Diagnosis and management of MIS-C

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OVERVIEW

- Acute coronavirus disease appears mild in children.
- **MIS-C** is **new serious emerging** disease in children/SARS-CoV-2
- First reports: RCPCH in April, 2020 www.thelancet.com Vol 395 May 23, 2020
- PIMS-TS, Post COVID-19, Kawasaki-like, TSS like, **MIS-C**
- **Incidence : 316/1.000.000** SARS-CoV-2 infections < 21 years

Last updated with cases reported to CDC on or before November 1, 2021*

TOTAL MIS-C PATIENTS MEETING CASE DEFINITION*	TOTAL MIS-C DEATHS MEETING CASE DEFINITION
5,526	48

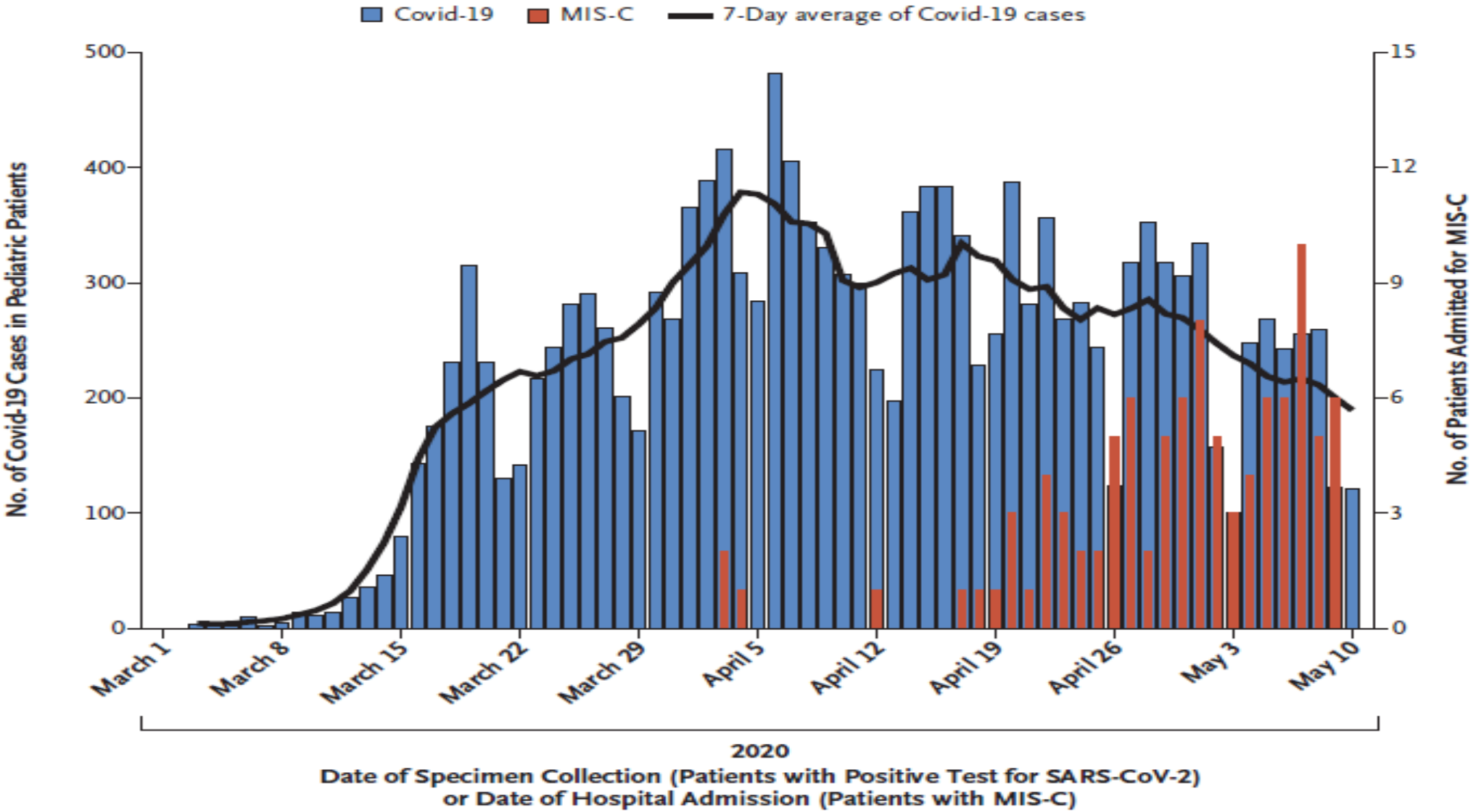
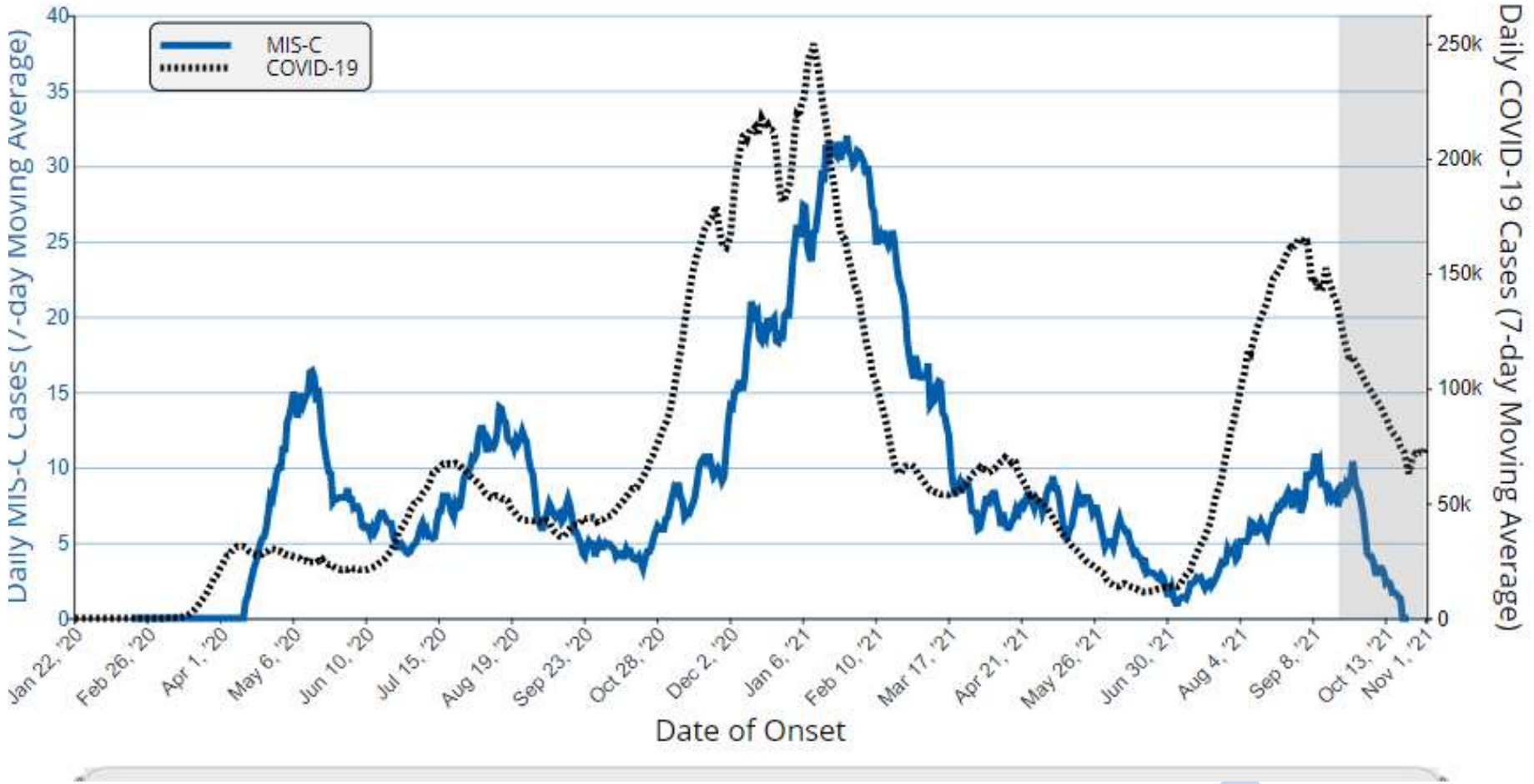


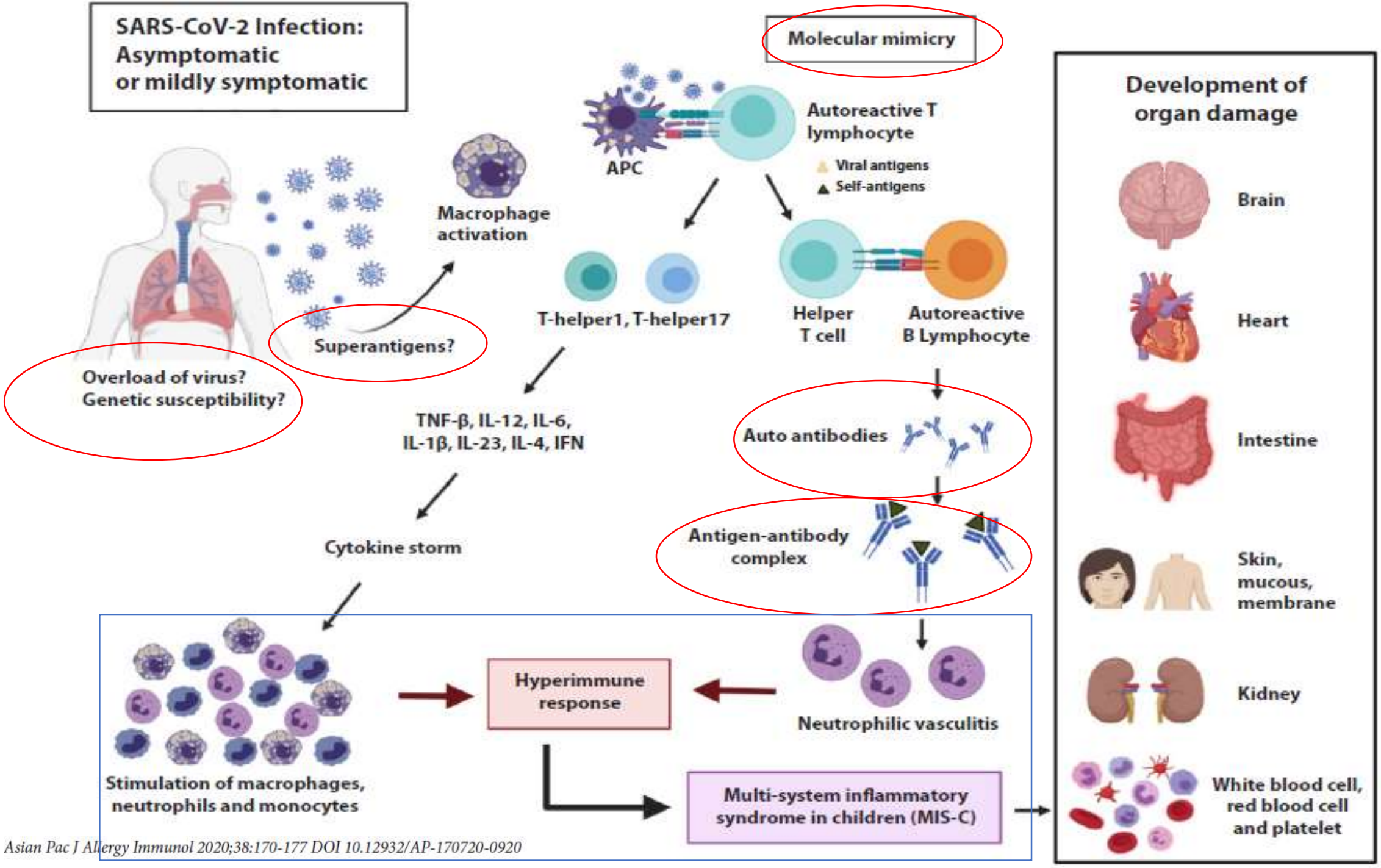
Figure 2. Pediatric Cases of Coronavirus Disease 2019 (Covid-19) and of MIS-C.

Daily MIS-C Cases and COVID-19 Cases Reported to CDC (7-Day Moving Average)



Hypothetical Pathogenesis

- **Immune dysregulation**.
- **Trigger** macrophage activation and cytokine release syndrome.
- Hypothesis :
  - Genetic susceptibility?
  - Superantigens
  - Overload of virus?
  - Molecular mimicry : host antigen?
  - Antigen- antibody complexes?



Asian Pac J Allergy Immunol 2020;38:170-177 DOI 10.12932/AP-170720-0920

Understanding SARS-CoV-2-related multisystem inflammatory syndrome in children

Anne H. Rowley[1,2,3]

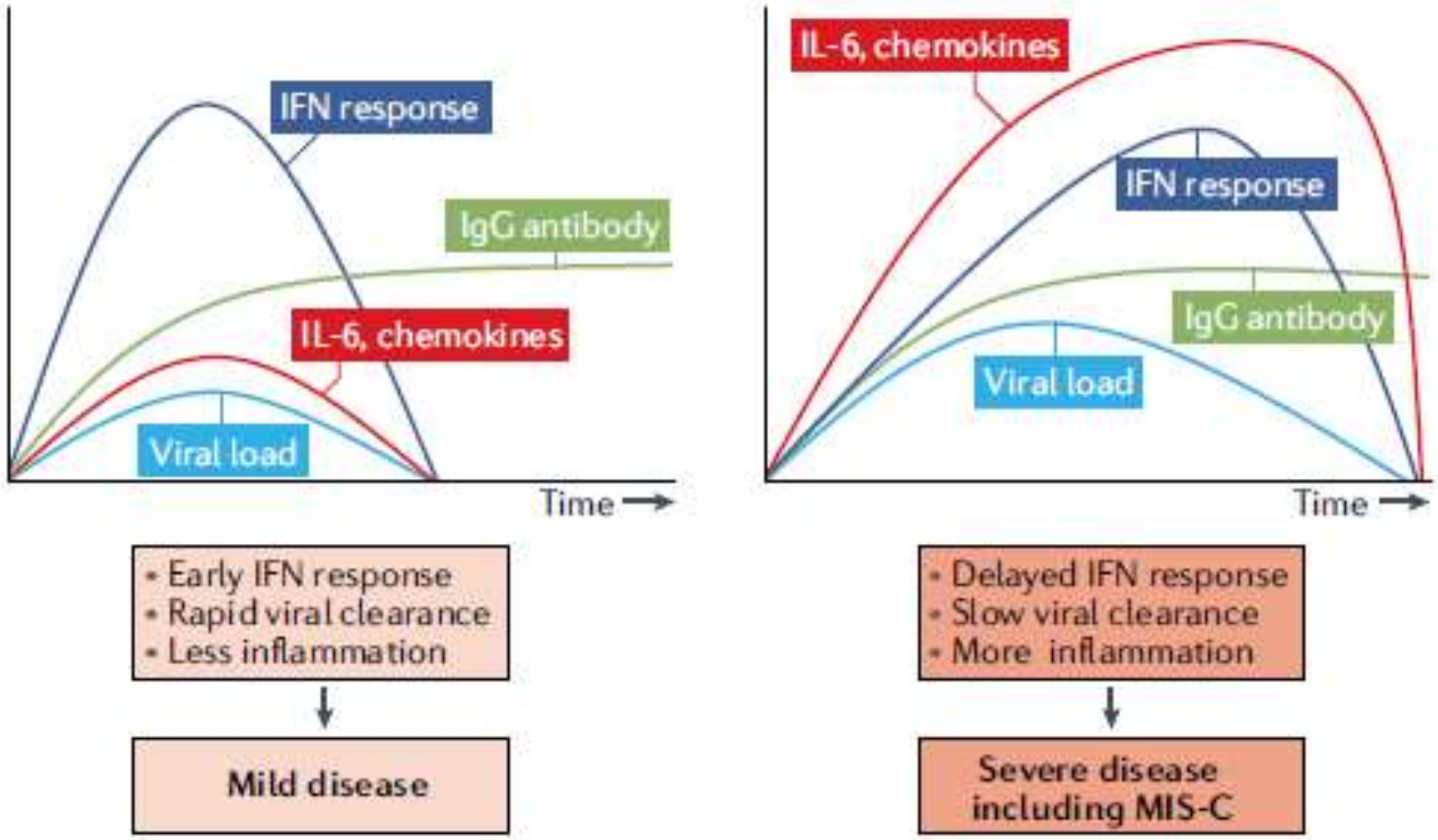


Fig. 1 | **Pathogenesis of multisystem inflammatory syndrome in children: a hypothesis.**

Nat Rev Immunol. 2020 Aug;20(8):453-454.

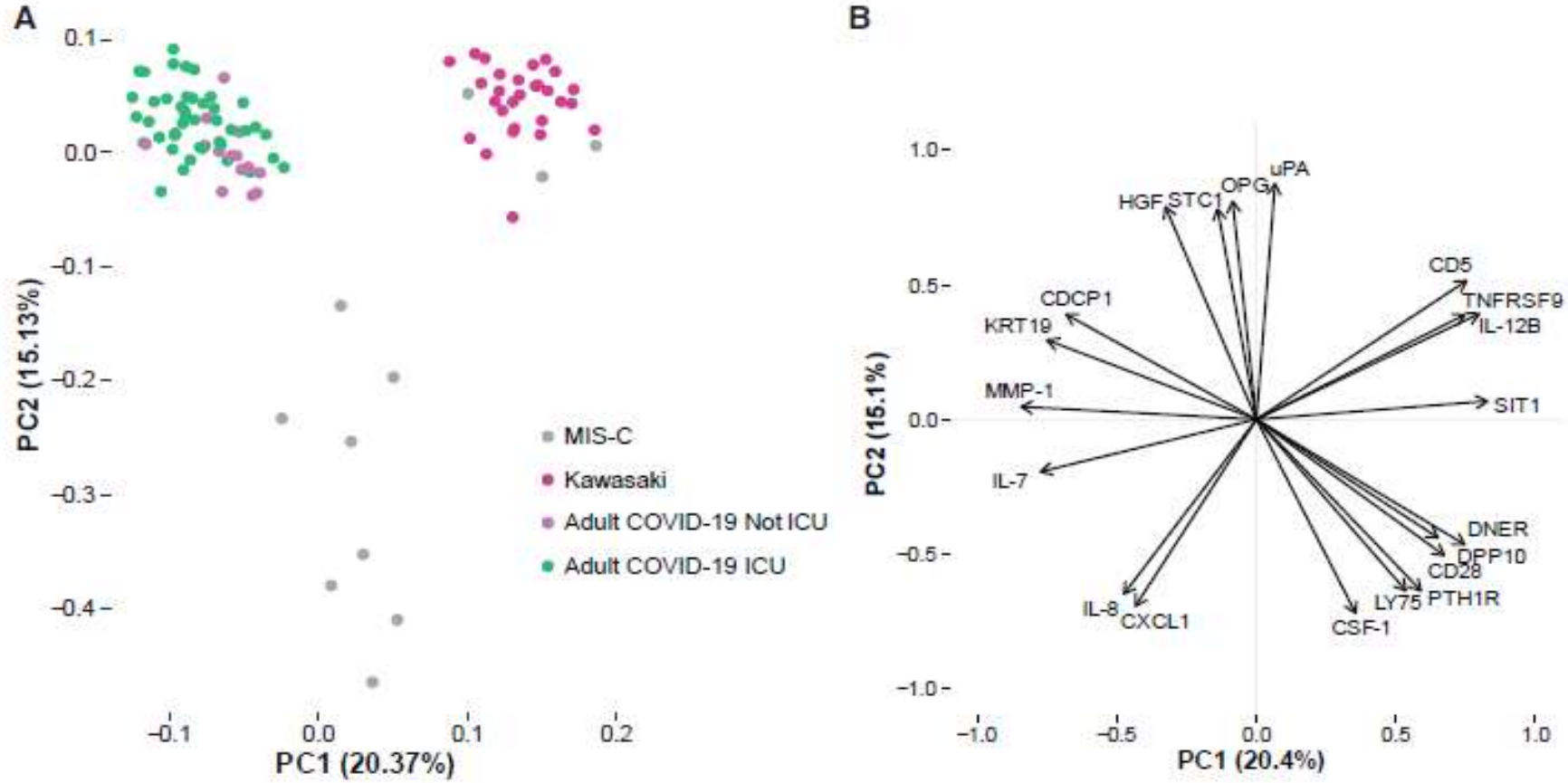


Figure 2. MIS-C Hyperinflammation Differs from Severe Acute COVID-19 Hyperinflammation

(A) Principal components 1 and 2 show variation in cytokine profiles among adult COVID-19 patients with severe disease treated in intensive care units (ICU) or not, and children with MIS-C or Kawasaki disease. n = 97 samples included, and 112 unique proteins included in the analysis.

(B) Top 20 proteins mostly contributing to the PCs 1–2.

See also Table S1.

Diagnosis
= case
definition

Table 1. Case Definitions of MIS-C.

Criteria	RCPCH[9] PIMS-TS	CDC[10] MIS-C	WHO[8] MIS-C
Age	All children (age not defined)	<21 years	0-19 years
Fever	Persistent fever ≥38.5°C	≥38.0°C for ≥24 hrs OR Subjective fever ≥24 hrs	Fever ≥3 days
Clinical Symptoms	1) Single or multi-organ dysfunction AND 2) Additional features*	1) Severe illness (hospitalized) AND 2) ≥2 organ systems involved	Two of the following: 1) Rash, conjunctivitis, mucocutaneous inflammation 2) Hypotension or shock 3) Cardiac involvement** 4) Coagulopathy 5) Acute GI symptoms
Inflammation	1) Neutrophilia 2) ↑CRP AND 3) Lymphopenia	Laboratory evidence of inflammation not limited to 1 or more of the following: 1) ↑CRP 2) ↑ESR 3) ↑Fibrinogen 4) ↑Procalcitonin 5) ↑D-dimer	Elevated inflammatory markers such as: 1) ↑ESR 2) ↑CRP 3) ↑Procalcitonin

		6) †Ferritin 7) †LDH 8) †IL-6 9) Neutrophilia 10) Lymphopenia 11) Hypoalbuminemia	
Link to SARS-CoV-2	PCR + or -	Current or recent: 1) +PCR 2) +Serology 3) +Antigen test OR 4) COVID-19 exposure within prior 4 weeks	Evidence of COVID-19: 1) +PCR 2) +Antigen test 3) +Serology OR 4) Likely COVID-19 contact
Exclusion	Exclusion of other infections	No alternative diagnosis	No obvious microbial cause

Adapted from[8-10]

WHO 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.

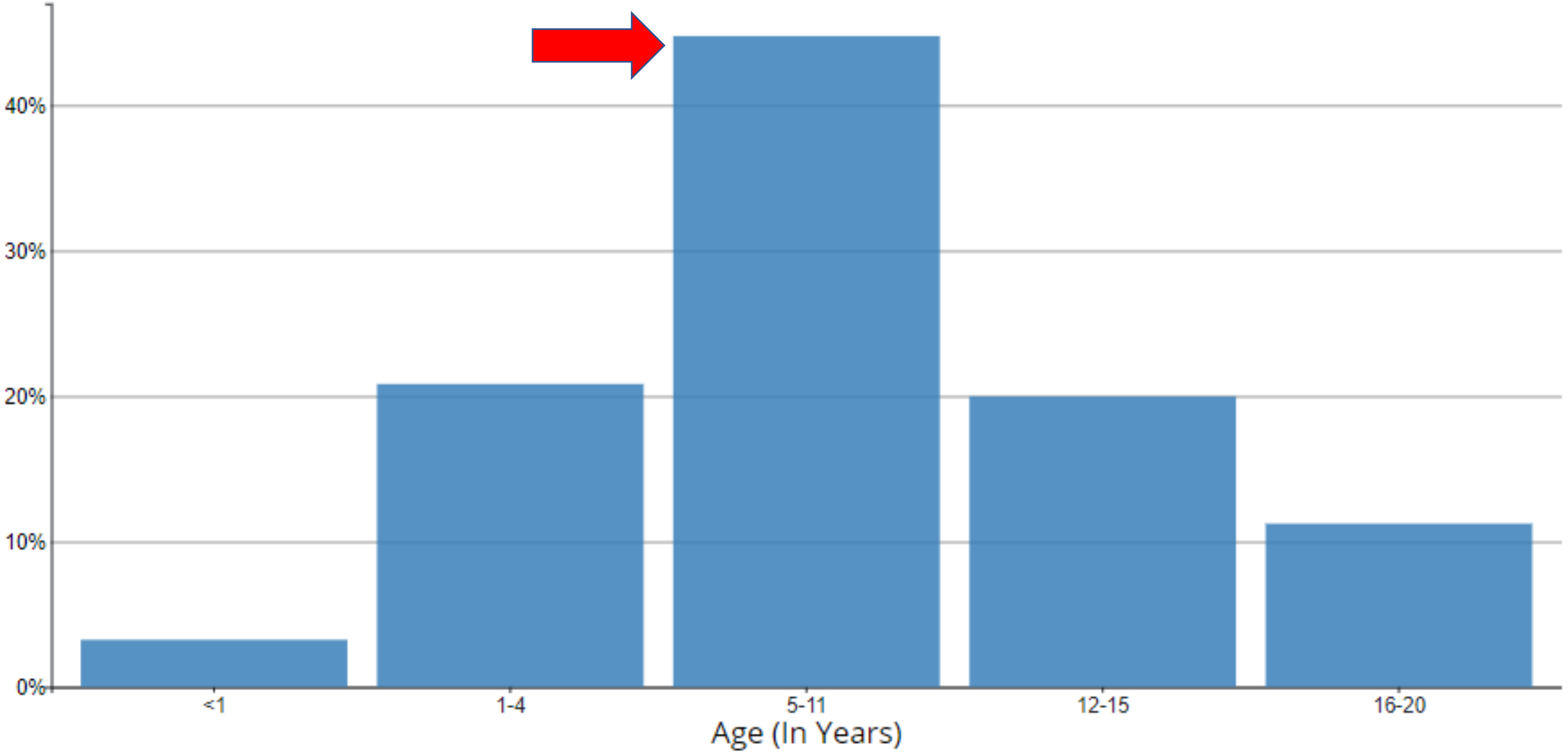
AND

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.

MIS-C Patients By Age Group



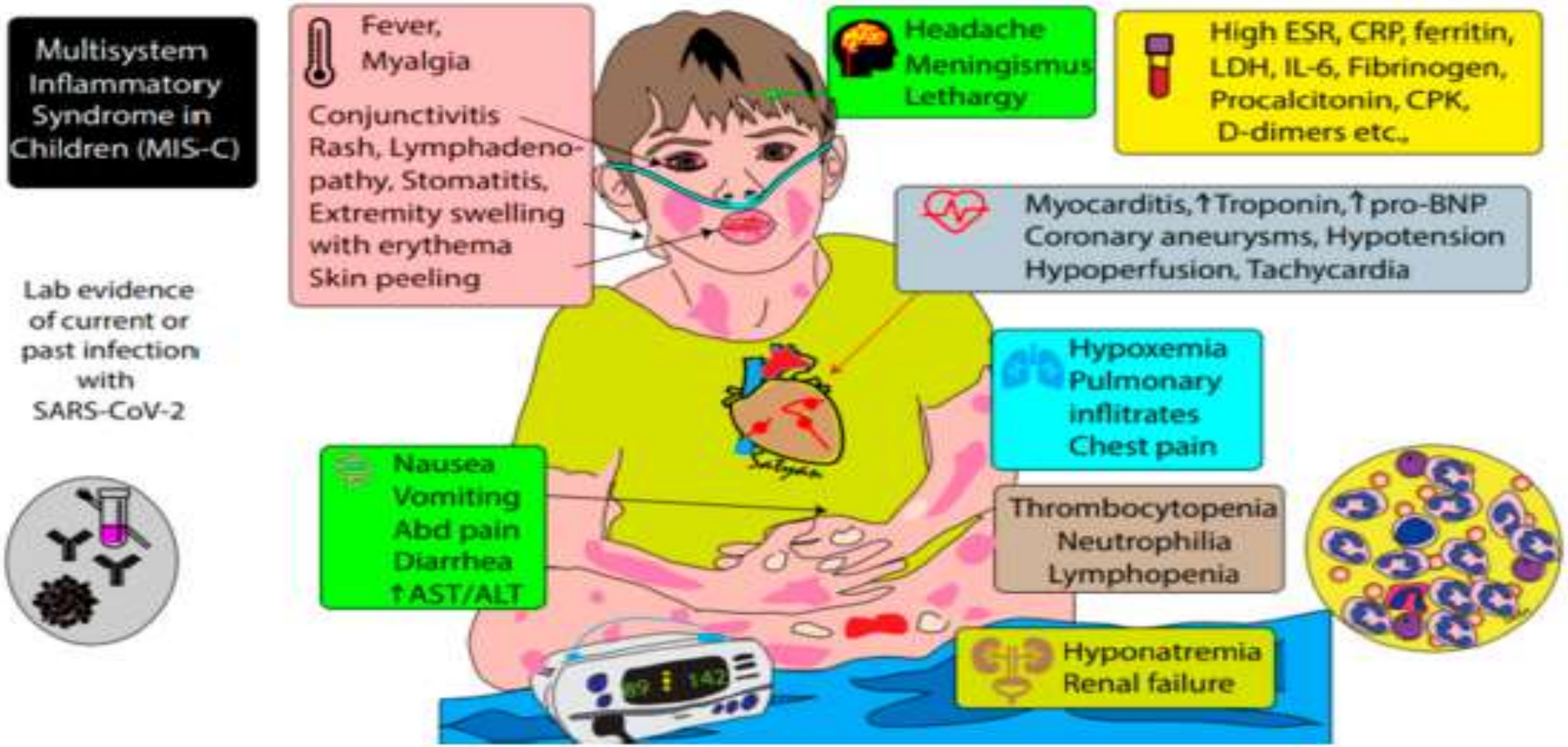


Figure 1. Infographic showing CDC criteria for the diagnosis of MIS-C. A combination of fever, evidence of inflammation, involvement of at least two organ systems, and prior evidence of SARS-CoV-2 infection are required to establish the diagnosis.


children

MDPI

Review

Multi-System Inflammatory Syndrome in Children (MIS-C) Following SARS-CoV-2 Infection: Review of Clinical Presentation, Hypothetical Pathogenesis, and Proposed Management

Natasha A. Nakra [1,*], Dean A. Blumberg [1], Angel Herrera-Guerra [2] and Satyan Lakshminrusimha [3,*]

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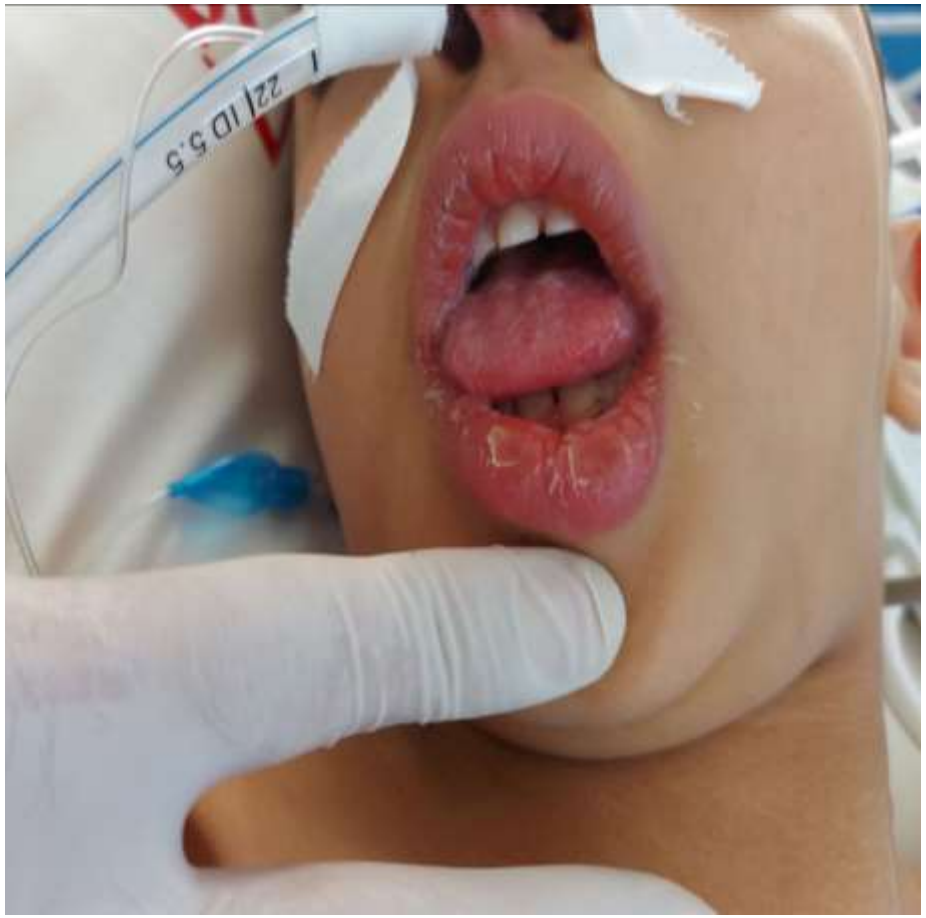
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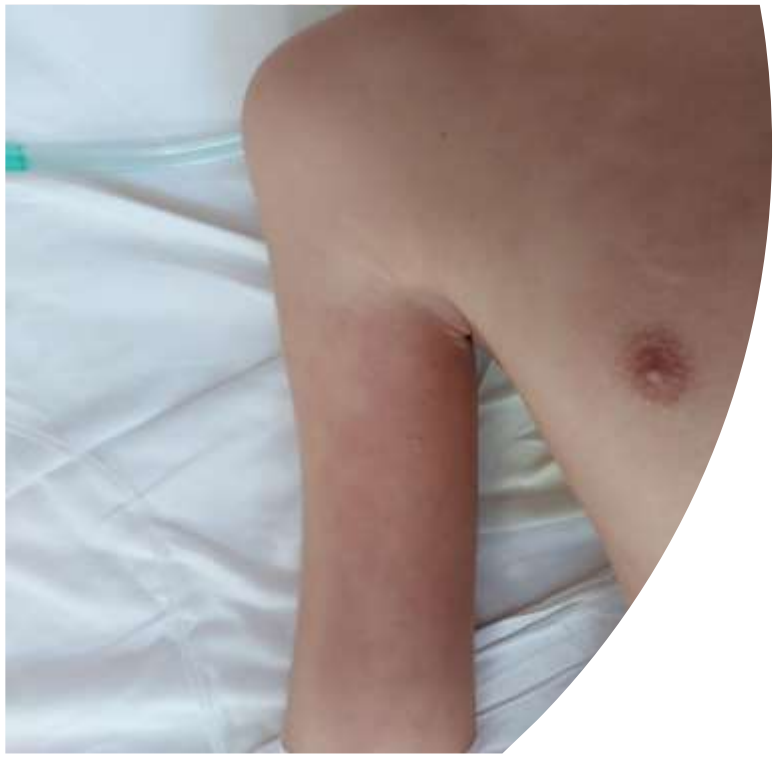

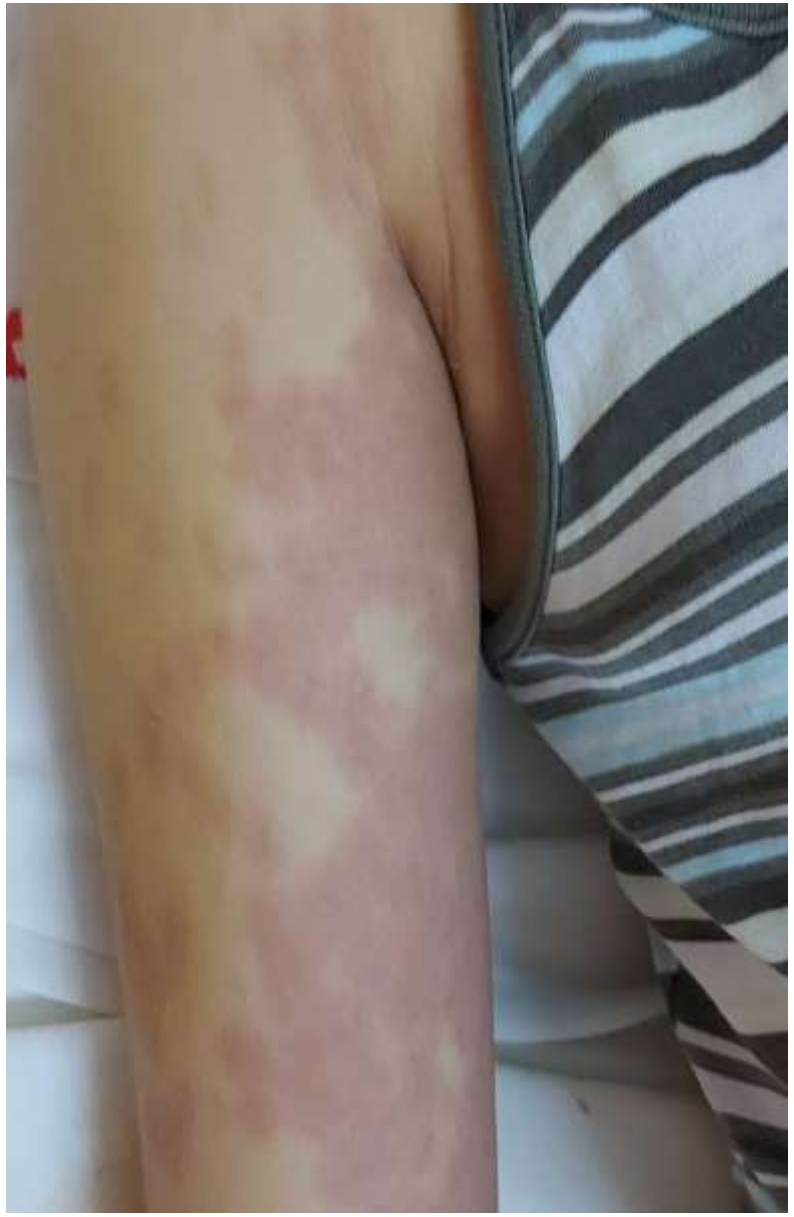

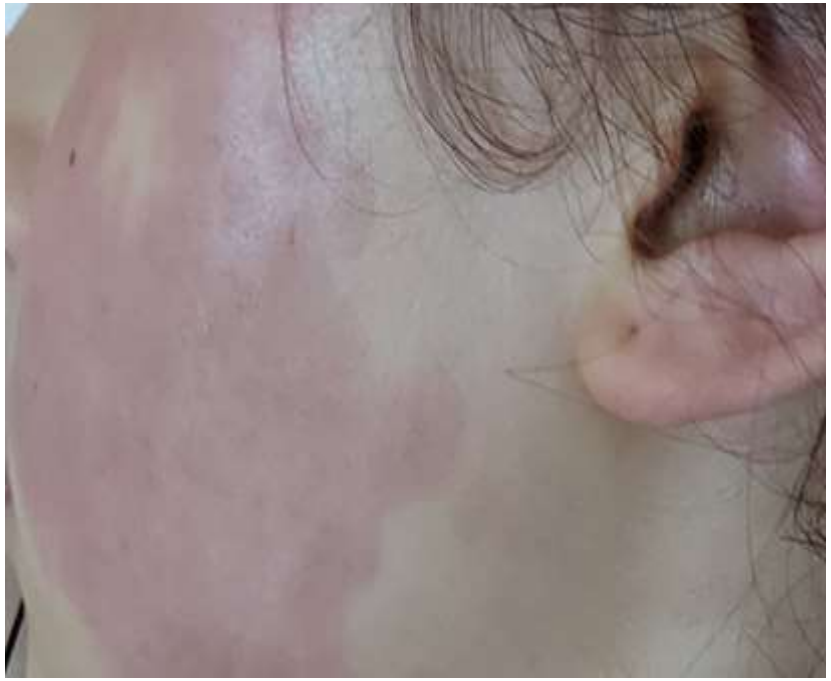

Presenting phenotype :

- 1.**Shock like presentation : signs of shock.**
- 2.Kawasaki disease-like presentation with cardiac involvement.
- 3.Undefined inflammatory presentation : persistant pyrexia with signes of MIS-C but not meeting shock criteria nor having cardiac involvement.

Mediterranean Journal of Hematology and Infectious Diseases

Original Article

First Tunisian Cluster Admissions of Critically Ill Patients with Multisystem Inflammatory Syndrome in Children (MIS-C)

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Pediatric intensive care unit, Children's Hospital Béchir Hamza of Tunis - Faculty of Medicine of Tunis-University of Tunis of EL-Manar. Tunis.

Competing interests: The authors declare no conflict of Interest.

Abstract. *Background:* **Multisystem inflammatory syndrome in children (MIS-C) is a new emerging severe disease that is temporally related to previous exposure to coronavirus infection disease (COVID-19).**
Aim: **To describe the clinical features, laboratory findings, therapies, and outcomes for the first Tunisian cluster admissions of critically ill children with severe MIS-C.**
Methods: **Retrospective study conducted from November 01 to November 30, 2020**
According to the WHO definition case, we included eight children aged less than 15 years who were admitted to our pediatric intensive care and met MIS-C criteria. We reviewed all patients' medical records to collect demographic and clinical data, severity scores, laboratory test results, echocardiographic findings, treatment, and outcomes.
Results: **The median age was 8 years (IQR: 4-10years). All children were previously fit and well. Seven patients were boys. Known exposure to COVID-19 was reported in 4 cases. Fever and gastrointestinal symptoms were reported in all cases. Five patients had marked abdominal pain and were examined by the surgeon for possible appendicitis. Seven patients had diarrhea. On examination, we found rash (n=7), conjunctivitis (n=7), cheilitis (n=5), and meningism (n=3). We reported cardiac dysfunction in 7 cases and shock with hypotension in 3 cases. All patients received immunoglobulins, methylprednisolone, and a low dose of aspirin. No deaths occurred.**
Conclusion: **We reported here the first Tunisian cluster admissions of 8 critically ill children with MIS-C to highlight the increase of a new severe emerging disease with evidence of prior COVID-19 infection in older children.**

Study period	Nov 2020 – nov 2021
N=	15
Sex-ratio	2 (10 male)
Median age (y)	9 (IQR: 5-10)
Underling conditions:	4 (2 overweight)
Median delay onset illness/ PICU admission (d)	6 (IQR: 5-7)
Clinical features :	
Fever	15
Gastrointestinal	15
Cardiovascular	15 (LV dysfunction (n =13) ,vasoplegic shock(n=2))
Respiratory	10
Dermatologic	15 (rash (n=13), conjunctivitis (n=13), cheilitis n=12))
Neurologic	4 (reduced level of consciousness)

Abnormal laboratory findings	values
Mean CRP (SD)	270 ±92
Mean lymphocyte (SD)	912 ± 447
Mean fibrinogen (SD)	4.7 ± 1.3
Mean Ddimers (SD)	5958± 5379
Median Toponin (IQR)	339 (36-879)
Median Pro-BNP (IQR)	9199 (28825-25000)
Renal failure	5
Liver failure	3
Median FEVG (IQR)	42 (33-50)
Management	
MV OFJ Dobutamine Milrinone Levosimendan Norepinephrine Ig+ steroids	4 11 15 3 1 3 15
Deaths	1

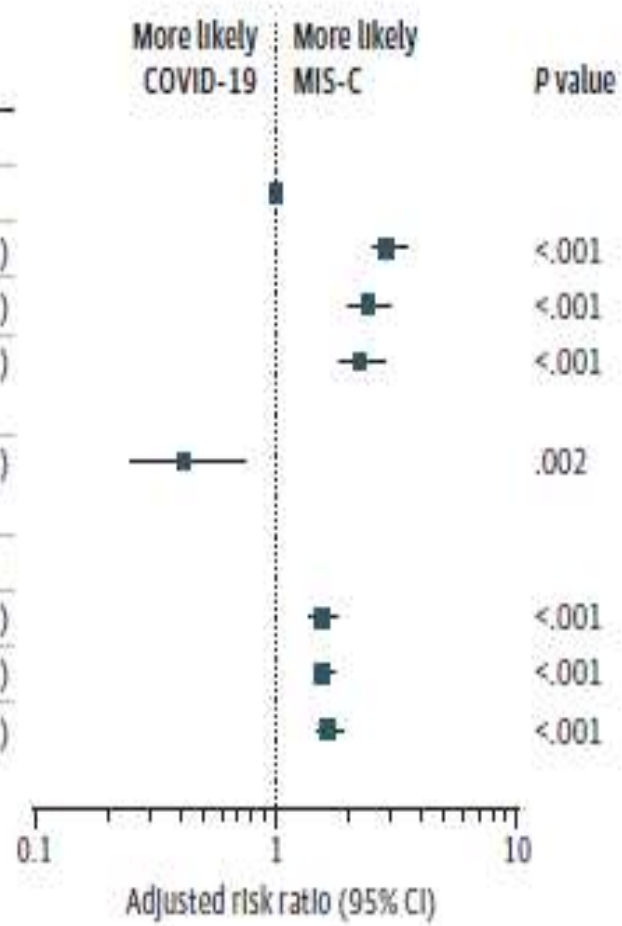
MIS-C versus severe acute COVID-19?

JAMA | Original Investigation

Characteristics and Outcomes of US Children and Adolescents With Multisystem Inflammatory Syndrome in Children (MIS-C) Compared With Severe Acute COVID-19

B Comparison of clinical phenotypes and laboratory values[a]

	No./total No. (%)				
	MIS-C (n = 539)	Severe acute COVID-19 (n = 577)	Absolute risk difference, % (95% CI)[b]	Adjusted risk ratio (95% CI)[c]	P value
Clinical group by complication					
Respiratory without cardiovascular	130/539 (24.1)	408/577 (70.7)	-46.6 (-51.8 to -41.4)	1 [Reference]	
Cardiorespiratory	302/539 (56.0)	51/577 (8.8)	47.2 (42.4 to 52.0)	2.99 (2.55 to 3.50)	<.001
Cardiovascular without respiratory	57/539 (10.6)	17/577 (2.9)	7.7 (4.7 to 10.6)	2.49 (2.05 to 3.02)	<.001
Mucocutaneous without respiratory or cardiovascular	38/539 (7.1)	13/577 (2.3)	4.8 (2.3 to 7.3)	2.29 (1.84 to 2.85)	<.001
Other without respiratory, cardiovascular, or mucocutaneous	12/539 (2.2)	88/577 (15.3)	-13.1 (-16.2 to -9.8)	0.43 (0.25 to 0.74)	.002
Laboratory value within first 48 h					
Neutrophil to lymphocyte ratio >5	321/515 (62.3)	154/464 (33.2)	29.1 (23.2 to 35.1)	1.59 (1.40 to 1.80)	<.001
Platelets <150 × 10^3/μL	212/523 (40.5)	84/486 (17.3)	23.2 (17.9 to 28.6)	1.58 (1.43 to 1.75)	<.001
C-reactive protein level >100 mg/L	325/491 (66.2)	67/285 (23.5)	42.7 (36.2 to 49.1)	1.70 (1.51 to 1.92)	<.001



Differential diagnoses :

- **Septic shock**
- **Toxic shock syndrome (TSS)**
- **Staphylococcal scaled skin syndrome (SSSS)**
- **Kawasaki disease (KD)**
- **Viral myocarditis (enterovirus, adenovirus)**
- **Acute appendicitis : acute surgical abdomen**

Management

RECOMMANDATIONS

RCPCH
Royal College of Paediatrics and Child Health
Leading the way in Children's Health

Guidance: Paediatric multisystem inflammatory syndrome temporally associated with COVID-19

OPEN

Caring for Critically Ill Children With Suspected or Proven Coronavirus Disease 2019 Infection: Recommendations by the Scientific Sections' Collaborative of the European Society of Pediatric and Neonatal Intensive Care*

frontiers in Pediatrics

REVIEW
published: 26 May 2021
doi: 10.3389/fped.2021.667507

OPEN ACCESS

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Best Practice Recommendations for the Diagnosis and Management of Children With Pediatric Inflammatory Multisystem Syndrome Temporally Associated With SARS-CoV-2 (PIMS-TS; Multisystem Inflammatory Syndrome in Children, MIS-C) in Switzerland

Arthritis & Rheumatology
Vol. 73, No. 4, April 2021, pp e13–e29
DOI 10.1002/art.41616

AMERICAN COLLEGE of RHEUMATOLOGY
Empowering Rheumatology Professionals

American College of Rheumatology Clinical Guidance for Multisystem Inflammatory Syndrome in Children Associated With SARS–CoV-2 and Hyperinflammation in Pediatric COVID-19: Version 2

Lauren A. Henderson,[1] Scott W. Canna,[2] Kevin G. Friedman,[1] Mark Gorelik,[3] Sivia K. Lapidus,[4] Hamid Bassiri,[5] Edward M. Behrens,[5] Anne Ferris,[6] Kate F. Kernan,[7] Grant S. Schulert,[8] Philip Seo,[9] Mary Beth F. Son,[1] Adriana H. Tremoulet,[10] Rae S. M. Yeung,[11] Amy S. Mudano,[12] Amy S. Turner,[13] David R. Karp,[14] and Jay J. Mehta[5]

Immunomodulory treatment:

Société tunisienne de pédiatrie –INEAS-2021

7.4.1 *Traitement immunomodulateur :*

1. Les immunoglobulines par voie intra veineuse (IGIV) :

- Les IGIV constituent la pierre angulaire du traitement.
- ***Dose :*** 2 grammes/kg sur 1 ou 2 jours (à passer sur 12heures). En cas d'obésité, faire le calcul de la dose selon le poids idéal sans dépasser 60g.
- En cas de défaillance cardiaque, passer lentement les IGIV en associant des diurétiques pour prévenir le risque de surcharge pulmonaire.

2. les corticoïdes :

Méthylprédnisolone

Forme modérée :

Dose : 2 mg/Kg IV en 2 prises jusqu'à apyrexie stable pendant 48 heures puis passage à la voie orale.

Diminution progressive par paliers.

Durée totale : 15 à 21 jours

Forme sévère avec choc ou défaillance d'organes mettant en jeu le pronostic vital :

Dose : 10 mg/Kg/j pendant 03jours puis 2 mg/Kg/j IV en2 prises jusqu'à apyrexie stable pendant 48 heures puis passage à la voie orale.

Diminution progressive par paliers.
Durée totale : 3 semaines à 1mois

Société tunisienne de pédiatrie –INEAS-2021

Anti platelet and anticoagulation therapy

Société tunisienne de pédiatrie –INEAS-2021

7.4.2 Traitement anti - agrégant plaquettaire : Aspirine :

- **Dose** : 3 à 5 mg/Kg/j (dose maximale : 100 mg/j)
- **Durée** 4 semaines si pas d'atteinte coronarienne
- **Contre-indications** : thrombopénie < 50 000 ou saignement actif

74.3 Traitement anticoagulant [42] :

Il sera discuté au cas par cas.

L'héparine de bas poids moléculaire (HBPM) (voir page 22) sera utilisée

Les principales indications sont :

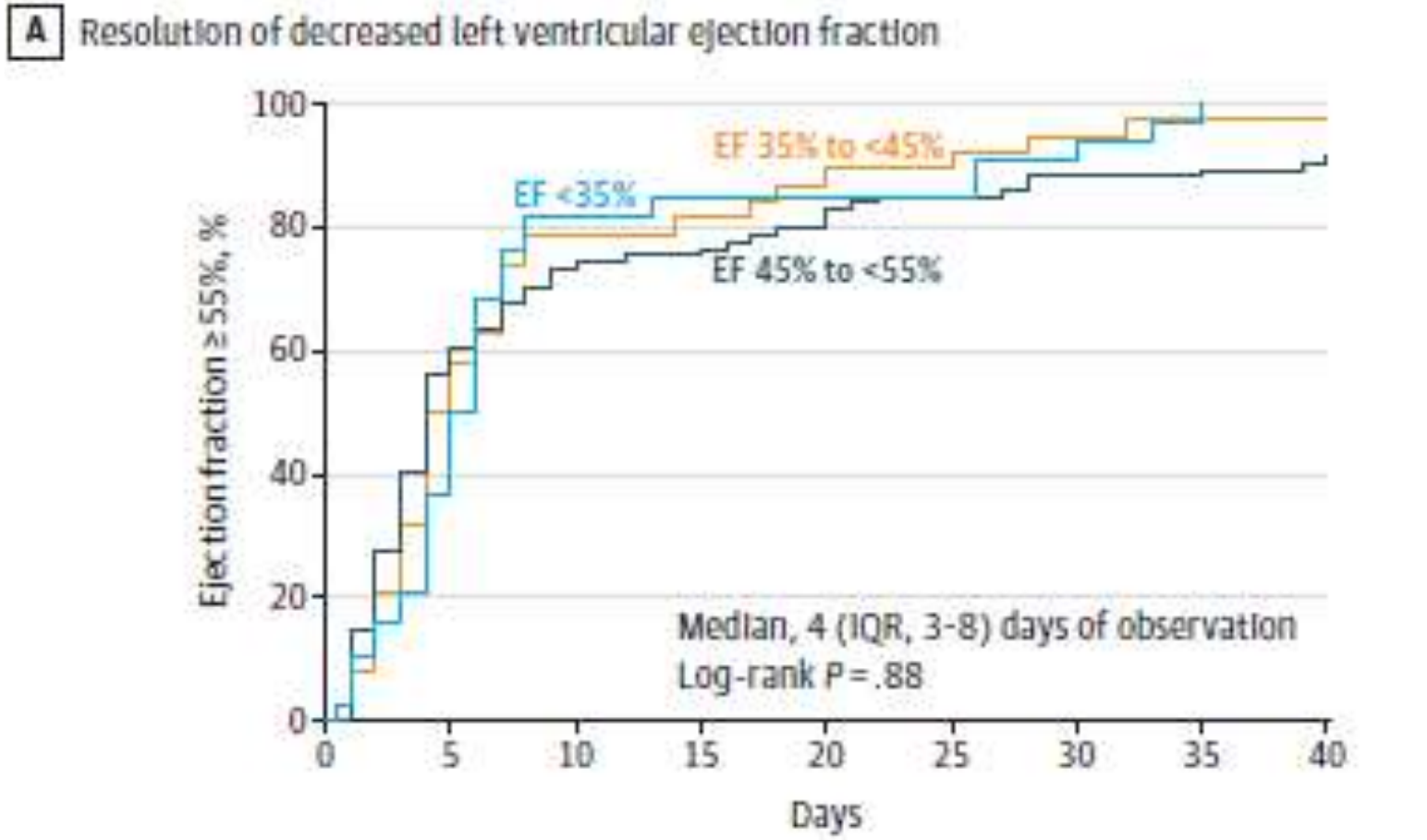
1. Terrain d'hypercoagulabilité (Mucoviscidose, MICI, Cancer, Drépanocytose, Lupus, AJI, Syndrome néphrotique)
2. Obésité
3. FEVG < 35 %
4. Dilatation ou anévrysme coronarien (Z score supérieure à 10)
5. Enfant pubère
6. D-Dimères ≥ 5fois les normales, associées à un autre facteur d'hypercoagulabilité.

IL1 or IL6 receptor antagonists

OUTCOMES

Mortality 1-2%

Figure 4. Cardiovascular Outcomes of Patients With MIS-C[a]



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Characteristics and Outcomes of US Children and Adolescents With Multisystem Inflammatory Syndrome in Children (MIS-C) Compared With Severe Acute COVID-19

Conclusion:

- MIS-C **a rare and serious** complication /SARS-CoV-2.
- **Clinical presentation:**
  - **-fever**
  - **-mutlisystem organ involvement (≥2)**
  - **-laboratory evidence of inflammation**
- Management : **multidisciplinary approach**
- **Good prognosis.**
- Close **follow-up with a pediatric cardiologist.**