PMIS-TS- SGH
Guideline for the management of Paediatric multisystem inflammatory syndrome temporally associated with COVID-19

Guideline Title	
Publication Date: 26/5/2020	Month Year: May 2020
Publication location: Online	SGH PICU Website: Yes
Review Date: 01/9/2020	Month Year: Sept 2020
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Paediatric multisystem inflammatory syndrome temporally associated with COVID-19 (PMIS-TS)

Quick guide:
NB: The full guide is below

Case definition (BPSU & WHO):

- Any child <18 years old, regardless of COVID-19 status
  AND
- Evidence of hyperinflammation:
  a. Fever >38 °C for ≥3 days **AND**
  b. CRP >100 mg/L **AND**
  c. One or more of the following:
    i. Cardiac involvement (any one of the following)
      - myocarditis/pericarditis/valvulitis OR
      - coronary artery involvement (echo) OR
      - cardiac failure/arrest.
    ii. Gastrointestinal involvement (any one of the following)
      - vomiting/diarrhoea OR
      - an acute abdomen OR
      - abnormal liver function (LFTs/clotting).
    iii. Respiratory failure (requiring any one of the following)
      - high flow and humidified oxygen (HFHO) OR
      - CPAP OR
      - ventilation.
    iv. Raised Ferritin (>500 µg/L) +/- Raised D-dimers (>2x upper limit of normal)

AND

3. No pathogen (except SARS-CoV-2) or diagnosis (e.g. confirmed appendicitis) identified.

If does not meet case definition:
-Manage as per standard clinical practice.

If being discharged:
-Advise parents low threshold to represent if symptoms continue.
-Email: PIDconsult@stgeorges.nhs.uk to organise telephone FU

Initial assessment **Paediatric Red ED** (PPE following Trust recommendations):
-ABCD
-Initial investigations (see below)
-Immediate management
- Careful fluid resuscitation
- Ceftriaxone +/- Clindamycin

-ED to contact: **PID consultant on call**, PICU SpR and General paeds consultant

To investigate **infectious cause** of this presentation:
1. Sepsis, staphylococcal/streptococcal toxic shock
2. Viral myocarditis

Notes:
1. During working hours contact PICU regarding on call paeds echo cover.
2. Consider the use of LMWH prophylaxis/treatment dose, after discussion with Haematology.

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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 and echo daily or if deterioration in inflammatory markers or clinical signs** (note 1)
- Abdominal US depending on symptoms

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 (viral panel including SARS-COV-2)

Consider recruiting to any research studies if appropriate

Scenario 1. Patient stable with no signs of cardiac involvement: Admission to **Pinckney ward & discuss with PID**:

- Close monitoring for any signs of deterioration
- Close monitoring of bloods: FBC, ferritin, CRP, PCT, ESR, LFTs, U+E, lipid profile, clotting including DD and troponin
- Consider use of IVIG and steroids
- Consider anticoagulation (aspirin/heparin)

Any patient in the ward to be reviewed by PICU if any concerns of clinical deterioration

Scenario 2. Patient unstable with one of more signs of organ failure or cardiac involvement:
Admission to PICU:

- Consider antiviral treatment (Consider enrolment in RECOVERY trial)
- Consider use of IVIG and steroids
- Consider anticoagulation (aspirin/heparin)
- Consider discussion and referral to ELCH/GOSH if enhanced cardiac management is required

Case definition (from RCPCH, BPSU and WHO):

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Considerations:

- Respiratory failure: increasing O_2, early or evolving ARDS. High suspicion of PE.
- Cardiovascular instability: requiring fluid boluses +/- inotropes, early signs of toxic shock syndrome
- Hyperinflammation: raised CRP > 100 mg/L, raised ferritin > 500 µg/L
- Gastrointestinal symptoms with features of shock: including gastroenteritis
- Neurological presentation: including confusion, meningism +/- cardiovascular instability

May present similarly to atypical Kawasaki or toxic shock syndrome, have a low threshold for consideration.

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
  - Use COVID intubation team on bleep 8011 and state paediatric COVID case
- 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
- Arrythmias
- Renal impairment
- Coronary artery aneurysms
- PE/ 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 consider risks of aerosol generation) for SARS-CoV-2
    - consider rectal swab for SARS-CoV-2
- Discuss need for alternative viral swabs and BAL for MC+S

Bloods:

Definitely required on admission and for monitoring:

- FBC – look specifically at platelet numbers and for lymphopenia, low/ falling Hb
- CRP (>100 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 arrythmias and further cardiac abnormalities.
- LFT, LDH - useful in monitoring response to treatment, likely to be raised initially as part of hyperinflammation.
- 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)

Consider on discussion with PICU / PID consultant. May be useful for diagnostics and monitoring:

- Troponin, NT-ProBNP - can present with myocarditis, potential cardiac failure
- 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 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

- On PICU
    - **Respiratory** support as required. Use COVID intubation team and escalate respiratory support as required. If oxygenation and ARDS an ongoing problem, then consider early referral to ECMO centre. Consider PE in differential diagnosis and management.

    - **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 re 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 cardiac tertiary centre for remote support.
            - Aim for first echo within 12hrs of admission
        - An echo rota for SGH PICU will be produced weekly, with external support from cardiology at RBH
        - If cardiac involvement suspected or confirmed, daily phone call to tertiary cardiology centre (ECH).
        - 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** – should be used routinely in patients with suspected / proven hyperinflammatory syndrome unless there are exclusion criteria **(discuss with haematology if ANY of these criteria are met):**

  - Exclusion criteria:
    - 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
    - If the patient has a suspected OR proven arterial OR venous thrombosis- discuss with haematology regarding therapeutic anticoagulation
  - Dosing

    If child being admitted to paediatric ward:

    Thromboprophylaxis (standard dose):
    - ≥12 years old AND 25-100kg: Dalteparin 5000 units SC OD
    - ≥12 years AND >100kg: Dalteparin 5000 units SC BD
    - ≥12 years old AND <25kg: Dalteparin 2500 units SC OD
    - <12 years old: Dalteparin 100 units / kg (max dose 5000 units) SC OD

    If child being admitted to PICU:
    - Continue thromboprophylaxis
    - Some patients may benefit from escalated dose thromboprophylaxis (see dosing information below) or therapeutic anticoagulation 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 echocardiogaraphy (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 (these should involve MDT discussion with PIC/ Haem and any other involved specialty):
  - Pulmonary haemorrhage
  - GI bleed
  - Intracranial bleed

Thromboprophylaxis (escalated dose):

- ≥12 years old AND <50kg: Dalteparin 100units/kg (max 5000 units) SC BD
- ≥12 years old AND 50 -100kg: Dalteparin 5000units SC BD
- ≥12 years old AND >100kg: Dalteparin 10,000 units SC BD
- <12 years old: Dalteparin 100 units/kg (max 5000 units) SC BD

- **On discharged from PICU to paediatric ward**: continue thromboprophylaxis- use dosing as above for paediatric ward patients or discuss with haematology.
- **On discharge from hospital:** Children discharged from hospital will usually be recommended to continue thromboprophylaxis for 7-14 days at home, dependent on speed of recovery. Discuss discharge planning with haematology.

- **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

Treatment:

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.

- Empirical antibiotic treatment –cefotaxime / ceftriaxone +/- clindamycin

- IVIG (2g/kg) treatment to be initiated early on PID agreement
- .DO NOT routinely prescribe aspirin- discuss with PID consultant if considering prescribing aspirin. Consider dipyridamole if significant gut involvement or renal failure.
    - If treating likely Kawasaki disease follow the aspirin dosing on Kawasaki guideline (high-dose aspirin [12.5mg/kg QDS, max 500mg/dose] followed by low dose aspirin [3-5mg/kg/day])
    - If treating hyperinflammatory syndrome: we would usually suggest low dose aspirin (3-5mg/kg/day) especially if using concomitant corticosteroid. In certain circumstance, high dose aspirin may be advised. **Please discuss all cases with PID consultant**.

- Consider high dose methylprednisolone (will need concomitant gastroprotection)
- PID to discuss and decide on antivirals
- PID to discuss and decide on further immunomodulatory therapy
    - May be dependent on ongoing evidence of hyperinflammation despite other treatments
    - PID and PICU to decide on clinical trial inclusions e.g. RECOVERY trial, DIAMONDS study, GenOMICCS study.
- 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

References:

- RCPCH guidance: https://www.rcpch.ac.uk/sites/default/files/2020-05/COVID-19-Paediatric-multisystem-%20inflammatory%20syndrome-20200501.pdf
- BPAIIG guidance: https://www.bpaiig.org/sites/default/files/National_paediatric_COVID19%20treatment%20v1.2_0.pdf
- STRS guidance: https://www.evelinalondon.nhs.uk/resources/our-services/hospital/south-thames-retrieval-service/pims-ts-paediatric-multisystem-inflammatory-syndrome-temporally-associated-with-sars-cov2.pdf