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VIEWPOINT

Update on the COVID-19-associated inflammatory syndrome in children and adolescents; paediatric inflammatory multisystem syndrome-temporally associated with SARS-CoV-2

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We provide an update on the state of play with regards a newly described inflammatory condition which has arisen during the current SARS-CoV-2 pandemic. The condition has been named paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 or multisystem inflammatory syndrome in children. This condition has shown significant similarities to Kawasaki disease and toxic shock syndrome.

Paediatricians and many families are aware of the recent reports of a novel multisystem inflammatory syndrome in children (MIS-C), which appears related to the ongoing SARS-CoV-2 pandemic. The condition has been named paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS) by the European Centre for Disease Prevention and Control[1] and MIS-C by the Centres for Disease Control and Prevention in the USA[2] and World Health Organization.[3] Henceforth, we use the term PIMS-TS to denote both of these described entities.

PIMS-TS was first reported in the UK in late April through the European Union's *Early Warning and Response System* and has now been reported from other European centres, the USA and Middle East. Anecdotally, up to 1000 cases have been reported formally and informally. Fewer than 10 deaths have been publicly reported to date. No confirmed cases have been reported in Australia or New Zealand to date.

Overall, the reported infection rates with SARS-CoV-2 (the novel coronavirus) are lower in children than adults, and children are often asymptomatic or have comparatively milder acute manifestations.[4] Few children have required hospitalisation or intensive care admission as part of the acute infection.[5]

Rather than a manifestation of primary infection, PIMS-TS appears to be a severe but delayed immune response to SARS-CoV-2 infection with uncontrolled inflammation resulting in host tissue damage.[6] The finding that many children with PIMS-TS have positive SARS-CoV-2 serology but are PCR negative on nasopharyngeal swabs supports the hypothesis of a post-infectious phenomenon.[7–9] This is also supported by the observation that the peak in PIMS-TS cases lags behind the peak in acute SARS-COV-2 cases by some weeks.[7] The mechanisms are unknown, but it seems plausible that genetic variation in affected children may contribute to this rare syndrome. Both innate (non-specific) and adaptive (both humoral and T-cell mediated) arms of the immune system have been suggested to be involved.[9,10]

A striking feature of PIMS-TS is the overlap with Kawasaki disease (KD) and toxic shock syndrome (TSS), both vasculitides likely triggered by infection.[9] While SARS-COV-2 is the suspected aetiological agent causing PIMS-TS, the cause of KD is unknown and may involve more than one infectious trigger.[11] Interestingly another novel coronavirus (coronavirus New Haven – HCoV-NH/HCoV-NL63) was previously implicated as the possible cause of KD in a series of cases in 2005,[11] but this finding could not be substantiated in other populations.[12]

Children with PIMS-TS seem to present with a severe illness characterised by shock and features often seen in KD or Kawasaki shock syndrome (KSS) (a rare, more severe form of KD that shares features with TSS).[13] These features include prolonged fever, rash, conjunctival injection, mucosal changes and raised inflammatory markers. While these features are common to both KSS and TSS, the inflammation seen in PIMS-TS seems to be far greater than that of KD.[7–9,13] Other differentiating features of PIMS-TS include an older age of onset (average of 10 years compared to 2 years for KD) and abdominal pain and diarrhoea as prominent presenting symptoms; myocardial and renal dysfunction have also been reported.[7–9,13] Additionally, children with PIMS-TS have shown marked lymphopaenia and thrombocytopaenia, coagulopathy, raised cardiac enzymes (troponin and brain natriuretic peptide, BNP), hyponatraemia,

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[Correction added on 5th September 2020, after first online publication: Kristine Macartney's name has been corrected.]

Table 1 Kawasaki disease (KD), Kawasaki shock syndrome (KSS), toxic shock syndrome (TSS) and paediatric inflammatory multisystem syndrome-temporally associated with SARS-CoV-2 (PIMS-TS): Comparison of key characteristics

Characteristic	KD	KSS	TSS	PIMS-TS
Biology				
Aetiology	Unknown. Infectious trigger in genetically susceptible host suspected.[18]	As for KD	*Staphylococcus aureus* producing TSST-1, SE-B, or SE-C. (A significant proportion of staphylococcal TSS cases are still menstrual associated.) *Streptococcus pyogenes* producing SPE-A or SPE-C[19]	Role of SARS-CoV-2 as trigger suspected, with a latent period of 1–4 weeks. Preceding SARS-CoV-2 infection may be asymptomatic
Pathophysiology	Systemic vasculitis with early activation of innate immune system (especially IL-1, IL-6, and TNF pathways)[18]	Unknown, but likely severe pathophysiology with shared features of both KD and TSS KD	SAG-mediated stimulation of T-cells causing massive cytokine release with capillary leak[19]	Unknown. Cardiogenic and distributive shock reported. Myocardial dysfunction may be related to acute systemic inflammation. Abnormal coagulation characteristic
Epidemiology (in paediatric population)				
Age, years – median	Peak age ~ 2 years[9,20]	Slightly older than KD[9,20]	Reported as a similar age (Whittaker *et al.*)[9] or older than KSS (mean 9.4 years in Lin *et al.*)[9,21]	Older than KSS (mean 9.6 years in Riphagen *et al.* and 9 years in Whittaker *et al.*)[7,9,22]
Sex ratio (male: female)	1.4:1[20]	Similar to KD[20,23]	1:9[24]	1.6:1[13] and 0.76:1[9]
Ethnicity	East Asian predominance[18,25]	No data	Caucasian predominance[24]	Afro-Caribbean prominence[9,13]
Incidence	Geographically widely variable. Australia: 17/100 000 *per annum* <5 years	5–7% of KD presentations[18,26]	~0.5/100000 *per annum*[19]	No data
Clinical presentation				
BP	N[18]	↓[27]	↓[28]	↓[7,13]
Oedema	Non-pitting, painful induration of hands and feet[18]	As for KD. May develop generalised oedema from capillary leak	Generalised non-pitting oedema from capillary leak	No data
Skin	Polymorphous rash, petechiae not typical. Late periungual desquamation	As for KD	Erythroderma, petechiae typical Late desquamation	Rash in around 50%[9,13]
Mucosa	Mucosal hyperaemia, ulceration not typical[18]	As for KD	Mucosal hyperaemia, ulceration typical[28]	Odynophagia in 3/8[13] and mucous membrane changes 29%[9]
Eyes	Non-purulent conjunctival injection	As for KD	Non-purulent conjunctival injection	Conjunctivitis in 45–62.5%[9,13]
Gastrointestinal	Abdominal symptoms (pain, diarrhoea, vomiting) common[18,20]	Abdominal symptoms (pain, diarrhoea, vomiting)more common than in KD[20]	Vomiting, diarrhoea, abdominal pain[28]	Diarrhoea in 50–87%[9,13] Abdominal pain in 50–75%[9,13]
Musculoskeletal	Arthralgia and arthritis common[18]	As for KD	Myalgia +++[28]	Myalgia in 1/8[13]
Neurological	Irritability common[18]	As for KD	Headache, confusion[28]	Headache in 25–25%[9,13]
Renal	Acute renal failure rare[20]	Acute renal failure more common than in KD[20]	Acute renal failure common[29]	22% with acute renal injury[9] and 1/8 required renal replacement therapy[13]
Echocardiogram findings				
Coronary changes	5–25%[22]	2–3 times more common than KD[20,27]	No data	14% have coronary lesions[9] Giant aneurysms in 12–25%[9,13]

(*Continues*)

Table 1 (Continued)

Characteristic	KD	KSS	TSS	PIMS-TS
Reduced EF	Rare[20]	Both cardiogenic and distributive shock reported frequently[20,23,30]	Reported, but distributive shock predominates[31,32]	Ventricular function abnormality in 31%[9] or 7/8.[13] Between 40 and 62% with shock had impaired EF[7,9]
Laboratory findings				
Total leukocyte count	N/↑[9,18,26]	↑[9,26]	N/↑[9,21]	N/↓[7,9]
Neutrophil count	N/↑[9,18,26]	↑[9,26]	N/↑[9,21]	N/↑[7,9]
Lymphocyte count	N[9,18]	N[9]	↑↑↑[9,28]	↓↓[7,9]
Haemoglobin	N/↓[9,26]	N/↓[9,26]	↓[9,21,28]	↓[7,9]
Platelet count	N, ↑↑ in 2nd–3rd week[18] ↓ in severe cases[18]	↑, however ↓ more common than in KD[9,21,27]	↓[9,21,28]	↓[7,9]
Fibrinogen	↑ initially, normalises rapidly[33,34]	N/↑[26,34]	↑[27]	↑[7,9]
D-Dimer	↑[34–37]	↑[9,34]	↑[9,28]	↑↑[7,9]
ESR	↑[21,26,34]	↑[21,26,34]	↑	↑[7,9]
CRP	↑[9,21,26,34]	↑↑[9,21,26,34]	↑↑[9]	↑↑[7,9]
Sodium	N	N/↓[38]	↓[28]	↓[7,9]
Creatinine	N[21]	↑[21]	↑[28]	
Albumin	N/↓ more in severe cases[9,18,20]	↓ more than in KD[9,20]	↓↓[9,28]	↓↓[7,9]
Bilirubin	N/↑[18]	No data	↑[39]	No data
Troponin	N[9]	N/↑[9,21,38]	No data	↑↑[7,9]
BNP	N	↑[37]	No data	↑↑[7]
Ferritin	N/↑[9,40,41]	↑[9]	No data	↑↑[7,9]
SARS-CoV-2 PCR	No data	No data	No data	Positive in 12–26%[7,9,13]
SARS-CoV-2 serology	No data	No data	No data	Positive in 80–87%[7,9]

BNP, brain natriuretic peptide; CRP, C-reactive protein; EF, ejection fraction; ESR, erythrocyte sedimentation rate; PCR, polymerase chain reaction; SAG, superantigen; TNF, tissue necrosis factor.

hypoalbuminaemia and raised lactate dehydrogenase and ferritin; these features have only infrequently been reported in KD.[7–9]

Early reports suggest that 20–25% of PIMS-TS patients demonstrate coronary artery changes (similar to the rate in untreated KD[13]); however giant coronary artery aneurysms were uncommon (<4%),[9] and most lesions have resolved relatively promptly (over a few weeks) with treatment.[7,8,13]

As paediatricians are aware, KD has a much higher incidence in children of North East Asian ancestry[14,15]; it is notable that PIMS-TS has not yet been reported from Asia. Cases of PIMS-TS reported to date have shown a possible over-representation of children from African, African-American and Afro-Caribbean ancestry.[9,12] Hypothesised explanations for this observation include the effect of relative social disadvantage on disease exposure and transmission, as well as the possibility of a specific genetic predisposition to PIMS-TS (analogous but distinct from that contributing to the ethnic differences in KD incidence[15]).

Patients with PIMS-TS have often required supportive treatment for hypotension and circulatory collapse.[7–9,13] Intravenous immunoglobulin (also the primary treatment for KD) and corticosteroids have also been used extensively,[7–9,13] with biologic agents and anticoagulants used in selected cases on appropriate subspecialty advice. There have been a small number of deaths, but generally the outcomes have been good, with few patients requiring extracorporeal membrane oxygenation. The long-term cardiovascular outcomes are yet to be determined.

Interestingly, in early April clinicians in the USA reported a case of KD with concurrent COVID-19,[16] and paediatricians in France and Italy (both of which have had high incidence of SARS-CoV-2 infection) reported marked increases in KD diagnoses (without shock but with positive SARS-COV-2 testing).[7,8] Many of the cases reported had incomplete KD with fever and less than four of the cardinal 5 clinical features of KD.[7,8] However, other regions have not reported any increases in KD overall during the pandemic. In Australia and New Zealand, where community transmission and incidence of SARS-CoV-2 remains low, there has not been any change in expected KD incidence in 2020 to date in as yet unpublished national surveillance data (http://www.paeds.org.au/covid-19-kawasaki-disease-kd-and-pims-ts-children).[17]

At present, little is known about PIMS-TS. It is unclear whether PIMS-TS represents a severe form of KD triggered by SARS-CoV-2, or a separate entity with a spectrum of disease extending from a mild febrile illness through a KD-like illness to a severe KSS/TSS-like disease. As KD, KSS and TSS are all syndromic, with no diagnostic test, as shown by Whittaker *et al.*,[9] it is difficult to define the boundaries between these phenotypes (Table 1).

We suggest that clinicians should be aware of this new condition and in the current pandemic should consider PIMS-TS when assessing children with fever and a differential diagnosis of KD, TSS, fever and rash, severe abdominal pain or shock without obvious cause. As with any serious paediatric condition, clinicians should follow recommended clinical management pathways for COVID-19, KD or TSS. For any patient with these conditions suspected to have PIMS-TS, it is important to ensure testing for SARS-CoV-2 by PCR on appropriate specimens but to also collect a blood sample for testing of antibodies (serology) to SARS-CoV-2 prior to IVIG therapy along with convalescent serology. Suspected cases should be discussed with local specialist paediatric services (infectious diseases, rheumatology, intensive care, cardiology) as appropriate.

In Australia and New Zealand, few if any cases of PIMS-TS would be expected if community transmission of SARS-CoV-2 is low – particularly in children. Nevertheless, the Paediatric Active Enhanced Disease Surveillance network, which already conducts national surveillance for KD and other conditions relevant to paediatrics (www.paeds.org.au) and The Influenza Complications Alert Network are working to establish active surveillance for PIMS-TS in Australia. These groups will be collaborating with other networks to ensure cases of PIMS-TS are rapidly detected and comprehensively investigated. For further information about surveillance and standardised data collection, please refer to http://www.paeds.org.au/covid-19-kawasaki-disease-kd-and-pims-ts-children

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