Guideline

# Paediatric Inflammatory Multisystem Syndrome Temporally Associated with COVID-19

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| **Author/custodian** | Director, Infection Management and Prevention Service<br>Director, Paediatric Intensive Care medicine | | | **Review date** | 08/12/2024 |
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## Purpose

Most children with a positive SARS-CoV-2 PCR are asymptomatic or suffer from a mild respiratory illness. A small proportion may present with a disease that spans from acute respiratory disease through to a later onset illness with three phenotypes of a hyperinflammatory response state called Paediatric Multisystem Inflammatory Syndrome Temporally Associated with COVID-19 (PIMS-TS, also called "multisystem inflammatory syndrome in children [MIS-C]). In patients with severe **COVID-19** disease, PIMS-TS has been reported to affect nearly half of the cohort. This guideline describes the presentation and management of severe **COVID-19 disease** followed by PIMS-TS.

## Scope

This guideline applies to children who present with signs and symptoms suggestive of Paediatric Multisystem Inflammatory Syndrome Temporally Associated with COVID-19 (PIMS-TS) also known as Multi-System inflammatory Syndrome in children (MIS-C).

## Related documents

**Procedures, Guidelines, Protocols**

- CHQ-WI-80135: Paediatric Respiratory Care during the COVID-19 Pandemic for all acute and chronic inpatients with respiratory disease.
- CHQ-GDL-63327: The management of children with COVID-19
- CHQ-PROC-63002: Infection Control Guidelines for the Management of Patients with Known or Suspected Coronavirus (COVID-19).

**Other**

- Fact Sheet: Paediatric inflammatory multisystem syndrome (For parents and guardians)

# Guideline

## Case definition for PIMS-TS

1. A child presenting with persistent fever, inflammation (neutrophilia, elevated CRP and lymphopaenia) and evidence of single or multi-organ dysfunction (shock, cardiac, respiratory, renal, gastrointestinal or neurological disorder) with additional features (Appendix 3). This may include children fulfilling full or partial criteria for Kawasaki disease.
2. **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).
3. SARS-CoV-2 PCR testing may be positive or negative.

For comparisons of definitions see Appendix 2.

## PIMS-TS Phenotypes in children

| Shocked cohort | Kawasaki-like Disease | Febrile and inflammatory |
|---|---|---|
| Median age 10.5 years<br>Clinically abdominal pain, diarrhoea +/- rash/erythema<br>Raised inflammatory markers<br>Raised cardiac enzymes<br>Echo - ventricular dysfunction and Coronary Artery Aneurysm | Median age 8 years<br>Clinically meet American Heart Association criteria - 4/5, mucocutaneous features<br>Raised inflammatory markers, milder increase cardiac markers<br>Echo - rare ventricular dysfunction +/- Coronary Artery Aneurysm | Median age 10 years<br>Range of features including abdominal pain, diarrhoea, mucocutaneous features, tachycardia common and mild hypotension<br>Raised inflammatory markers and cardiac enzymes<br>Echo - mild ventricular dysfunction +/- Coronary Artery Aneurysm |

Diagnosis of PIMS-TS in a child in a shocked state can be difficult due to diverse presentation and overlap with sepsis, appendicitis or gastric infection.

## Comparison of presentation of PIMS-TS to Kawasaki disease

PIMS-TS and Kawasaki disease (KD) do appear to be different entities, with differing, discrete gene expressions. In PIMS-TS, complement, platelet and neutrophil activation pathways are upregulated on gene expression. Clinically PIMS-TS patients are slightly older, have a higher white cell count, neutrophil count and CRP and lower lymphocyte count, haemoglobin and platelet count. The troponin, pro-BNP, d-dimer, cytokine, IgG, IgA are relatively elevated. IG1/3 ratio is abnormal. They may have lower neutralising antibody levels.
In practice, the distinction can be extremely difficult to make clinically. Thus, Multidisciplinary team (MDT) discussion of all cases is essential. Children aged < 6 years fulfilling complete or incomplete KD criteria should receive Intravenous Immunoglobulin (IVIG) without delay.

# Management of PIMS-TS

## ED assessment

- Consider in any unwell child especially if there has been high community transmission of COVID in the last few weeks.
- Routinely take a history of either COVID in patient or close contact.
- Initial assessment should follow usual practice as for any child who present with fever or is being managed for suspected sepsis.
- If inflammatory markers are raised and known previous COVID infection or contact – Liaise early with the Infectious Diseases (ID) team
- Admit to general paediatric ward if illness severity not high.
- All patients should be discussed with CHQ Paediatric Infectious Diseases team at presentation
- Consult with Children's Health Queensland Retrieval Services team through Retrieval Services Queensland early for advice and potential escalation of care where necessary.
- Admit to PICU if patient needs respiratory support in the form of HFNC with an oxygen requirement.
- A Multidisciplinary team (MDT) will be convened with paediatric infectious diseases, PICU, general paediatrics, rheumatology, haematology and immunology teams.
- Wear appropriate PPE at all times (See CHQ-PROC-63002: Infection Control Guideline for the Management of Patients with Known or Suspected Coronavirus (COVID-19)).
- Perform blood investigations (Appendix 1), respiratory viral PCR panel plus save serum and EDTA.
- Empiric antibiotics should include a toxin mediating antibiotic and be commenced as per the QLD Paediatric Statewide Sepsis pathway or local guidelines (where applicable), after blood cultures have been obtained. For example:
  - Cefotaxime
    - Over 1 month of age: 50 mg/kg (maximum 2 g) IV 6 hourly
    - Alternative: Ceftriaxone: Over 1 month of age: 50 mg/kg (maximum 2 g) IV 12-hourly
  - Lincomycin
    - Over 1 month of age: Lincomycin 15 mg/kg (maximum 1.2 g) IV 8 hourly
    - Alternatives: Clindamycin: Over 1 month of age: 10 mg/kg (maximum 600 mg) IV 6-hourly
- All cases will be reported to the Paediatric Active Enhanced Disease Surveillance (PAEDS) network by the Paediatric Infectious diseases Research team.

## Monitoring:

- Hourly CEWT (if on the ward) and regular full set of observations
- Monitor closely for signs of respiratory or cardiovascular deterioration
- Monitor for clinical signs of worsening inflammation by monitoring end organ function and inflammatory markers.

- Serial measurement of FBC, Chem20, CRP, Ferritin, Triglycerides, Coagulation screen will be required. The frequency will be determined by the attending clinician.

## Treatment principles

- Discuss early with PICU and paediatric infectious diseases / immunology / rheumatology teams. Multidisciplinary team (MDT) management of all cases is essential.
- All children should be treated as suspected COVID-19 cases

## Immunomodulatory therapy (see Appendix 4)

- Any child being considered for immunomodulatory therapy should be discussed at an MDT with immunology, rheumatology, general paediatrics, paediatric infectious diseases specialist and intensive care.
- There is no evidence so far to suggest that recovery from PIMS-TS is modified by treatment with IVIG alone, IVIG plus glucocorticoids or steroids alone.
- **First line therapy** - Intravenous Immunoglobulin 2 gram/kg.
  - In PIMS-TS shock (need for vasoactive support) add: Methylprednisolone – 10 mg/kg IV once daily (Maximum 1000 mg/day) for 3 days and then Prednisolone oral/enteral 2 mg/kg once daily (maximum 60 mg/day). Reduce dose every 3-5 days over a total of 2-3 weeks (discuss wean in MDT).
  - (Note 1: Alternative to IVIG: Methylprednisolone [10 mg/kg IV once daily (Maximum 1000 mg/day) for 3 days] may be used alone as first line in PIMS-TS shock > 5 years and if concern re adverse impact of IVIG fluid volume)
  - (Note 2: Steroids alone may be used as first line treatment in PIMS-TS undefined inflammatory presentation: Methylprednisolone 2 mg/kg IV once daily (Maximum 200 mg/day) for 3 days; after MDT discussion.
- **Second line therapy** - Corticosteroids should be considered as the next treatment option for children who remain unwell (continued fever, clinical or laboratory signs of inflammation) 24 hours after infusion of intravenous immunoglobulin. Methylprednisolone – 10 mg/kg IV once daily (Maximum 1000 mg/day) for 1 to 3 days and then prednisolone oral/enteral 2 mg/kg once daily (maximum 60 mg/day), reduce dose every 3-5 days over a total of 2 to 3 weeks (discuss dose and wean in MDT).
  - Note: all children receiving steroids should have gastroprotection with proton pump inhibitors
- **Third line therapy** – MDT to consider using Infliximab in patients with PIMS-TS refractory to initial treatment with IVIG and corticosteroids, and after exclusion of alternative causes.
- Dose:
  - Infliximab 5 mg/kg IV as a single dose. For administration information, refer to the CHQ-PMG-01209 Infliximab Paediatric Medication Guideline
  - If deterioration or no improvement and continued signs and symptoms of inflammation:
    - Anakinra 2 mg/kg/dose (maximum 100 mg/dose) by subcutaneous injection every 6 hours on day 1, every 8 hours on day 2, every 12 hours on day 3, every 24 hours days 4 to 5.

## Anticoagulation

- Thromboprophylaxis can be tailored to the requirements of each patients using D-dimers and a combination of non-COVID-19 risk factors. Consult with the haematology team.
- Prescribe oral/enteral Aspirin 3 to 5 mg/kg once daily (Maximum 100 mg/day) where platelets > 80
- Add Low molecular weight heparin (LMWH) for all children with shock in discussion with haematology:
  - Enoxaparin by subcutaneous injection twice a day targeting Anti Xa 0.2 to 0.5 OR unfractionated heparin at 10 to 15 units/kg/hr (in case of renal impairment or if procedures needed/other bleeding risks).
  - For more information, consult CHQ-PMG-01254 Enoxaparin or CHQ-PMG-01200 Heparin Sodium (Unfractionated Heparin)
- Consider LMWH in other phenotypes depending on risk factors
- Compression stockings (TEDS) should be used for all children > 12 years
- Marked thrombocytopenia and/or hypofibrinogenemia would be a relative contraindication. Haematology team will tailor these decision as per ISTH 2020 guidelines.

## Cardiac support

- Serial ECG, echocardiogram (frequency determined in consultation with the cardiology team), troponin, pro-BNP should be performed.
- Cardiac arrythmias have been reported. Monitor with continuous ECG and telemetry.
- Vasoactive support should follow routine intensive care principles of cardiovascular support.
- Patients admitted to PICU with a diagnosis of PIMS-TS and a severe disease should be discussed with the ECLS team early.

While PIMS-TS is uncommon, these are some of the sickest children clinicians are likely to encounter in paediatric practice. Management of these children should be within a collaborative multidisciplinary team environment. Parents will need advice and guidance to be shared decision makers in this relatively new disease entity. Patients presenting with COVID 19 related disease or PIMS-TS/MIS-C are likely to be enrolled in various research studies. The leads for PICU, immunology, the Paediatric Critical Care Research Group as well as the respective study coordinators should be contacted early for consultation.

## Discharge from PICU

Children should follow normal de-escalation pathways. Commonly these children will be discharged to the paediatric ward under the lead paediatric team.

## Abbreviations

| | |
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| CEWT | Child early warning tool |
| CHEM20 | Biochemistry Profile including electrolytes, urea, creatinine and liver function tests |
| CHQ | Children's Health Queensland |
| CK | Creatine kinase |
| CRP | C-reactive protein |
| ECG | Electrocardiogram |
| ECLS | Extracorporeal life support |
| FBC | Full blood count |
| IVIG | Intravenous Human Immunoglobulin |
| KD | Kawasaki's disease |
| LMWH | Low molecular weight heparin |
| MDT | Multi-disciplinary team |
| MIS-C | Multi-System inflammatory Syndrome in children |
| PAEDS | Paediatric infectious diseases Research network |
| PCR | Polymerase chain reaction |
| PICU | Paediatric Intensive care unit |
| PPE | Personal protective equipment |
| PIMS-TS | Paediatric Inflammatory Multisystem Syndrome Temporally Associated with COVID-19 |
| TEDS | Compression stockings |

## Consultation

Key stakeholders who reviewed this version:

- PICU SMO
- Infection Management and Prevention Service Director
- Paediatric Infection Specialists
- Critical Care Pharmacist Lead
- PICU Safety & Quality ANUM
- Clinical Pharmacist Lead- Antimicrobial Stewardship
- CHQ Medicines Advisory Committee – endorsed 18/11/2021

## References and suggested reading


1. Whittaker E et al. Clinical characteristics of 58 children with a Pediatric Inflammatory Multisystem Syndrome Temporally associated with SARS-CoV-2. JAMA. 8 June 2020. doi:10.1001/jama.2020.10369
2. United States Centers for Disease Control and Prevention. Multisystem Inflammatory Syndrome in Children (MIS-C) Associated with Coronavirus Disease 2019 (COVID-19). 2020. Available from: https://emergency.cdc.gov/han/2020/han00432.asp
3. Morbidity and Mortality Weekly Report. United States Centers for Disease Control and Prevention. Aug 14, 2020, Vol.69, No.32.
4. European Society of Paediatric and Neonatal Intensive Care conference 2021 presentation on Multisystem Inflammatory Syndrome in Children.
5. Royal College of Paediatrics and Child Health (RCPCH). Guidance - Paediatric multisystem inflammatory syndrome temporally associated with COVID-19 (PIMS). 2020. Available from: https://www.rcpch.ac.uk/resources/guidance-paediatric-multisystem-inflammatory-syndrome-temporally- associated-covid-19.
6. Royal College of Paediatrics and Child Health (RCPCH). COVID-19 - guidance for management of children admitted to hospital. Available from: https://www.rcpch.ac.uk/resources/covid-19-guidance-management-children-admitted-hospital
7. Pediatric acute respiratory distress syndrome: consensus recommendations from the Pediatric Acute Lung Injury Consensus Conference. Pediatr Crit Care Med. 2015 Jun; 16(5):428-39
8. McArdle AJ, Vito O, Patel H et al. Treatment of Multisystem Inflammatory Syndrome in Children. New England Journal of Medicine. 2021 Jun 16.
9. Acute Inflammatory Vasculitis working group and the Paediatric Active Enhanced Disease Surveillance (PAEDS) network. Advice for clinicians: Paediatric Inflammatory Multisystem Syndrome Temporally associated with SARS-COV-2 (PIMS-TS). Available from: https://www.ncirs.org.au/sites/default/files/2020-06/PIMS-TS%20statement_Final_June%202020.docx.pdf
10. Schlapbach et al. Best Practice Recommendations for the Diagnosis and Management of Children With Pediatric Inflammatory Multisystem Syndrome Temporally Associated With SARS-CoV-2 (PIMS-TS; Multisystem Inflammatory Syndrome in Children, MIS-C) in Switzerland. Front. Pediatr., 26 May 2021 | https://doi.org/10.3389/fped.2021.667507
11. Consensus-based clinical recommendations and research priorities for anticoagulant thromboprophylaxis in children hospitalised for COVID-19-related illness. Goldenberg et al. J Thombosis and Haemostasis. 28th Aug 2020.


## Guideline revision and approval history

| Version No. | Modified by | Amendments authorised by | Approved by |
|---|---|---|---|
| 1.0<br>05/10/2021 | PICU SMO<br>IMPS Director<br>Paediatric Infection Specialist<br>Clinical Pharmacist Lead - AMS | Director PICU | Divisional Director Critical Care |

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|---|---|
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| **Accreditation references** | NSQHS Standards (1-8): 1,3,7& 8<br>ISO 9001:2015 Quality Management Systems: (4-10): 8.1 & 8.5 |

## Appendix 1: PIMS-TS Investigation List

- FBC and Film
- Chem20
- Glucose
- Blood gas with lactate
- Coagulation + fibrinogen
- D-Dimer
- LDH
- CRP
- Triglycerides
- Ferritin
- Troponin
- Pro-BNP
- CK
- Vitamin D
- Amylase
- Urinalysis for protein
- Save EDTA and serum for PCR and serological studies (pre IVIG)
- Blood / Urine and stool / Throat swab culture
- NPA or throat swab for respiratory panel plus SARS-CoV-2 PCR
- Pneumococcal, Meningococcal, Blood PCR
- ASOT
- SARS-CoV-2 serology
- EBV, CMV, Adenovirus, Enterovirus PCR on blood
- Stool for bacterial and viral PCR
- *HBV/HCV/HIV and QTG before anti-cytokine therapy*
- CXR, ECG, abdominal Ultrasound, ECHO.

# Appendix 2: Comparison of the case definitions and terms

| Comparison of the case definitions and terms for an emerging inflammatory condition during the COVID-19 pandemic | | | | |
|---|---|---|---|---|
| **Differences** | **RCPCH** | **CDC** | **WHO** | **CPSP** |
| Name | PIMS-temporally associated with COVID-19 | Multisystem inflammatory syndrome in children (MIS-C) | MIS-C | PIMS-temporally associated with COVID-19 |
| Length of fever | Not specified | ≥24 h | ≥3 days | ≥3 days |
| Age | Child | <21 years | 0 to 19 years | <18 years |
| Evidence of inflammation | Yes | Yes | Yes | Yes |
| Multisystem | Single organ or multisystem | ≥2 systems involved | ≥2 systems involved | Not specified, but implied |
| Exclude other causes | Yes | Yes | Yes | Yes |
| SARS-CoV-2-PCR or antibody or exposure | Not necessary | Necessary | Necessary | Necessary |

CDC - Centers for Disease Control and Prevention; COVID-19 coronavirus disease 2019;
CPSP - Canadian Paediatric Surveillance Program;
PIMS - paediatric multisystem inflammatory syndrome;
RCPCH - Royal College of Paediatrics and Child Health;
SARS-CoV-2-PCR - severe acute respiratory syndrome coronavirus 2 polymerase chain reaction;
WHO - World Health Organization.

# Appendix 3: Additional features suggestive of PIMS-TS

| Clinical | Imaging-ECG | Laboratory |
|---|---|---|
| Persistent fever>38.5 C<br>Oxygen requirement<br>Hypotension<br>Abdominal pain<br>Confusion<br>Conjunctivitis<br>Cough<br>Diarrhoea<br>Headache<br>Lymphadenopathy<br>Mucus membrane changes<br>Neck swelling<br>Rash<br>Respiratory symptoms<br>Sore throat<br>Swollen hands and feet<br>Syncope<br>Vomiting | Echo and ECG – myocarditis, valvulitis, pericardial effusion, coronary artery dilatation<br>CXR – patchy symmetrical infiltrates, pleural effusion<br>Abdo USS – colitis, ileitis, lymphadenopathy, ascites, hepatosplenomegaly<br>CT chest – as for CXR – may demonstrate coronary artery abnormalities if with contrast | Abnormal Fibrinogen Absence of potential causative organisms (other than SARS-CoV-2)<br>High CRP<br>High D-Dimers<br>High ferritin<br>Hypoalbuminaemia<br>Lymphopenia<br>Neutrophilia in most<br>Acute kidney injury<br>Anaemia<br>Coagulopathy<br>High IL-10<br>High IL-6<br>Neutrophilia<br>Proteinuria<br>Raised CK<br>Raised LDH<br>Raised triglycerides<br>Raised troponin<br>Thrombocytopenia<br>Transaminitis |

# Appendix 4: PIMS-TS Diagnostic and Treatment Pathway