Clinical Illness Including MIS-C

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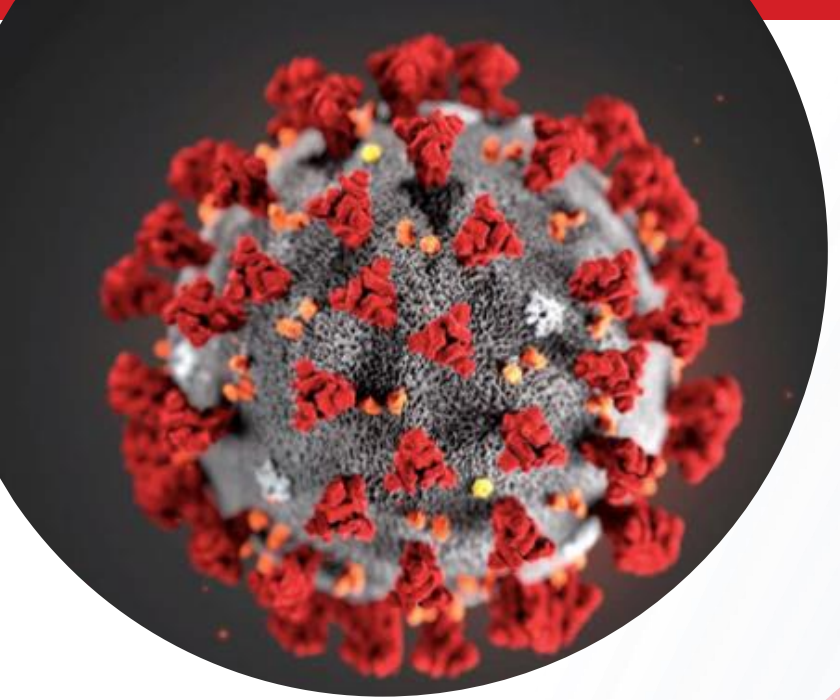


COVID-19 in Pediatrics

Clinical Illness Including MIS-C

Dr Liz Whittaker

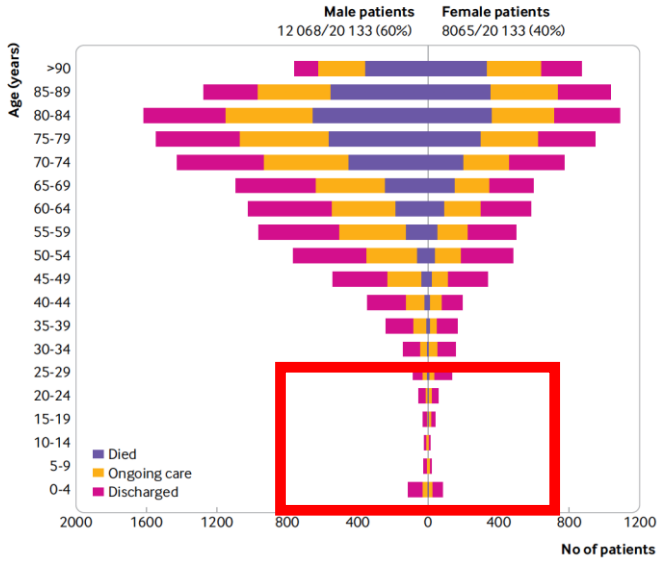
Consultant Paediatric infectious diseases

St Marys Hospital Paddington

Talk overview

- Severe COVID in children – epidemiology, cases, management
- PIMS vs MIS-C overview, management

Clinical COVID in children



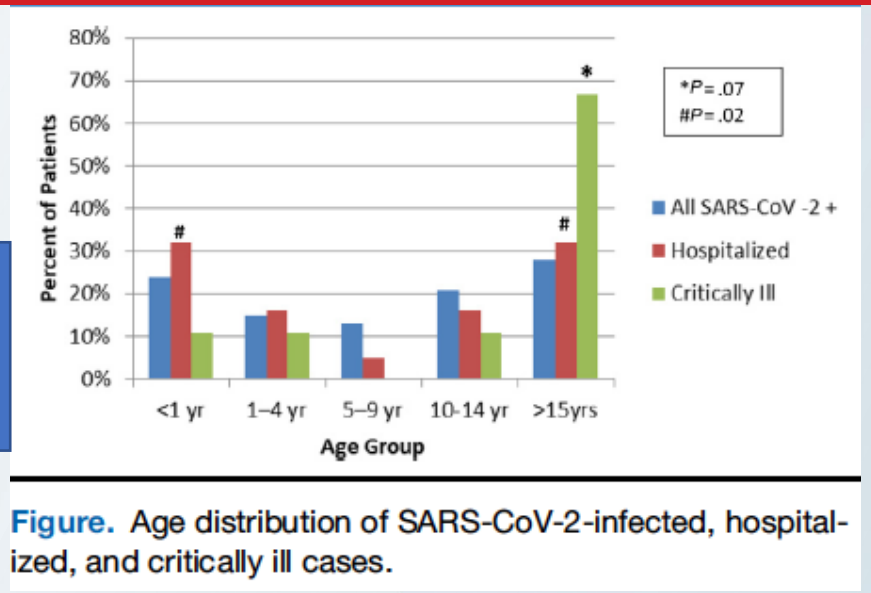
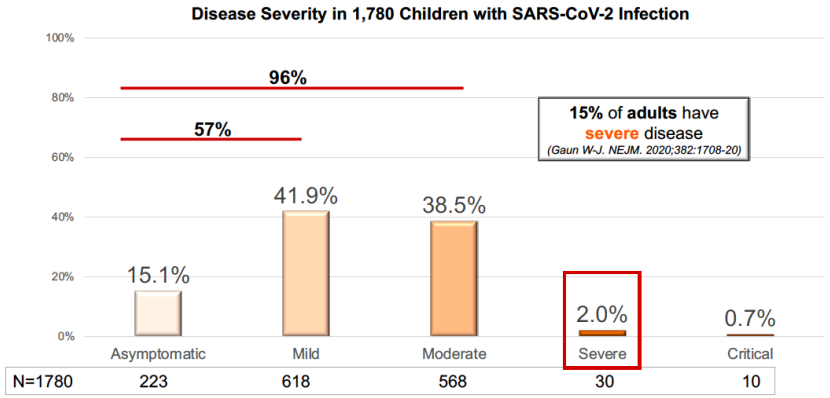
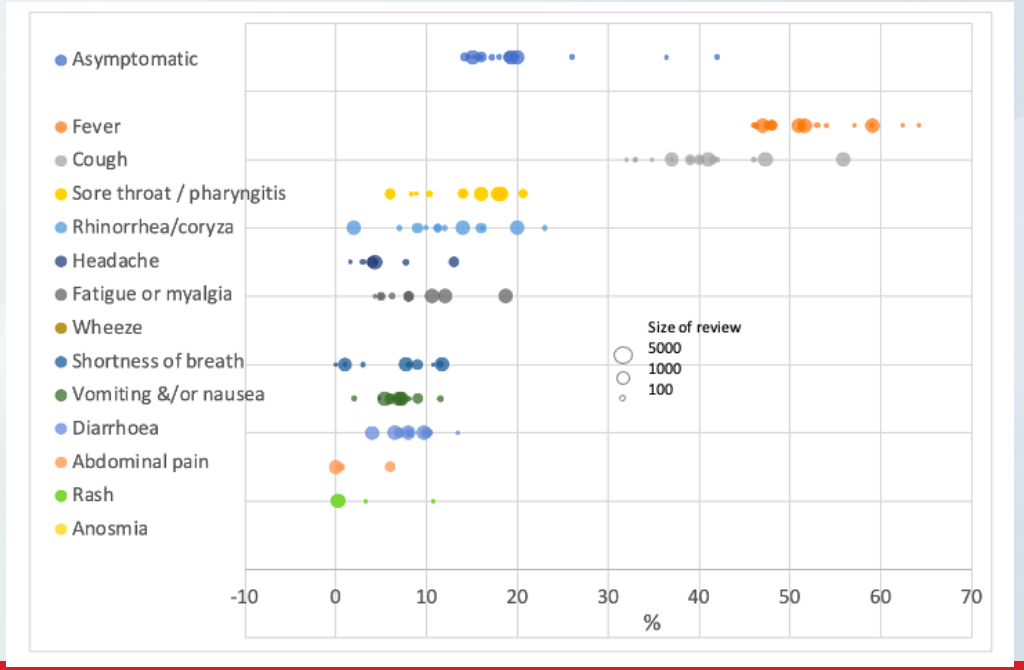


Figure. Age distribution of SARS-CoV-2-infected, hospitalized, and critically ill cases.

Data Continue to Show Children Generally Have Mild-Moderate Disease

Liguoro I et al. Eur J Pediatr. 2020 May 18





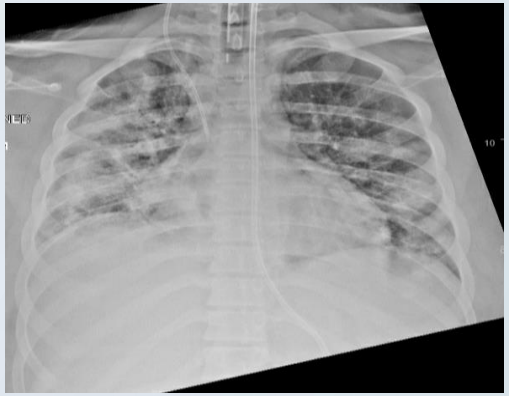
COVID- THE HIDDEN RISK

connecting care for children

Risks for children & families:

- 25% rise in domestic violence
- Unemployment
- Poverty
- Child abuse
- Social and emotional development
- Child development
- Education

SARS-CoV-2: 14 year ♂



Day -7	Day 1		Day 5	Day 10	Day 11	Day 20	Day 28
Contact: mother unwell	Unwell Fever Coryzal Cough Body ache	Shortness of breath Dizziness Weakness Anosmia Back pain Vomit	Admitted to local hospital: SARS-CoV-2 positive Respiratory distress Increasing oxygen need Intubation Inotropes	Transferred to GOSH ECMO referral	 **MDT, compassionate use Remdesivir**	Discharged to ward	Local hospital for rehabilitation

Risk factors – previously well, fully vaccinated incl BCG
BMI 38.6kg/m²

32+6/40
Maternal preeclampsia, twin
Small atrial septal defect,
Uneventful NICU/SCBU
Discharged home at 37/40

SARS-CoV-2: ex-premature (32+6/40) ♂

Day -7

Contact: NICU staff/ family ?

Day 1

3 days post DC
Acute respiratory distress
Hypoxia
Failed intubation in Emergency room
SARS-CoV-2 PCR +

Day 3

Transfer to GOSH
Laryngeal mask ventilation-
Intubated in theatre

Day 4

Steroids given prior to extubation,
Significant deterioration - ARDS
Prone position, HFOV, iNO2, inotropes

MDT, compassionate use Remdesivir

Day 9

SARS-CoV-2 pcr negative

Day 14

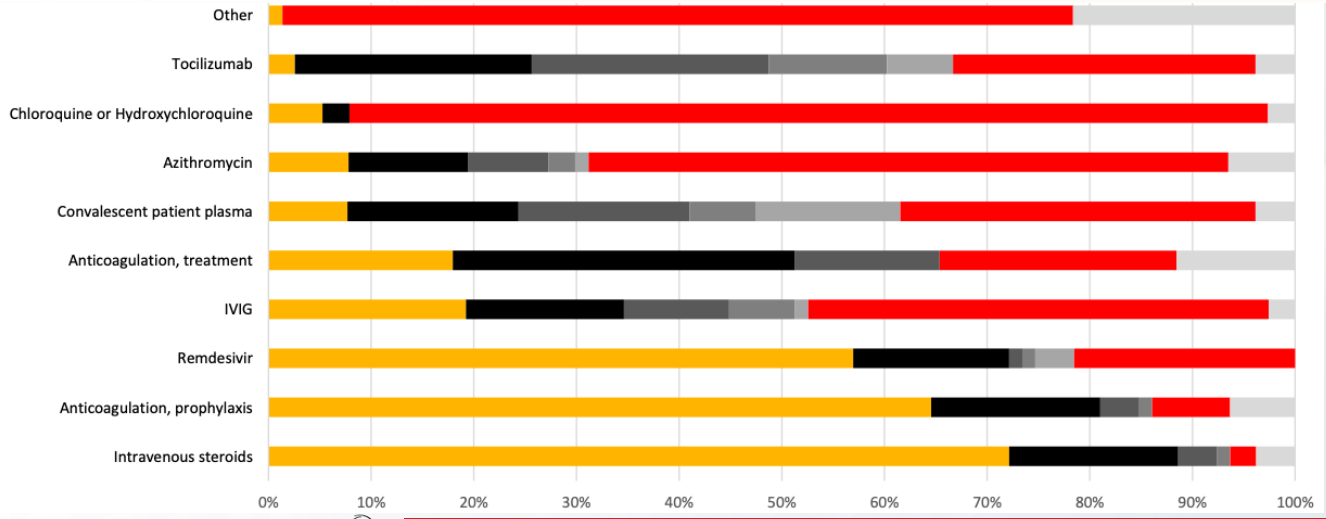
Day 18

Discharged to ward

Lynne Mofenson

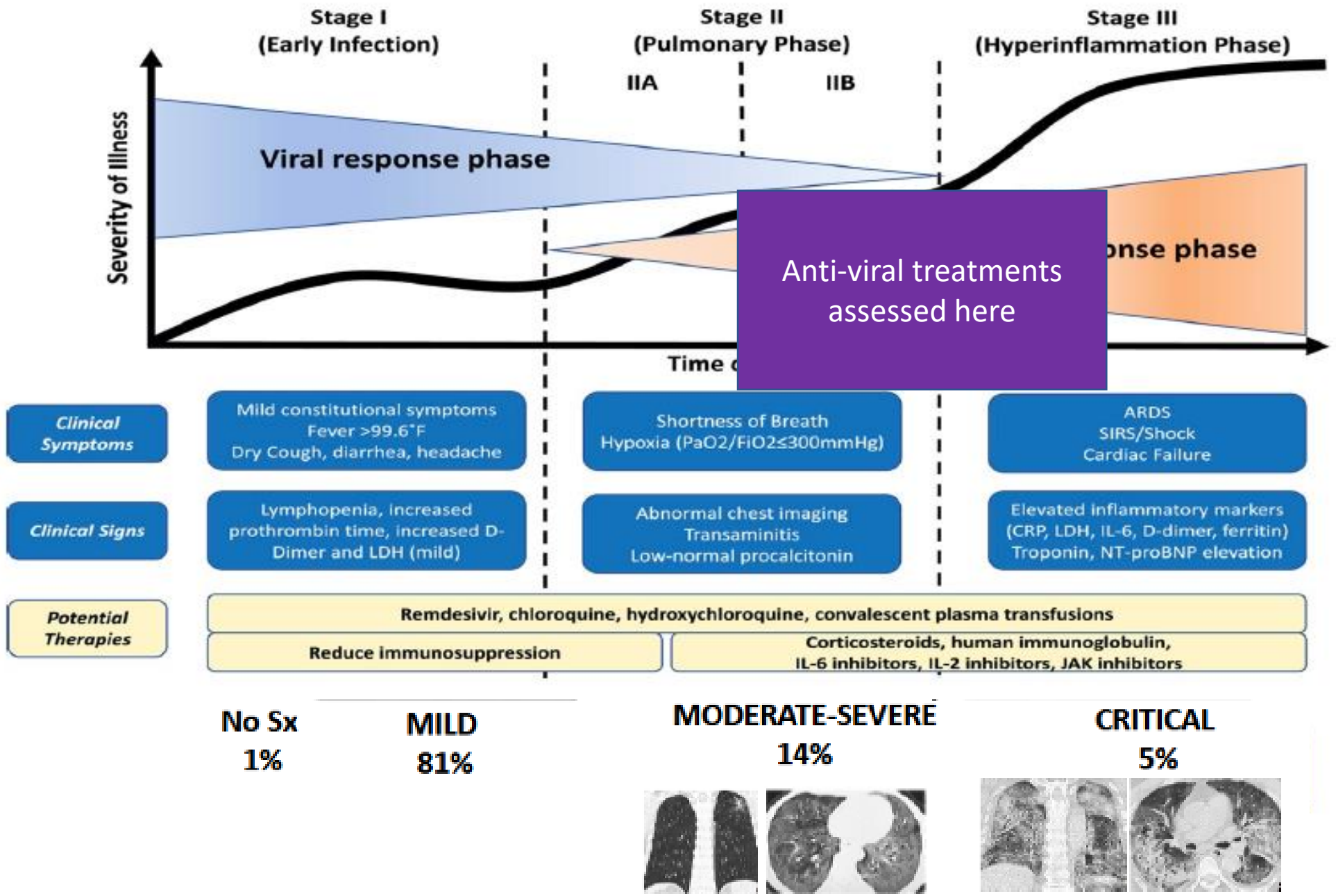
What are children with COVID-19 being treated with?

Participating PICUs by Country (n=78, n=1 not reported)			
United States	46	Chile	1
Spain	5	China	1
Argentina	2	Ghana	1
Canada	2	India	1
Colombia	2	Panama	1
Ecuador	2	Portugal	1
Italy	2	Puerto Rico	1
Japan	2	Saudi Arabia	1
United Kingdom	2	South Africa	1
Australia	1	Turkey	1
Brazil	1	Uruguay	1



Weekly survey of 78 PICU from 22 countries
Voluntary
Snapshot only

- 56% Remdesivir
- 72% Steroids
- 64% anti-coagulation
- 19% IVIG
- 8% convalescent plasma

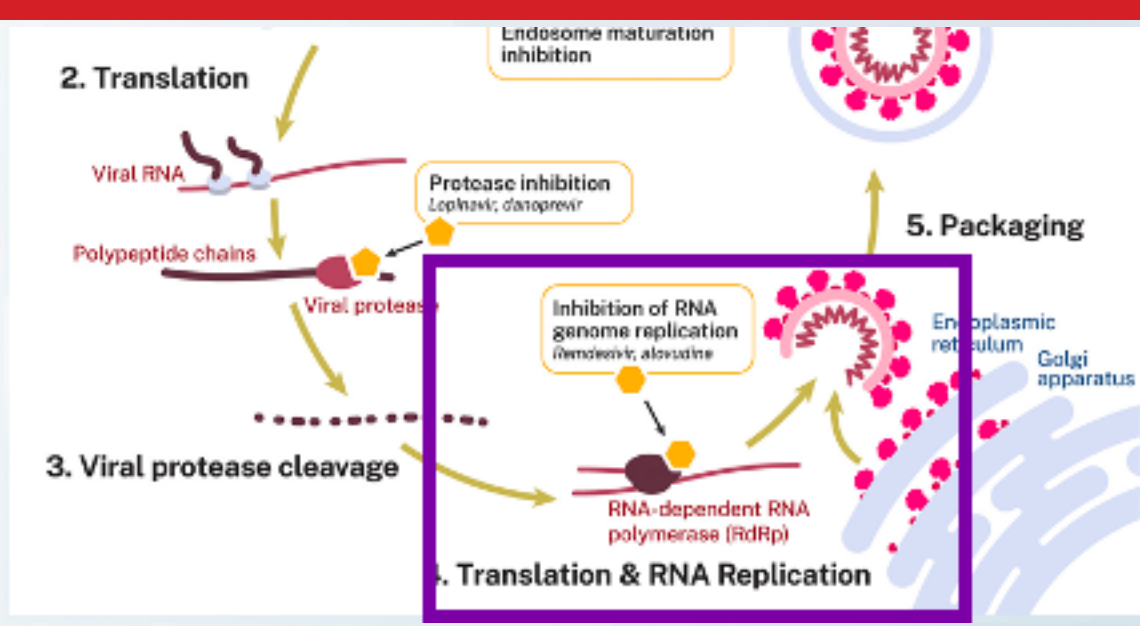


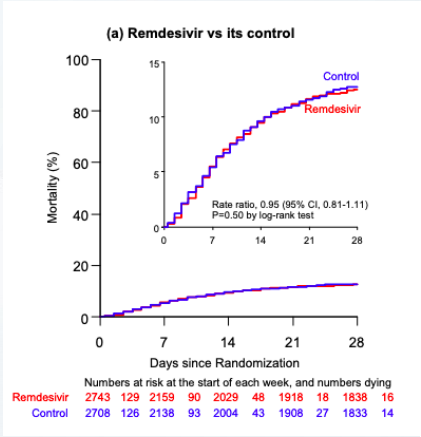
Classification of COVID-19 Disease States and Potential Therapeutic Targets. *Siddiqi and Mehra, J Heart Lung Transplant, 2020.*

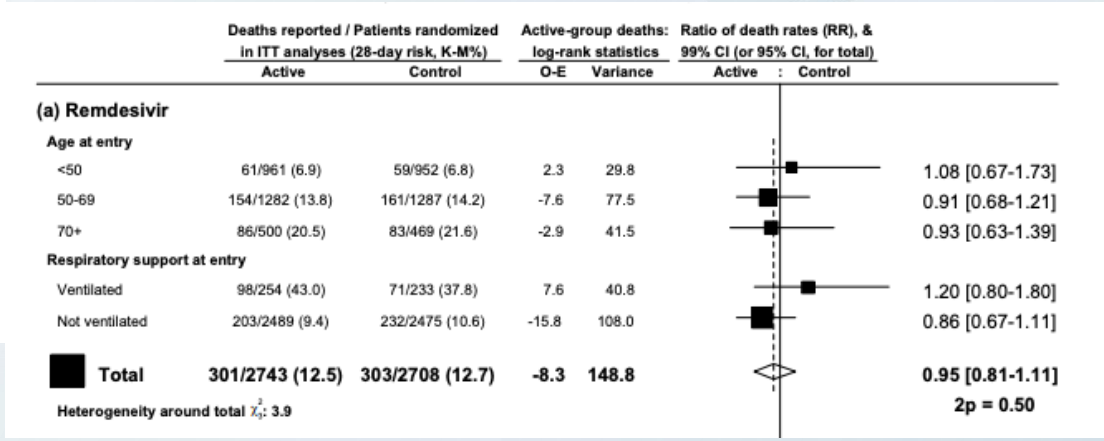
Remdesivir

- **Interesting** data in adults….
  - *SOLIDARITY trial vs. ACTT-1 vs. SIMPLE-severe vs. SIMPLE-moderate …. Still not definitive answer for lack of benefit in all scenarios*
- Children - safety data reassuring, no efficacy or outcome data
- Need RCT for children – CARAVAN

- Should we give it earlier?
- Need better preparations – nebulized
- Role alongside immunosuppression? Eg Dexamethasone…







Dexamethasone

RECOVERY
Randomised Evaluation of COVID-19 Therapy

- UK RECOVERY Trial: Large RCT of possible treatments for hospitalized patients with COVID-19
- Started March 2020; >11,500 participants have been randomized to SOC vs HCQ (stopped), low dose dexamethasone (6 mg), LPV/r, azithromycin, tocilizumab, convalescent plasma
- DSMB stopped dexamethasone arm for efficacy (including survival)

medRxiv preprint doi: https://doi.org/10.1101/2020.06.22.20137273 this version posted June 22, 2020.

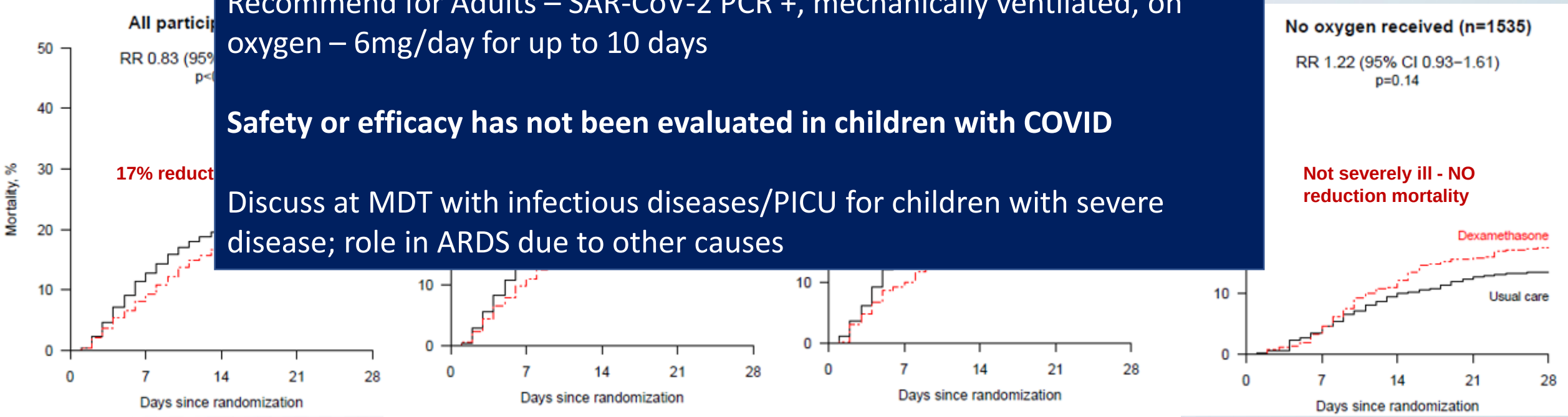
Effect of Dexamethasone in Hospitalized Patients with COVID-19 – Preliminary Report

Collaborative Group*

Recommend for Adults – SAR-CoV-2 PCR +, mechanically ventilated, on oxygen – 6mg/day for up to 10 days

Safety or efficacy has not been evaluated in children with COVID

Discuss at MDT with infectious diseases/PICU for children with severe disease; role in ARDS due to other causes



11 year old girl – SARS-CoV-2?

Day 0

3 days fever, abdominal pain, diarrhoea, myalgia, neck swelling

Day 1

SARS-CoV-2 pcr positive

sepsis

Surgical review
CT abdo
USS abdo

Broad spectrum AB

Deterioration

Day 2

60mlg/kg fluid

IVIG

ECHO – significant dysfunction

CRP doubled 300
Troponin
Pro-BNP rise

Day 3

High dose methylpred

Day 19

Normal cognition

Good ventricular function

Critical care myopathy
Right IJV thrombus

Day 28

ed to
e

Severe end of spectrum example of PIMS-TS

Differential – sepsis, COVID, toxic shock?

Intensive care admissions of children with paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS) in the UK: a multicentre observational study

Patrick Davies, Claire Evans, Hari Krishnan Kanthimathinathan, Jon Lillie, Joseph Brierley, Gareth Waters, Mae Johnson, Benedict Griffiths, Pascale du Pré, Zoha Mohammad, Akash Deep, Stephen Playfor, Davinder Singh, David Inwald, Michelle Jardine, Oliver Ross, Nayan Shetty, Mark Worrall, Ruchi Sinha, Ashwani Koul, Elizabeth Whittaker, Harish Vyas, Barnaby R Scholefield, Padmanabhan Ramnarayan**

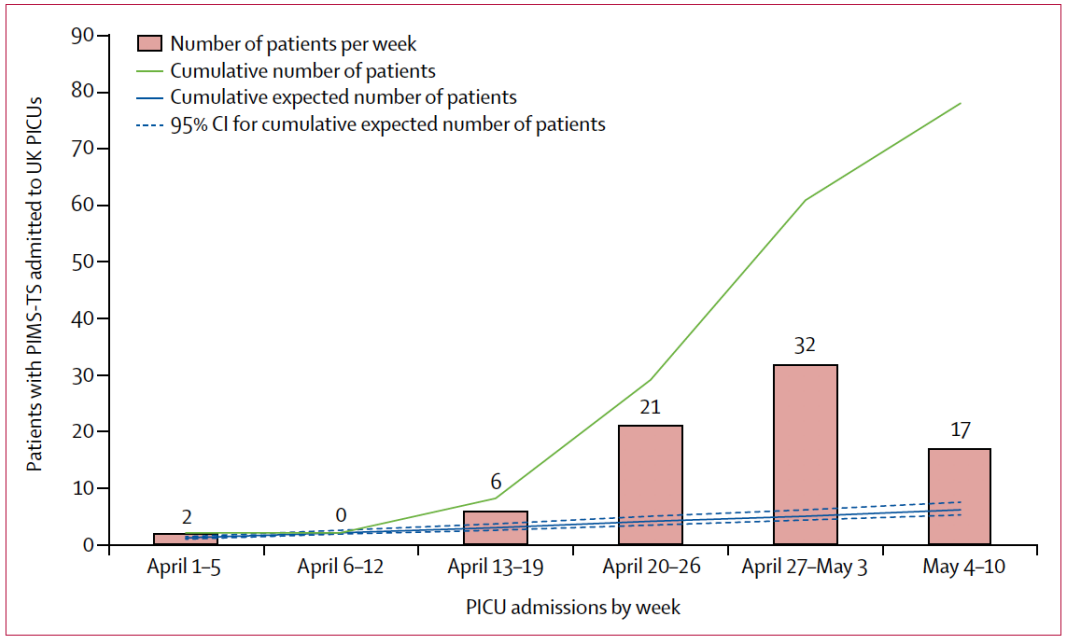


Figure 1: **PIMS-TS admissions per week to UK PICUs, April 1 to May 10, 2020**
The cumulative total, and the expected UK cumulative total of similar conditions (Kawasaki disease, toxic shock syndrome, haemophagocytic lymphohistiocytosis, and macrophage activation syndrome) from the previous 5 years are shown. PICU=paediatric intensive care unit. PIMS-TS=paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2.

21/23 PICUs in the UK

- 78 patients
- 67% male
- Median age 11 years (8-14)
- Median observed to expected weight ratio 1.22 (1.06-1.41)
- 78% no comorbidities
- 47% Afro-Caribbean, 28% Asian
- 22% PCR positive Majority of those tested serology positive
- Coinfection happens but is rare

Lancet Child Adolesc Health 2020: https://doi.org/10.1016/S2352-4642(20)30215-7

Paediatric Inflammatory Multisystem Syndrome, temporally associated with SARS-CoV-2 (PIMS-TS)

- Fever
- Rash
- Conjunctivitis
- Abdominal pain
- Diarrhoea
- Vomiting
- Headache

Specific lab biochemistry

Diagnosis of exclusion (sepsis, SJS, toxic shock etc)

Supportive care +/- immune modulation

MDT discussions

Shock

Myocardial dysfunction

ECG abnormalities

Coronary artery dilatation

Bowel inflammation

~250 children in UK

35-40% had 'shock'

PICU 3-4 days, inpatient 7

1 death

? Denominator, ~ 1/5000

Follow up data reassuring, but ongoing

Three phenotypes described in UK paper

Shocked cohort n=29

Median age 10.5

Clinically abdominal pain, diarrhea +/- rash/erythema

Raised inflammatory marker
Raised cardiac enzymes

Echo – ventricular dysfunction and CAA

Frequently given 2 or more treatments
Some resolved without immune modulation (early).

3 ECMO, 1 death

Kawasaki-like Disease n=13

Median age 8

Clinically meet AHA criteria – 4/5 mucocutaneous features

Raised inflammatory markers, milder increase cardiac markers

Echo – rare ventricular dysfunction +/- CAA

Manage as per KD guidelines – in our cohort, most had IVIG, Steroid and infliximab

No ECMO or death

Febrile and inflammatory n=23

Median age 10

Range of features including abdominal pain, diarrhea, mucocutaneous features. Tachycardia common and mild hypotension

Raised inflammatory markers and cardiac enzymes

Echo +/- mild ventricular dysfunction +/- CAA

Variety of treatments, including self-resolution

No ECMO or death

JAMA doi:10.1001/jama.2020.10369;

Three phenotypes described by CDC

MMWR / August 14, 2020 / Vol. 69 / No. 32

Shocked cohort n=203 (35.6%) Median age 9yrs

Clinically abdominal pain, diarrhea +/- rash/erythema

Raised inflammatory marker
Raised cardiac enzymes

Echo – ventricular dysfunction and CAA 21%

98% SARS-CoV-2 serology positive

Kawasaki-like Disease n=198 (34.7)

Median age 6yrs

Rash (62.6%), and mucocutaneous lesions (44.9%)

Raised inflammatory markers, milder increase cardiac markers

18.2% coronary artery dilatation

6.6% met KD AHA criteria

63% SARS-CoV-2 serology pos

Severe COVID phenotype? n=169 (29.6%)

Median age 10yrs

76% respiratory involvement (cough, SOB, ARDS)

84% SARS-CoV-2 PCR positive

Case Fatality rate 5.3%

Raised inflammatory markers and cardiac enzymes

Echo +/- mild ventricular dysfunction +/- CAA 15.8%

Mechanism?

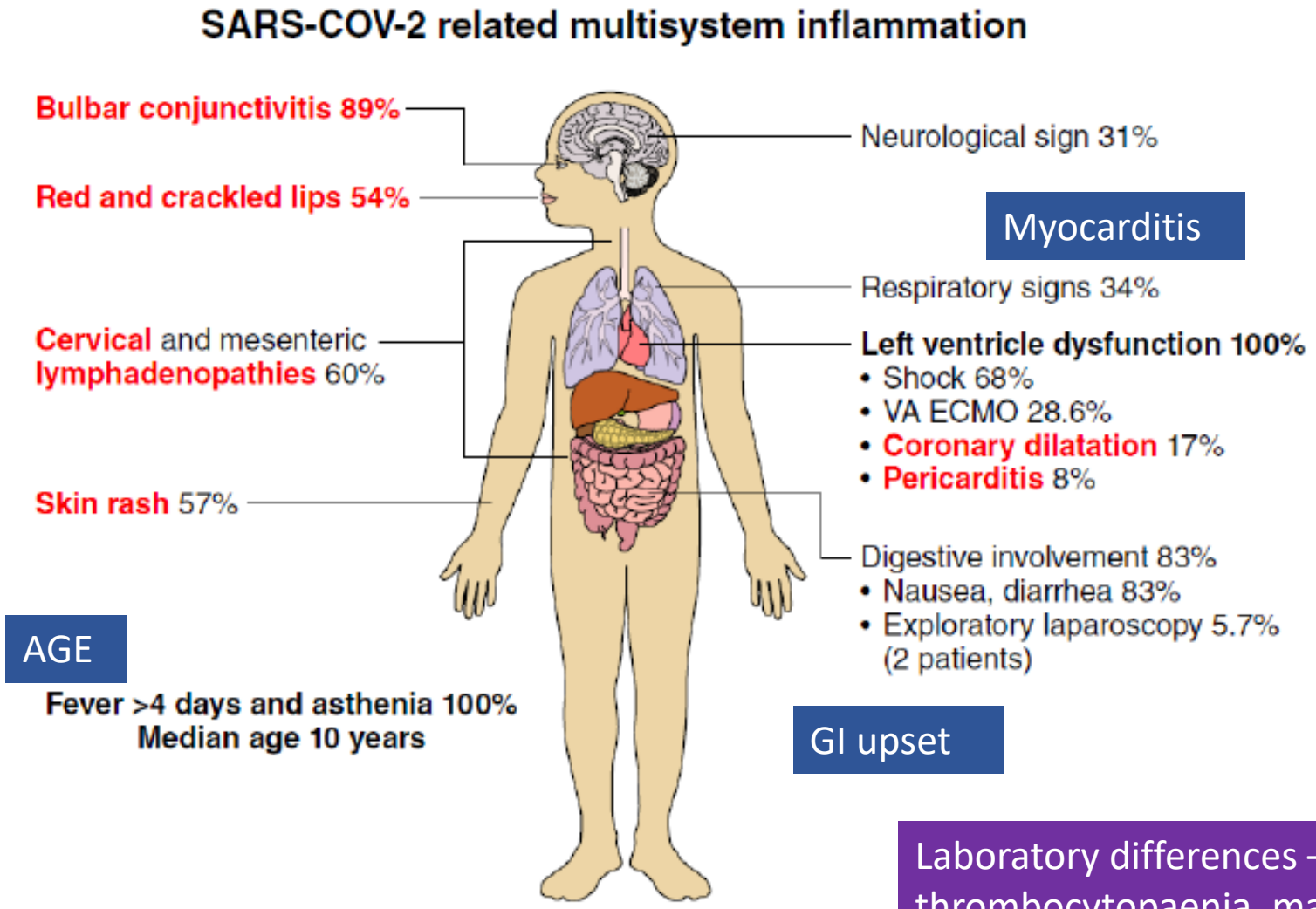
- Antibody Mediated
- Immune complex

- Is it Kawasaki disease?

- Other similar conditions in children
  - KD
  - KD –shock
  - Toxic shock syndrome
  - HLH/MAS

Comparison with historic Kawasaki disease, Kawasaki disease with shock and toxic shock syndrome cohorts

Manifestations of Paediatric inflammatory multi-system syndrome – compared to Kawasaki disease



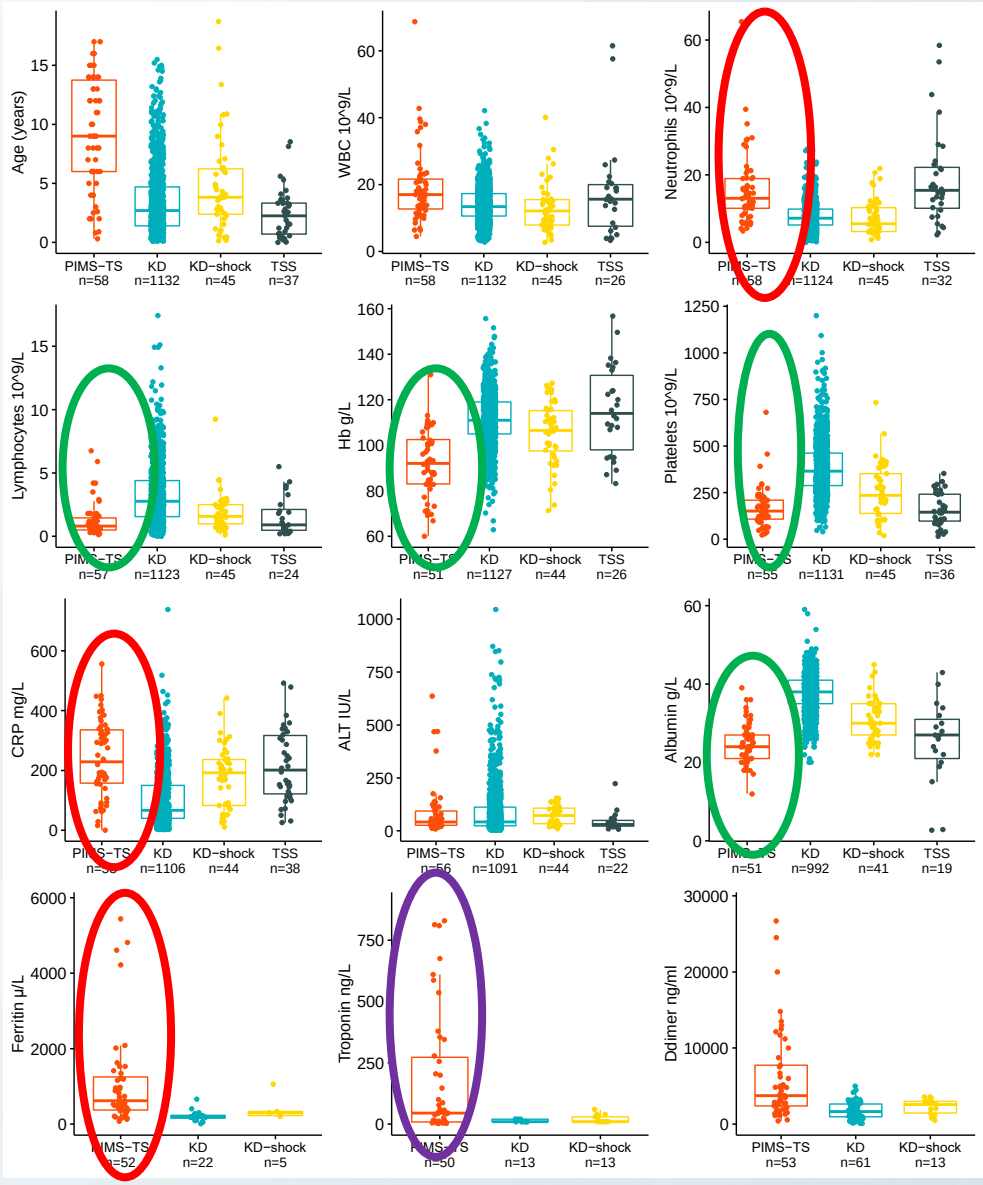
Laboratory differences – lymphopaenia, thrombocytopaenia, marked inflammation

Belhadjer Z et al. Circulation 2020 May 17 (epub)

Images from Adriana Tremoulet UCSD

Comparison KD/KD shock/TSS

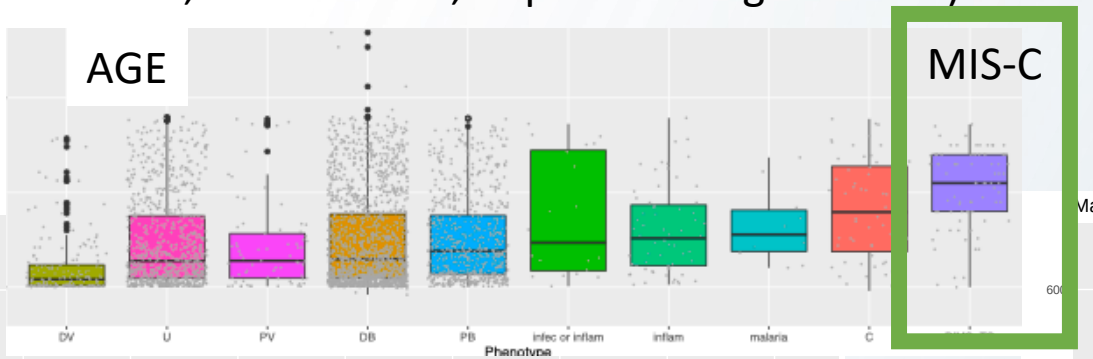
- Older
- More inflammatory (CRP, neutrophils, ferritin, LDH, fibrinogen)
- More lymphopaenic, anaemic and thrombocytopaenic, low albumin,
- Cardiac markers raised

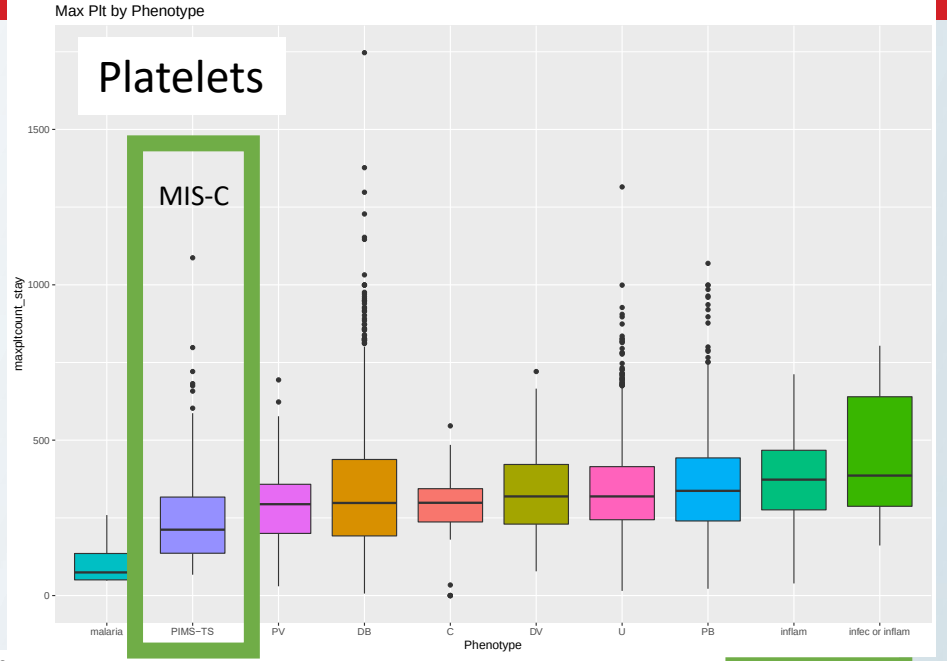


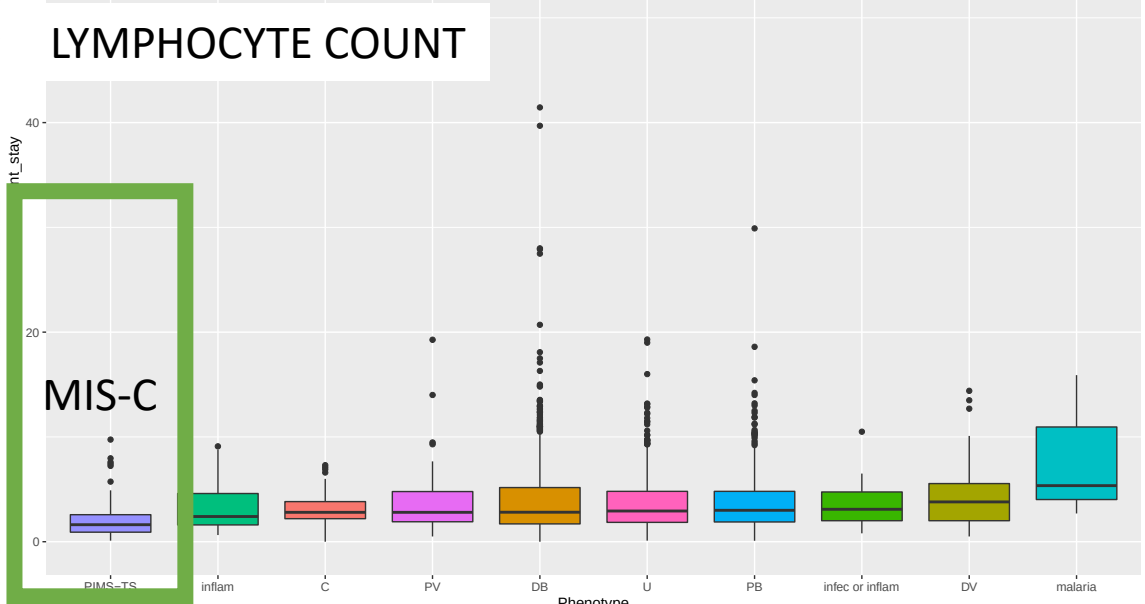
Comparison to other febrile illnesses

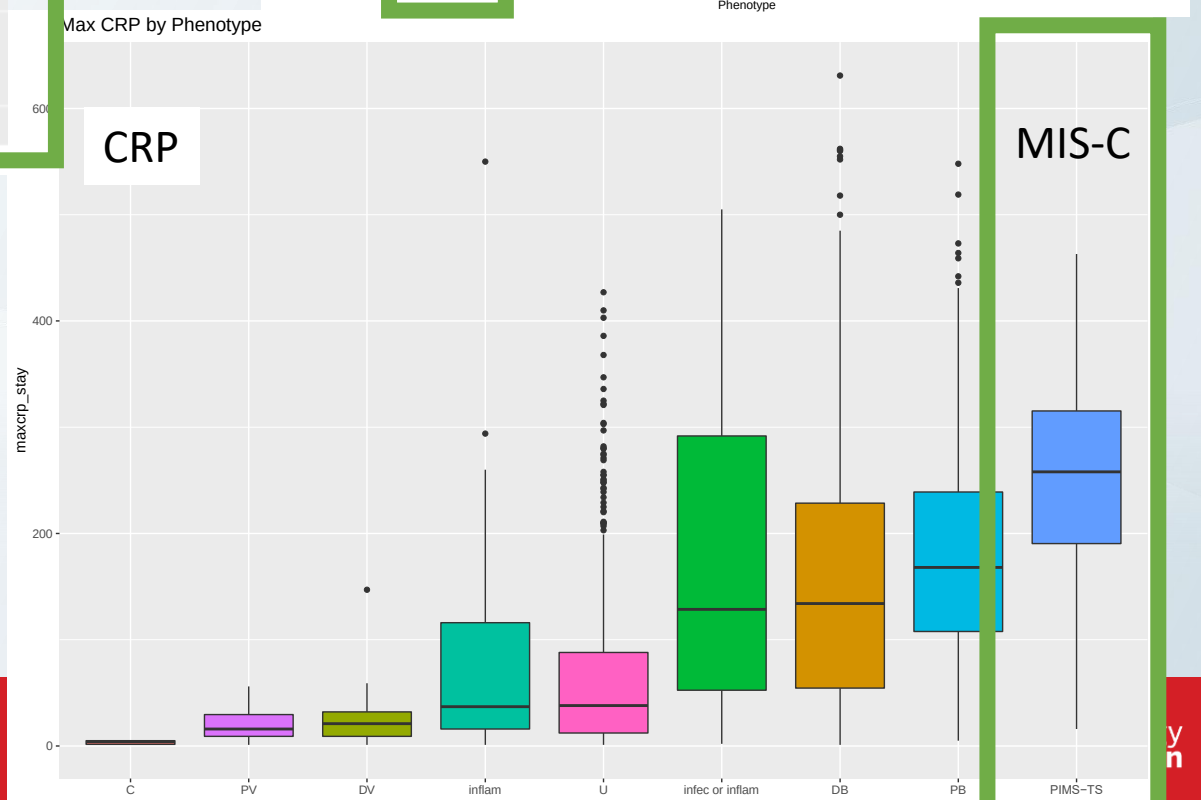
DIAMONDS
MAKING DIAGNOSIS PERSONAL

PIMS/MIS-C versus PERFORM & DIAMONDS Cohort
(Dr Clare Wilson, PhD Student, Imperial College London)



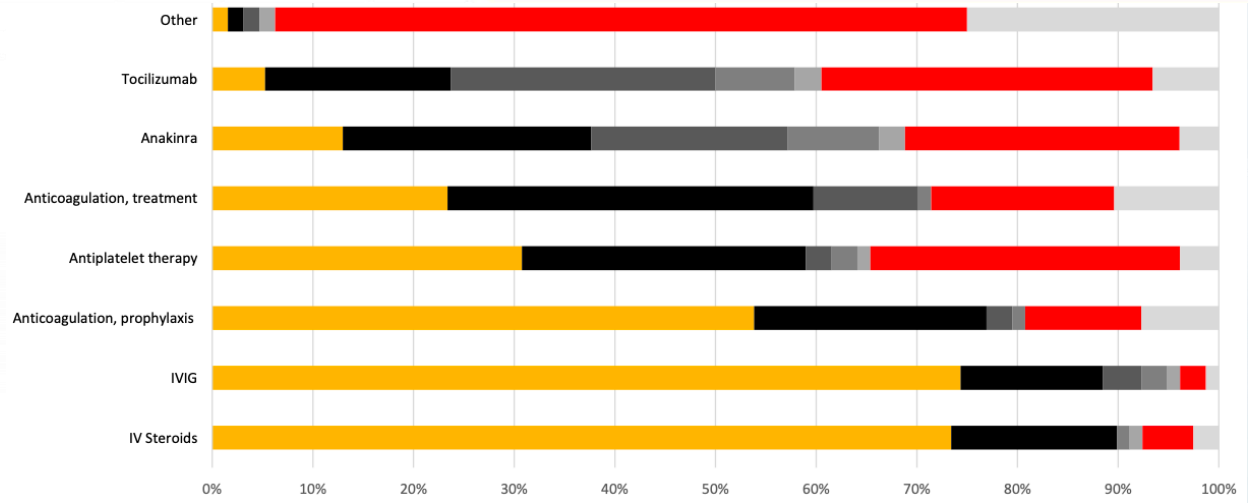






How are children with PIMS/MISC being treated?

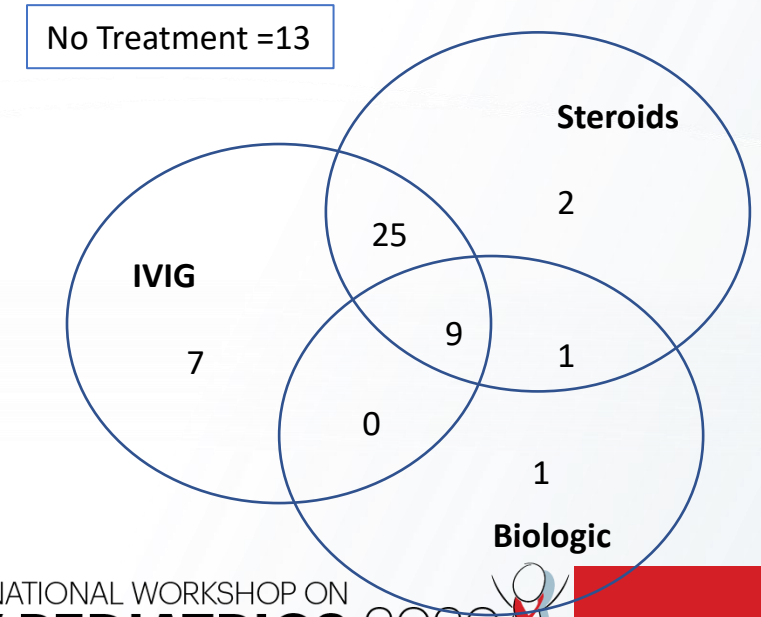
Participating PICUs by Country (n=78, n=1 not reported)			
United States	46	Chile	1
Spain	5	China	1
Argentina	2	Ghana	1
Canada	2	India	1
Colombia	2	Panama	1
Ecuador	2	Portugal	1
Italy	2	Puerto Rico	1
Japan	2	Saudi Arabia	1
United Kingdom	2	South Africa	1
Australia	1	Turkey	1
Brazil	1	Uruguay	1

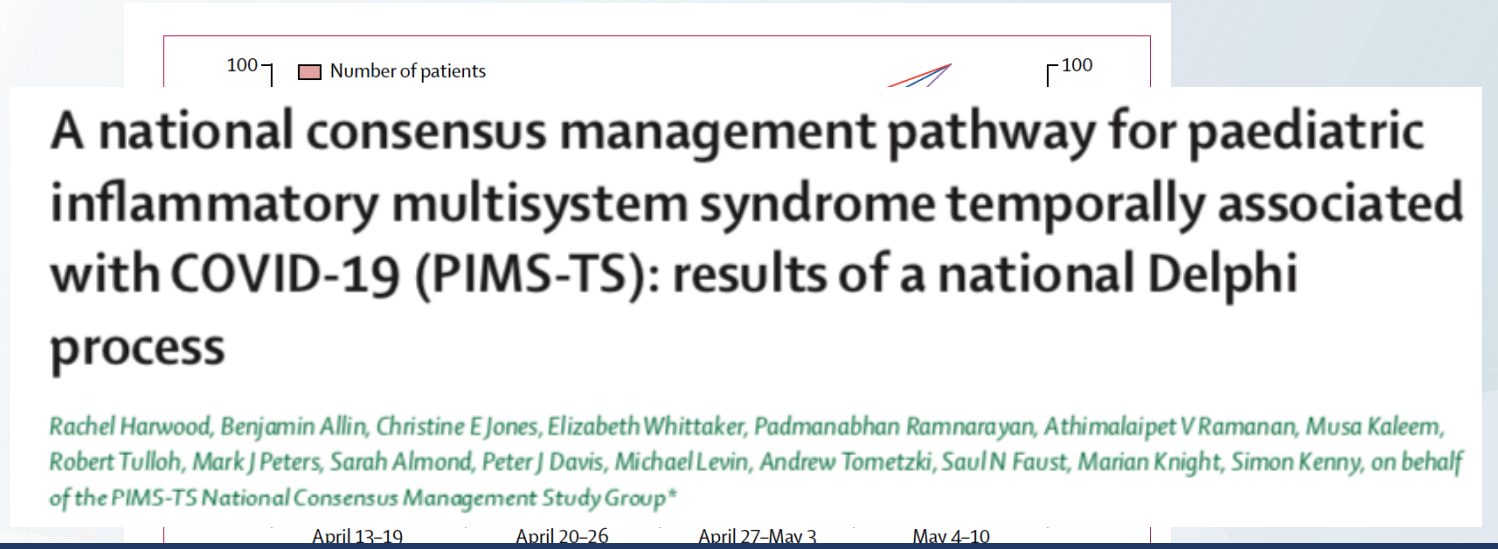


- IV steroids 72%
- IVIG 73%
- Anti-coagulation prophylaxis 54%
- Anti-platelet 31%
- Anakinra 12%, Toculizimab 6%

Treatment – what are we doing – anecdata and expert opinion rather than evidence

Treatment administered in 58 PIMS-TS patients in UK





--Consider all differentials!
--Recommend MDT within 24 hours of presentation/ if considering biologics
--Treatment based on phenotype (shock, Kawasaki like, other) & high risk features
- Supportive care (aspirin, LMWH, fluids, analgesia etc)
- Immune modulation (IVIG, Steroids, Anti-IL1/TNF/IL6)
- Ideally within a treatment trial

--Recruit to available studies (BPSU, DIAMONDS, ISARIC, RECOVERY etc)

Lancet Child Adolesc Health 2020: https://doi.org/10.1016/S2352-4642(20)30215-7 JAMA doi:10.1001/jama.2020.1103
Lancet https://doi.org/10.1016/S2352-4642(20)30304-7

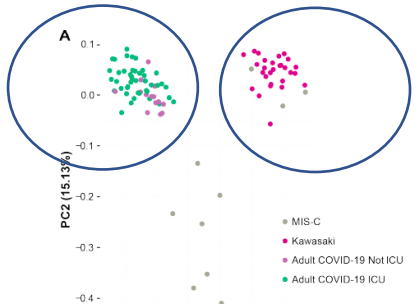
Follow up and outcomes

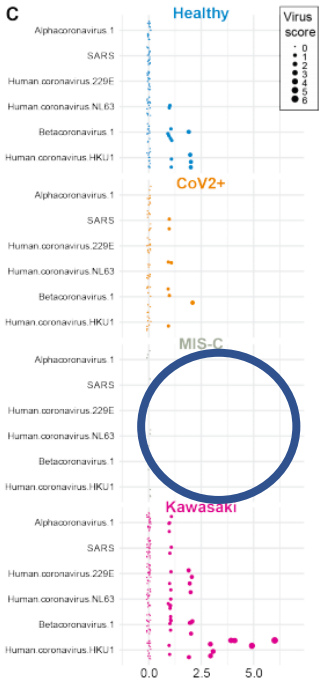
- Respiratory outcomes
- Thrombosis
- Cardiac outcomes – coronary artery aneurysms
  - PIMS –early outcome data reassuring
- COVID fatigue syndrome
- Behavioural and psychological

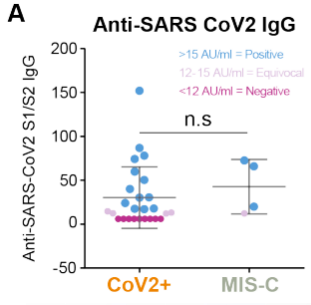
- Establishing multi-disciplinary clinics
- Logistics and cost

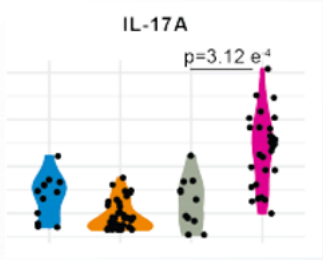
Understanding PIMS/MIS-C

Consiglio et al Cell 2020
DOI:https://doi.org/10.1016/j.cell.2020.09.016

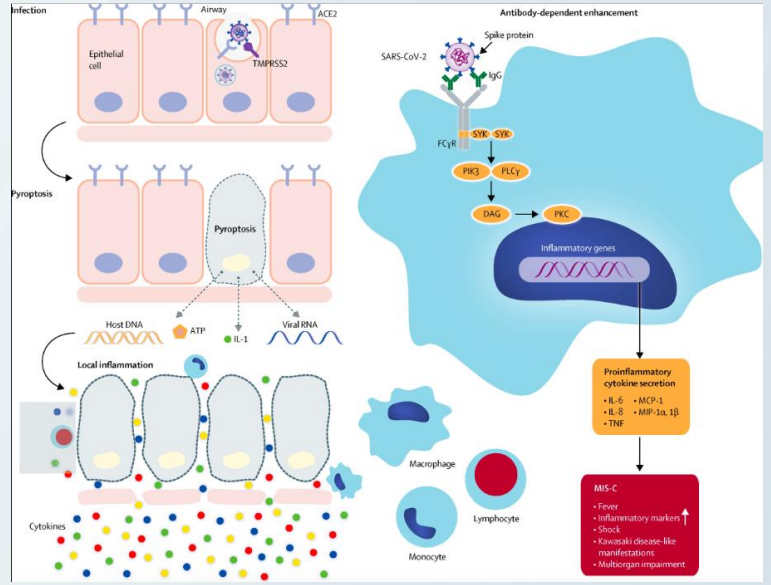




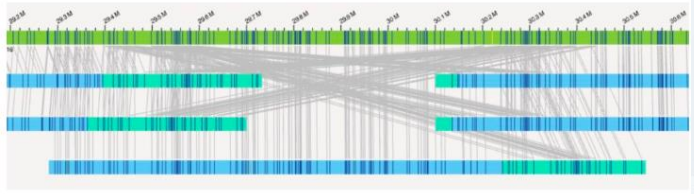




DIAMOND
MAKING DIAGNOSIS PERSONAL



Boston Children's Hospital



Probing MIS-C genetics: This readout from Saphyr shows areas of a patient's DNA that have "flipped" to a different location on the chromosome (indicated by the grey diagonal lines). The green line at the top represents the normal organization of DNA at that part of the chromosome. (Courtesy Bionano Genomics)

RECOVERY
Randomised Evaluation of COVID-19 Therapy

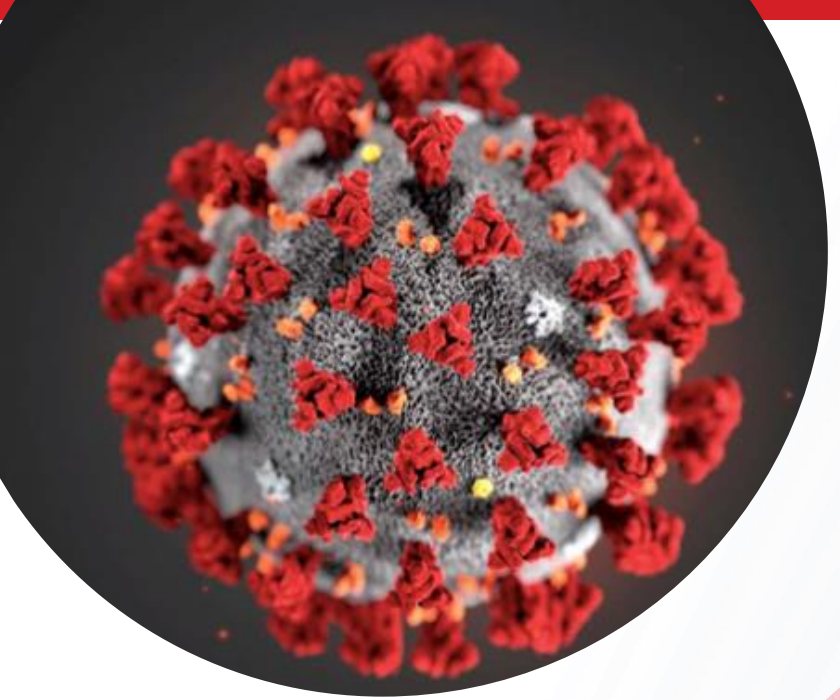
Best Available Treatment Study
for inflammatory syndromes associated with SARS-CoV-2

Summary

- Severe disease is rare
- MDT is crucial

- Treatments extrapolated from adult data
- Recruit to trial if available

- Need to follow up these children, within studies
- Understanding pathogenesis relevant for adults, and vaccine safety



Thank you
Questions?

virology education

Acknowledgements

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