West Midlands Guidance for the early recognition, investigation and management of the Paediatric Inflammatory Multisystem Syndrome - Temporally Associated with SARSCoV2 pandemic

Background:

The Royal College of Paediatrics and Child Health released a guidance on the 1st May 2020 warning that over the last few weeks there has been an apparent rise in the number of children presenting with an apparently new condition described as Paediatric Inflammatory Multisystem Syndrome - Temporally associated with SARSCoV2 pandemic. Despite the current COVID19 pandemic, most patients are testing negative for the SARS-CoV-2 virus using the rt-PCR on nasal and throat swabs. It is not clear what the number of children that might fit the above description within our hospital and region is. As of yet, there is no consensus on how this condition should be manged. This condition also overlaps with a wide differential including e.g. Kawasaki's Disease, other vasculitidies, Toxic Shock Syndrome, Haemophagocytic Lymphohistiocytosis, Malignancies, Myocarditis, or any other infection of viral or non-viral aetiology. Therefore, there is an urgent need to establish a protocol of management, with the RCPCH document at its heart, led by a multidisciplinary team until a better understanding of this new phenotype is established.

Scope:

This document refers to children who fulfil the case definition (Appendix 1) recently circulated by the RCPCH who are admitted or seen across Birmingham Women's and Children's Hospital NHS Foundation Trust or referred from other providers. Recognised patterns that require early referral for urgent management decisions are summarised in Appendix 2.

Aim:

This document aims to set out how BCH teams will facilitate the early identification of patients who may fulfil the case definition recently circulated by the RCPCH and facilitate an early MDT assessment to ensure equity of assessment and access to specialist assessment and treatment.

Underpinning principles:

1. This protocol does not replace the clinicians usual good practice, reasoning and clinical judgement.

2. Usual care pathways will still apply for patients who are not covered by the scope and aims of this document.
3. Patients presenting or admitted with a pyrexia of unknown origin, with or without personal or family history of confirmed or likely COVID19 infections need to be assessed against the case definition circulated by the RCPCH and the early referral cohorts defined by the BCH MDT. Appendix 1 and 2
4. Patients suspected to meet the case definition of PIMS-TS need to be fully investigated in line with the RCPCH investigation list on the day it is suspected. Appendix 4
5. Other diagnoses and investigations must still be performed as deemed necessary by the patient's team.
6. Other care pathways will still apply as per usual practice and must not be overlooked e.g. sepsis, cancer, vasculitis…etc.
7. A dedicated PIMS-TS BCH/West Midlands advisory group has been set up and is tasked with:
    a. Meet daily at a set time to discuss all suspected cases of PIMS-TS.
    b. Give advice to BCH and regional teams on diagnosis and management of PIMS-TS.
    c. Monitor and disseminate new information and link with national and international groups.
    d. Weekly update on patient numbers and outcomes.
    e. Facilitate the participation in research.
8. The dedicated PIMS-TS BCH/West Midlands advisory group is composed of:
    a. Paediatric Rheumatologist on service.
    b. Paediatric Cardiologist on service.
    c. Paediatric Infectious Diseases/Immunology specialist.
    d. Paediatrician on service. (NB children admitted to another hospital will be discussed with their local team)
    e. Paediatric intensivist for children admitted to PICU.
9. If required the PIMS-TS BCH/West Midlands advisory group will call on the expertise of:
    a. Paediatric intensivist for children on HDU or where there is concern that there is a clinical need to be admitted to PICU.
    b. KIDS consultant on service if the child is with another provider and there is a time critical need to transfer to PICU setting. NB children who do not have a time critical

need to be transfer may still need to be admitted on a tertiary referral basis without the need for KIDS referral.

c. Any other specialist depending on the systemic involvement

10. The meetings are organised and chaired by a clinician from silver command team at BCH
11. Referrals should be made as per the referral form below (Appendix 3) to rheumatology or cardiology depending on their presentations. The BCH team will in turn advise on the need for discussion with the PIMS-TS BCH/West Midlands advisory group and ensure the referring doctor has detail of zoom meeting.
12. The referring doctor should prepare the summary of the clinical phenotype a (Appendix 3) and investigation results (Appendix 4) to share during the zoom meeting.
13. The PIMS-TS BCH/West Midlands advisory group will recommend further investigations or the need for immunomodulatory treatment.

Plan of action:

Identifying patients:

1. Patients suspected with PIMS-TS who are retrieved by the KIDS team to PICU will be under the care of the most appropriate clinical team. Patients admitted to PICU from within BCH will remain under the care of their primary admitting team.
2. All patients should be discussed with the dedicated PIMS-TS BCH/West Midlands advisory group on daily basis initially.
3. Patients from outside BCH can be discussed at the PIMS-TS meeting (we strongly encourage the referral). Please highlight the features fulfilled in referral form (Appendix 3) and collate results as per Appendix 4. Please contact the meeting organiser who will share the zoom link to join the meeting at 3 pm that day if referred before 3 pm or 3 pm the following day.

Investigations:

4. The PIMS-TS BCH/West Midlands advisory group will oversee the completion of investigations as per the RCPCH document, agreed additional investigations by BCH (Appendix 4) as well as any necessary additional investigations required on case by case basis.

Patients referred for discussion from outside BCH out of hours:

1. Please follow normal care pathways that govern referrals to KIDS team where time critical transfers are required.
2. Non-time critical referrals will be processed as tertiary referrals if transfer to BCH is necessary.
3. Stable patients with predominantly cardiac manifestations should be referred to the cardiology consultant on service who will list the patient for discussion by the PIMS-TS BCH/West Midlands advisory group.
4. Stable PIMS-TS patients with an unexplained febrile illness should be referred to the rheumatology consultant on service who will list the patient for discussion by the MDT.

Management:

1. Suspect COVID19 and use appropriate PPE as per your local guidance.
2. Supportive care as per the normal care pathways remains the mainstay of management for all patients. There will be no deviation from normal care pathways where there is no clinical need.
3. Recommendations within the RCPCH document should be followed. Appendix 5
4. **The PIMS-TS BCH/West Midlands advisory group will discuss on case by case basis the need for additional treatment(s).**
5. The anticipated treatment decisions within the current standards of care pathways: (after exclusion of co-infection/sepsis)
    a. IVIG 2g/kg (possible repeat in 24-48 hours for poor responders): Required in Kawasaki's Disease (KD) predominant cases.
    b. In Kawasaki Disease phenotype: Aspirin 12.5mg/kg QDS (max dose 500mg) – anti-inflammatory dose (with PPI e.g. lansoprazole) until afebrile and inflammatory markers show improvement trend, then swap to anti-platelet dose of 2-5mg/kg (usually 75mg max) daily. **Avoid in patients with Platelet count <150 or if there is evidence of an acute kidney injury. Use alternative anti-platelet drug as per local guidelines.**
    c. Steroids: IV methylprednisolone 10mg / kg max 500mg up to 30mg/kg max 1g daily for 3 days (at discretion of rheumatologist). Indicated in IVIG resistant Kawasaki Disease, Immune complex mediated vasculitis and Macrophage Activation/ Haemophagocytic Lymphohistiocytosis Syndrome (MAS/HLHS)
    d. If MAS/HLHS diagnosed: Consider steroids and Tacrolimus as per standard of care.

6. The anticipated treatment decisions that are not currently covered by standards of care pathways: (Drugs and Therapeutics Committee application will be required)
    a. IVIG and steroid resistant KD: Consider Infliximab 1-2 doses. If fails, consider Anakinra, daily dose for 1-2 weeks.
    b. Steroids and Tacrolimus resistant MAS/HLHS: Consider Anakinra, daily dose for 2-4 weeks or Tocilizumab 1-2 doses.
7. Following Immunomodulatory treatment, monitor with:
    a. Echo/ECG as directed by the cardiologist on service.
    b. FBC, UE, LFT, LDH, CK, Clotting, D-Dimer, ESR, CRP, Troponin I, Ferritin and Triglycerides as directed by the rheumatologist.

Audit and research: (Appendix 7)

1. All patients presenting with the PIMS-TS phenotype must have 5ml EDTA and 5ml serum samples stored before receiving any immunomodulatory treatment.
2. All patients with the PIMS-TS phenotype should have the opportunity to be recruited to an appropriate research project available.
3. BCH will take active steps to open any relevant trials that may benefit patients or help better understand PIMS-TS.
4. BCH will support clinical and academic staff efforts to initiate research projects in collaborations with our partners in the region.
5. A database of all patients referred to the MDT has been set up on the cardiology database and will be analysed on weekly basis to inform short to medium term decision making.

Long-term surveillance:

While the disease process is new, and we cannot define the outcomes, it would be pragmatic that the children have a long term follow up to ensure that they are monitored.

1. The parallels that we have here are based on the surveillance for KD & LV functional assessment in patients at risk (family history, systemic-disease with associated cardiac involvement (e.g. neuro-muscular, post-chemo, etc.), and we would plan to set up a similar pathway for these children.
2. We would be led by national/international recommendations, but would set up a provisional regional programme.

MDT Development group

MDT member	Link person	Named Lead
Rheumatology	On service consultant (BCH switchboard 0121 333 9999)	Dr Eslam Al-Abadi
Cardiology	On service consultant (BCH switchboard 0121 333 9999)	Dr Ashish Chikermane
Infectious Disease	ID consultant at Heartlands (tel 0121 424 2000)	Dr Steve Welch
Critical Care (KIDS/PIC)	KIDS 03002001100 – or PIC Consultant	Dr Dave Ellis / Barney Scholefield / Zaf
General Paediatrics	On service consultant (BCH switchboard)	Dr Deepthi Jyothish
Chair of MDT	Medical Silver Adviser for Birmingham Women's and Children's	Contacted via email: bwc.covidmanagement@nhs.net marked for attention of Silver Adviser

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
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4. Tulloh RMR, Mayon-White R, Harnden A*, et al* Kawasaki disease: a prospective population survey in the UK and Ireland from 2013 to 2015 *Archives of Disease in Childhood* 2019;**104:**640-646.
5. Ramanan, A.V., 2017. I90. MACROPHAGE ACTIVATION SYNDROME: A REVIEW OF THE LITERATURE AND PRACTICAL APPROACH TO CLINICAL CASES. *Rheumatology*, *56*(suppl_2).

Appendix 1: RCPCH Guidance on case definition

Case definition:

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 (see listed in Appendix 1). 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 to ensure prompt treatment (paediatric infectious disease / cardiology / rheumatology*). There should be a low threshold for referral to Paediatric Intensive Care using normal pathways.

Clinical and laboratory features:

Clinical

All:

- Persistent fever >38.5°C

Most:

- Oxygen requirement
- Hypotension

Some:

- Abdominal pain
- Confusion
- Conjunctivitis
- Cough
- Diarrhoea
- Headache
- Lymphadenopathy
- Mucus membrane changes
- Neck swelling
- Rash
- Resp symptoms
- Sore throat
- Swollen hands and feet
- Syncope
- Vomiting

Laboratory

All:

- Abnormal Fibrinogen
- Absence of potential causative organisms (other than SARS-CoV-2)
- High CRP
- High D-Dimers
- High ferritin
- Hypoalbuminaemia
- Lymphopenia
- Neutrophilia in most – normal neutrophils in some

Some:

- Acute kidney injury
- Anaemia
- Coagulopathy
- High IL-10 (if available)*
- High IL-6 (if available)*
- Neutrophilia
- Proteinuria
- Raised CK
- Raised LDH
- Raised triglycerides
- Raised troponin
- Thrombocytopenia
- Transaminitis

*These assays are not widely available. CRP can be used as a surrogate marker for IL-6.

Imaging and ECG

- Echo and ECG – myocarditis, valvulitis, pericardial effusion, coronary artery dilatation
- CXR – patchy symmetrical infiltrates, pleural effusion
- Abdo USS – colitis, ileitis, lymphadenopathy, ascites, hepatosplenomegaly
- CT chest – as for CXR – may demonstrate coronary artery abnormalities if with contrast

QR code to RCPCH guidance

Appendix 2: Early referral criteria for urgent treatment decisions

Cardiovascular and Vasculitis spectrum:

1. Complete or incomplete Kawasaki's Disease
    a. who are in circulatory shock.
    b. with evidence of myocarditis or conductive abnormalities.
    c. who fail to respond to the first IVIG dose within 24hours.
    d. with significant gastrointestinal symptoms.
    e. with Central Nervous System features.
2. Complete or incomplete Kawasaki's Disease with low Platelets
3. Complete or incomplete Kawasaki's Disease in infants.
4. Non Kawasaki's Disease presentation with unexplained high inflammation markers &/or high or low platelets.

Hyperinflammation spectrum:

Fever >38 + Ferritin >500 with,

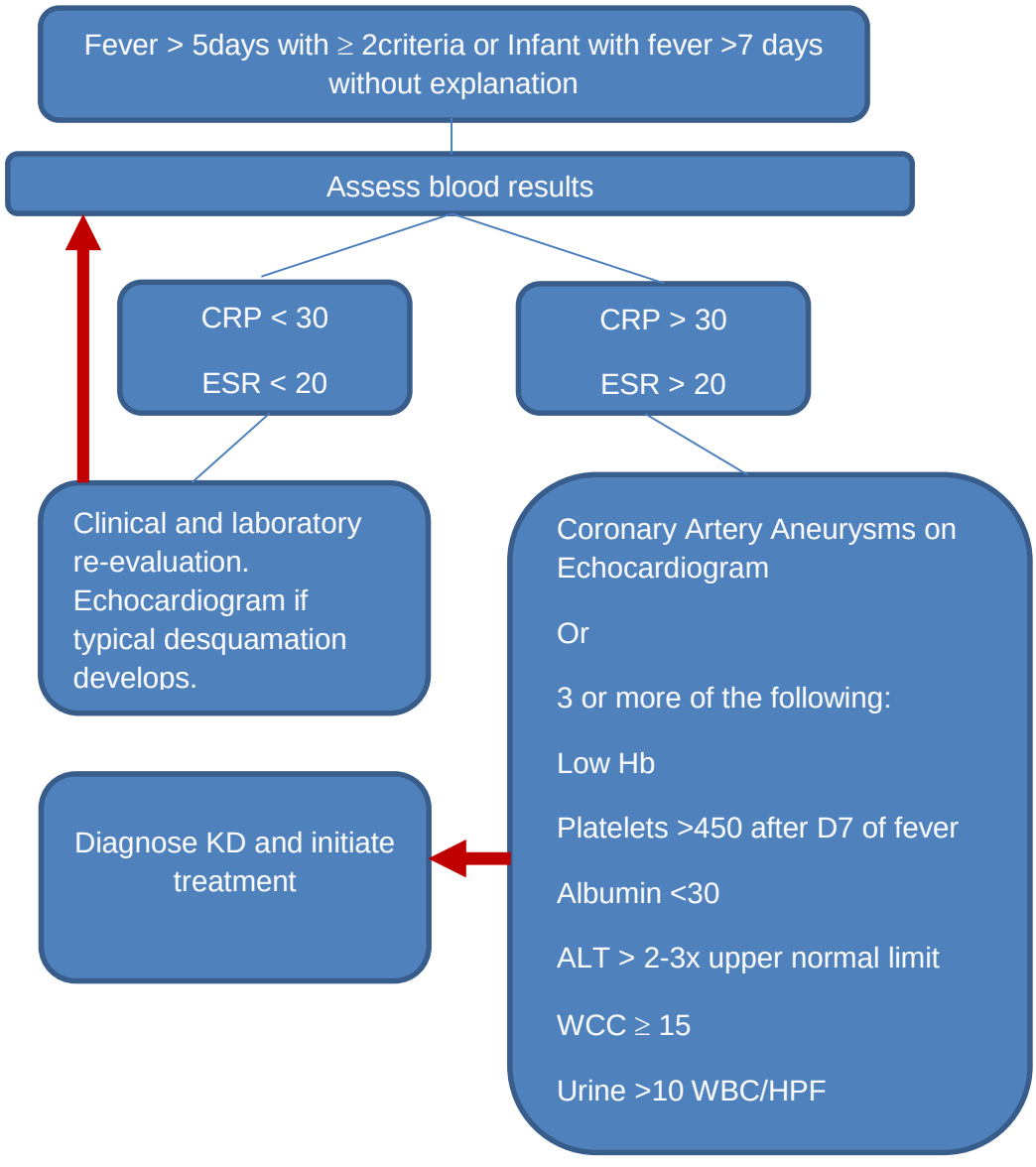
1. Increasing oxygen requirement and/or hypotension. Or
2. Evolving HLH/MAS without a clear cause +/- systemic involvement. Pragmatically defined as any 2 or more of the following:
    a. Hb < 90
    b. WCC < 4.0 or >15
    c. Neutrophils and/or Lymphocytes < 1.0
    d. Platelets < 150 or normal in the face of significant inflammatory response
    e. ALT > 3x Upper Normal Limit (UNL)
    f. Albumin <25
    g. LDH and or CK> 1.5x UNL
    h. Triglycerides >1.5x UNL
    i. Low or falling fibrinogen
    j. CRP and/or ESR >2xUNL
    k. ESR normal, falling or disproportionality less than the rise in other acute phase reactants.

Kawasaki disease diagnostic criteria	
Fever	Duration of 5 days or more PLUS 4 of 5 of the following:
1. Conjunctivitis	Bilateral, bulbar, non-suppurative
2. Lymphadenopathy	Cervical, often >1.5 cm
3. Rash	Polymorphous, no vesicles or crusts
4. Changes in lips or oral mucosa	Red cracked lips; 'strawberry' tongue; or diffuse erythema of oropharynx
5. **Changes of extremities**	Initial stage: erythema and oedema of palms and soles of feet Convalescent stage: peeling of skin from fingertips
KD can be diagnosed with less than 4 criteria or before day 5 if Coronary Artery Aneurysms are detected.	

Pitfalls in the diagnosis of Kawaski's Disease:

1. Features are often successive and do not need to be present at the time of the diagnosis to be counted.
2. A history of a clinical feature is sufficient to count a criterion as fulfilled.
3. The presence of an infection does not rule out the possibility of Kawasaki's Disease – consider and discuss with the MDT.

Algorithm for the diagnosis of Incomplete Kawasaki's Disease:



Appendix 3: Summary of clinical features List

Patient Demographics		
	Enter days	Comment
Number of days of Fever		
	Y/N	Comments
Rash		
Lymph nodes		
Conjunctivitis		
Mucosal changes		
Extremity Changes		
Hypotension		
Abnormal ECG		
Abnormal ECHO		
Vomiting		
Diarrhoea		
Abdominal pain		
Syncope		
Dizziness		
Disorientation		
Headache		
Photophobia		
Cough		
Difficulty in Breathing		
Hepatosplenomegaly		
Other 1 -		
Other 2 -		

Days of fever and yes/no are compulsory fields

Appendix 4 List of initial investigations

Request	Time/date sent	Result
FBC and Film		
U+E		
LFT		
CRP		
EST		
Glucose		
Blood gas with lactate		
Coagulation + fibrinogen		
D-Dimer		
LDH		
Triglycerides		
Ferritin		
Troponin		
Pro-BNP		
CK		
Vitamin D		
Amylase		
Urinalysis		
ECG		
Echocardiogram		
Save EDTA and serum for PCR and serological studies (pre IVIG)		
Blood culture		
Urine and stool culture		
Throat swab culture		
NPA or throat swab for respiratory Panel, mycoplasma plus SARS-CoV-2 PCR		
Consider Stool and blood for SARS-CoV-2 PCR – can be sent to PHE or GOSH		
Pneumococcal, Meningococcal, Group A strep, Staph aureus Blood PCR		
Anti-Steptolysin O Titer		
SARS-CoV-2 serology – if not available locally can send to GOSH/UHB		
EBV, CMV, Adenovirus, parvovirus Enterovirus PCR on blood		
Stool for virology		
HIV		
Request sending microbiological sample for enterotoxin/staph toxins		

Appendix 5 RCPCH: An approach to clinical management

A. Early medical management:

- _Wear appropriate PPE
- _Standard APLS resuscitation and supportive management
- _Empiric antibiotics should be commenced as per local sepsis protocols with blood cultures taken.
- _Take bloods for investigation as per plus save serum and EDTA for inclusion in research studies (see Appendix 4)
- _Call PIC retrieval teams early for advice, retrieving patients who are critically unwell or need ongoing specialist care.
- _Deterioration can be rapid and retrieval time will depend on the clinical situation.
- _Close cardiorespiratory monitoring including continuous saturations and ECG, with BP monitoring.
- _Early 12-lead ECG / echocardiography are indicated if possible (timing determined by clinical picture)
- _If the patient remains in the DGH ongoing regular support must be provided by regional services:
  - o Look for multisystem involvement (liver, renal, neurological etc.)
  - o If not already done, additional research samples including bloods and swabs should be taken prior to immunomodulatory treatment in discussion with tertiary centre (appendix 4). Consent may be taken retrospectively.
  - o Consider IVIG and aspirin early if fulfils criteria for Kawasaki Disease.
  - o Consider IVIG if fulfils criteria for toxic shock syndrome
  - o All cases with suspected myocardial involvement (elevated troponin I / ECG change and / or ECHO abnormalities) should be transferred to a cardiac centre with continuous infectious disease / immunology input.

Monitoring:

- _Hourly PEWS and full set of observations initially until stable > 12 hours
- _Monitor closely for signs of respiratory or cardiovascular deterioration
- _Monitor for clinical signs of worsening inflammation:
  - o Worsening fever
  - o Cardiorespiratory deterioration
  - o Worsening gastrointestinal symptoms
  - o Increasing hepatosplenomegaly or lymphadenopathy
  - o Extending rash
  - o Worsening neurological symptoms
  - o Laboratory signs of increasing inflammation
  - o Falling blood cell counts
  - o Rising ferritin
  - o Unexpectedly low or falling ESR
  - o Rising fibrinogen or new onset low fibrinogen
  - o Rising ALT, AST or LDH
  - o Rising triglycerides
  - o Rising D-dimers
  - o Low serum sodium with worsening renal function

Seek ongoing advice from specialist centre and consider transfer if deterioration is occurring.

Appendix 6: Cardiovascular management and follow up

The current clinical phenotypes show that the cardiac & circulatory systems may be involved. It not necessary that children presenting with this PIMS-ST will all have cardiac manifestations, and this should not preclude treatment.

Initial assessments of children presenting with this syndrome have shown that at presentation <50% had abnormal cardiac function, and about 20% had coronary artery involvement.

There is a proposed classification in this situation

1. Kawasaki's disease: (COVID negative outbreak in the context of Covid pandemic)
2. Corona related or "triggered" Kawasaki disease type syndrome (COVID positive)
3. Corona Shock Syndrome/ TSS (COVID)
    a. With normal cardiac function (with or without coronary dilatation)
    b. With impaired cardiac function (with or without coronary dilatation)

Presentations:

- Carditis presenting with
    - Pericardial effusion
    - Pathological valve regurgitation
    - Myocardial affectation with regional or global abnormalities
- Coronary arterial abnormalities
    - Dilatation
    - Aneurysms
- Rhythm changes
    - Bradycardia
    - Tachyarrhythmias
- Changing ECG patterns
    - Prolonged PR interval
    - QRS changes
    - Widespread ST/T changes
    - QT prolongation

We would recommend the following tests.

- Cardiac: ECG & echocardiogram
- Biochemical markers: BNP & troponin

ECG –

- At diagnosis
- In-patient: daily
- At discharge
- At all reviews subsequently
- Some patients may need a 24-hour Holter or other tests as clinically indicated

Echocardiogram

- At diagnosis
- Inpatient stay:
    - daily if on PICU/HDU
    - less frequently (as clinically indicated on ward)
- At all reviews subsequently

Troponin & BNP

- At presentation
- Troponin daily initially
- BNP every 8 days.
- Alternate day/less frequently depending on clinical progression
- At discharge
- At subsequent reviews

Suggested follow up guidelines:

- 1 week after discharge
- 3-4 weeks after discharge
- 6-8 weeks after discharge
- 4-6 months after discharge
- 12 months after discharge
- Subsequent reviews based on Kawasaki's Disease follow up (3-4 yearly)
- ? transfer to adult cardiology/discharge (depends upon evidence and recommendations)
- **FBC, ESR and CRP at the 1, 2-4 and 6-8 weeks follow up. If ESR, CRP or Platelets have not normalised please discuss with Rheumatology for possible other vasculitis.**

ECG:

- Rhythm (sinus/nodal)
- PR interval – look for 1st, 2nd or progressive blocks
- QRS interval & axis (look for widening QRS
- ST/T changes (pericarditis)
- Ischaemic/infarction
- QT interval (look for prolongation)

Echocardiograms: looking for function and coronary arteries

- LV Function
  - LV ejection fraction (Simpson)/ fractional shortening
  - LV dimension
  - Regional wall motion
  - Pericardial effusion
- Coronary artery
  - Coronary artery (z-scored on ref criteria)
  - Dilatation/aneurysm (comparison with previous scan)

In case of progressive changes to any cardiac parameter, consider transfer to BCH if not already there, and discussion with MDT team for specific treatment (IVIG, steroids, and if resistant potentially Toculizumab, Anakinra, etc.)

For out-of-hours, to contact the relevant MDT clinicians on-call

Appendix 7: Research

Due to the need to understand and define this condition and assess best treatment options research will be essential to allow a rigorous academic review of these patients and ensure an evidence based approach.

Dr Barney Scholefield is coordinating this activity with the Research leads at BWC (Prof J Kirk & University of Birmingham). Local research protocols may exist at DGHs.

RCPCH document recommends inclusion into the following studies:

DIAMONDS:

- DIAMONDS is recruiting children with infectious and inflammatory disorders https://www.diamonds2020.eu/
- DIAMONDS has approval for retrospective consent, so blood samples can be collected prior to treatment and consent obtained later.

ISARIC:

- ISARIC is recruiting children with confirmed or suspected COVID-19.
- Kits can be sent to sites for next day delivery
- Contact : ccp@liverpool.ac.uk https://isaric4c.net

RECOVERY:

- This intervention study isn't yet recruiting children, but will be updated when available**.**

Where immunomodulatory or antiviral therapy is advised, children should be recruited into the RECOVERY trial or similar when available.

A complementary BPSU study will be launching soon

BCH/UoB:

See Figure 1

Research at BCH is being conducted via:

1**) Observational studies:** data collection and bio-sample collection within the studies listed in figure 1.
2) **Interventional studies** (likely the two NIHR prioritised studies: RECOVERY and REMAP-CAP) both which are setting up paediatric arms of their studies.

Main route to biosampling, cytokine profiling and investigation is via existing studies at University of Birmingham (eg TRICICL study). As per RCPCH guidance, we should be saving samples and swabs for this type of process.

Please save & store serum & EDTA sample (10-15mls if possible) prior to any IVIG administration (as per RCPCH guidance).

Samples stored for later clinically relevant testing will not be used for research purposes before explicit consent is obtained. We will organise ethics/HRA protocols and consent permission to get proper approval for testing as soon as possible.

For information about enrolment of suitability of patients to ongoing studies, please email barney.scholefield1@nhs.net or this can be discussed via the MDT referral pathway.

The interventional studies are currently in development and will be considered when protocols are available.

Figure 1: BCH research pathways for COVID19 and PIMSTS patients.

(Note: These focus on BCH/PICU studies, other studies are also running at BWCH).