Syndrome de Kawasaki-like et COVID-19

Damien Bonnet,
M3C-Necker
Universités de Paris

La SFC répond à vos questions

COVID-19

Multisystem Inflammatory syndrome in children and adolescents (MIS-CA) related to SARS-CoV-2 infection

Damien Bonnet,
M3C-Necker
Universités de Paris

La SFC répond à vos questions

About this Attention Score

In the top 5% of all research outputs scored by Altmetric

Among the highest-scoring outputs from this source (#6 of 16,793)

High Attention Score compared to outputs of the same age (95th percentile)

High Attention Score compared to outputs of the same age and source (98th percentile)

Mentioned by

97 news outlets
1 blog
1218 tweeters
6 Facebook pages
1 Wikipedia page
2 Redditors

What is this page?

Cardiac Decompensation Seen in Children Following COVID-19
Physician's Briefing, 22 May 2020
(HealthDay News) -- Children may experience acute cardiac decompensation due to a severe inflammatory state (multisystem...

Cardiac Decompensation Seen in Children Following COVID-19
Drugs.com, 22 May 2020
-- Children may experience acute cardiac decompensation due to a severe inflammatory state (multisystem inflammatory syndrome...

COVID-19: TCTMD's Daily Dispatch for May 21
TCTMD, 21 May 2020
TCTMD reporter Todd Neale is keeping up on breaking news and peer-reviewed research related to COVID-19 and will update daily.

Immune Globulin Therapy Linked to Heart Function Recovery in COVID-Related Multisystem Inflammatory Syndrome
MPR, 21 May 2020
The use of immune globulin therapy appears to benefit children who experience acute heart failure caused by coronavirus disease...

Even Very Sick Kids Fare Well Despite Kawasaki-Like COVID-19 Symptoms
TCTMD, 21 May 2020
Physicians are still learning about the newly identified multisystem inflammatory syndrome in children (MIS-C).

COVID-19 Antibodies May Tame Inflammatory Condition in Kids: Study
Medicinenet, 21 May 2020
Latest Coronavirus News TUESDAY, May 19, 2020 (HealthDay News) -- Reports of children suffering from a serious coronavirus-linked...

Coronavírus causa nova doença em crianças e adolescentes
Superinteressante, 20 May 2020
(Alexandra Pavlovar /Superinteressante) Síndrome Inflamatória Multissistêmica Infantil (MIS-C) aparece semanas após a infecção...

Kawasaki-like Inflammatory Disease Affects Children With COVID-19
Diagnostic and Interventional Cardiology, 20 May 2020
A new, serious COVID-19 cardiovascular presentation emerged in late April and early May 2020 in the form of pediatric multi-syste...

Immunotherapy, steroids restore heart function in children with COVID-related multi-system inflammatory syndrome
The Medical News, 20 May 2020
Treatment with antibodies purified from donated blood - immune globulin therapy - and steroids restored heart function in the...

COVID-19 antibodies may tame Kawasaki-like condition in kids
UPI.com, 20 May 2020
Reports of children suffering from a serious coronavirus-linked inflammatory condition have scared parents everywhere, but new...

COVID-Linked Heart Failure in Kids; Transplant Survival in COVID-19; Waiting for Exercise
MedPage Today, 19 May 2020
Cardiology > Prevention Recent developments of interest in cardiovascular medicine The Washington Post and New York Times...

Antibodies May Tame Inflammatory Condition in Kids
WebMD News, 19 May 2020
(HealthDay News) -- Reports of children suffering from a serious coronavirus -linked inflammatory condition have scared parents...

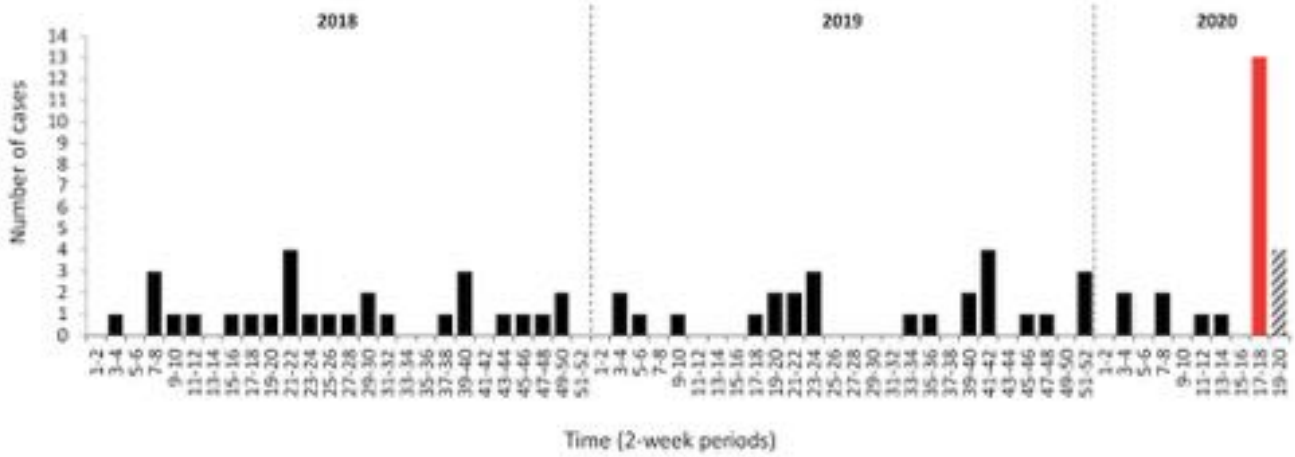
Immunotherapy, steroids had positive outcomes in children with COVID-related multi-system inflammatory syndrome
MedicalXpress, 19 May 2020
Rash on the skin of a child who has COVID-19 related multi-system inflammatory syndrome.

COVID-19 Antibodies May Tame Inflammatory Condition in Kids: Study
Health Day , 19 May 2020
(HealthDay News) -- Reports of children suffering from a serious coronavirus-linked inflammatory condition have scared parents...

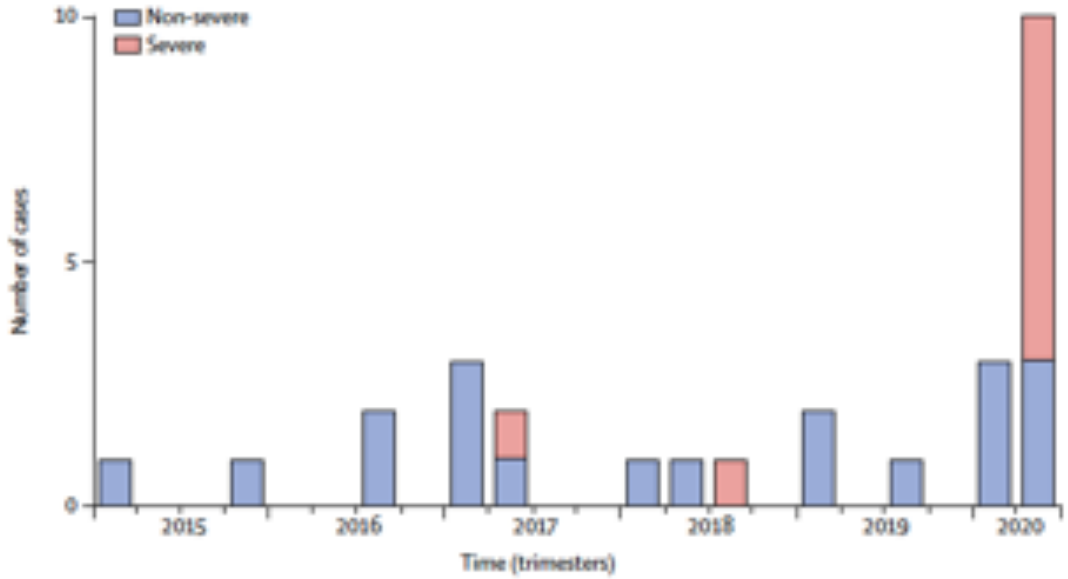
COVID-19 Antibodies May Tame Inflammatory Condition in Kids: Study
USNews.com, 19 May 2020
By Robert Preidt, HealthDay Reporter (HealthDay) TUESDAY, May 19, 2020 (HealthDay News) -- Reports of children suffering from a...

News story from Top Santé on Tuesday 19 May 2020
Top Santé, 19 May 2020

Incidence of Kawasaki disease at Necker Hospital since 2018



Necker hospital series BMJ, 2020



Verdoni L et al. Lancet 2020

Kawasaki disease Key points

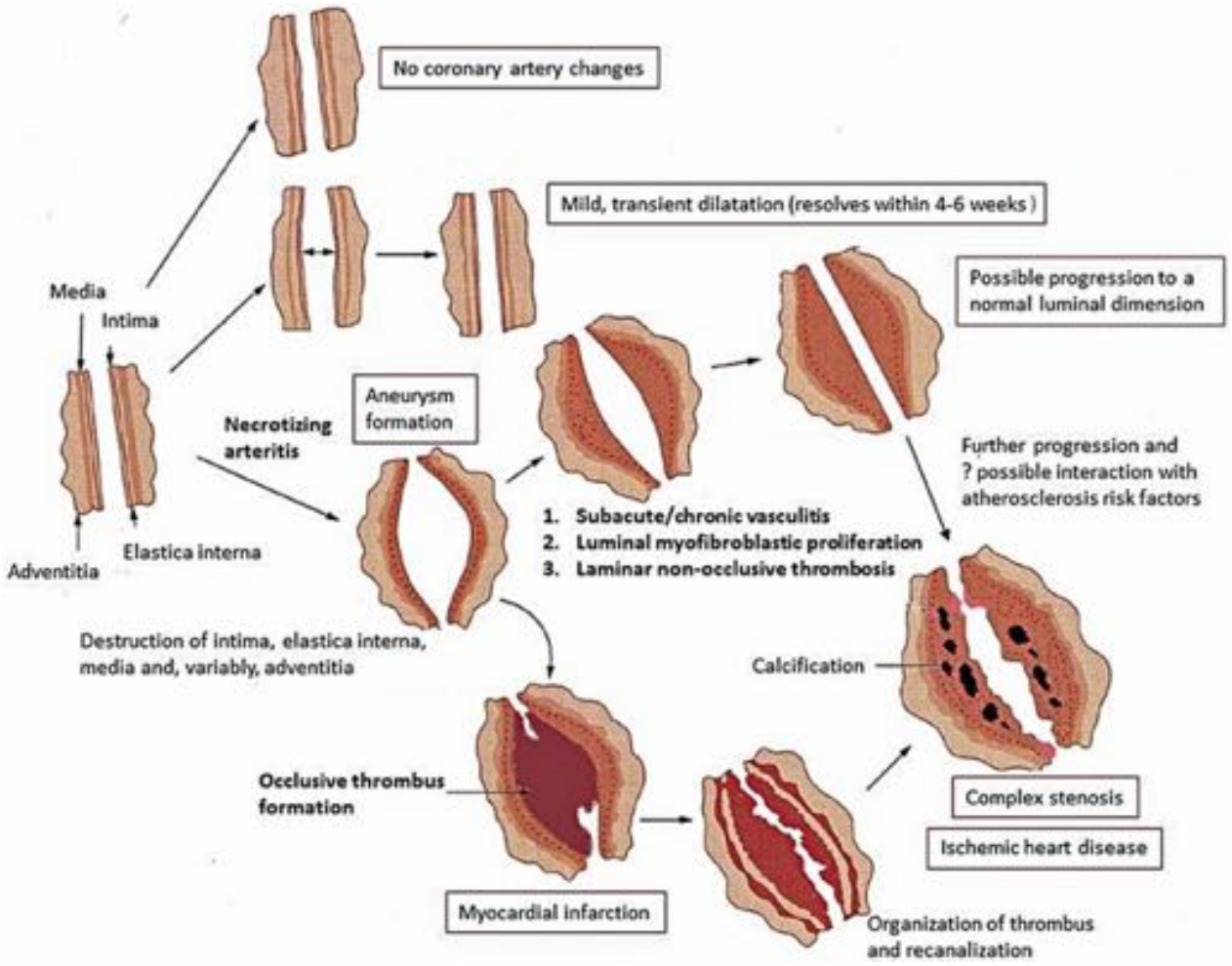
In Europe, KD is reported on average in 5–15/100 000 children under 5 years of age annually

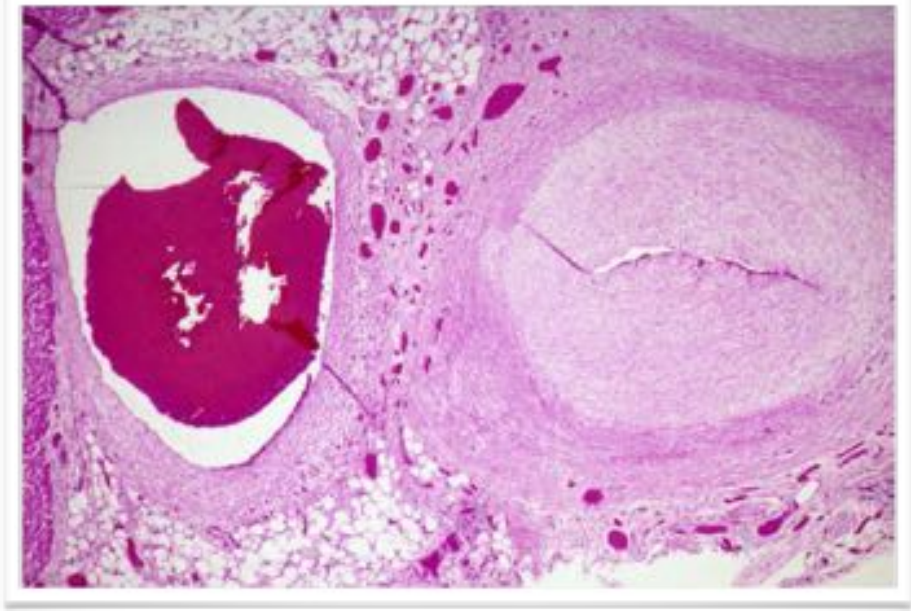
1. Kawasaki disease (KD) is an acute, self-limited febrile illness of unknown cause that predominantly affects children <5 years of age.

2. KD is now **the most common cause of acquired heart disease in children in developed countries**.

3. In the **absence of pathognomonic tests**, the diagnosis continues to rest on the **identification of principal clinical findings** and the exclusion of other clinically similar entities with known causes.

Coronary arteries in Kawasaki disease





Brian W. McCrindle et al. Circulation. 2017;135:e927-e999

Pathophysiology of Kawasaki disease

The main hypothesis includes **infection** with common pathogens, which causes an **immune-mediated response** resulting in KD in **genetically predisposed** children

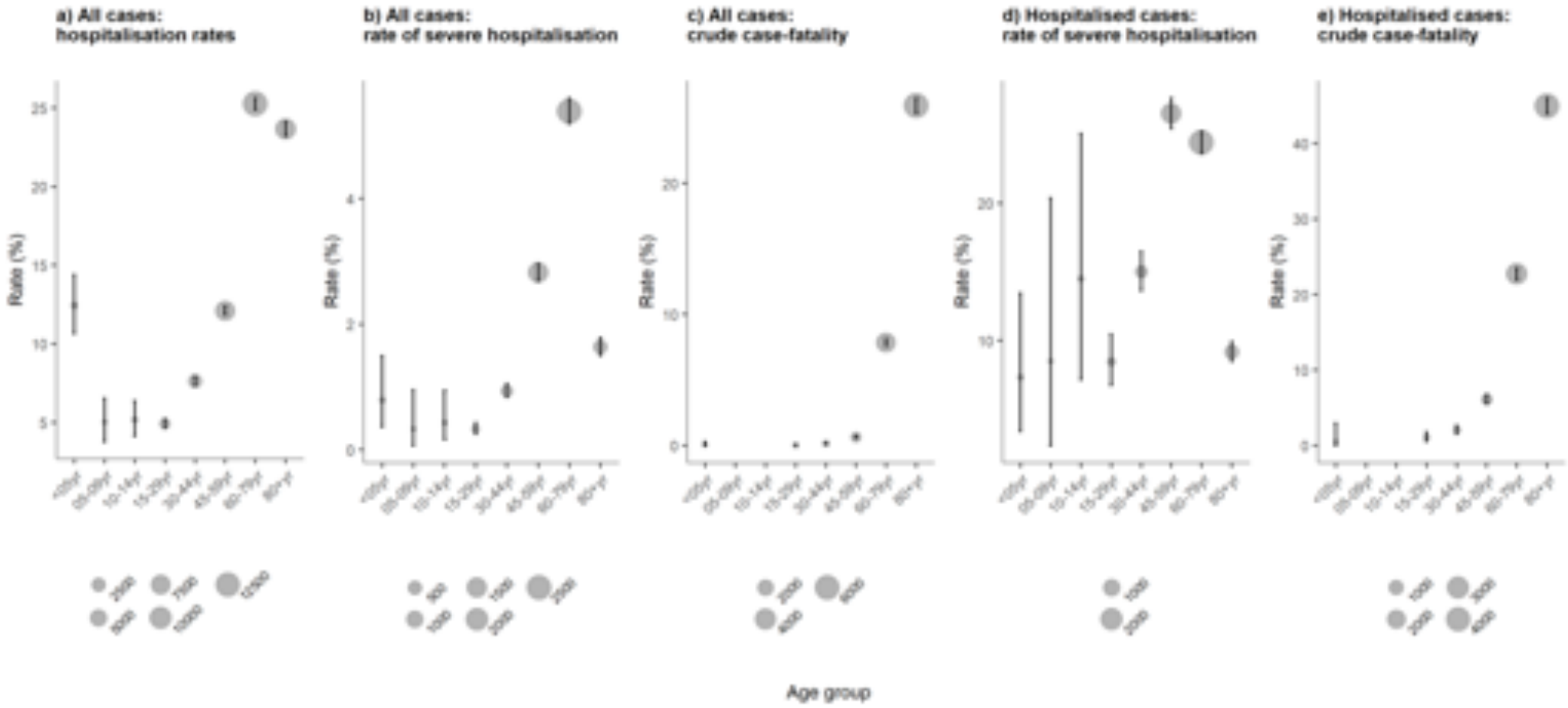
- It is most common in winter and early spring in Europe and North America
- The highest relative risk is in Asian children, especially of Japanese ancestry
- In Japan, the relative risk in siblings is 10-fold higher

COVID-19 in children

- **Less frequently** observed in children, and children tend to present with **milder symptoms** than adults.
- The most commonly reported symptoms include **fever and cough**.
- Due to the mild presentation of the disease in children, it appears that **children are also less likely to be tested**.
- Hospital admission are inversely related to age.
- Severe forms are observed in about 8-10% of hospitalised children.
- Fatalities do exist but are extremely rare.

https://covid19-surveillance-report.ecdc.europa.eu/

Age-specific rates of severe outcome, TESSy, EU/EEA and UK, 13 May 2020



European Centre for Disease Prevention and Control. Paediatric inflammatory multisystem syndrome and SARS-CoV-2 infection in children – 15 May 2020. ECDC: Stockholm; 2020.

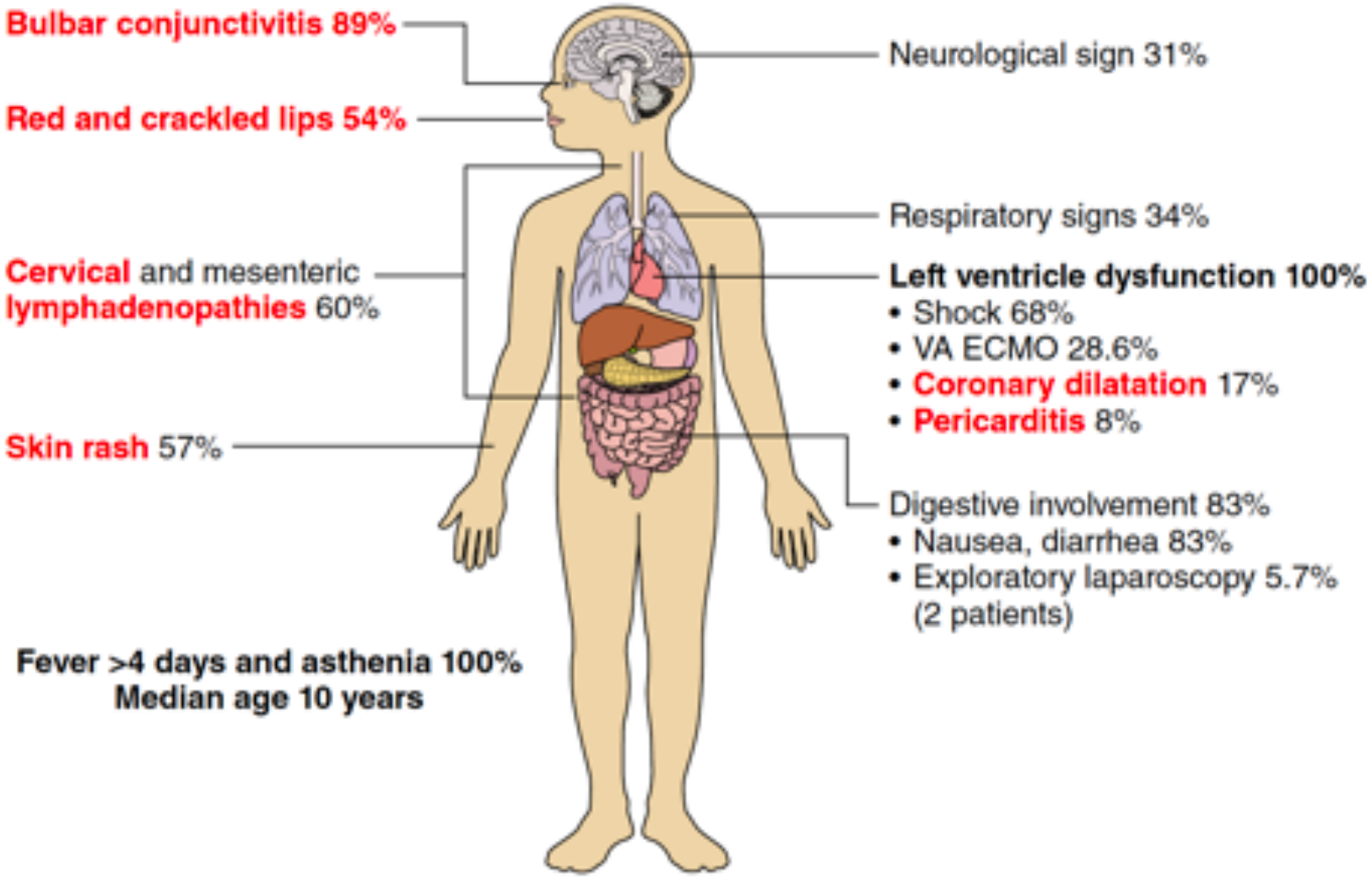
French series of MIS-CA

Table 1. Clinical signs and symptoms	
Median age yr	10
<1yr	0
1-5 years	1
6-16 years	34
Sex, n (%)	
Male/Female	18/17
Comorbidity, n (%)	10 (28)
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)

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 Aneurysms at day 10 (echography only)	6 (17) 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)

Belhadjer Z et al. Circulation 2020

MIS-CA presenting symptoms



Belhadjer Z et al. Circulation 2020

Cutaneous signs of MIS-CA

Belhadjer Z et al. Circulation 2020

French series of MIS-CA

Table 3. Laboratory findings		
	Baseline	**Normal values**
High sensitive troponin I (ng/L) (n=35)	347 (186-1267)	<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)	< 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

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)

Criteria for Kawasaki disease

Classic KD is diagnosed in the presence of **fever for at least 5 days** (the day of fever onset is taken to be the first day of fever) together **with at least 4 of the 5** following principal clinical features:

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


Multisystem inflammatory syndrome in children and adolescents MIS-CA

Paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 infection in children

European 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 other additional clinical, laboratory or imagining and ECG features. Children fulfilling full or partial criteria for Kawasaki disease may be included.
2. Exclusion of any other microbial cause, including bacterial sepsis, staphylococcal or streptococcal shock syndromes, infections associated with myocarditis such as enterovirus.
3. SARS-CoV-2 PCR testing positive or negative.

Multisystem inflammatory syndrome in children and adolescents MIS-CA

Paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 infection in children

WHO preliminary definition

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

6. Elevated markers of inflammation such as ESR, C-reactive protein, or procalcitonin.

AND

7. No other obvious microbial cause of inflammation, including bacterial sepsis, staphylococcal or streptococcal shock syndromes.

AND

8. Evidence of COVID-19 (RT-PCR, antigen test or serology positive), or likely contact with patients with COVID-19.

Association between SARS-CoV-2 infection and MIS-CA (Bradford Hill criteria)

1. Countries with large outbreaks of SARS-CoV-2 (France, Italy, Spain, UK, US) have seen the occurrence of cases of MIS-CA in the late stages of the first wave of the COVID-19 pandemic.
2. Repetition of findings, different populations
3. Cases have been observed in children negative by PCR but positive by serology, suggesting prior exposure to SARS-CoV-2 between one to up to 14 days. In addition, some children had confirmed and plausible COVID-19 exposure in their household or through contact with infected family members
4. Conceivable mechanism for the disease (KD pathophysiology)
5. The current hypothesis holds that SARS-CoV-2 triggers hyperinflammation in the MIS-CA cases, which is consistent with previous knowledge
6. Analogy with KD is an argument.

88% of positive serology in the first series and now 100% positive

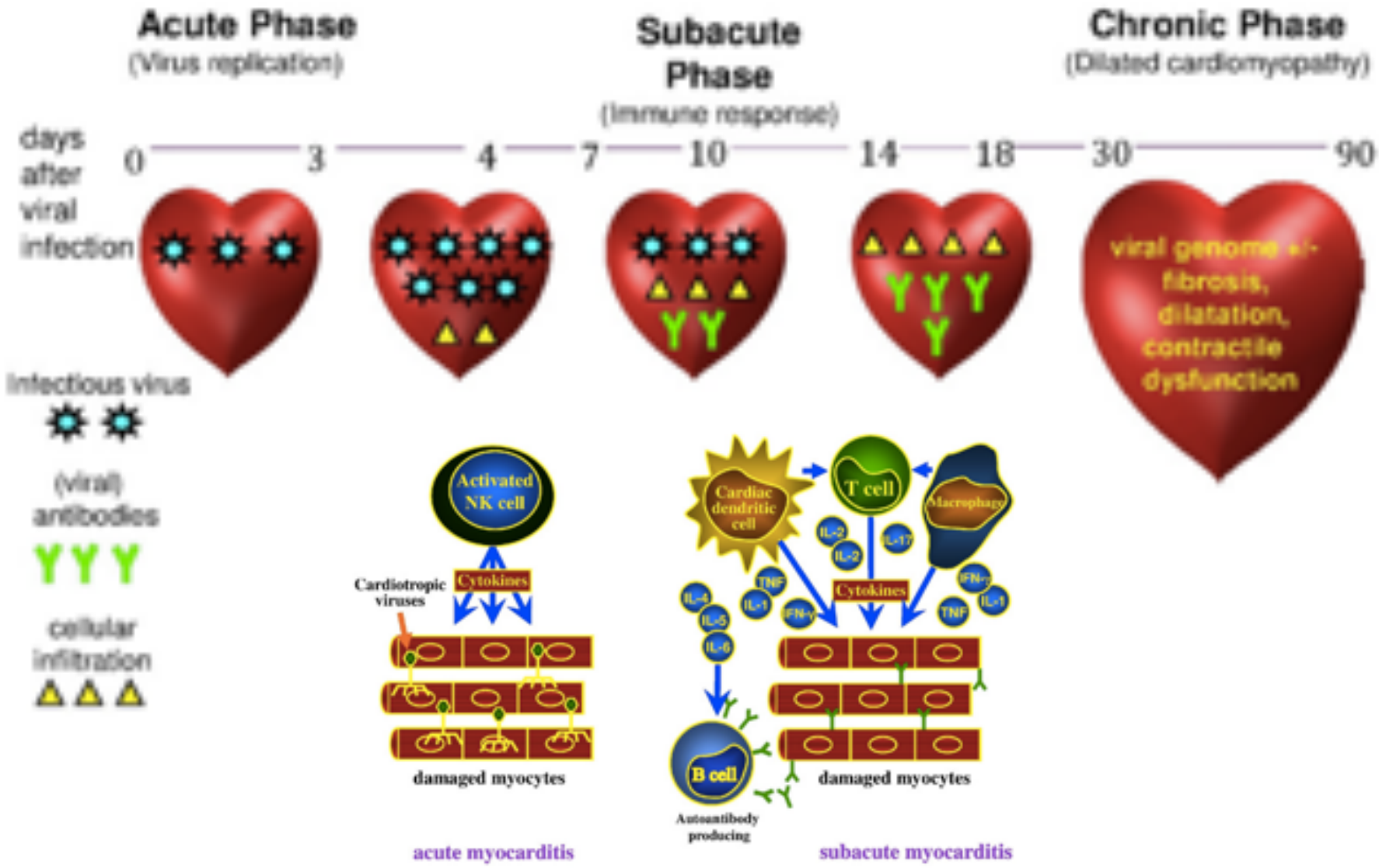
Stunning mechanism rather than necrotizing myocarditis

Takotsubo

Schoof F et al. J Am Coll Cardiol. 2010 Jan 19;55(3):e5.
Mattsson et al. BMC Med Genet. 2018 Mar 7;19(1):39

M3C NECKER

Myocarditis pathophysiology



Messages for the population

Maladie de Kawasaki : peut-on mettre ses enfants à l'école ?

Alors que le gouvernement a rouvert le 11 mai les écoles contre l'avis du Conseil scientifique, l'apparition d'une forme nouvelle de maladie inflammatoire chez les enfants ne présenterait pas de risque.

Par **Margaux d'Adhémar**
Publié le 15 mai 2020 à 18:37

Dans une école parisienne. *BENOIT TESSIER / REUTERS*

Le retour en classe de centaines de milliers d'élèves depuis le 11 mai, bientôt rejoints par les collégiens, pourrait-il être remis en question ? En effet, l'émergence d'un nouveau phénomène viral

Coronavirus : 135 enfants français atteints d'une forme proche de la maladie de Kawasaki, un mort

INFO LE FIGARO - La direction générale de la Santé annonce avoir recensé 135 cas de maladie de Kawasaki en France depuis plusieurs semaines. Une pathologie qui serait liée au coronavirus.

Par **Margaux d'Adhémar**
Publié le 15 mai 2020 à 14:20, mis à jour le 15 mai 2020 à 20:14

Fatigue intense, plusieurs jours de fièvre supérieure à 38°C, des ganglions, une forte inflammation et une éruption de boutons sont les caractéristiques typiques d'un Kawasaki (en photo, le personnel médical de l'hôpital Necker). *FRANCK FIFE / AFP*

Research and perspectives

- **Pragmatical issues**: informing our colleagues in areas that have not been affected yet by the SARS-CoV-2
  - predict those who will need intensive care and may have harder outcomes
  - understand the cardiac/hemodynamic presenting symptoms
  - organize follow-up: check for coronary aneurysms, myocardial sequelae, others…
- **Improve treatment**: IVIg, Steroids, Anti-IL1, Anti-IL6
- **Pathophysiological issues**: immune mechanisms, genetic susceptibility

Questions ?

M3C NECKER