PIMS/MIS-C
Au cours de la pandémie de Covid-19

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DES/C de Pathologie infectieuse et tropicale

4 octobre 2021

www.childfhu.com

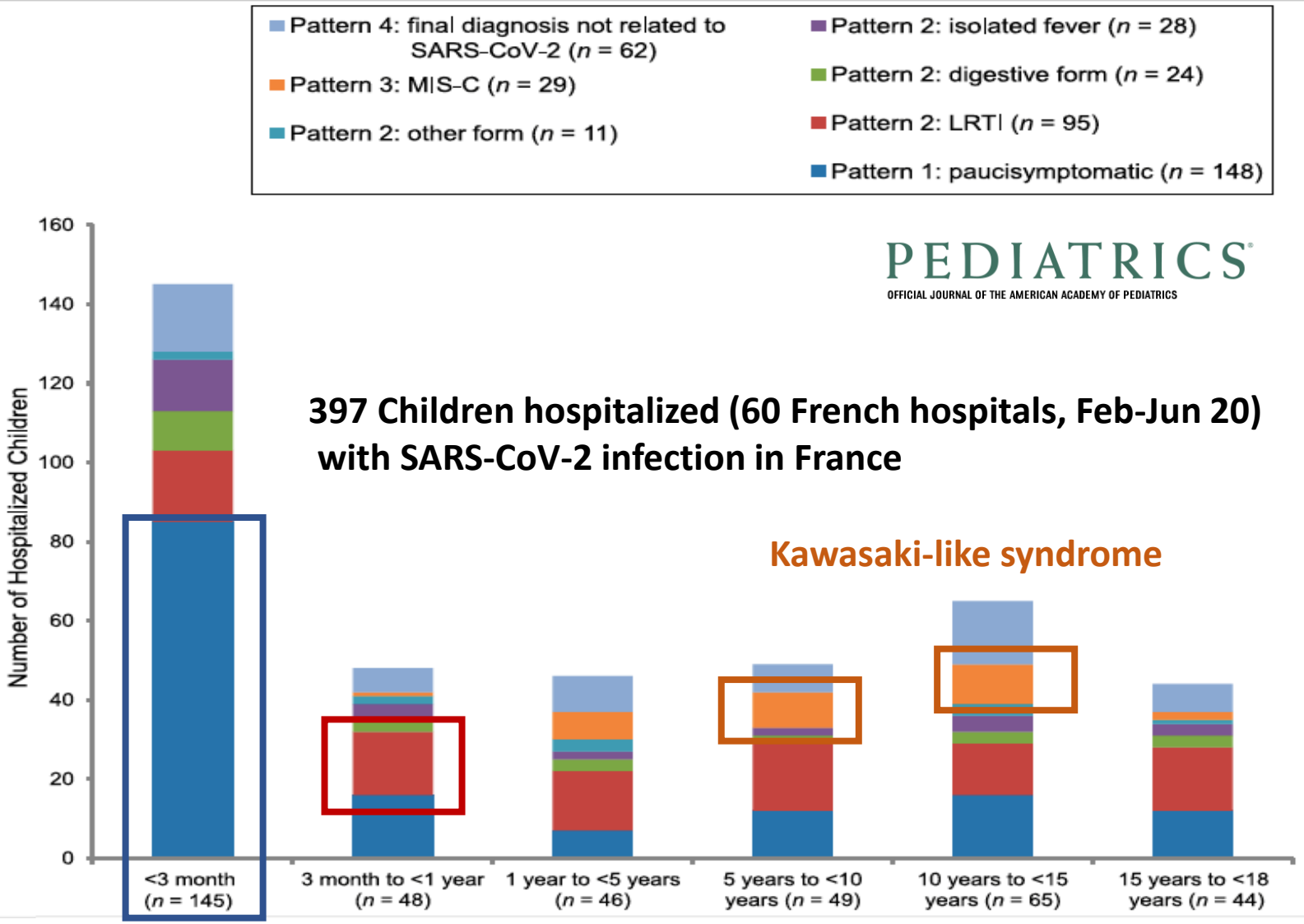
Université de Paris

Institut Pasteur

ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS

COVID-19 in hospitalized children

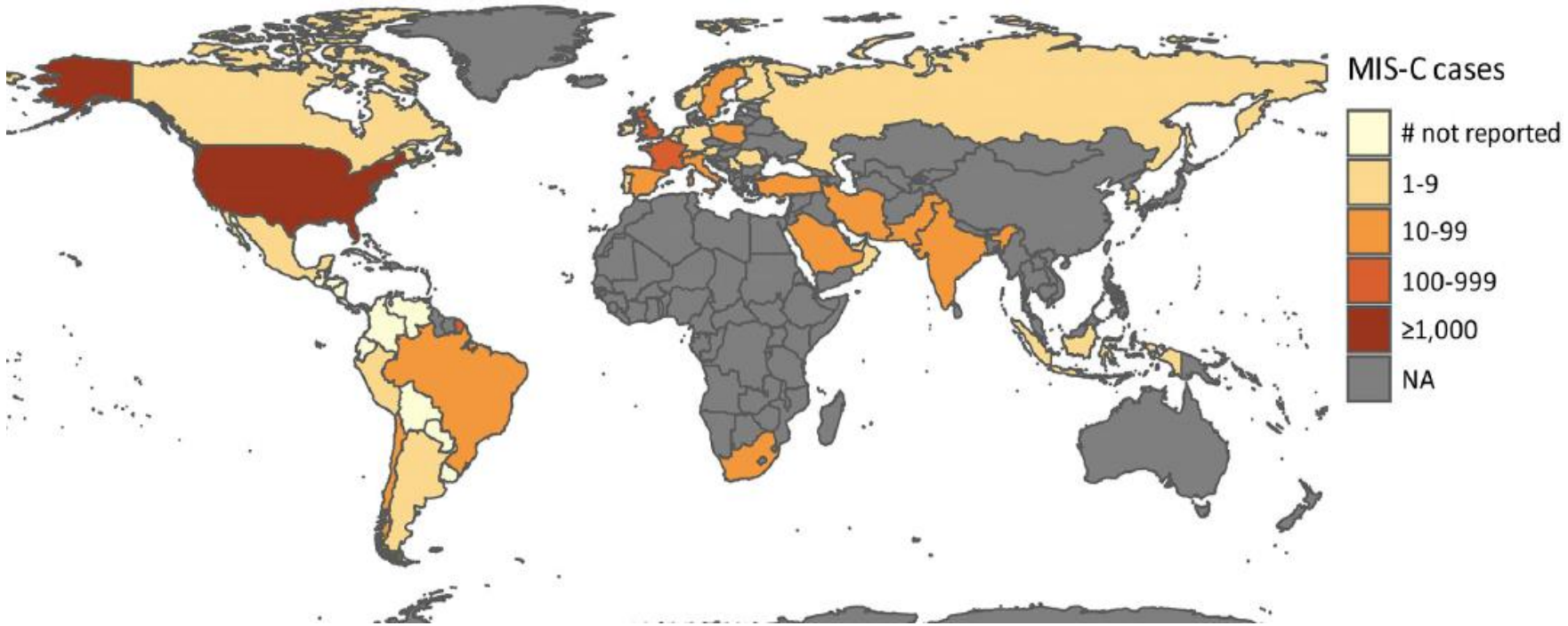
- Mild disease
- Death extremely rare
- Fever, mild respiratory symptoms
- Very rarely severe pneumonia
- PIMS-TS / MIS-C



Ludvigsson, Acta Paediatrica 2020 **Ouldali N, Pediatrics, Mar 2021**

April-May 2020
Alert on Myocarditis, shock, Kawasaki disease in children

Geographic Distribution of cases



Which name ?

- KD-SARS-CoV2, Kawa-COVID-19, Kawasaki-like multisystemic syndrome
- Paediatric inflammatory multisystem syndrome temporarelly associated with SARS-CoV-2 : PIMS-TS
- SARS-CoV-2 related multisystem inflammatory syndrome in children : MIS-C

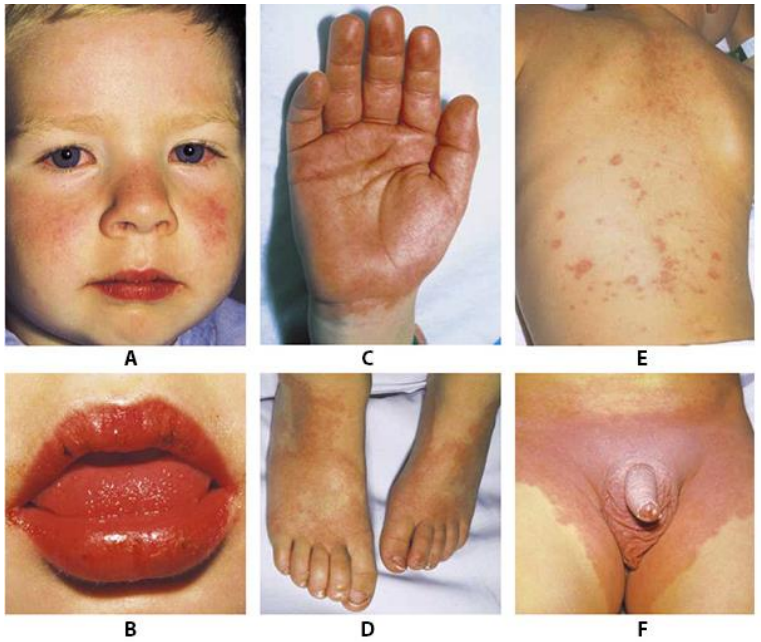
From WHO data, Feb 2021 ; Sancho-Shimizu J Exp Med

« Classic » Kawasaki disease

Connect to www.wooclap.com/SGNLDQ

- Multisystemic acute vascularitis aigue in children < 5 years
- Typical/complete form: fever > 4 days + at least 4 criteria among 5 major:

Cervical lymphadenopathy > 1.5 cm +, extremities changes, Bilateral bulbar conjunctival injection Lips and oral cavity changes , rash



Minor criteria
- Irritability
- Perineal or face desquamations
- Arthralgia
- Vomiting
- Otitis, Aseptic leucocyturia
- Inflammatory markers

Complications
- Seritis, Myocarditis, shock syndrome, Coronary abnormalities

Long-term complication: coronary dilatation/aneveurysm
-> Risk 23%, but falls to 4% if proper treatment!

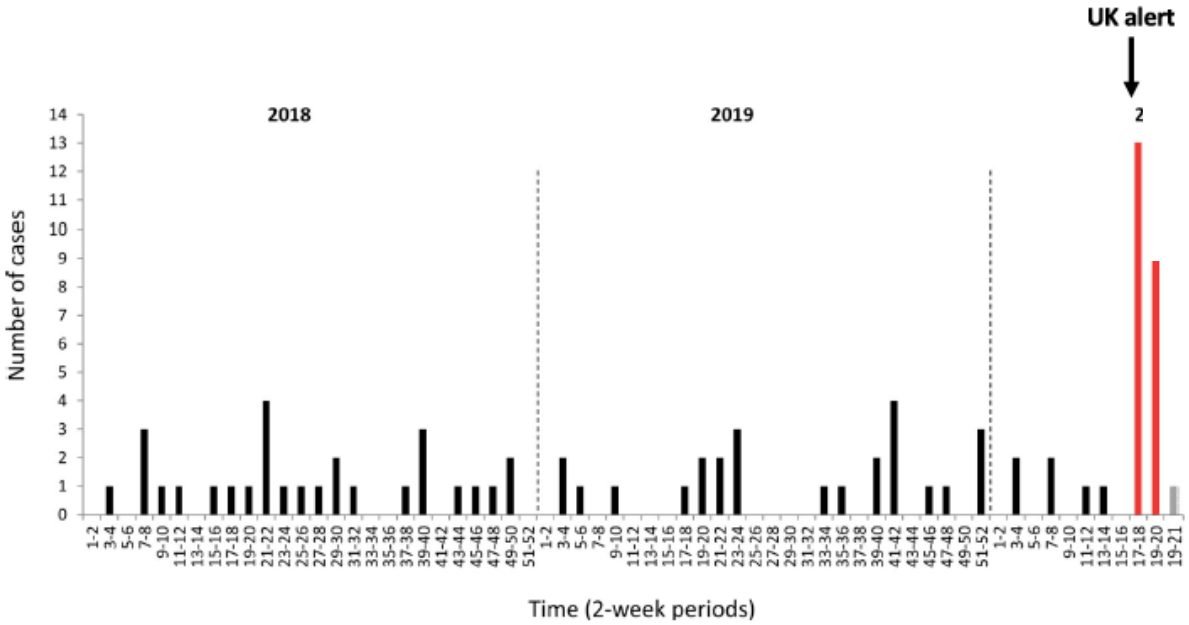
NEJM 1995, **AHA 2014, Mc Crindle 2017**

Journal of Clinical Immunology
https://doi.org/10.1007/s10875-020-00941-0

ORIGINAL ARTICLE

Distinctive Features of Kawasaki Disease Following SARS-CoV-2 Infection: a Controlled Study in Paris, France

Julie Toubiana[1,2] · Jérémie F. Cohen[1,3] · Joséphine Brice[1] · Clément Poirault[1] · Fanny Bajolle[4] · William Curtis[5] · Florence Moulin[6] · Soraya Matczak[1,2] · Marianne Leruez[7] · Jean-Laurent Casanova[8,9] · Martin Chalumeau[1,3] · Melissa Taylor[1] · Slimane Allali[1]



RAPID COMMUNICATION

Association between SARS-CoV-2 infection and Kawasaki-like multisystem inflammatory syndrome: a retrospective matched case–control study, Paris, France, April to May 2020

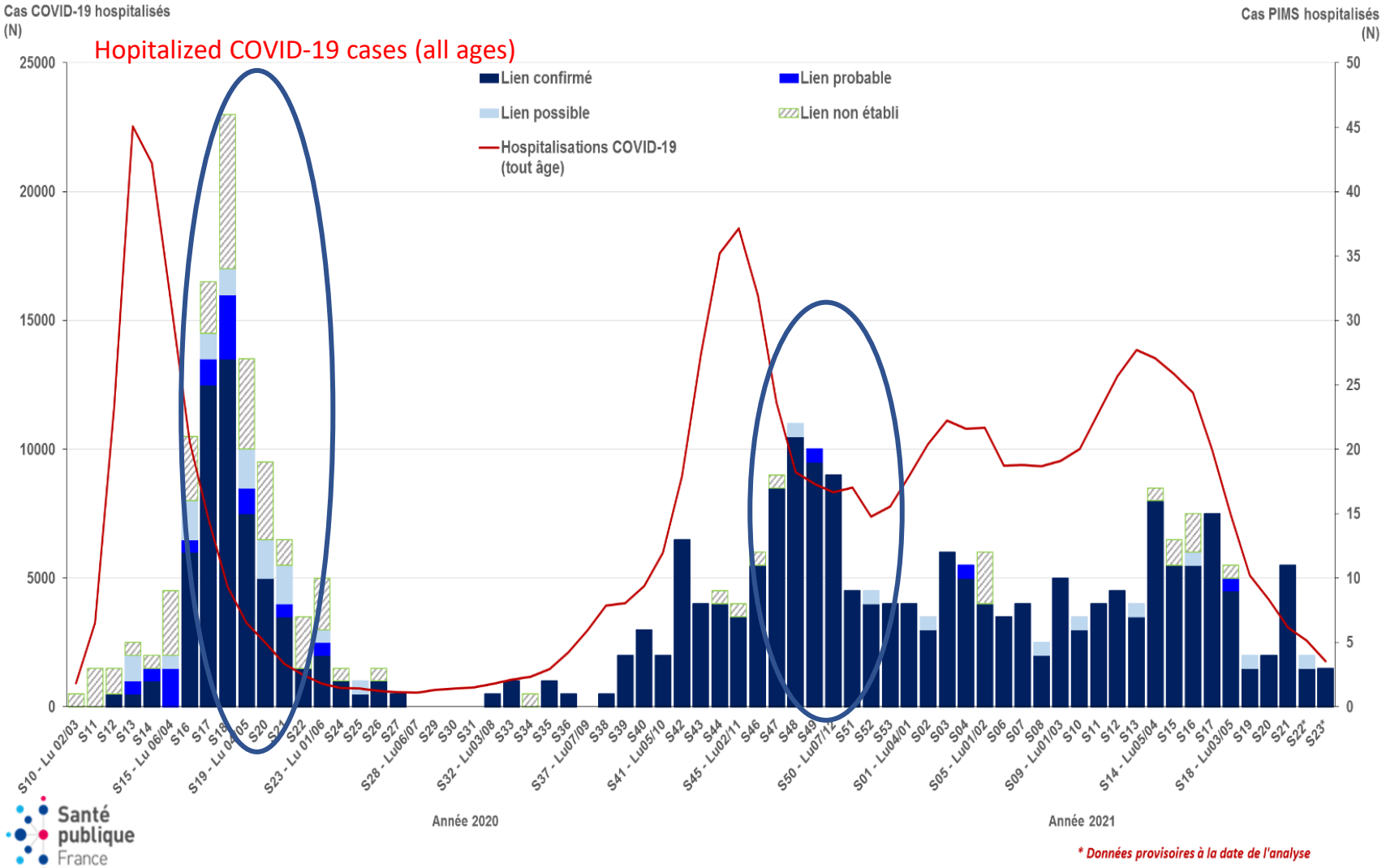
Julie Toubiana[1,2], Corinne Levy[3,4,5,6,7], Slimane Allali[1], Camille Jung[4,5], Marianne Leruez-Ville[8], Emmanuelle Varon[4,5,6,9], Fanny Bajolle[10], Naim Ouldali[3,6,11], Judith Chareyre[12], Stephane Béchet[3], Annie Elbez[3,7], Jean-Laurent Casanova[13,14], Martin Chalumeau[1,15], Robert Cohen[3,4,5,6,7,16], Jérémie F Cohen[1,15]

Characteristics	Cases (n = 23)		Controls (n = 102)		Matched OR (95% CI)a
	Number	%	Number	%	
Sex, females	11	48	48	47	NA
Age, mean in years (SD)	6.8 (4.8)	NA	5.8 (4.1)	NA	Matching criterion
Overall evidence of SARS-CoV-2 infection i.e. positive RT-PCR and/or serology					
Positive	17	74	11	11	26.4 (6.0–116.9)
Negative	6	26	91	89	Reference

MIS-C : 27-fold higher odds of previous exposure to SARS-CoV-2

Toubiana, J Clin Immunol 2020
Toubiana J Eurosurv 2020

PIMS Epidemiology in France

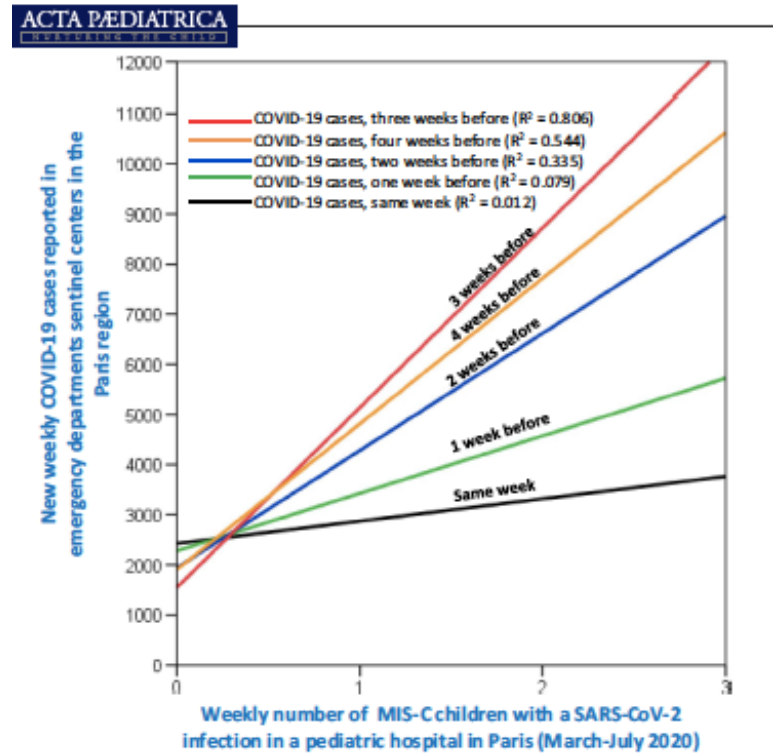


REGULAR ARTICLE

ACTA PÆDIATRICA WILEY

Multisystem inflammatory syndrome in children rose and fell with the first wave of the COVID-19 pandemic in France

Ricardo Carbajal[1] | Mathie Lorrot[2] | Yael Levy[3] | Emmanuel Grimprel[2] | Thibault Lecarpentier[1] | Sebastien Heritier[4] | Judith Faivre[5] | Aurélie Schnuriger[6] | Pauline Parisot[7] | Eléonore Blondiaux[8] | Solene Loschi[1] | Simon Rivière[1] | Julia Guilbert[3] | Anne-Sophie Romain[2] | Pierre-Louis Leger[3] | Romain Guedj[1]



2-4 weeks after COVID-19 waves (hospitalizations)

RESEARCH

Check for updates

FAST TRACK

Kawasaki-like multisystem inflammatory syndrome in children during the covid-19 pandemic in Paris, France: prospective observational study

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

Population 21 children

- Contact with a confirmed case 4-6 sem before symptoms
- Positive anti-SARS-CoV-2 IgG antibodies (+ positive PCR : 30%)
- All had fever + meeting definition for Kawasaki disease
- Some had coronary abdormalities (#20%)

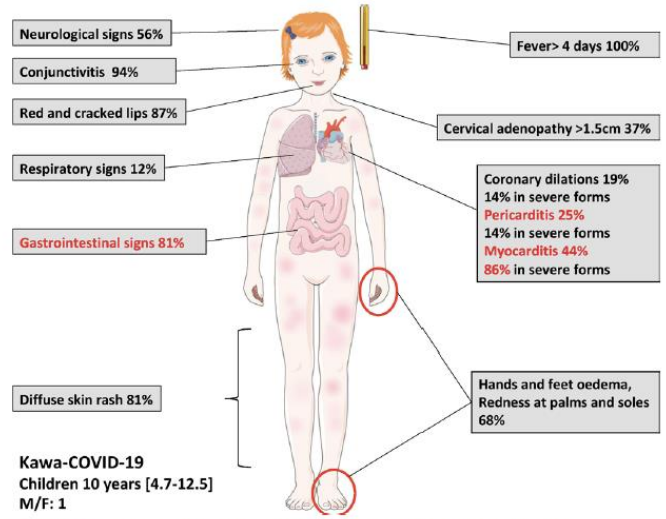


Figure 2 Main clinical features of Kawa-COVID-19 from the Paris region cohort, n=16 patients. In red: higher frequencies than classical Kawasaki disease.

Specificities compared to historical KD:

- **Older :** median age 8.2 vs. 4.0 yrs, p < 0.001
- **Almost all had acute abdominal pain** (surgical abdomen) : OR 84 [4.9–1456]
- **Neurological disorder** (meningitis/encephalitis) : OR 7.3 [1.9–27.7]
- **Shock** (vasoplegic or cardiogenic) : OR 13.7 [4.2–45.1]
- **Myocardial dysfunction** and markers of myocarditis (tropo, BNP): OR 387 [38–3933]
- **Higher levels of inflammatory** parameters : C-reactive protein, procalcitonin, ferritin
- **Lower lymphocyte** cell count

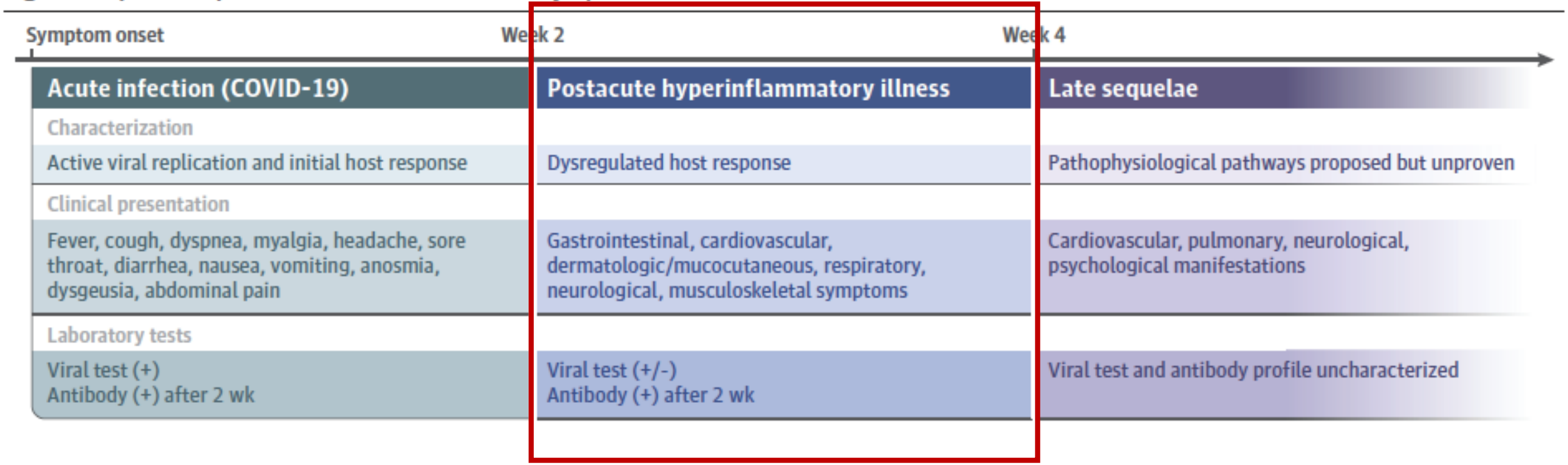
Toubiana, BMJ
Toubiana, J Clin Immunol
Pouletty, Ann Rheul Dis

VIEWPOINT

A Proposed Framework and Timeline of the Spectrum of Disease Due to SARS-CoV-2 Infection

Illness Beyond Acute Infection and Public Health Implications

Figure. Proposed Population-Based Framework for Symptomatic SARS-CoV-2 Infection[a]



Postacute Forms

Datta JAMA, Nov 2020

How to treat them ?: based on Kawasaki experience

A national consensus management pathway for paediatric inflammatory multisystem syndrome temporally associated with COVID-19 (PIMS-TS): results of a national Delphi process

*Rachel Harwood, Benjamin Allin, Christine E Jones, Elizabeth Whittaker, Padmanabhan Ramnarayan, Athimalaipet V Ramanan, Musa Kaleem, Robert Tulloh, Mark J Peters, Sarah Almond, Peter J Davis, Michael Levin, Andrew Tometzki, Saul N Faust, Marian Knight, Simon Kenny, on behalf of the PIMS-TS National Consensus Management Study Group**

- **First-line therapy for all children is intravenous immunoglobulins (IVIG)**
- 2 g/kg, can be administered in a single or divided dose depending on the clinical picture and cardiac function
- A second dose of intravenous immunoglobulin might be considered
- **High risk children/severe or IVIG resistance : methylprednisolone 2-10mg/kg daily**

COVID-19

JAMA | Original Investigation

Association of Intravenous Immunoglobulins Plus Methylprednisolone vs Immunoglobulins Alone With Course of Fever in Multisystem Inflammatory Syndrome in Children

Naïm Ouldali, MD, PhD; Julie Toubiana, MD, PhD; Denise Antona, MD; Etienne Javouhey, MD, PhD; Fouad Madhi, MD; Mathie Lorrot, MD, PhD; Pierre-Louis Léger, MD, PhD; Caroline Galeotti, MD, PhD; Caroline Claude, MD; Arnaud Wiedemann, MD, PhD; Noémie Lachaume, MD; Caroline Ovaert, MD, PhD; Morgane Dumortier, MD; Jean-Emmanuel Kahn, MD, PhD; Alexis Mandelcwajg, MD; Lucas Percheron, MD; Blandine Biot, MD; Jeanne Bordet, MD; Marie-Laure Girardin, MD; David Dawei Yang, MD; Marion Grimaud, MD; Mehdi Oualha, MD, PhD; Slimane Allali, MD, PhD; Fanny Bajolle, MD; Constance Beyler, MD; Ulrich Meinzer, MD, PhD; Michael Levy, MD, PhD; Ana-Maria Paulet, MD; Corinne Levy, MD; Robert Cohen, MD; Alexandre Belot, MD, PhD; François Angoulvant, MD, PhD; for the French Covid-19 Paediatric Inflammation Consortium

- **Etude retrospective**
- issue des notifications nationales : **Santé publique France**
- CRF information médicale
- Analyse de type **score de propension**

IGIV + methylprednisolone vs. IVIG alone

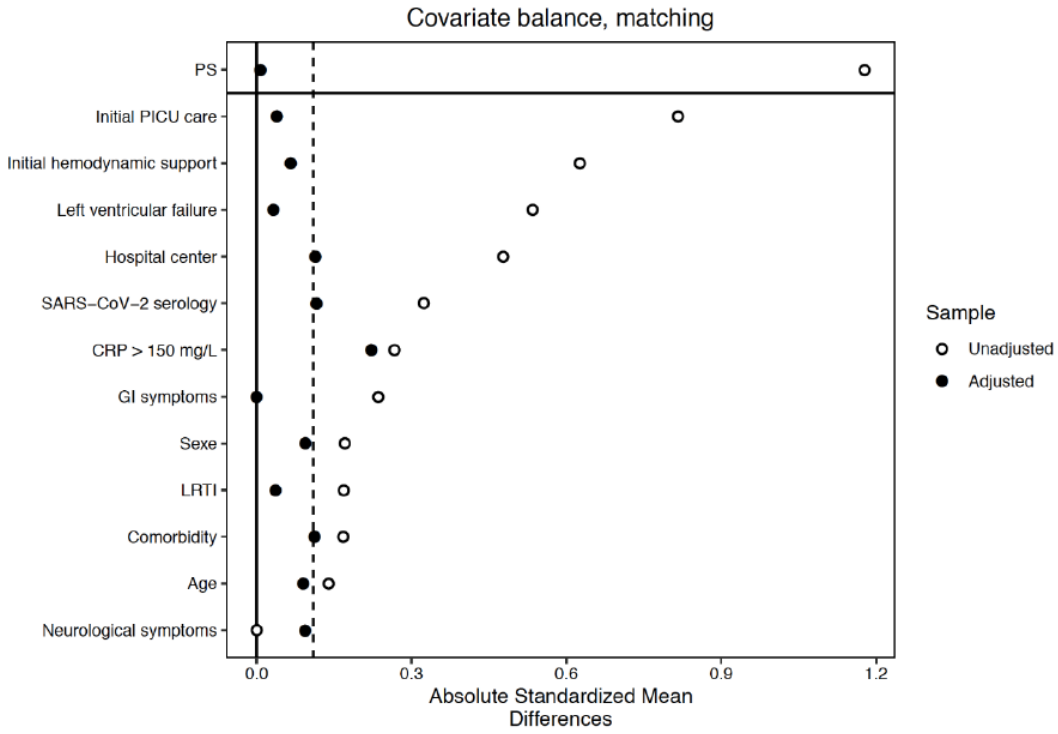
Non randomisation: risque de biais d'indication

Ex. : « on traite de façon plus intensive un patient plus grave »

Propensity score analysis

Principe: pour chaque patient, on établit une probabilité/score (PS) de recevoir le traitement 1 ou 2 en fonction de ses caractéristiques initiales

- On apparie ces patients en fonction de ce scor
- **On ajuste sur le poids de la caractéristique initiale « overlap weighting »**
  - Différence de poids (moyenne) des caractéristiques entre les 2 groupes de traitement divisé par écart type
  - On vérifie le poids de la caractéristique avant / après ajustement



Thomas L, JAMA 2020

JAMA | Original Investigation

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- **2 groupes: IVIG vs. IVIG + corticoides**
- **Patients PIMS/MISC selon les définitions OMS**

- **Critère de jugement principal:**
  - **Persistance de fièvre 48h après le traitement ou recrudescence thermique dans les 7 jours qui ont suivi le traitement**

- **Critère de jugement secondaire:**
  - Nécessité 2^{e} ligne
  - Support hémodynamique
  - Défaillance cardiaque
  - Durée hospitalisation en réanimation

JAMA | Original Investigation

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IGIV + corticos
Moins d'échec traitement
Moins de support hémodynamique
Moins de dysfonction VG

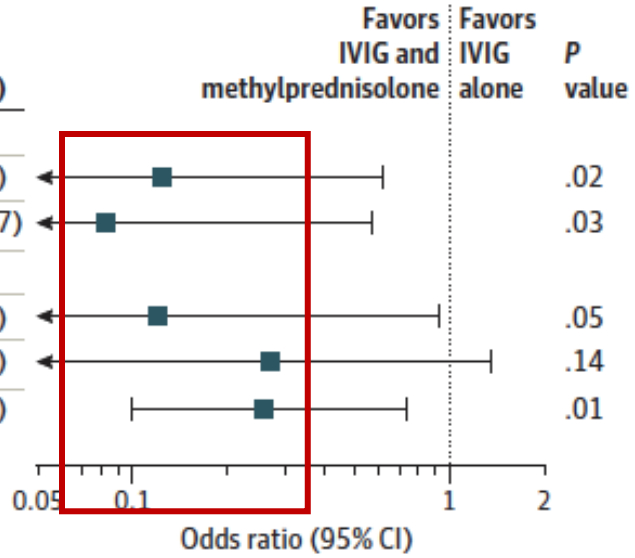
Table 2. Primary and Secondary Analyses in the Propensity Score–Matched Cohorts

Outcomes	After propensity score matching				
	No. (%)		Absolute risk difference between groups (95% CI) [reference: IVIG alone]	Odds ratio (95% CI) [reference: IVIG alone]	*P* value
	IVIG and methylprednisolone (n = 32)	IVIG alone (n = 64)			
Primary outcome					
Treatment failure[a]	3 (9)	24 (38)	−0.28 (−0.48 to −0.08)	0.25 (0.09 to 0.70)	.008
Secondary outcomes					
Second-line treatment[b]	3 (9)	20 (31)	−0.22 (−0.40 to −0.04)	0.19 (0.06 to 0.61)	.004
Hemodynamic support[c,d]	2 (6)	15 (23)	−0.17 (−0.34 to −0.004)	0.21 (0.06 to 0.76)	.01
LVEF <55%[c]	2/12 (17)	14/40 (35)	−0.18 (−0.35 to −0.01)	0.20 (0.06 to 0.66)	.007
Duration of PICU stay, median (IQR), d	4 (2 to 5)	6 (4 to 8.5)	Reduction of days: −2.4 (−4.0 to −0.7)		.005

Analyse en sous groupe

Figure 2. Association Between First-line Therapy Group and Treatment Failure Depending on Age and Acute Left Ventricular Dysfunction

	Risk of treatment failure						
	Before PS weighting, No. of events/patients (%)		After PS weighting, %		Absolute risk difference between groups (95% CI)	Odds ratio (95% CI)	*P* value
	IVIG and methylprednisolone	IVIG alone	IVIG and methylprednisolone	IVIG alone			
Age, y							
<10	2/17 (12)	22/39 (56)	12	52	-0.41 (-0.75 to -0.07)	0.12 (0.02 to 0.62)	.02
≥10	1/17 (6)	15/33 (45)	6	40	-0.34 (-0.66 to -0.03)	0.08 (<0.01 to 0.57)	.03
Ventricular dysfunction							
Absent	1/12 (8)	26/44 (59)	8	45	-0.37 (-0.73 to -0.02)	0.12 (0.01 to 0.93)	.05
Present	2/22 (9)	11/28 (39)	9	28	-0.19 (-0.46 to 0.08)	0.27 (0.04 to 1.35)	.14
All patients	3/34 (9)	37/72 (51)	9	38	-0.27 (-0.49 to -0.05)	0.17 (0.04 to 0.61)	.01



Autres études

Circulation

RESEARCH LETTER

Addition of Corticosteroids to Immunoglobulins Is Associated With Recovery of Cardiac Function in Multi-Inflammatory Syndrome in Children

Rapidité de normalisation fonction cardiaque

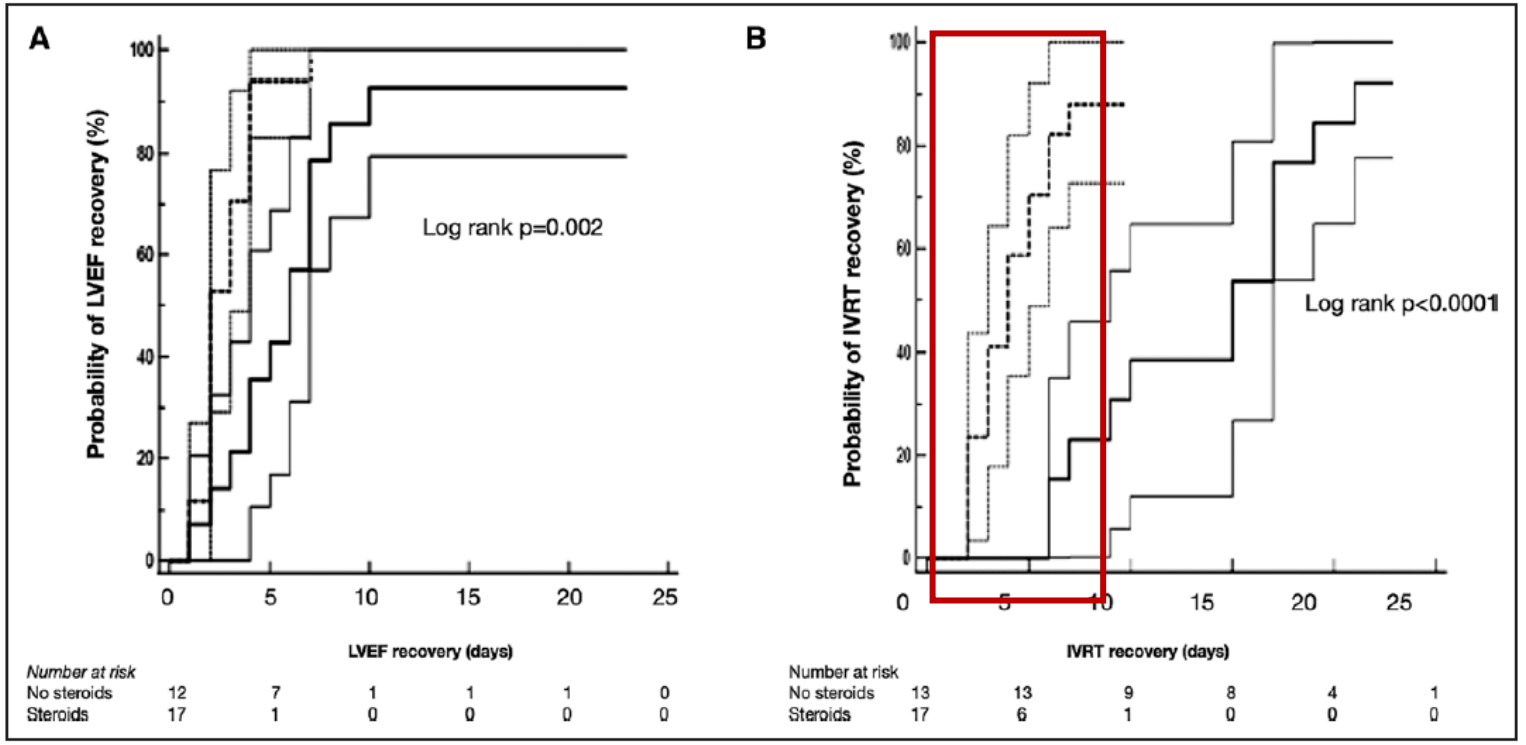


Figure. Kaplan-Meier recovery curves, along with the 95% confidence interval for patients who received intravenous immunoglobulin and steroid treatment (dashed line) versus those who were treated with intravenous immunoglobulin only (full line).
A, LVEF recovery. (Only 29 of 40 patients who had LVEF<55% at admission were included in this analysis.) **B**, IVRT recovery. (IVRT was measured at admission in 30 of 40 patients who all had sequential evaluations.) IVRT indicates isovolumic relaxation time; and LVEF, left ventricular ejection fraction.

Bithérapie fait mieux que monothérapie, mais ce ne sont pas des essais randomisés (possibles biais)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Multisystem Inflammatory Syndrome in Children — Initial Therapy and Outcomes

M.B.F. Son, N. Murray, K. Friedman, C.C. Young, M.M. Newhams, L.R. Feldstein,

CONCLUSIONS

Among children and adolescents with MIS-C, initial treatment with IVIG plus glucocorticoids was associated with a lower risk of new or persistent cardiovascular dysfunction than IVIG alone. (Funded by the Centers for Disease Control and Prevention.)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Treatment of Multisystem Inflammatory Syndrome in Children

A.J. McArdle, O. Vito, H. Patel, E.G. Seaby, P. Shah, C. Wilson, C. Broderick,
R. Niiman, A.H. Tremoulet, D. Munblit, R. Ulloa-Gutierrez, M.I. Carter, T. De.

CONCLUSIONS

We found no evidence that recovery from MIS-C differed after primary treatment with IVIG alone, IVIG plus glucocorticoids, or glucocorticoids alone, although significant differences may emerge as more data accrue. (Funded by the European Union's Horizon 2020 Program and others; BATS ISRCTN number, ISRCTN69546370.)

Physiopathologie du PIMS?

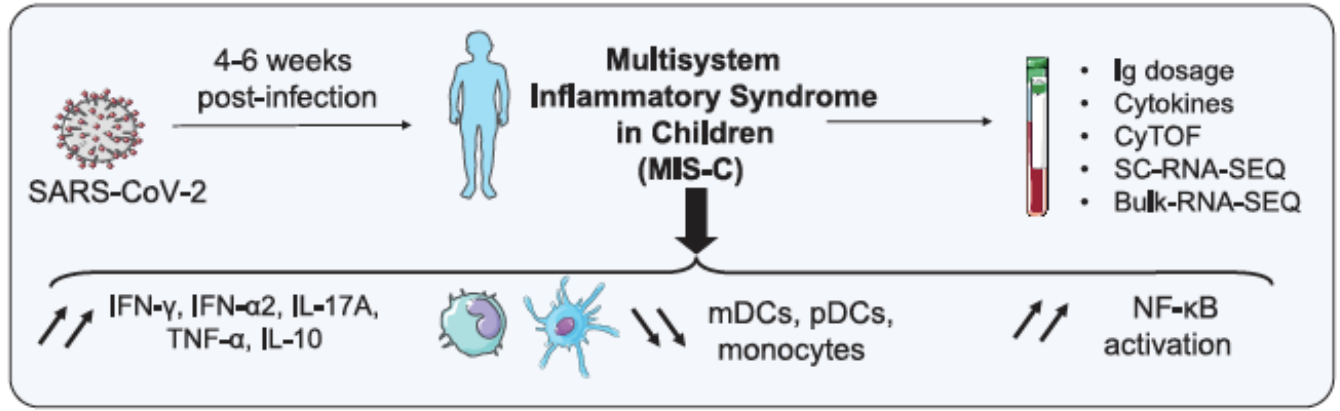
- **Dérégulation immunitaire**

Med

CellPress

Clinical and Translational Article

A monocyte/dendritic cell molecular signature of SARS-CoV-2-related multisystem inflammatory syndrome in children with severe myocarditis

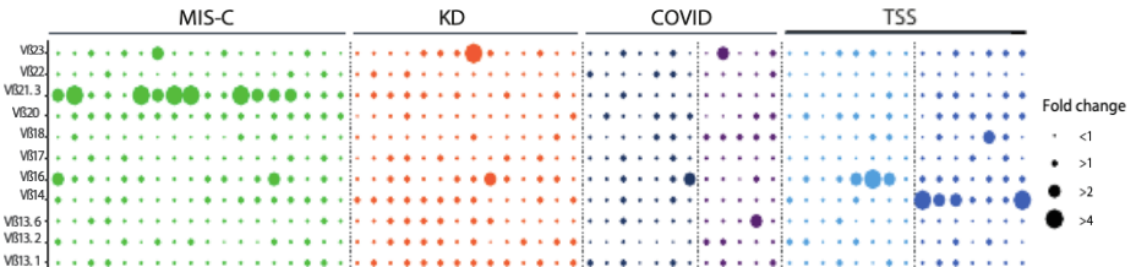


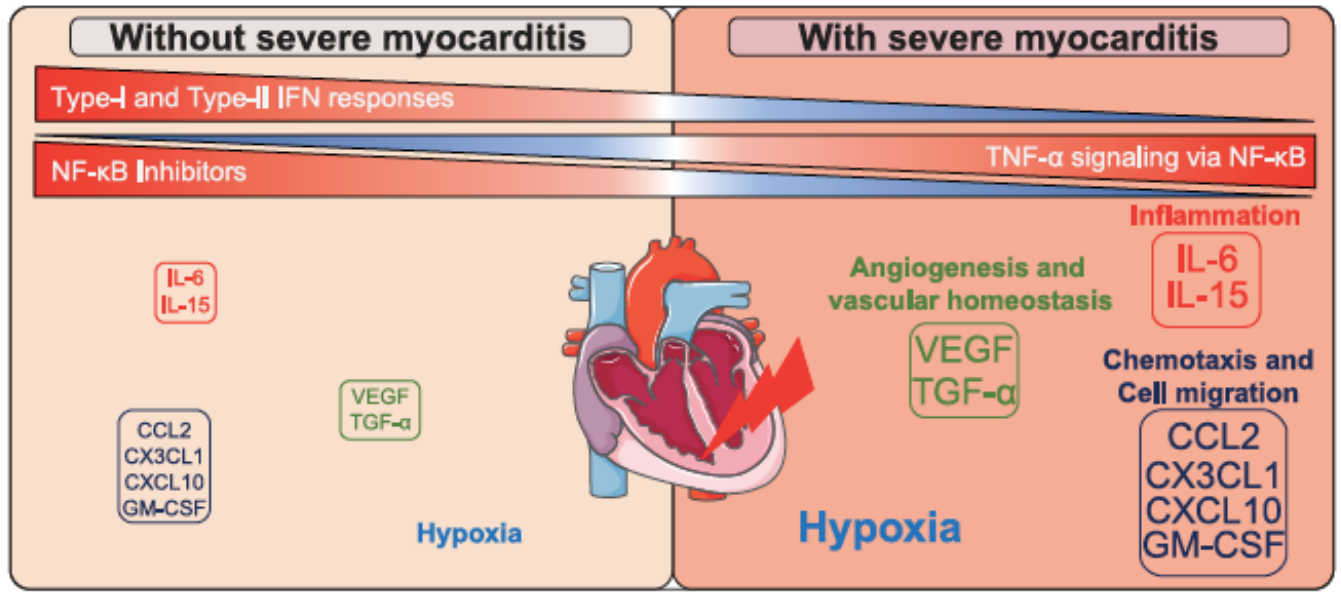
- **Répertoire Vbeta non dirigé contre antigènes SARS-CoV2**

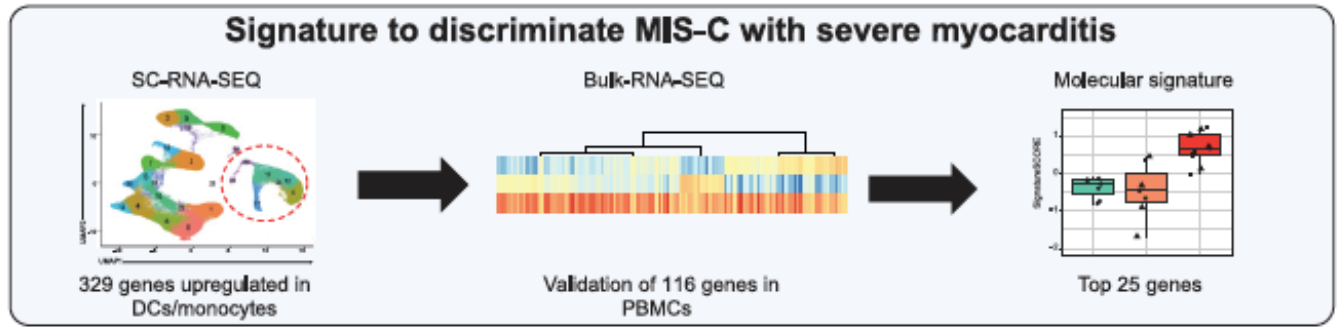
SCIENCE IMMUNOLOGY | RESEARCH ARTICLE

CORONAVIRUS

Polyclonal expansion of TCR Vβ 21.3$^+$ CD4$^+$ and CD8$^+$ T cells is a hallmark of multisystem inflammatory syndrome in children







Conclusion

- **Association between COVID-19 and these Kawasaki-like syndromes**
  - 2 weeks after adults peaks COVID-19
  - Cases : 4-6 weeks after mild COVID-19 symptoms or contact with SARS-CoV-2

Lessons from FHU teams experiences

- *The name (Kawa, PIMS, MIC…) is not important, the child health is important!*
- **Recognize quickly+++** *(do not wait for 5 days of fever!)*
  - Some have « incomplete forms » of KD
  - Gastro-intestinal symptoms can be inaugural
  - Troponin, BNP + call the cardiologist : systematic!

- **Treat well …**
  - … But do not miss another diagnosis.. **severe bacterial infection (e.g. meningo)**!

Definitions ?

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

World Health Organization[8]	Royal College of Paediatrics and Child Health (United Kingdom)[7]	Centers for Disease Control and Prevention (United States)[9]
Children and adolescents 0-19 y of age with fever >3 d AND 2 of the following: 1. Rash or bilateral nonpurulent conjunctivitis or mucocutaneous inflammation signs (oral, hands, or feet) 2. Hypotension or shock 3. Features of myocardial dysfunction, pericarditis, valvulitis, or coronary abnormalities (including ECHO findings or elevated troponin/NT-proBNP) 4. Evidence of coagulopathy (by PT, APTT, elevated D-dimers) 5. Acute gastrointestinal problems (diarrhea, vomiting, or abdominal pain) AND Elevated markers of inflammation such as ESR, CRP, or procalcitonin. AND No other obvious microbial cause of inflammation, including bacterial sepsis, staphylococcal or streptococcal shock syndromes. AND Evidence of COVID-19 (RT-PCR, antigen test, or serology positive), or likely contact with patients with COVID-19 Consider this syndrome in children with features of typical or atypical Kawasaki disease or toxic shock syndrome	A child presenting with persistent fever, inflammation (neutrophilia, elevated CRP, and lymphopenia) and evidence of single or multiorgan dysfunction (shock, cardiac, respiratory, kidney, gastrointestinal, or neurological disorder) with additional features (see listed in eAppendix in Supplement 2). This may include children fulfilling full or partial criteria for Kawasaki disease[a] Exclusion of any other microbial cause, including bacterial sepsis, staphylococcal or streptococcal shock syndromes, infections associated with myocarditis such as enterovirus (waiting for results of these investigations should not delay seeking expert advice) SARS-CoV-2 PCR test results may be positive or negative	An individual aged <21 y presenting with fever, laboratory evidence of inflammation, and evidence of clinically severe illness requiring hospitalization, with multisystem (>2) organ involvement (cardiac, kidney, respiratory, hematologic, gastrointestinal, dermatologic, or neurological) Fever >38.0 °C for ≥24 h or report of subjective fever lasting ≥24 h Laboratory evidence including, but not limited to, ≥1 of the following: an elevated CRP level, ESR, fibrinogen, procalcitonin, D-dimer, ferritin, lactic acid dehydrogenase, or IL-6; elevated neutrophils; reduced lymphocytes; and low albumin AND No alternative plausible diagnoses AND Positive for current or recent SARS-CoV-2 infection by RT-PCR, serology, or antigen test; or COVID-19 exposure within the 4 wk prior to the onset of symptoms Additional comments Some individuals may fulfill full or partial criteria for Kawasaki disease but should be reported if they meet the case definition for MIS-C Consider MIS-C in any pediatric death with evidence of SARS-CoV-2 infection

Whittaker, JAMA 2020