Paediatric Inflammatory Multisystem Syndrome Temporally Associated with COVID-19

**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).
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

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

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/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 arrhythmias 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

- 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


Guideline revision and approval history

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<th>Amendments authorised by</th>
<th>Approved by</th>
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<td>Divisional Director Critical Care</td>
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Keywords
COVID-19, coronavirus, PIMS-TS, Paediatric Multisystem Inflammatory Syndrome Temporally Associated with COVID-19, SARS-CoV-19 PCR, 63400

Accreditation references
NSQHS Standards (1-8): 1,3,7& 8
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

<table>
<thead>
<tr>
<th>Differences</th>
<th>RCPCH</th>
<th>CDC</th>
<th>WHO</th>
<th>CPSP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name</td>
<td>PIMS-temporally associated with COVID-19</td>
<td>Multisystem inflammatory syndrome in children (MIS-C)</td>
<td>MIS-C</td>
<td>PIMS-temporally associated with COVID-19</td>
</tr>
<tr>
<td>Length of fever</td>
<td>Not specified</td>
<td>≥24 h</td>
<td>≥3 days</td>
<td>≥3 days</td>
</tr>
<tr>
<td>Age</td>
<td>Child</td>
<td>&lt;21 years</td>
<td>0 to 19 years</td>
<td>&lt;18 years</td>
</tr>
<tr>
<td>Evidence of inflammation</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Multisystem</td>
<td>Single organ or multisystem</td>
<td>≥2 systems involved</td>
<td>≥2 systems involved</td>
<td>Not specified, but implied</td>
</tr>
<tr>
<td>Exclude other causes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>SARS-CoV-2-PCR or antibody or exposure</td>
<td>Not necessary</td>
<td>Necessary</td>
<td>Necessary</td>
<td>Necessary</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Clinical</th>
<th>Imaging-ECG</th>
<th>Laboratory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Persistent fever&gt;38.5 C</td>
<td>Echo and ECG – myocarditis, valvulitis, pericardial effusion, coronary artery dilatation</td>
<td>Abnormal Fibrinogen Absence of potential causative organisms (other than SARS-CoV-2)</td>
</tr>
<tr>
<td>Oxygen requirement</td>
<td>CXR – patchy symmetrical infiltrates, pleural effusion</td>
<td>High CRP</td>
</tr>
<tr>
<td>Hypotension</td>
<td>Abdo USS – colitis, ileitis, lymphadenopathy, ascites, hepatosplenomegaly</td>
<td>High D-Dimers</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>CT chest – as for CXR – may demonstrate coronary artery abnormalities if with contrast</td>
<td>High ferritin</td>
</tr>
<tr>
<td>Confusion</td>
<td></td>
<td>Hypoalbuminaemia</td>
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<tr>
<td>Conjunctivitis</td>
<td></td>
<td>Lymphopenia</td>
</tr>
<tr>
<td>Cough</td>
<td></td>
<td>Neutrophilia in most</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td></td>
<td>Acute kidney injury</td>
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<tr>
<td>Headache</td>
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<td>Anaemia</td>
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<tr>
<td>Lymphadenopathy</td>
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<td>Coagulopathy</td>
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<tr>
<td>Mucus membrane changes</td>
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<td>High IL-10</td>
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<tr>
<td>Neck swelling</td>
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<td>High IL-6</td>
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<tr>
<td>Rash</td>
<td></td>
<td>Neutrophilia</td>
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<tr>
<td>Respiratory symptoms</td>
<td></td>
<td>Proteinuria</td>
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<tr>
<td>Sore throat</td>
<td></td>
<td>Raised CK</td>
</tr>
<tr>
<td>Swollen hands and feet</td>
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<td>Raised LDH</td>
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<tr>
<td>Syncope</td>
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<td>Raised triglycerides</td>
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<tr>
<td>Vomiting</td>
<td></td>
<td>Raised troponin</td>
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<td></td>
<td></td>
<td>Thrombocytopenia</td>
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<td>Transaminitis</td>
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Appendix 4: PIMS-TS Diagnostic and Treatment Pathway

Evaluation for Possible PIMS-TS

Consider and Investigate alternate diagnoses: sepsis, toxic shock, bacterial enteritis, appendicitis, viral infection (adenovirus, EBV, CMV), Kawasaki Disease (KD), HLH/MAS, drug reactions (Appx 1, 3)

First Line Treatment based on most likely Phenotype

Shock (requirement for fluid boluses / inotropes / raised lactate / prolonged capillary refill)

Features of complete KD with or without cardiac involvement

Other undefined Inflammation (GI, neuro, renal, other including incomplete KD)

PIMS-TS shock
Admission to PICU
Perform and collate Investigations (Appendix 1)
MDT support

Resuscitate as per ABC
Antibiotics as per Sepsis guideline
Cefotaxime plus Lincomycin (or Clindamycin) IV

• IVIG 2 gram/kg
• Methylprednisolone (MP) 10 mg/kg IV once daily (Maximum 1000 mg/day) for 3 days and then Prednisolone oral/enteral 2 mg/kg once daily /day (maximum 60 mg/day). Reduce dose every 3-5 days over a total of 2-3 weeks (discuss wean in MDT).
• Oral Aspirin 3-5mg/kg/day (Max 100mg) when platelets > 80
• LMWH as per Haematologist
• Compression stockings if >12yrs
• Proton pump inhibitor

No clinical improvement 24 hours after first IVIG and MP

MDT consider:
• Infliximab 5 mg/kg IV as a single dose

If no improvement or deterioration, consider:
• Anakinra 2 mg/kg/dose (max 100 mg/dose) SC 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

No clinical improvement 24 hours after first IVIG +/- MP

MDT consider:
• Methylprednisolone 10 mg/kg IV once daily (Maximum 1000 mg/day) for 3 days, followed by oral/enteral prednisolone 2 mg/kg once daily (maximum 60 mg/day) and wean as directed.
• Second dose IVIG 2 gram/kg
• Infliximab IV or Anakinra SC

Kawasaki like PIMS-TS
Perform and collate Investigations (Appx 1)
Treat as per KD

• IVIG 2 gram/kg
• Oral Aspirin 3-5mg/kg/day (Max 100mg) when platelets > 80
• Consider LMWH as per Haematologist

Consider in High risk KD: Methylprednisolone IV 2mg/kg (Max 200mg/day) for 3 days or until CRP normalizes, followed by prednisolone oral/enteral 2mg/kg (max 60 mg/day) weaning over 2 weeks.

MDT discussion
• IVIG 2 gram/kg
• Oral Aspirin 3-5mg/kg/day (Max 100mg) when platelets > 80
• Consider LMWH as per Haematologist

Consider with IVIG or alone: Methylprednisolone 2 mg/kg (Max 200mg/day) IV for 3 days or until CRP normalizes, followed by prednisolone oral/enteral 2mg/kg (max 60 mg/day) weaning over 2 weeks.

PIMS-TS undefined inflammatory
Perform and collate Investigations (Appendix 1)

No clinical improvement 24 hours after first IVIG and MP

MDT consider:
• Methylprednisolone 10 mg/kg IV once daily (Maximum 1000 mg/day) for 3 days, followed by oral/enteral prednisolone 2 mg/kg once daily (maximum 60 mg/day) and wean as directed.
• Second dose IVIG 2 gram/kg
• Infliximab IV or Anakinra SC