Sheffield Children's NHS
NHS Foundation Trust

PIMS-TS: Diagnosis and Management

Reference:	CG2015v2
Written by:	Karen Bourne, Carmen Gonzalez, Daniel Hawley, Caroline Kerrison Madeleine Mackay, Sarah Maltby, Anne-Marie McMahon, Clare Nash, Fiona Shackley, Rupa Talekar, Jessica Wan
Peer reviewer:	Rachel Riddell, Rum Thomas
Approved:	November 2021
Review Due:	November 2024

Purpose

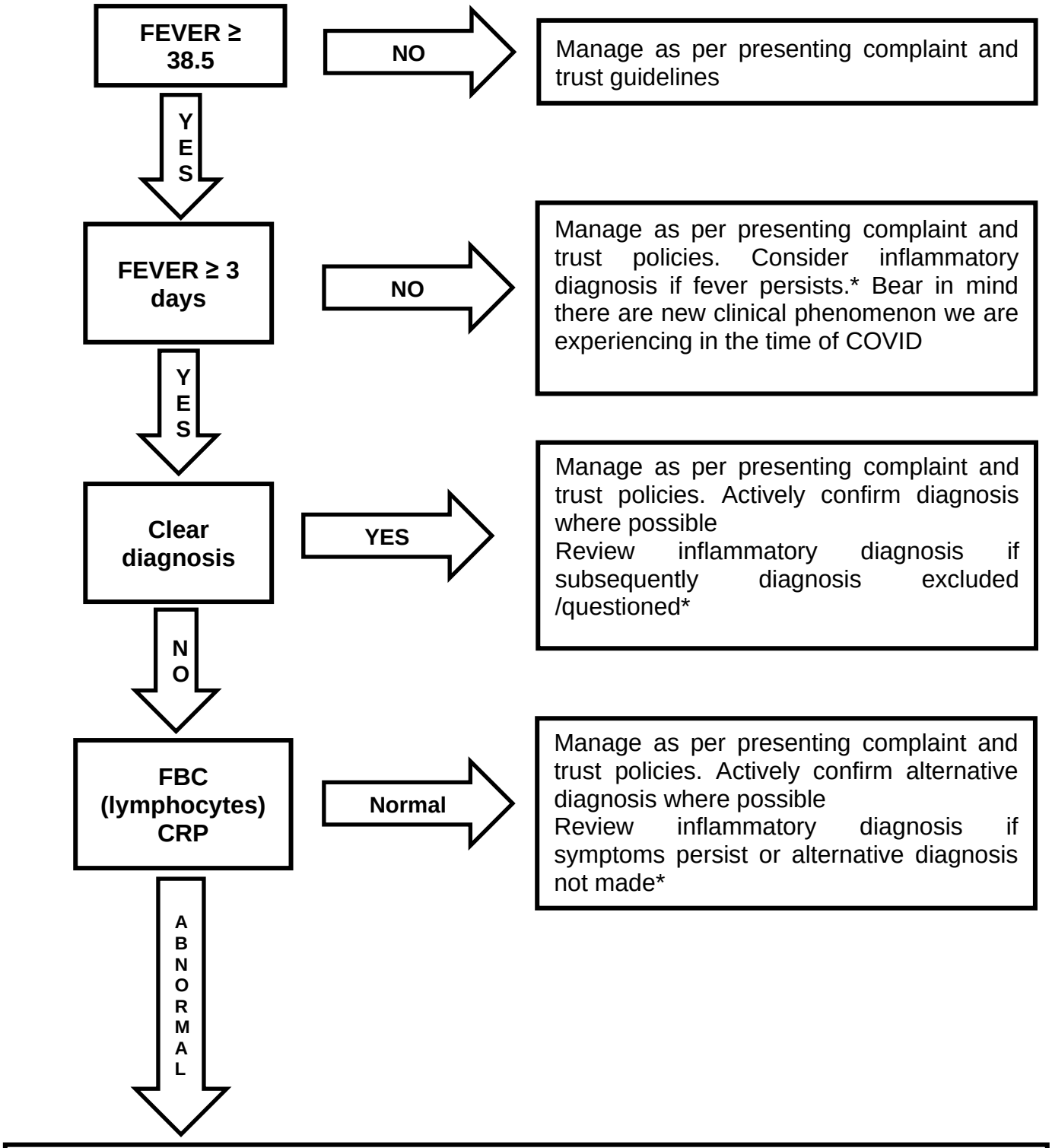
To provide guidance to clinical staff regarding the diagnosis and management of Paediatric Multisystem Inflammatory Syndrome temporally associated with COVID-19 (PIMS-TS).

Intended Audience

This guideline is for use by clinical staff within Sheffield Children's NHS Foundation Trust.

Table of Contents

Is it PIMS-TS Flow Chart



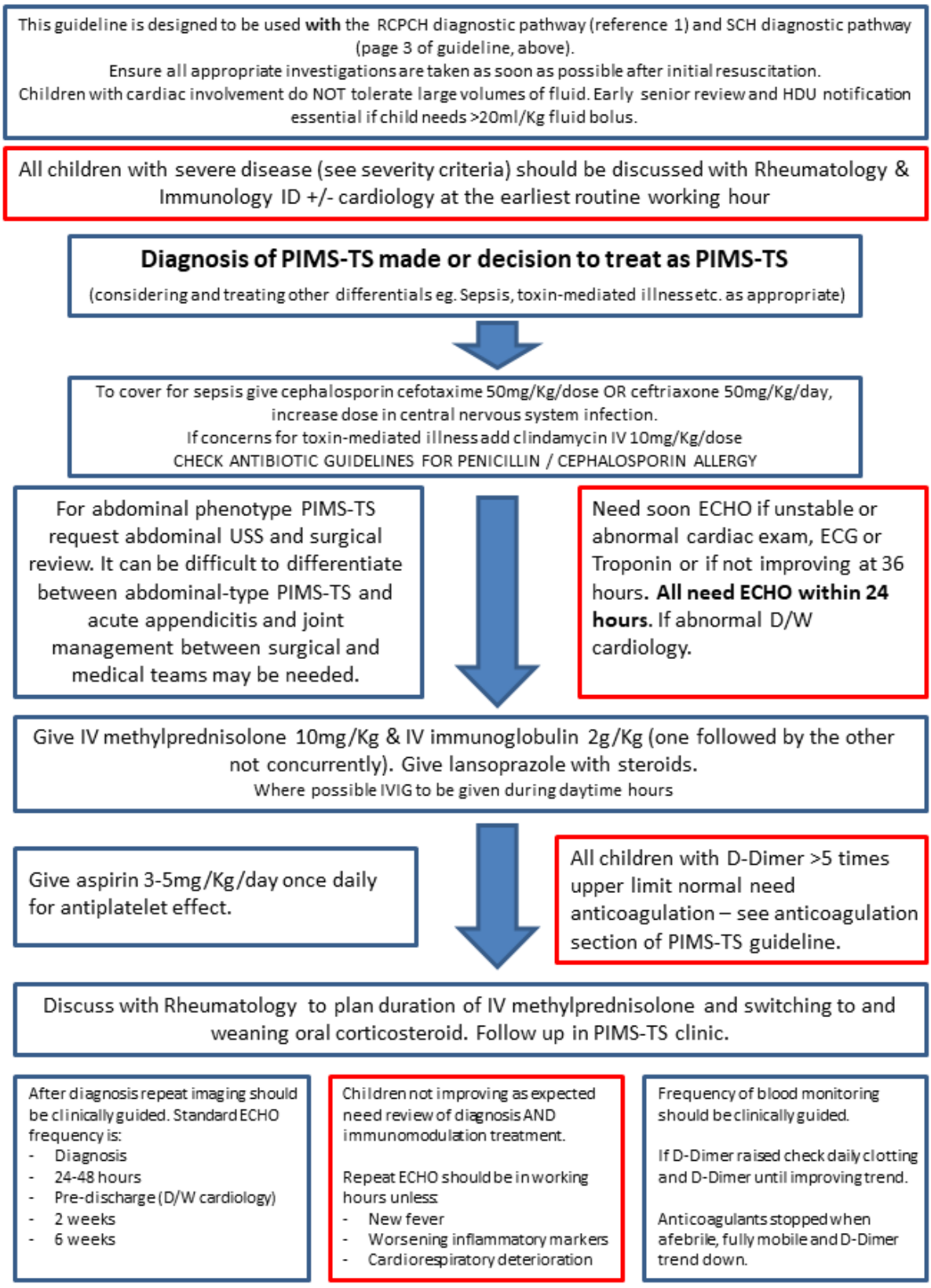
Manage (&/- resuscitate) as per presenting complaint and trust guidelines.
Actively work through PIMS-TS case definition checklist below to aid referral discussions. If uncertain request early senior review. Bear in mind other diagnoses could fit these criteria and should be actively excluded.

Authors: Karen Bourne, Carmen Gonzalez, Daniel Hawley, Caroline Kerrison, Madeleine Mackay, Sarah Maltby, Anne-Marie McMahon, Clare Nash, Fiona Shackley, Rupa Talekar, Jessica Wan

Is it PIMS-TS Check List

Fever ≥ 38.5 ^{o}C for ≥ 3 days (most of the day, not made normal by antipyretics)	☐
AND two of the following:	
Rash or bilateral non-purulent conjunctivitis or muco-cutaneous inflammation signs (oral, hands or feet).	☐
Hypotension or shock. *resuscitate appropriately before specialist tests*	☐
Clinically evaluate for possible features of myocardial dysfunction, (ECHO findings or elevated Troponin/NT-proBNP may be indicated if concerned enough to request these)	☐
Evidence of coagulopathy (by PT, PTT, elevated d-Dimers).	☐
Acute gastrointestinal problems (diarrhoea, vomiting, or abdominal pain).	☐
AND	
Elevated markers of inflammation such as ESR, C-reactive protein	☐
AND	
No other obvious microbial cause of inflammation, including bacterial sepsis, staphylococcal or streptococcal shock syndromes.	☐

Sheffield Children's PIMS-TS Treatment Flow Chart



Authors: Karen Bourne, Carmen Gonzalez, Daniel Hawley, Caroline Kerrison, Madeleine Mackay, Sarah Maltby, Anne-Marie McMahon, Clare Nash, Fiona Shackley, Rupa Talekar, Jessica Wan

1. Introduction

Most children are asymptomatic or exhibit mild symptoms from COVID-19 infection. However a small number of children have been identified who develop a significant systemic inflammatory response. 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 (1).

2. RCPCH case definition of PIMS-TS

A child presenting with persistent fever, inflammation (neutrophilia, elevated CRP and lymphopenia) 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. 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)(1).

SARS-CoV-2 PCR testing may be positive or negative (1).

There should be a low threshold for referral to Paediatric Intensive Care (1).

3. Classification of PIMS-TS

Primary classification of PIMS-TS should be based on the presenting phenotype (2)

- Kawasaki disease-like: complete and incomplete, classified using the American Heart Association criteria (3)
- Non-specific: children presenting with shock or fever, or both, and symptoms that might include abdominal pain, gastrointestinal, respiratory, or neurological symptoms that do not meet the criteria for Kawasaki disease

Subsequent classification of severity is recommended as below

4. Investigations

See appendix A for appropriate investigations and investigation checklist which should be completed for all patients with a suspected PIMS-TS. This appendix includes two tables, which guide initial investigations and suggested daily monitoring investigations.

5. Cardiology Investigations

Examine the patient for signs of impaired Ventricular function such as low volume pulse, tachycardia out of proportion to their temperature, hepatomegaly, reduced central capillary refill.

Investigations

ECG and Transthoracic Echocardiogram

Daily ECGs:
Look for evidence of arrhythmias and ischemia in the form of ST elevation and / or T wave inversion in Leads V5-V6

Echocardiogram:
All patients with a diagnosis of PIMS-TS should have an Echocardiogram within 24 hours of presentation. This should be arranged via the Radiology department at the earliest opportunity during working hours. Ideally utilise the reserved 8:45 am week-day morning PIMS-TS Echo slot to enable timely management during the day.

An urgent Echo is required if the patient has any of the following:

- An Abnormal ECG
- Hypotension unresponsive to Fluid boluses (20ml/kg and still displaying signs of shock)
- On Inotropic support
- Other signs of shock (including persistent tachycardia)
- Raised Troponin even in the absence of all of the above

Urgent out of hours echo can be arranged via switchboard who have the Echo rota.

Similar to Kawasaki disease a normal Echocardiogram does not rule out PIMS-TS so do not use an Echocardiogram to diagnose PIMS-TS but as an adjunct to guide management and / or escalation of care.

If the initial Echocardiogram is normal and the child responds rapidly to PIMS-TS first line treatment, including resolution of blood inflammatory markers, then they only need a pre-discharge Echocardiogram. If this is abnormal please discuss with Cardiology.

If the initial Echocardiogram is abnormal it will need repeating. The timing for this is dependent on the abnormality and the child's clinical condition, blood markers and other systemic information.

6. Severity Criteria

Features of severe disease may be indicated by any of the following and should prompt early referral to paediatric intensive care, and discussion with the sub-specialist team (including PICU Consultant, Paediatric Consultant, Immunology/ID Consultant, Rheumatology Consultant and Cardiology Consultant). In particular, children who are haemodynamically unstable should be discussed early with PICU.

Severity Criteria	
Age	Less than 1 year old
Physiological Features	Prolonged central capillary refill time Persistent hypotension Persistent tachycardia Requirement of 20ml/Kg fluid bolus Oxygen saturation <92% in room air
Haematological / Biochemical Features	Significant increase in CRP (>150mg/L) Increased troponin Increased NT-Pro-BNP Increased ferritin Increased D-Dimer High or low fibrinogen Increased creatinine Lymphopenia
Cardiac Features	Abnormal Echocardiogram: - Coronary artery dilatation, ectasia or aneurysms - Impaired left ventricular function - Regional wall motion abnormalities (RWMA) - Mitral or Aortic regurgitation - Pericardial effusion - Intracardiac thrombus Abnormal ECG*: - Ventricular ectopics - Junctional rhythm - Brady- or tachyarrhythmias - ST segment changes - T wave inversion in V5 & V6 *Cardiology opinion to be sought urgently in any patient who has signs of ischaemia on ECG

7. Management

Antimicrobials

- Cover with antibiotics until results of blood culture available.
- Ceftriaxone 50 mg/kg OD IV. if concerns CNS involvement increase dose to 80 mg/kg OD IV.
- If concerns about toxin-mediated disease and in all children presenting in shock add Clindamycin 10 mg/kg QDS IV.
- Review antibiotics at 48 hours with results of infection investigations. Continue with Clindamycin for 48-72 hours for anti-toxin effect.

Discuss with ID any query about antibiotic therapy.

Intravenous Immunoglobulin

- Dose recommended of IVIG is 2 g/kg. Aim to infuse in 12 hours, but adjust rates and duration of infusion depending on fluid tolerance and/or potential side effects.
- If concerns about cardiac function and/or possibility of fluid overload split in 2 lots of 1 g/kg. Aim to give second 1g/kg 12 to 24 hours after first infusion depending on clinical severity of illness. Reassess clinically between infusions. Consider Furosemide 0.5 mg/kg IV if signs of fluid overload.
- Ideally IVIG infusion should be started during working hours, provided that the patient has started treatment with IV Methylprednisolone.
- It is not currently indicated to repeat IVIG if no complete response to treatment. This decision should be individualised and discussed jointly with sub-specialties (Immunology/ID and Rheumatology).

Liaise with pharmacy for infusion rates as depend on immunoglobulin product available.

IVIG for this indication does not require panel approval, but paperwork for pharmacy needs to be completed as soon as practically possible.

Corticosteroids

Intravenous Methylprednisolone (IVMP) at 10mg/kg should be given to all children who meet the severe criteria as above for PIMS-TS and considered for those children who did not initially meet the severe criteria, but remain unwell 24 hours after receiving IVIG, particularly if they remain pyrexial.

Methylprednisolone can be made up in an infusion (usually with 100mls of 0.9% sodium chloride, but any reasonable volume may be used and smaller volumes may be appropriate in younger children or where fluid restriction is desirable) and given over 1 hour. If the patient is hypertensive consider giving this over 2 hours.

Please see the Rheumatology Trust guideline on patient monitoring during IVMP infusion (4).

IVMP as above is usually given for 3-5 days (based on clinical status and response) and then switched to oral prednisolone (2mg/kg), or an IVMP dose of 1.6mg/Kg (equivalent to 2mg/kg oral prednisolone). Once the patient has been changed to oral prednisone this can gradually be weaned over 4-6 weeks. Please seek Rheumatology advice on this.

Gastric protection (PPI) should be given to all children receiving corticosteroid regimens described above.

Biologic therapy

Biological therapy should be considered as a third-line option in children who do not respond to intravenous immunoglobulin and methylprednisolone; the decision to commence a biological therapy should be made only after seeking Rheumatology advice.

Early discussion with Rheumatology, Immunology/ID and Cardiology is recommended in any child who remains unresponsive to any of the above treatments.

Anticoagulation

See Appendix B

Follow up

All patients should be followed up at 2 weeks and 6 weeks from discharge in the PIMS-TS clinic. At discharge, please request Echocardiograms to be done on the same day as the 2 week and 6 week PIMS-TS clinics, via ICE requesting.

On discharge, please also request a follow up appointment 2 weeks and 6 weeks from discharge (Medicine A).

8. References

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

(2) Harwood R 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. 2021 Feb;5(2):133-141.

(3) McCrindle BW, Rowley AH, Newburger JW et al. Diagnosis, treatment, and long-term management of Kawasaki disease: a scientific statement for health professionals from the American Heart Association. Circulation. 2017; 135: e927-e999.

(4) Sheffield Children's NHS Foundation Trust (2019) McMahon AM, Hawley D. Guideline for Methylprednisolone Infusions for Patients with Rheumatological Conditions. Sheffield Children's Hospital Clinical Guideline Ref 1539v3.

(5) De-Graeff N, Groot N, Ozen S, Eleftheriou D, Avcin T, Bader-Menier B, Dolezalova P, Feldman BM, Kone-Paut I, Lahdenne P, McCann L, Pilkington C, Ravelli A, van Royen-Kerkhof A, Uziel Y, Vastert B, Wulffraat N, Kamphuis S, Brogan P, Beresford MW. European consensus-based recommendations for the diagnosis and treatment of Kawasaki disease – the SHARE initiative. Rheumatology (Oxford). 2019 Apr 1;58(4):672-682.

(6) Schlapbach, Luregn J. et al. Best Practice Recommendations for the Diagnosis and Management of Children With Pediatric Inflammatory Multisystem Syndrome Temporally Associated With SARS-CoV-2 (PIMS-TS; Multisystem Inflammatory Syndrome in Children, MIS-C) in Switzerland. Front. Pediatr . 26 May 2021. Available from: https://doi.org/10.3389/fped.2021.667507 Date accessed 12/11/21.

(7) University Hospitals of Bristol and Weston NHS Foundation Trust. (2020) Paediatric Multisystem Inflammatory Syndrome Temporarily Associated with COVID-19 (PIMS-TS) Clinical Guideline. Available from https://www.watch.nhs.uk/wp-content/uploads/2021/01/Bristol-PIMS-TS-Guideline.pdf . Date accessed 12/11/21.

(8) Evalena London, Guy's and St Thomas' NHS Foundation Trust. (2020). Paediatric Critical Care: PIMS-TS Paediatric Multisystem Inflammatory Syndrome temporally associated with SARS-CoV2. Clinical Guideline. Available from: 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 Date accessed. 12/11/21.

(9) UptoDate. COVID-19: Multisystem inflammatory syndrome in children (MIS-C) management and outcome. October 2021. Available from: https://www.uptodate.com/contents/covid-19-multisystem-inflammatory-syndrome-in-children-mis-c-management-and-outcome#H1599219637 Date accessed 12/11/21.

9. Appendix A

PIMS TS *INITIAL* LABORATORY INVESTIGATIONS
(at time of considering PIMS) (15-20ml blood excluding blood cultures)
All cultures should ideally happen BEFORE antibiotics but if they have not been done prior take samples anyway.
If it is difficult to get the bloods volumes required, **do NOT delay** resuscitation and empiric treatment.
All viral PCRs can be taken after adequate resuscitation, antibiotics and vascular access established.
Clinical details must include at a minimum ?PIMS-TS

Tests	**Bottles**	**Date and time sent**	**Results** (normal, high/low – see ICE for details)
Haematology: Pink forms			
FBC and film	EDTA pink (1ml)		
Coagulation &fibrinogen	Citrate purple (1ml)		
D-Dimer	Ensure filled to line or send 2 bottles		
Biochemistry: Green Forms			
U&E	Li-Hep orange (2 ml)		
LFT			
CRP			
Triglycerides			
Ferritin			
LDH			
CK			
amylase			
Vitamin D	s.gel Green(0.5 ml) green form		
Troponin	s.gel green (0.5 ml) green form		
Pro-BNP (call SCH biochem inform urgent)	s.gel green (0.75ml) green form		
Glucose	Fluoride-Hep yellow (0.5ml		
Blood gas with lactate	-		
Microbiology: Blue Forms			
Blood Culture blue form	2-10 ml		
Blood Viral PCR EBV, CMV, adenovirus, enterovirus, HSV & VZV	EDTA pink 2ml **plus** IF POSSIBLE extra 2 ml – please store		
***ASOT & save serum	s.gel green (2ml)		
SARS-CoV2 serology	s.gel green (2ml)		
NPA or throat & deep nose swab: Resp virus& mycoplasma SARS-CoV-2 PCR	Green swab		
Urinalysis	-		
Urine culture	-		
Stool culture +/-bacterial PCR	-		
Stool viral pathogen PCR	-		
Throat swab culture	BLACK SWAB		
Immunology: Blue forms			
***IgG, IgA, IgM	s.gel green (2ml)		

PID panel (can wait if limited blood)	EDTA pink 1ml		

PRIOR TO IVIG

If abdominal symptoms Abdo USS +/- Abdo CT

	Comment	**Date**	**Result**
Radiology:			
ECHO	**ECHO – ASAP by PEC/suitable sonographer**.		
CXR	Even if no respiratory symptoms		
Abdomen If abdominal symptoms	AUSS or CT as per local decision		
Other:			
ECG:	Most commonly: sinus tachycardia with non-specific ST segment and T wave changes.		

PIMS TS *DAILY MONITORING* LABORATAORY INVESTIGATIONS

If PIMS-TS is diagnosed or until excluded please monitor bloods. These bloods should be done daily ideally before 8am (or at 9am if not possible earlier) to inform management.

PiMS-TS and acute severe COVID-19 are new clinical syndromes in children. There is little known about the clinical progression and these bloods are **vital** in assisting management decisions.

As a default once on a "PIMS-TS pathway" the bloods below should be done AS A MINIMUM 24 hourly.

Please ✓when bloods done and specify time for next sample in next column see grey text as example

Tests	Bottles	Date/time	Date/time	Date/time	Date/time	Date/time
		19/11 8am				
Haematology: Pink forms						
FBC and film	EDTA pink (1ml)	✓				
Coagulation &fibrinogen D-Dimer	Citrate purple (1ml) Ensure filled to line or send 2 bottles	✓				
Biochemistry: Green Forms						
U&E LFT CRP Triglycerides Ferritin LDH CK amylase	Li-Hep orange (2 ml)	✓				
Troponin & BNP can go in same bottle but need >1ml for both. **Please call biochemistry and inform coming**						
Troponin	s.gel green (0.5 ml) green form	✓				
Pro-BNP	s.gel green (0.75ml) green form	✓				

Other: (please specify)						

ECHO		
Date of scan Eg 19/11/20	Planned date of next ECHO 21/11/20	Indication to alert cardiology sooner New fever, CVS unstable

46703

Initiating thromboprophylaxis for PIMS-TS (Page 1 of 2)

Appendix B: Guideline for PIMS-TS: Diagnosis and Management

Name:		Age:	Date form completed:
Hospital no:		BMI:	BMI centile for age:
Date of birth NHS Number:		D-dimer:	D-dimer upper limit for age: 5 x D-dimer upper limit for age:
		Serum Creatinine:	
Weight (kg):	Height (cm):	eGFR:	

BMI: weight ÷ (height)^2 *BMI centile for age: Plot on EDMS/RCPCH charts*
eGFR: k x height (cm) ÷ serum creatinine. K = 40 if > 1 month old. K = 30 if < 1 month old

Step 1: Consider thrombosis and bleeding risk factors for hospital acquired VTE associated with PIMS-TS (tick all that apply)

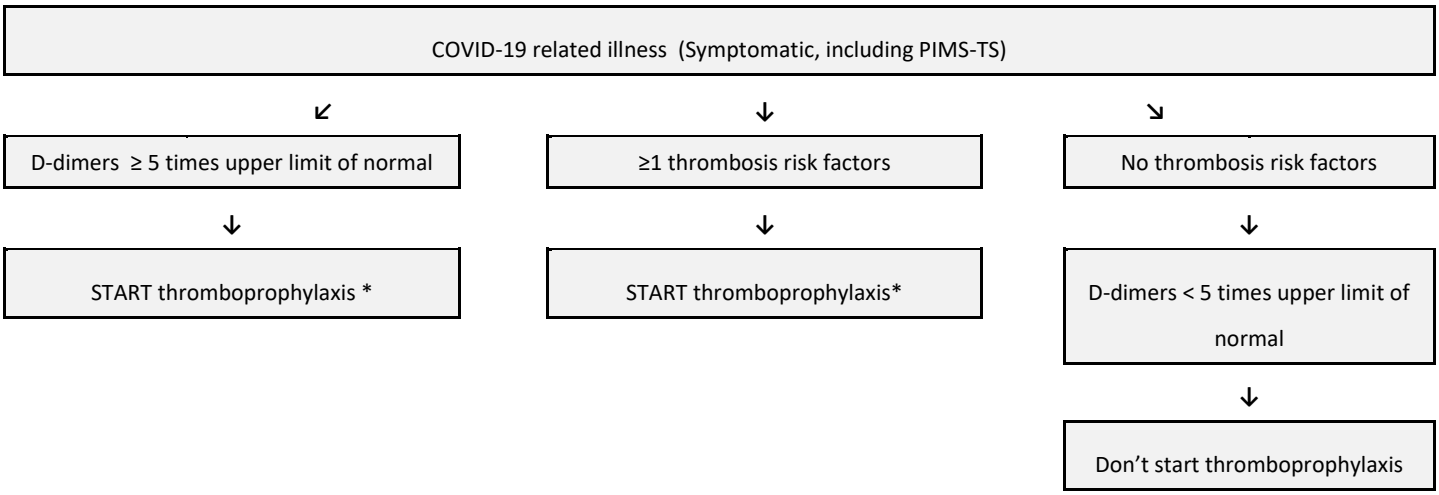
THROMBOSIS RISK FACTORS	Tick	BLEEDING RISK FACTORS *	Tick
Pubertal, post pubertal, or age > 12 years		Thrombocytopenia (platelets < 20-50)	
Central venous catheter		Low fibrinogen (fibrinogen <1)	
Mechanical ventilation		Major bleeding	
Prolonged length of stay (e.g. anticipated >3 days)		Acquired bleeding disorders (e.g. liver failure)	
Complete immobility		Aspirin > 5 mg/kg/day for conditions other than PIMSTS	
Obesity (i.e. BMI > 95th percentile)		Uncontrolled systolic hypertension (>230/120 mmHg)	
Active malignancy, nephrotic syndrome, cystic fibrosis exacerbation, sickle cell disease vaso-occlusive crisis, or flare of underlying inflammatory disease (e.g. inflammatory bowel disease, lupus, juvenile idiopathic arthritis)		Untreated inherited bleeding disorders (e.g. haemophilia, vWD)	
Congenital or acquired cardiac disease with venous stasis or impaired venous return		Concurrent use of anticoagulants known to increase risk of bleeding (e.g. warfarin with INR>2)	
Previous history of VTE		Acute stroke	
First degree family history of VTE before age 40 years or unprovoked VTE		Neurosurgery, spinal surgery, eye surgery	
Known thrombophilia (e.g. protein S, protein C, antithrombin deficiency, factor V leiden, factor II G20210A, persistent antiphospholipid antibodies		Other procedure with bleeding risk e.g. LP	
Receiving oestrogen-containing oral contraceptive pill			
Post splenectomy for underlying haemoglobinopathy			

*** If any bleeding risk factor is present, a consultant decision is needed to start thromboprophylaxis.**

Step 2: Flowchart to determine whether to start thromboprophylaxis **

If bleeding risk is present - discuss with consultant before starting thromboprophylaxis

***** Add mechanical thromboprophylaxis if the child is post-pubertal or over 40kg regardless of risk factors***



Step 3: Prescribe thromboprophylaxis appropriately and document in notes

- Anticoagulant thromboprophylaxis should not be routinely prescribed in hospitalised children with asymptomatic COVID-19 infection in the absence of risk factors for hospital associated VTE
- **eGFR determines the choice of thromboprophylaxis medication**
  - If eGFR>30, use enoxaparin (low molecular weight heparin)
  - If eGFR is <30, consider use of unfractionated heparin instead of low molecular weight heparin – see SCH Heparin guidelines
- **What about mechanical thromboprophylaxis?**
  - Add mechanical thromboprophylaxis (TED stockings or flowtron boots) in all post-pubertal children, >40kg or if possible in those who cannot have anticoagulation – see SCH thromboprophylaxis guidelines
- **Dose of enoxaparin:**

Age/Actual body weight	***Dose (subcutaneous)***
<2 months	*0.75mg/kg/dose 12 hourly*
2 months of age and <40kg	*0.5mg/kg/dose 12 hourly*
40-100kg	*40mg 24 hourly*
100-150kg	*40mg 12 hourly*
>150kg	*60mg 12 hourly*

Next steps: Consider need for monitoring

- **Anti-Xa level monitoring is not routinely done for prophylactic doses**
  - Consider monitoring in cases of obesity (BMI >30), renal insufficiency, clinically unstable (for senior discussion)

Outcome on thromboprophylaxis	**Indicated? *(tick)***		**Date prescribed**
No thromboprophylaxis indicated			N/A
Mechanical thromboprophylaxis			
Enoxaparin (low molecular weight heparin)			
Unfractionated heparin			
	Monitoring		
Is anti-Xa monitoring indicated?		YES / NO ***(circle)***	
When is anti-Xa monitoring due?		***(Date)***	

Signed:…….. Name…….. GMC…….. Date……