Welcome!

DEPARTMENT OF PEDIATRICS
CALGARY

Before we get started:

- Please ensure your microphone is muted
- If you have any questions/comments, feel free to join the Zoom group chat at any time
- There will also be a Q&A period at the end of the meeting
- If you are experiencing technical difficulties, please contact daren.powell@ahs.ca

PIMS-TS/MIS-C/KD/TSS What is all the fuss about?

Dr. Shelley Riphagen
PICU Attending Physician, Evelina London Children's Healthcare

Dr. Susa Benseler
Pediatric Rheumatology, Alberta Children's Hospital

Background

- April 27, 2020 - Health authorities in the UK issue a report
  - Seriously ill children presenting with circulatory shock and hyperinflammatory state
  - Features consistent with toxic shock or KD
  - Some of the tested children were positive for SARS-CoV-2 infection
- May 4, 2020
  - NYC Department of Health issue an alert
- May 6, 2020
  - 8 British children are described in the Lancet by Dr. Riphagen and colleagues
- May 10, 2020
  - NYC - at least 85 children have presented with an inflammatory syndrome
  - 3 have died due to TSS with links to SARS-CoV-2 infection
  - Another 2 deaths are under investigation

Riphagen S, Gomez X, Gonzalez-Martinez C, Wilkinson N, Theocharis P. Hyperinflammatory shock in children during COVID-19 pandemic. Lancet. 2020 06/05/2020

Case Definitions

- Royal College of Paediatrics and Child Health (PIMS-TS)
  -Persistent fever
  -Inflammation (neutrophilia, elevated CRP and lymphopaenia)
  -Organ dysfunction
  -Children fulfilling full or partial criteria for KD may be included
  -Exclusion of any other microbial cause
  -SARS-CoV-2 PCR testing positive or negative

- CDC MIS-C Associated with COVID-19
  -Fever
  -Laboratory evidence of inflammation
  -Clinically severe illness requiring hospitalization
  -Multisystem organ involvement
  -No alternative plausible diagnoses
  -Positive for 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

Inflammatory Multi-system Syndrome-Temporally associated with SARS CoV2

PIMS-TS

Shelley Riphagen
Paediatric Intensivist Evelina London Children's Hospital
Clinical lead South Thames Retrieval Service

Evelina London
Celebrating 150 years of caring for children

South Thames RETRIEVAL SERVICE

Guy's and St Thomas' NHS Foundation Trust

STRS Evelina Public health alert, end April

- 4 cases “Toxic shock” in one day
- All one borough
- 3 more in next 24 hours, different boroughs
- All exact same clinical picture

Setting

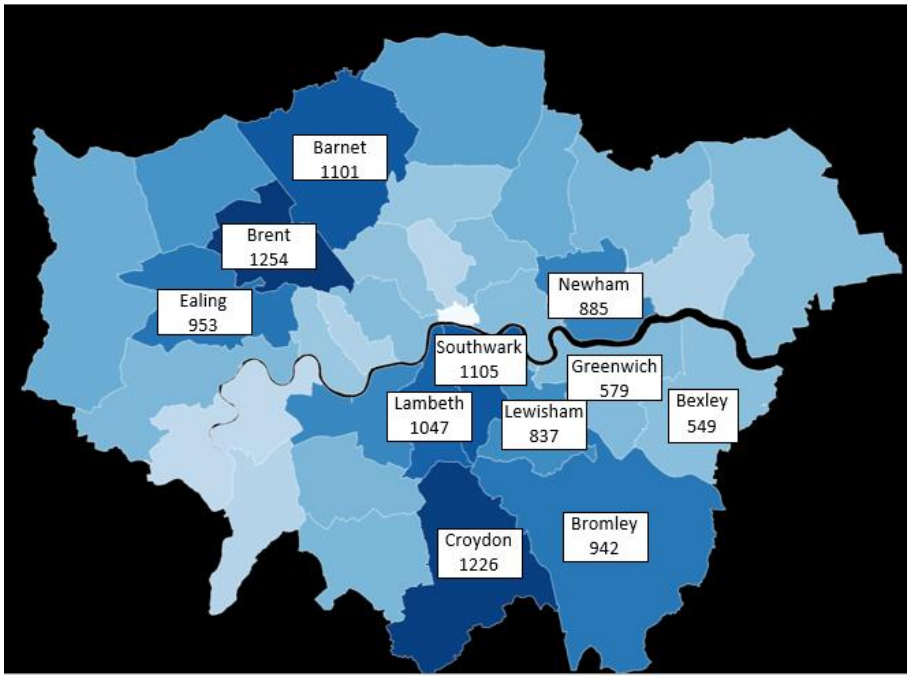
Previously “fit and well” children

Significant viral exposure in community

Multiple children in London (and internationally) presenting with similar clinical picture

- High fever
- Loose stools & abdominal pain
- Lethargy
- Shock
- Rash
- Myocardial dysfunction
- Biochemical evidence of hyper-inflammation

Covid cases in adults April 22, 2020



Hyperinflammatory shock in children during COVID-19 pandemic

South Thames Retrieval Service in London, UK, provides paediatric intensive care support and retrieval to 2 million children in South East England. Over a period of 10 days in mid-April, 2020, we noted an unprecedented cluster of eight children with hyperinflammatory shock with features similar to atypical Kawasaki disease, Kawasaki disease shock syndrome,[1] or toxic shock syndrome (typical number is one or two children per week). All children were previously fit and well. Six of the children were of Afro-Caribbean descent, and five of the children were boys. All children except one were well above the 75th centile for weight. Three children had known family exposure to coronavirus disease 2019 (COVID-19). Demographics, clinical findings, imaging findings, treatment, and outcome from the paediatric intensive care unit (PICU) are shown in the appendix.

Clinical presentations were similar, with unrelenting fever (38–40°C), variable rash, conjunctivitis, peripheral oedema, and generalised extremity pain with significant gastro-intestinal symptoms (appendix). All progressed to warm, vasoplegic shock, refractory to volume resuscitation and eventually requiring noradrenaline and milrinone for haemodynamic support. Most of the children had no significant respiratory involvement, although seven of the children required mechanical ventilation for cardiovascular stabilisation. Other notable features (besides persistent fever and rash) included development of small pleural, pericardial, and ascitic effusions, suggestive of a diffuse inflammatory process.

All children tested negative for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) on bronchoalveolar lavage or nasopharyngeal aspirates. Despite being critically unwell, with laboratory evidence of infection or inflammation[2] including elevated concentrations of C-reactive protein, procalcitonin, ferritin, triglycerides, and D-dimers (appendix), no pathological organism was identified in seven of the children. Adenovirus and enterovirus were isolated in one child (appendix).

Baseline electrocardiograms were non-specific; however, a common echocardiographic finding was echo-bright coronary vessels (appendix), which progressed to giant coronary aneurysm in one patient within a week of discharge from paediatric intensive care (appendix). One child developed arrhythmia with refractory shock, requiring extracorporeal life support, and died from a large cerebrovascular infarct. The myocardial involvement[2] in this syndrome is evidenced by very elevated cardiac enzymes during the course of illness.

All children were given intravenous immunoglobulin (2 g/kg) in the first 24 h, and antibiotic cover including ceftriaxone and clindamycin. Subsequently, six children have been given 50 mg/kg aspirin. All of the children were discharged from PICU after 4–6 days. Since discharge, two of the children have tested positive for SARS-CoV-2 (including the child who died, in whom SARS-CoV-2 was detected post mortem). All children are receiving ongoing surveillance for coronary abnormalities.

We suggest that this clinical picture represents a new phenomenon affecting previously asymptomatic children with SARS-CoV-2 infection manifesting as a hyperinflammatory syndrome with multiorgan involvement similar to Kawasaki disease shock syndrome. The multifaceted nature of the disease course underlines the need for multispecialty input (PICU, cardiology, infectious diseases, immunology, and rheumatology).

The intention of this report is to bring this subset of children to the attention of the wider paediatric community, in order to optimise early recognition and management. As this Correspondence goes to press, 1 week after the initial submission, the Evelina London Children's Hospital PICU has managed more than 20 children with similar clinical presentation, the first ten of whom tested positive for antibody (including the original eight children in the cohort described above).

We declare no competing interests.

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South Thames Retrieval Service for Children, Evelina London Children's Hospital Paediatric Intensive Care Unit, London SE1 7EH, UK (SR, XG); and Evelina London Children's Hospital, London, UK (CG-M, NW, PT)

1 Zhang M-M, Shi L, Lin Y, Liu Y. Clinical analysis of Kawasaki disease shock syndrome. *Chin Med J (Engl)* 2017; 130: 2891–92.
2 Liu P, Blet A, Smyth D, Li H. The science underlying COVID-19: implications for the cardiovascular system. *Circulation* 2020; published online April 15. DOI:10.1161/CIRCULATIONAHA.120.047549.
3 Li Y, Zou L, Wu J, et al. Kawasaki disease shock syndrome: clinical characteristics and possible use of IL-6, IL-10 and IFN-as biomarkers for early recognition. *Pediatr Rheumatol Online J* 2019; 17: 1.

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Table: Demographics, clinical findings, imaging findings, treatment and outcome from PICU

Patient	Clinical presentation		Organ support	Pharmacological treatment	Imaging	Laboratory	Micro	PICU LOS (days) /Outcome
	Initial	*PICU referral*				*Max. or min.*		
P1- 14y, M *95kg, BMI 33* *Afro* *Nil comorbid*	4/7 >40C, 3/7 non-bloody diarrhea, abdo. pain, headache	BP 80/40, HR 120 RR 40, WOB, StO2 99% NCO2	MV, RRT, VA-ECMO,	Dopamine, NA, VP, Adr, Milrinone, Hydroxicortisone IVIG, ceftriaxone, clindamycin	RV dysfunction/elevated RVSP Ileitis, GB edema and dilated biliary tree, ascites, bilateral basal lung consolidations and diffuse nodules	Ferr 4220 D-dimers 13.4 Trop 675 proBNP >35000 CRP 556 PCT>100 Alb 20 Plat 123	PM COVID-19 PCR+	6 / Demise *(Right MCA & ACA ischemic infarct)*
P2- 8y, M *30kg, BMI 18* *Afro* *Nil comorbid*	5/7 >39C, non-bloody diarrhea, abdo. pain, conjunctivitis, rash	BP 81/37, HR 165 RR 40 , SVIA	MV	NA, Adr, IVIG, Infliximab, Methylpred. Ceftriaxone, clindamycin	Mild biventricular dysfunction, severely dilated coronaries Ascites, pleural effusions	Ferr 277 D-dimers 4.8 Trop 25 CRP 295 PCT 8.4 Alb 18 Plat 61	Nil, LCE-Mother	4 / Alive
P3- 4y, M *18kg, BMI 17* *Middle-east* *Nil comorbid*	4/7 >39C, D+V, abdo. pain, rash, conjunctivitis	BP 90/30, HR 170 RR 35, SVIA	MV	NA, Adre, IVIG Ceftriaxone, Clindamycin	Ascites, pleural effusions	Ferr 574 D-dimers 11.7 Trop 45 CRP 322 PCT 10.3 Alb 22 Plat 103	Adenovirus+ ERV+	4 / Alive
P4- 13y, F *64kg, BMI 33* *Afro* *Nil comorbid*	5/7 >39C, non-bloody diarrhea, abdo. pain, conjunctivitis	BP 77/41, HR 127 RR 24 , SVIA	HFNC	NA, Milrinone, IVIG, Ceftriaxone, Clindamycin	Moderate-severe LV dysfunction Ascites	Ferr 631 D-dimers 3.4 Trop 250 proBNP 13427 CRP 307 PCT 12.1 Alb 21 Plat 146	Nil	5 / Alive
P5- 6y, M *22kg, BMI 14* *Asian* *Autism, ADHD*	4/7 >39C, odynophagia, rash, conjunctivitis	BP 85/43, HR 150, RR 50, SVIA	NIV	Milrinone, IVIG, Methylpred, Aspirin, Ceftriaxone	Dilated LV, AVVR, peri-coronary hyperechogenicity	Ferr 550 D-dimers 11.1 Trop 47 proBNP 7004 CRP 183 Alb 24 Plat 165	COVID-19 PCR+, LCE-Father	-/-
P6- 6y, F *26kg, BMI 15* *Afro* *Nil comorbid*	5/7 >39C, myalgia, 3/7 D+V, conjunctivitis	BP 77/46, HR 120, RR 40, SVIA	NIV	Dopamine, Noradrenaline, Milrinone, IVIG, Methylpred, Aspirin, Ceftriaxone, Clindamycin	Mild LV systolic impairment	Ferr 1023 D-dimers 9.9 Trop 45 proBNP 9376 CRP 169 PCT 11.6 Alb 25 Plat 158	Nil, CCE-Grandfather	-/-
P7- 12y, M *50kg, BMI 20* *Afro* *Alopecia areata, hayfever*	4/7 >39C, 2/7 D+V, abdo. pain, rash, odynophagia, headache	BP 80/48, HR 125, RR 47, SatO2 98% HFNC FiO2 0.35	MV	Noradrenaline, Adrenaline, Milrinone, IVIG, Methylpred, Heparin, Ceftriaxone, Clindamycin, Metronidazole	Severe biventricular impairment Ileitis, ascites, pleural effusions	Ferr 958 D-dimers 24.5 Trop 813 proBNP >35000 CRP 251 PCT 71.5 Alb 24 Plat 273	Nil	-/-
P8- 8y, F *50kg, BMI 25* *Afro* *Nil comorbid*	4/7 >39C, odynophagia, 2/7 D+V, abdo. pain	BP 82/41 HR 130, RR 35, SatO2 97% NCO2	MV	Dopamine, NA, Milrinone, IVIG, Aspirin, Ceftriaxone, Clindamycin	Moderate LV dysfunction	Ferr 460 D-dimers 4.3 Trop 120 CRP 347 PCT 7.42 Alb 22 Plat 296	Nil, LCE-Paren	-/-

Afro- Afrocaribbean; Abdo.- Abdominal; RA- Room air; NA- Noradrenaline; MV- Mechanical ventilation via ETT; RRT- Renal replacement therapy; VA-ECMO- Veno-arterial extracorporeal membrane oxygenation; Adre- Adrenaline; VP- Argipressin; IVIG- Human intravenous immunoglobulin; LV- left ventricle; PM- Post-mortem; CCE- Confirmed

Disclaimer

Not expert at this disease

An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study

Lancet May 13 2020

Lucio Verdoni, Angelo Mazza, Annalisa Gervasoni, Laura Martelli, Maurizio Ruggeri, Matteo Ciuffreda, Ezio Bonanomi, Lorenzo D'Antiga

Why and How Is Hyperferritinemic Sepsis Different From Sepsis Without Hyperferritinemia?*

Carcillo PCCM May 2020

10.1161/CIRCULATIONAHA.120.047549

The Science Underlying COVID-19:

Implications for the Cardiovascular System

Running Title: *Liu et al.; Science & COVID-19*

Endothelial cell infection and endotheliitis in COVID-19

Varga. Lancet April 20

Evidence Supports a Causal Model for Vitamin D in COVID-19 Outcomes

Davies G, Garami AR, Byers J

NHS
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Cytokine storm in Covid adults

- Over reaction to infectious trigger
- Response may be delayed
- Diagnosis
  - History compatible with infectious trigger
  - Clinical features to support multi-organ involvement
  - Lab results to support hyper-inflammation

	Number of points
Temperature	
<38·4°C	0
38·4–39·4°C	33
>39·4°C	49
Organomegaly	
None	0
Hepatomegaly or splenomegaly	23
Hepatomegaly and splenomegaly	38
Number of cytopenias*	
One lineage	0
Two lineages	24
Three lineages	34
Triglycerides (mmol/L)	
<1·5 mmol/L	0
1·5–4·0 mmol/L	44
>4·0 mmol/L	64
Fibrinogen (g/L)	
>2·5 g/L	0
≤2·5 g/L	30
Ferritin ng/ml	
<2000 ng/ml	0
2000–6000 ng/ml	35
>6000 ng/ml	50
Serum aspartate aminotransferase	
<30 IU/L	0
≥30 IU/L	19
Haemophagocytosis on bone marrow aspirate	
No	0
Yes	35
Known immunosuppression†	
No	0
Yes	18

The HScore[11] generates a probability for the presence of secondary HLH. HScores greater than 169 are 93% sensitive and 86% specific for HLH. Note that bone marrow haemophagocytosis is not mandatory for a diagnosis of HLH. HScores can be calculated using an online HScore calculator.[11] HLH=haemophagocytic lymphohistiocytosis. *Defined as either haemoglobin concentration of 9·2 g/dL or less (≤5·71 mmol/L), a white blood cell count of 5000 white blood cells per mm³ or less, or platelet count of 110 000 platelets per mm³ or less, or all of these criteria combined. †HIV positive or receiving long-term immunosuppressive therapy (ie, glucocorticoids, cyclosporine, azathioprine).

www.thelancet.com Vol 395 March 28, 2020

Clinical picture in children

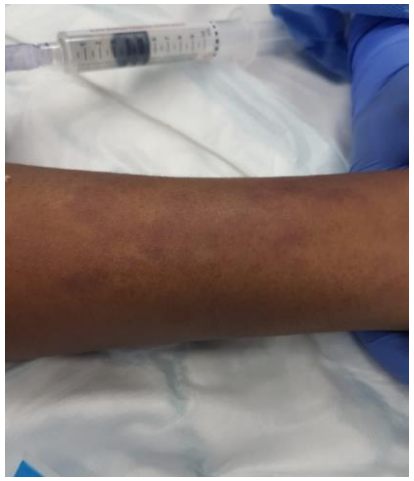
No obvious primary infection

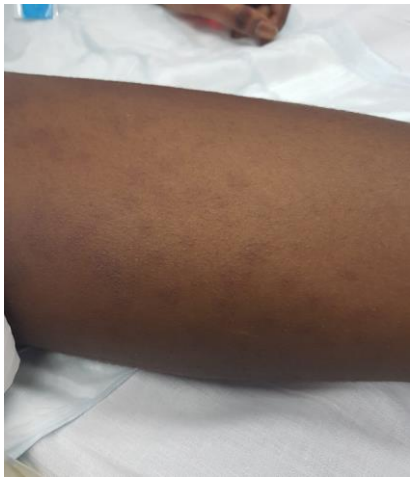
Delayed severe clinical illness characterised by unrelenting fever, rash, myalgia and abdominal pain, conjunctivitis and vasoplegic shock

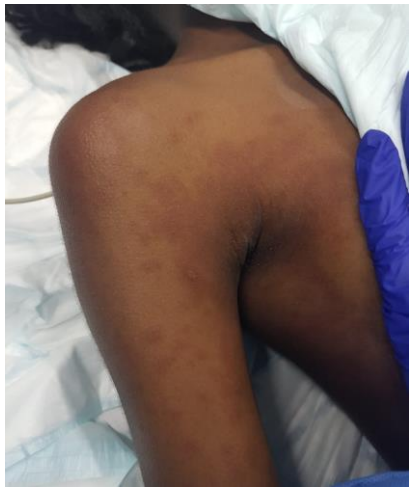
Hyper-inflammation

Cross over picture

Kawasaki shock syndrome, toxic shock syndrome and HLH



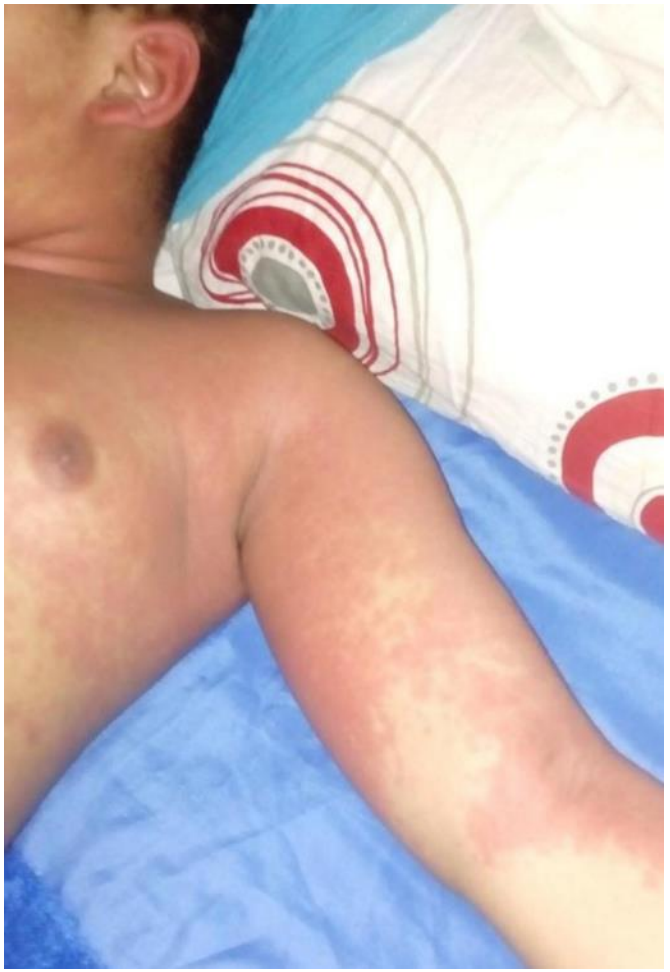




Acutely presenting rash with PIMS-TS

Macular, non blanching areas of tender redness, not hot

Adjacent areas of extreme pallor with no cap refill



Kawasaki Disease

Clinical features

Children <5yo

Fever ≥5 days +

4 of 5

- Rash
- Significant cervical lymphadenopathy
- Conjunctivitis
- Oral mucosal changes
- Peripheral extremity changes

Development of coronary artery aneurysms without all of above + atypical KD

Small subset with shock KDSS: GI sx & shock

Laboratory findings

- Slightly low Na
- Elevated ESR, CRP, WCC
- Thrombocytosis by end of disease progression
- Transaminitis
- Sterile pyuria and aseptic meningitis

Treatment

Early IVIG 2g/kg

Aspirin

Steroids in IVIG resistance/ TNFa blockade- infliximab

Other important points

Definite genetic susceptibility

sHLH

Clinical features

5 of 8 clinical and lab features

Fever >38C

Splenomegaly

Defined trigger (infection, malignancy, rheumatoid disease = MAS)

Laboratory findings

- Cytopaenia (2 of 3 lines)
- Hypertriglyceridaema (>3 mmol/l) UL1.7
- Hypofibrinogenaemia (<1.5 g/l) UL 3.9
- Hyperferritinaemia (>500ug/l) UL 114
- Low/ absent NKC
- Elevated soluble CD25 (soluble Il-2 receptor) and reduced perforin

Treatment

- Multi-organ support
- High dose steroids, etopside, cyclosporinA
- IVIG
- Cytokine targeted treatment: Anakinra

Other important points

Multiple well described genetic associations in pHLH and some in sHLH

Toxic shock syndrome

Clinical features

- Severe illness d/t GAS (throat/URTI/ peri-menstrual) or Staph (skin lesion)
- Erythematous rash
- GI symptoms (pain/ Diarrhoea/ vomiting)
- Shock, classically starting with vasodilated shock (toxic vasculopathy)
- Severe limb pain-Soft tissues necrosis esp necrotising fasciitis, myositis or distal gangrene)

Laboratory findings

- Abnormal relevant microbiology
- Elevated CRP
- Renal impairment
- Coagulopathy with DIC (low plt, clotting deranged with elevated D- dimers)
- Transaminitis
- ARDS

Treatment

- Source control early
- Broad spectrum antibiotics & Clindamycin (Tissue penetration and immune modulation)
- IVIG 1g/kg over 2 days

14th - 28th April
(1 case 14th March)

PICU, all received noradrenaline

22 Cases

19 cases excluding "possible" cases

Shock *n = 21*

- **Cardiac dysfunction** *n = 19*
  - Ventilated *n = 10*
    - ECMO n=2
    - No ECMO n=8
  - HFNC *n = 3*
  - Nil n=6
- **Nil dysfunction** n =2
  - Ventilated *n = 0*
  - Nil *n = 2*

Respiratory *n = 1*

- Vent *n = 1*
  - Alive n=1

One death
Majority respond to immunsuppression+norad

Evelina London 150

NHS Guy's and St Thomas' NHS Foundation Trust

Demographics

Patient	Age	Centile
1	14	99
2	8	80
3	4	75
4	13	91
5	6	75
6	15	91
7	8	99
8	6	92
9	12	91
10	7	30
11	12	92
12	11	96
13	9	70
14	15	90
15	4	99
16	16	95
	Med	**91**
	Q1	**76.25**
	Q3	**95.75**

Ethnicity

11/16 African

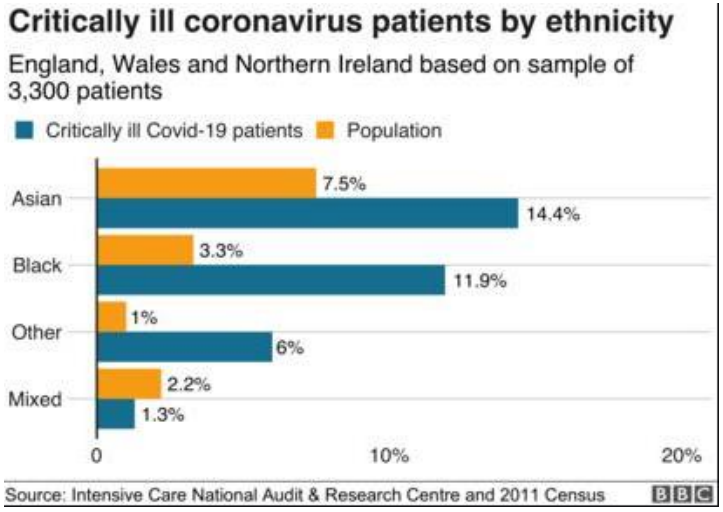
4/16 Middle east/

Indian

Ethnic minority children completely over-represented in London cohort

Vast majority in group in higher weight centiles

London ethnicity 2007



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6yo, Afro-caribbean

female

26kg (75th C)

Completely well

5 d fever & lethargy

Muscle pain, diarrhoea

and conjunctivitis

oedematous

✔		✔	✔
		No	No
38.3 °C		38.0 °C	
135	138	137	136
		NSR	ST
31	37	37	35
99 %	98 %	100 %	99 %
63/25 (36)	68/38 (46)	81/47 (57)	86/47 (59)

Local treatment

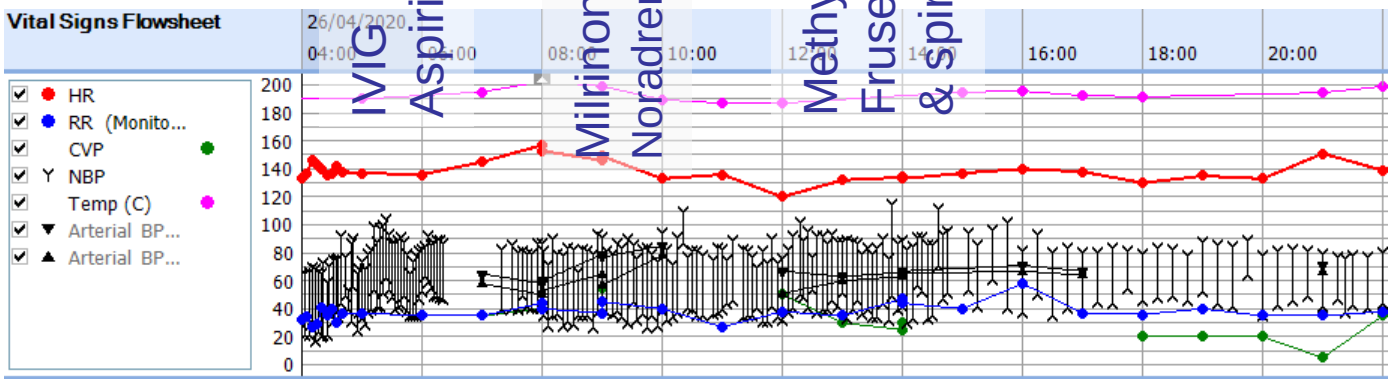
Ceftriaxone &

Clindamycin

40ml/kg volume

resuscitation

Referral STRS



First blood

WC	10.7
Lymphs	1
Hb	96
Plt	158
Fibrinogen	4.1
D dimers	9.95
Ferritn	924
Trop T	45
NT-proBNP	9376
Alb	31

Typical presentation and course in first cohort- but management changing rapidly based on ID/ rheum advice

Evelina London 150

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Biochemical findings

FBC:

- Normal-High WBC 5-30
- Lymphopaenic <1
- Borderline low plt 100-140

Fibrinogen

- Elevated 5-10 g/l (N=1.9-3.7)

D Dimers

- Elevated 5-20mg/l (N=0-0.5)

Ferritin

- Elevated 500-5000mcg/l (N<100)

Hyponatraemic 125-135mmol/l

Hypoalbuminaemic 20-30g/l

Normal renal & Liver fxn

CRP very elevated 150-600mg/l

PCT slightly elevated (5-15)

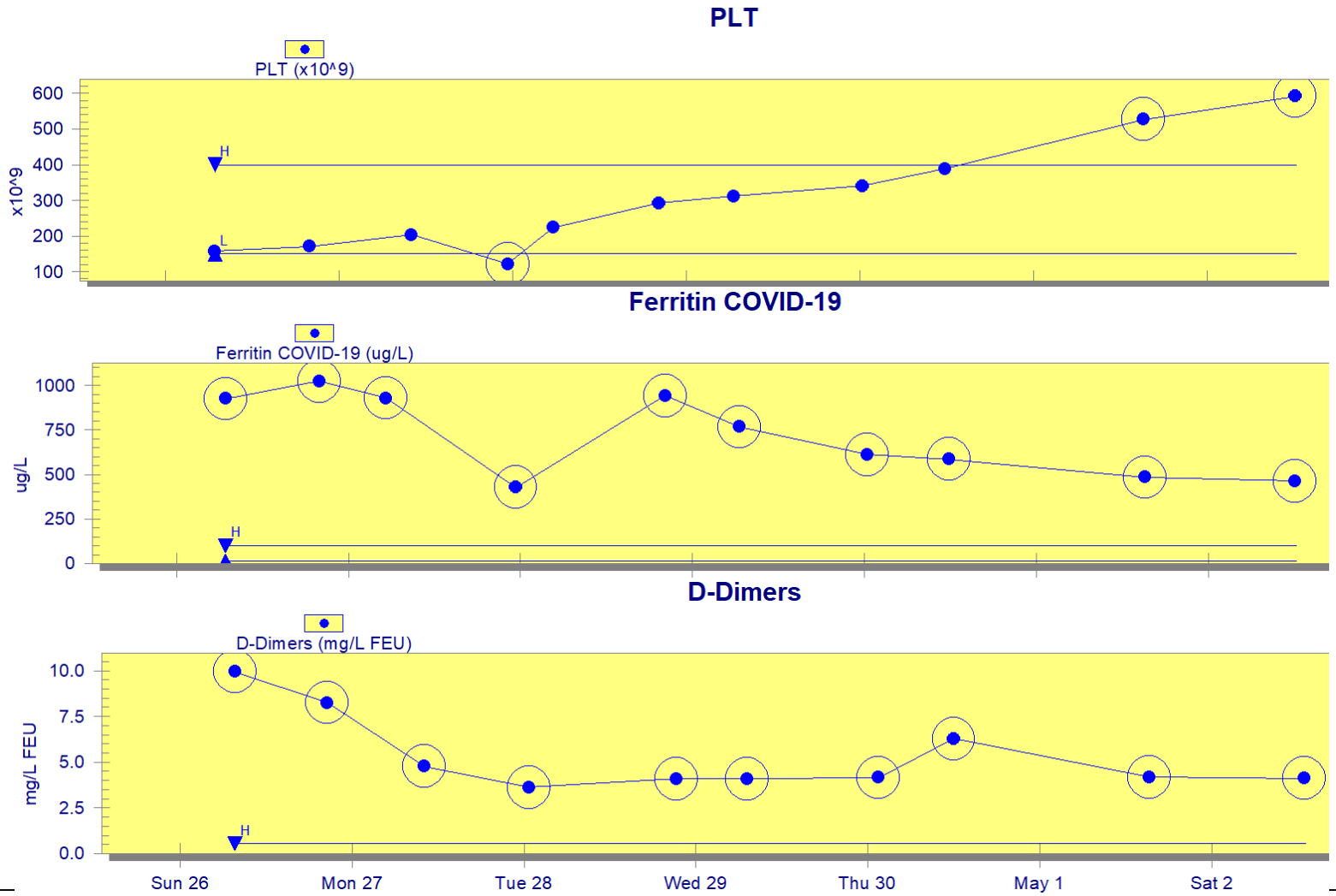
Troponin elevated 40-1000 ng/l (N<12)

NT pro- BNP 5000-14 000 ng/l (N<400)

Vit D low <50, some very low <20nmol/l

Triglycerides high >2mmol/l fasting

Biochemical course of illness



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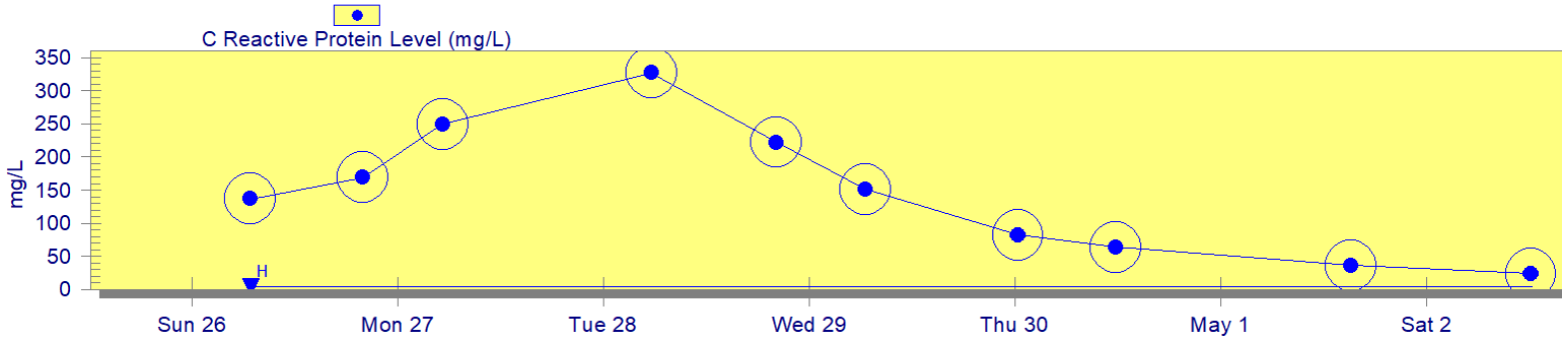
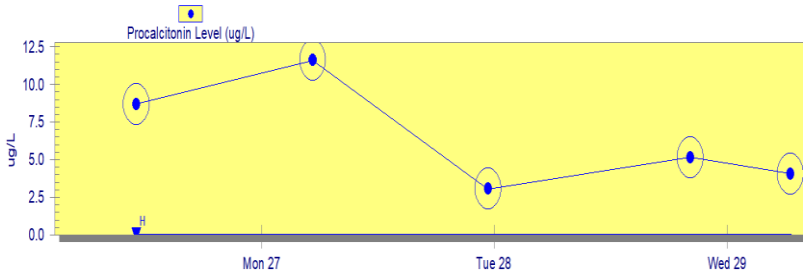
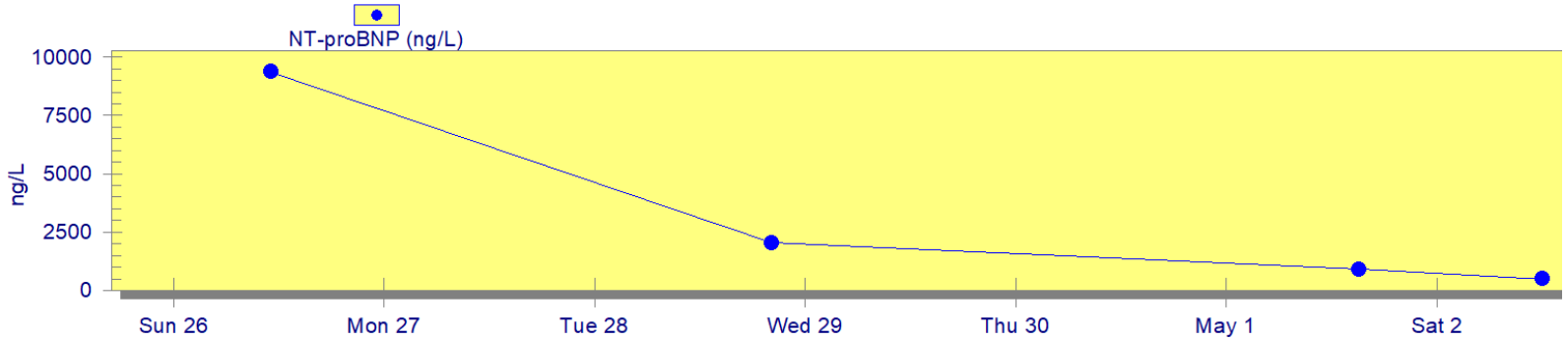
C Reactive Protein Level



Procalcitonin Level



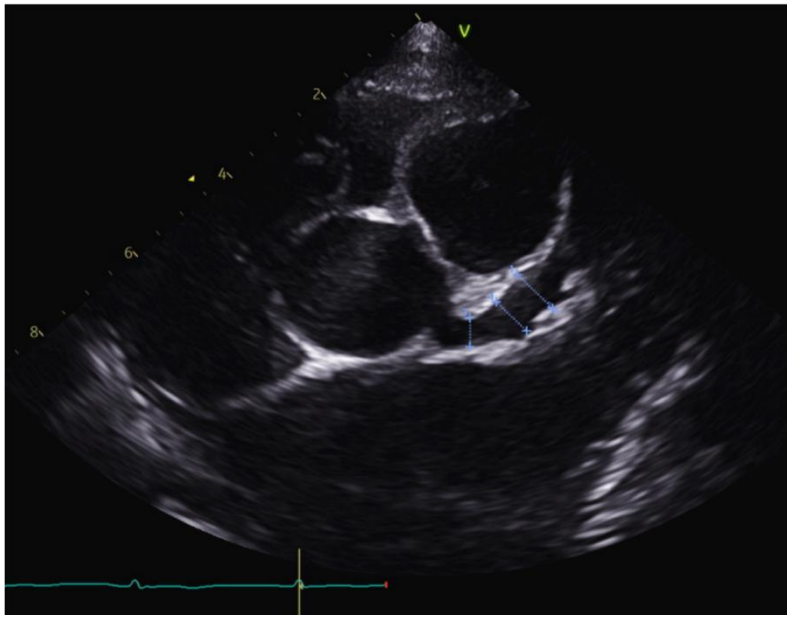
NT-proBNP



Cardiac manifestations

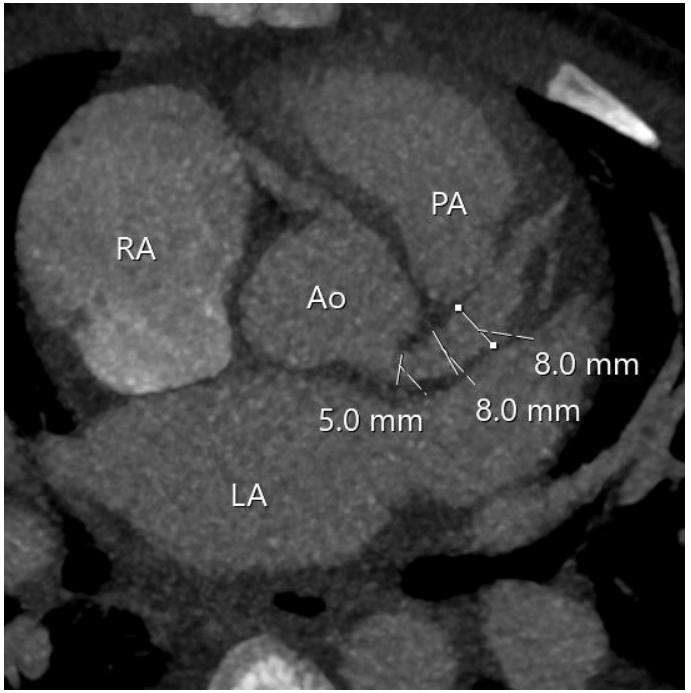
Vasoplegic shock, depressed longitudinal ventricular function, pancarditis, pericardial effusion, transient Wenckebach phenomenon, VF in one

Bright & dilated coronaries



Echocardiogram: Parasternal short axis.
Showing origin and proximal course of left coronary artery. There is aneurysmal dilatation of the left main and left anterior descending coronary artery.

Development of coronary aneurysm



Current management for critically ill children

- Steroids
  - Methylprednisilone 10mg/kg (max 1000mg) – 5 days, then wean 2 wks
  - Non-shocked 1- 2mg/kg x 5 days
- Aspirin
  - Low dose 3-5mg/kg, capped at 75mg
  - Then low molecular weight heparin
- IVIG
  - 2g/kg if clinically stable/ no concern about volume overload
- Vit D
  - 100 000 IU

Investigations

Core investigations:

- FBC, Full biochemical profile (Na, K, Ur, Cr, Ca, Phos, Mg, LFTs)
- CRP, PCT, ESR
- Ferritin, Triglycerides, Trop-T, D-Dimers, CK, NT-proBNP, LDH
- Coagulation profile (Including Fibrinogen)
- Blood / Urine culture
- Save serum & EDTA sample
- Chest X-ray
- Consider abdominal imaging to exclude abdominal pathology

Additional investigations (PICU admission)

- Vitamin D, amylase, ASOT
- Group and Save (crossmatch if considering ECMO)
- Blood film
- Virology for SARS-CoV-2 PCR on Stool, NPA, BAL and blood, serology for SARS-CoV-2
- DIAMOND Trial pack
- M C & S: BAL, urine, throat swab
- Standard Respiratory Viral panel - NPA or throat swab
- Viral serology blood PCR: EBV, CMV, Adeno, Enterovirus
- Blood PCR: Pneumococ., Meningococ., Group A strep, Staph A

Learning points

Completely under-evaluated (15yo 54kg sBP 59 Red eyes & dizziness)

Abdominal pain significant feature (beware surgical mimics)

Many like toxic shock

(beware some will be and will need source control, cover Ceftriaxone & clindamycin)

Most atypical KD- TSS cross over

myocardial involvement totally under–evaluated without Echo; careful volume resuscitation, early milrinone & nor adrenaline

Very hyper-inflammatory, possibly vasculitic

Rash, leaky- pleural, pericardial, ascitic and generalised leak, peri-vascular enhancement)- need aggressive anti-inflammatory control- aspirin, methylprednisolone

Probably post-infection antibody/ cytokine mediated response?

No primary disease history, no acute infectious swabs positive, IgG positive- IVIG

Most NB

Team effort

Early involvement

- Immunology/ Infectious diseases
- Cardiology
- Rheumatology

Support of DGH

- When to refer
- What to look out for
- What blood tests
- Save serum!

Paediatric Critical Care

Paediatric Multisystem Inflammatory Syndrome temporally associated with SARS-CoV2

Covid-19 pandemic has been temporally associated with the emergence of a paediatric presentation of severe inflammation and shock. This syndrome has some clinical similarities to Kawasaki shock and toxic shock syndromes. Patients have presented with mild to severe symptoms. In the majority of patients, coronavirus has not been detected by PCR, however serological evidence of Sar2 infection has been present. The likeliest mechanism is a delayed antibody-mediated dysrequlated host immune response.

Clinical features

May include one or more of the following:
- Persistent Fever > 39 C
- Lethargy and Myalgia
- Abdominal Symptoms: Pain, Diarrhoea and Vomiting
- Rash/Conjunctivitis
- Hypotension (Wide pulse pressure) +/- Shock

Laboratory features

Hyponatraemia
Raised Ferritin (>500)
Raised Fibrinogen
neutrophilia
Raised D-Dimer
Renal dysfunction
Raised CRP
Raised Troponin and B-NP
Lymphopenia /
Platelets initially low or normal

Significant similarity in presentation with other paediatric diagnoses

Septic shock - may require higher volume fluid resuscitation and source control -senior clinical review
Peritonitis -negative laparotomy reported in some cases -cautious specialist surgical review with appropriate radiology

Initial Management

Examination:
- Exclude potential septic foci and careful cardiac assessment (liver, JVP,cardiac / thoracic ratio on CXR)

Resuscitation:
- Ceftriaxone and Clindamycin as sepsis impossible to exclude
- If signs of shock – fluid resuscitation (10ml/kg aliquots) with re evaluation after each bolus and discuss with STRS
- If no improvement with fluid, start inotropes: Dopamine@ 5 - 10mcg/kg/min, until central access (consider noradrenaline)
- Anaesthetic team review
- Early IVIG 2g/kg (must save serum prior to administration)

Severe myocardial dysfunction common:
- If intubation required: cardio-stable induction (ketamine+ arrest drugs ready)
- Caution on moving or transferring ventilated patients - instability observed in presence of severe cardiac dysfunction (extremely pre load dependant)

Investigations

Core investigations:
- FBC, Full biochemical profile (Na, K, Ur, Cr, Ca, Phos, Mg, LFTs)
- CRP, PCT, ESR
- Ferritin, Triglycerides, Trop-T, D-Dimers, CK, LDH,
- Coagulation profile, (Including Fibrinogen)
- Blood / Urine culture
- Save serum & EDTA sample
- Chest X-ray
- Consider abdominal imaging to exclude abdominal pathology

Additional investigations (PICU admission)
- Vitamin D, amylase, ASOT
- Group and Save
- Blood film
- Virology for SARS-CoV-2 PCR on Stool, NPA, BAL and blood, serology for SARS-CoV-2
- DIAMOND Trial pack
- M C & S: BAL, urine, throat swab
- Standard Respiratory Viral panel - NPA or throat swab
- Viral serology blood PCR: EBV, CMV, Adeno, Enterovirus
- Blood PCR: Pneumococ., Meningococ., Group A strep, Staph A

PICU Management at Specialist Center

Patient to be managed as COVID (even if PCR negative for Sar2-coV)- full PPE and management in appropriate area

- Central access: awake femoral line preferable in self ventilating patients
- Temperature control – regular paracetamol, active cooling if ventilated
- Ensure adequate IVIG administered (2g/kg – max weight to be capped at 70Kg). (note out of hours stock kept on PICU to avoid delay), monitor for fluid overload during infusion.
- Enteral Aspirin 12.5mg/kg QDS (max 500mg) with high dose PPI (Pantoprazole /Omeprazole)
- Methylprednisolone if shocked (30mg/day- max 1g) for 3 days
- Pubescent teenagers to commence DVT prophylaxis: TED Stockings consider LMW heparin or IV UF heparin (check coagulation profile prior to starting)

Monitoring:
- Urgent Echo at ICU admission and repeat as clinically indicated
- 12 lead ECG at admission and repeat daily
- If oxygen requirement repeat CXR
- Regular Blood gas – measure lactate
- Repeat Core investigations 12 hourly – if rising inflammatory markers discuss urgently with ID team.

Further immunomodulation may include (MDT discussion):
- Repeat IVIG at 48 hours if remains febrile
- Infliximab (monoclonal antibody)
- Anakinra (IL-1 receptor antagonist)

Cardiac Manifestations and Management

Pancarditis may include: bi-ventricular impairment, mitral/ tricuspid valve regurgitation, pericardial effusion, coronary artery dilatation / aneurysm.
- Clinical course unpredictable with rapid deterioration observed in some.
- 12 lead ECG – Arrhythmias reported
- Urgent Echocardiogram (transfer to ELCH)
- Low threshold for Milrinone infusion
- Severe cases consider Levosimendan and discuss need for anticoagulation
- VA ECMO used in refractory shock – Cross match blood urgently

Therapy Complications
- Fluid overload risk with IVIG infusion – consider diuretics
- Hypertension: high dose methyl prednisolone associated with severe hypertension and PRES. Treatment with Ca channel blockade or SNP if severe cardiac dysfunction.
- Hyperglycaemia – may require insulin infusion.
- Gastritis patients to start high dose PPI.

Step down
- Consider HDU step down when off Noradrenaline 6-12 h
- Milrinone to continue on HDU if impaired cardiac function
- Leave central line in situ – if twice daily bloods required
- Aspirin: reduce to 5mg/kg OD once afebrile and falling CRP
- If improving after 3 doses of Methylprednisolone, change to prednisolone 2mg/kg OD (max 60mg).

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Ongoing management questions

Right dose steroids?.....started too high, major side effects, reduced/ stratified

Aspirin….started too high, lower dose. Important in recovery phase with thrombocytosis

When to escalate treatment/ de-escalate?

When to use targeted biological antibody management?

- Which one better?
  - Infliximab
  - Tocilizumab
  - Anakinra

Predictors of severity?....Cardiac involvement

- Public Health England alert
- NHS England alert
- Royal College of Paediatrics
- Paediatric intensive care society
- ELCH PIMS-TS resource

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

Guidance: Paediatric multisystem inflammatory syndrome temporally associated with COVID 19

https://www.rcpch.ac.uk/resources/guidance

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NHS
Guy's and St Thomas' NHS Foundation Trust

Unanswered questions

What are the predictors of critical care disease severity

- ?Trop/ BNP

Is there a specific genetic predisposition similar to SLE, SARS,MERS, KD?

Is the adult disease that has been identified as sHLH/ cytokine storm just a spectrum of the same pathology in children

- Pulmonary embolus, stroke in young adults?

Follow up

Over 60 children in Evelina since mid-April

2nd follow up clinic

“All 8 children seen looked really well,

cardiac function either stable or significant improvement.

Few readmissions amongst whole group-ongoing carditis with depressed function

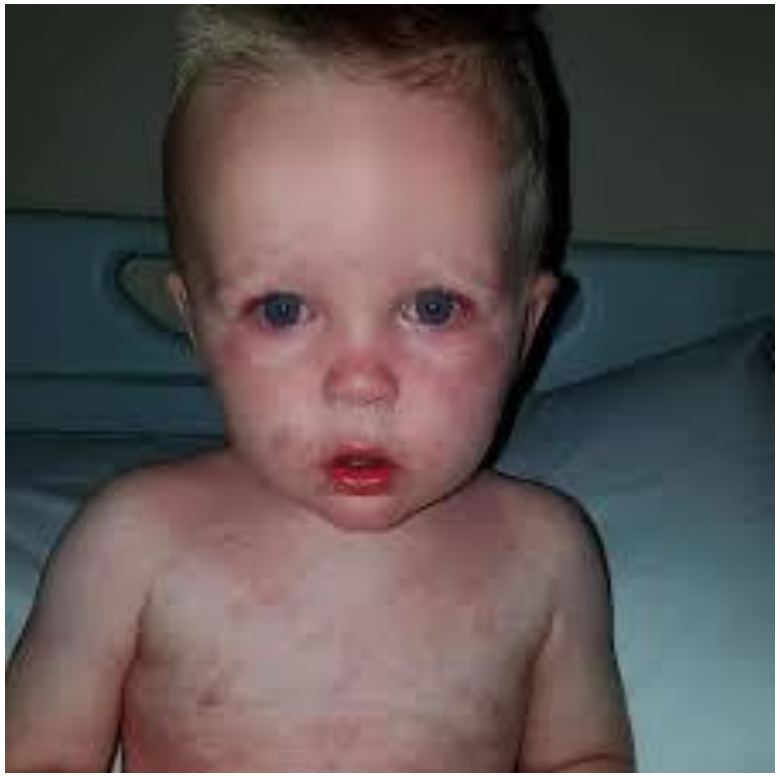
Bloods all good.

The cohort were mostly from the week when …were on, week before last (3 weeks ago)

All had been through PICU. Many of the families said how much they had valued the care they received whilst on PICU”

Multisystem Inflammatory Syndrome in Children temporally related to COVID at ACH

Infection → immune response → immune dysregulation/hyperinflammation



https://www.mirror.co.uk/news/uk-news/mum-details-kawasaki-disease-symptoms-22045811

Cytokine release

- Systemic inflammation (fever, malaise)
- Vessel inflammation (hyperemia, rashes, vascular leakage, LN, dilatations/aneurysms)
- Inflammatory shock (hypotension, myocardial dysfunction/myocarditis)

WHO: Preliminary Case Definition

Multisystem Inflammatory Syndrome in Children temporally related to COVID

Children 0-19 years of age with Fever ≥3 days

AND **one/two** of the following:

a) Rash or bilateral non-purulent conjunctivitis or muco-cutaneous inflammation signs (oral, hands or feet)

b) Hypotension or shock, or features of myocardial dysfunction, or pericarditis, or valvulitis, or coronary abnormalities (ECHO findings or elevated Troponin/NT-proBNP)

c) 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 test positive or serology), or likely contact with patients with COVID

Kawasaki and Coronavirus

Association between a Novel Human Coronavirus and Kawasaki Disease

Frank Esper,[1] Eugene D. Shapiro,[1,2,3] Carla Weibel,[1] David Ferguson,[4] Marie L. Landry,[4] and Jeffrey S. Kahn[1,3]

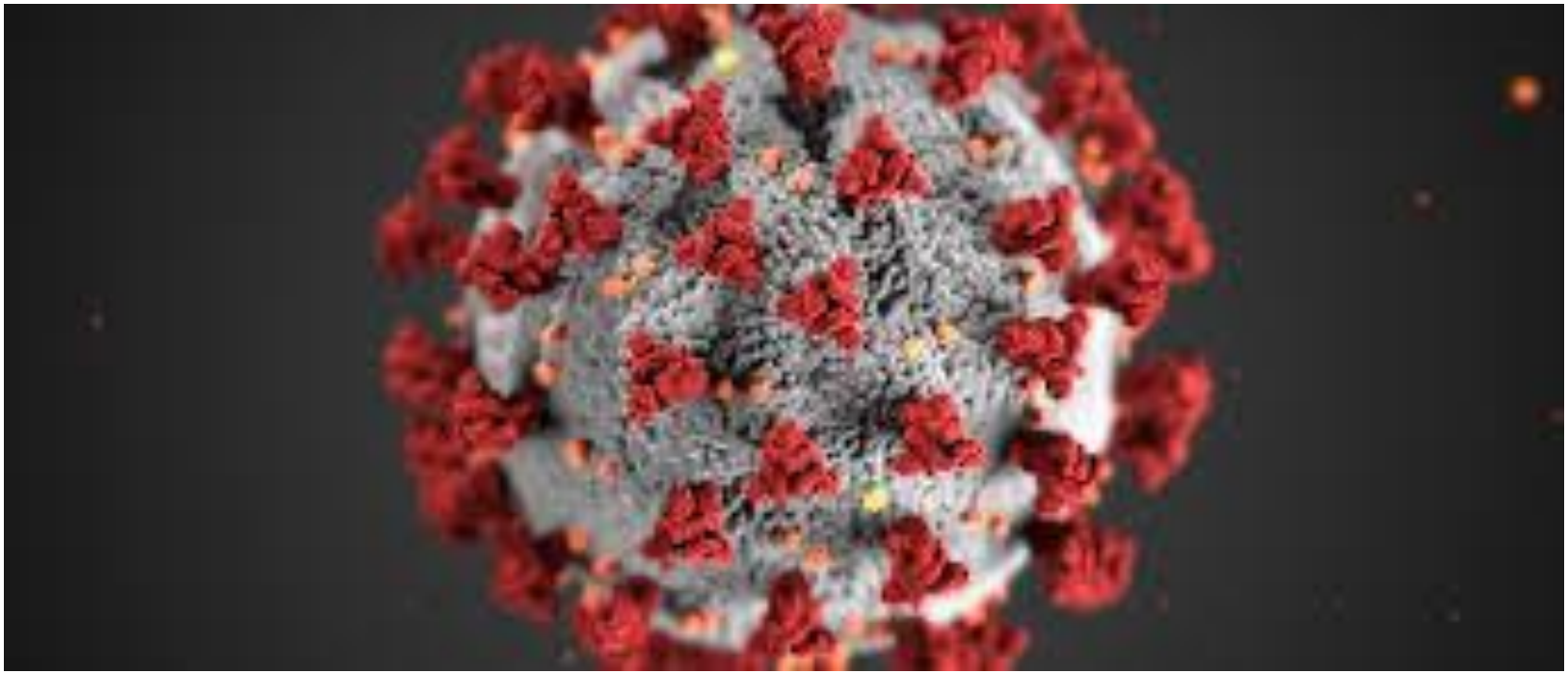
[1]Department of Pediatrics, Division of Infectious Diseases, [2]Department of Pediatrics, Division of General Pediatrics, and Departments of [3]Epidemiology and Public Health and [4]Laboratory Medicine, Yale University School of Medicine, New Haven, Connecticut

(See the article by Esper et al., on pages 492–8, and the editorial commentary by McIntosh, on pages 489–91.)

Lack of Association between Infection with a Novel Human Coronavirus (HCoV), HCoV-NH, and Kawasaki Disease in Taiwan

Luan-Yin Chang,[1] Bor-Luen Chiang,[1] Chuan-Liang Kao,[2,3] Mei-Hwan Wu,[1] Pei-Jer Chen,[4] Ben Berkhout,[5] Hui-Ching Yang,[1] and Li-Min Huang,[1] for the Kawasaki Disease Research Group[a]

Departments of [1]Pediatrics, [2]Laboratory Medicine, [3]Medical Technology, and [4]Internal Medicine, National Taiwan University Hospital, College of Medicine, National Taiwan University, Taipei, Taiwan; [5]Department of Human Retrovirology, Academic Medical Center, University of Amsterdam, The Netherlands



Kids with hyperinflammation at ACH

Diagnosing hyperinflammation

Clinical features

- Typical clinical features: fevers, fatigue, malaise/crankiness
- KD features: red eyes, cracked lips, swollen lymph nodes, puf hands/feet, rash
- COVID in kids phenotypes:
  - GI symptoms (abdominal pain, nausea/vomiting, diarrhea)
  - Loss of smell/taste, headaches, neck pain, chilblain-like rashes toes
- **Inflammatory shock**: hypotension, tachycardia, myocardial dysfunction, HSM, non-responsiveness to fluid recussitation

Laboratory and other tests

- Blood/urine:
  - Inflammation: CRP, ferritin, D-Dimers, CBC – lymphopenia, platelets low normal, low albumin, (high procalcitonin)
  - Heart/vessels/coags: troponin, BNP, PTT, INR, fibrinogen
  - Organ function: LFTs including bili, LDH, creatinine, urine, electrolytes
- COVID: PCRs NPS, stool, blood
- Chest x-rays, ECG
- Cytokines and receptors * (IL1/6/18, CXCL10, macrophage markers)

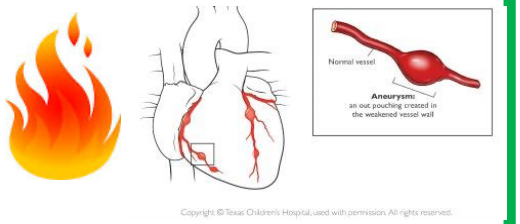
* APL permission needed

Managing hyperinflammation

Multidisciplinary team, early testing

- ED/ICU/Hospital Paediatrics, Infectious Diseases, Cardiology, Rheumatology/Immunology, others as appropriate (GI, Neurology)
- Include peds COVID study coordinator, commitment to peds COVID studies
- Rapid completion of testing (store serum/plasma for further testing)
- Early ECHO, early repeat

Treatment of hyperinflammation



- Shock management, early start of vasopressors
- IVIG 2g/kg for KD management
- Antithrombotic therapy
  - High dose ASA for KD, low dose when afebrile
  - Escalation to heparin, if coronary aneurysms
- Corticosteroid pulses (30mg/kg) x 3 days
- Biologic therapies – options IL-1 inhibition (anakinra) or IL-6 inhibition (tocilizumab) after team considerations (high risk child, failure to other immunosuppression) or anti-TNFa (advanced coronary artery disease)

* being hired
**APL permission needed

-doctors-immediate/index.html

CNN health Food Fitness Wellness Parenting Vital Signs • LIVE TV Edition

Kids with suspected Covid-related syndrome need immediate attention, doctors say

By Maggie Fox, CNN
Updated 10:57 PM ET, Tue May 19, 2020

Doctors warn of strange new symptoms in children

This is how sharing dinner table items can make you sick

White House asked for his advice on hydroxychloroquine

A look at the potential long term effects of Covid-19

CDC 'muzz White Hou say

(CNN) — Kids who may have multisystem inflammatory syndrome in children, or MIS-C, a troubling complication of Covid-19 infection, need immediate attention and will probably need to be hospitalized, doctors said Tuesday.

Symptoms do not look like the classic symptoms of coronavirus and may mostly include stomach pain and vomiting, along with fever and perhaps a rash, the experts told other doctors during a meeting Tuesday organized by the US Centers for Disease Control and Prevention.

It's becoming clear that many of the children with the new syndrome have damage to their hearts and need immediate treatment, they said at the Clinician Outreach and Communication Activity (COCA) briefing. And they believe it's increasingly clear that Covid-19 is involved, even though many of the children test negative for the virus at first and never seemed to have had symptoms of infection.

Thank you
On behalf of the ACH
COVID team