Guideline for treatment of suspected and confirmed paediatric multisystem inflammatory syndrome temporally associated with COVID-19 (PIMS-TS)

Introduction

This document outlines the pharmacological treatment options for the management of suspected and confirmed paediatric multisystem inflammatory syndrome / hyper-inflammatory patients associated with COVID-19 (PIMS-TS)

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For information including definition, clinical management, monitoring and the general principles to treatment, refer to RCPCH guidance entitled: **Guidance: Paediatric multisystem inflammatory syndrome temporally associated with COVID-19.**

The following treatments are changing rapidly
Please ensure you are using the most up to date version of this guidance.

- Treatment must only be initiated once the MDT has been consulted.
- Consideration for enrolment into RECOVERY trial must be considered for all patients with suspected COVID-19 OR PIMS-TS, except those displaying a kawasaki like presentation.
- Patients enrolled in the RECOVERY trial are advised to follow the doses as outlined in the trial document.

TREATMENT

1. Intravenous antibiotics – do not delay.

   Clindamycin must only be prescribed if suspicion of toxic shock syndrome is present.

   Children under the age of 1 month: Cefotaxime, Amoxicillin and Clindamycin (See Paediatric microguide)

   Children over the age of 1 month:
   Ceftriaxone
   Child 1 month–12 years: 80mg/kg IV once daily
   Child 12-18 years: 2-4g daily

   Clindamycin
   Child 1 month–18 years: 10mg/kg (max 1.2g) qds IV in severe infections
   Total daily dose may alternatively be given in 3 divided doses

   Duration: Until Review by MDT

2. Human iv immunoglobulin (IVIG) – Must be prescribed by brand

Formulation: Choose brand based on the nearest vial size to limit wastage.

a. **INTRATECT 50 mg/ml – 20ml (1g), 50ml (2.5g), 100ml (5g) and 200ml (10g)**

b. **IQYMUNE 100 mg/mL - 20ml (2g), 50ml (5g), 100ml (10g) and 200ml (20g)**

Supply permitting, otherwise any available product

Dose: 2g/kg - usually a single dose infusion, may be repeated according to clinical status. To avoid hyper viscosity, the second dose should be reduced to 1g/Kg if given within 48 hours of the first dose.

Administration: Medusa

Use **ideal body weight** for patients who are overweight. (Appendix 1)
Notes: Indicated for all clinical presentations of PIMS-TS including Toxic Shock Syndrome, typical or atypical Kawasaki Disease +/- Myocarditis. Myocardial inflammation/coronary artery abnormalities.
Round down to closest whole vial size

Procurement: Not stored in pharmacy, obtain from Blood Bank.

3. Aspirin – (As per All Wales PIMS-TS Pathway)

Dose: 5mg/kg OD (Higher doses may only be used after discussion with cardiology).

Max dose: Weight: 15kg – 49kg = **75mg**
Weight: ≥50kg **= 150mg**

Adverse effects: Gastritis – Max dose Lansoprazole must be prescribed alongside aspirin therapy. See appendix TWO for Lansoprazole dosage and administration.

Duration: Until ECHO performed at 6-8 weeks and then reviewed.

Administration: 75mg soluble tablets, round to a measurable dose, fractions of tablets can be given.

4. VTE prophylaxis - On advice of PIMS-TS Core MDT

Children over the age 16: See adult guidelines on intranet (reducing the risk of venous thromboembolism in adult patients Admitted with suspected or confirmed covid-19.)

All children over 12 years of age should wear compression stockings.

Prophylactic enoxaparin

Indication: Significantly immobilised **or** central line

Contraindication: Active bleeding/high risk of bleeding, lumbar puncture or epidural anaesthesia within the past 6h or due in the next 24h, severe hypertension over the 99th centile, thrombocytopenia: platelet count < 50 x 109 /L, acute bacterial endocarditis

For invasive procedures (LP or operations) must be >24hours off last dose before needle/knife to skin.

Dose:
Children under the age of 1 month
750micrograms/kg twice daily (Round to the nearest mg for ease of administration)

Children over the age of 1 month – 16 years
500micrograms/kg twice daily. MAX: 40mg

Renal impairment: If eGFR under 30ml/min – discuss options with renal.

Age	**Estimated eGFR equation** (mL/minute/ 1.73 m2)
Child over 1 year:	40 x height (cm)/serum creatinine (micromol/ litre)
Child between 1 month and 1 year:	35 x height (cm)/serum creatinine (micromol/ litre)
Neonate	30 x height (cm)/serum creatinine (micromol/ litre)

Administration: See Paediatric Thrombosis and Anticoagulation Guidelines (2014).

Treatment dose enoxaparin

Indication: Confirmed thromboembolism/significant coronary artery aneurysm

If platelets <50 x10^9/L then discuss with paediatric haematology. As a guide: in first month of treatment support platelets with transfusion and keep above 50. Once out of first month then stop when platelets fall to < 50

For invasive procedures (LP or operations) must be >24hours off last dose before needle/knife to skin.

Refer to Paediatric Thrombosis and Anticoagulation Guidelines (2014) or Cardiology clinical guidelines (2019) for information on Dosage, Monitoring and Factor Xa Levels. Both can be found on the "Paediatric Cardiology" section of intranet

5. Steroids – On advice of PIMS-TS Core MDT

Methylprednisolone – 1st line steroid

Formulation: Injection as **sodium succinate**, 40mg, 500mg and 1g

Dose: 10mg/kg IV Once daily (up to 30mg/kg on advice of PIMS-TS Core MDT)

Maximum daily dose: 1g

Duration: 3 days without weaning (up to 5 days on advice of PIMS-TS Core MDT)

Monitoring: TPR and BP before the start and every 15 minutes during infusion.
Monitor urine sugar before and after infusion and 2 hours later.

Common side effects: Light-headed, dizzy, nauseous, or has increasing headache.
- Action required: check TPR and BP and consider slowing or stopping the infusion.

Inform the medical team.
Specific intervention required if:
• BP rises by >30mmHg (hypertension)
• BP falls accompanied by symptoms such as light-headedness
• Severe tachycardia (>150 bpm or patient feels palpitations or light-headed)
• Altered conscious state, seizures and psychosis
STOP infusion and obtain immediate medical review
Common mild side effects not requiring intervention: facial flushing, metallic taste, hyperactivity, mood changes.

Notes: Indicated for clinical presentations which include atypical Kawasaki Disease or persistent systemic inflammation following IVIG administration.
Aim to adjust doses to morning as soon as possible as interferes with sleep.
If multiple patients present aim for similar administration timings to enable vial sharing.

Prednisolone – (on advice from PIMS-TS Core MDT)

Conversion: 5mg of prednisolone = 4mg of methylprednisolone.

Formulation: 5mg tablets

Dose: 2mg/kg in acute phase if IV access not available, round to nearest 5mg.

Max dose: 40mg (60mg may be used on Paediatric Rheumatology advice).

Weaning: Time frame and dose (usually 1mg/kg (max 40mg)) as directed by PIMS-TS Core MDT.

Adverse Effect: Gastritis - Max dose Lansoprazole must be prescribed alongside steroid treatment.

6. Immune Modulation Therapy – On advice of PIMS-TS Core MDT

The choice of which agent to use will be decided on a case-by-case basis

Tocilizumab via **Recovery Trial** if clinical equipoise as per All Wales PIMS-TS Treatment Pathway.
Standard treatment:
If features are representative more of an atypical Kawasaki picture with cardiac involvement then infliximab would usually be first choice.
If features are representative more of a macrophage activation syndrome (MAS)/ sHLH picture then anakinra would usually be first choice.

Infliximab (Inflectra) (TNFα)

Formulation: IV powder for reconstitution 100mg

Dose: 5-6mg/kg (rounded to the nearest vial size) on advice of PIMS-TS Core MDT

Duration: ONCE only – not to be repeated unless under cardiology advice

Administration: See MEDUSA

Notes: Hypersensitivity reactions reported during the infusion and up to 2 hours after. Ensure rescue medications are prescribed prior to administration:

Drug	Dose	Route
Chlorphenamine	6months – 6 years:2.5mg 6-12 years: 5mg 12-18 years: 10mg	IV
Paracetamol	15mg/kg/dose	PO
Hydrocortisone	6months – 6 years: 50mg 6-12 years: 100mg 12-18 years: 200mg	IV infusion (see medusa)

Anakinra (IL-1 Inhibitor)

The choice of route will be determined by the PIMS-TS Core MDT. Either intravenous or subcutaneous route will be chosen depending on the clinical severity of the patient.
Note: intravenous dosing of anakinra achieves a higher and faster maximal plasma concentration (higher Cmax and shorter Tmax), compared with subcutaneous delivery. I/V route also preferred if:
- High doses (>2 mg/kg per day or >100 mg daily) required
- Platelets <20 × 109/L or haemorrhagic complications
- SC skin oedema
- Neurological symptoms

Subcutaneous:

See BNFc for dosing, adverse effects, monitoring requirements, cautions and contraindications.

Max dose: 8mg/kg per day or 600mg per day.

Intravenous:

Formulation: 100mg in 0.67ml pre-filled syringes

Dose: I/V 2mg/kg BD increasing by 2mg/kg/day until response/max dose achieved

Max dose: IV 12mg/kg per day (6mg/kg BD) – **only to be used in PCCU** on advice of Paediatric Rheumatology ONLY.

Maximum daily dose: 400mg (i.e. 200mg per dose)

Administration: Dilute in a suitable volume of Sodium Chloride 0.9% and give as IV bolus over 3-5mins or add anakinra dose to 50ml NaCl 0.9% before infusing intravenously, over 30 minutes.
Adverse effects: Headache; infection; neutropenia; thrombocytopenia
Cautions:
- confer an increased risk of infection, so careful assessment of co-infection should be made prior to use
- Ensure absolute neutrophil count is more than 1.5 x 10^9/litre
- Ensure **IL6 and soluble CD25 levels** are taken prior to use (if locally available)
- Duration depending on clinical response, review daily

Continuous Intravenous Infusion:

Continuous IV infusion is only to be used in patients who are critically unwell with significant oedema and capillary leak or unresponsive or has a contraindication to subcutaneous or IV bolus anakinra. Only on the advice of a Paediatric Rheumatology Consultant.

Change to subcutaneous administration as soon clinically appropriate.

Loading dose: 2mg/kg stat

Dose: 2mg/kg/day increasing by 2mg/kg/day every 12 hours if unresponsive to previous dose.

Max dose: 12mg/kg/day

Maximum daily dose: 400mg (excluding loading dose)

Administration (Via Syringe pump)

Weight	Concentration	Diluent	Starting rate of infusion (dose)
<20kg	100mg in **24ml** total volume	Sodium Chloride 0.9%	**0.02ml**/kg/hour (2mg/kg/hour)
>20kg	100mg in **12ml** total volume	Sodium Chloride 0.9%	**0.01ml**/kg/hour (2mg/kg/hour)

SYRINGE MUST BE CHANGED EVERY 8 HOURS

Compatibility: Anakinra should not be administered concomitantly via Y-site or mixed with any other medications due to lack of compatibility information.

Toculizumab (IL- 6 Inhibitor)

See RECOVERY trial.

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Appendix One – IBW

As there is no consensus on the best method or formula to use to calculate IBW, consistency in the method used is essential. The reverse BMI method (demonstrated below) is most preferable as it can be applied consistently to all children between 2 and 20 years.

BMI Method

The equation for BMI can be used in reverse to determine IBW:

$IBW = BMI_{50} \times \text{height } (m^2)$

Where BMI_{50} represents the 50th centile of a BMI chart, which is the ideal BMI for their height, age and gender (4). BMI charts[i] are available from the Royal College of Paediatrics and Child Health website.

[i] Royal College of Paediatrics and Child Health. Body Mass Index (BMI) Chart [accessed 20/08/18]. Available from: https://www.rcpch.ac.uk/resources/body-mass-index-bmi-chart

Box 1: Example of IBW calculation using the BMI method

A 7 year old girl who is 1.2m tall

$BMI_{50} = 15.6 kg/m^2$ (using Girls UK Body Mass Index 2-20 years chart)

$IBW = BMI_{50} \times \text{height } (m^2) = 15.6 \times 1.2 \times 1.2 = 22.5 kg$

Appendix Two - Lansoprazole

Body weight	Dose	Notes
>30kg	15-30mg daily in the morning	
15-30kg	15mg daily in the morning	
7.5-15kg	7.5mg daily in the morning	Use half 15mg FasTab
2.5-7.5kg	3.75mg daily in the morning	Use quarter of 15mg FasTab
<2.5kg	1mg/kg daily in the morning	

Administration – See “Lansoprazole in children - C&V Guideline for administration” located on INFORM under lansoprazole