PIMS-TS- SGH
Guideline for the management of paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2

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<td>Primary Author(s): S. Drysdale (PID), D. Sangaran (PICU), S. Manna (PICU), E. Bolton (Pharmacy), A. Thomas (Haematology)</td>
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Paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS)

**Management flowcharts:**

NB: The full guide is below

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**Case definition (WHO):**

- Any child <19 years old

**AND**

- Evidence of hyperinflammation:
  - a. Fever >38°C for ≥3 days **AND**
  - b. Raised inflammatory markers (CRP, ESR, procalcitonin) (e.g. CRP >50 mg/L) **AND**
  - c. Two or more of the following:
    - i. Rash or bilateral non-purulent conjunctivitis or muco-cutaneous inflammation signs (oral, hands or feet)
    - ii. Hypotension or shock
    - iii. Features of myocardial dysfunction, pericarditis, valvulitis, or coronary abnormalities (including echo findings or elevated Troponin/NT-proBNP)
    - iv. Evidence of coagulopathy (by PT, PTT, elevated d-Dimers).
    - v. Acute gastrointestinal problems (diarrhoea, vomiting, or abdominal pain).

**AND**

- 3. No other obvious microbial cause of inflammation, including bacterial sepsis, staphylococcal or streptococcal shock syndromes.

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**Initial assessment Paediatric Red ED (PPE following Trust recommendations):**

- ABCD
- Initial investigations (see below)
- Immediate management:
  - Careful fluid resuscitation
  - Ceftriaxone (add Clindamycin if shock present)
- ED to contact: PID consultant on call, PICU SpR and General paed consultant

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**Critical thinking:**

**Child with fever ≥3 days and clinical signs / symptoms of:**

- Cardiac involvement including hypotension or shock
- Gastrointestinal symptoms (diarrhoea, vomiting, or abdominal pain)
- Neurological symptoms
- Rash / mucosal changes
- Oedema of hands / feet
- Bilateral conjunctivitis

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**Initial bloods:**

- FBC and film
- Blood gas with lactate
- CRP, Procalcitonin
- U+E, bone profile, LFTs, LDH
- Ferritin, lipid profile.
- Clotting including D-dimers + fibrinogen
- Troponin, NT-ProBNP, CK
- Vitamin D
- Save serum (pre IVIG administration)
- ANA, ASOT

**Imaging:**

- Chest x-ray
- ECG (+ echo if PIMS-TS likely- see note 1)
- Abdominal US depending on symptoms

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**Microbiology:**

- Blood and urine culture
- SARS-COV-2 PCR (respiratory) and serology.
- Throat swab (bacterial)

**Based on symptoms/signs:**

- Viral PCR in blood enterovirus, CMV, EBV, adenovirus).
- Pneumococcal, Meningococcal Blood PCR
- Viral PCR respiratory extended panel (prior discussion with PID/Micro)
- Viral PCR in stools

Consider recruiting to any research studies if appropriate (DIAMONDS, GENOMICCS)

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If patient haemodynamically stable:
- 1st line: Human IV immunoglobulin (IVIG) (dosing below) as soon as possible. Patients with cardiovascular instability may deteriorate suddenly and should be monitored closely.
- 2nd line if no improvement/deteriorates after 1st line treatment: IV methylprednisolone (dosing below)*

If patient shocked / signs fluid overload:
- Referral to PICU
- Consider discussion and referral to ELCH/GOSH if enhanced cardiac management is needed
- IV methylprednisolone (dosing below)*
- Request IVIG (dosing below) and commence as soon as available (only in PICU)

Patients can still be recruited to RECOVERY even if received IVIG and/or methylprednisolone

- Re-evaluate antibiotics in 48 hrs
- Further specialist therapies (including Biologics) should only be used following agreement in MDT (Evelina have a PIMS-TS daily (including weekends) at 11am via Bluejeans videoconferencing system)
**Case definition (from WHO):**

- Any child <19 years old

AND

- Evidence of hyperinflammation:
  
  a. Fever >38 °C for ≥3 days **AND**
  
  b. Raised inflammatory markers (CRP, ESR, procalcitonin) (e.g. CRP >50 mg/L) **AND**
  
  c. Two or more of the following:
     
    i. Rash or bilateral non-purulent conjunctivitis or muco-cutaneous inflammation signs (oral, hands or feet)
    
    ii. Hypotension or shock
    
    iii. Features of myocardial dysfunction, pericarditis, valvulitis, or coronary abnormalities (including echo findings or elevated Troponin/NT-proBNP)
    
    iv. Evidence of coagulopathy (by PT, PTT, elevated d-Dimers).
    
    v. Acute gastrointestinal problems (diarrhoea, vomiting, or abdominal pain).

AND

3. No other obvious microbial cause of inflammation, including bacterial sepsis, staphylococcal or streptococcal shock syndromes.

AND

4. Evidence of COVID-19 (RT-PCR, antigen test or serology positive), or likely contact with person with COVID-19.

**History taking:**

Need to consider non-COVID related disease presentations too. Ask about:

- Unwell contacts
- Known/suspected COVID contacts
- Previous recent illnesses
- Recent injuries/ wounds: need to consider NAI as differential
- Any documented travel in last 6 months
- Comorbidities including overgrowth, obesity

**Presenting features** can include:

- Rash
- Abdominal pain
- Diarrhoea
- Conjunctivitis
- Headache
- Meningism
- Cough
- SOB
- Syncope
- Lymphadenopathy
- Sore throat
- Shock
- Hypoxia
- Oedema
- Fever
- Confusion
Initial Medical Management and Considerations:
- ABCDE management of presenting situation
  - Call for senior help as soon as you need
- Early and close cardiorespiratory management: use cardiac monitor at presentation
- Early referral to PICU for supportive management
- Early referral to PID for treatment specific management
- Is this a primary infection or is there secondary infection?
  - Differentials include sepsis and toxin mediated disease.
- Remember to wear appropriate PPE as per trust guidance
- If patient is initially well enough for ward will need ongoing daily PID and PICU involvement
  - Admission to PICU will be based on evolving single or multi organ failure requiring HDU level or greater support. This will need to be discussed with the PICU consultant on call

Types of presentation/ Potential pitfalls:
- Myocarditis
- Arrhythmias
- Renal impairment
- Coronary artery aneurysms
- Pulmonary embolus / cerebral infarcts
- Toxic shock like syndrome leading to gross vasoplegia
- Underestimation of gastrointestinal symptoms – check for splenomegaly and/or hepatomegaly
- Macrophage activation syndrome (MAS) / Haemophagocytic lymphohistiocytosis (HLH)
  - Can use http://saintantoine.aphp.fr/score/ to determine H score for HLH

Investigations
Swabs:
- SARS-CoV-2 throat swab in ED/Ward/PICU
  - On PICU:
    - consider deep ETT secretions (NB risks of aerosol generation) for SARS-CoV-2
  - Discuss need for alternative viral swabs and BAL for MC+S

Bloods:
- FBC – look specifically at platelet numbers and for lymphopenia, low/ falling Hb
- CRP (>50 mg/L)
- Procalcitonin will be useful in monitoring treatment response to treatment
- U+E - may present with AKI
- Bone profile – need to ensure normal Na, K, Ca and Mg levels to prevent arrhythmias and further cardiac abnormalities.
- LFT, LDH - useful in monitoring response to treatment, likely to be raised initially as part of hyperinflammation.
- Troponin, NT-ProBNP - can present with myocarditis, potential cardiac failure
- Clotting including D-dimers – looking for raise in d-dimer and fibrinogen, potentially hypercoagulable and high risk of thrombosis (PE/Stroke)
- Blood culture
- Viral PCRs inc EBV, CMV, Adenovirus
- Save serum (pre IVIG administration)
- HLH / MAS panel: include ferritin (> 800), lipid profile, triglycerides, fibrinogen – potential crossover between multisystem hyperinflammatory syndromes
- ANA / ANCA
- CK
- Vitamin D
Other:
- Urine MC+S
- CXR – looking at lung fields (consider COVID and non-COVID changes) but also cardiothoracic size
- ECG – strain patterns
- ECHO – look for cardiac function and coronaries – brightness and size.
- Abdominal USS – if GI symptoms: looking for intra-abdominal inflammation, quality and size of liver and spleen

Management:
- Supportive treatment as required
  - High potential to deteriorate – ongoing conversation with PICU about best place to manage these patients
  - On Ward will need HDU level management – continuous \( \text{O}_2 \) sats and cardiac monitoring with hourly BP. For early escalation of supportive management. Be wary of fluid overload with strict input / output charts and daily weights where possible
- All patients should receive aspirin (dosing below) and thromboprophylaxis (dosing below)
- Follow flowchart above with regards to IVIG, methylprednisolone and biologics.
- Discuss all treatment from admission with PID team. Call PID consultant (on call) via switchboard. PICU consultant to be involved in all discussion re: management of patient, including escalation of treatment or futility of offering treatment.
  - PID and PICU to decide on clinical trial inclusions e.g. RECOVERY trial, DIAMONDS study, GenOMICCS study.
- On PICU
  - **Respiratory** support as required. If oxygenation and ARDS an ongoing problem, then consider early referral to ECMO centre.
  - **Cardiac** - will need support for potential vasoplegia including fluids and pressors. Use of inodilator e.g. milrinone as allowed. Low threshold for considering myocarditis and concerns about subsequent cardiac failure +/- arrhythmias.
  - **Cardiac complications include:**
    - Decreased myocardial contractility:
    - Pericardial effusion
    - Coronary arteries affected (dilatation/aneurysm)
    - Mitral or aortic valve insufficiency
    - Myocardial ischemia / infarction
  - Be aware of ECG changes including:
    - Prolonged PR interval
    - Prolonged QT interval
    - Low voltage complexes
    - Abnormal Q wave
    - ST or T wave changes
    - Initial daily echo and low threshold for referring to tertiary cardiac centre for remote support.
    - Low threshold for early referral for ECMO for myocardial failure +/- vasoplegic shock
  - **Renal** – early use of CRRT in AKI. For judicious fluid management in view of potential ARDS and cardiac failure. Care with venous clots with central lines and vascaths in hypercoaguable state.
  - **Thromboprophylaxis** (dosing below)– should be used routinely in patients with suspected / proven hyperinflammatory syndrome unless there are exclusion criteria (**PID/PICU consultant to discuss with haematology if ANY exclusion criteria**).
  - **Feeding** - enteral if appropriate, may need to consider PN.
- **Neurology** - sedation levels +/- paralysis will depend on clinical condition of patient. Low threshold for neuroimaging if clinical concerns. Infarcts and haemorrhages will be a contraindication for ECLS.
- **Monitoring** - regular neurological assessment, daily bloods including those for monitoring hyperinflammation, checking for rashes, new bruising, daily assessment of organomegaly

**Follow up:**
- All patients with PIMS-TS need to be referred to the Evelina London Children’s Hospital (ELCH) for ongoing cardiac review after discharge from St George’s:
  - Complete a cardiology referral to the RAS cardiology clinic (use the form and e-mail for urgent referrals) available at: https://www.evelinalondon.nhs.uk/our-services/hospital/heart-services/referrals.aspx
  - Also e-mail a discharge/referral letter to the PIID secretary Lee Makin (Lee.makin@gstt.nhs.uk), and cc Jenny Handforth, PIID consultant (Jennifer.handforth@gstt.nhs.uk)
- Some children may have an earlier review at SGH as a ward attendant on Pinckney ward (e.g. if need further monitoring of blood tests, etc).
- Aspirin should be continued for 6 week or at least until seen at ELCH.

**MEDICATIONS**

For patients on multiple medications, discuss with pharmacy and check for interactions http://www.covid19-druginteractions.org

1. **Immune Modulation Therapy**

**Monitoring:** For all medications: baseline FBC, ESR, CRP, U&Es and LFTs

**BMI Ideal body weight methodology:**
The equation for BMI can be used in reverse to determine IBW: \[ IBW = \frac{BMI}{50} \times (\text{height in m})^2 \]
where BMI50 represents the 50th centile of a BMI chart, which is the ideal BMI for height, age and gender. BMI charts are available from: https://www.rcpch.ac.uk/resources/body-mass-index-bmi-chart

**Example:**
A 7 year old girl who is 1.2m tall
BMI50 = 15.6kg/m² (using Girls UK BMI 2-20 years chart)
IBW = BMI50 x (height in m)² = 15.6 x 1.2 x 1.2 = 22.5kg
*The 7 year old girl’s IBW is 15.6kg/m² x 1.2m² = 22.5kg*

- **HUMAN IV IMMUNOGLOBULIN (IVIG)**
  - **Dose:** 2g/kg - usually a single dose infusion, may be repeated according to clinical status. Use BMI ideal body weight to calculate the dose using methodology stated above. Doses are rounded to the nearest vial size (within 10% of the total dose) (vial sizes are 5g, 10g and 20g). If the child is at risk of cardiovascular instability and/or fluid overload consider:
    - dose reduction
    - cautious use of furosemide
    - or consider Methylprednisolone instead
  - **Common side effects:** Flushing, hypo/hypertension, possible fever, dizziness and GI disturbances – usually rate related. **Action required:** stop the infusion, do not disconnect the line. Monitor the patient and restart at the previous rate and continue at this rate (do not increase the rate again).
If symptoms worsen or patients show signs of anaphylaxis **STOP infusion and obtain immediate medical review.**

b) **METHYLPREDNISOLONE IV**

**Dose:** Day 1-3: Depending on severity: 10mg/kg OD (max 1 gram)
Consider 2 additional days of corticosteroids depending on severity after MDT discussion. Aim to adjust to morning dosing as soon as possible as interferes with sleep.
No weaning regime is required routinely if treatment duration does not exceed 5 days.
Ensure gastro-protection with omeprazole.

**Common side effects:** Light-headed, dizzy, nauseous, or has increasing headache. **Action required:** check TPR and BP and consider slowing or stopping the infusion. Inform the medical team.

**Common mild side effects** not requiring intervention: facial flushing, metallic taste, hyperactivity, mood changes.

c) **BIOLOGICS**

For biologics (e.g. Tocilizumab): baseline HIV, Hepatitis B+C, Quantiferon and CXR should be done. These tests must be requested and samples sent prior to initiation of treatment. However, treatment may be commenced prior to results being available due to urgency of the clinical indication

**Only use after discussion in MDT (Evelina PIMS-TS MDT is daily, including weekends, at 11am via Bluejeans videoconferencing).**

2. **Other Co-Medication**

a) **ASPIRIN**

**Dose:**
-PO/NG: 5mg/kg once daily (max dose 75mg), for a min of 6 weeks and until echocardiogram normal

All patients should be treated with aspirin (unless contra-indications) and continue until outpatient follow up. Continue in patients who are also on Dalteparin.

b) **DALTEPARIN**

Thromboprophylaxis should be used routinely in all patients with suspected / proven PIMS-TS and continued until discharge, unless there are exclusion criteria (see below). Children with a protracted disease course and ongoing risk factors for thrombosis may be recommended to continue thromboprophylaxis for 7-14 days at home, dependent on speed of recovery.

Children under 5 years of age who are active and whose presentation is more akin to Kawasaki Disease do not need dalteparin routinely.

Exclusion criteria (if any present, PID/PICU consultant to discuss with haematology):

- Platelet count <50 x 10^9/L
- Fibrinogen < 1.5 g/L
- APTT ratio and/or INR (PT) >2.0
- Significant abnormal renal function (e.g. creatinine clearance <30 ml/min)
- If a patient has any acute / active bleed - defined as:
  - otherwise unexplained drop in [Hb] ≥20g/L AND / OR
• otherwise unexplained haemodynamic instability AND / OR
• obvious macroscopic haemorrhage e.g. frank blood via nose, mouth, nasogastric tube or per rectum

  o If the patient has a suspected OR proven arterial OR venous thrombosis- discuss with haematology regarding therapeutic anticoagulation

Dosing:

-If child being admitted to general paediatric ward:

  Thromboprophylaxis (standard dose):
  
  o ≥12 years old AND 25-100kg: Dalteparin 5000 units SC OD
  o ≥12 years AND >100kg: Dalteparin 5000 units SC BD
  o ≥12 years old AND <25kg: Dalteparin 2500 units SC OD
  o <12 years old: Dalteparin 100 units / kg (max dose 5000 units) SC OD
  o (NB: in children <5 years old dalteparin is not routinely prescribed)

If child being admitted to PICU:

  • Continue thromboprophylaxis

  • Some patients may benefit from enhanced dose thromboprophylaxis (see dosing information below) taking into account:

    • Degree of organ failure (e.g. respiratory, cardiac, renal)

    • Concomitant factors that may increase bleeding risk (e.g. dosage of concomitant aspirin)

    • Consideration should be given to the adoption of adult protocols, particularly in patients 16-18 years old

  • Consider therapeutic anticoagulation in children with impaired systolic function on echocardiography (provisionally FS<25%)

    • Choice of heparin will be determined by clinical context and PICU consultant, taking into account renal function, evidence of multi organ failure and if there is need to consider surgical/ interventional input e.g. cardiac catheter or thrombectomy.

  • Contraindications will include:

    • Pulmonary haemorrhage

    • GI bleed

    • Intracranial bleed

  • Thromboprophylaxis (enhanced dose):

    • ≥12 years old AND <50kg: Dalteparin 100 units/kg (max 5000 units) SC BD

    • ≥12 years old AND 50 -100kg: Dalteparin 5000 units SC BD

    • ≥12 years old AND >100kg: Dalteparin 7,500 units SC BD

    • <12 years old: Dalteparin 100 units/kg (max 5000 units) SC BD
• (NB: in children <5 years old dalteparin is not routinely prescribed)

If the patient experiences a thrombotic event, contact the paediatric haematology team.

c) OMEPRAZOLE
Dose: PO/IV: dose as per BNFc
Note: Continue treatment while on aspirin and/or steroids

d) ANTIBIOTICS
Antibiotics should be commenced on all patients at presentation, in accordance with antibiotic guidelines for severe sepsis:
All patients: Ceftriaxone (cefotaxime in PICU) IV: as per formulary
Patients presenting with shock: Ceftriaxone (cefotaxime in PICU) (as above) and Clindamycin IV
dosing as per formulary

All antibiotic therapy should be reviewed at 48 hours; consider stopping if blood cultures negative
and no other evidence of ongoing bacterial infection.

References:

• Adapted from the Evelina Children's Hospital PIMS-TS pathway (v1, November 2020)
• BPAIIG guidance: https://www.bpaiig.org/sites/default/files/National_paediatric_COVID19%20treatment%20v1.2_0.pdf
• National treatment guidance (RCPCH) for COVID-19 is available at: https://www.bpaiig.org/sites/default/files/National_paediatric_COVID19%20treatment%20v1.2_0.pdf