APPENDIX C:

Paediatric **I**nflammatory **M**ultisystem **S**yndrome- **T**emporally associated with **S**ARS CoV-2 (PIMS-TS) **/**
Multisystem **I**nflammatory **S**yndrome in **C**hildren (**MIS-C)**

Version 2. For updated document please see online version here

Authors: Helena Rabie, Kate Webb, Christiaan Scott, Eric Decloet, Helmuth Reuter, Mignon McCulloch, John Lawrenson, Deepthi Abrahams, Mark Cotton, Liesl Zühlke.
Stellenbosch University and University of Cape Town Paediatrics Departments

Introduction:
In May 2020, a paediatric inflammatory multisystem syndrome was observed in association with CoVID-19. Clinical features varied between a Kawasaki-Disease (KD) like illness with both typical and atypical features and toxic shock syndrome presentations. Tables with the clinical features of these conditions are below. The full spectrum of disease is not known, and management not been studied prospectively. It may be difficult to distinguish this from typical KD (that may occur with an increased frequency) and incomplete KD and toxic shock due to gram positive infections. [1,2,3] There are slight differences in the case definitions between the UK, WHO and USA but the principles of the diagnosis are similar and are highlighted in table 1.[4-7]

Table 1: Essential components for the diagnosis of PIMS-TS /MIS-C [(4-7)] *Please see* Figure 1 as well	
	Description
1. Child	In the USA this includes adolescents up to 21 years of age.
2. Fever	> 38.5ºC
3. Single OR multiorgan dysfunction	**Organ dysfunction includes**: Shock, cardiac, respiratory, renal, gastrointestinal or neurological disorder **Feature may include:** Hypotension, tachycardia confusion, headache, syncope, conjunctivitis, respiratory symptoms including cough or supplemental oxygen requirement, sore throat, mucous membrane changes lymphadenopathy, neck swelling abdominal pain, diarrhoea, vomiting, rash, swollen hands and feet
4. Clear evidence of inflammation (Not all test on all patients)	**Laboratory parameters include features of an exaggerated inflammatory response and cytokine storm and include:** **Raised** C-Reactive protein (CRP), erythrocyte sedimentation rate (ESR), procalcitonin (PCT), fibrinogen, d-dimer, ferritin, lactic acid dehydrogenase (LDH), neutrophils, troponin T and Pro BNP. **Reduced** lymphocytes and low albumin
5. No clear other cause	**Consider:** 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 or management)
6. **SARS-CoV-2 PCR testing** may be positive or negative, if possible/available antibody test should be performed	

Table 2: Principles of early general management and investigations of PIMS-TS /MIS-C	
Principle	**Action**
Discuss all cases with possible PIMS-TS /MIS-C with paediatric rheumatology (Rheum) and Infectious diseases (ID) as soon as you suspect it.	
1. Treated as PUI for suspected COVID-19	Cohort or isolate and do the SARS-COV-2 PCR
2. Consider sepsis as a possibility	Early appropriate antibiotic that covers the clinical presentation and refer to local guidance with appropriate cover of *Staphylococcus aureus* and group A streptococci, if toxic shock criteria are met clindamycin can be considered as an addition and if vasculitis present tick born illness should be considered.
3. Monitor cardio-respiratory function closely.	Mild disease • May only require supportive care. Moderate to severe disease • Early referral to intensive care or hospital with intensive care
4. Laboratory investigations	In all suspected cases Blood culture FBC and differential diagnosis Electrolytes, urea and s-creatinine, AST and ALT CRP, PCT, ESR, ferritin Clotting profile, fibrinogen and d-dimers

	Other tests depending on the clinical presentation and after discussion e.g. Troponin T and pro BNP (Refer to appendix 1 – investigation checklist)[4]
5. Other investigations	CXR, ECG, serial echocardiography

Specific Treatment
The following treatment guidelines serve as an interim, local, consensus-based guidance as evidence-based guidelines do not currently exist. The guidance will be updated as evidence becomes available. Children that clearly meet the KD clinical definition AND are of a typical age for KD should be managed as KD and this guide does not aim to replace management guidelines for KD.

Table 3. Suggested initial targeted therapy		
INITIAL therapy **Review the diagnosis and particularly in the case of children with TSS ensure that a source on infection was not overlooked**		
*Kawasaki criteria met and typical age stable and not shocked Child less than 4 with incomplete KD and stable	IVIG**	2g/kg over 12-48 hours
	/Anti-coagulation	Aspirin: 3-5mg/kg/day Heparin/LMWH*** if evidence of thrombosis or if large coronary artery aneurysm (Discuss with cardiology) Avoid Aspirin if platelets below 80 000
	Steroids	Oral prednisone 2mg/kg/day per os for 5 days if Kobayashi risk score ≥ 4 for children of Asian descent and ≥5 for other children. Tapering of oral steroids should be discussed and depends on the clinical response. D/W Rheum
Kawasaki-like illness but in PICU with shock OR MAS (particularly consider the age of the child)	IVIG**	2g/kg over 12-24 hours
	/Anti-coagulation	Aspirin: 3-5mg/kg/day Heparin/LMWH*** if evidence of thrombosis or if large coronary artery aneurysm or if EF < 30% (Discuss with cardiology) Avoid Aspirin if platelets below 80 000
	Steroids	IVI methylprednisolone 10mg /kg/day pulse 3 days followed by an oral tapering
Toxic shock like illness(definition) with out MAS (definition) and not Catecholamine resistant	IVIG**	2g/kg over 12-24 hours
	/Anticoagulation	Heparin/LMWH*** if evidence of thrombosis or if large coronary artery aneurysm or if EF < 30% (Discuss with cardiology/ICU)
	Steroids	Only after review
Toxic shock-like illness with Catecholamine resistant shock AND / OR MAS	IVIG**	2g/kg over 12-24 hours
	Aspirin	Heparin/LMWH*** if evidence of thrombosis or if large coronary artery aneurysm or if EF < 30% (Discuss with cardiology/ICU)
	Steroids	IVI methylprednisolone 10 mg/kg/day pulse 3 days followed by oral tapering
***Follow established KD guidelines for diagnosis and management**		

Table 4. Suggested management of IVIG failure		
THERAPY FOR INITIAL FAILURE of IVIG Failure of initial therapy should be considered with if continued fever after 36 hours post initial therapy and increasingly raised or poorly responding inflammatory markers (note that ESR should not be used after IVIG Discuss ALL children with paediatric rheumatology Review the diagnosis and particularly in the case of children with TSS ensure that a source on infection was not overlooked Consider additional investigations as indicated and repeat ECHO		
Typical Kawasaki with IVIG resistance and not shocked and initial treatment did NOT include any steroids	IVIG repeat**	2g/kg over 12-24 hours
	Aspirin/Anticoagulation	3-5mg/kg/day
	Steroids	IVI methylprednisolone 10-30mg/kg pulse/day (max 800mg) plus 3 days oral taper with oral prednisone 2m/kg/day(do not exceed 60 mg) and wean further as discussed with Rheumatologist

IVIG resistant Kawasaki disease and not shocked but initial treatment DID include oral steroids	IVIG repeat**	2g/kg over 12-24 hours
	Aspirin/anticoagulation	Aspirin: 3-5mg/kg/day Heparin/LMWH*** if evidence of thrombosis or if large coronary artery aneurysm (Discuss with cardiology) Avoid Aspirin if platelets below 80 000
	Steroids	Escalate to IVI methylprednisolone 10-30mg/kg/day (max 800mg) pulse 3 days and taper with oral prednisone 2m/kg/day (do not exceed 60 mg) and wean further as discussed with Rheumatologist
	Biologics	Consider infliximab after consultation with Rheumatologist
Kawasaki like illness but in PICU with shock OR MAS (particularly consider the age of the child)	IVIG**	2g/kg over 12-24 hours
	Aspirin/Anticoagulation	Aspirin: 3-5mg/kg/day Heparin/LMWH*** if evidence of thrombosis or if large coronary artery aneurysm (Discuss with cardiologists) Avoid Aspirin if platelets below 80 000
	Steroids	Consider escalation to IVI methyl prednisolone 10-30mg/kg pulse and then taper with oral prednisone 2m/kg/day (do not exceed 60 mg) and wean further as discussed with Rheumatologist .
	Biologics	Disease process more typical of KD consider toclizumab, infliximab or anakinra* after consultation with Rheumatologist
Toxic shock like illness initially treated with only IVIG	IVIG**	Consider repeating BUT discuss with rheumatolog
	Aspirin/Anticoagulation	Heparin/LMWH*** if evidence of thrombosis or if large coronary artery aneurysm (Discuss with cardiology)
	Steroid	IVI methyl prednisolone 10mg/kg/d pulse for 3 days followed by oral tapering of 2m/kg/day (do not exceed 60 mg) and wean further as discussed with Rheumatologist .
	Biologics	Consider tocilizumab after discussion with rheumatology. In case use of tocilizumab contraindicated, Anakinra* may be considered.
Toxic shock like illness Catecholamine resistant shock OR MAS on steroid pulse	IVIG**	Consider repeating BUT discuss with rheumatology
	Aspirin/Anticoagulation	Heparin/LMWH*** if evidence of thrombosis or if large coronary artery aneurysm (Discuss with cardiology)
	Steroid	Complete 3 day IVI pulse and continue to oral tapering starting at 2mg/kg/day oral prednisone (do not exceed 60 mg) and wean further) as discussed with Rheumatologist
	Biologics	Consider tocilizumab after discussion with rheumatologist. In case use of tocilizumab contraindicated, Anakinra* may considered.

Follow up: If criteria for KD are met children should be followed up as per KD guidelines.

Case Reporting: As this is an evolving disease, patients should all be offered recruitment into a paediatric data registry and clinical data. Were additional biomarker studies can be done of if clinical studies are available on research protocol patients should be offered enrolment

Table 5: DIAGNOSTIC GUIDE TO KAWASAKI DISEASE - Adapted from 8 and 9	
KAWASAKI DISEASE "TYPICAL" presentation"	
Fever persisting for at least 5 days, PLUS 4 of the 5 criteria:	
1. Conjuntivitis	Typically Bilateral, "dry" or non-purulent, painless and in the bulbar distribution.
2. Lymphadenopathy	Cervical, most commonly unilateral, tender. At least one node >1.5cm.
3. Rash	Polymorphous; without vesicles, bullae or crusts; occurring in the first few days, involves the trunk and extremities. Variable presentations such as urticarial, morbilliform, maculopapular, or resembling scarlet fever
4. Lips and mucosa	Intense hyperaemia of lips leading to redness and cracking and/or diffuse erythema of oropharynx. Strawberry tongue.
5. Extremities	Hyperaemia and painful oedema of hands and feet that progresses to desquamation in the convalescent stage. Perineal desquamation frequently associated.
Consider the following as well • Typically KD is an illness affecting children younger than 4 years of age • Irritability is very frequently present, although not included as a diagnostic criterion. • Diagnostic features may present sequentially. • Common findings outside the diagnostic criteria include arthritis, aseptic meningitis, sterile pyuria and dysuria • Diagnosis in children less than 6 months may be more difficult	
KAWASAKI DISEASE "INCOMPLETE presentation"	
Fever for ≥5 days plus two or three of the aforementioned clinical criteria.	
In these children consider the following laboratory criteria Anaemia for age Platelet count ≥450,000 after the seventh day of fever Albumin ≤30 g/L Elevated ALT level WBC count ≥15,000/mm^3 ≥10 WBC/hpf on urinalysis	Also look at the ECHO

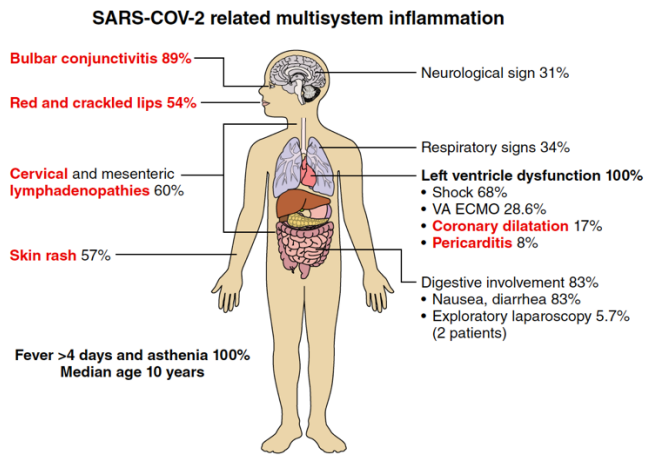

Table 6 KOBAYSHI SCORE [10$]		
Variable	Definition	Points
Sodium	≤133 mmol/l	2
Days of illness at time of initial treatment	≤4	2
AST	≥100IU/L	2
%neutrophils	≥80%	2
CRP	≥100mg/L	1
Age	≤12 months	1
Platelets	$\leq 300 \times 10^{9/L}$	1

$: Note this score has not been validated in children who are not of Japanese ethnicity. It is included here as a guide to features of severity and likely IVIG failure.

Table 7 Diagnostic criteria for Group A streptococcal and staphylococcal toxic shock [Adapted from 11,12]	
A] Hypotension. systolic blood pressure <5th percentile for age in children <16 years)	
Group A Streptococcal toxic shock Infection can be at any site but most often occurs in association with infection of a cutaneous lesion. Signs of toxicity and a rapidly progressive clinical course are characteristic	**Staphylococcal toxic shock diagnostic criteria**
CLINICAL CRITERIA	
Hypotension. systolic blood pressure <5th percentile for age in children <16 years) AND	**Hypotension.** systolic blood pressure <5th percentile for age in children <16 years)
	Fever: greater than or equal to 38.9°C)
	Rash: diffuse macular erythroderma
	Desquamation: 1-2 weeks after onset of rash
Multi system disease with **2 or more** of the following:	Multi system disease with **3 or more** of the following
• Renal involvement: Creatinine greater than or equal to twice the upper limit of normal for age	Renal involvement: Urea or Creatinine greater than or equal to twice the upper limit of normal for age OR pyuria (>5 leukocytes/high-power field) in the absence of urinary tract infection
• Coagulopathy: Platelets less than or equal to 100,000/mm^3 (less than or equal to 100 x 10^6/L) or disseminated intravascular coagulation, defined by prolonged clotting times, low fibrinogen level, and the presence of fibrin degradation products	Coagulopathy: Platelets less than or equal to 100,000/mm^3
• Liver involvement: Alanine aminotransferase, aspartate aminotransferase, or total bilirubin levels greater than or equal to twice the upper limit of normal for the patient's age	Liver involvement: Alanine aminotransferase, aspartate aminotransferase, levels greater than or equal to twice the upper limit of normal for the patient's age
• Acute respiratory distress syndrome: defined by acute onset of diffuse pulmonary infiltrates and hypoxemia in the absence of cardiac failure or by evidence of diffuse capillary leak manifested by acute onset of generalised oedema, or pleural or peritoneal effusions with hypoalbuminemia	
• A generalized erythematous macular rash that may desquamate.	
• Soft-tissue necrosis, including necrotizing fasciitis or myositis, or gangrene.	
	Gastrointestinal: Vomiting or diarrhoea at onset of illness
	Muscular: Severe myalgia or creatine phosphokinase elevation >2 times the upper limit of normal
	Mucous membranes: Vaginal, oropharyngeal, or conjunctival hyperaemia
	Central nervous system: Disorientation or alterations in consciousness without focal neurologic signs when fever and hypotension are absent

MICROBIOLOGICAL	
Culture POSITIVE only for Group A Streptococcus or NEGATIVE with no aetiology identified	Cultures (blood or cerebrospinal fluid) negative for alternative pathogens (blood cultures may be positive for *Staphylococcus aureus*)
Probable diagnosis: Meet the above clinical criteria (in the absence of another identified aetiology for the illness) with isolation of GAS from a nonsterile site **Confirmed diagnosis**: Meet the above clinical criteria, with isolation of GAS from a normally sterile site	**Probable case**: A case which meets the laboratory criteria and four of the five clinical criteria **Confirmed case**: A case which meets the laboratory criteria and all five of the clinical criteria, including desquamation

Table 8: Ravelli diagnostic criteria for macrophage activation syndrome [13] (Developed for rheumatological disorders)
Fever AND Ferritin >684ng/mL AND
2 or more of the following • Platelet count ≤181 X 109/L; • Aspartate aminotransferase >48 units/L; • Triglycerides >156 mg/dL; or fibrinogen ≤360 mg/dL.

Appendix 1 Investigation checklist [4](Discuss with Rheumatology ID team)				
Initial investigations	**KD Classic**	**KD- Associated SARS-COVID 2**	**PIMS TS**	**Result**
Blood culture	All	All	All	
FBC and Film	All	All	All	
ESR	All	All	All	
CRP	All	All	All	
PCT	Local policy Discuss with ID	Local policy Discuss with ID	Local policy Discuss with ID	
U+E	Sodium for all and rest as needed	Sodium for all and rest as needed	All	
AST, ALT, Albumin	All	All	All	
Blood gas with lactate	Clinical indication	Clinical indication	All	
Coagulation + fibrinogen+ D-Dimer	MAS/Shock	MAS/Shock	All	
LDH	MAS/Shock	MAS/Shock	All	
CK	If shocked	If shocked	All	
Triglycerides	If MAS suspected	If MAS suspected	All	
Ferritin	If MAS suspected	If MAS suspected	All	
Troponin	OR Abn ECG Shock	OR Abn ECG Shock	OR Abn ECG Shock	
Pro-BNP	(after discussion with Cardiology)	(after discussion with Cardiology)	(after discussion with Cardiology)	
LP	Clinical need	Clinical need	Clinical need	
ECHO	All	All	All	
RV16 respiratory testing	If diagnosis unsure	If diagnosis unsure	All	
SARS-CoV-2 PCR respiratory test	All	All	All	
Throat swab	If scarlet fever concerning	If scarlet fever concerning	If scarlet fever concerning	
ASOT/Anti-DNASE B	If scarlet fever concerning	If scarlet fever concerning	All	
SARS-COV2 serology	If possible or store	If possible or store	If possible or store	
Stool for enterovirus	If shocked Guided by ID	If shocked Guided by ID	If shocked Guided by ID	

Urinalysis an urine dipsticks	All	All	All	
Assessment for rickettsia	Only of diagnosis in doubt and after d/w Micro and ID should not prevent therapy if tick byte suspected			
Other testing for infections	D/w ID			
Save EDTA and serum for PCR and	WITH CONSENT AND AS PART OF A RESEARCH PROJECT			
CXR	All	All	All	
ECG	All	All	All	
Ultrasound Abdomen	As needed	As needed	As needed	

Reference

1. Verdoni L et al. An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study. The Lancet. Published online. 13 May 2020. https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)31103-X/fulltext
2. Viner RM and Whittaker E. Kawasaki-like disease: emerging complication during the COVID-19 pandemic. Published online 13 May 2020. https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)31129-6/fulltext
3. Riphagen S et al. Hyperinflammatory shock in children during COVID-19 pandemic. The Lancet. Published online 6 May 2020. https://www.thelancet.com/pdfs/journals/lancet/PIIS0140-6736(20)31094-1.pdf (PDF
4. Royal College of Paediatrics and Child Health Guidance –Paediatric multisystem inflammatory syndrome temporally associated with COVID-19. 5 May 2020. https://www.rcpch.ac.uk/resources/guidance-paediatric-multisystem-inflammatory-syndrome-temporally-associated-covid-19
5. European Centre for Disease Prevention and Control Paediatric inflammatory multisystem syndrome and SARS-CoV-2 infection in children. https://www.ecdc.europa.eu/sites/default/files/documents/covid-19-risk-assessment-paediatric-inflammatory-multisystem-syndrome-15-May-2020.pdf
6. Centre for Disease Control Multisystem Inflammatory Syndrome in Children (MIS-C) Associated with Coronavirus Disease 2019 (COVID-19)https://www.cdc.gov/mis-c/hcp/
7. World Health organization. Multisystem inflammatory syndrome in children and adolescents with COVID-19. Scientific brief 15 May 2020https://www.who.int/publications/i/item/multisystem-inflammatory-syndrome-in-children-and-adolescents-with-covid-19https://www.who.int/publications/i/item/multisystem-inflammatory-syndrome-in-children-and-adolescents-with-covid-19
8. 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: e927–99.
9. Belhadjer Z,et al. Acute heart failure in multisystem inflammatory syndrome in children (MIS-C) in the context of global SARS-CoV-2 pandemic [published online ahead of print, 2020 May 17]. *Circulation*. 2020;10.1161/CIRCULATIONAHA.120.048360. doi:10.1161/CIRCULATIONAHA.120.048360
10. Kobayashi T, Saji T, Otani T, et al. Efficacy of immunoglobulin plus prednisolone for prevention of coronary artery abnormalities in severe Kawasaki disease (RAISE study): a randomised, open-label, blinded-endpoints trial. Lancet 2012; 379: 1613–20.
11. Center for Disease Control Streptococcal Toxic Shock Syndrome (STSS) (*Streptococcus pyogenes*) 2010 Case Definition. https://wwwn.cdc.gov/nndss/conditions/streptococcal-toxic-shock-syndrome/case-definition/2010/#:~:text=Clinical%20Description,infection%20of%20a%20cutaneous%20lesion.
12. Center for Disease Control Toxic Shock Syndrome (Other Than Streptococcal) (TSS) 2011 Case Definition https://wwwn.cdc.gov/nndss/conditions/toxic-shock-syndrome-other-than-streptococcal/case-definition/2011/
13. Ravelli A, Minoia F, Dav. S, et al. 2016 Classification criteria for macrophage activation syndrome complicating systemic juvenile idiopathic arthritis: a European League Against Rheumatism/American College of Rheumatology/Paediatric Rheumatology International Trials Organisation Collaborative Initiative. Ann Rheum Dis 2016; 75: 481–89.
14. Clinical Guidance for Pediatric Patients with Multisystem Inflammatory Syndrome in Children (MIS-C) Associated with SARS-CoV-2 and Hyperinflammation in COVID-19. https://www.rheumatology.org/Portals/0/Files/ACR-COVID-19-Clinical-Guidance-Summary-MIS-C-Hyperinflammation.pdf?ver=2020-07-02-140939-180. Accessed 4 July 2020.