

Clinical Management and research questions from the emerging spectrum of Inflammatory disorders associated with SARSCov 2. IPA Webinar

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Rady Children's Hospital San Diego- Jane Burns, Adriana tremoulet, Chisato Shimizu.

BATS study group. Ortensia vito, priyen Shah, TishamDe, Ruud Nijman Harsita Patel, Andre Mcardle, Clare Wilson, Aubrey Cunnington



In march 2020 as COVID19 evolved in UK Paediatricians noticed unusual Illness

- Severe illness admitted to paediatric ward, or PICU
- Varied presentations - prolonged fever, sore throat, headache, abdominal pain and vomiting, rash, conjunctivitis
- Some developed shock, organ dysfunction
- In common - \uparrow CRP, \uparrow Neutrophil, \downarrow lymphocytes, \uparrow D-Dimers
- Some -typical Kawasaki disease features
- Majority SARS-CoV-2 PCR negative

58 cases from 8 hospitals in England and systematically reviewed

Development of a case definition

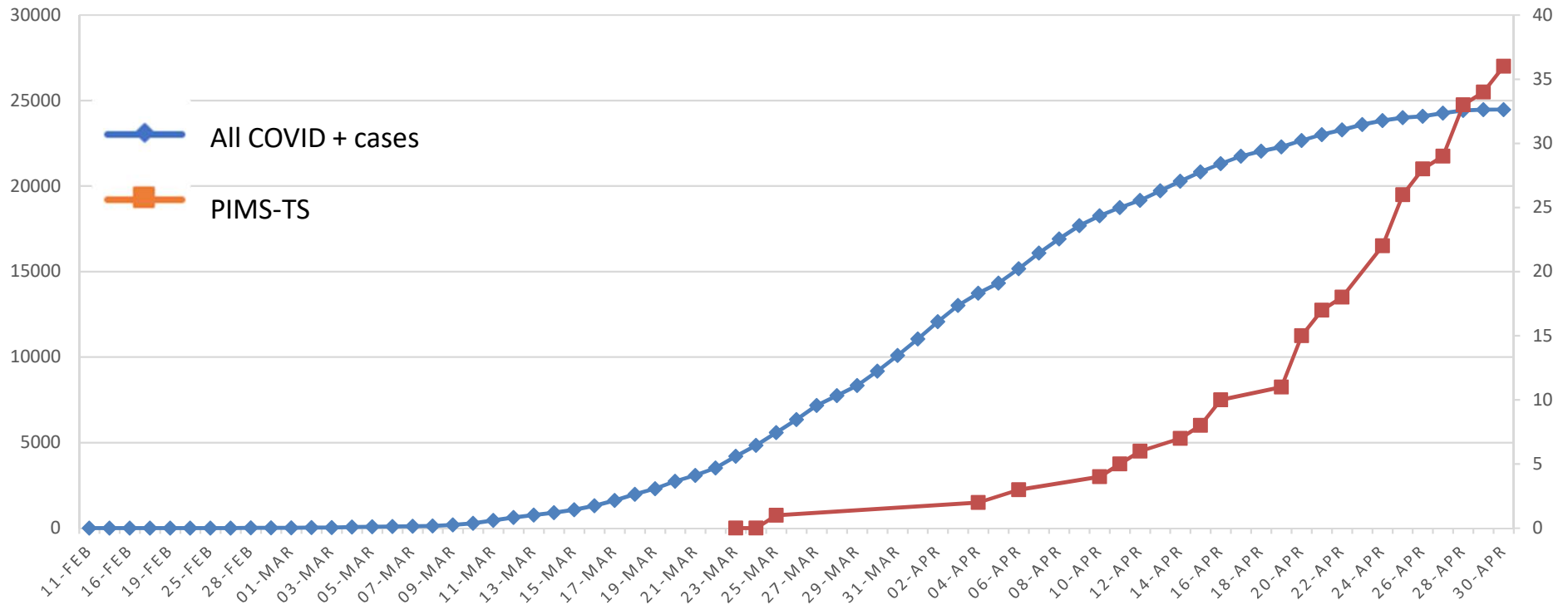
- Case note review, data collated on a data base
- Panel of infectious diseases and PICU specialists
- Initial report only Included children admitted to HDU/PICU
- **Exclusion of any other microbial cause, including bacterial sepsis, staphylococcal or streptococcal shock syndromes; infections associated with myocarditis such as enterovirus and Macrophage activation syndromes**
- **NHS UK alerted on 24 April emerging new disorder**

PIMS-TS appear to be a month Behind the COVID19 peak in the population



Public Health
England

Laboratory Confirmed COVID-19 cases, London



Clinical presentations

- **50% shock, Myocardial involvement**
- 52% rash
 - 45% conjunctivitis, 29% mucus membrane
- **53% abdominal involvement**
- 38% acute kidney injury,
- Unlike adults - only 32% respiratory symptoms

3 Groups

- Shock
- Kawasaki disease definition
- Fever and inflammation

	N (%)
Characteristic	PIMS-TS all cases N=58
Age, median (Range) year	9 (5.7-13)
Male	25 /58 (43)
Ethnicity	
Black	22 /58 (38)
White	12 /58 (21)
Asian	18/58 (31)
Other	6/58 (10)
Clinical Features at Presentation	
Shock	29/58 (50)
Diarrhoea	30.58 (52)
Abdominal pain	31/58 (53)
Rash	30/58 (52)
Vomiting	26/58 (45)
Conjunctival injection	26/58 (45)
Headache	15 /58 (26)
Respiratory symptoms	12/58 (21)
Mucus membrane changes	17/58 (29)
Sore throat	6/58 (10)
Confusion	5/58 (9)
Lymphadenopathy	9/58 (16)
Swollen hands and feet	9/58 (16)

Inflammation and cardiac Injury

- Striking elevation of CRP, Ferritin, D Dimers, Fibrinogen
- Anaemia, Low Lymphocytes, low albumin
- Elevated Troponin and Pro-BNP

Haemoglobin (g/L)	92 (83-103)
Total white cell count (x10 ⁹ /L)	17 (12-22)
Neutrophil count (x10 ⁹ /L)	13 (10-19)
Lymphocyte count (x10 ⁹ /L)	0.8 (0.5-1.5)
Platelet number (x10 ⁹ /L)	151 (104-210)
D-Dimer (ug/L)	3578 (2085-8235)
Ferritin (ug/L)	610 (359-1280)
Troponin (ng/L)	45 (8-294)
ALT (U/L)	42 (26-95)
Albumin (g/L)	24 (21-27)
Lactate dehydrogenase (U/L)	419 (319-887)
Fibrinogen (g/L)	5.7 (4.37-7)
C reactive protein (CRP) (mg/L)	229 (156-338)
Pro-BNP (pg/ml)	788 (174-10548)

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

Case definition:

1. A child presenting with persistent fever, inflammation (neutrophilia, elevated CRP and lymphopaenia) and evidence of single or multi-organ dysfunction (shock, cardiac, respiratory, renal, gastrointestinal or neurological disorder) with additional features (see listed in [Appendix 1](#)). This may include children fulfilling full or partial criteria for Kawasaki disease.
2. Exclusion of any other microbial cause, including bacterial sepsis, staphylococcal or streptococcal shock syndromes, infections associated with myocarditis such as enterovirus (waiting for results of these investigations should not delay seeking expert advice).
3. SARS-CoV-2 PCR testing may be positive or negative



Emergency Preparedness and Response

Multisystem Inflammatory Syndrome in Children (MIS-C) Associated with Coronavirus Disease 2019 (COVID-19) May 14, 2020,

Case Definition for Multisystem Inflammatory Syndrome in Children (MIS-C)

- An individual aged <21 years presenting with feverⁱ, laboratory evidence of inflammationⁱⁱ, and evidence of clinically severe illness requiring hospitalization, with multisystem (≥ 2) organ involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic or neurological); **AND**
- No alternative plausible diagnoses; **AND**
- Positive for current or recent SARS-CoV-2 infection by RT-PCR, serology, or antigen test; or COVID-19 exposure within the 4 weeks prior to the onset of symptoms

ⁱFever $\geq 38.0^{\circ}\text{C}$ for ≥ 24 hours, or report of subjective fever lasting ≥ 24 hours

ⁱⁱIncluding, but not limited to, one or more of the following: an elevated C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), fibrinogen, procalcitonin, d-dimer, ferritin, lactic acid dehydrogenase (LDH), or interleukin 6 (IL-6), elevated neutrophils, reduced lymphocytes and low albumin

Multisystem inflammatory syndrome in children and adolescents with COVID-19

Scientific brief

15 May 2020



Preliminary case definition^a

Children and adolescents 0–19 years of age with fever ≥ 3 days

AND 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, pericarditis, valvulitis, or coronary abnormalities (including ECHO findings or elevated Troponin/NT-proBNP),
- d) Evidence of coagulopathy (by 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.

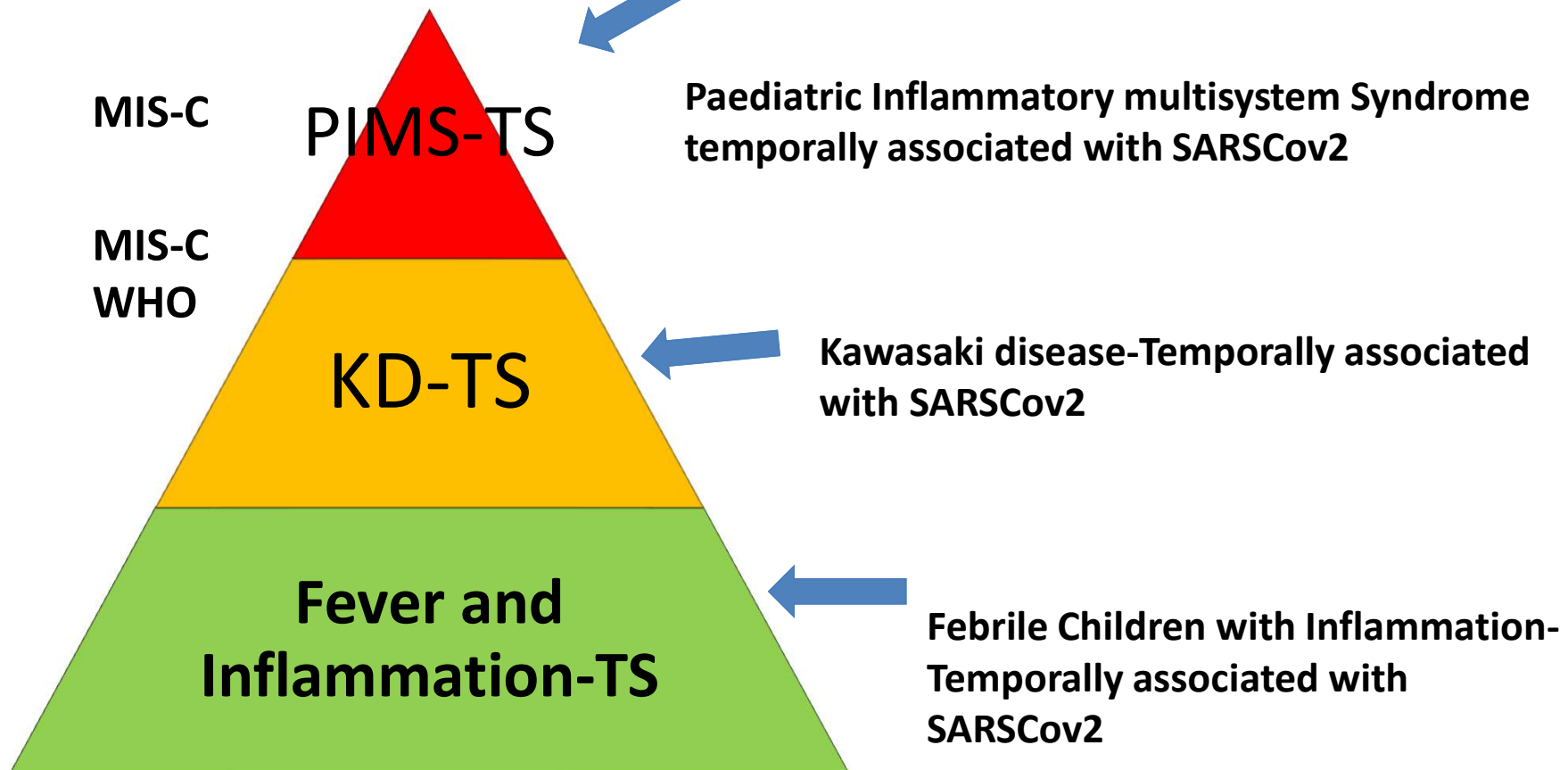
AND

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

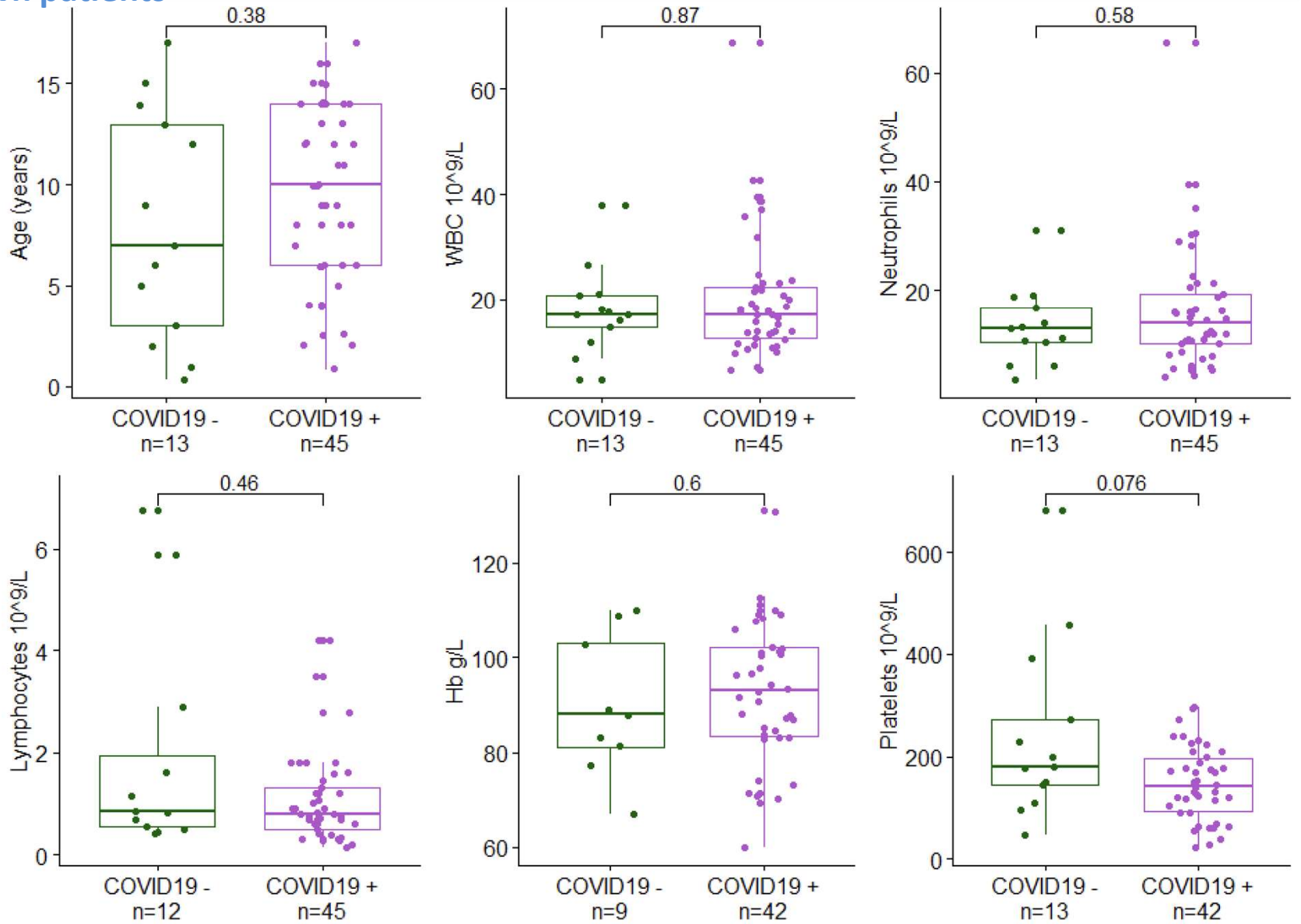
An emerging new spectrum of SARSCov2 in children

COVID 19 in children: generally mild or asymptomatic

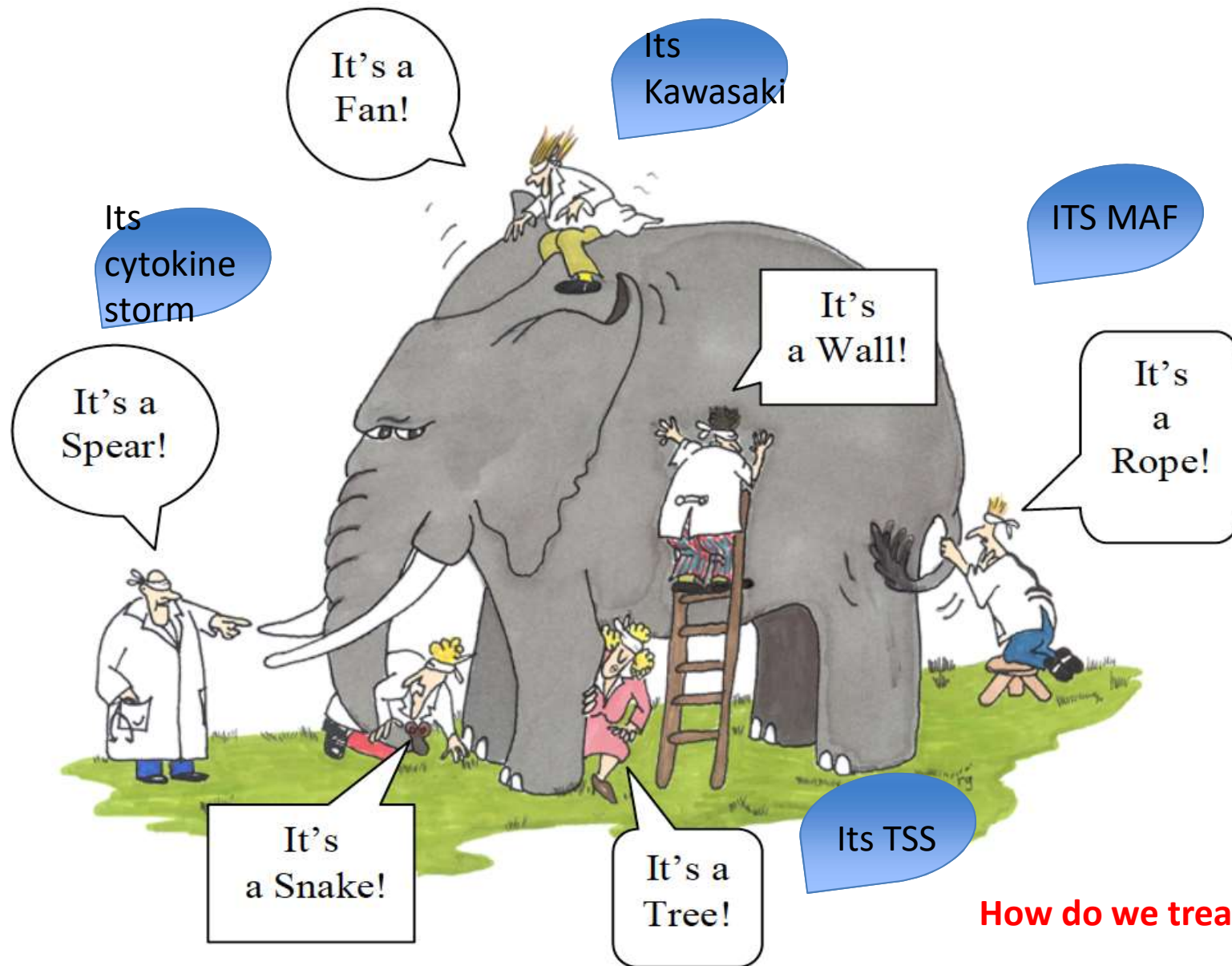
POST SARSCov2 Inflammatory syndromes



Do we need proof of Previous or current SARS COv2: No clinical or Laboratory differences between SARSCov2 positive and unknown patients



What is this new disease?



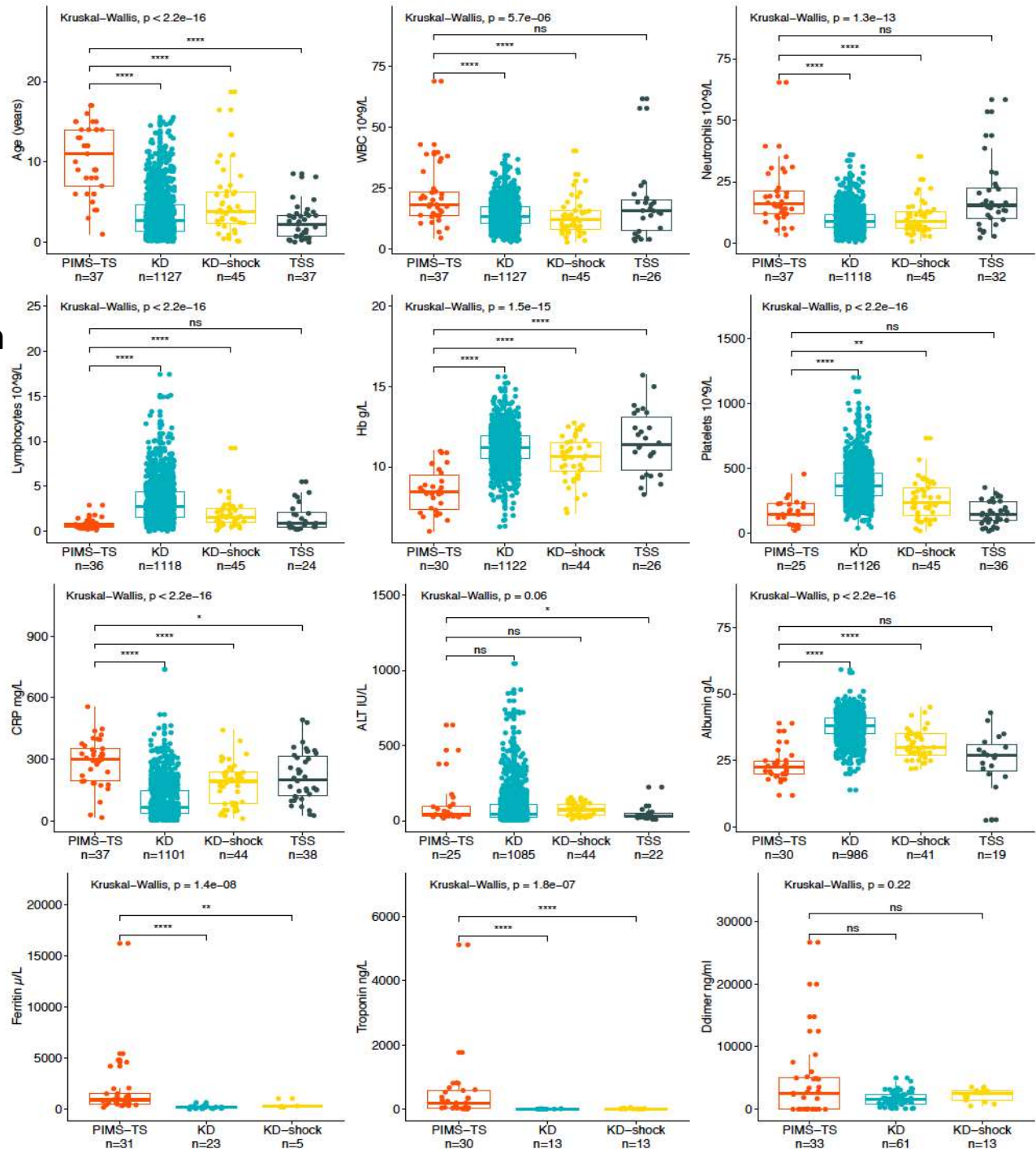
How do we treat it ?

**Kawasaki disease
 ,Kawasaki shock syndrome
 And Toxic Shock syndrome
 Have clear differences from
 PIMS-TS**

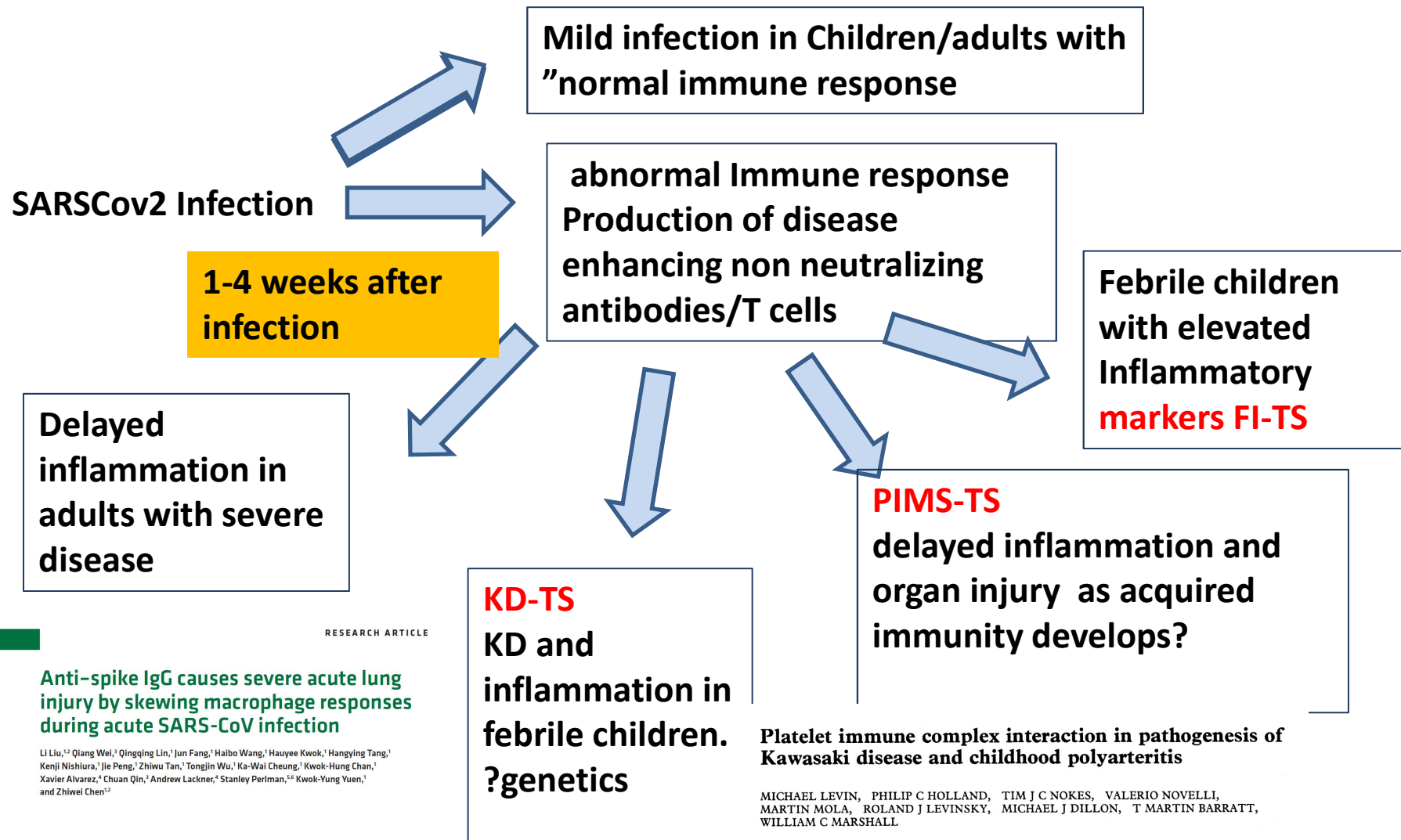
Comparison of PIMS-TS(UK)
 with >1000 Kawasaki
 disease patients(SanDiego)
 and KD shock and TSS

Clear differences:

**We cannot assume the
 same treatments for KD
 will work in PIMS/MIS**



Possible mechanism for acquired immunity mediating inflammation and organ damage ??



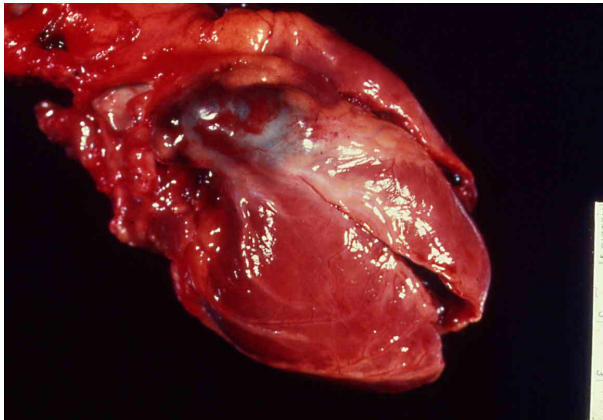
Anti-spike IgG causes severe acute lung injury by skewing macrophage responses during acute SARS-CoV infection

Li Liu,^{1,2} Qiang Wei,³ Qingqing Lin,¹ Jun Fang,¹ Haibo Wang,¹ Haoyee Kwok,¹ Hangying Tang,¹ Kenji Nishiura,¹ Jie Peng,¹ Zhiwu Tan,¹ Tongjin Wu,¹ Ka-Wai Cheung,¹ Kwok-Hung Chan,¹ Xavier Alvarez,⁴ Chuan Qin,⁵ Andrew Lackner,⁶ Stanley Perlman,^{4,6} Kwok-Yung Yuen,¹ and Zhiwei Chen^{1,2}

Platelet immune complex interaction in pathogenesis of Kawasaki disease and childhood polyarteritis

MICHAEL LEVIN, PHILIP C HOLLAND, TIM J C NOKES, VALERIO NOVELLI, MARTIN MOLA, ROLAND J LEVINSKY, MICHAEL J DILLON, T MARTIN BARRATT, WILLIAM C MARSHALL

Clinical questions :Inflammation and Fever Temporally associated with SARSCov2



What is the risk of Coronary artery aneurysms

Inflammation Shock, Organ failure

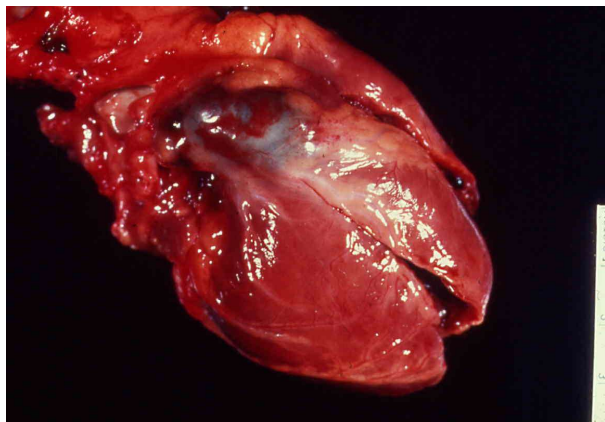
“Kawasaki Disease”

Febrile child With Inflammation

What is the risk of progression to KD and Multiorgan failure?

Mild Symptomatic COVID

Treatment questions on Febrile Inflammation spectrum associated with SARS COV2



What is the risk of
Coronary artery
aneurysms

Febrile child
With
Inflammation

“Kawasaki
Disease”

Inflammation
Shock, Organ failure

What TREATMENT prevents
progression to KD and
Multiorgan failure?

What Biomarkers predict progression

Mild
Symptomatic
COVID

Which treatment prevents Coronary artery aneurysms

?

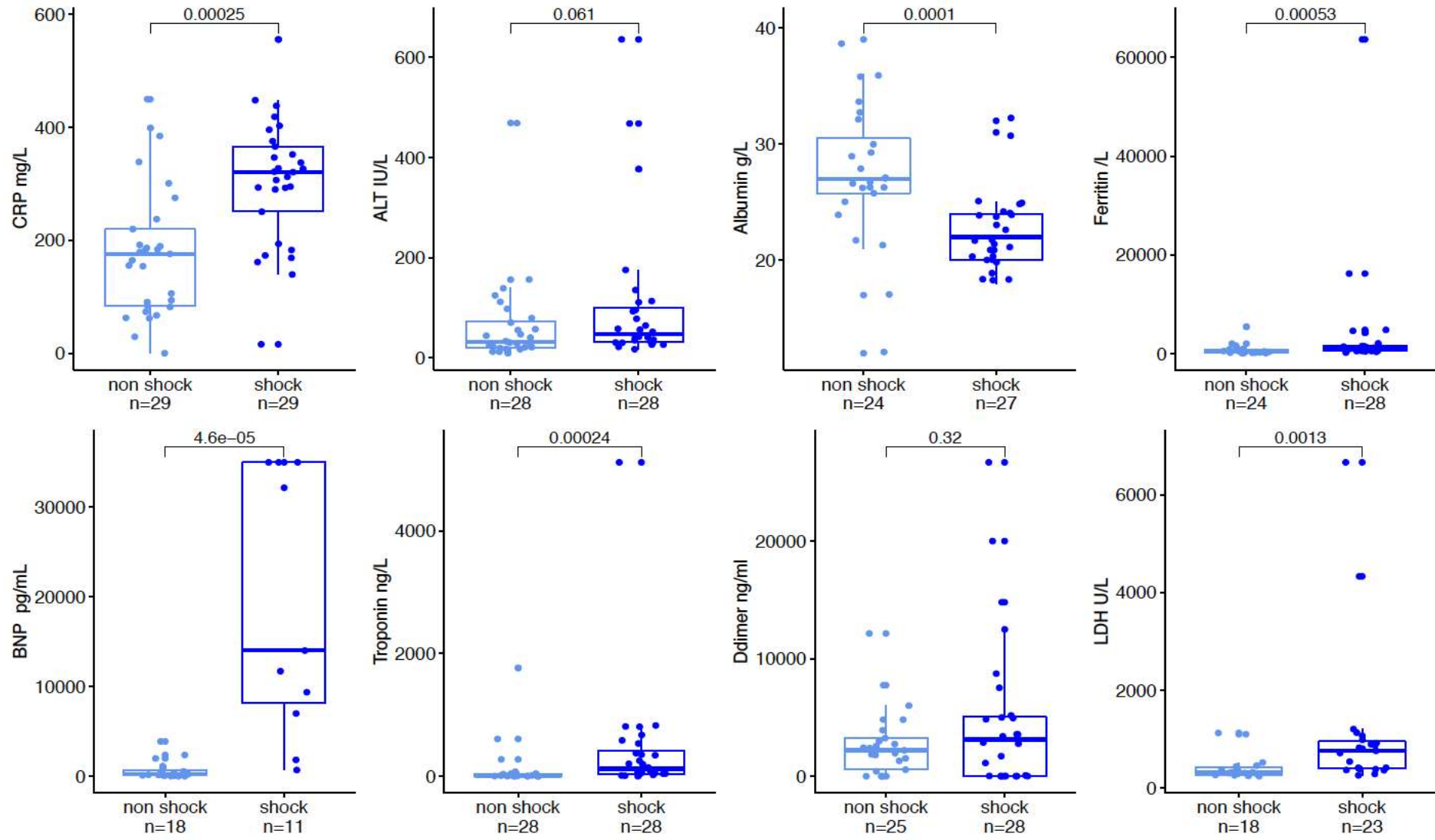
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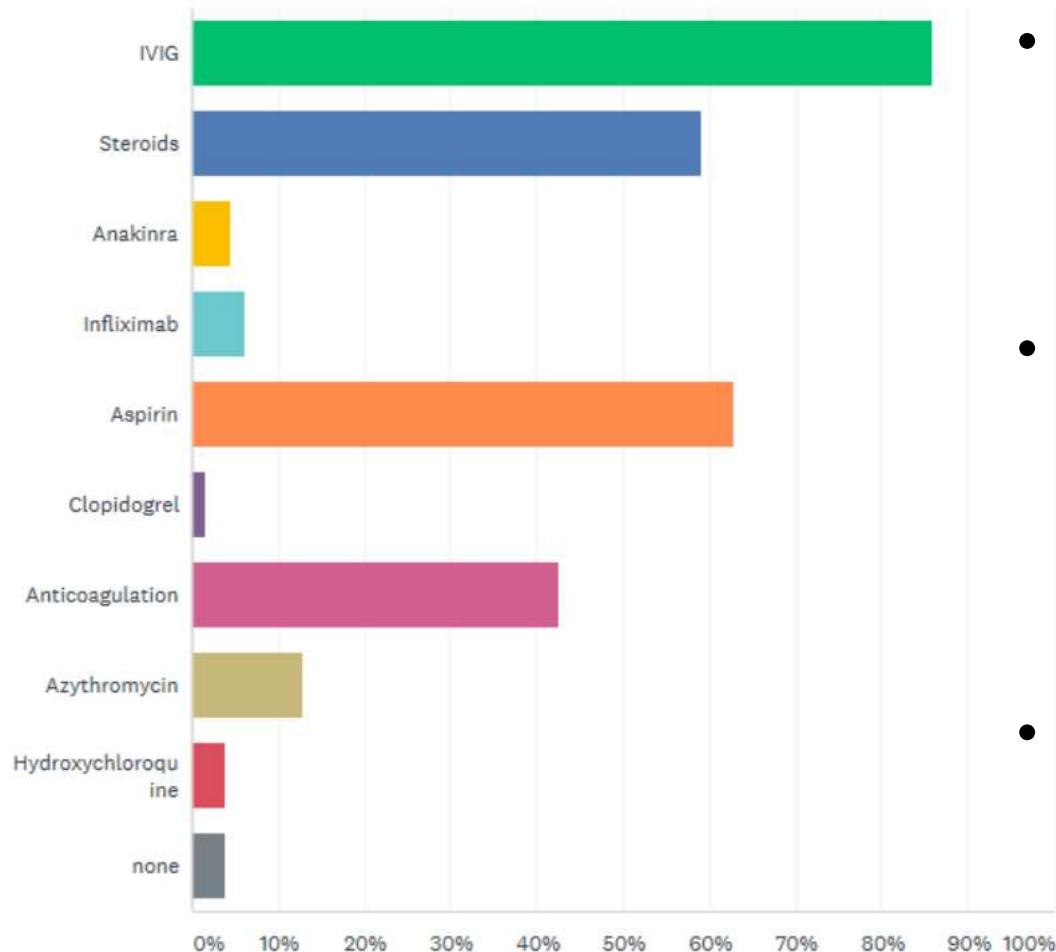
Urgent Clinical Management question

- Do patients progress from the less severe to more serious categories? ie. Febrile inflammation → KD → PIMS/MIS-C
- What is the risk of Coronary artery aneurysms in each group?
- What is the relationship between KD-TS and KD prior to the pandemic? Are the mechanisms different.
- Do anti-inflammatory and immuno-modulating treatments such as immunoglobulin, steroids, anti-TNF, anti-IL1, anti-IL6 agents improve outcome AND reduce risk of coronary artery aneurysms?
- **What treatment should be given in Less resourced countries**
- What are the mechanism
- Are there biomarkers to distinguish each group (Febrile inflammation/KD/PIMS) and COVID from other conditions

Can we identify patients at risk of progression to shock



What treatment should be given to prevent progression, prevent Coronary damage , improve outcome



Unpublished 3 centre survey 134 patients
courtesy Prof Alain Fraisse RBH

- **Pediatricians have used "Best Guess "Of available treatments.**
- **We do not know which of the agents given have been beneficial or harmful**
- **Treatments for Kawasaki disease may or may not be optimal**
- **Need data to inform Practice**

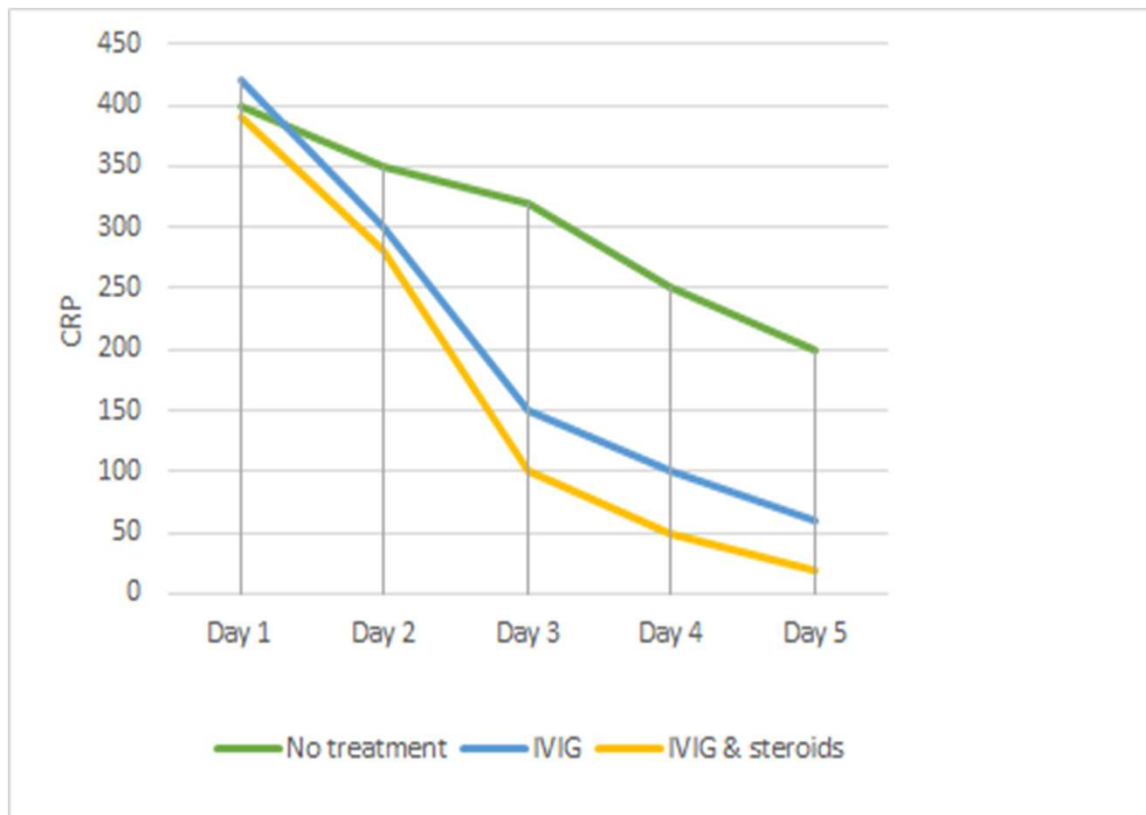
International study of Best available treatment for paediatric inflammatory syndromes associate with SARS-Cov-2- “Best available treatment(Do your Best study).”

- **Randomised trials are needed to resolve best therapy**
- **However patients in many countries presenting now**
- **Unlikely to have Randomised trials up and running in time to help clinicians decisions**
- **Over 1000 children already treated with Clinicians “Best guess”**
- **Many countries have shortages or no availability of IVIG or biologicals**
- **Can we use the data on children already treated- and those presenting now to answer the therapeutic questions, and inform the design of Randomised trials?**

The hypothesis underlying this study

administration immunomodulating agents such as immunoglobulin, anti TNF, anti IL1, or anti IL6 therapies , will result in more rapid resolution of inflammatory markers, prevent progression from FIS-TS to KD-TS or PIMS-TS ,reduce the need for intensive care or organ support and reduce coronary artery aneurysm rate and severity.

Although Not randomised Each Institution and clinician chose best treatment which can be compared if patients are matched for severity



Large numbers of patients

Modelled curve of rate of change of CRP(Ferritin, Troponin, BNP, D Dimers

Corrected for severity, day of illness, age, level of marker at start of treatment

How to Participate ?

- **To enter the trial and provide data: log onto the online study entry site and provide contact details (email, address, country and institution). (Live next week)**

<https://bit.ly/36BEvxz>

bestavailabletreatmentstudy@gmail.com

Analysis

Electronically captured data following treatment with any of the agents will be analysed by the machine learning and data monitoring group at Imperial College who have expertise in application of machine learning techniques to large scale patient data.

Acknowledgement, participation and ownership of data

All clinicians submitting patients to this study will be listed as a member of the international consortium, have access to their own data for their own analyses and included in all subsequent reports.

Open to all countries

We also need to study the Biology of a new spectrum of diseases

- Detailed clinical phenotyping and sample collection is needed
- RNA, DNA, serum Plasma, cells, post mortem tissue in acute stage and convalescence will enable :
- Study of Genetics, Biomarkers of severity and diagnosis, immunopathology .
- **Contribute to local studies**



THANKS

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