Clinical Guideline

Paediatric Multisystem Inflammatory Syndrome Temporarily Associated with COVID-19 (PIMS-TS)

SETTING	Bristol Royal Hospital for Children (BRHC) and South West Paediatric Specialist Network
FOR STAFF	Paediatric staff at BRHC and associated networks
PATIENTS	Children with suspected or confirmed PIMS-TS

Background

In countries with a high incidence of COVID-19 infection there have been increasing reports of children presenting with significant multisystem inflammatory pathology. At present, the cause of this presentation remains unclear but a temporal association with SARS-CoV-2 infection has been identified and the majority of children in reported case series have evidence of previous or concomitant SARS-CoV-2 infection.

The clinical presentation shares features with other paediatric inflammatory conditions such as Kawasaki Disease, Staphylococcal and Streptococcal Toxic Shock Syndrome, bacterial sepsis, HLH and Macrophage Activation Syndrome. Abdominal symptoms have also featured prominently and several cases have required intensive care.

As this is a new clinical entity, understanding and management are evolving rapidly and this guidance will likely need to change to reflect this. Early discussion with Paediatric Infectious Diseases, Rheumatology, Cardiology and PICU/WATCh teams is advised.

This guidance is intended to be used alongside the local Kawasaki Disease guideline (DMS) and the RCPCH guidance:

https://www.rcpch.ac.uk/sites/default/files/2020-05/COVID-19-Paediatric-multisystem-%20inflammatory%20syndrome-20200501.pdf.

It aims to facilitate initial investigations and management discussions, both within BRHC and across the South West Paediatric Network.

Case Definition

1. A child presenting with persistent fever, inflammation (neutrophilia, elevated CRP and lymphopaenia) and evidence of single or multi-organ dysfunction with additional features (see RCPCH guidance). 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 discussion with Paediatric Infectious Diseases and WATCh teams).

3. SARS-CoV-2 PCR testing may be positive or negative.

Diagnosis

PIMS-TS is a clinical diagnosis and there is no specific investigation that will confirm or exclude the diagnosis. Diagnostic investigations are therefore targeted towards excluding other significant pathology and helping to characterise the inflammatory response to guide decision-making.

It is important to consider the diagnosis early to prevent unnecessary delays in treatment. However, in children initially presenting with a febrile illness, where there is a broad differential diagnosis, it may be appropriate to obtain a more limited set of initial investigations (eg. FBC, U&E, LFT, CRP, cultures). This can then be extended if there is evidence of significant inflammation without a clear cause.

Investigations

1. In a child presenting with suspected PIMS-TS the recommended initial investigations are listed in Table 1.
2. Table 1 should be printed and included in the patient's notes, with the date each investigation is obtained completed.
3. All children meeting the case definition should be commenced on a broad-spectrum antibiotic whilst awaiting the results of these investigations.
4. Blood cultures, and other microbiology samples, should be obtained prior to starting antibiotics.
5. **Serology samples, including a serum sample for storage, must be obtained prior to giving immunoglobulin**.
6. All children presenting with suspected PIMS-TS should have a baseline ECG.
7. If there is a strong clinical suspicion of PIMS-TS an echocardiogram should be obtained within 24 hours of presentation. If paediatric echo is not available locally the case should be discussed with Paediatric Cardiology and Infectious Diseases to determine if the child requires transfer to BRHC.
8. **All children should be discussed with the Paediatric Infectious Diseases team and Paediatric Cardiology prior to initiating specific treatment**.

Patients presenting to BRHC with suspected PIMS-TS should be admitted under the General Paediatric team with input from Paediatric Infectious Diseases and Cardiology as needed. Children transferred from other centres for management of suspected PIMS-TS should be admitted under joint care of General Paediatrics and Paediatric Infectious Diseases with input from Cardiology and other specialties as needed.

	Table 1. **Investigation**	**Date Sent**	**Result**
Bloods	**FBC & blood film**		
	U&E		
	LFT		
	Amylase		
	CRP		
	LDH		
	CK		
	Glucose		
	Triglycerides		
	Blood gas (including lactate)		
	NT-proBNP*		
	Troponin		
	Ferritin		
	ESR*		
	Coagulation Screen (including fibrinogen)		
	D-dimer		
	C3, C4		
	von Willebrand factor**		
	ADAMTS 13**		
	Vitamin D		
	Blood culture		
	COVID-19 PCR & serology★		
	EDTA sample for storage		
	Serum sample for storage		
	EBV/CMV/Enterovirus & Adenovirus PCR		
	EBV/CMV/Mycoplasma serology		

	Meningococcal/Pneumococcal/Group A Strep/Staphylococcal PCR		
	ASOT & anti-DNAse B		
Micro/Virology	NPA or throat swab for respiratory viral PCR including SARS-CoV-2		
	Bacterial throat swab		
	Urine culture		
	Stool culture		
	Stool for virology		
	Stool for SARS-CoV-2 PCR★		
Imaging/Other	Urinalysis (please also send protein:creatinine and albumin:creatinine ratios if proteinuria is present)		
	ECG		
	Echocardiogram (within 24h)		
	CXR		
	Abdominal ultrasound		

Investigations in bold should be checked daily in children with PIMS-TS until clinically stable
Please ensure all serology and serum samples are taken prior to giving IVIG

The listed investigations are all available at BRHC.

In other centres some investigations may not be available locally:
*If available locally.
**If available locally. At BRHC this can be performed on a standard coagulation sample however please contact the Haematology lab prior to sending.
★If not available locally this can be sent to Bristol, PHE, or GOSH

PIMS-TS Management Pathway

This flowchart is for guidance only. All children with suspected PIMS-TS should be discussed regularly with Paediatric Infectious Diseases, Cardiology +/- PICU/WATCh.

Consult RCPCH definition and guidelines*

Child presents with features of **Paediatric Multisystem Inflammatory Syndrome**

Early discussion with local Paediatric Consultant on call
If clinically unstable discuss with WATCh team/PICU

Kawasaki Disease | **Sepsis/Toxic Shock Syndrome** | **Hyperinflammatory Syndrome**

General principles

Obtain investigations as detailed in **Table 1**.

Cautious fluid resuscitation if needed
Use 5 ml/kg boluses and titrate to clinical response
Consider early use of inotropes (discuss with WATCh team)

Ensure ECG & Echo obtained within 24h
Daily bloods and alternate day echo until clinically stable

Ensure regular review by an experienced Paediatrician.
Can deteriorate rapidly. Discuss clinical progress with ID team daily.

Antibiotics
*doses given for guidance only, please consult BNFc

IV Ceftriaxone 80 mg/kg*
(or cefotaxime, according to local protocols)

+ IV Clindamycin
10mg/kg QDS*

Discuss with Paediatric ID Consultant at BRHC (07769960542) prior to any additional treatment. All children requiring immunomodulatory treatment should be recruited to the RECOVERY trial.

0-24h

+ Aspirin
7.5 mg/kg QDS

IVIG 2 g/kg
or
IV Methylprednisolone 10 mg/kg OD for 3 days (max 1g)
or
No additional treatment

Review response to treatment

If ongoing fever and inflammation, or clinical deterioration, discuss with Paediatric ID Consultant at BRHC regarding 2nd line interventions.

Management

The clinical presentation of PIMS-TS can be highly variable but appears to cluster into three distinct clinical phenotypes; a Kawasaki Disease-like presentation; a Toxic Shock-like presentation; and a hyperinflammatory presentation without shock that does not meet the criteria for Kawasaki Disease. These different clinical presentations may require different management strategies.

General Principles

1. At present the most effective treatment strategy for PIMS-TS is unknown.
2. Management should ensure good supportive care and treatment of treatable conditions.
3. Children with PIMS-TS can deteriorate rapidly and an experienced Paediatrician should review all children with suspected PIMS-TS regularly.
4. All children who meet the case definition should be commenced on a broad-spectrum antibiotic (eg. IV ceftriaxone) after obtaining appropriate cultures.
5. Ventricular dysfunction is common in published case series of PIMS-TS patients presenting with shock. If children require fluid resuscitation this should be given as small volume boluses (5 ml/kg, 0.9% Sodium Chloride), titrated to clinical response.
6. If children require significant fluid resuscitation, or do not respond to repeated fluid boluses, they should be discussed with PICU/WATCh. Early consideration of inotropic support may be needed.
7. All children with suspected PIMS-TS should be discussed with the Paediatric Infectious Diseases team and Paediatric Cardiology prior to specific treatment. All treatment decisions should be taken within a multi-disciplinary team.
8. All children with suspected PIMS-TS requiring immunomodulatory treatment should be considered for inclusion in the RECOVERY trial. This now has a PIMS-TS specific treatment arm that includes IVIG, IV methylprednisolone, and tocilizumab.
9. The use of immunomodulatory treatments outside a clinical trial setting should be avoided. If treatment outwith a clinical trial is felt necessary this should be discussed with the Paediatric Infectious Diseases Consultant on call.
10. Children presenting with mild to moderate symptoms may not require specific treatment.
11. **Children <1 year presenting with PIMS-TS appear at high risk of rapid deterioration, severe disease, and cardiac complications.** Clinicians should therefore have a low threshold for early discussion and transfer of these patients.
12. The bloods indicated in **bold** in Table 1 should be repeated daily until the child is clinically stable.
13. Timing of repeat echocardiograms will be guided by Paediatric Cardiology.

Specific Management

1. For children presenting with a Toxic Shock-like syndrome the addition of IV clindamycin is advised, in keeping with current guidelines for Staphylococcal and Streptococcal Toxic Shock.
2. Intravenous immunoglobulin (IVIG) 2 g/kg is also recommended for children presenting with a Toxic Shock-like syndrome, in keeping with current guidelines.
3. Children presenting with classical/complete Kawasaki Disease should be managed according to the Kawasaki Disease guideline (link). The UK diagnostic criteria for complete Kawasaki Disease are highlighted in Table 2. IVIG treatment should not be delayed in children who meet the diagnostic criteria for complete Kawasaki Disease.

Table 2. **UK Diagnostic Criteria for Complete Kawasaki Disease**
Fever (remitting) > 38°C ≥ 5 days **PLUS** ≥ 4 of the following
1. Bilateral, non-purulent conjunctivitis
2. Rash, polymorphous erythematous maculopapular (no vesicles or crusts)
3. Oral changes. Red cracked lips, strawberry tongue or diffuse oropharynx
4. Cervical Lymphadenopathy, often unilateral >1.5cm lesions
5. Changes to extremities (erythema and swelling of the palms and soles, 2-3 weeks later may be desquamation of palms and soles).

1. Intravenous immunoglobulin should be administered according to the BRHC IVIG (Privigen) Guidelines (DMS).
2. Verbal consent should be obtained from parents and documented in the child's clinical notes prior to administering IVIG. Children who receive IVIG should not receive live vaccines for 3 months after treatment. It is important that this information is included on the child's discharge letter and communicated to the parents and GP.
3. **Serology samples, including a serum sample for storage, must be obtained prior to giving immunoglobulin**.
4. Response to treatment should be assessed 24 hours after immunomodulatory treatment.
5. Children who do not respond to initial immunomodulatory treatment should be discussed with the Paediatric Infectious Diseases Consultant on call and considered for randomisation to 2nd line interventions in the RECOVERY trial. The Paediatric Infectious Diseases Consultant will guide further immunomodulatory management.
6. Children presenting with a Kawasaki Disease-like syndrome should be started on high

dose aspirin, in keeping with the Kawasaki Disease guidelines. The aspirin dose can be reduced once they are afebrile for ≥48 hours.

7. The duration of aspirin treatment will be guided by Paediatric Cardiology. This is likely to be for at least 6 weeks.
8. All children receiving high dose aspirin or steroids should also be started on gastric protection (eg. omeprazole).
4. All children weighing over 40kg should be assessed using the VTE prophylaxis guidelines (link) and provided with TED stockings where appropriate.
5. Other forms of thromboprophylaxis will be discussed on a case-by-case basis.

BPSU

The British Paediatric Surveillance Unit (BPSU) is currently collecting information on children presenting with suspected/confirmed PIMS-TS to better understand the incidence, presenting features, laboratory features, management and clinical course.

All cases of suspected/confirmed PIMS-TS should be reported to BPSU (https://www.rcpch.ac.uk/work-we-do/bpsu/study-multisystem-inflammatory-syndrome-kawasaki-disease-toxic-shock-syndrome.

Table A

REFERENCES	1. Rachel Harwood, Christine E Jones, Elizabeth Whittaker et al. A national consensus management pathway for paediatric inflammatory multisystem syndrome temporally associated with COVID-19 (PIMS-TS): results of a national Delphi process. Lancet Child Adolesc Health, September 18, 2020 https://doi.org/10.1016/ S2352-4642(20)30304-7. 2. Guidance: Paediatric Multisystem Inflammatory Syndrome Temporarily Associated with COVID-19. Royal College of Paediatrics and Child Health. 1st May 2020. https://www.rcpch.ac.uk/sites/default/files/2020-05/COVID-19-Paediatric-multisystem-%20inflammatory%20syndrome-20200501.pdf. 3. Paediatric inflammatory multisystem syndrome and SARS-CoV-2 infection in children. European Centre for Disease Prevention and Control. 15th May 2020. https://www.ecdc.europa.eu/sites/default/files/documents/covid-19-risk-assessment-paediatric-inflammatory-multisystem-syndrome-15-May-2020.pdf 4. Whittaker E, Bamford A, Kenny J, et al. Clinical Characteristics of 58 Children With a Pediatric Inflammatory Multisystem Syndrome Temporally Associated With SARS-CoV-2. *JAMA.* 2020. 5. Perez-Toledo M, Faustini SE, Jossi SE, et al. Serology confirms SARS-CoV-2 infection in PCR-negative children presenting with Paediatric Inflammatory Multi-System Syndrome. *medRxiv.* 2020. 6. Ramcharan T, Nolan O, Lai CY, et al. Paediatric Inflammatory Multisystem Syndrome: Temporally Associated with SARS-CoV-2 (PIMS-TS): Cardiac Features, Management and Short-Term Outcomes at a UK Tertiary Paediatric Hospital. *Pediatr Cardiol.* 2020. 7. Feldstein LR, Rose EB, Horwitz SM, et al. Multisystem Inflammatory Syndrome in U.S. Children and Adolescents. *N Engl J Med.* 2020. 8. Kaushik S, Aydin SI, Derespina KR, et al. Multisystem Inflammatory Syndrome in Children (MIS-C) Associated with SARS-CoV-2 Infection: A Multi-institutional Study from New York City. *J Pediatr.* 2020. 9. Miller J, Cantor A, Zachariah P, Ahn D, Martinez M, Margolis K. Gastrointestinal symptoms as a major presentation component of a novel multisystem inflammatory syndrome in children (MIS-C) that is related to COVID-19: a single center experience of 44 cases. *Gastroenterology.* 2020. 10. McCrindle BW, Manlhiot C. SARS-CoV-2-Related Inflammatory Multisystem Syndrome in Children: Different or Shared Etiology and Pathophysiology as Kawasaki Disease? *JAMA.* 2020. 11. Chiotos K, Bassiri H, Behrens EM, et al. Multisystem Inflammatory Syndrome in Children during the COVID-19 pandemic: a case series. *J Pediatric Infect Dis Soc.* 2020. 12. Verdoni L, Mazza A, Gervasoni A, et al. An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study. *Lancet.* 2020;395(10239):1771-1778.

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RELATED DOCUMENTS AND PAGES	
AUTHORISING BODY	
SAFETY	No safety concerns
QUERIES AND CONTACT	• **Paediatric Infectious Diseases & Immunology Registrar** (Mon-Fri, 08:30-17:30) – Bleep 3997, or via BRHC Switchboard (0117 342 8460) • **Paediatric Infectious Diseases & Immunology Consultant** (Consultant to Consultant advice is available 24h but cases should be discussed with local responsible clinician prior to calling) – 07769960542 or via BRHC Switchboard (0117 342 8460) • **WATCh service** – 0300 0300 789 • **Paediatric Cardiology Registrar** – Bleep 2424, or via BRHC Switchboard (0117 342 8460)