

Guidance: Paediatric multisystem inflammatory syndrome temporally associated with COVID-19

Most children are asymptomatic or exhibit mild symptoms from COVID-19 infection. However, in the last two months a small number of children have been identified who develop a significant systemic inflammatory response. All children have been diagnosed and managed appropriately along standard referral pathways. Affected children may require paediatric intensive care and input from paediatric infectious diseases, cardiology, and rheumatology.

This rare syndrome shares common features with other paediatric inflammatory conditions including: Kawasaki disease, staphylococcal and streptococcal toxic shock syndromes, bacterial sepsis and macrophage activation syndromes. It can also present with unusual abdominal symptoms with excessive inflammatory markers.

Early recognition by paediatricians and specialist referral including to critical care is essential. Advice currently given to families and carers of children and young people (for example RCPCH parent advice during COVID-19 leaflet) supports appropriate referral to health services.

This document is to raise awareness and gives management advice to clinicians and has been developed after expert review of the cases.

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.

See [Appendix 1](#) for further Clinical and diagnostic features and for initial recommended investigations.

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 Appendix 2 plus save serum and EDTA for inclusion in research studies (see [Appendix 3](#))
- 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:
 - Look for multisystem involvement (liver, renal, neurological etc.)
 - If not already done, additional research samples including bloods and swabs should be taken prior to immunomodulatory treatment in discussion with tertiary centre (appendix 3). Consent may be taken retrospectively.
 - Consider IVIG and aspirin early if fulfils criteria for Kawasaki Disease.
 - Consider IVIG if fulfils criteria for toxic shock syndrome
 - 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:
 - Worsening fever
 - Cardiorespiratory deterioration
 - Worsening gastrointestinal symptoms
 - Increasing hepatosplenomegaly or lymphadenopathy
 - Extending rash
 - Worsening neurological symptoms
 - Laboratory signs of increasing inflammation
 - Falling blood cell counts
 - Rising ferritin
 - Unexpectedly low or falling ESR
 - Rising fibrinogen or new onset low fibrinogen
 - Rising ALT, AST or LDH
 - Rising triglycerides
 - Rising D-dimers
 - Low serum sodium with worsening renal function

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

B. Treatment:

General principles

- **Discuss early with PICU and paediatric infectious diseases/immunology/rheumatology* team**
- All children should be treated as suspected COVID-19
- Refer to local policy on management of COVID-19 or suspected COVID-19 as well as empiric or targeted antimicrobial guidelines.
- For mild to moderate disease supportive care only is recommended
- If clinically deteriorating or severe disease discuss transfer with PICU retrieval teams
- Candidate antiviral therapies should only be given in the context of a clinical trial if available (e.g. RECOVERY trial)
- As this an evolving condition, all children should be considered for recruitment in research studies such as DIAMONDS and ISARIC-CCP
- Any child being considered for antiviral therapy should be discussed at MDT including a clinician from an external trust as per RCPCH guidance
- Immunomodulatory therapy should be discussed with paediatric ID and/or clinicians with appropriate experience in their use (e.g. rheumatology, immunology, haematology) on a case by case basis and used in the context of a trial if eligible and available.

* Each Region may have a different specialty delivering support for inflammatory conditions including immunology, infectious diseases and rheumatology.

Thank you to all those paediatricians who contributed to this guidance from infectious disease, rheumatology, paediatric intensive care, immunology and cardiology.

Special thanks to the BPAIIG, North Thames Paediatric Network and South Thames Paediatric Network.

Appendix 1

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

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

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.

Appendix 2

Initial investigations (frequency of repeat depends on clinical need)

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

Appendix 3

Research

Research blood samples should be taken prior to IVIG.

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.

Additional samples to be collected include ideally before IVIG if given: throat swab, serum, EDTA, PAXGENE or equivalent

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>

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

A complementary BPSU study will be launching soon

