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 United Kingdom (the UK),[1] Europe[2,3,4] and the United States of America (the USA)[5] 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 SARS-CoV-2 infection. This condition has been provisionally named Paediatric Inflammatory Multisystem Syndrome Temporally associated with SARS-COV-2 (PIMS-TS).[6] The United States Centers for Disease Control and Prevention has named this syndrome Multisystem Inflammatory Syndrome in Children associated with COVID-19 (MIS-C).[7]

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, suggests 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 and Toxic Shock Syndrome

Kawasaki disease (KD) is a well described but uncommon disease that predominantly affects children under 5 years of age but also occurs in older children.[8] 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 Toxic Shock Syndrome (TSS). TSS is an infrequent manifestation of streptococcal and staphylococcal infections in children and adults. Children with KSS and TSS usually require management in intensive care units with vasopressor or inotropic support.

Many aspects of PIMS-TS resemble KSS: patients have fever and shock, rash, and red hands and feet. Importantly, around 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 versus 2 years, respectively) and limited, early data suggest that in the UK and US populations, African and Afro-Caribbean children may be at greater risk of PIMS-TS in contrast to KD occurring with the 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.

Initial reports show patients with PIMS-TS may have elevated inflammatory markers, including erythrocyte sedimentation ratio (ESR), C-reactive protein (CRP) and ferritin, along with abnormal coagulation studies, which is not significantly different from patients with other presentations such as KD/KSS, bacterial sepsis and TSS. However, other laboratory parameters appear more specific for PIMS-TS, including lymphopaenia and thrombocytopaenia 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 of patients with PIMS-TS.

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 the involvement of a senior clinician.

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.

Both KD and TSS are treated with intravenous immunoglobulin (IVIG), and children with PIMS-TS have also been managed with IVIG.[2,9,10] Further expert advice on additional treatment modalities should be sought as needed and may be obtained from specialist services such as paediatric infectious diseases, paediatric rheumatology, paediatric cardiology and paediatric immunology, where appropriate.

While case definitions of PIMS-TS or PIMS have been proposed,[6,11] it is important to emphasise that these are for surveillance purposes and not to guide clinical management.

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

Tests for children with suspected PIMS-TS

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

At presentation (and ideally before 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 **before** the administration of blood products such as IVIG)
- full blood count and film
- electrolytes and liver function testing
- lbumin
- creatine phosphokinase (CPK)
- troponin
- lactate dehydrogenase (LDH)
- ferritin
- inflammatory markers – ESR and 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.

After the acute illness

- serum for SARS-CoV-2 serology (at 2–3 weeks after illness, using well-validated assay)
- echocardiography assessing for myocardial function and coronary artery lesions (at 4–6 weeks after illness)

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 (three in the USA and one each in the UK[9] and France[4,10]).

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 SARS-CoV-2 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 SARS-CoV-2 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 had 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 6,975 cases as at 13 May 2020. In New Zealand, 68 probable or definite cases of COVID-19 have been diagnosed in children aged ≤15 years out of 1,503 probable or definite cases as at 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[12] 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).[13] 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.[14] 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,[15] which means that cases are well documented and aids in understanding the epidemiology of this emerging issue.

If you suspect PIMS-TS in a child, seek clinical advice from your local paediatric infectious diseases, rheumatology and/or immunology specialist(s).

Please contact the PAEDS network to contribute surveillance data, and for support in data submission, by emailing schn-paeds@health.nsw.gov.au or calling 0428 424 610 during 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, the UK and Europe, regions that are experiencing widespread community-based transmission of SARS-CoV-2 and thus, much higher rates of paediatric infection/exposure. COVID-19 generally is uncommon and typically an asymptomatic or mild disease in children. 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.

For more information, also see the AHPPC statement: https://www.health.gov.au/news/australian-health-protection-principal-committee-ahppc-coronavirus-covid-19-statements-on-14-may-2020

The Acute Inflammatory Vasculitis working group and the Paediatric Active Enhanced Disease Surveillance (PAEDS) network include David Burgner, Davinder Singh-Grewal, Ryan Lucas, Allen Cheng, Nicholas Wood, Philip Britton and Kristine Macartney.

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