

Paediatric Inflammatory Multi-system Syndrome – temporally associated with SARS-CoV 2 (PIMS-TS): Critical Care guidance

A rapid dissemination summary report of a facilitated ‘knowledge sharing session’ between clinicians with collective experience of the critical care management of children with PIMS-TS.

The webinar, attended by 278 clinicians, was hosted on 7th May 2020 by the Paediatric Intensive Care Society (PICS). The session involved invited clinicians from Great Ormond Street Hospital, Evelina Children’s Hospital, Birmingham Children’s Hospital, and Nottingham Children’s Hospital.

This paper is not a clinical guideline. It summarises the knowledge, practice and experience discussed at the session, including an analysis of the web chat content, and these may change in this rapidly developing situation. It also highlights emerging unanswered questions where data sharing and research may help to inform clinical practice.

RCPC Case Definition ¹

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. 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.

All stable children should be discussed as soon as possible with specialist services (paediatric intensive care, paediatric infectious disease, cardiology, rheumatology/immunology), and there should be a low threshold for referral to Paediatric Intensive Care **through normal pathways**. Clinical, laboratory features, and list of initial investigations are set out in the [RCPC guidance](#)

General principles

1. The essential basis for the management of this condition remains high quality general paediatric intensive care.
2. The commonest presenting feature in critically ill children is shock. Other features include pyrexia and abdominal symptoms (pain, vomiting, diarrhoea). Respiratory failure is uncommon.
3. Blood tests reveal elevated markers of inflammation (CRP, ferritin) and abnormalities of coagulation (elevated D-dimers and fibrinogen). Troponin and BNP have been used to indicate degree of cardiac involvement.
4. Regular cardiac echocardiogram is recommended to track cardiac dysfunction and evolution of coronary artery abnormalities. Abdominal imaging may be valuable to exclude significant abdominal pathology.
5. A multidisciplinary team approach is encouraged to ensure treatment decisions are co-ordinated. This should engage colleagues from cardiology, infectious diseases, and rheumatology/immunology (depending on local circumstances). Transport team conference call facilities may assist with triage decisions at first presentation.
6. This is an emerging condition and uncertainty regards best treatment requires a need for engagement in national audit, service evaluation, observational and interventional clinical trials.

Fluids and inotropes	
SIRS response	<ul style="list-style-type: none"> • Vasodilated 'warm' shock, relatively refractory to fluid boluses, is a common feature. • Cardiac dysfunction may evolve rapidly and unexpectedly. • Cardiac output can be exquisitely sensitive to inotropes and fluids. • Great caution urged when moving patients as CVS instability reported.
Inotropes	<ul style="list-style-type: none"> • Common advice to referring hospitals to begin peripheral inotropes (e.g. dopamine and/or adrenaline). Noradrenaline, vasopressin may be needed once central access gained. • If evidence of cardiac dysfunction: adrenaline, milrinone, (levosimendan)
Coronary aneurysms	<ul style="list-style-type: none"> • Coronary aneurysms seen in some patients. Coronary artery 'brightness' appears a more common feature.
ECLS	<ul style="list-style-type: none"> • A few children (n=3) have required ECMO. Since progression of cardiac dysfunction can be rapid and unpredictable, early transfer to an ECMO centre should be considered. Refractory arrhythmia/shock are indications for VA ECMO. Caution: many patients are prothrombotic.
RRT	<ul style="list-style-type: none"> • Not required in great majority of patients.

Mechanical ventilation
1. Mechanical ventilation is required in about 60% patients, usually for support of cardiac output or to enable optimal conditions for line insertion.
2. Non-invasive ventilation and HFNC also used successfully.

Antibiotics and infection control
1. SARS-RT-PCR testing inconsistent. Serology commonly positive if done.
2. Full PPE advised pending results of SARS-CoV2 PCR testing, although full PPE may need to continue if clinical suspicion is high even if SARS-CoV-2 testing negative due to the risk of false negative test results.
3. Although evidence of viral/ bacterial co-infections is rare, antibiotics as per local guidelines should be started at presentation.

Immunomodulatory/ anticoagulation considerations
1. Risk of venous thrombosis (especially large vessels). Approach to anticoagulation (LMWH, high dose aspirin) very variable. Discuss with local haematology team.
2. Approach to immunomodulation (IVIg, steroids, anakinra, tocilizumab) very variable. Discuss with local MDT team.

Outcomes
Length of stay in PICU is generally short (3-4 days) and the great majority of patients survive.

Emerging questions for consideration:



- Whether this condition is unique from variant Kawasaki disease, SARS-CoV2 infection and other sepsis syndromes (to be part addressed through ongoing PICANet / BPSU surveillance)
- ‘Biology’ of the immune response and its association with SARS- Cov-2 disease. Essential to better understand approaches to:
 - Anticoagulation: Unit variation between use of high dose aspirin, alternative antiplatelet agents and prophylactic low molecular weight heparin.
 - Immunotherapy: Many patients presenting with Kawasaki’s disease phenotype are commonly given IVIG and steroids. Use of anakinra and tocilizumab is partly dependent on local MDT advice
 - Role of antiviral agents e.g. Remdesivir or Lopinivir-Ritonavir (to be partly addressed through trials e.g. RECOVERY).

References:

1. Guidance: Paediatric multisystem inflammatory syndrome temporally associated with COVID-19. Royal College of Paediatrics and Child Health.
<https://www.rcpch.ac.uk/sites/default/files/2020-05/COVID-19-Paediatric-multisystem-%20inflammatory%20syndrome-20200501.pdf>

Webinar hosts:

Dr. Padmanabhan Ramnarayan, PICS Honorary Secretary
Dr. James Fraser, PICS President

With thanks to our panel members:

Dr. Barney Scholefield, PICS-SG Chair, Consultant in Paediatric Intensive Care, Birmingham Women and Children’s Hospital NHS Foundation Trust
Dr. Jon Lillie, Consultant in Paediatric Intensive Care, Evelina London Children’s Hospital
Dr. Patrick Davies, Consultant in Paediatric Intensive Care, Nottingham Children’s Hospital
Dr. Harikrishnan, Consultant in Paediatric Intensive Care, Birmingham Women and Children’s Hospital NHS Foundation Trust
Drs Mae Johnson, Pascale du Pré and Nicholas Lanyon, Great Ormond Street Hospital NHS Foundation Trust

Upcoming Research:

The following is a list of current studies available for UK PICUs to consider for PIMS-TS

Study Name	Group	Full Title	Design/ Status/ Age	Link	Notes
NIHR & RCPCH LINK FOR PRIORITY STUDIES				https://www.nihr.ac.uk/covid-19/urgent-public-health-studies-covid-19.htm https://www.rcpch.ac.uk/resources/covid-19-data-collection	
BPSU	RCPCH	Surveillance of the Paediatric Inflammation and Multi-system syndrome patients	National Audit Active All children	https://www.rcpch.ac.uk/work-we-do/bpsu/study-multisystem-inflammatory-syndrome-kawasaki-disease-toxic-shock-syndrome	Our aim is to understand the incidence, presenting features, laboratory features, management, clinical course and the outcome of this potentially new syndrome characterised by hyperinflammation which is temporally associated with COVID-19
PICANET COVID19 custom audit	PICANET	COVID-19 real time reporting via PICANet	National Audit Active PICU Pts	https://www.picanet.org.uk/covid-19/	A custom audit is being developed to streamline COVID patient data collection from PICUs. Allows data from 1/1/2020 to be include.
ISARIC	WHO	ISARIC/WHO Clinical Characterisation Protocol for Severe Emerging Infections in the UK (CCP-UK)	Observational Active All Ages	https://isaric.tghn.org/	Acute respiratory illness patients of all ages with a history of fever or measured fever of >H1 AND at least one respiratory symptom - AND high suspicion or confirmed infection with a respiratory pathogen relevant to the objectives of this protocol - AND admitted to a healthcare facility
DIAMOND	Imperial/EU	Diagnosis and Management of Febrile Illness using RNA Personalised Molecular Signature Diagnosis. CPMS ID: 45537 IRAS ID: 278651	Observational Active PICU Pts	https://www.nihr.ac.uk/covid-studies/study-detail.htm?entryId=278651	Development of novel host RNA-based diagnostic devices that can diagnose COVID-19
GenOMICC	Edinburgh	Genetics Of Mortality In Critical Care	Observational Active All Ages	https://genomicc.org/	Including COVID-19 patients in addition to sepsis. Burns and severe respiratory disease. Centres can choose patient cohort to study (eg just COVID).

Interventional Clinical Trials Paediatrics and Adults

Study Name	Group	Full Title	Design/ Status/ Age	Link	Notes
RECOVERY	NIHR	RECOVERY: Randomised Evaluation of COVID-19 Therapy Comparison of existing HIV treatment (Lopinavir-Ritonavir) and antiinflammatory steroid (dexamethasone) in treating COVID-19.	RCT Active ALL AGES	https://www.recoverytrial.net/	Inclusion criteria – New protocol developed 5/5/2020 Opening to paediatric patients Note: 2 nd level randomisation to Tocilizumab – which may include PIMSTS patients.
REM-CAP	NIHR	A Randomised, Embedded, Multi-factorial, Adaptive Platform Trial for Community-Acquired Pneumonia	RCT Active >18yrs	https://www.remapcap.org/	Currently not open to paediatric patients, but this may change in the future.