OPENING A NEW PANDORA'S BOX

Melanie Hau

HKSCCM grand round

22nd Sep 2020

HPI

M/52

Lives with family

Property manager

Good past health

Presented with productive cough, GE symptoms for 6 days

Admitted to another hospital's medicine department 19-31/7/2020

FIRST HOSPITALIZATION

SARS-CoV-2 RT PCR +ve with CT value 20.67

Enrolled into HKU group A study, treated with:

1. clofazimine + IFN 20-22/7
2. IFN 26-28/7
3. Ribavirin 26-29/7
4. Dexamethasone 25-27/7

Ab +ve 28/7, off O2 and discharged 31/7

Discharge CT value 25.54

READMISSION

Readmitted QEH MED 1 week later (7/8)

for fever, productive cough, mild shortness of breath

Repeated NP swab RT-PCR x SARS-CoV2 CT= 30.97

CRP (304mg/l) and procalcitonin (8.89ng/ml) elevated

Treated as CAP/secondary bacterial pneumonia

Empirical augmentin → tazocin for 2 days

DETERIORATION

Progressive Deterioration

High fever

Septic shock, requiring dopamine infusion

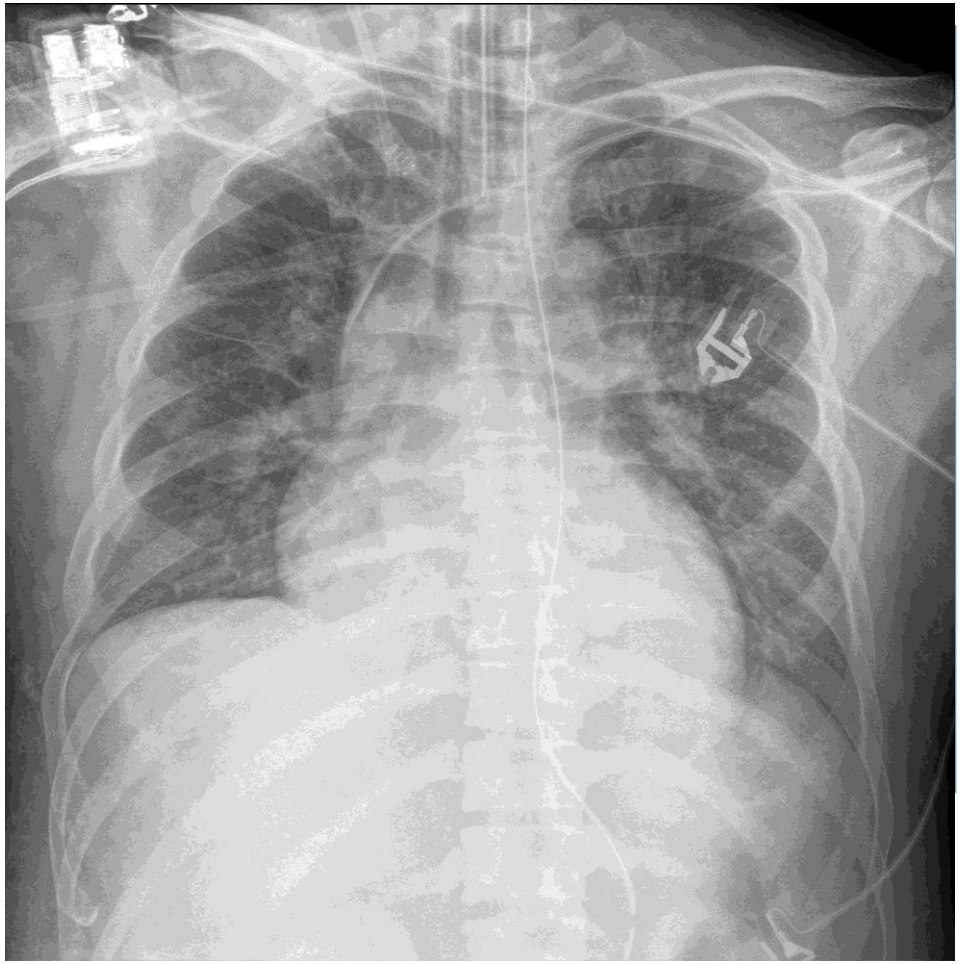
Antibiotics : →Vancomycin + meropenem

Respiratory failure: SpO2 88-90% on 6L O2

→ Intubated on day 5

Started Hydrocortisone for stress cover

ON ADMISSION TO ICU



BP 83/65 mmHg (MAP 72) on Noradrenaline 10mcg/min

SpO2 94-96% on FiO2 0.6 PEEP 10;

→ istat PaO2 10: PaO2/FiO2 ratio 134mmHg;

Urine output 50-80ml/hr

PHYSICAL EXAM

Sedated and paralysed

Chest: bilateral fine crepitations

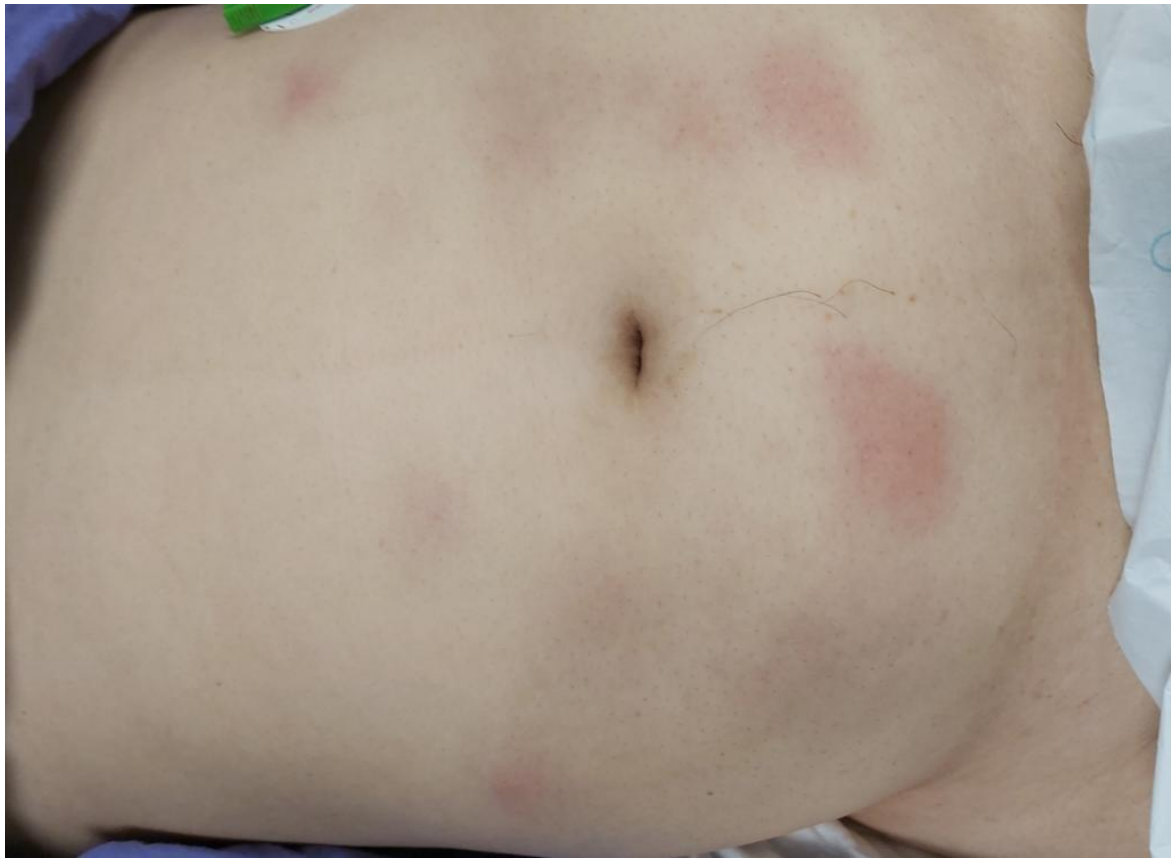
Abdomen: soft

Blancheable erythematous rash on the abdomen

No conjunctival injection

No cervical lymphadenopathy

No limbs/joint swelling



INVESTIGATIONS

- Hb11.8 WBC 25.1 Platelets 89; neutrophil 32, no lymphopenia
- Clotting: APTT 41.5s; INR/PT normal
- ABG: pH 7.29; pCO2 4.6 kPa; pO2 10.0 on FiO2 0.6 ; HCO3 23.2 BE -3
- Lactate 3.5 mmol/L
- Creatinine 88umol/L
- Liver Function
  - Bilirubin 11 umol/L → 29 umol/L in ICU
  - ALP 141 IU/L on hospital admission → 1994 IU/L in ICU
  - AST 53 IU/L → 3973 IU/L in ICU
  - ALP 155 IU/L → 212 IU/L in ICU
  - NH3 107 umol/L

INVESTIGATIONS – INFLAMMATORY MARKERS

	On hospital admission	On ICU admission
WBC (x 10^9/L)	12.9	25.1
Lymphocyte (x 10^9/L)	3.9	4.2
Neutrophil (x 10^9/L)	11.7	23.3
APTT (sec)	34.5	45.1
PT (sec)	13.1	19.5
D-dimer (ng/ml)	on admission in UCH: 675	> 5000
LDH (IU/L)	271	5254
CRP (mg/L)	152	304
Ferritin (pmol/L)	3033 on D3	154848
Procalcitonin (ng/ml)	0.63	8.89
Albumin (g/L)	32	13

Autoimmune panel unremarkable, no positive bacterial cultures, TA for common respiratory viruses -ve

INVESTIGATIONS - CARDIAC

ECG: no ischaemic changes

Hs-TnI 1425 ng/L ; CK normal

ECHO: LVEF 30% global hypokinesia, moderate MR, mild TR. No pericardial effusion

Coronary angiogram: mid to distal LAD total occlusion with retrograde from left system ; minor RCA and LCx lesions

- For medical treatment meanwhile in view of sepsis and DIC. Plan for elective PCI to LAD lesion.
- Endomyocardial biopsy done

INVESTIGATIONS - IMAGING

- CT abdomen with contrast: Thickened gallbladder wall, Duodenitis.

INVESTIGATIONS - HISTOPATHOLOGICAL

Endomyocardial biopsy: No pathological diagnosis

Skin biopsy:

Mild **mononuclear perivascular infiltrates in the dermis** accompanied by subtle endothelial swelling. Eosinophil is inconspicuous. Thrombosis or fibrinoid necrosis of blood vessel seen. Mild papillary dermal edema. No evidence of vasculitis found.

Imp: The histopathological changes are nonspecific, Although they can be seen in Kawasaki- like condition. They are not diagnostic.

MANAGEMENT

Immunomodulatory:

Hydrocortisone 100mg Q8H from day 1 ICU admission

IVIG 60g/day (1g/kg/day) on day 2 and 3

Antimicrobials:

Meropenem continued until day 6 ICU

Vancomycin continued until day 2 ICU

ACS: Aspirin/enoxaparin

CLINICAL COURSE-

Haemodynamic:

Required up to 22mcg/min noradrenaline on day 1

Weaned off vasopressors on day 4 ICU

Repeated echo on day 5 ICU: LVEF improved to 40%

Repeated echo on day 7 ICU: LVEF improved to 50%

Renal:

Oliguric on day 3-5, Creatinine 366umol/L, metabolic acidosis with BE up to -10

CVVH with EMiC filter from day 3-5

Urine output recovered to 1.4L/day on day 6 ICU

Resp:

High ventilatory support requirement and paralysed from day 1-2

Gradually improved and extubated on day 6 ICU

BIOCHEMICAL PROGRESS

IVIG on days 2-3

	Day 1 ICU	Day 3	Day 4	Before discharge
LDH (IU/L)	5254	821	349	472
CRP (mg/L)	304	164	83	7
Ferritin (pmol/L)	154848	84395	28604	1027
Procalcitonin (ng/ml)	4.87	8.89	4.30	
Neutrophil x 10^9/L	23.3	22.8	17.6	8.2

Creatinine (umol/L): 88 on day 1 ICU→ 366 on day 3 → 107 before discharge

ALP (IU/L): 212 on day 1 ICU→ 97 on discharge

ALT (IU/L): 1994 on day 1 ICU → 177 before discharge

AST (IU/L): 3973 on day 1 ICU → 23 before discharge

POST HOSPITAL DISCHARGE FOLLOW UP

Total ICU length of stay 8 days (discharged 18/8)

Total hospital length of stay 18 (discharged 25/8)

Discharged on prednisolone 30mg with tapering plan and aspirin.

Cardiac MRI appointment defaulted due to claustrophobia

DISCUSSION

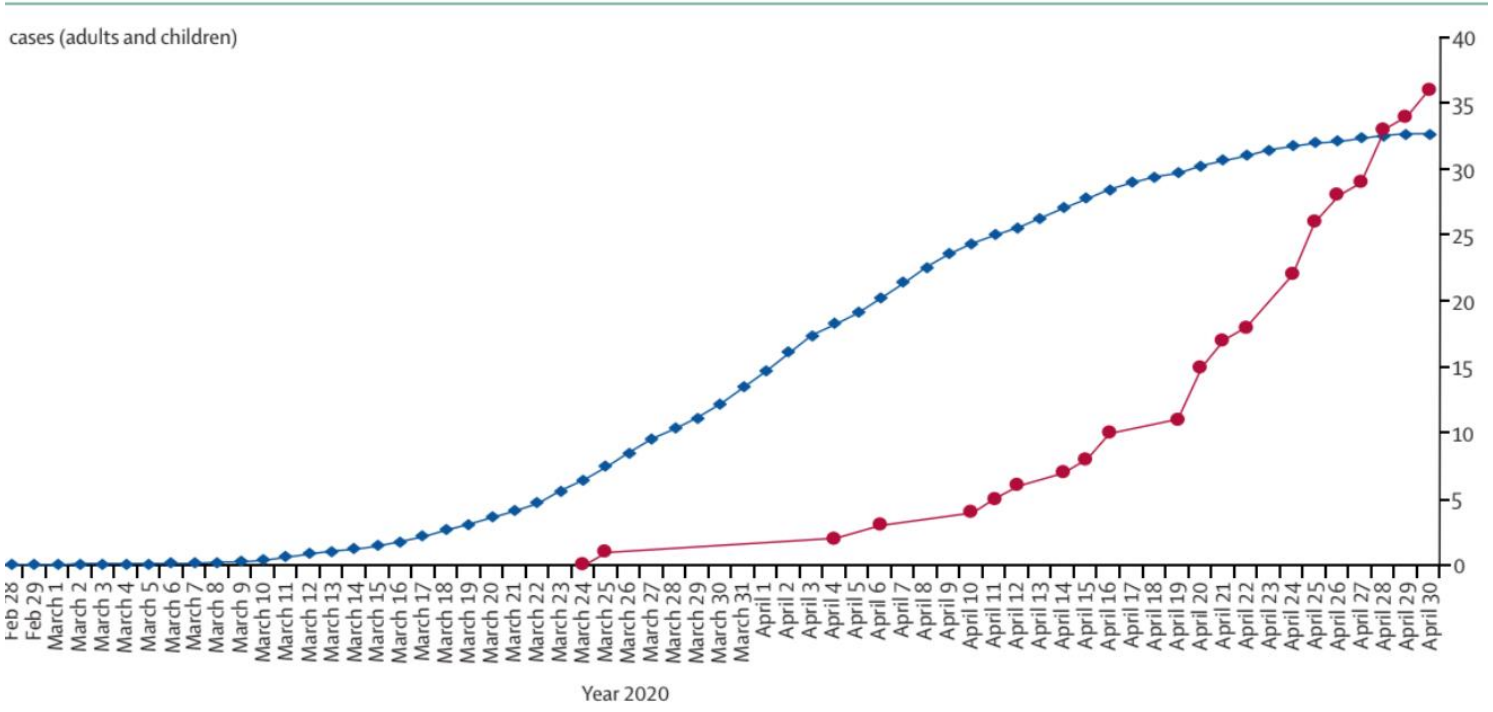
Children (MIS-C) Associated with Coronavirus Disease 2019 (COVID-19)

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

Paediatric Inflammatory Multisystemic Syndrome (PIMS-TS)

Multisystemic Inflammation Syndrome in Children (MIS-C)

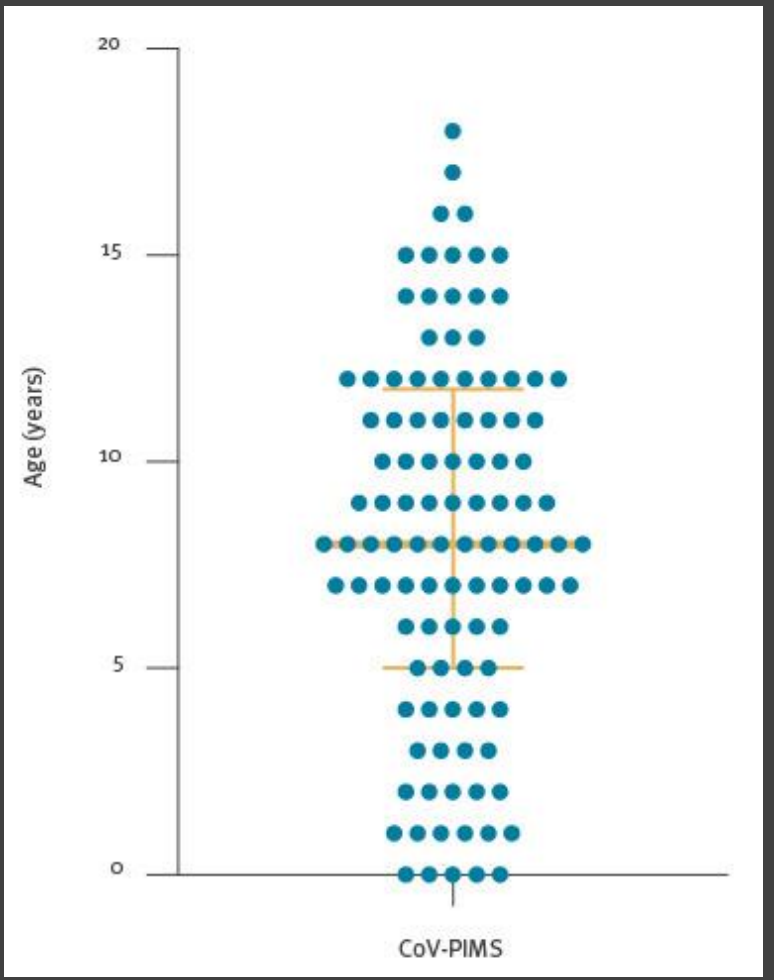
- Kawasaki-like disease
- Kawasaki disease toxic shock syndrome
- Myocarditis
- Macrophage activation Syndrome



PCR-positive COVID-19 cases

London, UK. Data taken from Public Health England.[89] Figure courtesy of Alasdair Bamford and Myrsini Kaforou. MIS-C=multisystem inflammatory syndrome in
e respiratory syndrome coronavirus 2.

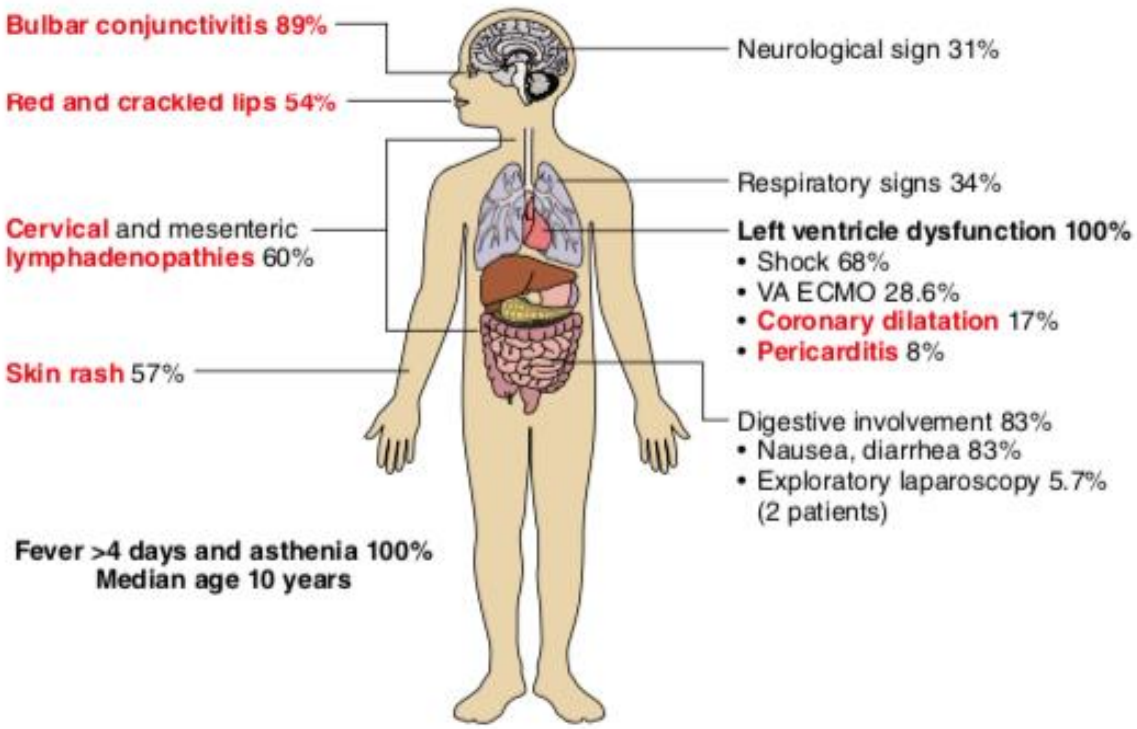
EPIDEMIOLOGY[3]



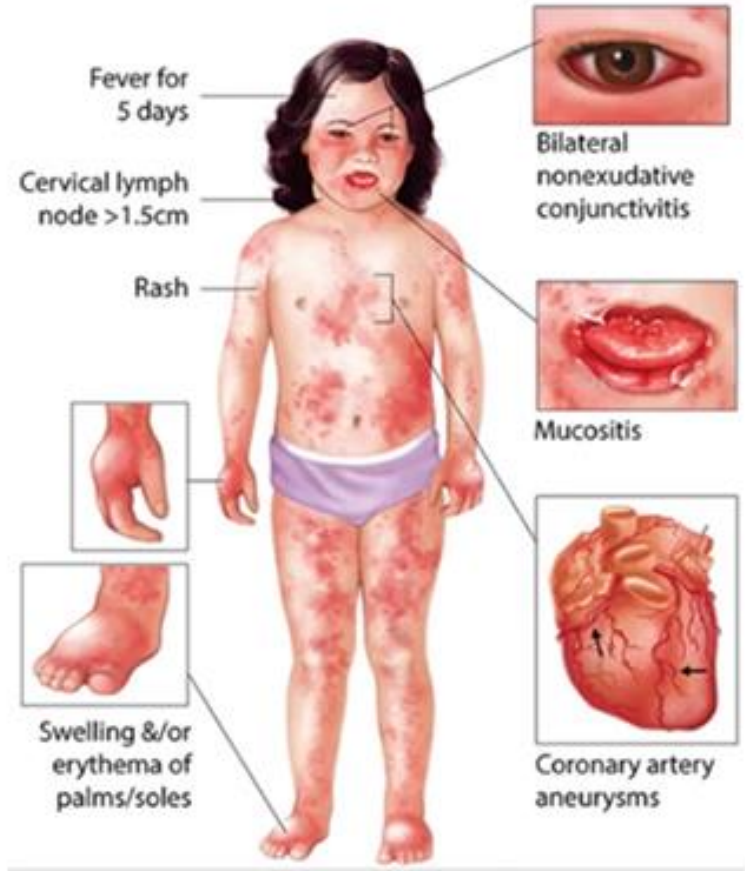
CDC: 71% Blacks and Hispanics

	Complete Kawasaki disease	Incomplete Kawasaki disease	Kawasaki disease shock syndrome
Organisation or publication	AHA	AHA	Kanegaye et al,[41]
Age	Child (age not specified)	Child (age not specified)	Child (age not specified)
Inflammation	Fever lasting 5 days or more*	Fever lasting 5 days or more*	Fever
Main features	>/= 4 of these clinical features: 1. erythema and cracking of lips, strawberry tongue, oral mucosa 2. bilateral bulbar conjunctival injection without exudate; 3. rash 4. acute phase: erythema and oedema of the hands and feet; subacute phase: periungual desquamation 5. cervical lymphadenopathy	2/3 principal clinical features or a positive echocardiogram	Kawasaki disease-like clinical features + Any of the following causing initiation of volume expansion, vasoactive agents, or ICU admission: systolic hypotension based on age/ decrease in systolic blood pressure from baseline by 20% or more/ clinical signs of poor perfusion
Exclusion	..	..	Other microbial cause

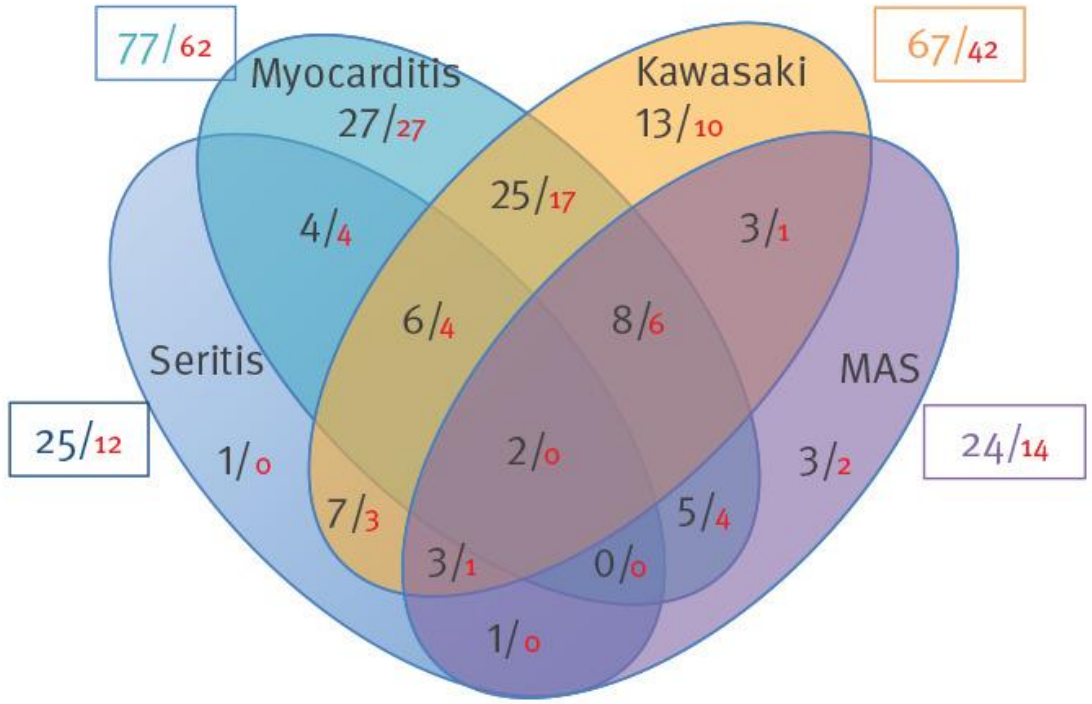
SARS-COV-2 related multisystem inflammation



Kawasaki disease



CLINICAL FEATURES



ALL COV-PIMS (n = 108)
Confirmed CoV-PIMS (n = 79)

	Events	Total	Pooled mean proportion (95%CI)	Heterogeneity I^2 (%)
Demographic				
Male sex	374	660	55·8 (50·3–61·2)	30·7
Female sex	287	660	44·2 (38·8–49·7)	30·7
Ethnicity				
Black African	173	542	35·6 (28·5–43·4)	56·5
Hispanic	101	375	27·5 (16·8–41·6)	69·5
Non-Hispanic white	193	539	19·5 (15·1–24·7)	29·4
Asian	39	349	10·5 (4·9–21·0)	72
Other	109	491	22·4 (15·7–31·0)	63·2
Clinical features				
Abdominal pain	127	660	68·9 (56·8–78·8)	43·2
Diarrhoea	48	99	50·3 (37·0–63·6)	24·2
Vomiting	62	91	69·2 (58·8–78·2)	0
Other gastrointestinal tract symptoms (not specified)	410	465	86·9 (81·8–90·8)	25·7
Neurological symptoms	133	370	38·7 (29·0–49·4)	65·8
Complete Kawasaki disease	105	312	41·1 (27·9–55·8)	70·6
Incomplete Kawasaki disease	34	76	45·6 (34·4–57·2)	0
Myocarditis	124	243	57·8 (43·3–71·1)	61·3
Shock	238	438	66·5 (52·0–78·5)	81·4
Laboratory and radiological features				
RT-PCR	275	655	34·7 (26·3–44·1)	67·6
Serological test	445	634	80·3 (70·9–87·2)	78·3
Elevated D-dimer	330	356	93·3 (84·5–97·3)	69·5
Abnormal renal function tests	84	257	43·2 (24·1–64·6)	87·6
Coronary artery dilatation	27	193	15·5 (10·9–21·6)	0
Coronary aneurysm	33	442	8·9 (6·2–12·6)	7·3
Cardiac dysfunction	218	327	63·3 (52·9–72·6)	47·6
Treatment				
Intensive care unit admission	481	606	79·1 (70·8–85·5)	61·7
Mechanical ventilation	187	648	29·2 (19·9–40·5)	79·3
Extracorporeal membrane oxygenation	32	525	7·6 (4·1–13·8)	57·1
Outcomes				
Recovered	530	619	91·1 (82·3–95·7)	76·8
Death	11	625	3·5 (2·2–5·5)	0

Figure 3: **Pooled meta-analysis of patient characteristics in multisystem inflammatory syndrome in children associated with COVID-19**[8-36]
Three case series were not included in the meta-analysis because of the overlap in cases. Cases reported in two studies[34,35] were also included in the case series reported by Feldstein and colleagues.[22] Cases reported by Riphagen and colleagues[10] were also included in the study by Whittaker and colleagues.[18] The random-effect model is applied.

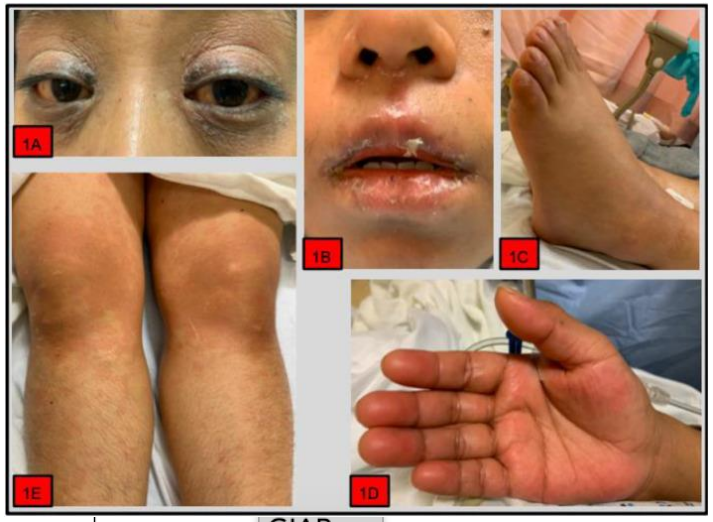
CASE DEFINITIONS [3]

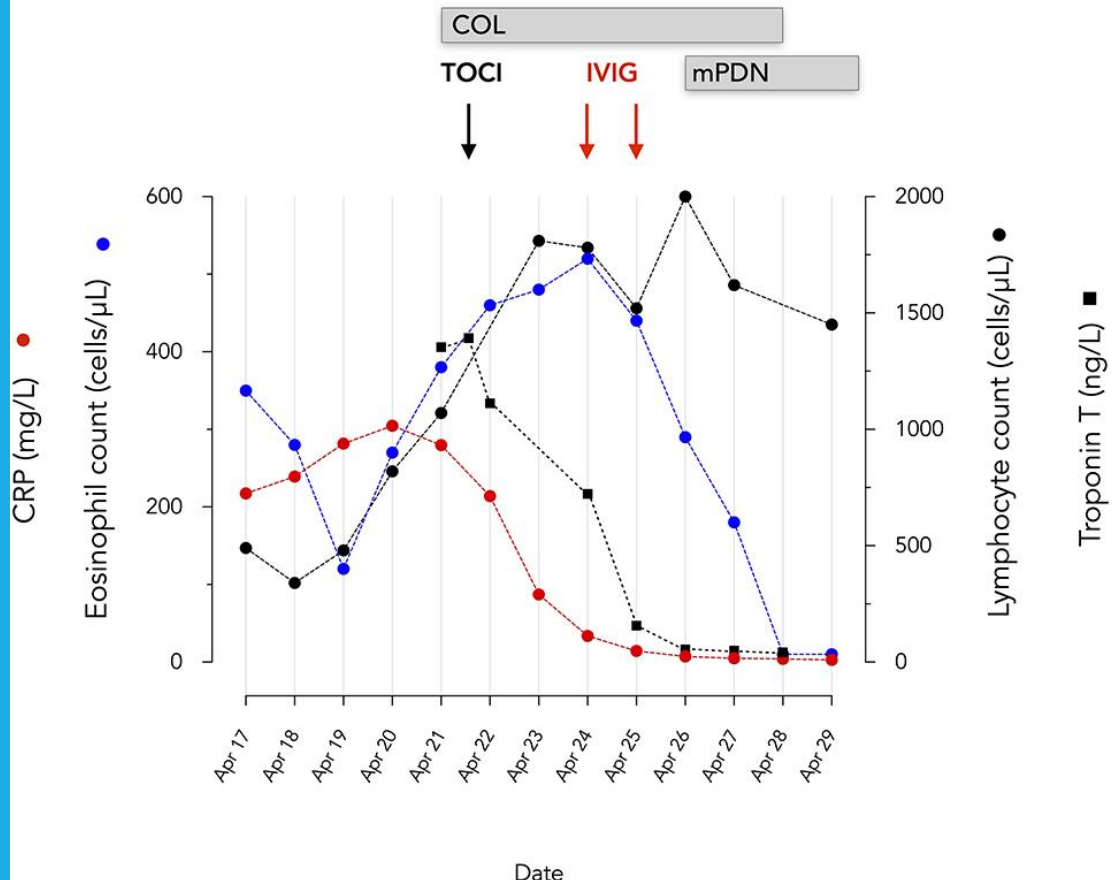
	MIS-C associated with COVID-19	PIMS-TS	MIS-C associated with COVID-19
Organisation or publication	WHO[6]	RCPCH	US CDC
Age	0–19 years	Child (age not specified)	<21 years
Inflammation	Fever and elevated inflammatory markers for 3 days or more	Fever and elevated inflammatory markers	Fever and elevated inflammatory markers
Main features	Two of the following: 1. rash/bilateral non-purulent conjunctivitis/mucocutaneous inflammation signs (oral, hands, or feet); 2. hypotension/shock; 3. features of myocardial dysfunction, pericarditis, valvulitis, or coronary abnormalities 4. coagulopathy (↑ PT/APTT/D-dimer) 5. acute GI problems	Single or multiple organ dysfunction (shock/respiratory/ renal/ gastrointestinal/neurological disorder	1. Clinically severe illness requiring hospitalisation 2. Multisystem organ involvement (2+) (cardiac, renal, respiratory, haematological, gastrointestinal, dermatological, or neurological)
Exclusion	Other microbial cause of inflammation	Any other microbial cause	Other plausible alternative diagnoses
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

REPORTED CASES OF ADULT-MIS TO DATE

Location	New York City[4]	US[5]	London[6]	France[7]	Belgium[8]
Patient	45/M, Hispanic	36/F	21/M	21/caucasian	19/F
1st exposure	2 weeks ago				3 weeks ago (anosmia)
SARS-CoV-2 PCR	+ve	+ve	-ve (nasal/ stool)	-ve (nasal swab, saliva, stool, skin bx)	-ve (nasal, BAL)
COVID Serology		+ve	+ve	+ve	+ve (IgG and IgM)
			Symptoms		
Fever	+	+		+	+
Lymphadenopathy		+	+		+
Mucositis	Conjunctivitis* chelitis	Conjunctivitis Cracked lips	Conjunctivitis Cracked Lips Pominent lingual papillae	Conjunctivitis	Conjunctivitis Red, swollen lips
Resp	Sore throat		Required HFNO	Pleural effusion	ARDS
Cutaneous	Erythema Multiforme Skin bx: nonspecific inflammatory infiltrates Extremity pain	Diffuse MP rash Acral oedema Palmar erythema	Palmar MP rash	MP rash over trunk and palms Skin bx: upper dermis inflammatory infiltrates	Morbilliform rash on ULs and buttock
MSK		Arthalgias			
GI	Diarrhea #	CT abdomen: GB thickening, colitis	CT abdomen: mesenteric adenopathy, terminal ileitis	diarrhea	
Cardiac	↑TnI ↑BNP Echo: impaired ventricular function	Echo and CT coro normal (done after IVIG)	↑TnT ECG/Echo/CT coro normal	Echo: hyperdynamic LV, normal EF	↑↑TnT Echo: LVEF 15%. pericardial effusion Cardiac MRI: myocardial edema
Shock			+	+	+ (PiCCO: distributive +cardiac depression)
			Investigations		
Inflammatory markers	↑CRP/ESR ↑neutrophil ↓lymphocyte ↑ Procalcitonin ↑ IL6	↑CRP ↑ D-dimer	↑inflammatory markers ↑neutrophil ↓lymphocytes ↑eosinophils	↑CRP ↑procalcitonin ↑ferritin	↑CRP ↑IL6 ↑D-dimer ↑WCC
Others	↑↑ferritin, ↑TG ↑AST (suggestive of HLH)	Anaemia Hyponatraemia ↑ AST/ALT/ALP/bilirubin		↑lactate	
Treatment	LMWH IVIG (2g/kg over 2 days) Tocilizumab	Aspirin 650mg IVIG Pulsed Methylprednisolone	IVIG Methylprednisolone	None	Tocilizumab IVIG
Course	-Discharged day 9 Resolution of symptoms -Normal repeated echo	-Recovery in 1 day Discharged on prednisolone	-Discharged on low dose aspirin on day 8	- Discharged from ICU on day 8 - CT coro at 4 weeks no coronary aneurysms - Cardiac MRI at 4 weeks no myocarditis	- Discharged 3 weeks later - Repeated CT angiogram: a coronary artery aneurysm, methylprednisolone started

A CLOSER LOOK





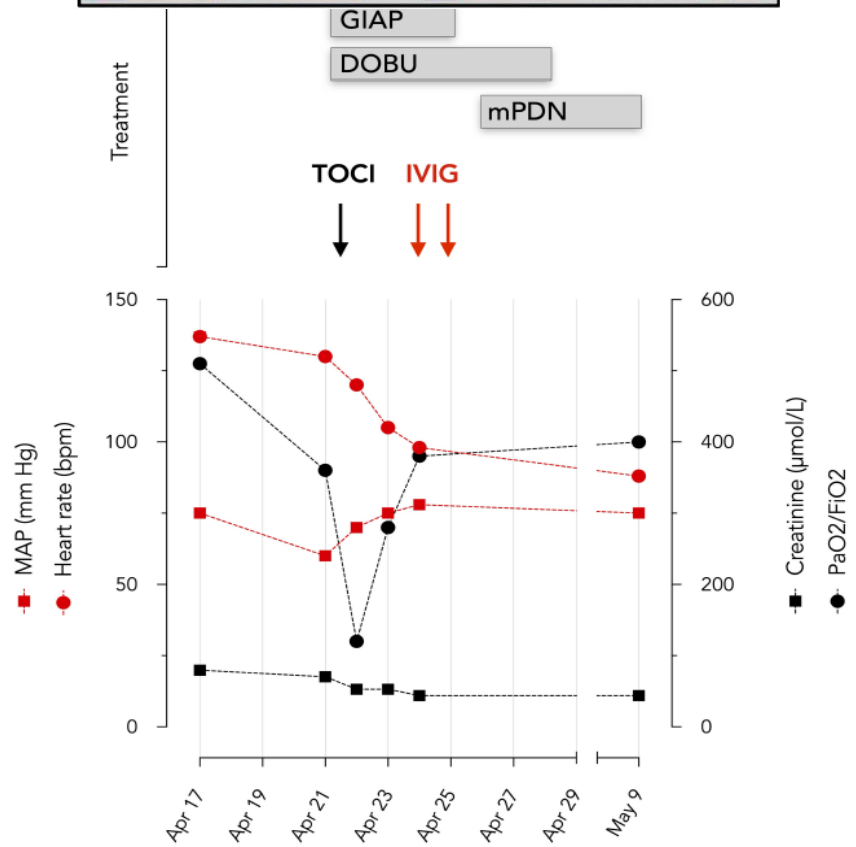
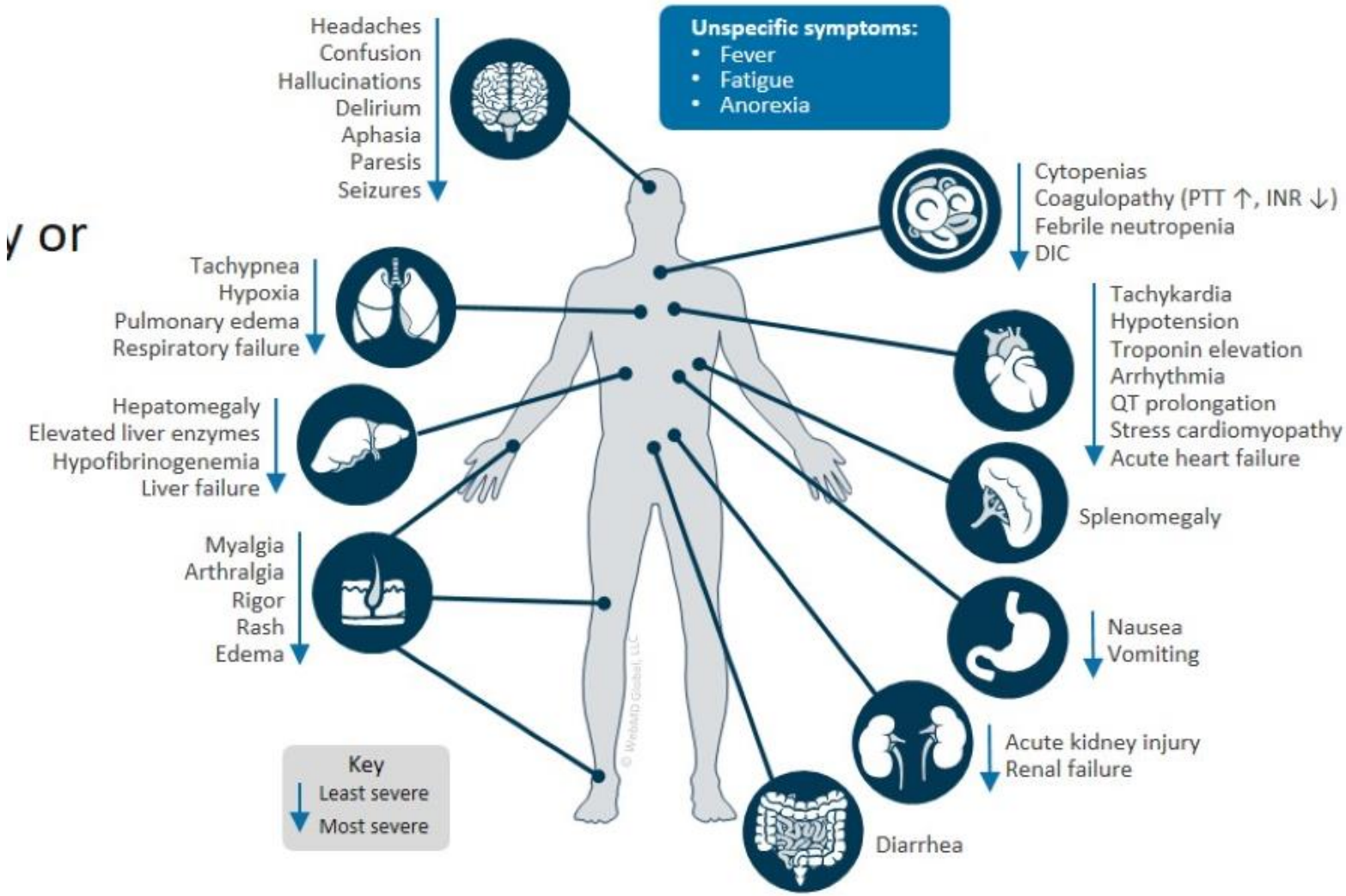
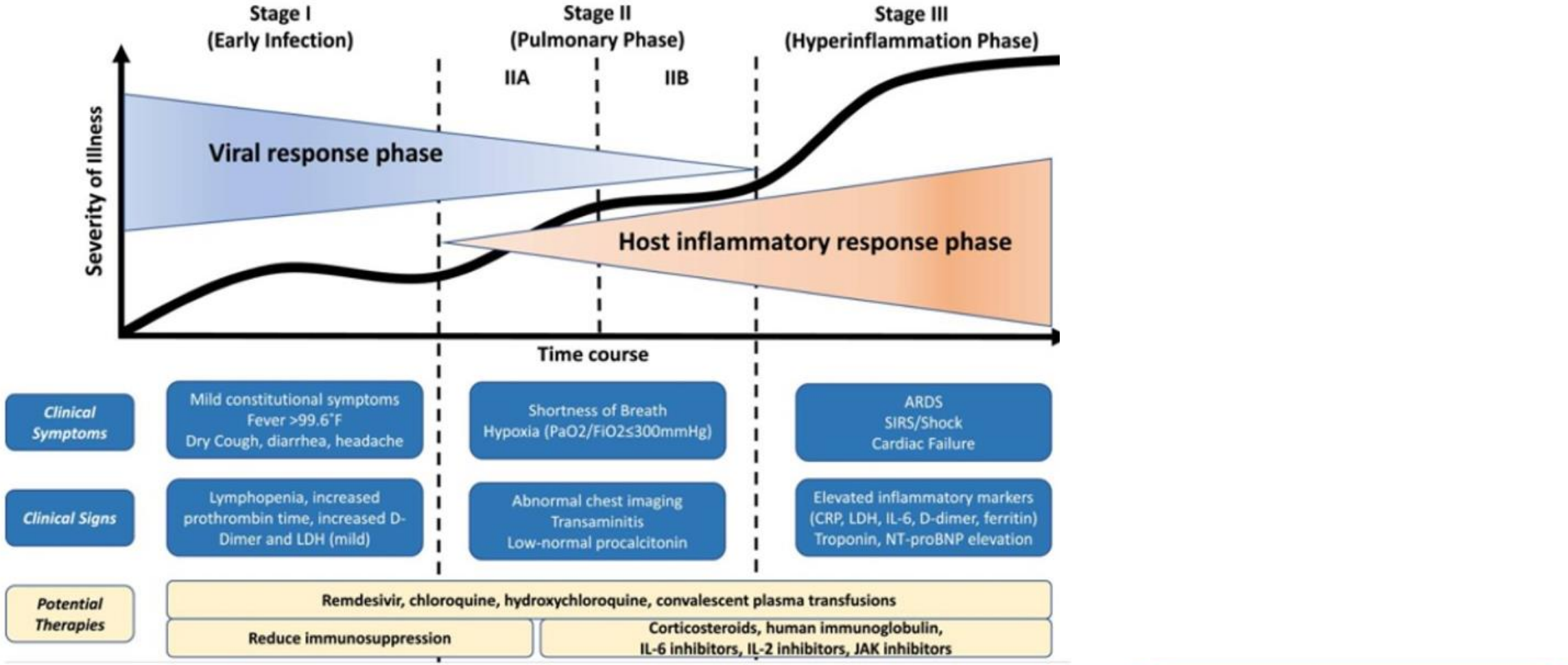


FIGURE 3 | Evolution of hemodynamic and organ function variables. Oxygenation was assessed by PaO_2/FiO_2 ratio and renal function by serum creatinine levels BPM beats per minute. TOCI, tocilizumab; COL, colchicine; DOBU, dobutamine; mPDN, methylprednisolone; IVIG, Privigen 60 g; GIAP, Giapreza.

Clinical presentation of the cytokine storm



COVID-19 AND INFLAMMATORY RESPONSE[9]



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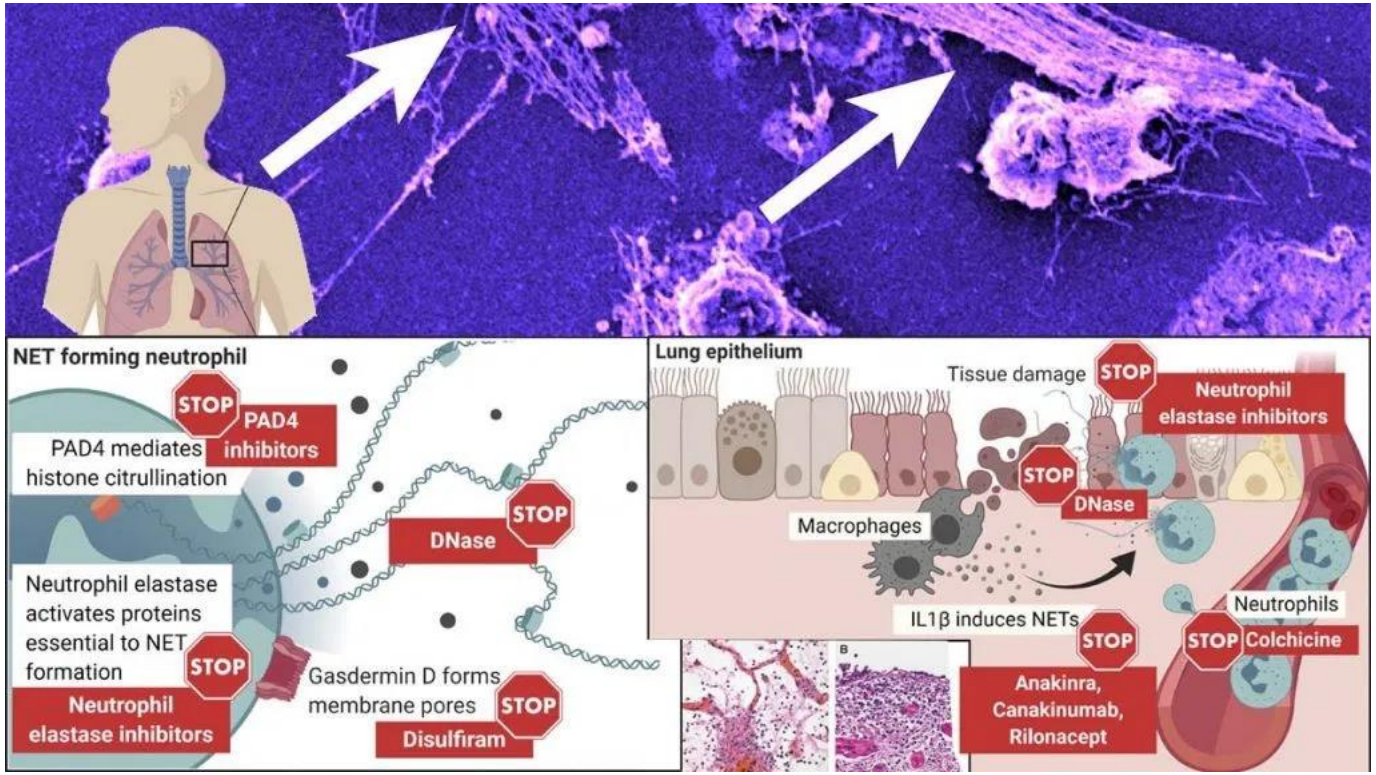
PATHOPHYSIOLOGY

POSSIBLE MECHANISM FOR INNATE IMMUNE RESPONSE[11]

NET (Neutrophil Extracellular Traps)



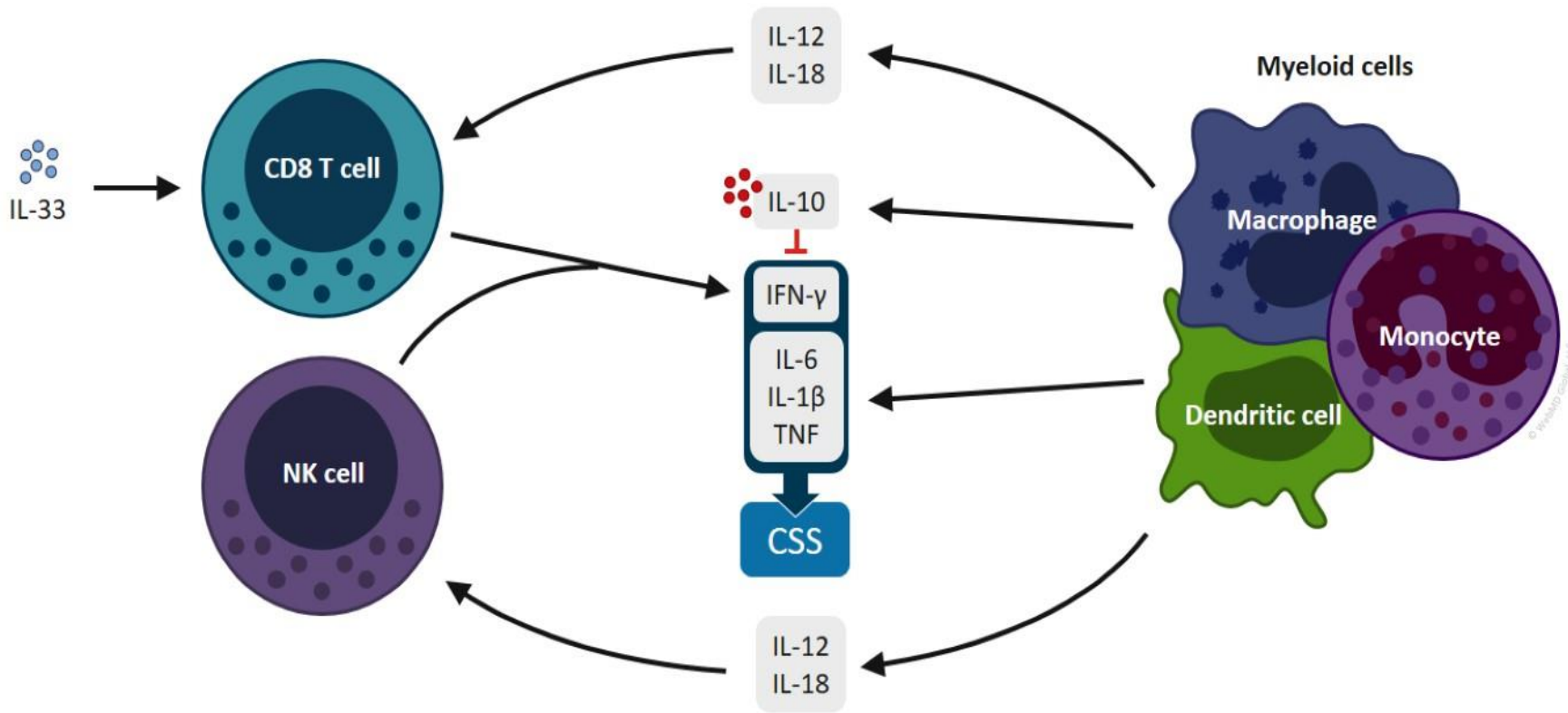
ARDS

Excessive thrombosis

Cytokine storm

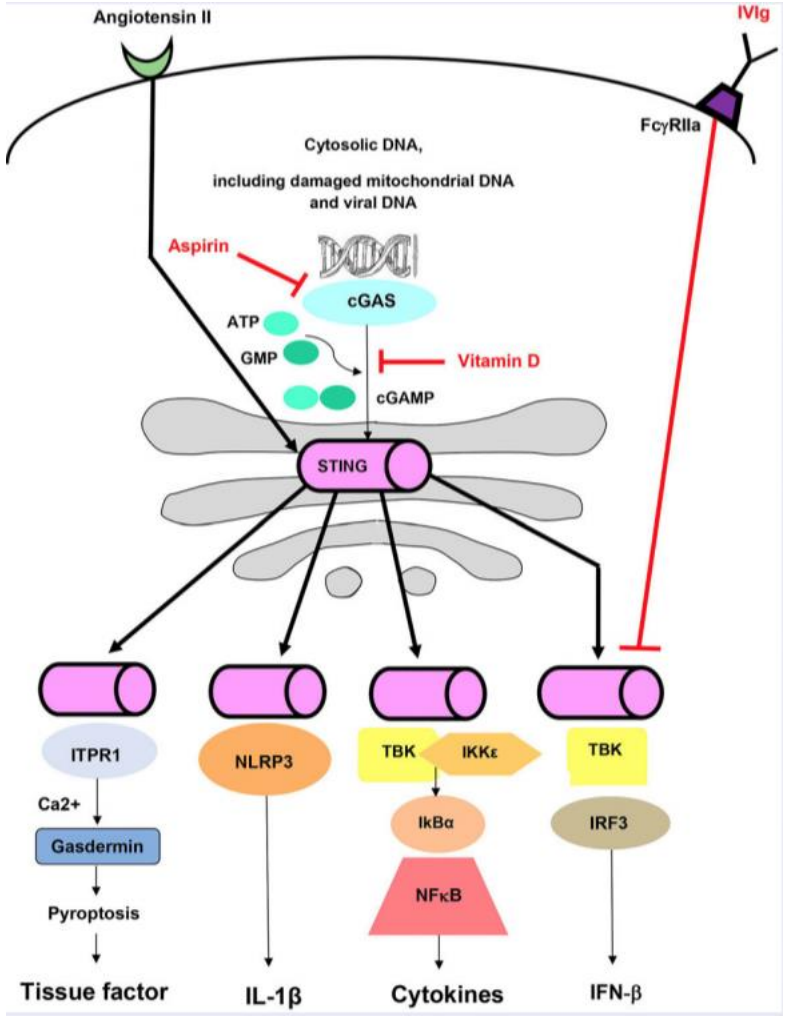
IL1β, IL2, IL6, IL7, IL8, IL10, IL17, IFNγ,TNFa etc..

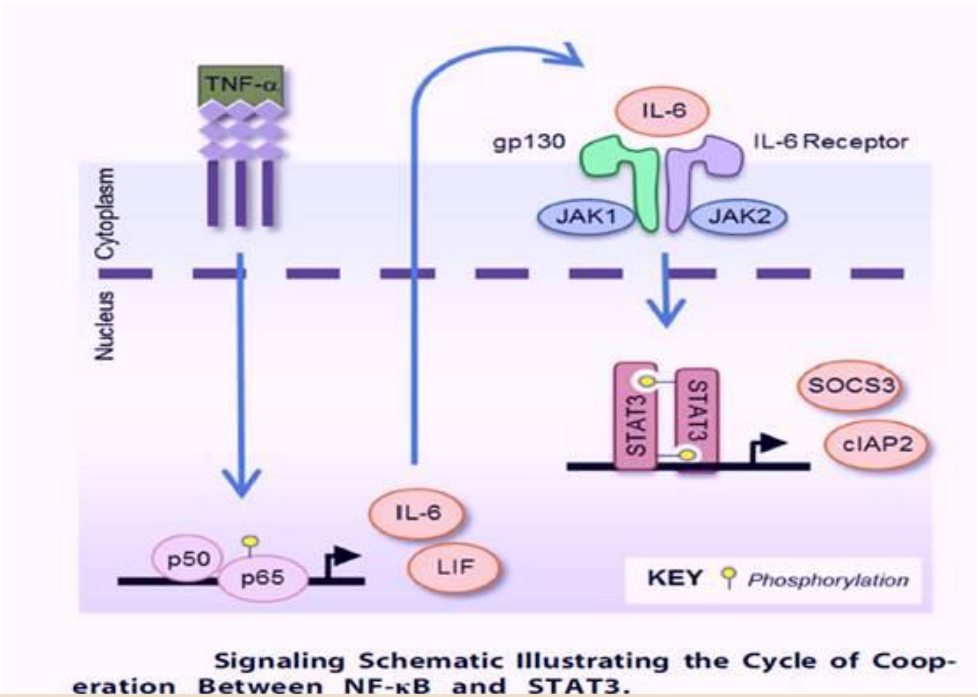
Cytokine Storm Pathway



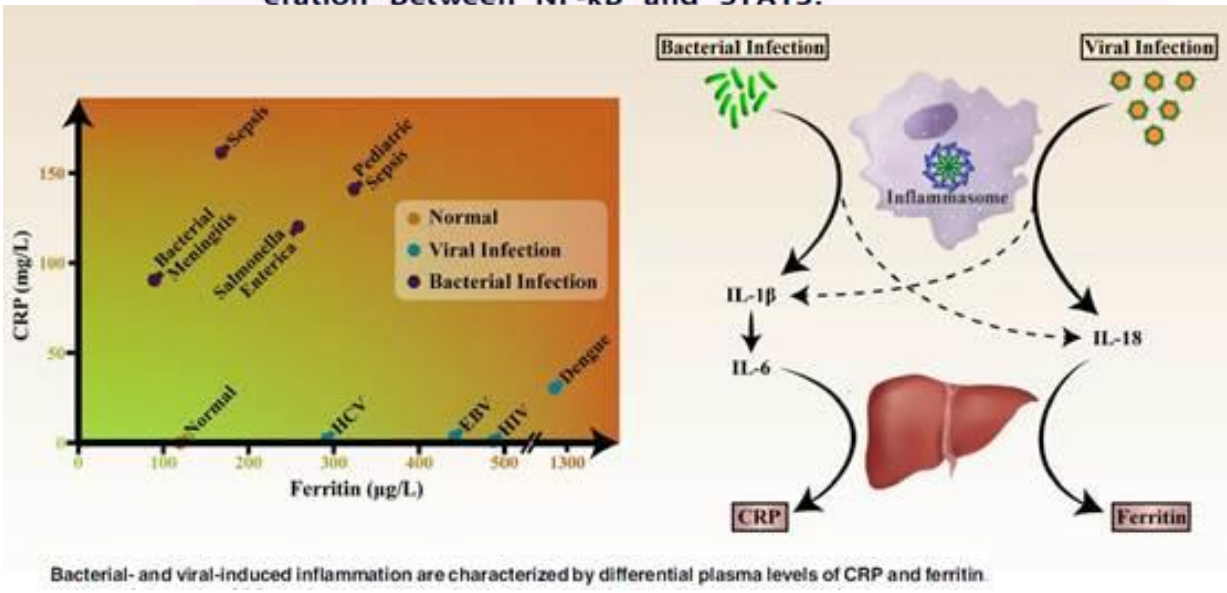
Cron RQ, et al. *Cytokine Storm Syndrome*. 2019.

CYOTKINE DISREGULATION RESPONSE[12]



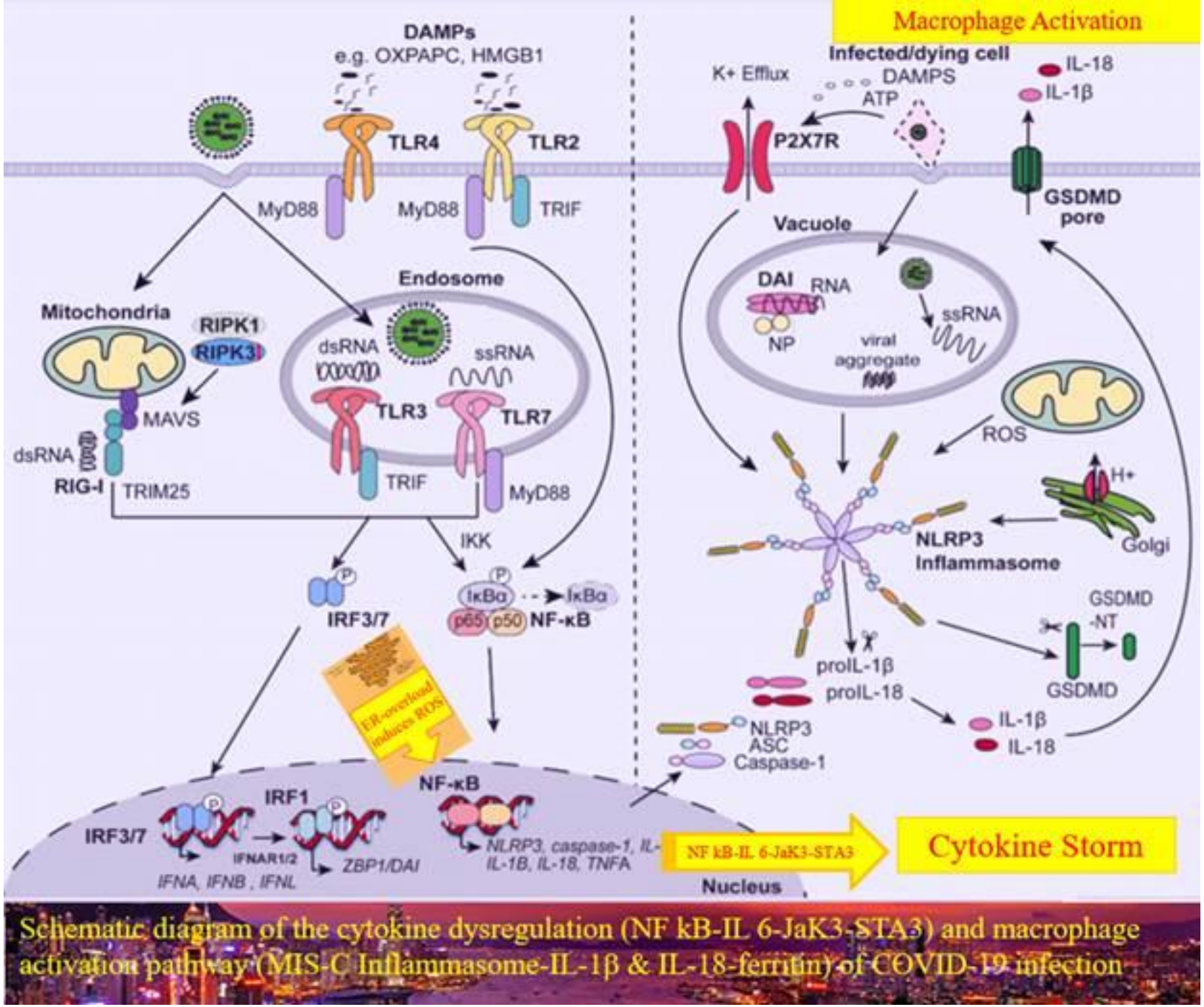


Signaling Schematic Illustrating the Cycle of Coop-
eration Between NF-κB and STAT3.



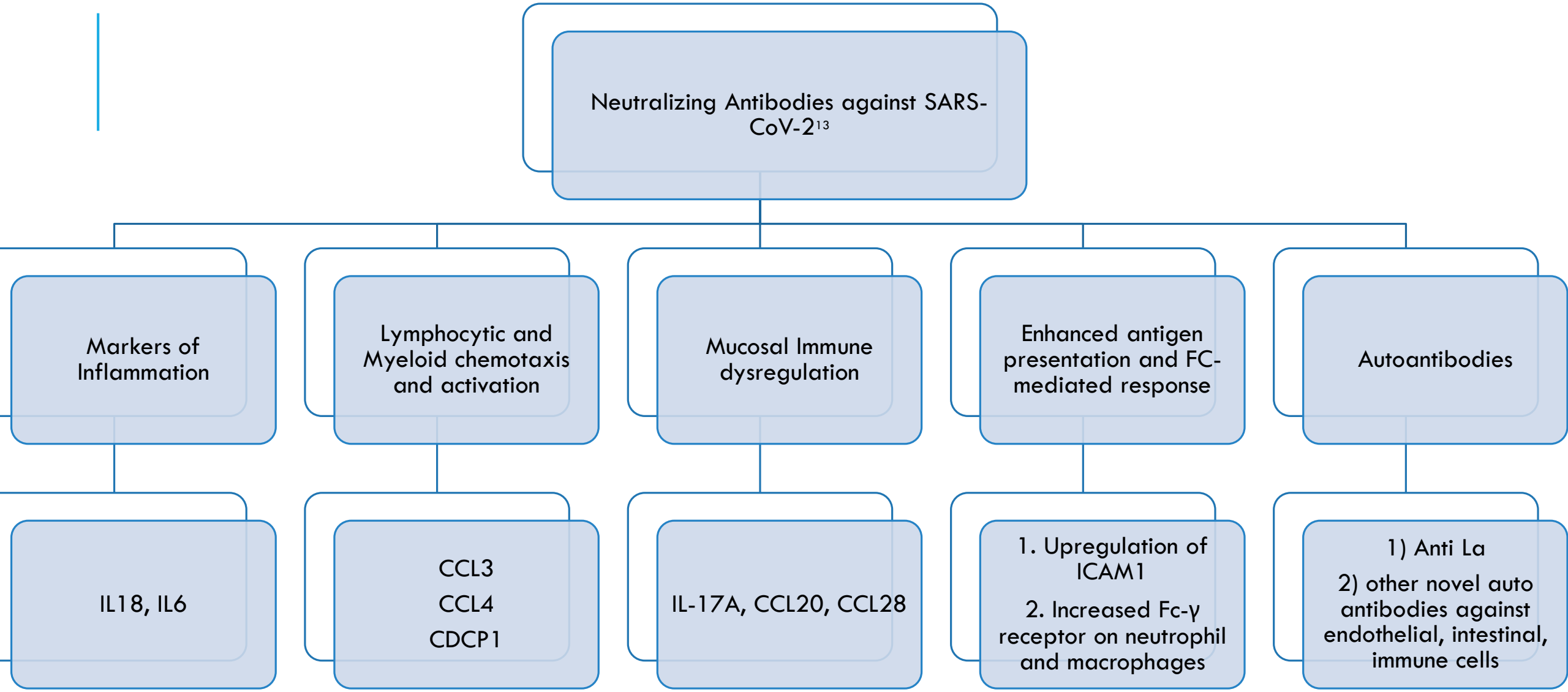
Bacterial- and viral-induced inflammation are characterized by differential plasma levels of CRP and ferritin

Courtesy to Dr. K.Y. Lai for the images



Schematic diagram of the cytokine dysregulation (NF kB-IL 6-JaK3-STA3) and macrophage activation pathway (MIS-C Inflammasome-IL-1β & IL-18-ferritin) of COVID-19 infection

Courtesy to Dr. K.Y. Lai for the image


Neutralizing Antibodies against SARS-CoV-2[13]
Markers of Inflammation
Lymphocytic and Myeloid chemotaxis and activation
Mucosal Immune dysregulation
Enhanced antigen presentation and FC-mediated response
Autoantibodies
IL18, IL6
CCL3
CCL4
CDCP1
IL-17A, CCL20, CCL28
1. Upregulation of ICAM1
2. Increased Fc-γ receptor on neutrophil and macrophages
1) Anti La
2) other novel auto antibodies against endothelial, intestinal, immune cells

POSSIBLE SARS-COV ANTIBODY MEDIATED RESPONSES

1) Antibody dependent enhancement of viral entry and amplification of viral replication

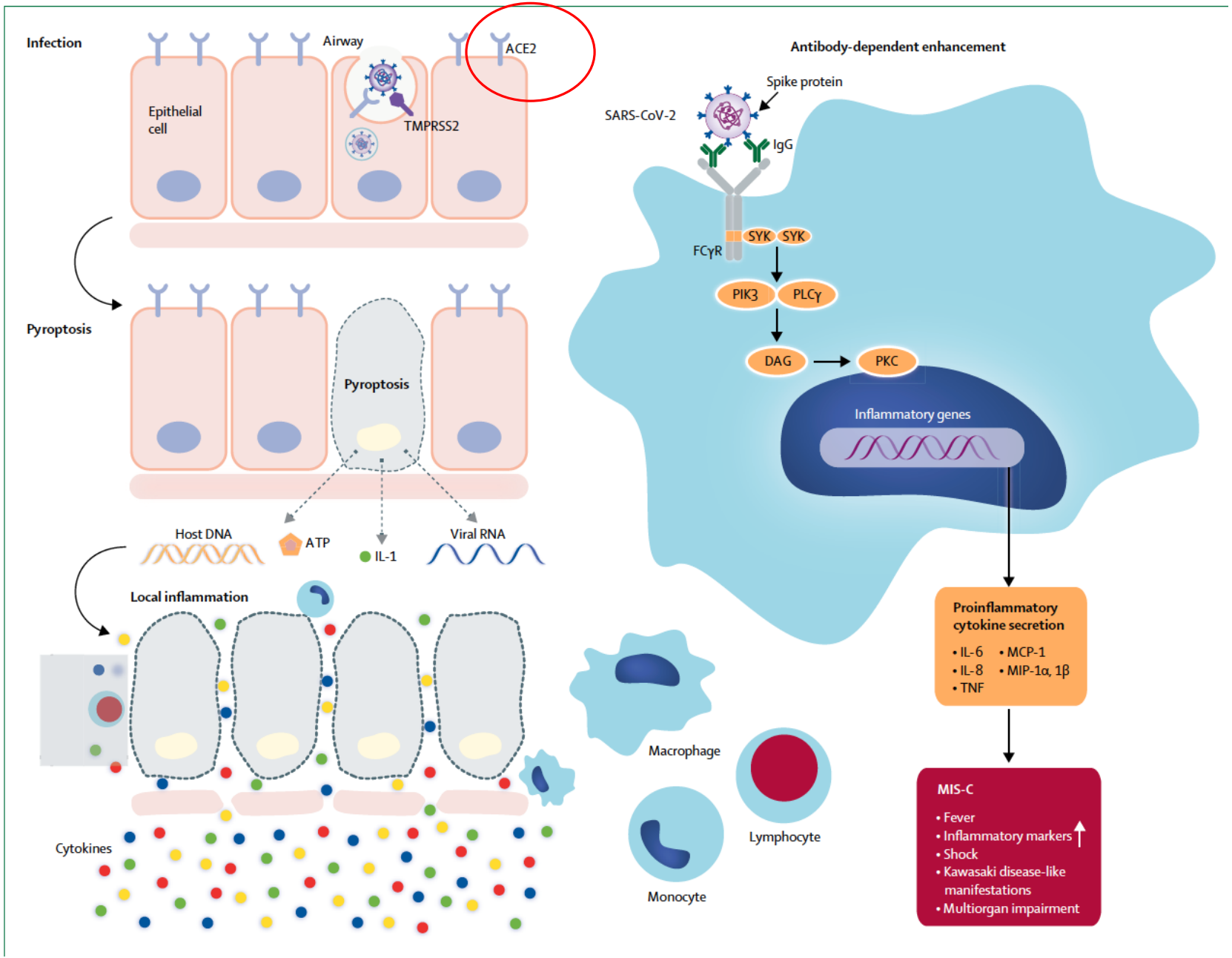
2) Formation of immune complexes which activate inflammation

3) Antibody or T cell recognition of self antigens → autoantibodies

- Viral mimicry of the host

4) Antibody or T-cell recognition of viral antigens expressed on infected cells

5) Viral super antigen sequences which activate host immune cells

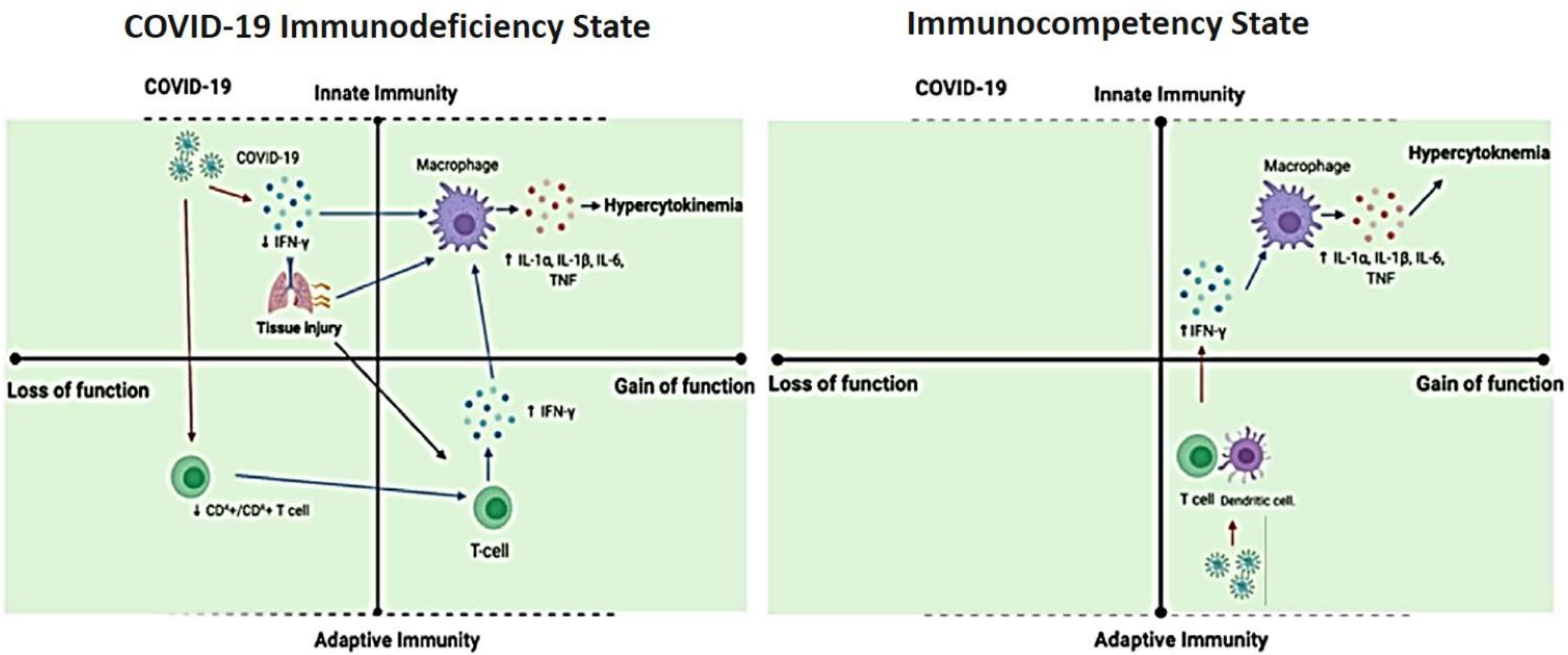

Infection
Airway
ACE2
Epithelial cell
TMPRSS2
Pyroptosis
Pyroptosis
Host DNA
ATP
IL-1
Viral RNA
Local inflammation
Cytokines
Antibody-dependent enhancement
Spike protein
SARS-CoV-2
IgG
FCγR
SYK
SYK
PIK3
PLCγ
DAG
PKC
Inflammatory genes
Proinflammatory cytokine secretion
• IL-6
• IL-8
• TNF
• MCP-1
• MIP-1α, 1β
Macrophage
Lymphocyte
Monocyte
MIS-C
• Fever
• Inflammatory markers
• Shock
• Kawasaki disease-like manifestations
• Multiorgan impairment

IMMUNOLOGICAL LINK TO KAWASAKIS DISEASE?

Immune complexes → FcγR/Complement activation → vascular injury and inflammatory response

Increased T-cell responses

Classification of COVID-19 Macrophage Activation Syndrome-Like Disease



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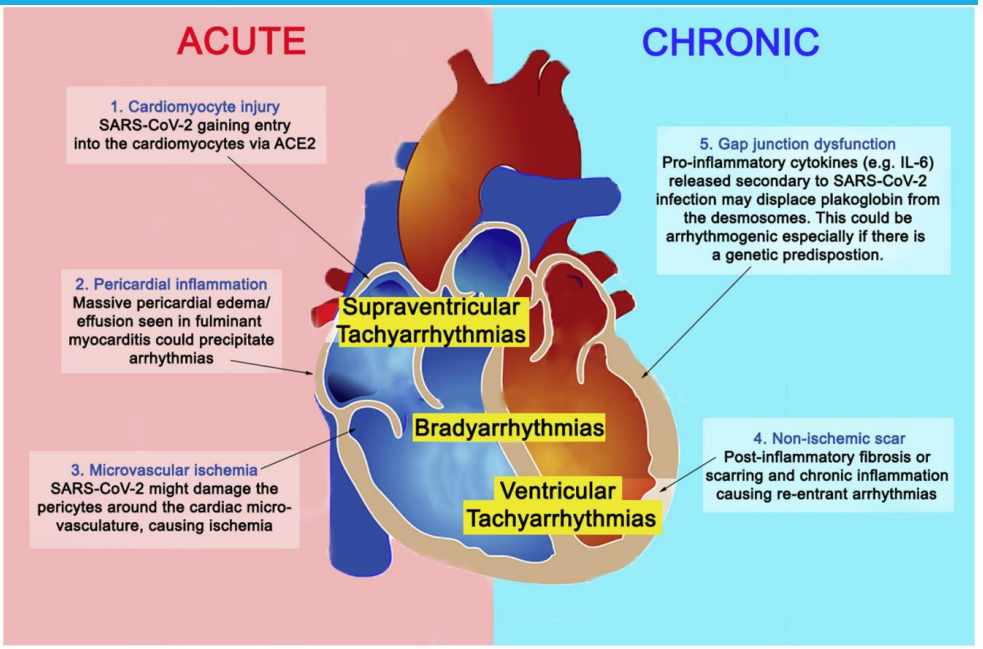
COVID-19 CYTOKINE STORM AND HLH [15]

HLH-04 Criteria	HScore	Ferritin:ESR ratio	COVID-19 Features
Fever	Fever		Yes
Splenomegaly	Splenomegaly		Unknown
	Hepatomegaly		Unknown
Anemia	Anemia		Yes
Thrombocytopenia	Thrombocytopenia		Yes
Neutropenia	Neutropenia		Yes
Hypertriglyceridemia	Hypertriglyceridemia		Unknown
Hypofibrinogenemia	Hypofibrinogenemia		Yes
Hemophagocytosis	Hemophagocytosis		Unknown
Low NK cell activity			Unknown
Hyperferritinemia	Hyperferritinemia	Hyperferritinemia	Yes
Elevated soluble CD25	Elevated soluble CD25		Yes
	Elevated serum GGT		Unknown, but AST and ALT ↑
	Underlying immunosuppression		Some with HIV infection
		Falling ESR	Unknown

Cron RQ, et al. *J Rheumatol*. 2020;47:639-642.

CARDIAC INVOVEMENT



ure 2 Arrhythmogenesis in SARS-CoV-2–related myocarditis. Possible mechanisms responsible for arrhythmias in SARS-CoV-2–related myocarditis are own. Mechanisms 1, 2, and 3 could occur in the acute setting, whereas mechanisms 4 and 5 occur in chronic/healed myocarditis. Abbreviations as in Figure 1.

Coronary artery dilatation was observed in 8.9% (CI 6.2-12.6) of patients

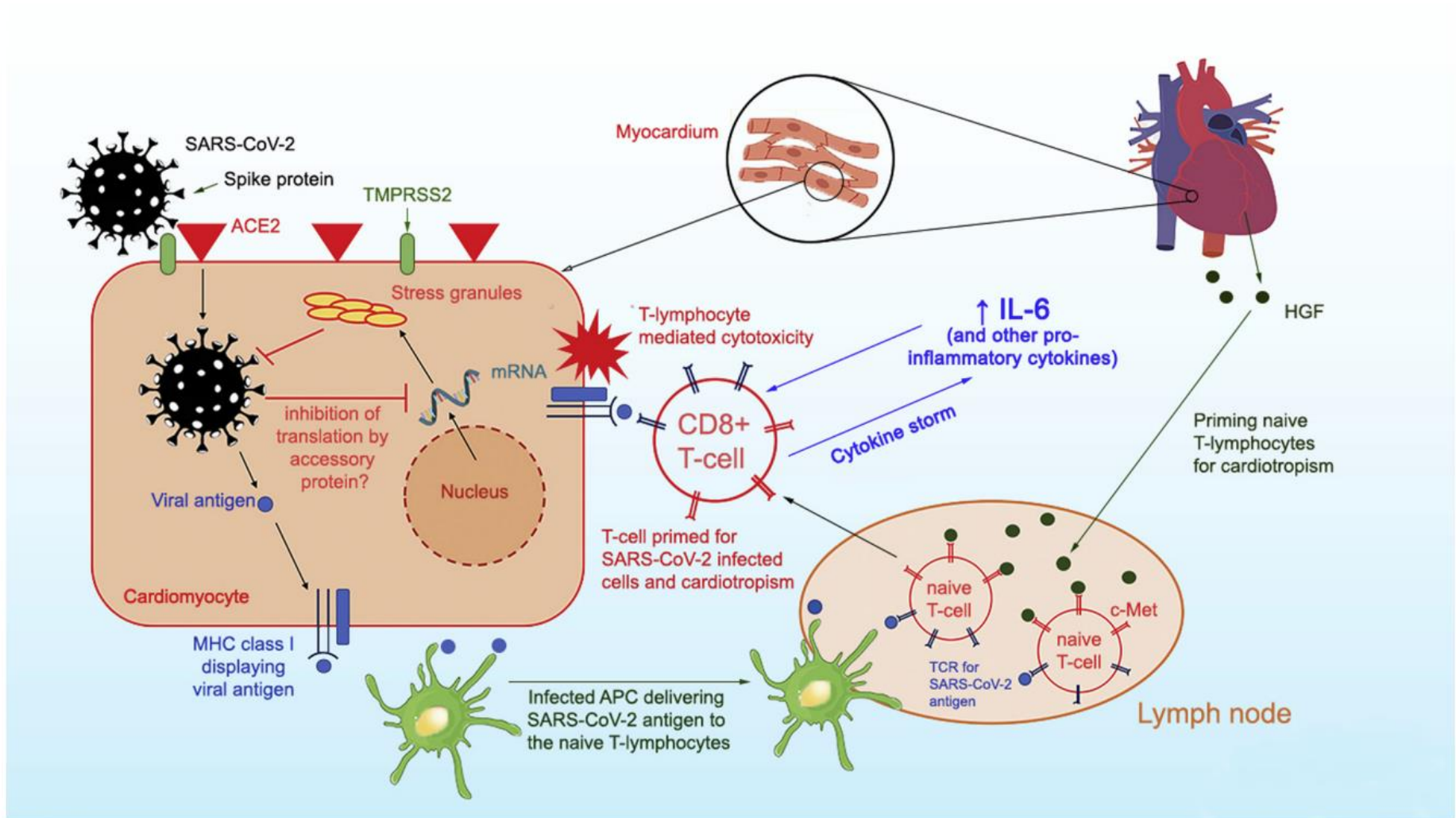
Aneurysm seen in 15.5% (10.9-21.6) at presentation

Smaller proportion with persistent coronary artery aneurysm after discharge from hospital (incidence unknown)

Elevated troponin (80.9%) /

Elevated BnP (84.9%) /

Arrhythmia/ left ventricular dysfunction (63.3%)


SARS-CoV-2
Spike protein
ACE2
TMPRSS2
Stress granules
mRNA
inhibition of translation by accessory protein?
Nucleus
Viral antigen
Cardiomyocyte
MHC class I displaying viral antigen
Myocardium
T-lymphocyte mediated cytotoxicity
↑ IL-6
(and other pro-inflammatory cytokines)
Cytokine storm
CD8+ T-cell
T-cell primed for SARS-CoV-2 infected cells and cardiotropism
HGF
Priming naive T-lymphocytes for cardiotropism
naive T-cell
c-Met
naive T-cell
TCR for SARS-CoV-2 antigen
Lymph node
Infected APC delivering SARS-CoV-2 antigen to the naive T-lymphocytes

MANAGEMENT

EXISTING PUBLISHED GUIDELINES

	Royal College of Paediatrics and Child Health	**US Centres for Disease control and prevention**
Supportive Care	Only recommended for mild to moderate disease. Discuss with pediatric ICU and pediatric infectious disease, immunology and rheumatology team. If clinical deteriorating or in case of severe disease, discuss transfer with paediatric ICU team	Fluid resuscitation, inotropic support, respiratory support, and in rare cases, extracorporeal membranous oxygenation
Directed care against underlying inflammatory processes	Immunotherapy should be discussed with paediatric infectious disease unit and experienced clinicians on a case by case basis and use din the context of a trial if eligible and available	Intravenous Immunogloblin, 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	

ROLE OF REMDESIVIR,DEXAMETHASONE AND IVIG

- Remdesivir
  - could be considered if viral PCR+ve

- Steroid-
  - Supported by RECOVERY trial
  - Suppress immune response and subsequent inflammation

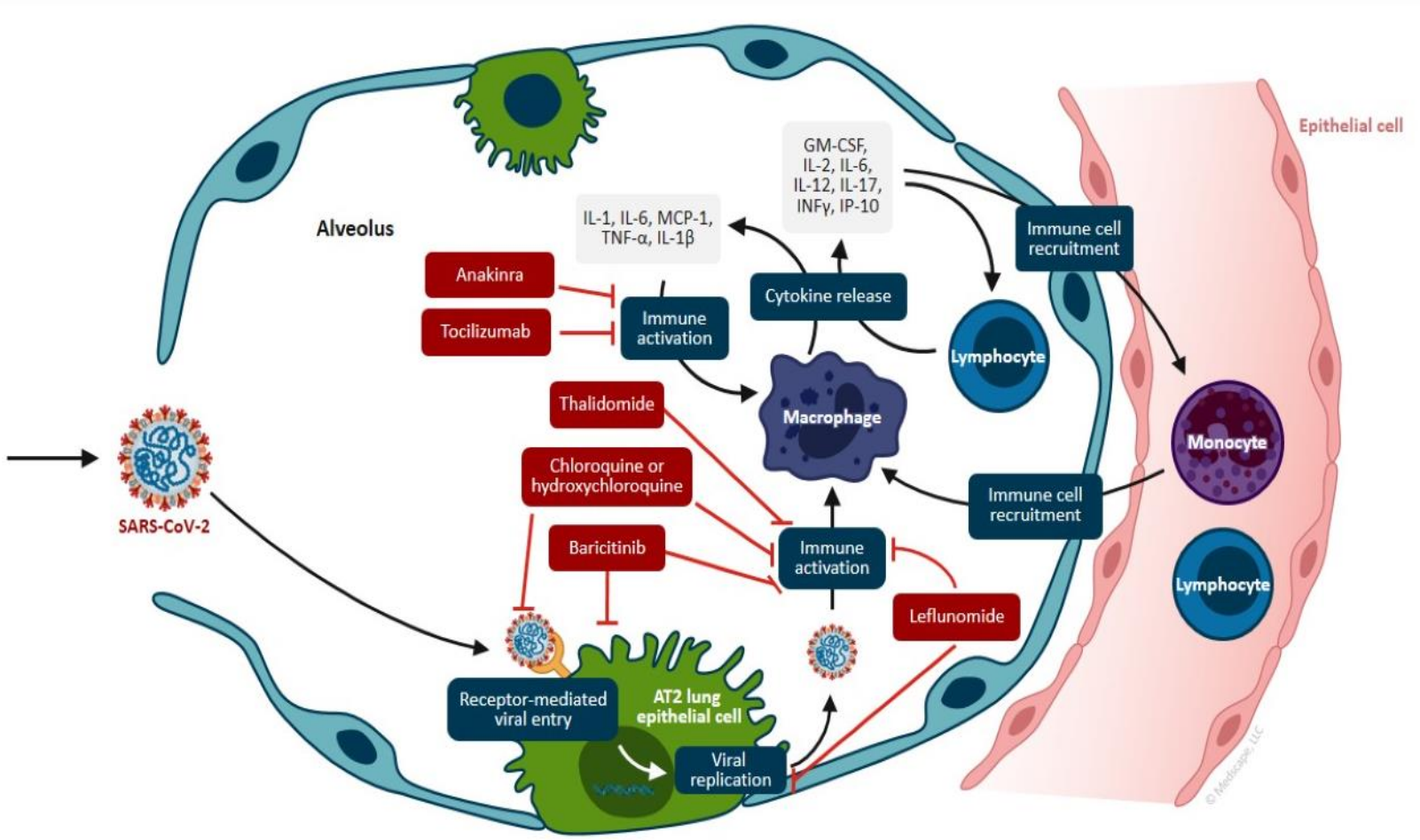
- IVIG
  - Immunoglobulin fraction from serum collected from 1000-15000 humans
  - Essential treatment in Kawasaki's disease
  - IVIG refractory KD show higher incidence of coronary artery aneurysms
  - Inhibits CD40 ligand on CD4 T cells → therapeutic anti-inflammatory effect

OTHER IMMUNOMODULATORY AGENTS TRIED

Infliximab

Tocilizumab

Anakinra



Zhong J, et al. *Lancet Rheumatol.* 2020. [Epub ahead of print]

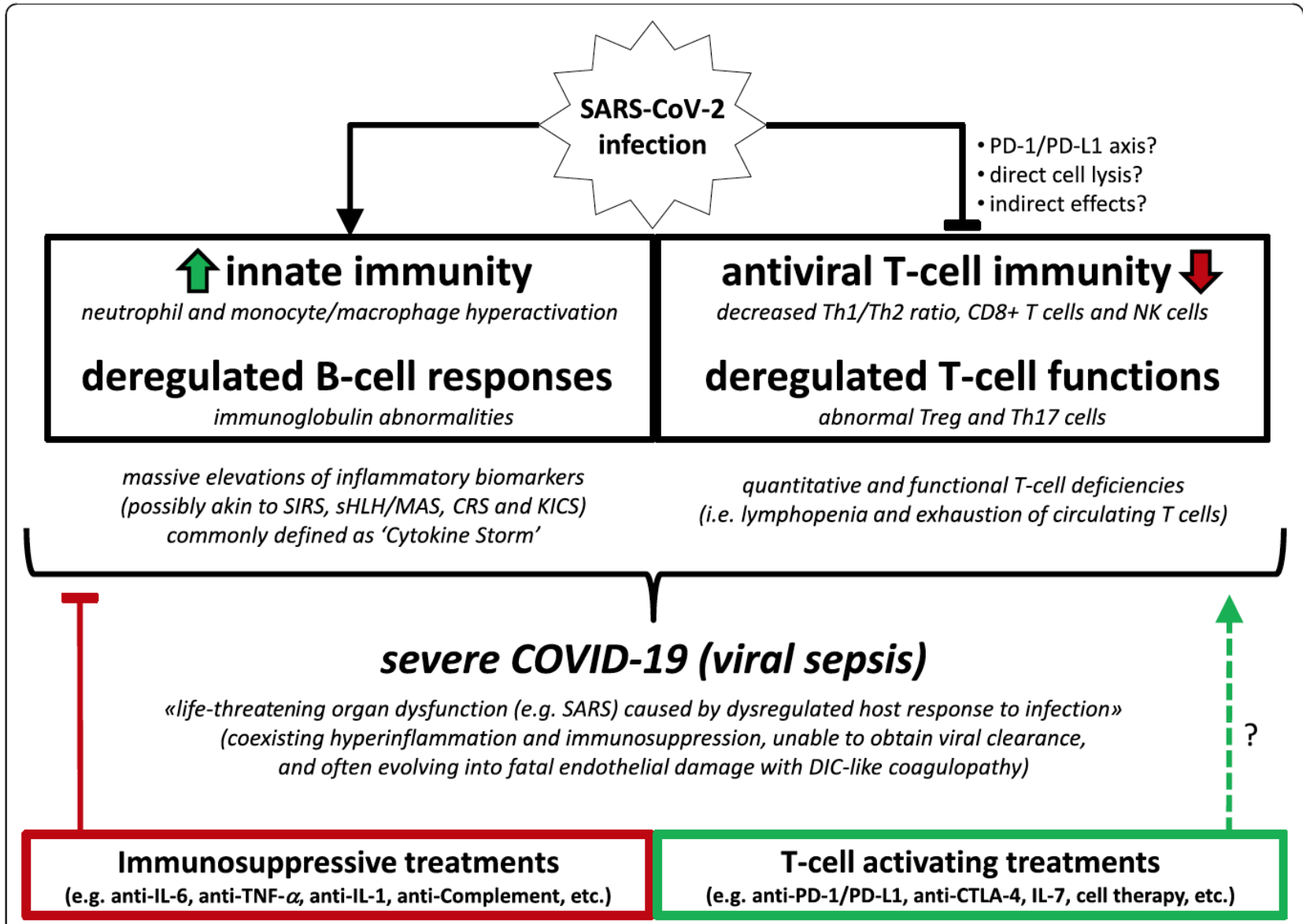


Fig. 1 Working model for COVID-19 immunopathogenesis and related immunomodulatory treatments. Acronyms: SARS-CoV-2 severe acute respiratory syndrome-coronavirus-2, SARS severe acute respiratory syndrome, SIRS severe inflammatory response syndrome, sHLH secondary hemophagocytic lymphohistiocytosis, MAS macrophage activation syndrome, CRS cytokine release syndrome, KICS Kaposi sarcoma herpesvirus-associated inflammatory cytokine syndrome, COVID-19 coronavirus disease-19, DIC disseminated intravascular coagulation

SUPPORTIVE THERAPY

Shock

- Volume expansion using buffered or balanced crystalloids
- Vasopressors for distributive shock
- Inotropes for cardiogenic shock

Respiratory Support

ECMO in rare cases (esp. if severe myocarditis)

CARDIAC MONITORING AND FOLLOW UP

Echographic assessment for all on presentation

Daily ECG on severe cases

Follow up echocardiogram at discharge from hospital and after 2-6 weeks

consider Cardiac MRI to look for persistent myocardial damage

Cardiology follow up recommended

COAGULOPATHY AND PREVENTION

High incidence of coagulopathy/major vessel thrombosis in both adults and children

Lack of consensus on anticoagulation

WHO interim guidance: Anticoagulation recommended for severe COVID-19

- Heparin/LMWH

Low dose aspirin used in Kawasaki disease have been used for MIS-C

- given until follow up echograms exclude persistent coronary artery aneurysms and injury

D-dimer level used as a guide in some institutions

Anticoagulation and antiplatelet therapy generally recommended if severe inflammatory syndrome, raised D-dimer and high fibrinogen

Dose/Duration/Choice of anticoagulation? : liaise with haematologists.

OUTCOMES AND FOLLOW UP

Most paediatrics patient with MIS-C often require special care

Most patients showed favourable outcomes

Can be discharged from hospital once inflammatory laboratory markers normalized, afebrile, normotensive, not require supplemental oxygen.

Close follow up important because natural history of MIS-C is still unclear

Subspecialties involved: primary care/ID/rheumatology/cardiology/haematology

https://www.who.int/publications/i/item/WHO-2019-nCoV-MIS_Children_CRF-2020.2

https://www.cdc.gov/mis-c/hcp/

REPORTING SYSTEMS

WHO REPORT FORM

World Health Organization

PARTICIPANT ID |___|___|___|___|___|___|___|___|___|___|___|___|___|___|

Global COVID-19 Clinical Platform: Case Record Form for suspected cases of Multisystem inflammatory syndrome (MIS) in children and adolescents temporally related to COVID-19

Preliminary case definition

Children and adolescents 0–19 years of age with measured or self-reported fever ≥ 3 days
AND at least two of the following:

a) Rash or bilateral non-purulent conjunctivitis or muco-cutaneous inflammation signs (oral, hands or feet)
b) Hypotension or shock
c) Features of myocardial dysfunction, or pericarditis, or valvulitis, or coronary abnormalities (ECHO findings or elevated Troponin/NT-proBNP)
d) Evidence of coagulopathy (abnormal PT, PTT, elevated d-Dimers)
e) 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 (RT-PCR, antigen test or serology positive) or likely contact with patients with COVID

NB Consider this syndrome in children with features of typical or atypical Kawasaki disease or toxic shock syndrome.

MODULE 1. Complete this module for all children aged 0–19 suspected to have multisystem inflammatory disorder (even if all criteria in the case definition are not met – to capture the full spectrum of the condition). Complete the module at the time the disorder is suspected. Submit module when initial investigations included in case definition are available

Facility name_____ **Country**_____

Date of patient assessment [_D_][_D_]/[_M_][_M_]/[_2_][_0_][_Y_][_Y_]
Date of admission to hospital [_D_][_D_]/[_M_][_M_]/[_2_][_0_][_Y_][_Y_]

1a. DEMOGRAPHICS *(complete when MIS is first suspected)*

Sex at birth ☐Male ☐Female ☐Not specified. **Date of birth** [_D_][_D_]/[_M_][_M_]/[_Y_][_Y_][_Y_][_Y_]
If date of birth is unknown, record **Age** [_____][___][___]years OR [_][_]months
Ethnicity (as reported by family) (please pre-specify main groups in the population and choose from the list) _____

1b. DATE OF ONSET OF CURRENT ILLNESS AND VITAL SIGNS *(complete when MIS is first suspected)*

Date of onset of first symptom or sign [_D_][_D_]/[_M_][_M_]/[_2_][_0_][_Y_][_Y_]
Date of onset of fever [_D_][_D_]/[_M_][_M_]/[_2_][_0_][_Y_][_Y_]
Temperature [_][___.] [_]°C **Heart rate** [___][___][_]beats/min
Respiratory rate [_][___]breaths/min
BP [_] [_] [_](systolic) [___][_][_](diastolic) mmHg **Dehydration** ☐Severe ☐Some ☐None
Capillary refill time > 2 seconds ☐Yes ☐No ☐Unknown
Oxygen saturation [__][ ][__]% on ☐Room air ☐Oxygen therapy ☐Unknown
Conscious state ☐Alert ☐Response to verbal stimuli ☐Response to painful stimuli ☐Unresponsive
Mid-upper arm circumference [_][_][___]mm **Length / Height** [___] [___][___]cm **Weight** [_][_][___]kg

World Health Organization

PARTICIPANT ID |___|___|___|___|___|___|___|___|___|___|___|___|___|___|

1c. POSSIBLE SIGNS AND SYMPTOMS OF MULTISYSTEM INFLAMMATORY SYNDROME *(complete when MIS is first suspected)*

Fever (measured or self-reported) ☐Yes ☐No ☐Unknown
Duration of fever ___ days
Rash ☐Yes ☐No ☐Unknown If yes type of rash _____
Bilateral conjunctivitis ☐Yes, purulent ☐Yes, non-purulent ☐No ☐Unknown
Oral mucosal inflammation signs ☐Yes ☐No ☐Unknown
Peripheral cutaneous inflammation signs (hands or feet) ☐Yes ☐No ☐Unknown
Hypotension (age-appropriate) ☐Yes ☐No ☐Unknown
Tachycardia (age-appropriate) ☐Yes ☐No ☐Unknown
Prolonged capillary refill time ☐Yes ☐No ☐Unknown
Pale/mottled skin ☐Yes ☐No ☐Unknown
Cold hands/feet ☐Yes ☐No ☐Unknown
Urinary output < 2 mL/kg/hr ☐Yes ☐No ☐Unknown

Chest pain ☐Yes ☐No ☐Unknown
Tachypnoea (age-appropriate) ☐Yes ☐No ☐Unknown
Respiratory distress ☐Yes ☐No ☐Unknown

Abdominal pain ☐Yes ☐No ☐Unknown
Diarrhoea ☐Yes ☐No ☐Unknown
Vomiting ☐Yes ☐No ☐Unknown

1d. OTHER SIGNS AND SYMPTOMS *(complete when MIS is first suspected)*

Cough	☐Yes ☐No ☐Unknown		Fatigue/malaise	☐Yes ☐No ☐Unknown	
Sore throat	☐Yes ☐No ☐Unknown		Seizures	☐Yes ☐No ☐Unknown	
Runny nose	☐Yes ☐No ☐Unknown		Headache	☐Yes ☐No ☐Unknown	
Wheezing	☐Yes ☐No ☐Unknown		Hypotonia/floppiness	☐Yes ☐No ☐Unknown	
Swollen joints	☐Yes ☐No ☐Unknown		Paralysis	☐Yes ☐No ☐Unknown	
Cervical lymphadenopathy	☐Yes ☐No ☐Unknown		Irritability	☐Yes ☐No ☐Unknown	
Joint pain (arthralgia)	☐Yes ☐No ☐Unknown		Photophobia	☐Yes ☐No ☐Unknown	
Muscle aches	☐Yes ☐No ☐Unknown		Hyposmia/anosmia (loss of smell)	☐Yes ☐No ☐Unknown	
Skin ulcers	☐Yes ☐No ☐Unknown		Hypogeusia (loss of taste)	☐Yes ☐No ☐Unknown	
Stiff neck	☐Yes ☐No ☐Unknown		Not able to drink	☐Yes ☐No ☐Unknown	
Other? Specify _____			Bleeding (haemorrhage) ☐Yes ☐No ☐Unknown If yes, specify site _____		

1e. RECENT HISTORY

Has the child been admitted to hospital in the last 3 months? ☐Yes ☐No ☐ Unknown
If yes, date of discharge from hospital [_D_][_D_]/[_M_][_M_]/[_2_][_0_][_Y_][_Y_]
If yes, was it related to this illness episode or for the same or similar problems? ☐Yes ☐No ☐ Unknown
History of COVID-19 infection in the previous 4 weeks prior to current illness?
☐Yes - Lab confirmed ☐Yes - Clinically diagnosed ☐No ☐Unknown
History of any respiratory infection in the previous 4 weeks prior to current illness? ☐Yes ☐No ☐ Unknown
Any household member (or other contact) with confirmed COVID-19 in previous 4 weeks? ☐Yes ☐No ☐Unknown
Past history of Kawasaki disease? ☐Yes ☐No ☐ Unknown

Family history of Kawasaki disease? ☐Yes ☐No ☐ Unknown

World Health Organization

PARTICIPANT ID |___|___|___|___|___|___|___|___|___|___|___|___|___|___|

1f. CO-MORBIDITIES, PAST HISTORY *(complete when MIS is first suspected)*

Inflammatory or rheumatological disorder If yes, specify_____	☐Yes ☐No ☐Unknown	Asplenia	☐Yes ☐No ☐Unknown
Hypertension (age-appropriate)	☐Yes ☐No ☐Unknown	Congenital or acquired immune-suppression If yes, specify_____	☐Yes ☐No ☐Unknown
Other chronic cardiac disease If yes, specify_____	☐Yes ☐No ☐Unknown	Chronic kidney disease	☐Yes ☐No ☐Unknown
Asthma	☐Yes ☐No ☐Unknown	Chronic liver disease	☐Yes ☐No ☐Unknown
Tuberculosis	☐Yes ☐No ☐Unknown	Chronic neurological disorder	☐Yes ☐No ☐Unknown
Other chronic pulmonary disease If yes, specify_____	☐Yes ☐No ☐Unknown	Haematologic disorder	☐Yes ☐No ☐Unknown
Diabetes	☐Yes type 1 ☐Yes type 2 ☐No ☐Unknown	HIV ☐Yes (on ART) ☐Yes (not on ART) ☐No ☐Unknown	
Malignant neoplasm	☐Yes ☐No ☐Unknown	Other? If yes, specify _____	

1g. PRE-ADMISSION AND CHRONIC MEDICATION
Were any of the following taken within 14 days of admission: *(complete when MIS is first suspected)*

Non-steroidal anti-inflammatory (NSAID)? ☐Yes ☐No ☐Unknown
If yes, specify name _____; Route ☐Oral/rectal ☐Parenteral (IM/IV) ☐Unknown

Steroids? ☐Yes ☐No ☐Unknown
If yes, specify name _____; Route ☐Oral/rectal ☐Parenteral (IM/IV) ☐Inhaled ☐Topical ☐Unknown

Antibiotics? ☐Yes ☐No ☐Unknown
If yes, specify name _____; Route ☐Oral/rectal ☐Parenteral (IM/IV) ☐Unknown

Any other medication? ☐Yes ☐No ☐Unknown
If yes, specify name _____; Route ☐Oral/rectal ☐Parenteral (IM/IV) ☐Inhaled ☐Topical ☐Unknown
If yes, specify name _____; Route ☐Oral/rectal ☐Parenteral (IM/IV) ☐Inhaled ☐Topical ☐Unknown
If yes, specify name _____; Route ☐Oral/rectal ☐Parenteral (IM/IV) ☐Inhaled ☐Topical ☐Unknown

1h. LABORATORY RESULTS
(complete with results of tests ordered at the time MIS is first suspected) (record units if different from those listed)*
Record the worst value between 00:00 to 24:00 on day of assessment (if Not Available write 'N/A'):

Parameter	Value*	Not done	Parameter	Value*	Not done
Markers of inflammation/coagulopathy			**Markers of organ dysfunction**		
Haemoglobin (g/L)		☐	Creatinine (µmol/L)		☐
Total WBC count (x10⁹/L)		☐	Sodium (mmol/L)		☐
Neutrophils (x10⁹/L)		☐	Potassium (mmol/L)		☐
Haematocrit (%)		☐	Glucose (mmol/L)		☐
Platelets (x10⁹/L)		☐	Pro-BNP (pg/mL)		☐
APTT/APTR		☐	Troponin (ng/mL)		☐
PT (seconds)		☐	Creatine kinase (U/L)		☐
INR		☐	LDH (U/L)		☐
Fibrinogen (g/L)		☐	Triglycerides		☐
Procalcitonin (ng/mL)		☐	ALT/SGPT (U/L)		☐
CRP (mg/L)		☐	Total bilirubin (µmol/L)		☐
ESR (mm/hr)		☐	AST/SGOT (U/L)		☐
D-dimer (mg/L)		☐	Albumin (g/dL)		☐
IL-6 (pg/mL)		☐	Lactate (mmol/L)		☐
IL-10 (pg/mL)		☐	Ferritin (ng/mL)		

World Health Organization

PARTICIPANT ID |___|___|___|___|___|___|___|___|___|___|___|___|___|___|

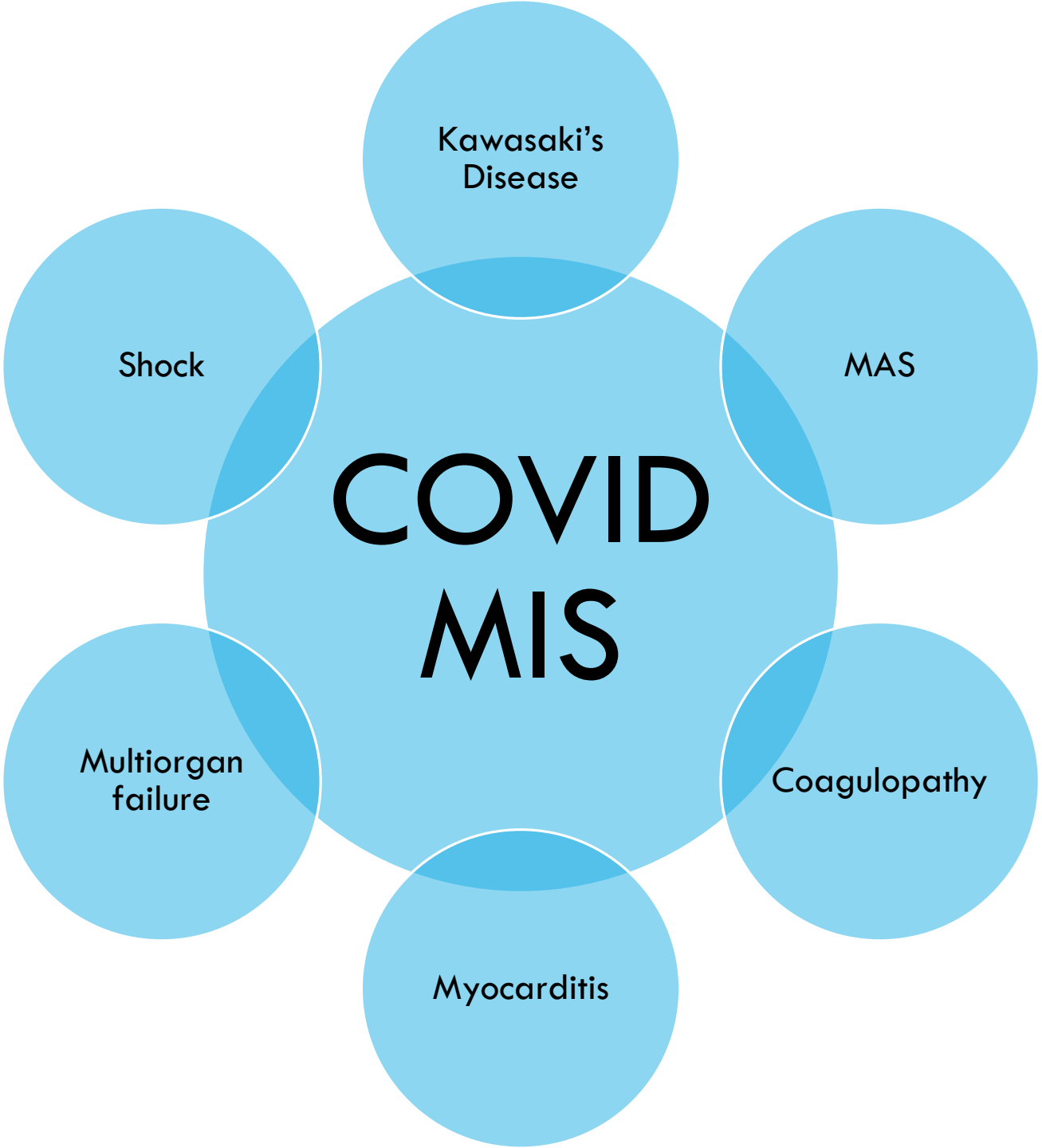
1i. IMAGING AND PATHOGEN TESTING
(complete when results of tests ordered at the time MIS is first suspected are available)

Chest X-ray/CT performed ☐Yes ☐No ☐Unknown **If yes, findings** _____

ECG performed? ☐Yes ☐No ☐ Unknown
On that ECG what were the findings? _____

Echocardiography performed ☐Yes ☐No ☐Unknown
If yes, features of myocardial dysfunction? ☐Yes ☐No ☐Unknown
features of pericarditis? ☐Yes ☐No ☐Unknown
features of valvulitis? ☐Yes ☐No ☐Unknown
coronary abnormalities? ☐Yes ☐No ☐Unknown

Other cardiac imaging performed ☐Yes ☐No ☐Unknown
If yes, specify name of imaging and results _____


Kawasaki's Disease
Shock
MAS
COVID MIS
Multiorgan failure
Coagulopathy
Myocarditis

SUMMARY- MIS AT A GLANCE

Case definition:

- Fever >24hrs
- Laboratory evidence of inflammation
- Evidence of clinically severe illness requiring hospitalization
- Multisystem (>/= 2) organ involvement
- No alternative plausible diagnosis
- Positive for current or recent SARS-CoV-2 infection by RT PCR, serology or antigen test; or exposure to suspected or confirmed COVID-19 case within the 4 weeks prior to onset of symptoms

Presentation:

- Fever, GI symptoms, Mucocutaneous lesions
- Hypotension, Shock, Cardiac Injury, AKI

Investigations

- Inflammatory markers:
  - Raised CRP/ESR/Fibrinogen/Procalcitonin/D-dimer/Ferritin/LDH/IL-6/neutrophils)
  - Reduced lymphocytes and albumin
- Cardiac injury: Elevated Troponin, BNP, ECG, echocardiogram
- Testing for SARS-CoV-2 infection: RT PCR / serology

Treatment

- Supportive
- Ant-inflammatory measures: Steroid, IVIG
- ?Concerns for coronary artery involvement: aspirin
- ?Hypercoagulable state: anticoagulation (?treatment/prophylactic)

QUESTIONS YET TO BE ADDRESSED

How does MIS pathophysiology differ from Kawasaki's disease/toxic shock syndrome/ macrophage activation syndrome?

Do the same or different genetic factors influence MIS-C as they do in Kawasaki's disease?

Will patients with fever and inflammation following SARS-CoV-2 infection progress to Kawasaki disease, shock and organ failure if untreated?

What's the optimal treatment?

Which treatment can prevent coronary artery aneurysms?

Do infection at different ages (childhood/adolescence/adults) influence severity of disease and prognosis?

Are there differences in underlying immunology of MIS-C between children and adults?

Medium and long term adverse outcomes?

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THANK YOU

SPECIAL THANKS TO ALL THE COLLEAGUES WHO CARED FOR OUR PATIENT, DR ANNE LEUNG AND DR K.Y. LAI FOR THEIR GUIDANCE

Pandora's box had been opened and monsters had come out. But there had been something hidden at the bottom of Pandora's box. Something wonderful. Hope

Lisa Marie Rice