Sickle cell disease and COVID-19

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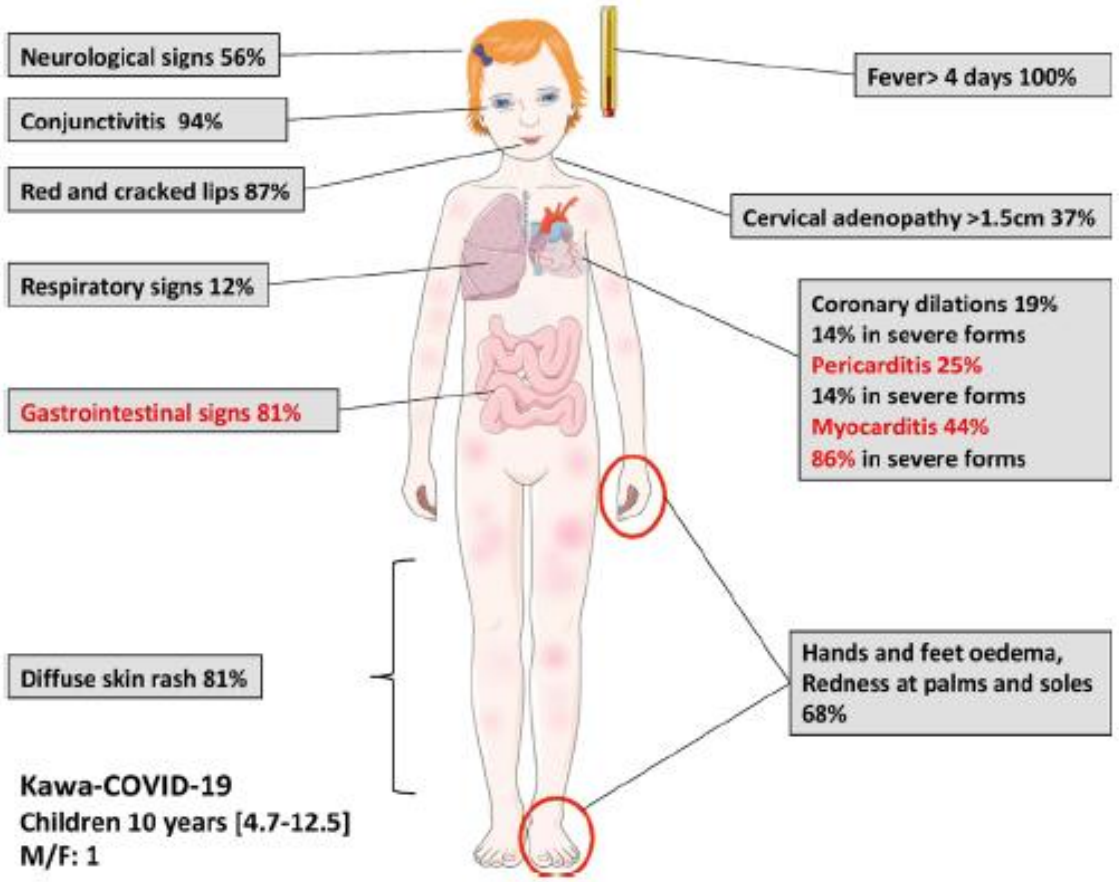
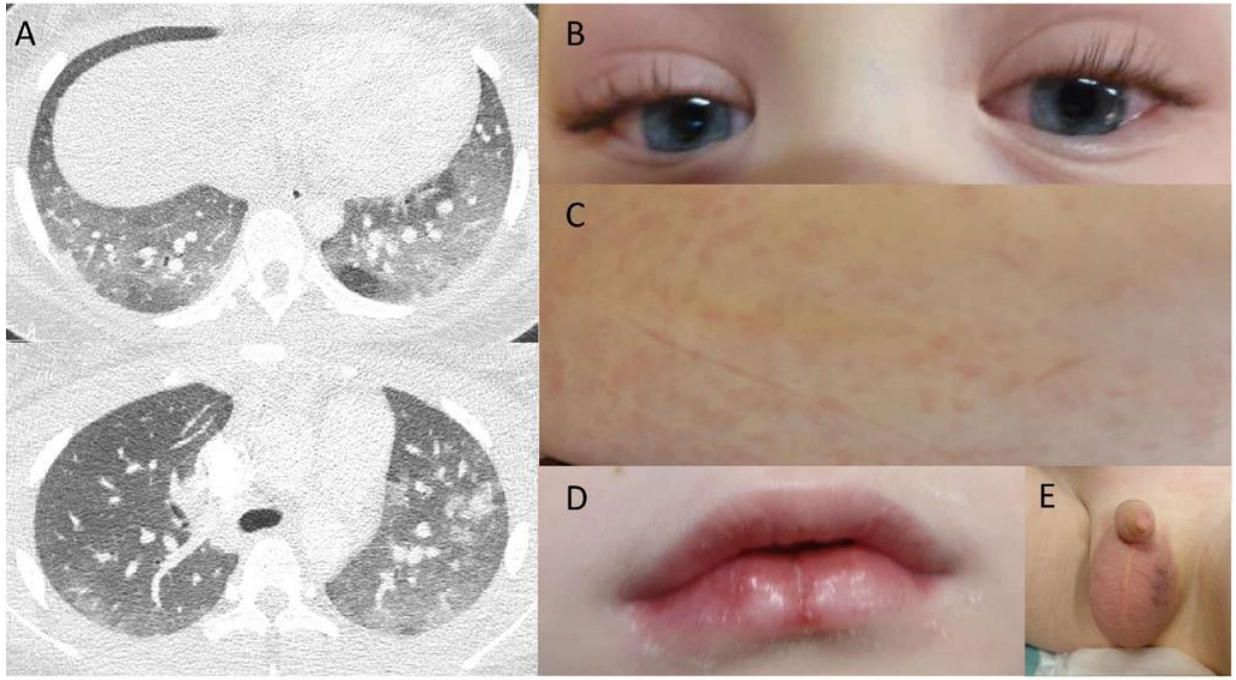
Kawa-COVID-19/PIMS-TS/MIS-C

Origin:			164
Afro-Caribbean	67/187 (36%)	10/16 (62%)	56
Middle East	44/187 (23%)	2/16 (12%)	532
European	48/187 (27%)	4/16 (25%)	1
Asia	28/187 (15%)	0/16	136





Pouletty M, et al. Ann Rheum Dis 2020;0:1–8. doi:10.1136/annrheumdis-2020-217960

How easy is it to diagnose PIMS-TS

	PIMS-TS/Kawa-COVID-19	Classical Kawasaki Disease
Age (years)	10	2
Resistance to IVIG	10/16	45/220
Platelet count (x10*9/l)	188	383
Myocarditis	7/16	3/220

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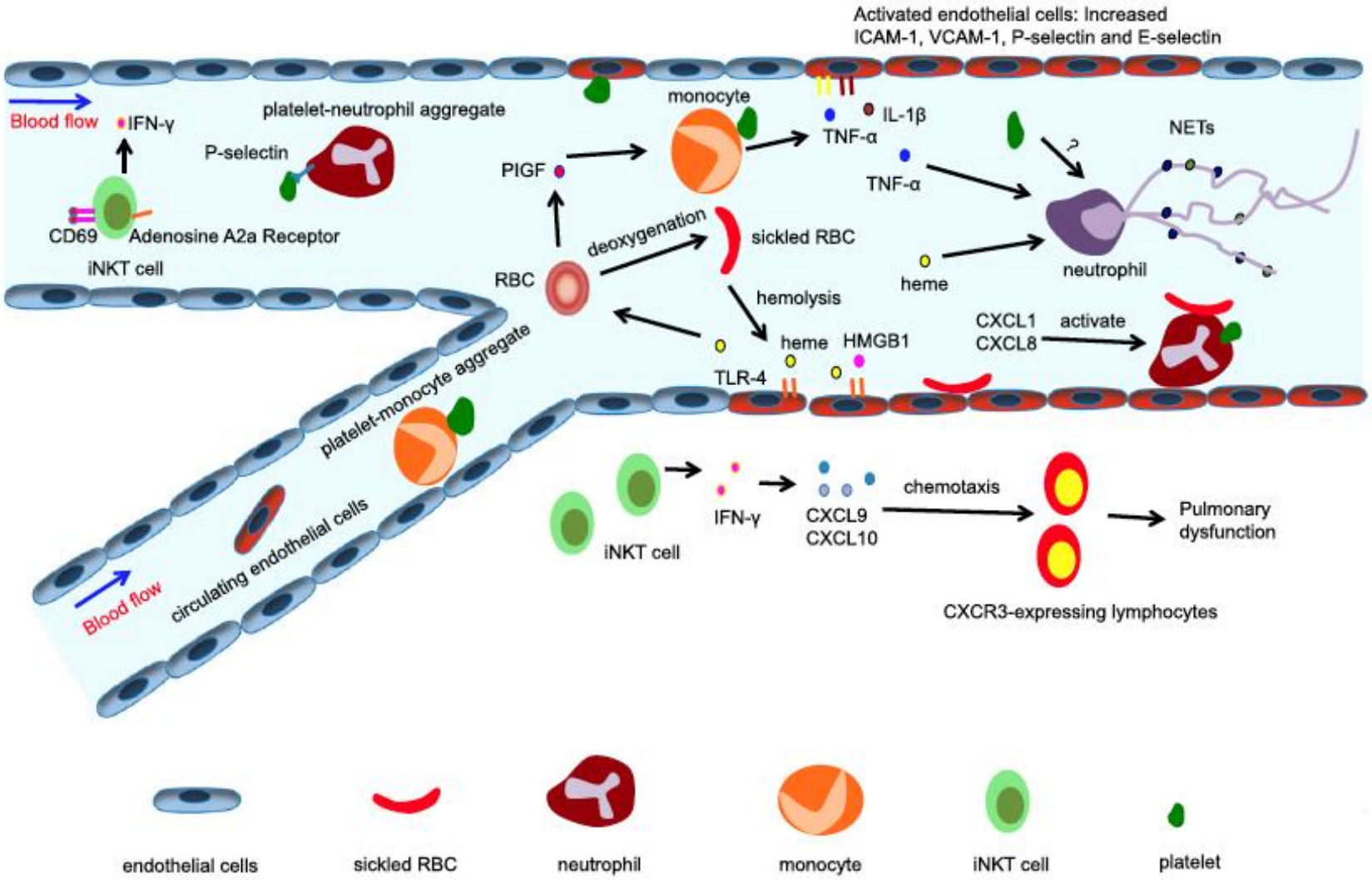
Sickle cell disease and PIMS-TS



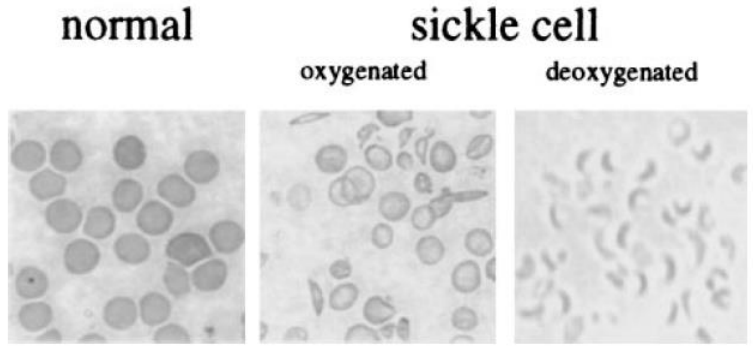
Zang et al Blood. 2016;127(7):801-809

Hallmarks of SCD inflammation

- Laboratory attributes:
  - Leucocytosis
  - Thrombocytosis
  - Increased markers of inflammation and oxidative stress
  - Procoagulant phenotype
- Other cells implicated in sickle-associated vaso-occlusive events:
  - Neutrophils
  - Monocytes
  - Platelets
  - Invariant NKT
  - Lymphocytes
  - Endothelium

Mouse models in SCD

- Redefined the pathophysiology of vaso-occlusion
- Exhibit varying degrees of severity, haemolytic anaemia, leucocytosis, markers of inflammation and activated coagulation
- Mimic the pathology of human disease in response to stimuli, including hypoxia/re-oxygenation, cytokines, lipopolysaccharide and haemoglobin/heme



Chang et al. PNAS Vol. 95, pp. 14886–14890, 1998

Landmark observations in SCD pathobiology using mouse models

- Kaul and Hebbel[1] showed that pathological stimuli, such as hypoxia-re-oxygenation, resulted in decreased blood flow, enhanced leucocyte rolling, adhesion, emigration, and enhanced oxidant production, strongly supporting the concept that SCD is a disease of inflammation, oxidative stress and reperfusion/injury physiology
- Turhan and Frenette[2] demonstrated that leucocytes mediate TNF-α–induced vaso-occlusion which leads to reduced blood flow and death. Leucocyte-dependent vaso-occlusion was prevented in mice lacking both P- and E-selectins
- Belcher and others[3] showed that treatment with antibodies targeting multiple adhesion molecules, including VCAM-1, ICAM-1, P-selectin, E-selectin, α4β1, αVβ3, vWF, or PECAM-1, inhibits microvascular stasis in response to hypoxia-reoxygenation or hemoglobin/heme infusion

1. Kaul and Hebbel *JCI* 2000;106(3):411–420
2. Turhan and Frenette *PNAS U S A*. 2002;99(5):3047–3051
3. Belcher et al. *Blood*.2014;123(3):377–390

Characteristics	All patients ($N=61$)	No microbiological documentation ($N=49$)	With microbiological documentation ($N=12$)	P-values
Sex				
Male (%)	29 (47)	23 (47)	6 (50)	1.000
Female (%)	32 (52)	26 (53)	6 (50)	
Mean age (years) (standard deviation)	31.2 (±9.28)	31.4 (±9.91)	30.3 (±6.34)	0.716
Type of sickle cell disease				
SS (%)	55 (90)	44 (90)	11(92)	0.748
SC (%)	3 (5)	2 (4)	1(8)	
S-beta-thal (%)	3 (5)	3 (6)	0	
Treatment				
Hydroxyurea (%)	24 (39)	16 (33)	8 (67)	0.047
Chronic transfusion therapy (%)	9 (15)	6 (12)	3 (25)	0.361
Bloodletting (%)	4 (7)	2 (4)	2 (17)	0.170
Vaccinations				
Seasonal flu vaccination (%)	38 (74)	28 (57)	10 (83)	0.250
Haemophilus influenzae type B vaccination (%)	55 (90)	43 (88)	12 (100)	0.572
Pneumococcal vaccination (%)	50 (82)	40 (82)	10 (83)	1
Characteristics of acute chest syndrome episodes				
Fever > 38 °C (%)	61(100)	49(100)	12(100)	
Cough (%)	28(46)	19(39)	9(75)	0.049
Chest pain (%)	58(95)	46(94)	12(100)	1
Expectoration (%)	21(34)	12(25)	9(75)	0.002
Tachypnea (%)	42(69)	31(63)	11(92)	0.083
Oxygen saturation (median %) [range]	96[96–98]	97[96–98]	95[94–98]	0.086
Baseline laboratory values (median) [range]				
Leucocytes (Giga/l)	1.52[1.11–1.95]	1.54[1.11–2.02]	.435[1.105–1.585]	0.284
Hemoglobin (g/dL)	8.3[7.3;9.1]	8.3[7.3–8.9]	8.2[6.8–10.6]	0.554
CRP (mg/L)	104.2[35.1–156.0]	96.7[32.7–136.0]	06.50[59.0–164.8]	0.231
LDH (IU/L)	559[396–728]	553[392–725]	698[510;941]	0.132
PCT (µg/L)	0.4[0.2–1.0]	0.4[0.2–1]	0.6[0.2–2.4]	0.549

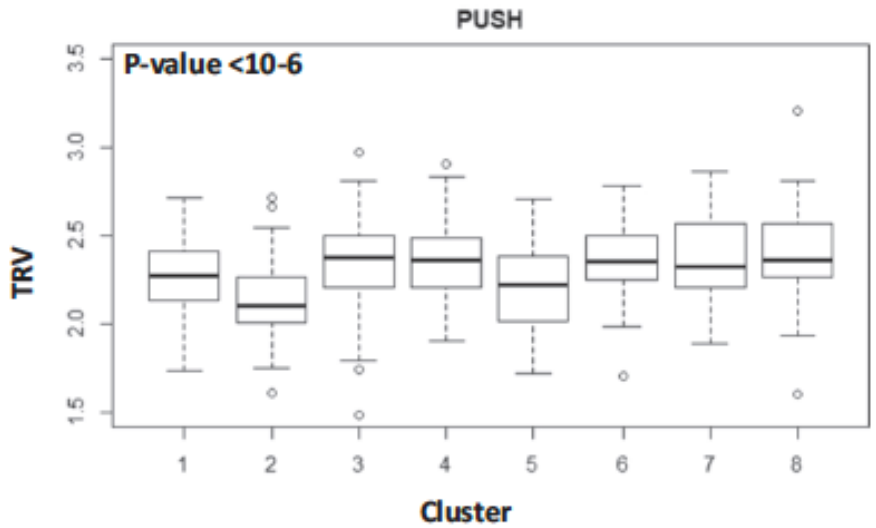
Raffetin et al. Médecine et maladies infectieuses 50 (2020) 49–56

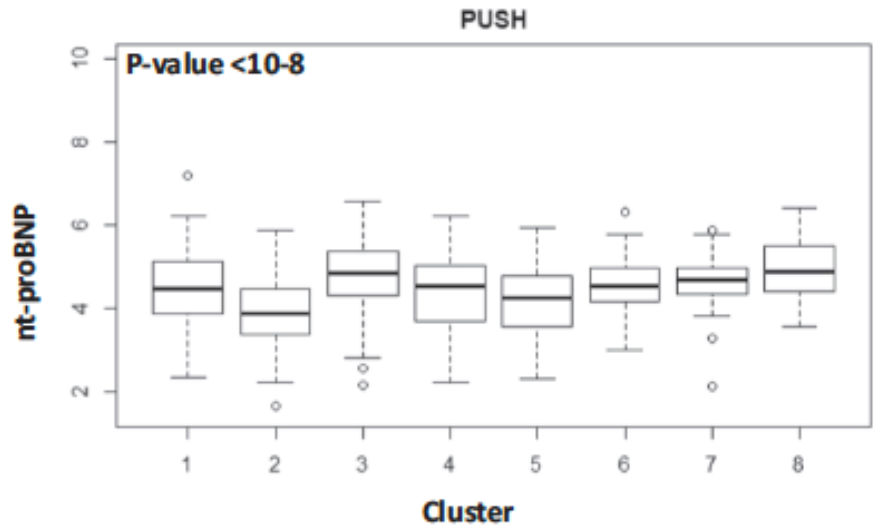
Biomarkers in SCD

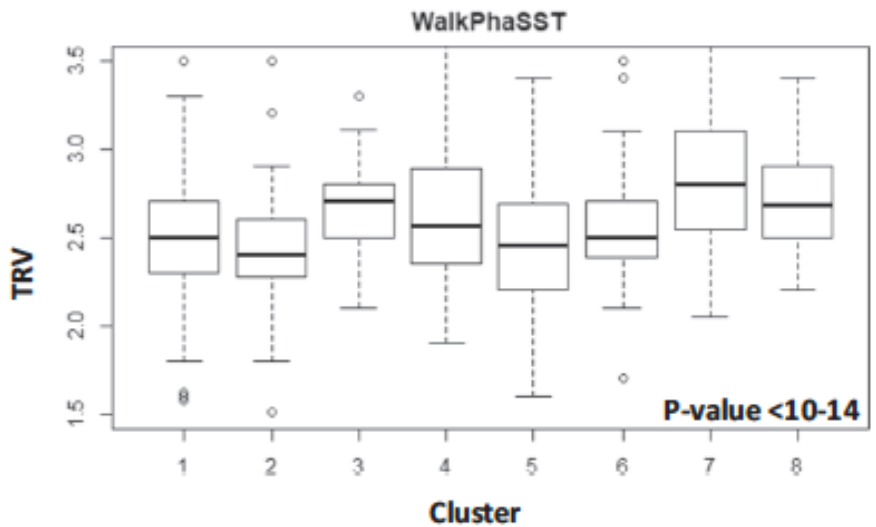
Table 1
Demographic characteristics of sickle cell disease patients by cluster.

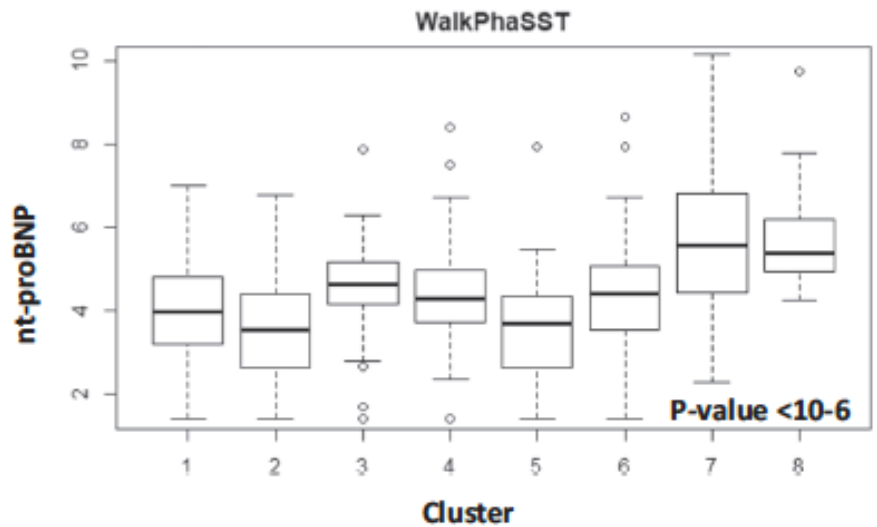
	Overall	Cluster 1	Cluster 2	Cluster 3	Cluster 4	Cluster 5	Cluster 6	Cluster 7	Cluster 8
n	2320	657	437	364	341	273	91	52	47
Age (years, mean (sd))	15.30 (12.15)	14.97 (11.30)	15.46 (13.13)	14.91 (11.61)	16.26 (11.72)	15.04 (12.89)	12.69 (10.78)	18.98 (14.57)	15.40 (12.34)
Follow-up years (mean (sd))[a]	6.44 (2.32)	6.49 (2.27)	6.50 (2.78)	6.17 (2.09)	6.44 (2.10)	6.45 (2.42)	6.63 (1.86)	6.16 (1.92)	6.56 (2.12)
Sex = Male (%)	1217 (52.5)	327 (49.8)	229 (52.4)	188 (51.6)	208 (61.0)	144 (52.7)	41 (45.1)	26 (50.0)	28 (59.6)
Fetal hemoglobin (%, mean(sd))[b]	8.47 (11.89)	8.76 (10.83)	11.56 (15.97)	7.23 (9.42)	10.04 (13.81)	3.99 (5.42)	7.42 (9.62)	6.20 (7.44)	4.94 (3.72)
Hemolytic score[c]	0	0.31	−1.38	0.86	0.84	−1.31	0.48	0.72	1.28
Hemoglobin (g/dL)	9.23 (1.76)	8.81 (1.34)	10.88 (1.53)	8.05 (1.11)	8.35 (1.05)	10.97 (1.24)	9.04 (1.82)	7.73 (1.45)	7.49 (0.94)

Dui et al. Blood Cells, Molecules and Diseases 72 (2018) 1–9









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Downstream effects of Anti inflammatory agents

Table 1. Agents targeting neutrophils, platelets, and inflammatory pathways

Category*	Therapeutic Agent	Mechanism of Action	Phase (Study ID #)
Neutrophils	Rivipansel (GMI-1070)	Pan-selectin inhibitor	3 (NCT02187003)
	IVIG	Inhibits neutrophil activation and RBC capture	2 (NCT01757418)
	SelG1	Humanized anti–P-selectin mAb	2 (NCT01895361)
	Hydroxyurea	Myelosuppression, NO donor	FDA-approved
	PF04447943	PDE9 inhibitor	1 (NCT02114203)
	Unfractionated heparin	Inhibits P-selectin and Mac-1 ligand binding	2 (NCT02098993)
Platelets	Prasugrel	ADP receptor blockade	3 (NCT01794000)
	Ticagrelor	ADP receptor blockade	2 (NCT02482298)
Inflammation	Regadenoson	$A_{2A}R$ agonist, blocks iNKT activation	2 (NCT01788631)
	NKTT120	Humanized mAb, depletes iNKT cells	1 (NCT01783691)
	Montelukast	Inhibits leukotriene receptors and mast cell degranulation	2 (NCT01960413)
	Mometasone	Inhaled corticosteroids	2 (NCT02061202)
	Rivaroxaban	Anti-Xa, inhibits IL-6 and VCAM-1	2 (NCT02072668)
	Ω-3 fatty acids	Reduces endothelial activation	2 (ISRCTN80844630)
	Glutamine	Increases NADPH, reduced oxidative stress	3 (NCT01179217)
	N-acetylcysteine	Increases glutathione, reduces oxidative stress	3 (NCT01849016)
	Simvastatin	Activates endothelial NO synthase	2 (NCT01702246)
	Atorvastatin	Activates endothelial NO synthase	2 (NCT01732718)
	L-arginine	Substrate for NO	2 (NCT02447874)
	Vaporized cannabis	Targets cannabinoid receptors to reduce chronic pain and inflammation	1, 2 (NCT01771731)

NADPH, nicotinamide adenine dinucleotide phosphate.
*Several therapies have multiple mechanisms of action.

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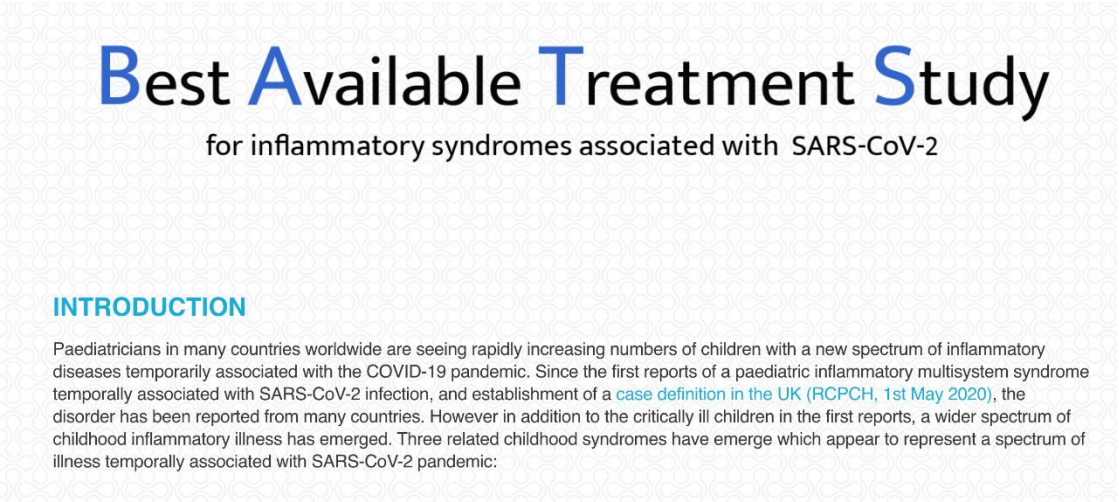
PIMS TS and SCD has overlaps

- Both are systemic inflammatory syndromes
- PIMS-TS specific treatment may be harmful to children
- High dose corticosteroids can cause intracranial haemorrhage in SCD and is associated with risk of PRES

Strouse et al. Pediatrics . 2006 Nov;118(5):1916-24.

In conclusion

- MDT discussion involving SCD specialist needed
- Current PIMS-TS diagnostic criteria have many overlaps with SCD-related acute inflammatory vaso-occlusion
- Treatment should eb given if very high degree of suspicion,
- Treatment should be given under a study umbrella



Best Available Treatment Study

for inflammatory syndromes associated with SARS-CoV-2

INTRODUCTION

Paediatricians in many countries worldwide are seeing rapidly increasing numbers of children with a new spectrum of inflammatory diseases temporarily associated with the COVID-19 pandemic. Since the first reports of a paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 infection, and establishment of a case definition in the UK (RCPCH, 1st May 2020), the disorder has been reported from many countries. However in addition to the critically ill children in the first reports, a wider spectrum of childhood inflammatory illness has emerged. Three related childhood syndromes have emerge which appear to represent a spectrum of illness temporally associated with SARS-CoV-2 pandemic:

- **PAEDIATRIC INFLAMMATORY MULTISYSTEM SYNDROME – TEMPORALLY ASSOCIATED WITH SARS-COV-2 (PIMS-TS).**
  - A child presenting with persistent fever, inflammation (which may be characterised by neutrophilia, elevated CRP and lymphopenia) and evidence of single or multi-organ dysfunction (shock, cardiac, respiratory, renal, gastrointestinal or neurological disorder) with additional features. This may include children meeting 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 (waiting for results of these investigations should not delay seeking expert advice).
  - SARS-CoV-2 PCR testing may be positive or negative.
-
- **TYPICAL KAWASAKI DISEASE – TEMPORALLY ASSOCIATED WITH SARS-COV-2 (KD-TS).**
  - Increasing numbers of children meeting the classical criteria for Kawasaki disease, but with evidence of SARS-CoV-2 infection or exposure. SARS-CoV-2PCR may be positive or negative, and SARS-CoV-2 antibodies positive or negative.
-
- **FEBRILE INFLAMMATORY SYNDROME – TEMPORALLY ASSOCIATED WITH SARS-COV-2 (FIS-TS).**
  - Definition: Febrile children, without features of 1 or 2, but with inflammatory blood markers (such as raised CRP, neutrophilia, lymphopenia, elevated D-Dimers, ferritin), in whom other infectious or inflammatory causes cannot be identified, SARS-CoV-2 may be positive or negative by PCR and antibody.