

MIS-C (multisystem inflammatory syndrome – children) and immune responses in COVID-19: timing is everything

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First cases of PIMS/MIS-C

 Late March 2020, in Italy and the UK, a small number of children were admitted critically ill with GI symptoms and signs of Kawasaki disease
 most negative for SARS-CoV-2 by PCR

As of 6/1/20, estimating about 300 cases of MIS-C in US

At least five children in the US have died: three in New York State, a 15-year-old girl in Maryland, and a child in Louisiana

57,026 COVID-19 cases in children <18 years of age



Children's

Overview

Recognition

- One recent and clear case of MIS-C
- MIS-C definitions, European reports
- Comparison to related conditions (focus on Kawasaki disease)

Mechanism

 how does our immune system help or hurt us in acute COVID-19 versus MIS-C

Management

 How does what we know so far of mechanism help us manage MIS-C





A clear-cut case from Oregon

- 14 year old girl, previously healthy
- In early May, 6 days PTA, had fever to 104°, HA, abdominal pain and nausea
- SARS-COV-2 PCR negative. IV fluids and Zofran →home, GI symptoms improved.
- She then developed conjunctivitis and swollen lips, later "strawberry tongue"
- Back in clinic, low blood pressure (70/40) → ED.
- In the ED, continued hypotensive despite fluid boluses, given low-dose dopamine
- Labs: lymphopenia, very high CRP/ESR, elevated ferritin, normal lactate. Elevated troponin, mild hypoalbuminemia, elevated IL-6.
- Initial treatment clindamycin and ceftriaxone for possible toxic shock syndrome.

(Adenovirus, EBV, CMV, enterovirus negative. Blood and urine cultures negative. ASO and throat culture were negative.)

Case from Oregon (continued)



In the PICU, echocardiogram showed moderately depressed LV function and coronary ectasia.

- Given 2g/k IVIG (Kawasaki dosing), had a reaction to IVIG→ 40mg IV Solumedrol.
- Given concerning cardiac disease, given 100mg anakinra.
- Given concern for thrombotic microangiopathy, given heparin in lieu of high dose ASA.
- Fever and conjunctivitis better in <1 day.
- Current status: out of the ICU, on lisinopril, cardiac function better but still decreased
- SARS-COV-2 IgG positive. No known COVID-19 Sx in weeks prior.
- Exposure? possibly her 19 year old brother who had returned 4 weeks prior from a naval base in Mississippi.

Thanks for Dr. Gillepsie at Randall Children's for case

Case definitions – UK (PIMS-TS) and CDC (MIS-C)



- A child presenting with persistent fever, inflammation (neutrophilia, high CRP, lymphopenia) and evidence of single or multi-organ dysfunction with additional features
 - may include children fulfilling full or partial criteria for Kawasaki disease.
- Exclusion of any other microbial cause, including bacterial sepsis, staphylococcal or streptococcal shock syndromes, infections associated with myocarditis such as enterovirus
- SARS-CoV-2 PCR testing may be positive or negative

April 27, 2020: Royal College of Paediatrics and Child Health

https://www.rcpch.ac.uk/sites/default/files/2020-05/COVID-19-Paediatric-multisystem-%20inflammatory%20syndrome-20200501.pdf

- An individual under 21 years presenting with fever, laboratory evidence of inflammation 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 reverse-transcriptase polymerase chain reaction, serology or antigen test; or COVID-19 exposure within the four weeks prior to the onset of symptoms.

https://emergency.cdc.gov/han/2020/han00432.asp



Recap of Kawasaki Disease

Kawasaki disease (KD) definition

Fever lasting at least 5 days without other explanation and at least 4 of the 5 following criteria: (fever and <4 criteria = "incomplete KD")

- Bilateral bulbar (limbic sparing) non-exudative conjunctival injection early
- Oral mucous membrane changes, including injected or fissured lips, injected pharynx, or strawberry tongue
- Peripheral extremity changes, including erythema of palms or soles, edema of hands or feet (acute phase), inflammation at BCG site and periungual desquamation (convalescent phase)
- Polymorphous rash
- Cervical lymphadenopathy (at least 1 lymph node >1.5 cm in diameter, often unilateral) – least frequent finding







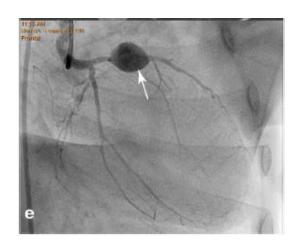




Kawasaki disease, continued



- Clinical signs result of acute inflammatory small/medium vessel vasculitis
- Coronary arteries are particularly susceptible: 30-50% develop transient (<2mo) dilatation, 20% develop aneurysms if untreated→5% if IVIG in first 10d.
 - 1% with "giant aneurysms"
- Myocarditis common, rarely significant decrease in myocardial function
- 80% of cases between 6 months and 5 years of age, M/F ratio 1.5/1
- Susceptibility varies among ethnic/genetic groups higher in NE Asian children (~200/10k) versus European origin (5-10/10K)
- Winter/spring seasonality, geographic clustering and lack of recurrence suggests an infectious trigger, though no one cause known





Kawasaki disease, labs and treatment

- Elevated WBC and ANC, anemia, progressively increasing platelet count
- Elevated inflammatory markers, CRP>3.5 in 80% of cases, ESR >60 in 60% of cases (note further increase in ESR after IVIG)
- Lowered sodium, albumin, elevated liver enzymes
- CSF with lymphocytic pleocytosis, normal protein and glucose
- 2 grams/k of IVIG within 10 days of fever → 85-90% of children be afebrile within 36 hours and have significant decrease in coronary artery aneurysm risk
- Second dose of IVIG if fever recurs, 10-20% do not response to IVIG
- Aspirin (dosing variable) for thrombocytosis and irritated/prothrombotic vascular endothelium
- Some recover without treatment



Case reports of PIMS/MIS-C



Summary of the first European reports:

- 8-17 children per report, age range 7-9 years of age
- GI symptoms notable
- 50%-100% presented in shock
- Most with myocarditis, some with coronary artery aneurysms
- Most PCR negative, most IgG positive

Riphagen et al, Toubniana, et al, Verdoni, et al



European PICU case series:

- 35 children from France and Switzerland
- Median age at admission was 10 years (range 2-16 years).
- Gastrointestinal symptoms were prominent. ALL presented with fever.
- 29/35 straight to ICU and remaining 6 to ICU within 24 hours
- 80% in cardiogenic shock/requiring inotropes, LV EF was <30% in one third, 10/25 38% ECMO
- ** more myocardial dysfunction than coronary artery changes (6/35, 17%)
- (88%) patients tested positive for SARS-CoV-2 infection by PCR of nasopharyngeal swab or serology.
- 28/35 IVIG, 12/35 steroids, 3/25 anakinra

"The high levels of BNP in our series suggest a mechanism of myocardial edema or stunning"

Belhadjer, Z et al



CHOP PICU experience

- 6 children in PICU: 3 weak-PCR positive, all IgG positive (one not tested)
- Severe prominent cardiac dysfunction with troponin leak and extremely elevated BNPs
- Enteropathy 66%, in contrast to 15-26% of patients diagnosed with KD prior to the COVID-19 pandemic
- 66% experienced neurologic symptoms
 - HA in patient 1, altered mental status in patient 2, irritability and nuchal rigidity in patients 4 and 5.
- Relative thrombocytopenia in 50% (instead of thrombocytosis)
- All had hyponatremia at presentation
- ALL given IVIG and methylprednisolone

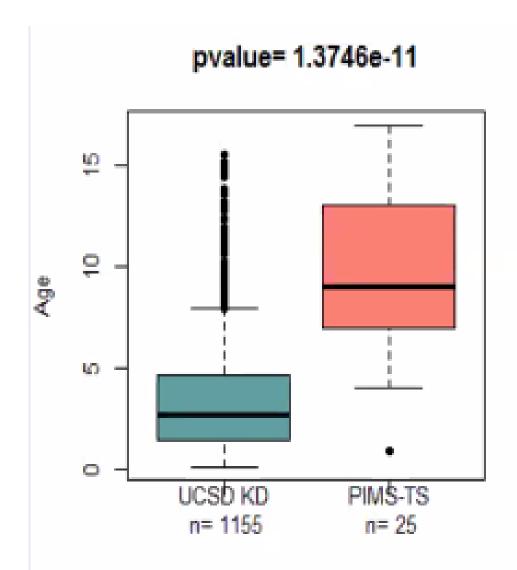
Chiotos, K et al.



Comparison of UK PIMS-TS MIS-C cohort to USCD Kawasaki cohort

Children with PIMS-TS/MIS-C are older than those with KD





pvalue= 6e-12

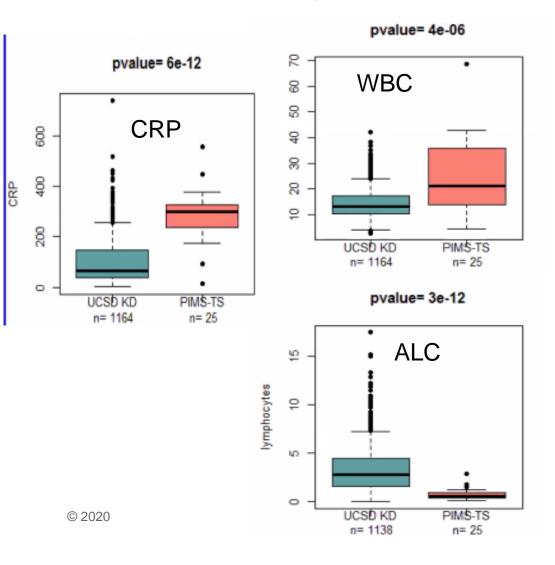
Data shown by Prof. Mike Levin, Imperial College – COCA call

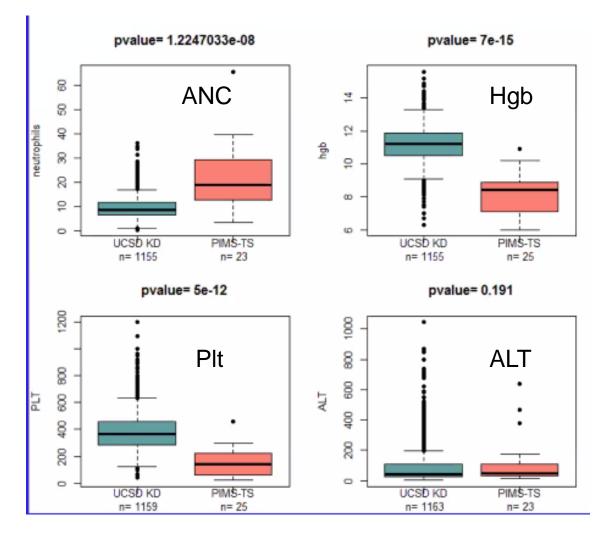
Comparison of Kawasaki (and KD shock) pre-IVIG versus PIMS-TS/MIS-C



CRP, WBC, ANC higher;

ALC, platelets, Hgb, albumin (not shown) lower





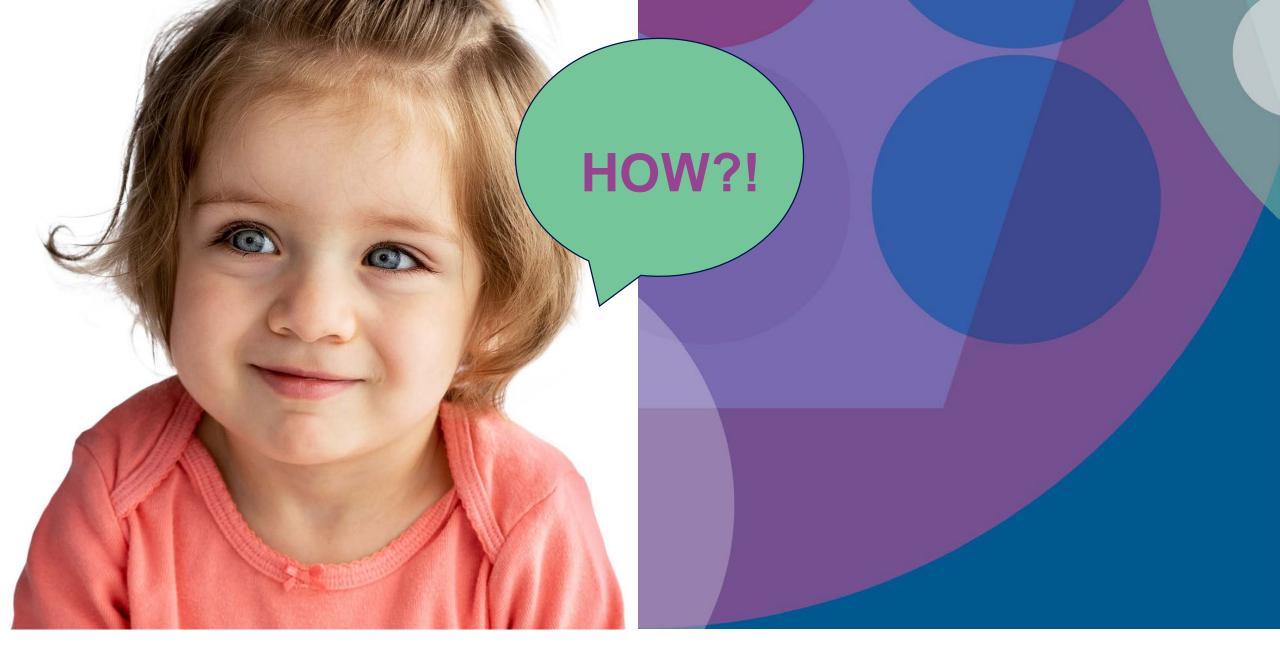


MIS-C distinct from KD, and more closely resembles Kawasaki shock syndrome (KDSS)

- KDSS is 1-5% of KD cases
- Children are older than typical KD (4 yr vs 2 yr in Li et al, still generally <5 years of age)
- Similar presentation to septic shock, toxic shock syndromes
- WBC and inflammatory markers are higher; IL-6 levels, IL-10, IFNγ higher
- Low platelets, low hemoglobin, low albumin, high D-dimer
- Elevated troponin; higher risk of coronary artery aneurysms, 1/3 with LV dysfunction
- "IVIG resistance" defined as persistent fever >36 hr after end of IVIG
 - 70% in Li, Y et al compared to 2.3% in KD control group

Differences from MIS-C:

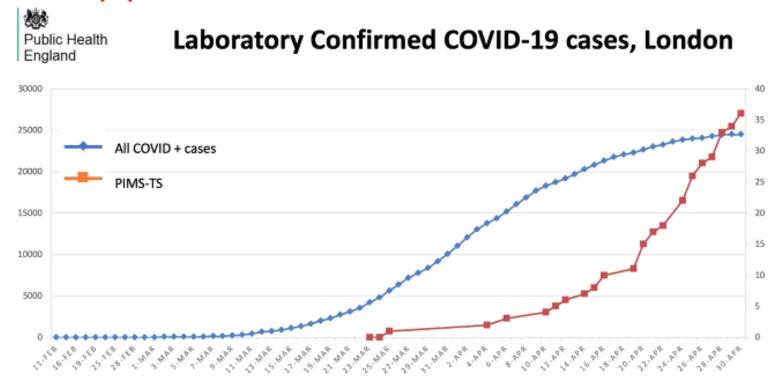
MIS-C has more lymphopenia, and more myocarditis/myocardial dysfunction vs. coronary aneurysms





Timing of MIS-C cases suggests an <u>post-viral</u> immune response, even though some still PCR+

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



4 week delay also seen in New York City/State (PIDS talk)

Tempo of Immunity



Rapid

<5 Days

Innate (pre-existing)
Immunity

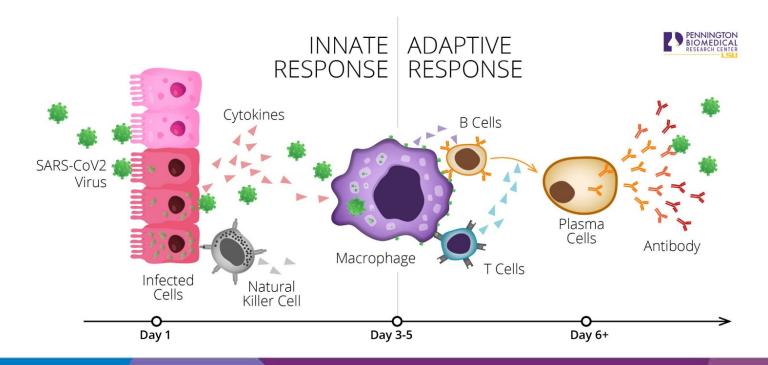
Intermediate

5-10 Days

Innate & Antigenspecific/Adaptive Immunity Slow

> 10 Days

Antigenspecific/Adaptive (memory) Immunity



Immune responses in children evolve with age and are different than adults'

- Innate "ready to go" immunity (neutrophils, macrophages, complement):
 - Compared to adults, infant neutrophils more quickly depleted
 - Complement levels lower than adults



- Lymphocytes from infants respond poorly to some (eg, polysaccharide) antigens
- Naïve T cells mount less robust cytokine responses
- Immunoglobulin (antibody) levels very fluid especially in the first 4-5 years





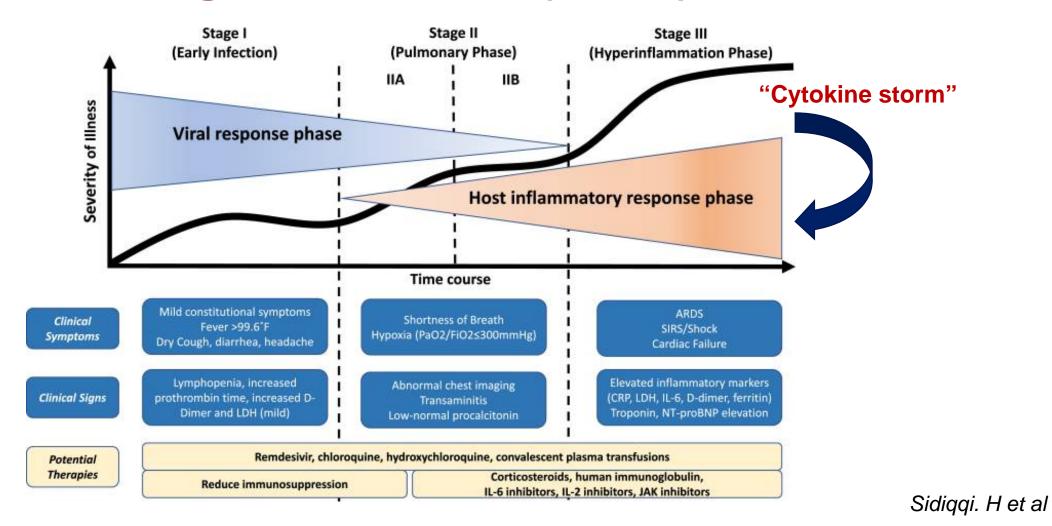
(among many other differences...)



Immune responses <u>soon</u> after SARS-CoV-2 infection

Stages of COVID-19 (adults)

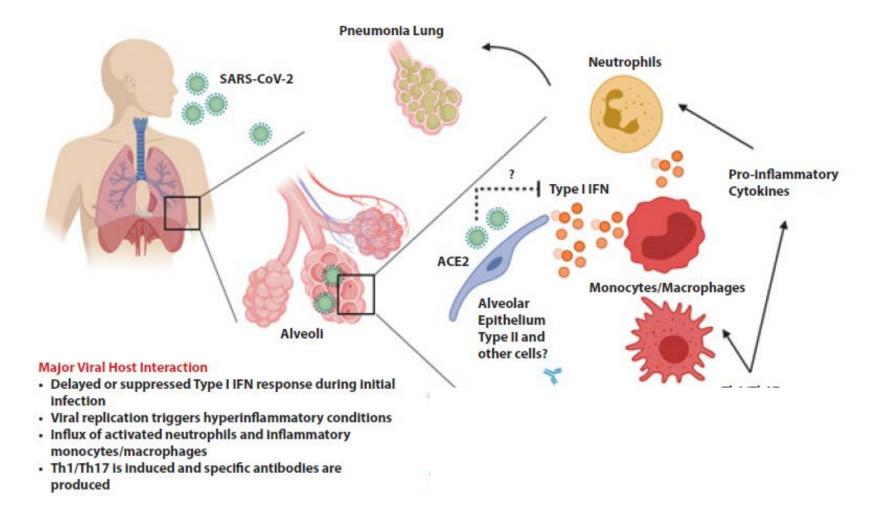




Innate response in COVID-19: early evasion



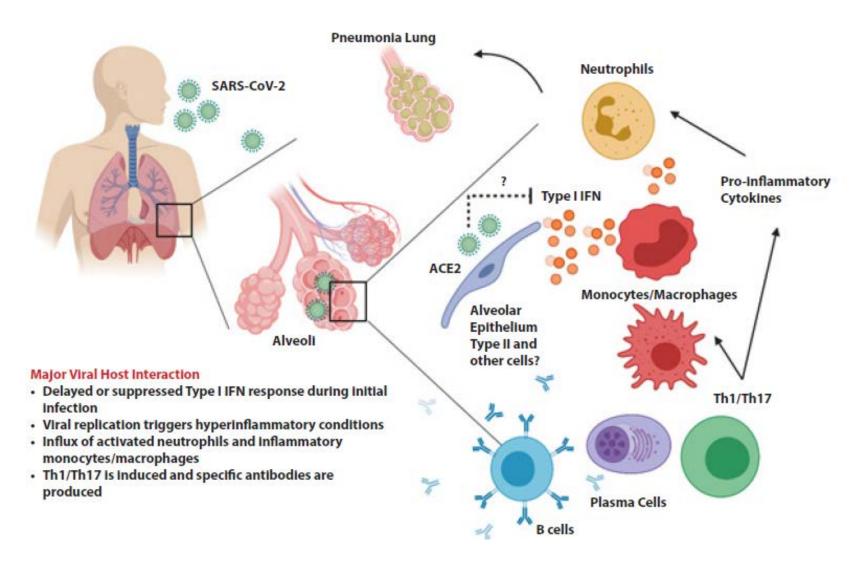
- Multiple cell types infected
- Innate pathogen sensors (TLR3, RIG-I) and JAK signaling important for type 1 interferon response.
- * SARS-CoV and MERS-COV suppress the type 1 interferon response → less control of the virus and more innate cell influx



Innate response in COVID-19, continued



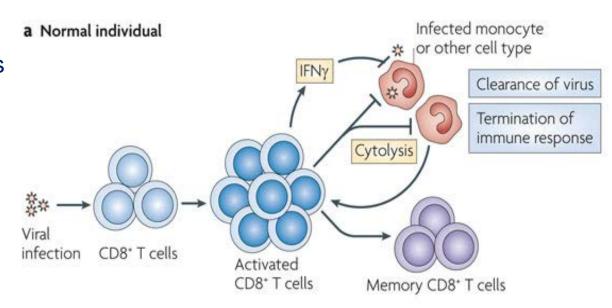
- Increase in chemokines like CXCL8 (neutrophil attractant) CCL2/7 cytokines like MCP-1, TNFα, IL1β, IL-6 and type II IFN (IFNγ more destructive to lungs)
- Immune complex and complement consumption microthrombosis throughout the body
- Bridging to adaptive immune response - downregulation of MHC in infected APCs with MERS-CoV decreases appropriate T cell activation





T cell immunity

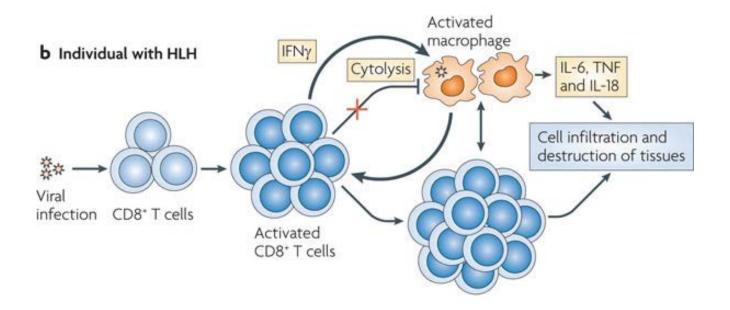
- Direct infection of T cells:
 - Like MERS, virus cannot replicate in T cells and extent of T cell depletion/lymphopenia associated with severity for SARS CoV
- In vitro, T cells are more permissive to SARS-CoV-2 than SARS CoV even though ACE2 expression is low
- Interesting/?good news that SARS CoV-2 spike protein reactive T cells are detectable in 83% of COVID-19 patients, and 34% of SARS-CoV-2 seronegative healthy donors



Braun, et al, de Saint Basile, G et al, Wang, X., et al

Children's

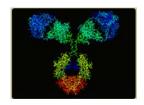
How ACUTE cytokine storm MAY be mechanistically similar to MAS/HLH



Cytokine profiles severe COVID-19 are similar to those observed in cytokine release syndromes (MAS/HLH), with increased IL-6, IL-7 and TNF α , and soluble IL-2R

Nature Reviews | Immunology

de Saint Basile, G et al





Humoral (B cells and antibodies) immunity

- Time to seroconversion in this viral class:
 - SARS-CoV seroconversion by day 4, IgM peak ~ 1 month, IgG peak 2-4 months.
 - MERS CoV seroconversion took 2-3 weeks
 - In adults SARS CoV-2 IgM appears at day 8-12, IgG by day 14 durability and height and efficacy of IgG under investigation
- Higher levels of specific IgA, IgM and IgG in adults with the worst outcomes
- 4 patients with XLA (no antibody production) developed COVID-19 PNA and recovered-?protected by not being able to make a normal humoral response?



Summary of how "acute" responses after infection can lead to immune dysregulation

- SARS-CoV-2 replicates in various cell types (lung epithelia, intestinal, immune) and suppresses early type I interferon responses.
- Infection/killing of innate immune cells leads to cell death, more viral replication and more pro-inflammatory cytokines
- Viral replication results in tissue damage and excessive recruitment of innate and adaptive immune cells, which mediates a dysregulated hyperinflammatory response



MIS-C as a "later" immune stage - reported 4-6 weeks after SARS CoV-2 infection/exposure

Possible/speculative mechanisms of "late" immune injury in MIS-C



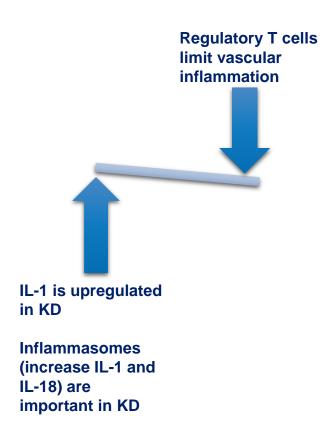
- Antibody dependent enhancement (ADE)?
 - One mAb against SARS spike protein facilitated viral entry into host cells and enhanced infectivity (similar to dengue)
- Antispike IgG reported to cause severe acute lung injury by skewing macrophage responses
- Immune complex formation? activating neutrophils and platelets
- Second wave of viral exposure triggering HLH?
- Molecular mimicry (like ARF)
- ?autoimmunity (perhaps less likely given widespread effects)
- T cell: Effect on regulatory T cells (less IL-10), superantigen mechanisms? (like TSS)

Other ways MIS-C MAY be mechanistically similar to KD



 Neutrophil/macrophage infiltration into elastic lamina, then infiltration of CD8+ T cells, plasma cells and macrophages

Antagonistic roles of IL-1 and regulatory T cells



Marrani et al, Deitz et al



More mechanistic clues from geography



Host/pathogen balance: only some regions with high incidence of COVID-19 cases are reporting cases of MIS-C

Different viral strains in different regions

There are few reported cases of PIMS/KD like disease in Asian countries (Korea this past week), yet KD is more common in children of Asian descent

(preliminary) There may be an increase of MIS-C cases in Black children – UK, NY



Korber, et al

https://www.cato.org/blog/two-supertypes-coronavirus-east-asian-european

Host susceptibilities to KD and TSS and HLH, so likely also to MIS-C



• Innate:

– people who have had KD or TSS have a persistent pro-inflammatory innate immune phenotype <u>years later</u>, including decreased IL-1r α production after viral infection

Adaptive:

- KD susceptible people have different polymorphisms in B cell development genes, ITPKC (negative regulator of T cell function)
- People with certain MHC haplotypes are more susceptible to toxic shock syndromes and severe viral disease --- MHC susceptibility map for SARS-CoV-2 has been reported!
- A growing number of host susceptibility genes for HLH



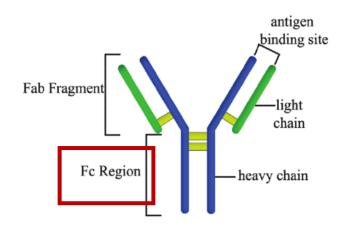
IMPLICATIONS FOR TREATMENT OF MIS-C

(in addition to the usual epic cares from ED, PICU, ID, Hematology, Cardiology, everyone for children presenting in early heart failure or shock)



IVIG - how does it work in KD?

- 1981, IVIG used for immunomodulation to treat ITP and then KD
- Lower-dose IVIG regimens have been studied in KD and NOT as successful - associated with more coronary abnormalities
- Mechanism of IVIG is not completely understood.
 - Speed of action suggests neutralization of a toxin or superantigen, or neutralization of pro-inflammatory cytokines
 - Blockade of Fc receptors on monocyte/macrophages
 - Affect on tolerogenic dendritic cells IVIG induces expression of IL-10 and dendritic cell-mediated expansion of regulatory T cells (Tregs lower in acute KD)



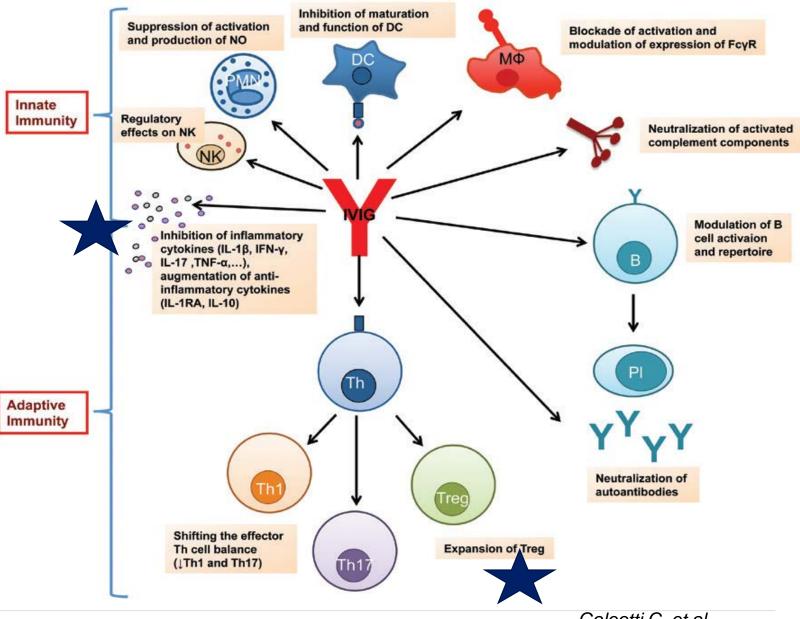
Lo, MS et al © 2020 Page 38

IVIG for MIS-C?

 Passive immunity to virus, cross-reactivity with other coronaviruses?

 Immunomodulation of both innate and adaptive responses

– Both?



Galeotti C, et al

© 2020

Direct cytokine inhibition – IL-1 blockade makes sense for MIS-C



- IL-1 high in KD and plays an important role in the vasculitis of KD
 - Giving IL-1 α/β induces myocarditis and aneurysms in mouse model of KD; KO are protected
- A precedent for using anakinra (IL-1 α/β RA) in refractory KD with decrease in CAA
- IL-1 inhibition has been used in MAS/HLH
- Relatively safe biologic since short half-life, rare opportunistic infections
- For <u>acute cytokine storm</u> Cavalli et al, 29 <u>adults</u> with COVI9-19, ARDS, hyperinflammation on HCQ, Kaletra +/-anakinra (5mg/k BID IV or 100mg BID subcu, stopped early) – higher dose led to lower CRP, respiratory improvement with 90% survival in high-dose anakinra group and 56% in standard treatment group
 - Rationale hyperinflammation was similar to MAS/HLH
- Other agents: rilonacept and canakinumab



Direct cytokine inhibition: IL-6 blockade – perhaps not for MIS-C/KD

- Tocilizimab has a longer half-life, 2-3 weeks
- Nozawa, T, et al NEJM— 4 patients with KD given tocilizumab on day 7-8 (after IVIG) none had coronary artery aneurysms at beginning, fever decreased, but 2 patients <u>developed</u> giant coronary artery aneurysms! ?decreased remodeling of vascular epithelia?
- For acute cytokine storm, there are many reports of using IL-6 inhibition in adults (Luo, J Med Vir; Xu PNAS, Pereira AM J Transplantation see COCA call notes)
- Other agents: sarilumab, siltuximab, sirukumab
- CAVEAT the distinction between acute cytokine storm and MIS-C may not be clear

What about steroids – for MIS-C not clear



Steroids currently NOT recommended for ADULTS with acute COVID-19

Steroids and TNF inhibitors (infliximab) have been studied in refractory KD, (as well as IVIG + TNFi)

MIS-C:

- Of the 38 patients in Levin's/UK cohort, 50% were given steroids
- Belhadjer: 33% given steroids
- NY Northwell (30 patients): 70% given steroids
- Montefiore, NY ?steroids; only 50% received IVIG. Still with good outcomes improving in 3-7 days

So many other immunosuppressive treatments being considered for all stages of COVID-19



- GM-CSF inhibition
- JAK inhibition
- Calcineurin inhibitors
- Anti-complement agents

Convalescent serum

Concluding thoughts



Related diagnoses still need to be carefully considered – TSS, HLH/MAS, sepsis

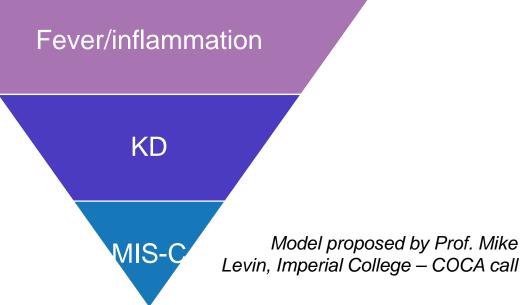
RECOGNITION of MIS-C in children

Most children exposed to or infected with SARS-CoV-2 are **not** going to be affected by MIS-C, and nearly all who have had this syndrome have recovered

A proposed continuum –

 SARS-COV2 with fever/cytokine storm – likely still detectable virus

- SARS associated/triggered KD
- SARS associated/triggered shock/MIS-C





Summary of <u>SIMILARITIES</u> between MIS-C, classic (pre-COVID) KD, TSS, HLH/MAS

- Susceptible child (likely genetic differences)
- Exposure to infectious trigger or antigen (speculative for Kawasaki disease)
- Fever, inflammatory symptoms including diffuse rash and myalgias
- Exaggerated immune response involving both innate and adaptive immune responses

Children's

Summary of <u>DIFFERENCES</u> between MIS-C and classic (pre-COVID) KD

- MIS-C patients are older
 - (mean age 8-10yr, but also young adults: 20 y/o in San Diego, many in 20s in NYC)
- More children with GI symptoms, preceding other symptoms in some cases
- Higher levels of inflammatory responses
- More myocardial injury/LV dysfunction
- Higher incidence of coronary artery abnormalities, earlier in the illness
- Timing: weeks after presumed exposure to SARS-CoV-2

Concluding thoughts



TREATMENT

- For now, most are using KD pathway/high dose IVIG to start – if recurrence of fever or significant cardiac disease, consider escalation sooner
- Anti IL-1, but perhaps not Anti IL-6 if MIS-C esp. if coronary dilatation
- Steroids have a role, if not acutely infected
- Antivirals if significant positive PCR?
- May need more vigilance with convalescent serum if a late adaptive immune response could be deleterious in some children

Children's multidisciplinary guideline on our website (Hester, Nowak, Garland, Pozos, Pomputius, Koutsari, B. Chu, Bergmann)

Thank you for your time and attention!



Children's Immunology





Tamara Pozos, MD PhD





Manar Abdalgani, MBBS

- Telehealth visits
- Primary center in MN for referrals for abnormal newborn screen for SCID



Diana Vilkama, CNP

- DiGeorge/VCF clinic
- Rare Diagnosis Clinic with Genetics

Cheryl Hale, RN 651-220-7148



3 RECENT TALKS TO WATCH ON MIS-C

1) COCA call 5/18/20

https://emergency.cdc.gov/coca/ppt/2020/COCA_Call_Slides_05_19_2020.pdf

2) PIDS Virtual Town Hall 5/19/20

https://societycentral.zoom.us/rec/play/75MrJeGqqzw3T4fD5ASDC6 UqW424L66s1HAc-

aBZyky8UXdVY1T1ZrsRM7eRmozEXrizM9ImHoqkbcey?startTime=1 589904002000& x zm rtaid=91zZPhJaR5Gu PbosJ8OaQ.15900009 89205.e849c09c58ee9728ba7ae121c0a8e427&_x_zm_rhtaid=396

3) Contemporary Pediatrics 5/20/20

https://event.on24.com/eventRegistration/console/EventConsoleApollo.jsp?&eventid=2367492&sessionid=1&username=&partnerref=&format=fhvideo1&mobile=&flashsupportedmobiledevice=&helpcenter=&key=C363AE087661DCDCA5C680BE6F888AB7&newConsole=false&nxChe=true&text_language_id=en&playerwidth=748&playerheight=526&eventuserid=303117078&contenttype=L&mediametricsessionid=257962893&mediametricid=3349695&usercd=303117078&mode=launch



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