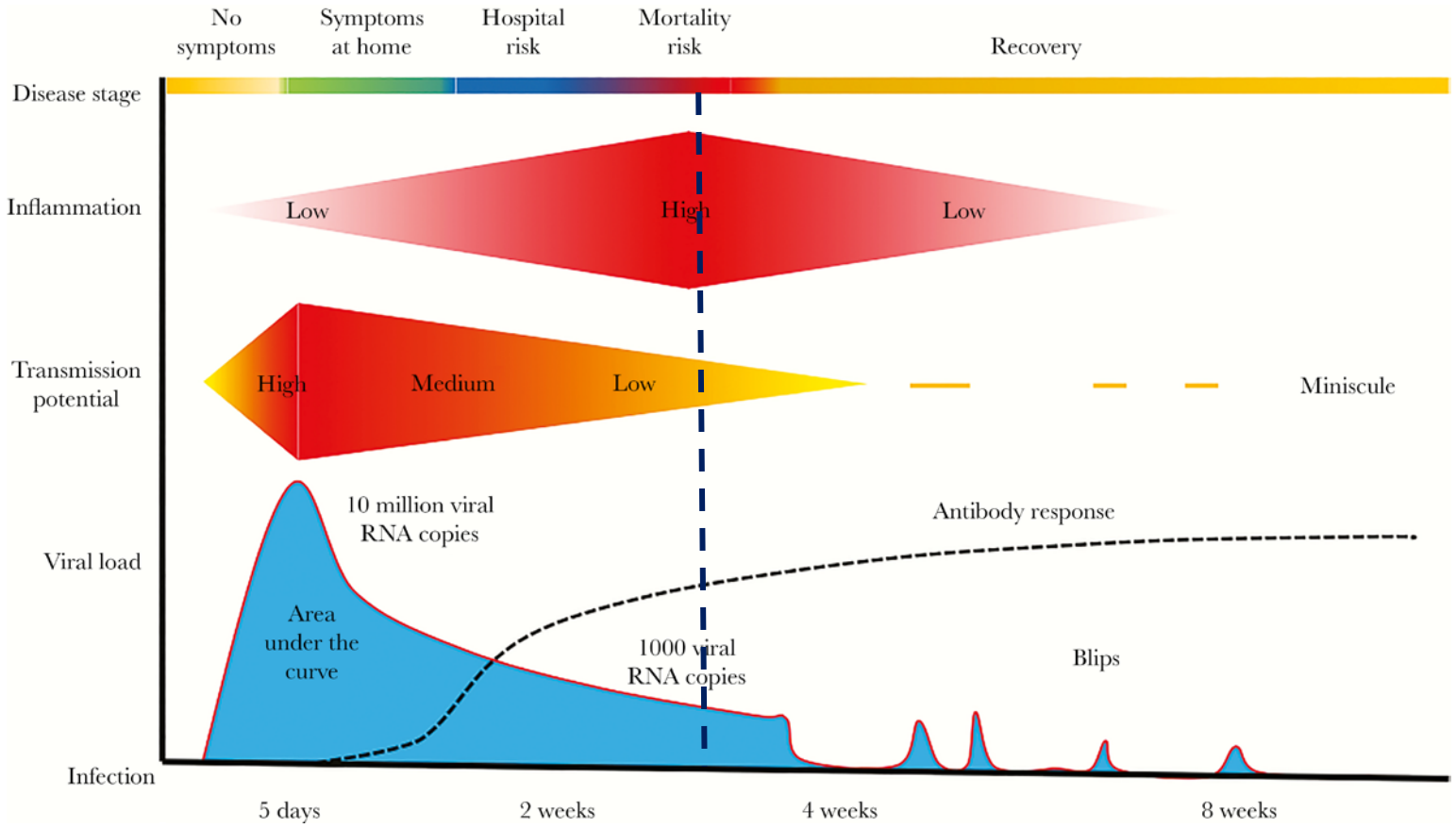
Symptom onset

Hallmarks: dyspnea, tachypnea, hypoxemia

* Acute Mild Phase: nonspecific symptoms. Most commonly fevers, cough, myalgias, fatigue. Nausea, diarrhea reported <50% of the time

Pan Lancet ID 2020 https://doi.org/10.1016/S1473-3099(20)30113-4
Zou NEJM 2020 DOI: 10.1056/NEJMc2001737
Zhou Lancet 2020 https://doi.org/10.1016/S0140-6736(20)30566-3
Li NEJM 2020 DOI: 10.1056/NEJMoa2001316
Wang JAMA 2020 doi:10.1001/jama.2020.1585
Siddiqi JHLT 2020 doi:10.1016/j.healun.2020.03.012

Figure 1. Schematic of severe acute respiratory syndrome coronavirus 2 infection in a symptomatic person. RNA, ...



Open Forum Infect Dis, Volume 7, Issue 7, July 2020, ofaa232, https://doi.org/10.1093/ofid/ofaa232

Pathophysiology

- Immune dysregulation (Cytokine are elevated, CRP is very high)
  - Post infectious
  - Many children with negative SARS CoV2 PCR
  - Many children with positive Serology
  - *Active investigation*
- Myocardial injury
  - Systemic inflammation
  - Acute myocarditis
  - Hypoxia
  - Stress
  - Cardiomyopathy
  - Ischemia due to Coronary artery inflammation

Presentation

- Daily call for Infectious Disease teams in the world
- Along the lines of other illnesses that we see in the ID service
- COVID19 in the community long enough (more than 1 month)
- Age: 8-10 year old, some young adults with similar symptoms
- Fever
  - GI category
  - KD, TSS
  - Neurological involvement: ataxia, headache, confusion, headache, focal signs
- Differential diagnosis:
  - TSS, risk factors, portal of entry
  - Kawasaki disease shock syndrome

Pediatric Post-COVID-19 Inflammatory Syndrome

Patients presenting with this inflammatory syndrome may have had a preceeding illness consistent with COVID-19, or had a COVID-19 sick contact.

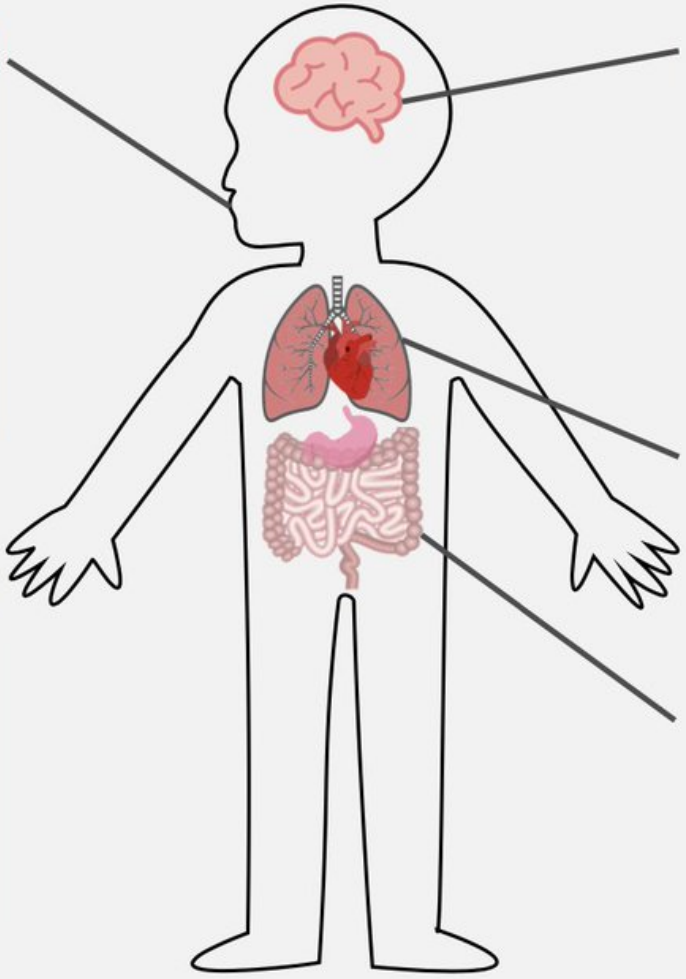
30%-80%

MUCOCUTANEOUS

- ☐ Rash - reticular, morbilliform, purpuric
- ☐ Lip Swelling / Cracking
- ☐ Strawberry Tongue
- ☐ Extremity Swelling / Peeling
- ☐ Conjunctivitis
- ☐ Blisters / Erosions

SYSTEMIC INFLAMMATION

- ☐ Fever
- ☐ Myalgias
- ☐ Tachycardia
- ☐ Hypotension
- ☐ Hypoperfusion or Hyperperfusion
- ☐ Lymphadenopathy / Lymphadenitis



30%-60%

NEUROLOGIC

- ☐ Headache
- ☐ Altered Mental Status
- ☐ Meningismus
- ☐ Focal Deficits
- ☐ Seizure

20%-60%

CARDIOPULMONARY

- ☐ Respiratory Distress
- ☐ Chest Pain

60%-100%

GASTROINTESTINAL

- ☐ Nausea / Vomiting
- ☐ Diarrhea
- ☐ Abdominal Pain

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Cook Children's Medical Center Guidelines

CDC Case Definition for MIS-C from May 2020

This statement derived from the Centers for Disease Control.

As described in the Health Advisory, "Multisystem Inflammatory Syndrome in Children (MIS-C) Associated with Coronavirus Disease 2019 (COVID-19)," the case definition for MIS-C is:

- An individual aged <21 years presenting with fever*, laboratory evidence of inflammation**, 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 exposure to a suspected or confirmed COVID-19 case within the 4 weeks prior to the onset of symptoms.

*Fever ≥ 38.0°C for ≥ 24 hours, or report of subjective fever lasting ≥ 24 hours
**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.

EMORY INTERNAL MEDICINE RESIDENCY: COVID-19 VISUAL SERIES

An Emory educational initiative in partnership with Baylor Infectious Disease

CDC Defines New Syndrome: Multisystem Inflammatory Syndrome in Children (MIS-C)

MIS-C should be diagnosed and reported in a patient ≤21 years old with all of the following:

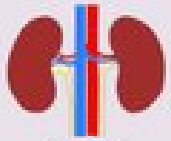
Fever

38°C or subjective fever for ≥ 24 hours

SARS-CoV-2 Positive

- RT-PCR Serology or
- Antigen test or
- COVID-19 exposure within 4 weeks

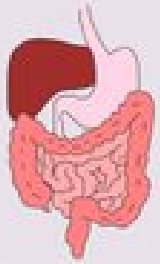
Hospitalized with involvement of ≥ 2 of the following organ systems



Renal

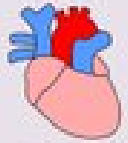
Neurologic

Respiratory



Gastrointestinal

Hematologic



Cardiac

Dermatologic

Evidence of Inflammation

- CRP
- ESR
- IL-6
- Neutrophils
- D-Dimer
- Procalcitonin
- Ferritin
- LDH
- Fibrinogen

- Lymphocytes
- Albumin

*Only need one of these lab values or other lab evidence of inflammation

No alternative plausible diagnoses

All patients meeting MIS-C criteria should be **diagnosed and reported** to the local, state, or territorial health department (even if also meeting Kawasaki criteria).

Where to report: https://www.naccho.org/membership/lhd-directory

24-hour support:

- Local Health Department Phone Numbers: https://resources.cste.org/epiafterhours
- CDC Emergency Operations Center: 770-488-7100

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

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Evaluation

- Physical exam
  - If ill appearing: broad differential diagnosis and extensive work up
- Labs:
  - Inflammatory markers: CRP, ESR, ferritin, fibrinogen, LDH, SARS CoV2 igg
    - CRP is very telling (very high- >10 mg/dl or 100 mg/liter)
  - CBC: Anemia and Thrombocytopenia
  - Cardiac labs: **BNP** (*myocardial strain*), **troponin** (*indicates myocardial inflammation)*
  - Rheumatology work up
  - ID work up

Admitting Labs and Imaging Work Up

- ❑ SARS-CoV-2 PCR swab
- ❑ Respiratory pathogen panel
- ❑ CBC with differential, C reactive protein, erythrocyte sedimentation rate, ferritin, procalcitonin, D-dimer, LDH, PT/PTT, fibrinogen, BNP, troponin, CK-MB, renal panel, liver function test, triglycerides
- ❑ Urinalysis, urine culture, blood culture
- ❑ CXR
- ❑ EKG on admission and q48h
- ❑ Echo – on the indication, note "concern for Kawasaki Disease"
- ❑ *Consider* after specialist consultation: ANA, C3, C4, cytokine panel

Special Considerations in the Work-Up

- Call a Stroke Alert as usual for patients who meet criteria. The 2nd Floor iMRI will be used for suspected COVID-19 patients.
- For patients presenting with a rash:
  - ❑ Add pictures to the patient's chart in EPIC
  - ❑ HSV and VZV PCR of erosion, blister, or varicella-like lesions
- Obtain before giving IVIG or FFP:
  - ❑ Quantitative Immunoglobulins, Fibrinogen
- *Consider* obtaining before giving IVIG or FFP:
  - ❑ COVID ELISA serology testing
  - ❑ Double stranded DNA, Smith Antibody, lupus anti-coagulant panel
  - ❑ Viral serologies

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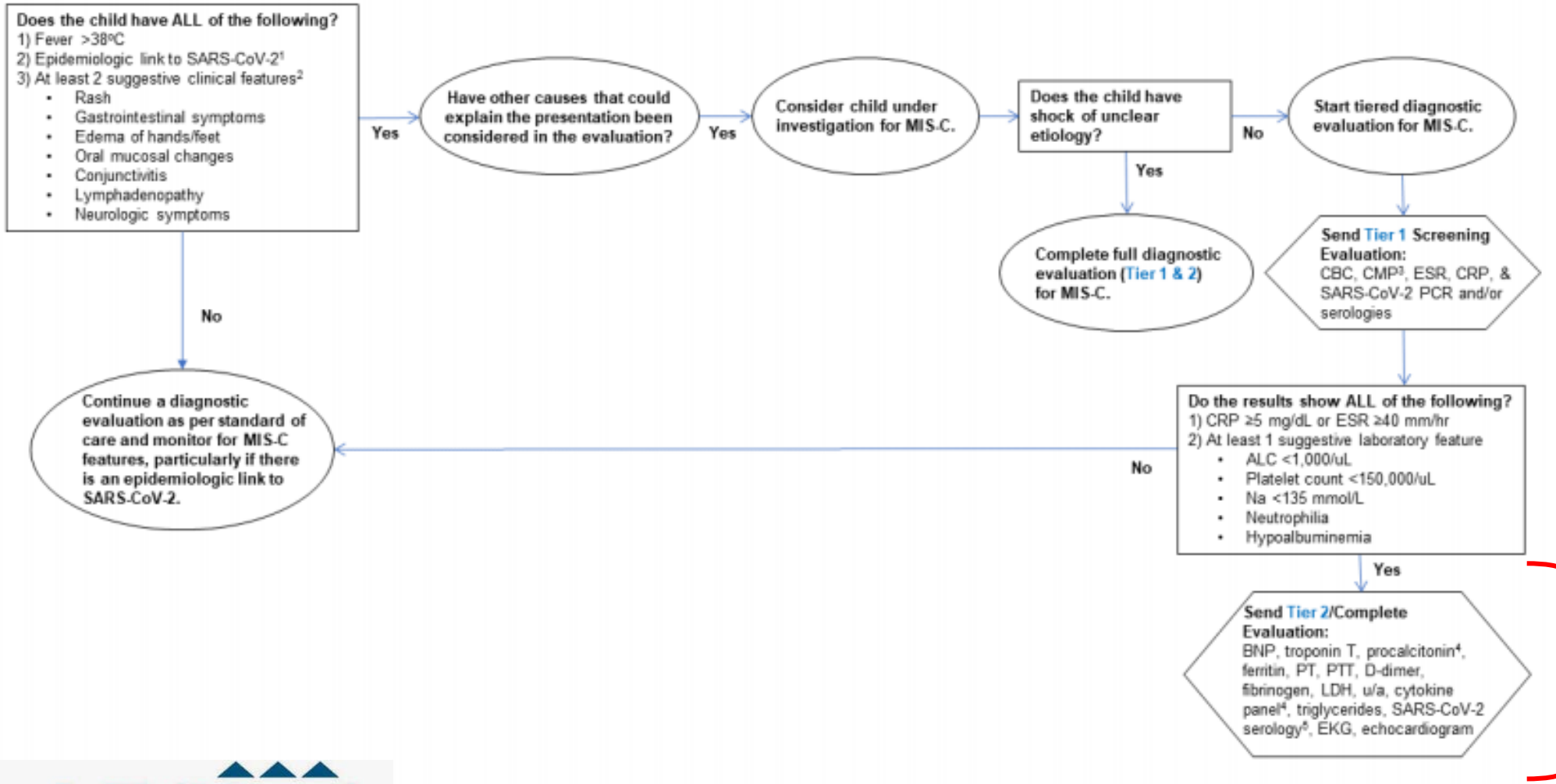

First phase

More
Fancy labs

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Classic Presentation

- Clinical picture
- Labs:
  - Lymphocytopenia
  - Anemia
  - Thrombocytopenia
  - Elevated CRP
  - +/- ESR
  - Elevated D-dimer
  - Elevated ferritin
  - Elevated fibrinogen
  - Elevated procalcitonin
  - Elevated IL-6
- Elevated BNP
- Elevated troponin
- Echocardiogram
  - LV dysfunction
  - Decreased Ejection fraction
  - Abnormal coronaries
- EKG

Cardiovascular work up

Echocardiogram

- Predictor of disease severity
- Function: Left ventricular function, ejection fraction (EF)
- Coronary arteries

EKG

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How do you distinguish KD from MIS-C?

Differential Diagnosis

- Phenotypic overlap with MIS-C andKD
- 40-50 % patients meets criteria for complete/incomplete KD
- MIS-C older children and adolescents vs younger children
- MIS-C affect mostly black and Hispanic versus Asian
- MIS-C with GI symptoms >> than in KD
- MIS-C with more myocardial dysfunction and shock presentation
- MIS-C with higher inflammatory markers (CRP, Ferritin, D-Dimer)
- MIS-C: >> LV dysfunction, >>cardiac markers
- KD: >> coronary changes, Less GI sx
- *COVID 19 exposure*

Previously reported possible coronavirus-Kawasaki disease association

Table 1. Clinical and laboratory features of children with Kawasaki disease.

Case subject[a] (sex)	Age (month/year of diagnosis), months	Interval,[b] days	Bilateral conjunctivitis	Erythema of the mouth or pharynx	Polymorphous rash	Erythema or edema of the hands or feet	Lymphadenopathy[c]	No. of criteria[d]	Echocardiographic result[e]	HCoV-NH by PCR
1 (M)[f]	6 (2/02)	4	+	+	+	+	−	4	CA-D	+
2 (M)	8 (1/04)	6	+	−	+	−	+	3	CA-D	+
3 (M)	12 (4/03)	5	+	+	+	+	−	4	Normal	+
4 (M)	15 (1/04)	4	+	+	+	−	−	3	CA-D	+
5 (F)	21 (3/04)	5	+	+	+	−	+	4	Normal	+
6 (F)	27 (2/04)	10	+	+	+	+	−	4	Normal	+
7 (M)	60 (4/04)	5	+	+	+	−	+	4	Normal[g]	+
8 (M)	67 (3/04)	9	+	+	+	−	−	3	CA-abnl	+
9 (M)	2 (11/02)	5	−	+	+	−	+	3	CA-abnl	−
10 (M)	15 (1/03)	13	+	−	+	+	−	3	Normal	−
11 (M)	34 (12/02)	7	+	+	+	−	+	4	Normal	−

Note. −, negative; +, positive; CA-abnl, abnormal echogenicity of the coronary arteries without evidence of dilation; CA-D, abnormal echogenicity of the coronary arteries with evidence of dilation; F, female; HCoV-NH, New Haven coronavirus; M, male; PCR, polymerase chain reaction.

[a] All case subjects had fever for >5 days.
[b] Between onset of fever and the date the specimen was collected.
[c] Cervical lymph node enlargement with at least 1 node >1.5 cm.
[d] No. of diagnostic criteria met (in addition to fever).
[e] Echocardiograms were obtained at the time of diagnosis of Kawasaki disease.
[f] First case identified.
[g] Subsequent echocardiogram revealed dilation of the origin of the left coronary artery.

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Esper JID 2005 https://doi.org/10.1086/428291

Other DDx?

Other DDx

- Toxic shock syndrome
- Sepsis
- Appendicitis
- Other viral illnesses
- HLH
- SLE
- Vasculitis

Treatment

1. **IVIG or not?**
   - Not recommended a second IVIG- risk for hemolytic anemia

2. +/-Low dose steroids vs high dose steroids (solumedrol 2m/kg/d vs 30 mg/kg/day)

3. +/- Anakindra (very favored here in Cook Children's Hospital The darling of rheumatology

4. +/- Anti IL-6 *(tocilizumab- more used in adults, more risk of bacterial infections)*

5. ***+/- Infliximab***

Cook Children's Medical Center Guidelines

Initial Inpatient Consults

- Infectious Disease, Rheumatology, Hematology
- Consult Cardiology if any abnormality noted on echo or initial cardiac labs
- Consult Oncology for suspected HLH

Management Guidelines

MANAGEMENT BY CLINICAL SEVERITY			
Therapeutic Category ǂ	**Mild**	**Moderate**	**Severe**
IVIG	Consider	Yes	Yes
Remdesivir	Consider for positive Covid-19 PCR	Consider for positive Covid-19 PCR	Consider for positive Covid-19 PCR
Immunomodulation	Consider	Anakinra + solumedrol	Anakinra + solumedrol
GI prophylaxis	*Indicated when receiving solumedrol*		
Anticoagulation	*Recommendations per Hematology*		
Broad-spectrum antibiotics	*see Other Management Considerations [a] for specific guidance*		

PATIENTS WITH GI SYMPTOMS: These patients have a higher risk of bowel perforation with pulse steroids. Consider risk/benefit of therapy in these patients.

Anakindra

- Interleukin receptor antagonist.
- Interleukin 1 is a highly active pro inflammatory cytokine that lower pain threshold and damages tissues
- Blocking IL-1 activity results in rapid and sustained reduction of disease severity, decreases pro inflammatory cytokine expression
- Off label use for MIS-C during this pandemic
- Less side effects that anti IL-6
- Reduces mortality in sepsis patients
- Relatively safe

www.thelancet.com/rheumatology Published online May 15, 2020 https://doi.org/10.1016/S2665-9913(20)30137-5

Classification of Clinical Severity

- **Mild**
  - No vasoactive requirement, minimal or no respiratory support, minimal organ injury
- **Moderate**
  - Vasoactive-inotropic score <10, significant oxygen supplement, mild or isolated organ injury
- **Severe**
  - Vasoactive inotropic score >10, non invasive or invasive respiratory support, moderate or severe organ injury including moderate to severe ventricular dysfunction.

Management

- *If hemodynamically unstable?*
  - Aggressive approach
    - Antibiotics, IVF,
    - Treat as MIS-c

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Isolation

- SARS CoV2 PCR
  - If positive, COVID19 isolation and admission to COVID19 unit
  - If negative on admission, will repeat in 24 hours,
    - If negative- No isolation even if positive IGG for COVID19
    - Consider family members

Follow up

- Cardiac monitoring
  - Symptoms can get worse with no therapy
- Serial labs
  - CRP is very helpful
  - BNP if elevated
- Follow up echo, if abnormal repeat every 48 hours
- EKG repeat every 48 hours

Discharge and outpatient F/U

- "Most do well"
- Quick turn around
- No need to be back to baseline 100%
- Afebrile for 24 hours
- KD signs improving
- Cardiac function improving
- If neurology symptoms, in resolution

- 2 weeks follow up echo and EKG
- 6 weeks follow up echo and EKG
- If arrhythmia- Holter follow up
- If cardiac dysfunction: stress echo, cardiac MRI
- Echo 1 year after presentation if cardiac abnormalities in the acute phase
- ASA low dose for at least 6 weeks

"Long consequences remain to be determined"

Summary

- Different names
- Temporal association with COVID19
- Time and comprehensive evaluation will help to understand pathogenesis
- Clinical findings overlap with KD, TSS, MAS- this is distinct syndrome
- Varied symptoms
- Lab characteristics
- Echo with decreased LV
- Treatment with best practice evolving
- A lot of unknowns.

Questions?

Thank you!!!

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