Multisystem Inflammatory Syndrome in Children

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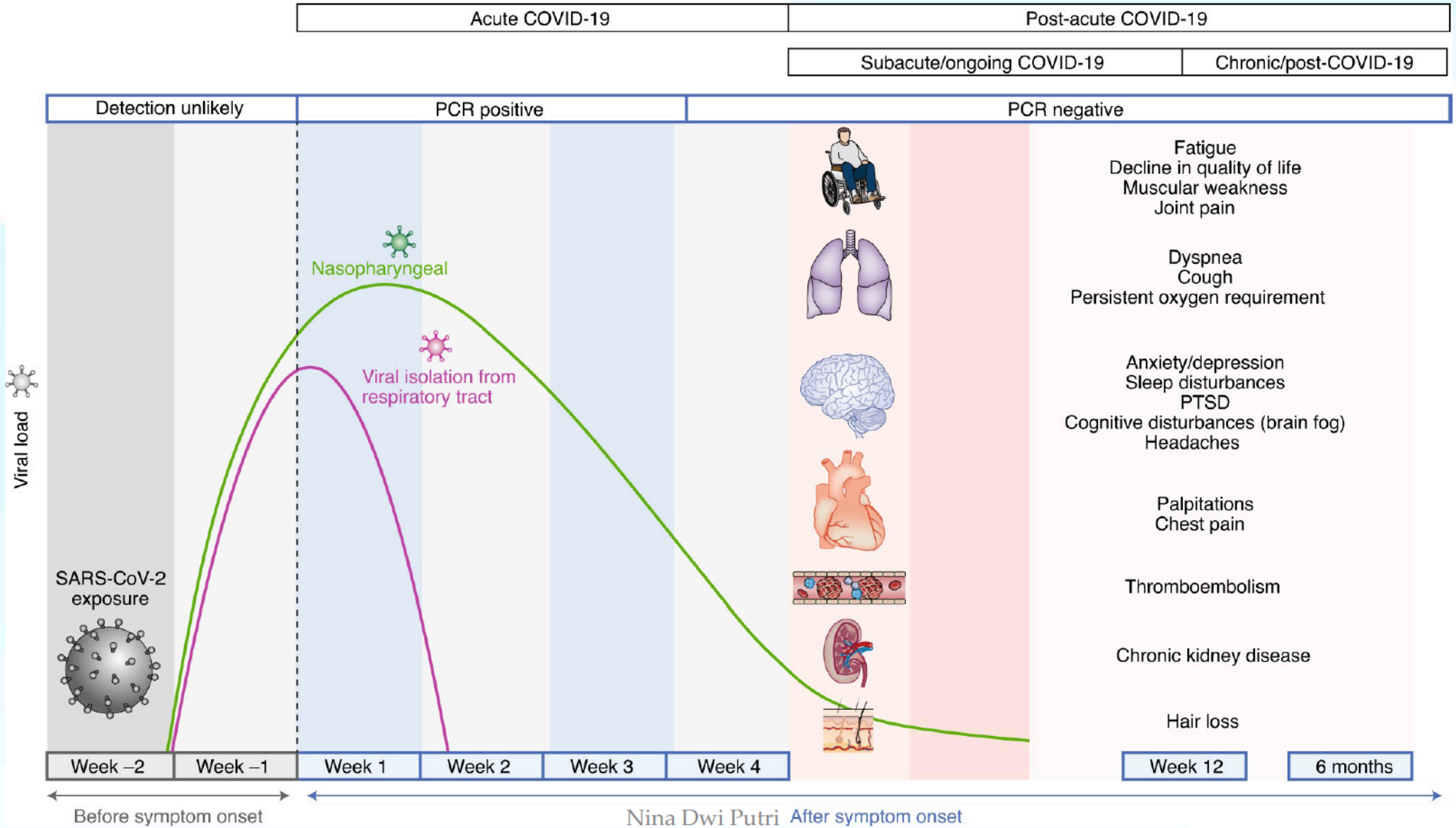
Disclaimer

All data is preliminary

Evidence is mostly change on daily basis

Need more robust data

Slide Courtesy of Satgas Covid-19 IDAI



Nina Dwi Putri

https://www.nature.com/articles/s41591-021-01283-z

Clinical Spectrum of COVID-19 in Children

Acute COVID-19		COVID-19-associated MIS-C		
Mild	**Severe**	**Febrile inflammatory state**	**KD-like illness**	**Severe MIS-C**
In most children, COVID-19 causes no or only mild symptoms.	A small minority of children present with severe acute COVID-19 manifestations, including respiratory failure, ARDS, neurologic symptoms, coagulopathy, and shock. This occurs most commonly in children with underlying medical conditions. Some children with severe acute COVD-19 may develop signs of cytokine storm.	Some children may present with persistent fevers and mild symptoms (eg, headache, fatigue). Inflammatory markers may be elevated, but signs of severe multisystem involvement are lacking.	Some children meet criteria for complete or incomplete KD and do not develop shock and severe multisystem involvement.	Children with severe MIS-C have markedly elevated inflammatory markers and severe multisystem involvement. Cardiac involvement and shock are common.

MIS-C

- Post COVID-19 inflammation
- Delayed hyperinflammation associated with COVID-19
- Other names:
  - PIM-TS: Pediatric Inflammatory Multisystem Syndrome temporally associated with SARS-CoV-2
  - PCAID: Pediatric COVID-19 Associated Inflammatory Disorder

Multisystem inflammatory disease temporally associated with SARS-CoV-2 infection

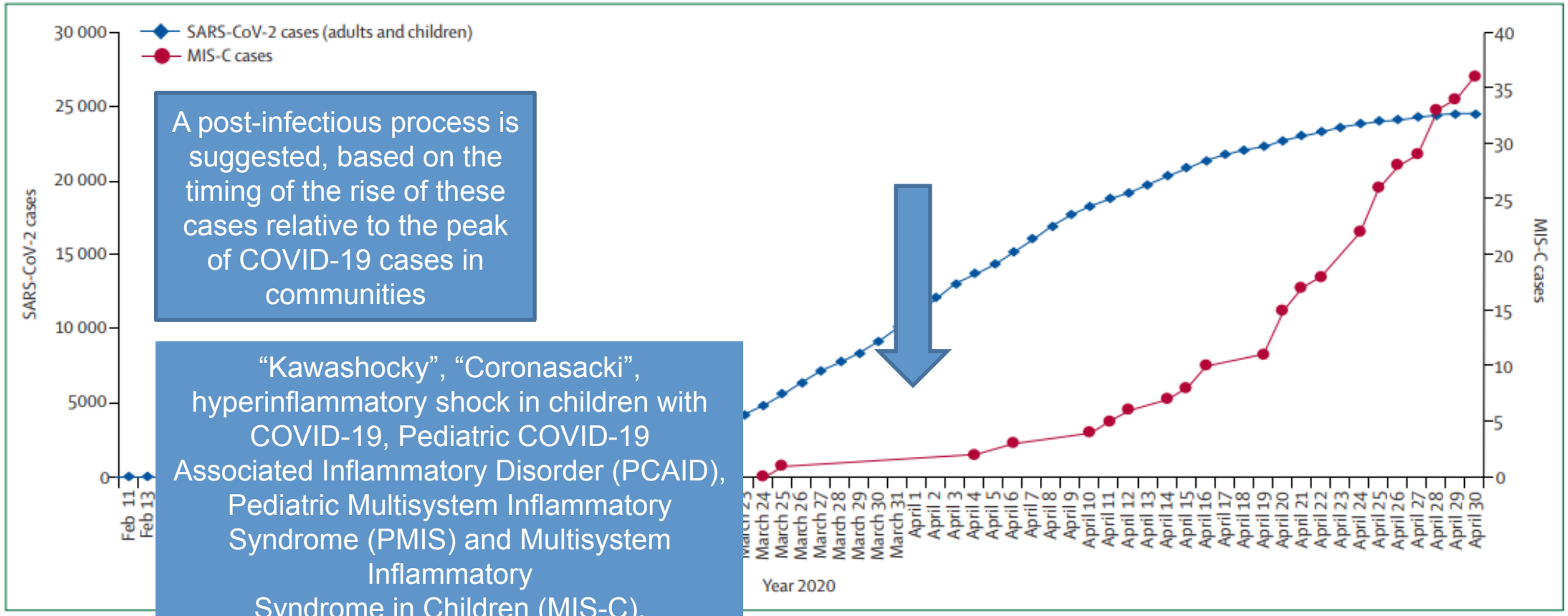
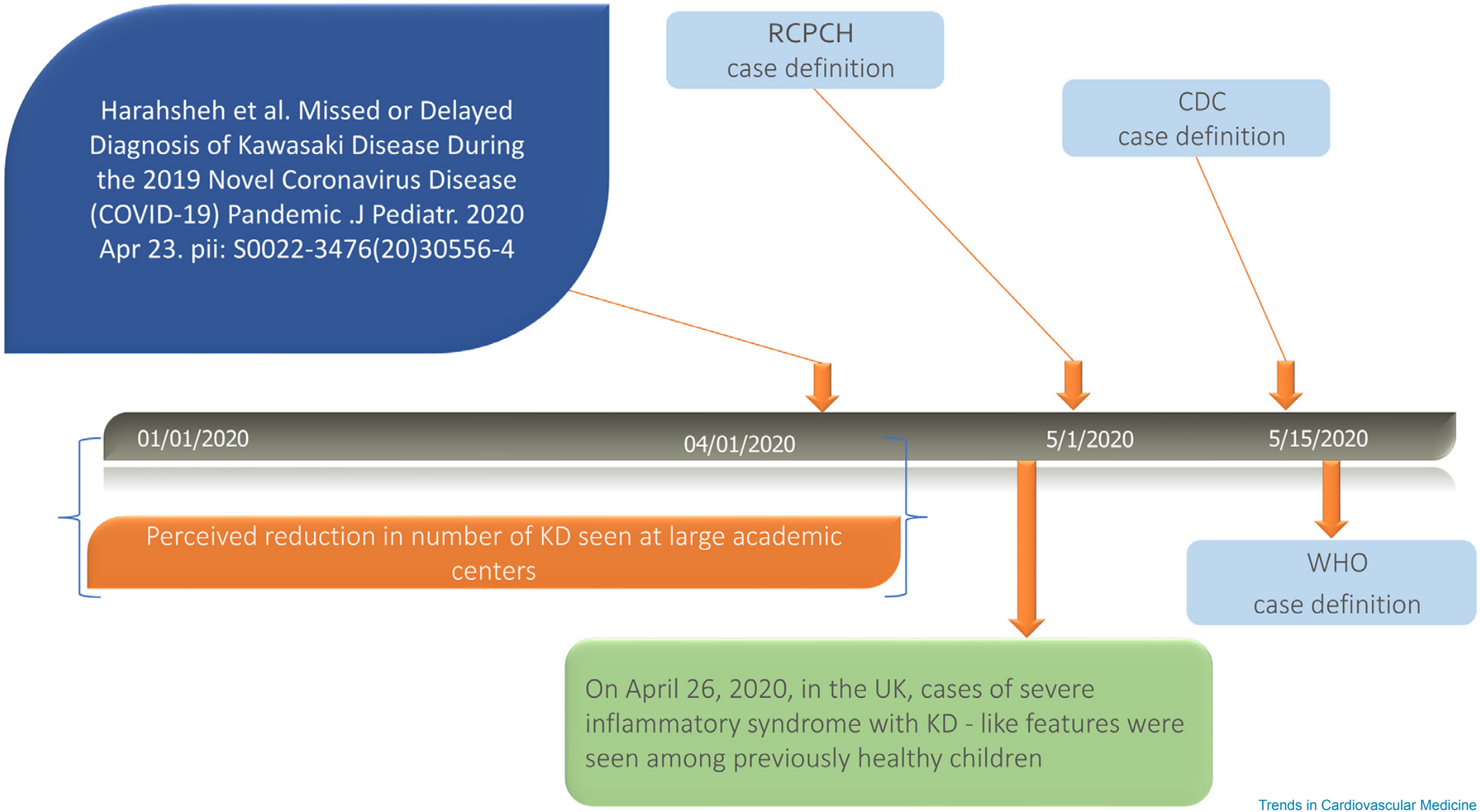


Figure 1: **Time course of MIS-C in PCR-positive COVID-19 cases**

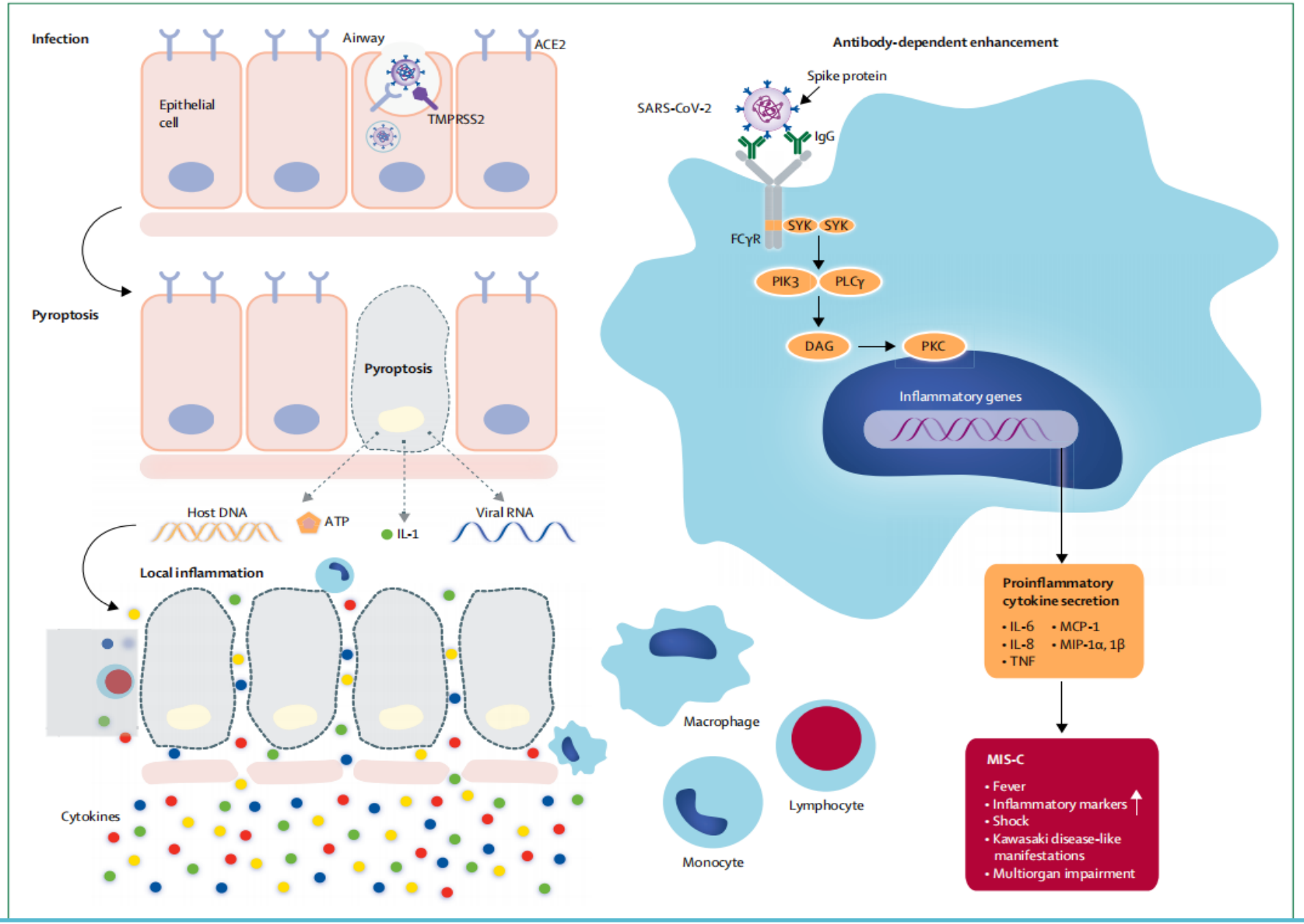
Only incudes PCR-positive cases in London, UK. Data taken from Public Health England.[89] Figure courtesy of Alasdair Bamford and Myrsini Kaforou. MIS-C=multisystem inflammatory syndrome in children. SARS-CoV-2=severe acute respiratory syndrome coronavirus 2.

Jiang Li, et all. COVID-19 and multisystem inflammatory syndrome in children and adolescents. Lancet Infect Dis 2020; 20: 276-88.

Timeline of MIS-C



Trends in Cardiovascular Medicine 30 (2020) 389–39



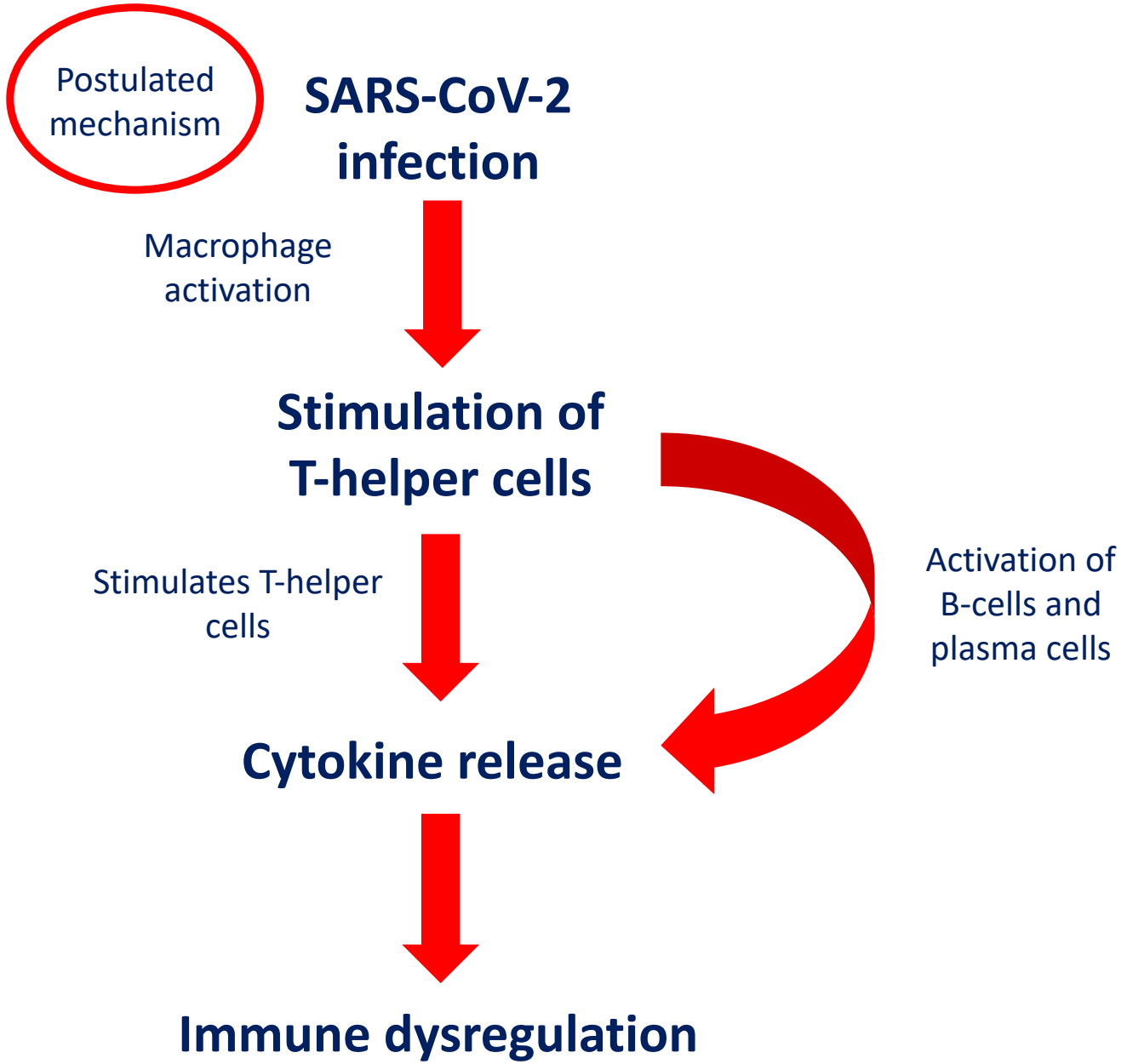
ACE2=angiotensin-converting enzyme 2. DAG=diacylglycerol. FcγR=Fc-gamma receptor. IL=interleukin. MCP=monocyte chemoattractant protein.
MIS-C=multisystem inflammatory syndrome in children. MIP=macrophage inflammatory protein. PIK3=phosphoinositide 3 kinase. PKC=protein kinase C. PLCγ=phospholipase C gamma.
SARS-CoV-2=severe acute respiratory syndrome coronavirus 2. SYK=tyrosine protein kinase SYK. TMPRSS2=transmembrane serine protease 2. TNF=tumour necrosis factor.

Jiang Li, et all. COVID-19 and multisystem inflammatory syndrome in children and adolescents. Lancet Infect Dis 2020; 20: 276-88.

Pathophysiology of MIS-C
in the literature

The hyperinflammation occurring in MIS-C is different to that found in severe acute COVID-19!

- Different cytokines involved:
  - IL-17 more often seen in severe acute COVID-19 → pertaining to T-cell regulation and leukocyte count
  - IL-8 more often seen in MIS-C → pertaining to lymphopenia
  - IL-6 also more commonly observed in MIS-C → leading to antibody-mediated cytokine storm



Cell

The Immunology of Multisystem Inflammatory Syndrome in Children with COVID-19

Highlights

- Hyperinflammation in MIS-C differs from that of acute COVID-19
- T cell subsets discriminate Kawasaki disease patients from MIS-C
- IL-17A drives Kawasaki but not MIS-C hyperinflammation
- Global profiling reveals candidate autoantibodies with pathogenic potential

Proposed Case Definition

	MIS-C associated with COVID-19	PIMS-TS	MIS-C associated with COVID-19	Complete Kawasaki disease	Incomplete Kawasaki disease	Kawasaki disease shock syndrome
Organisation or publication	WHO[6]	Royal College of Pediatrics and Child Health[39]	US Centers for Disease Control and Prevention[37]	American Heart Association[40]	American Heart Association[40]	Kanegaye et al,[41]
Age	0–19 years	Child (age not specified)	<21 years	Child (age not specified)	Child (age not specified)	Child (age not specified)
Inflammation	Fever and elevated inflammatory markers for 3 days or more	Fever and elevated inflammatory markers	Fever and elevated inflammatory markers	Fever lasting 5 days or more*	Fever lasting 5 days or more*	Fever
Main features	Two of the following: (A) rash or bilateral non-purulent conjunctivitis or mucocutaneous inflammation signs (oral, hands, or feet); (B) hypotension or shock; (C) features of myocardial dysfunction, pericarditis, valvulitis, or coronary abnormalities (including echocardiogram findings or elevated troponin or N-terminal pro B-type natriuretic peptide); (D) evidence of coagulopathy (elevated prothrombin time, partial thromboplastin time, and elevated D-dimers); and (E) acute gastrointestinal problems (diarrhoea, vomiting, or abdominal pain)	Single or multiple organ dysfunction (shock or respiratory, renal, gastrointestinal, or neurological disorder; additional features (appendix 6 pp 3–4)	Clinically severe illness requiring hospitalisation; and multisystem (two or more) organ involvement (cardiac, renal, respiratory, haematological, gastrointestinal, dermatological, or neurological)	Four or more principal clinical features: (A) erythema and cracking of lips, strawberry tongue or oral and pharyngeal mucosa; (B) bilateral bulbar conjunctival injection without exudate; (C) rash; (D) erythema and oedema of the hands and feet in acute phase and periungual desquamation in subacute phase; and (E) cervical lymphadenopathy	Two or three principal clinical features or a positive echocardiogram	Kawasaki disease-like clinical features and any of the following causing initiation of volume expansion, vasoactive agents, or transfer to the intensive care unit: systolic hypotension based on age, or a decrease in systolic blood pressure from baseline by 20% or more, or clinical signs of poor perfusion
Exclusion	Other microbial cause of inflammation	Any other microbial cause	Other plausible alternative diagnoses	..	..	Other microbial cause
SARS-CoV-2 status	Positive RT-PCR, antigen test, or serology; or any contact with patients with COVID-19	RT-PCR positive or negative	Positive RT-PCR, serology, or antigen test; or COVID-19 exposure within the past 4 weeks before symptom onset	..	..	..

MIS-C=multisystem inflammatory syndrome in children. PIMS-TS=paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2. SARS-CoV-2=severe acute respiratory syndrome coronavirus 2. *In the presence of four or more principal clinical features, particularly when redness and swelling of the hands and feet are present, the diagnosis of Kawasaki disease can be made with only 4 days of fever.

Table 1: **Preliminary case definitions for MIS-C**

Jiang Li, et all.. Lancet Infect Dis 2020; 20: 276-88.

Comparison of Case Definition

Table 1. Comparison of the case definitions and terms for an emerging inflammatory condition during the COVID-19 pandemic

Differences	RCPCH	CDC	WHO	CPSP
Name	PIMS-temporally associated with COVID-19	Multisystem inflammatory syndrome in children (MIS-C)	MIS-C	PIMS-temporally associated with COVID-19
Length of fever	Not specified	≥24 h	≥3 days	≥3 days
Age	Child	<21 years	0 to 19 years	<18 years
Evidence of inflammation	Yes	Yes	Yes	Yes
Multisystem	Single organ or multisystem	≥2 systems involved	≥2 systems involved	Not specified but implied
Exclude other causes	Yes	Yes	Yes	Yes
SARS-CoV-2-PCR or antibody or exposure	Not necessary	Necessary	Necessary	Necessary

CDC Centers for Disease Control and Prevention; COVID-19 coronavirus 19; CPSP Canadian Paediatric Surveillance Program; PIMS paediatric multisystem inflammatory syndrome; RCPCH Royal College of Paediatrics and Child Health; SARS-CoV-2-PCR severe acute respiratory syndrome coronavirus 2 polymerase chain reaction; WHO World Health Organization

MIS-C

- Children or adolescence age 0-18 y.o with high grade temperature ≥3 days with two or more symptoms:

a. Rash or bilateral non purulent conjungtivitis or mucocutaneous inflammation at oral region, upper or lower extremities

b. Shock or hypotensive

c. Myocardial dysfunction, pericarditis, vasculitis, coronary abnormalities (abnormal ECG or echocardiography findings, elevated Troponin/ NT-proBNP levels

d. Coagulopathy (Prolonged PT, APTT, or elevated D-dimer level)

e. Acute gastrointestinal symptoms (Diarhea, vomiting, or abdominal pain)

- Besides fever with two or more symptoms, MIS-C must also have below features:

a. Elevated inflammatory markers, i.e ESR, CRP or procalcitonin;

b. Exclusion of other microbial cause of inflammation, i.e bacterial sepsis, toxic shock syndrome due to Staphylococus/ Streptococcus; and

c. Evidence of SARS-CoV-2 infection (Positive RT-PCR, antigen test or serology) or any contact with patient with COVID-19

MIS-C is a **clinical diagnosis**, NOT based on RT-PCR

Table 1. Comparison of clinical and laboratory features of MIS-C with KD, KDSS, and TSS.

	Pediatric MIS-C	**Kawasaki Disease (KD)**	**Kawasaki Disease Shock Syndrome (KDSS)**	**Toxic Shock Syndrome (TSS)**
Age of affected children	Older (range 6 m–16 y)	Younger	Younger	Older
Hypotension	±	−	++	++
Mucous membrane involvement	±	+	+	±
Rash	+	+	+	Typically erythroderma
Desquamation	+	+	+	+
Altered mental status or encephalopathy	+	Rare	+	+
Vomiting, diarrhea, and/or abdominal pain	++	Rare	+	+
Respiratory distress	+	Rare	+	±
Myalgias	+	−	−	+
WBC differential	Neutrophilia, lymphopenia	Neutrophilia	Neutrophilia	Neutrophilia
Platelets	↓	↑	↓, normal, or ↑	↓
PT/PTT	↑	normal	normal or ↑	↑
Fibrinogen	↓, normal, or ↑	normal	normal, or ↑	↓
D-dimer	↑	normal	normal, or ↑	↑
ALT	normal, or ↑	normal, or ↑	normal, or ↑	normal, or ↑
Creatinine	↑	normal	↑	↑
Troponin	↑	normal, or ↑	↑	ID
Pro-BNP	↑↑	normal, or ↑	↑	ID
Ferritin	↑	normal, or ↑	normal, or ↑	normal
CRP	↑↑	↑	↑↑	↑
Coronary artery dilation or aneurysms	+	+	++	−
Cardiac ventricular dysfunction	+	±	+	Rare
Valvular regurgitation	+	+	++	Rare

Abbreviations: +, generally present; ++, almost always present; −, generally absent; ±, may be present or absent; ↑ increased; ↑↑, highly increased; ↓ decreased; ALT, alanine transaminase; pro-BNP, pro-B-type natriuretic peptide; CRP, C-reactive protein; ID, insufficient data; KD, Kawasaki Disease; KDSS, Kawasaki Disease shock syndrome; m, months; MIS-C, multisystem inflammatory syndrome in children; PT/PTT, prothrombin time and partial thromboplastin time; TSS, toxic shock syndrome; WBC, white blood cell count; y, years.

Symptoms	%
Persistent fever (4-6 days)	100
GI symptoms (abdominal pain, vomiting, diarrhea)	60-100
Rashes	45-76
Conjungtivitis	30-81
Mucosal membrane involvement	27-76
Neurocognitive symptoms (headache, lethargic, convulsion)	29-58
Respiratory symptoms (tachypnea, dyspnea)	21-65
Sore throat	10-16
Myalgia	8-17
Edema in extremities	9-16
Lymphadenopathy	6-16

Clinical Manifestation	%
Shock	32-76
Complete Kawasaki Criteria	22-64
Myocardial dysfunction (echo OR increased troponin/BNP)	51-90
Arrhyhtmia	12
Acute respiratory failure (Invasive or NIV)	28-52
AKI	8-52
Serocytis (Pleural effusion, Pericardial effusion, Ascites)	24-57
Hepatitis or hepatomegaly	5-21
Encephalopathy, convulsion, coma, meningoencephalitis	6-7

https://uptodate.com/contents/covid-19-multisystem-inflammatory-syndrome-in-children-mis-c-clinical-features-evaluation.

Laboratory Findings	%
Abnormal cell count	
Lymphophenia	85-95
Neutrophilia	68-90
Mild anemia	70
Thrombocytopenia	31-80
Increased Inflammatory Markers	
CRP	90-100
LED	75-80
D-dimer	67-100
Fibrinogen	80-100
Procalcitonine	80-95
Interleukin-6	80-100
Elevated Cardiac Marker	
Troponin	50-90
BNP or NT-pro-BNP	73-90
Hypoalbuminemia	48-95
Elevated AST/ALT	62-70
Elevated LDH	10-60
Hypertrigliceridemia	70

Radiological Findings	
Echocardiography	
LV dysfunction	31-58%
Coronary artery dilatation/anurysm	8-38
Others, i.e: MR and pericardial effusion	
Chest X Ray	
Mostly normal	
Abnormal findings, i.e: mild pleural effusion, patchy consolidation, focal consolidation, atelectasis	
CT thorax	
Similar to X ray findings	
Nodular GGO in several patients	
USG and/or CT	
Unspesific findings: free fluid, ascites, inflammation in the gut and mesenteric, incl. ileitis, adenopathy/mesenteric adenitis, and pericolecystic oedema	

https://uptodate.com/contents/covid-19-multisystem-inflammatory-syndrome-in-children-mis-c-clinical-features-evaluation.

Clinical Management of MIS-C

	Royal College of Paediatrics and Child Health[39]	US Centers for Disease Control and Prevention[37]
Supportive care	Only recommended for mild to moderate disease; discuss early with paediatric intensive care unit and paediatric infectious disease, immunology, and rheumatology team; if clinically deteriorating or in cases of severe disease, discuss transfer with paediatric intensive care unit retrieval teams	Fluid resuscitation, inotropic support, respiratory support, and in rare cases, extracorporeal membranous oxygenation
Directed care against underlying inflammatory process	Immunotherapy should be discussed with a paediatric infectious diseases unit and experienced clinicians on a case-by-case basis and used in the context of a trial if eligible and available	Intravenous immunoglobulin, steroids, aspirin, and anticoagulation treatment
Antiviral therapy	Should be given only in the context of a clinical trial and should be discussed at multidisciplinary team meetings with a clinician from an external trust	..
Antibiotics for sepsis	..	Given while waiting for bacterial cultures
Other	All children treated as if they have COVID-19 and all should be considered for recruitment in research studies	..

Table 2: **Published guidance on the management of multisystem inflammatory syndrome in children associated with COVID-19**

Jiang Li, et all. COVID-19 and multisystem inflammatory syndrome in children and adolescents. Lancet Infect Dis 2020; 20: 276-88.

A stepwise approach to immunomodulatory treatment in MIS-C is recommended, IVIG and/or glucocorticoids considered first tier agents

Either alone or in combination

There is insufficient data available to compare the efficacy of IVIG vs. glucocorticoids in MIS-C or to determine if these treatments should be provided individually or as dual therapy.

TABLE 1 Potential Treatment Options for Children With MIS-C

Treatment	Indications	Dosing	Precautions	Side Effects
Immunomodulators				
IVIG				Infusion reactions, anaphylaxis, transaminitis, aseptic meningitis, hemolysis (dose-dependent effect, highest risk in non-O blood type)
Corticosteroids	• Consider for high-risk patients with KD features (age <6 months, coronary artery z-score >2.5 on baseline echocardiography, IVIG resistance) • Consider for MIS-C with cytokine storm (rheumatology/ID consult) • Consider for ARDS	• 1-2 mg/kg divided bid (prednisone, prednisolone, methylprednisolone)		• Hypertension • Hyperglycemia
Anikinra (IL-1 inhibitor)	• Consider for MIS-C with cytokine storm (rheumatology/ID consult) • Consider for high-risk patients with KD in whom steroids are not an option			
Canakinumab	• Consider for MIS-C with cytokine storm (rheumatology/ID consult) • Consider for high-risk patients with KD in whom steroids are not an option		• Avoid live viral vaccines	
Tocilizumab (IL-6 inhibitor)	• Consider for MIS-C with cytokine storm (rheumatology/ID consult)	• <30 kg: 12 mg/kg IV • ≥30 kg: 8 mg/kg IV • Maximum dose 800 mg	• Treatment with more than 1 biologic agent is not recommended • Avoid live viral vaccines	

Some patients with mild symptoms may require only close monitoring without IVIG and/or glucocorticoids.

Based on Whittaker et al reported (*2).

Once the patient has defervesced and is improved clinically → transitioned to an equivalent oral dose of prednisolone or prednisone by the time of discharge and then tapered off over 3-4 weeks.

Henderson et al. American College of Rheumatology clinical guidance for pediatric patients with Multisystem Inflammatory Syndrome in Children (MIS-C) associated with SARS-CoV-2 and hyperinflammation in COVID-19. Version 1.2020

Beroukhim RS, et al. Children at risk multisystem inflammatory syndrome and COVID-19. JACC. 2020;2:1271-4.

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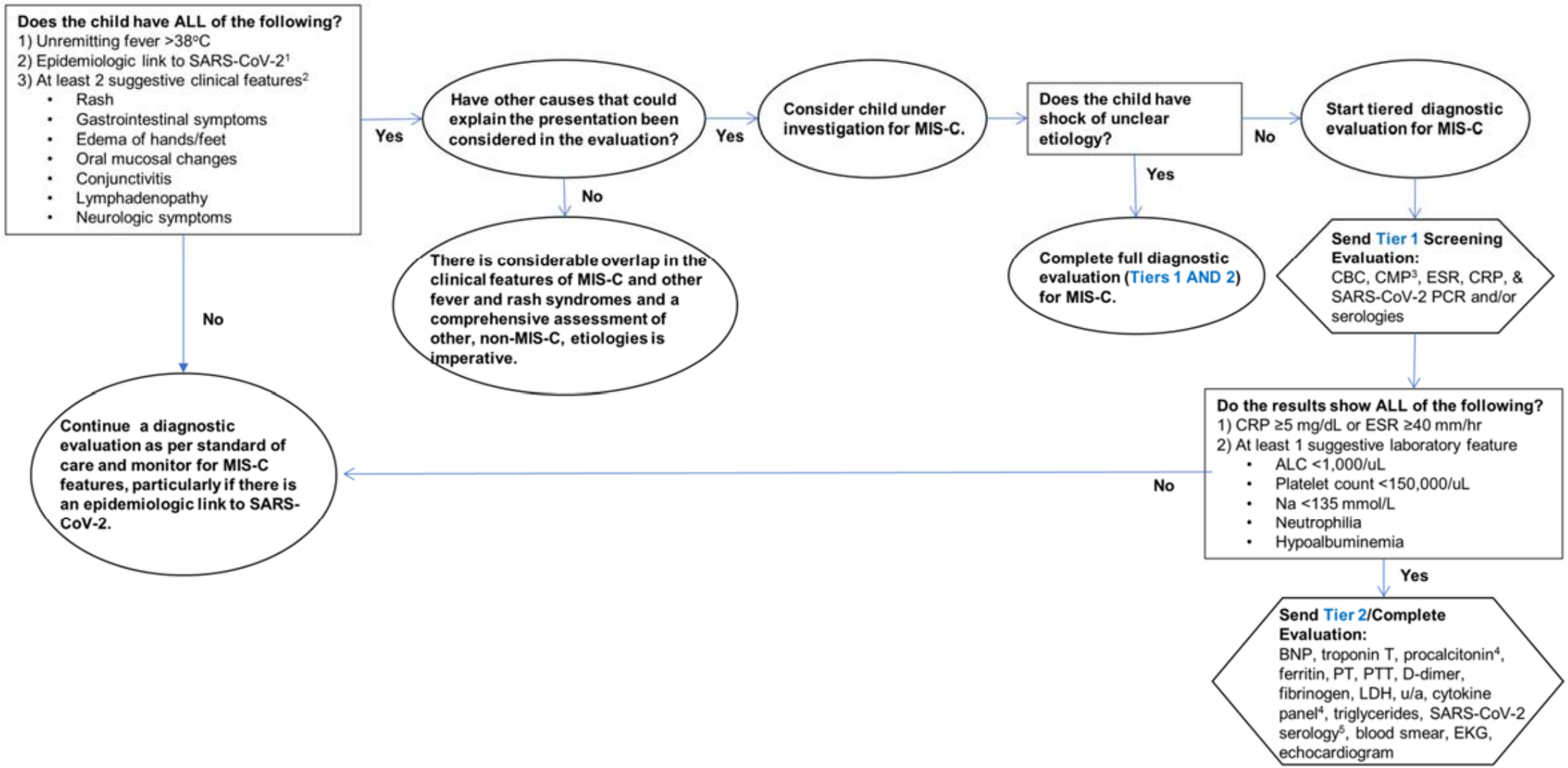

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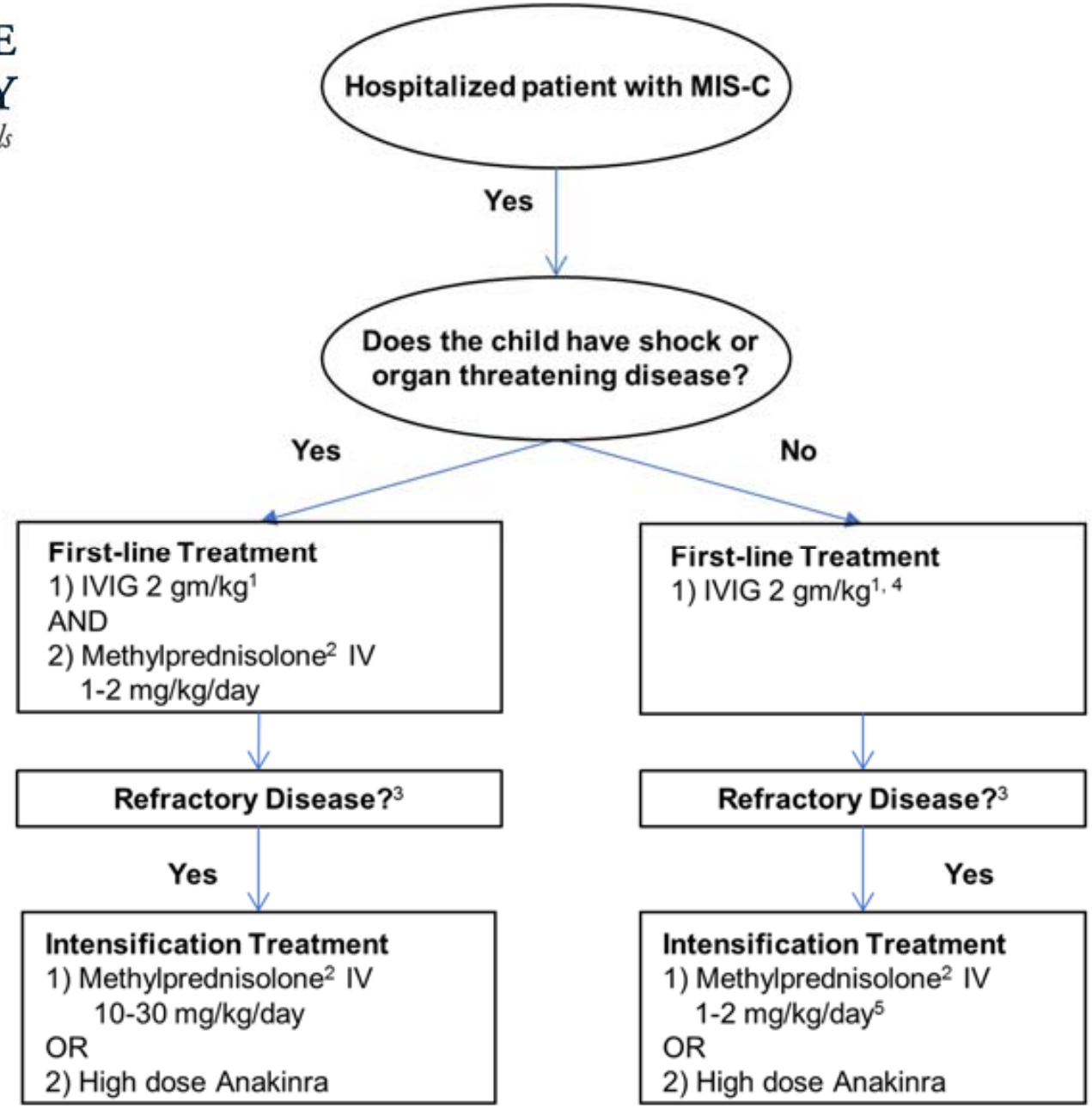

Cardiac Management of MIS-C

Table 4. Cardiac management of MIS-C*

Guidance statement	Level of consensus
Patients with MIS-C and abnormal BNP and/or troponin T levels at diagnosis should have these laboratory parameters trended over time until they normalize.	High
EKGs should be performed at a minimum of every 48 hours in MIS-C patients who are hospitalized and during follow-up visits. If conduction abnormalities are present, patients should be placed on continuous telemetry while in the hospital, and Holter monitors should be considered during follow-up.	Moderate to high
Echocardiograms conducted at diagnosis and during clinical follow-up should include evaluation of ventricular/valvar function, pericardial effusion, and coronary artery dimensions with measurements indexed to body surface area using z-scores.	High
Echocardiograms should be repeated at a minimum of 7–14 days and 4–6 weeks after presentation. For those patients with cardiac abnormalities occurring in the acute phase of their illness, an echocardiogram 1 year after MIS-C diagnosis could be considered. Patients with LV dysfunction and/or CAAs will require more frequent echocardiograms.	Moderate to high
Cardiac MRI may be indicated 2–6 months after MIS-C diagnosis in patients who presented with significant transient LV dysfunction in the acute phase of illness (LV ejection fraction <50%) or persistent LV dysfunction. Cardiac MRI should focus on myocardial characterization, including functional assessment, T1/T2-weighted imaging, T1 mapping and extracellular volume quantification, and late gadolinium enhancement.	High
Cardiac CT should be performed in patients with suspected presence of distal CAAs that are not well seen on echocardiogram.	Moderate

* MIS-C = multisystem inflammatory syndrome in children; BNP = B-type natriuretic peptide; EKG = electrocardiogram; LV = left ventricular; CAAs = coronary artery aneurysms; MRI = magnetic resonance imaging; CT = computed tomography.

Henderson LA, Canna SW, Friedman KG, Gorelik M, Lapidus SK, Bassiri H, et al. American College of Rheumatology Clinical Guidance for Pediatric Patients with Multisystem Inflammatory Syndrome in Children (MIS-C) Associated with SARS-CoV-2 and Hyperinflammation in COVID-19. Version 1. Arthritis Rheumatol 2020; 72; 1791-1805. doi: https://onlinelibrary.wiley.com/doi/10.1002/art.41454..

Immunomodulary Treatment in MIS-C

Table 5. Immunomodulatory treatment in MIS-C*

Guidance statement	Level of consensus
Patients "under investigation" for MIS-C without life-threatening manifestations should undergo diagnostic evaluation for MIS-C, as well as other possible infections and non–infection-related conditions, before immunomodulatory treatment is initiated.	Moderate
Patients "under investigation" for MIS-C with life-threatening manifestations may require immunomodulatory treatment for MIS-C before the full diagnostic evaluation can be completed.	High
After evaluation by specialists with expertise in MIS-C, some patients with mild symptoms may only require close monitoring without immunomodulatory treatment. The panel noted uncertainty around the empiric use of IVIG to prevent CAAs in this setting.	Moderate
A stepwise progression of immunomodulatory therapies should be used to treat MIS-C with IVIG and/or glucocorticoids considered as first-tier treatments.	Moderate to high
High-dose IVIG (typically 1–2 gm/kg) may be considered for treatment of MIS-C. Cardiac function and fluid status should be assessed in MIS-C patients with shock before IVIG treatment is provided, and IVIG should be administered when cardiac function is restored.	Moderate to high
Low-to-moderate doses of glucocorticoids may be considered for treatment of MIS-C. High-dose IV pulse glucocorticoids may be considered to treat patients with life-threatening complications, such as shock, and specifically, if a patient requires high-dose or multiple inotropes and/or vasopressors.	Moderate to high
Anakinra (IV or SC) may be considered for treatment of MIS-C refractory to IVIG and glucocorticoids or in patients with contraindications to these treatments.	Moderate to high
Serial laboratory testing and cardiac assessment should guide the immunomodulatory treatment response and tapering. Patients will often require a 2–3-week taper of immunomodulatory medications.	High

* MIS-C = multisystem inflammatory syndrome in children; IVIG = intravenous immunoglobulin; CAAs = coronary artery aneurysms; SC = subcutaneous.

Henderson LA, Canna SW, Friedman KG, Gorelik M, Lapidus SK, Bassiri H, et al. American College of Rheumatology Clinical Guidance for Pediatric Patients with Multisystem Inflammatory Syndrome in Children (MIS-C) Associated with SARS-CoV-2 and Hyperinflammation in COVID-19. Version 1. Arthritis Rheumatol 2020; 72; 1791-1805. doi: https://onlinelibrary.wiley.com/doi/10.1002/art.41454..

Antiplatelet and anticoagulation therapy in MISC-C

Table 6. Antiplatelet and anticoagulation therapy in MIS-C*

Guidance statement	Level of consensus
Low-dose aspirin (3–5 mg/kg/day; maximum 81 mg/day) should be used in patients with MIS-C and KD-like features and/or thrombocytosis (platelet count ≥450,000/μl) and should be continued until the platelet count is normalized and normal coronary arteries are confirmed at ≥4 weeks after diagnosis. Treatment with aspirin should be avoided in patients with a platelet count of ≤80,000/μl.	Moderate
MIS-C patients with CAAs and a maximal z-score of 2.5–10.0 should be treated with low-dose aspirin. Patients with a z-score of ≥10.0 should be treated with low-dose aspirin and therapeutic anticoagulation with enoxaparin (factor Xa level 0.5–1.0) or warfarin.	Moderate to high
Patients with MIS-C and documented thrombosis or an EF of <35% should receive therapeutic anticoagulation with enoxaparin until at least 2 weeks after discharge from the hospital.	High
Indications for longer outpatient therapeutic enoxaparin dosing include the following: CAAs with a z-score of >10.0 (indefinite treatment), documented thrombosis (treatment for ≥3 months pending thrombus resolution), or ongoing moderate-to-severe LV dysfunction.	High
For MIS-C patients who do not meet the above criteria, the approach to antiplatelet and anticoagulation therapeutic management should be tailored to the patient's risk for thrombosis.	High

* MIS-C = multisystem inflammatory syndrome in children; KD = Kawasaki disease; CAAs = coronary artery aneurysms; EF = ejection fraction; LV = left ventricular.

Henderson LA, Canna SW, Friedman KG, Gorelik M, Lapidus SK, Bassiri H, et al. American College of Rheumatology Clinical Guidance for Pediatric Patients with Multisystem Inflammatory Syndrome in Children (MIS-C) Associated with SARS-CoV-2 and Hyperinflammation in COVID-19. Version 1. Arthritis Rheumatol 2020; 72; 1791-1805. doi: https://onlinelibrary.wiley.com/doi/10.1002/art.41454..

Hyperinflammation in COVID-19

Table 7. Hyperinflammation in COVID-19*

Guidance statement	Level of consensus
Children with a complex medical history and those taking immunosuppressive medications, including moderate-to-high–dose glucocorticoids, may be at higher risk for severe outcomes in COVID-19.	Moderate to high
Children and adults admitted to the hospital with COVID-19 present with similar symptoms, including fever, upper respiratory tract symptoms, abdominal pain, and diarrhea.	Moderate
Children with severe respiratory symptoms due to COVID-19 should be considered for immunomodulatory therapy if any of the following are present: ARDS, shock/cardiac dysfunction, substantially elevated LDH, D-dimer, IL-6, IL-2R, CRP, and/or ferritin levels, and depressed lymphocyte count, albumin levels, and/or platelet count.	Moderate to high
Glucocorticoids may be considered for use as immunomodulatory therapy in patients with COVID-19 and hyperinflammation (as outlined in the above statement).	Moderate
Anakinra treatment appears safe in severe infections and in children with hyperinflammatory syndromes. In children with COVID-19 and hyperinflammation, anakinra (>4 mg/kg/day IV or SC) should be considered for immunomodulatory therapy. Initiation of anakinra before invasive mechanical ventilation may be beneficial.	High
Children with COVID-19 treated with anakinra should be monitored for LFT abnormalities.	Moderate
Compared to standard care, tocilizumab may be effective in reducing mortality and ICU admission in patients with severe COVID-19 pneumonia and signs of hyperinflammation; however, patients treated with tocilizumab may be at higher risk for bacterial and fungal infections.	Moderate
When tocilizumab is used to treat children with COVID-19, weight-based dosing should be employed (body weight <30 kg, 12 mg/kg IV; body weight ≥30 kg, 8 mg/kg IV, maximum 800 mg). Children treated with tocilizumab should be monitored for LFT abnormalities and elevated triglyceride levels.	Moderate to high
In the absence of randomized controlled trials or comparative effectiveness studies, if immunomodulation is to be used at all, the balance of risks and benefits suggests that anakinra be used as first-line immunomodulatory treatment of children with COVID-19 and hyperinflammation. There is insufficient evidence to support the use of other immunomodulatory agents, unless glucocorticoids, IL-1–blocking therapies, and/or IL-6–blocking therapies are contraindicated or have failed.	Moderate

* COVID-19 = coronavirus disease 2019; ARDS = acute respiratory distress syndrome; LDH = lactate dehydrogenase; IL-6 = interleukin-6; IL-2R = interleukin-2 receptor; CRP = C-reactive protein; IV = intravenous; SC = subcutaneous; LFT = liver function test; ICU = intensive care unit.

Henderson LA, Canna SW, Friedman KG, Gorelik M, Lapidus SK, Bassiri H, et al. American College of Rheumatology Clinical Guidance for Pediatric Patients with Multisystem Inflammatory Syndrome in Children (MIS-C) Associated with SARS-CoV-2 and Hyperinflammation in COVID-19. Version 1. Arthritis Rheumatol 2020; 72; 1791-1805. doi: https://onlinelibrary.wiley.com/doi/10.1002/art.41454..

Table 3. Possible doses for immunomodulatory agents in the treatment of MIS-C, depending on phenotypic characteristics.

Medication Class	Dose	Important Notes
IVIG [16,34]	• If they meet KD criteria: 2 g/kg IV typically given in a single dose • If they meet SHLH criteria: 1–2 g/kg IV	Use with caution if fluid overload, renal dysfunction. Consider alternate dosing strategy.
Aspirin	• If they meet KD criteria: 30–50 mg/kg/d, decrease to 3–5 mg/kg/d once afebrile × 48 h	Precaution in severe thrombocytopenia
Corticosteroids [34,39]	For severe KD *: ○ Dosing strategy 1: Methylprednisone 0.8 mg/kg BID IV for 5–7 d or until CRP normalizes followed by PO prednisone/prednisolone 2 mg/kg/d with wean over 2–3 w ○ Dosing strategy 2: Methylprednisolone 10–30 mg/kg IV QD for 3 d followed by PO prednisone/prednisolone 2 mg/kg/d until d 7 or until CRP normalizes and then wean over 2–3 w For SHLH ** ○ Methylprednisone pulsed dosing of 30 mg/kg IV QD × 3 doses followed by 1 mg/kg IV q12 h, wean to be determined by peds rheumatology, immunology, or H/O	Precaution if positive RT-PCR for SARS-CoV-2, suggesting active infection
Anakinra [16,34]	• 2–6 mg/kg/day IV/SQ, length of therapy to be decided with input from pediatric rheumatology or immunology	
Tocilizumab	• <30 Kg: 12 mg/kg IV • >30 Kg: 8 mg/kg IV	Trials ongoing for safety and efficacy in the setting of active coronavirus infection [40]

Abbreviations: BID, twice daily; d, days; g, gram; h, hours; H/O, hematology–oncology; IV, intravenous; IG, immune globulin; KD, Kawasaki disease; kg, kilograms; mg, milligrams; PO, by mouth; q, every; QD, every day; RT-PCR, reverse transcriptase PCR; SHLH, secondary hemophagocytic lymphohistiocytosis; SQ, subcutaneous; w, weeks. *—see text for definition. **—per clinical discretion.

Usage of Anti-coagulation and Anti-platelet

- Aspirin or enoxaparin → reduce venous thromboembolism (MIS-C has a high risk criteria)

GI complications in MIS-C patients on steroids and aspirin. Risk of coronary artery thrombosis is directly related to size of the CAA with exponentially increased probability in coronary arteries with dimensions above a z-score of 10.0.(22, 59, 60) Thus, anticoagulation with enoxaparin (factor Xa level 0.5-1.0) or warfarin in MIS-C patients with a coronary artery z-score greater than 10.0 is advised. Patients with more than mild LV dysfunction are at risk for intracardiac thrombosis.(61, 62) Given the lack of clarity about the exact risk of hypercoagulability in MIS-C, the Task Force recommended considering anticoagulation for MIS-C with moderate or severe LV dysfunction (EF <35%).

Henderson LA, Canna SW, Friedman KG, Gorelik M, Lapidus SK, Bassiri H, et al. American College of Rheumatology clinical guidance for pediatric patients witl multisystem inflammatory syndrome in children (MIS-C) associated with SARSCoV-2 and hyperinflammation in COVID-19.
Version 1. Arthritis Rheumatol 2020.

Prophylaxis of thrombosis

TABLE 1 Summary of consensus-based clinical recommendations on use/non-use of anticoagulant thromboprophylaxis in children hospitalized for COVID-19–related illness and children hospitalized with asymptomatic SARS-CoV-2 infection

Scenario	D-dimer >5 times upper limit of normal values	Non-COVID-19 clinical risk factors for HA-VTE (see Table 2)	Anticoagulant thromboprophylaxis suggested
Hospitalized for COVID-19–related illness (includes MIS-C)	Yes	N/A	Yes
	No	One or more[a]	Yes
		None	No
Hospitalized with asymptomatic SARS-CoV-2 infection	N/A	Multiple[b]	Yes
		Few or none	No

Abbreviations: HA-VTE, hospital-associated venous thromboembolism; N/A, not applicable.

[a]While there was consensus among experts surveyed for the stated recommendations, specific risk factors endorsed by survey respondents varied. Please see also Table 2 for risk factor examples.

[b]Several studies in critically ill and non–critically ill children without COVID-19 (analyzed in Mahajerin et al.18 or published subsequently) have suggested a clinically meaningful increase in the risk of hospital-associated VTE in association with the co-existence of multiple (eg, ≥3) specific risk factors. We presume that these findings also apply to hospitalized children with asymptomatic SARS-CoV-2 infection, until data may emerge that indicate otherwise.

Panduan Antitrombotik-Antikoagulan MIS-C

MIS-C

Aspirin
3-5 mg/kg/hari (max 81 mg/hari)

- VTE/prior VTE
- Severe LV dysfunction
- Large CAA
- D-Dimer ≥ 5x normal
- D Dimer <5x normal + > 2 faktor risiko tambahan

TIDAK → **Profilaksis antikoagulan**

LMWH/Enoxaparin

- < 2bulan: 0.75 mg/kg setiap 12 jam
- > 2bulan: 0.5 mg/kg setiap 12 jam

Obesitas: >120 kg atau BMI>30

- 0.5 mg/kg (max 150 mg) tiap 12 jam

Pasien dengan CrCl <30

- 0.5mg/kg 1 x sehari

atau

UFH 10-15 unit/kg/jam

YA → **Terapi antikoagulan**

LMWH/Enoxaparin

Dosis LMWH sesuai usia:
< 2bulan: 1.5 mg/kg setiap 12 jam
> 2bulan: 1.0 mg/kg setiap 12 jam

Obesitas: >120 kg atau BMI>30
1.0 mg/kg setiap 12 jam
Dosis maksimal 150 mg

Bila CrCl <30: 1.0 mg/kg 1x sehari

Faktor risiko:

- Riwayat *venous thrombotic events* (VTE), riwayat keluarga VTE (1st *degree relative*)
- Terpasang *central venous line* (cvl) atau alat intravaskular/jantung lain
- Immobilisasi komplit
- Malignansi aktif
- Sakit autoimmune/*inflammatory disease* aktif/flare
- Obesitas
- Usia pubertal atau usia >12 tahun
- Dehidrasi berat
- Luka bakar luas
- Pasca operasi/trauma berat
- Mendapat terapi estrogen

Modifikasi
Pediatric Blood & Cancer, 06 May 2021, DOI: (10.1002/pbc.29049)
Son, MBFCOVID-19: Multisystem inflammatory syndrome in children (MIS-C) management and outcome. UpTodate, July 2021

Medications	Dose	Route	Notes
Aspirin (ASA)	3-5mg/kg/day, max=81mg	PO	Continue approximately 4-6 weeks.
Enoxaparin (Prophylaxis dosing)	< 2months: 0.75mg/kg/dose q12 hours ≥ 2months and < 60kg: 0.5mg/kg/dose q12 hrs ≥60kg: 40mg daily (40mg q12 hours in adolescent, & critically ill	SQ	Monitoring for prophylaxis dosing is optional. Obtain if there is new bleeding, change in liver or renal function, or in critically ill pts. If monitoring, check LMWH level 4 hours after 3rd - 5th dose. Target 0.2-0.4 units/mL
Enoxaparin (Therapeutic dosing)	< 2months 1.5 mg/kg/dose q12 hours ≥ 2months: 1 mg/kg/dose q12 hours	SQ	Not to be used in acute kidney injury & CrCl <30 mL/minute Check LMWH level 4 hours after 3rd - 5th dose Target > 0.5-1.0 units/mL, Dose adjustment by Heme/Onc
Unfractionated Heparin (Prophylaxis dosing)	Any dose ≤ 10 units/kg/hr	IV	No monitoring required unless signs or symptoms of bleeding, or patient was coagulapathic to begin with.
Unfractionated Heparin (Therapeutic dosing)	Any dose > 10 units/kg/hr	IV	aPTT may be unreliable lab. If aPTT is prolonged at baseline, use Unfractionated Heparin assay (anti-Xa for UFH)

Usage of Immunomodulators

- IVIG (2 g/kg) prevents coronary artery aneurysm in KD[1]
- There have been reports of benefit from IVIG therapy in COVID-19 associated myocarditis[2]
- Glucocorticoids shows reduce coronary artery aneurysm in KD patients with high risk of IVIG failure[3]

1. Furusho K, Nakano H, Shinomiya K, Tamura T, Manabe Y, Kawarano M, et al. High-dose intravenous gammaglobulin for Kawasaki disease. Lancet 1984;324 (8411):1055–8.
2. Kociol RD, Cooper LT, Fang JC, Moslehi JJ, Pang PS, Sabe MA, et al. Recognition and initial management of fulminant myocarditis: a scientific statement from the American Heart Association. Circulation 2020;141(6):e69–92.
3. Kobayashi T, Saji T, Otani T, Takeuchi K, Nakamura T, Arakawa H, et al. Efficacy of immunoglobulin plus prednisolone for prevention of coronary artery abnormalities in severe Kawasaki disease (RAISE study): a randomised, openlabel, blinded-endpoints trial. Lancet 2012;379(9826):1613–20.

Why was IVIG treatment provided in this patient?

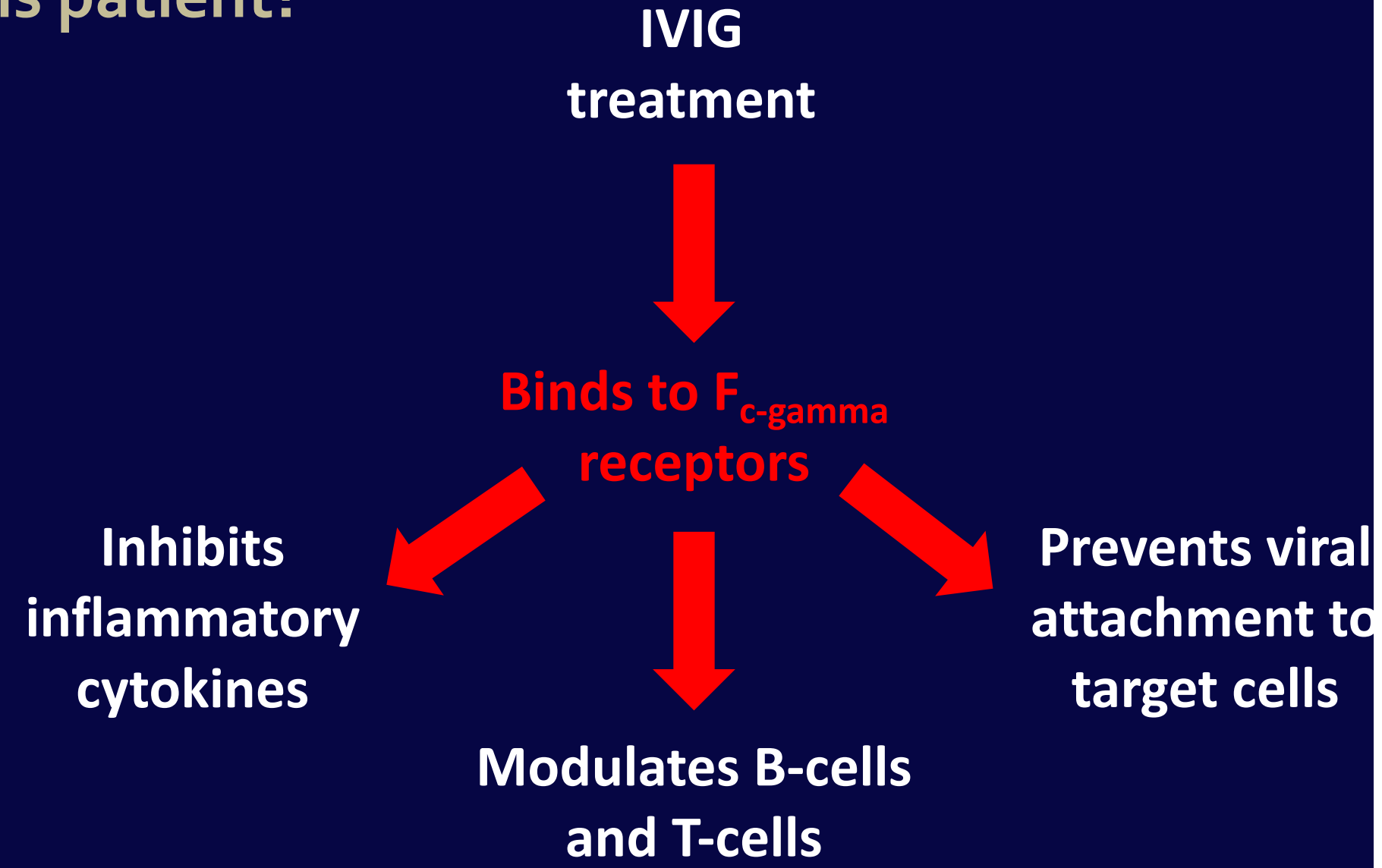

Table 5
Medications.

Total n = 662	N (%)
Intravenous immunoglobulin	506 (76.4)
Vasoactive support	347 (52.3)
Corticosteroids	347 (52.3)
Antibiotics	108 (16.3)
Anticoagulants	172 (25.9)
Aspirin	111 (16.8)
Interleukin-1ra inhibitor	56 (8.5)
Interleukin-6 inhibitor	40 (6.0)
Remdesivir	6 (0.9)
Hydroxychloroquine	5 (0.8)

Because many cases met the diagnostic criteria of classic or incomplete Kawasaki disease, most reported MIS-C cases were treated using the standard protocol for Kawasaki disease → intravenous immunoglobulin with our without aspirin

Type of steroid and durations

Usage of Specific Immunotherapies

- IL-6 Inhibitor prevents
  - Megakaryocyte maturations → leads to thrombocytosis[1]
  - Triggering cascade that stimulates polyclonal B cell autoantibody production → endothelial damage → vasculatis[1]
- Tocilizumab → used to treat systemic onset juvenile idiopathic arthritis[2] (shares many features with MIS-C)
- Anakinra[3] (IL-1 receptor antagonist) → commonly used to treat systemic juvenile arthritis induced cytokine release syndrome
- Infliximab (TNF-α blocker) → reduce significant elevated TNF-α levels in the states of cytokine storm[4]

1. Ueno Y, Takano N, Kanegane H, Yokoi T, Yachie A, Miyawaki T, et al. The acute phase nature of interleukin 6: studies in Kawasaki disease and other febrile illnesses. Clin Exp Immunol 1989;76(3):337.
2.] Beukelman T, Patkar NM, Saag KG, Tolleson-Rinehart S, Cron RQ, DeWitt EM, et al. 2011 American College of Rheumatology recommendations for the treatment of juvenile idiopathic arthritis: initiation and safety monitoring of therapeutic agents for the treatment of arthritis and systemic features. Arthritis Care Res 2011;63(4):465–82.
3. Food and Drug Administration. Anakinra (kineret) prescribing information [Internet]. 2012 [cited 2020 Jul 15]. Available from: https://www.accessdata. fda.gov/drugsatfda_docs/label/ 2012/103950s5136lbl.pdf.
4. Cheng MH, Zhang S, Porritt RA, Arditi M, Bahar I. An insertion unique to SARSCoV-2 exhibits superantigenic character strengthened by recent mutations. bioRxiv. 2020.

Usage of Supportive Therapy

SPECIAL ARTICLE OPEN

COVID-19 PICU guidelines: for high- and limited-resource settings

Saraswati Kache[1], Mohammod Jobayer Chisti[2], Felicity Gumbo[3], Ezekiel Mupere[4], Xia Zhi[5], Karthi Nallasamy[6], Satoshi Nakagawa[7], Jan Hau Lee[8], Matteo Di Nardo[9], Pedro de la Oliva[10], Chhavi Katyal[11], Kanwaljeet J. S. Anand[12], Daniela Carla de Souza[13], Vanessa Soares Lanziotti[14] and Joseph Carcillo[15]

BACKGROUND: Fewer children than adults have been affected by the COVID-19 pandemic, and the clinical manifestations are distinct from those of adults. Some children particularly those with acute or chronic co-morbidities are likely to develop critical illness. Recently, a multisystem inflammatory syndrome (MIS-C) has been described in children with some of these patients requiring care in the pediatric ICU.
METHODS: An international collaboration was formed to review the available the care of critically ill children with SARS-CoV-2 infection. Where the evider consensus-based guidelines.
RESULTS: This process has generated 44 recommendations related to pedia distress or failure, sepsis or septic shock, cardiopulmonary arrest, MIS-C, thos explain the milder disease patterns in children and the potential to use repu thrombotic therapies are also described.
CONCLUSION: Brief summaries of pediatric SARS-CoV-2 infection in different are capturing this data globally. These guidelines seek to harmonize the stanc children with COVID-19 receive across the world.

Pediatric Research (2020) 88:705–716; https://doi.org/10.1038/s41390-020-105

IMPACT:

- At the time of publication, this is the latest evidence for managing critically ill children infected with SARS-CoV-2.
- Referring to these guidelines can decrease the morbidity and potentially the mortality of children effected by COVID-19 and its sequalae.
- These guidelines can be adapted to both high- and limited-resource settings.

Eight recommendations from the document were related to MIS-C treatment with the best practice suggestions being supportive management and close monitoring, use of a multidisciplinary team, laboratory tests (SARS-CoV2 antigens, inflammatory markers, organ system dysfunction), and empirical antibiotics until bacterial causes are excluded

JAMA | Original Investigation

Clinical Characteristics of 58 Children With a Pediatric Inflammatory Multisystem Syndrome Temporally Associated With SARS-CoV-2

Elizabeth Whittaker, MD; Alasdair Bamford, MD; Julia Kenny, MD; Myrsini Kaforou, PhD; Christine E. Jones, MD; Priyen Shah, MD; Padmanabhan Ramnarayan, MD; Alain Fraisse, MD; Owen Miller, MD; Patrick Davies, MD; Filip Kucera, MD; Joe Brierley, MD; Marilyn McDougall, MD; Michael Carter, MD; Adriana Tremoulet, MD; Chisato Shimizu, MD; Jethro Herberg, MD; Jane C. Burns, MD; Hermione Lyall, MD; Michael Levin, MD; for the PIMS-TS Study Group and EUCLIDS and PERFORM Consortia

Treatment

Inotropic support was required in 47%; 71% were treated with intravenous immunoglobulin and 64% with corticosteroids. Three patients received anakinra and eight infliximab (Table 3); 22% of the patients recovered with supportive care alone.

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, L.L. Loftis, K.M. Tarquinio, A.R. Singh, S.M. Heidemann, V.L. Soma, B.J. Riggs, J.C. Fitzgerald, M. Kong, S. Doymaz, J.S. Giuliano, Jr., M.A. Keenaghan, J.R. Hume, C.V. Hobbs, J.E. Schuster, K.N. Clouser, M.W. Hall, L.S. Smith, S.M. Horwitz, S.P. Schwartz, K. Irby, T.T. Bradford, A.B. Maddux, C.J. Babbitt, C.M. Rowan, G.E. McLaughlin, P.H. Yager, M. Maamari, E.H. Mack, C.L. Carroll, V.L. Montgomery, N.B. Halasa, N.Z. Cvijanovich, B.M. Coates, C.E. Rose, J.W. Newburger, M.M. Patel, and A.G. Randolph, for the Overcoming COVID-19 Investigators*

RESULTS

A total of 518 patients with MIS-C (median age, 8.7 years) received at least one immunomodulatory therapy; 75% had been previously healthy, and 9 died. In the propensity-score–matched analysis, initial treatment with IVIG plus glucocorticoids (103 patients) was associated with a lower risk of cardiovascular dysfunction on or after day 2 than IVIG alone (103 patients) (17% vs. 31%; risk ratio, 0.56; 95% confidence interval [CI], 0.34 to 0.94). The risks of the components of the composite outcome were also lower among those who received IVIG plus glucocorticoids: left ventricular dysfunction occurred in 8% and 17% of the patients, respectively (risk ratio, 0.46; 95% CI, 0.19 to 1.15), and shock resulting in vasopressor use in 13% and 24% (risk ratio, 0.54; 95% CI, 0.29 to 1.00). The use of adjunctive therapy was lower among patients who received IVIG plus glucocorticoids than among those who received IVIG alone (34% vs. 70%; risk ratio, 0.49; 95% CI, 0.36 to 0.65), but the risk of fever was unaffected (31% and 40%, respectively; risk ratio, 0.78; 95% CI, 0.53 to 1.13). The inverse-probability-weighted analysis confirmed the results of the propensity-score–matched analysis.

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.)

Thank You

“People don’t care how much you know,
until they know how much you care”
(Theodore Roosevelt)