Advice for clinicians: Paediatric Inflammatory Multisystem Syndrome Temporally associated with SARS-COV-2 (PIMS-TS)

A statement from the Acute Inflammatory Vasculitis working group and the Paediatric Active Enhanced Disease Surveillance (PAEDS) network.

Background Information

Reports from the UK\(^1\), Europe\(^2,3\), and the USA\(^4\) since late April have described a number of severely ill children and adolescents with fever and shock frequently associated with abdominal pain and rash associated with of SARS-CoV-2 infection. This condition has been provisionally named Paediatric Inflammatory Multisystem Syndrome Temporally associated with SARS-COV-2 (PIMS-TS)\(^5\). The United States Centers for Disease Control and Prevention has named this syndrome Multisystem Inflammatory Syndrome in Children associated with COVID-19 (MIS-C)\(^6\).

The exact link between SARS-CoV-2 and PIMS-TS remains unclear. The epidemiology, particularly a delay in timing between peak SARS-CoV-2 infection in the community and PIMS-TS cases in several locations, as well as the timing of infection and clinical presentation in individual patients, suggest that this condition may be due to a delayed immune-mediated phenomenon triggered by the virus. Many, but not all, of the reported cases have tested positive for SARS-CoV-2 on PCR and/or serological testing.

PIMS-TS shows similarities to Kawasaki Disease (KD) and Toxic Shock Syndrome (TSS)

KD is a well described but uncommon disease predominantly affecting children under 5 years of age but also occurs in older children\(^7\). It is suspected that KD results from an excessive inflammatory response to an unknown trigger, probably an infection in genetically susceptible children. This inflammation can damage blood vessels, particularly the coronary arteries. Less than 5% of children with KD present with shock (Kawasaki shock syndrome, KSS), which shares features with TSS. TSS is an infrequent manifestation of streptococcal and staphylococcal infection in children and also adults. Children with KSS and TSS usually require management in intensive care units with vasopressor or inotropic support.

3 Toubiana J et al, Medrxiv 2020. Available from: https://www.medrxiv.org/content/10.1101/2020.05.10.20097394v1
Many aspects of PIMS-TS resemble KSS; patients have fever and shock, as well as rash, and red hands and feet. Importantly, ~25% of PIMS-TS cases reported to date have evidence of damage to the coronary arteries, which is also a hallmark of KD and KSS. This raises the possibility that there may be a pathophysiological link between KD, KSS and PIMS-TS.

However, there are some significant differences; PIMS-TS appears to affect older children than typical KD does (average age around 11 years vs 2 years, respectively) and limited, early data suggest that in UK and US populations African and Afro-Caribbean children may be at greater risk of PIMS-TS, in contrast to KD occurring with highest frequency in East Asian children. In PIMS-TS, gastrointestinal symptoms (particularly abdominal pain) predominate and there appears to be a higher frequency of myocarditis and renal impairment.

From initial reports, patients with PIMS-TS may have elevated inflammatory markers including ESR, CRP and ferritin along with abnormal coagulation studies which is not highly differential from other presentations such as KD/KSS, bacterial sepsis and TSS. However, other laboratory parameters appear more specific for PIMS-TS including lymphopaenia and thrombocytopenia on full blood count, and hyponatraemia. An elevated troponin may occur. Echocardiography has also been reported to show myocardial dysfunction and coronary artery abnormalities in a significant proportion.

**Recommendations for management of patients with possible PIMS-TS**

Initial management of children presenting with features of PIMS-TS should include the usual assessment of a child with fever. Differential diagnoses, including TSS, KD and bacterial sepsis should be considered, investigated and treated according to local guidelines with senior clinician involvement.

Appropriate supportive management should be commenced and specific measures for hypotension or shock instituted urgently if required. Children with shock should be referred to intensive care as appropriate.

KD and TSS are both treated with intravenous immunoglobulin and children with PIMS-TS have also been managed with IVIG. Further expert advice on additional treatment modalities should be sought as needed and may be obtained from the following specialist services where appropriate - paediatric infectious diseases, paediatric rheumatology, paediatric cardiology and paediatric immunology.

While case definitions have been proposed, it is important to emphasise that these are for surveillance purposes and not to guide clinical management.

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Specialist advice on SARS-CoV-2 testing, including for current or previous infection can be obtained from paediatric infectious diseases specialists and clinical microbiologists.

In addition to any clinically indicated investigations, the following tests are recommended for children with suspected PIMS-TS:

**At presentation (and ideally prior to IVIG administration):**

- Patient height and weight (so coronary artery z-scores can be calculated from BSA)
- Nasopharyngeal and throat swab for SARS-CoV-2 PCR
- Serum for SARS-CoV-2 serology (wherever possible this should be taken prior to the administration of blood products such as IVIG)
- Full blood count and film
- Electrolytes and liver function testing
- Albumin
- Creatine Phosphokinase (CPK)
- Troponin
- Lactate Dehydrogenase (LDH)
- Ferritin
- Inflammatory markers – Erythrocyte Sedimentation Ratio (ESR) and C-Reactive Protein (CRP)
- Coagulation studies – International Normalised Ratio (INR), Activated Prothrombin Time (APTT), fibrinogen, D-Dimer, Fibrin Degradation Products (FDP)
- Echocardiography assessing for myocardial function and coronary artery lesions. Frequency of further echocardiograms depends on initial findings and consultation with paediatric cardiology and paediatrician experienced in management of KD and/or paediatric COVID-19.

4-6 weeks after the acute illness

- Serum for SARS-CoV-2 serology
- Echocardiography assessing for myocardial function and coronary artery lesions

The outcome of PIMS-TS is generally good. While the majority of children reported to date have recovered, five deaths have been reported to date (3 in the USA and 1 each in the UK and France).

**How common is PIMS-TS overseas, and have there been any cases in Australia?**

To date, PIMS-TS has only been reported in small numbers internationally and only from countries with a high incidence of COVID-19 infection. The reported case numbers of PIMS-TS in New York are small relative to the total population of children. In the UK report, 8 PIMS-TS cases were noted in an estimated catchment area of 2 million children; the number of COVID-19 infections in children in this population is not known but was certainly much higher – by at least 10-fold - than Australia. Overall, 246,406 COVID-19 cases in the UK, and 1,550,294 cases in the USA have been reported as at 18 May 2020.

In Australia and New Zealand there have been no reported cases of PIMS-TS or of either KD or TSS in children with SARS-CoV-2 infection. As in other countries, the proportion of all COVID-19 cases that
occur in children is low (<4%). Since January there have only been 150 cases of COVID-19 diagnosed in children aged <15 years in Australia, out of a total of 6975 cases as at 13 May 2020. In New Zealand, 68 probable or definite cases of COVID-19 have been diagnosed in children 15 years or less out of 1503 probable or definite cases as of 19 May 2020.

The public health measures that have been effective in controlling COVID-19 are also likely to reduce, but not completely eliminate, the risk that PIMS-TS will occur in Australian children.

**What activities exist and are proposed to address the potential issue of PIMS-TS in Australia?**

The PAEDS network, established across seven major children’s hospitals in Australia, is currently undertaking surveillance for COVID-19 in children (in collaboration with FluCAN, supported by the Commonwealth Department of Health). A registry for KD using PAEDS and other sources (supported by the National Blood Authority), is also ongoing.

Outside of the COVID-19 pandemic, approximately 400 cases of typical KD per year are reported in Australia. Since the onset of the pandemic in 2020, no increase in KD case numbers has been detected compared to previous years. If numbers of KD do rise in the coming months, we are confident that our existing surveillance mechanisms will identify and report this. Furthermore, a process is underway to establish a specific surveillance program for PIMS-TS leveraging off existing networks, particularly PAEDS.

Clinicians must inform their local public health units of patients with probable and confirmed COVID-19 as a matter of urgency, which means that cases are well documented and aids in understanding the epidemiology of this emerging issue.

Should you suspect a case of PIMS-TS in a child, clinical advice should be first sought from your local paediatric infectious diseases, rheumatology and/or immunology specialists. To contribute surveillance data and support surrounding data collection please contact the PAEDS network by emailing schn-paeds@health.nsw.gov.au or calling 0428 424 610 in business hours.

Further information including a case definition for surveillance in Australia will be available on the PAEDS website (www.paeds.org.au/) in the near future.

**Summary**

PIMS-TS is a newly described syndrome in children with features that overlap with KD, KSS and TSS but also with some distinct symptoms and signs. It appears to be linked to COVID-19. To date, PIMS-TS has been reported in children from the USA, UK and Europe, regions that are experiencing widespread community-based transmission of SARS-CoV-2 and thus, much higher rates of paediatric 11

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13 Most recent estimate of incidence in Australia is 17.5 cases per 100,000 children under the age of 5 per year. (Unpublished data - Lucas, Singh-Grewal, Burgner, et al.)

infection/exposure. COVID-19 generally is uncommon in children and typically an asymptomatic or mild disease. PIMS-TS appears to be a rare, but clinically significant, complication of SARS-CoV-2 infection. The overall risk for any severe COVID-19 outcomes in children in the Australian context remains extremely low.