Version 1.0, date 30.12.2020

Best Practice Recommendations for the Diagnosis and Management of Children with Paediatric Inflammatory Multisystem Syndrome Temporally Associated with SARS-CoV-2 (PIMS-TS; Multisystem Inflammatory Syndrome in Children, MIS-C) in Switzerland

Endorsed by

- ***the Swiss Society of Intensive Care (SGI)***
- ***the Swiss Interest Group for Pediatric and Neonatal Intensive Care (IGPNI)***
- ***the Pediatric Infectious Diseases Group Switzerland (PIGS)***
- ***the Swiss Society of Pediatrics (SGP)***

Authors

Luregn J Schlapbach[1,2], MD, PhD, FCICM, Maya C Andre[3,4], MD, PhD, Serge Grazioli[5], MD, Nina Schöbi, MD[6,7], Nicole Ritz[8], MD, Christoph Aebi[6], MD, Philipp Agyeman[6], MD, Manuela Albisetti[9], Douggl GN Bailey[10], Christoph Berger[11], MD, Géraldine Blanchard Rohner[12], MD, DPhil, Michael Hofer[12,13], MD, Arnauld G L'Huillier[12], MD, Mark Marston[3], MScN, Patrick M Meyer-Sauteur[11], MD, PhD Jana Pachlopnik Schmid[14], MD, PhD, Marie-Helene Perez[15], MD, Bjarte Rogdo[10], MD, Johannes Trück[11,14], MD, DPhil, Andreas Woerner[16], MD, Petra Zimmerman[17,18], MD, PhD, Peter C Rimensberger[5] MD, *for the PIMS-TS working group of the Interest Group for Pediatric and Neonatal Intensive Care (IGPNI) of the Swiss Society of Intensive Care and the Pediatric Infectious Diseases Group Switzerland (PIGS)*

[1] Pediatric and Neonatal Intensive Care Unit, and Children`s Research Center, University Children's Hospital Zurich, Zurich, Switzerland
[2] Child Health Research Centre, The University of Queensland, and Paediatric Intensive Care Unit, Queensland Children`s Hospital, Brisbane, Australia
[3] University of Basel Children´s Hospital, Division of Respiratory and Critical Care Medicine, Basel, Switzerland.
[4] University Children´s Hospital, Department of Pediatric Hematology and Oncology, Eberhard Karls University, Tuebingen, Germany
[5] Division of Neonatal and Pediatric Intensive Care, Department of Child, Woman and, Adolescent Medecine, Geneva University Hospitals and Faculty of Medicine, Geneva, Switzerland
[6] Department of Pediatrics, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland
[7] Alder Hey Children's Hospital, NHS Foundation Trust, Liverpool, United Kingdom
[8] Department of Infectiology and Vaccinology, University Children's Hospital Basel, Basel, Switzerland
[9] Department of Haematology, and Children`s Research Center, University Children's Hospital Zurich, Zurich, Switzerland
[10] Department of Pediatric Intensive Care, Children's Hospital St. Gallen, St. Gallen, Switzerland
[11] Division of Infectious Diseases and Hospital Epidemiology, University Children's Hospital Zurich, Zurich, Switzerland
[12] Unit of Immunology and Vaccinology, Division of General Pediatrics, Department of Pediatrics, Gynecology and Obstetrics, Geneva University Hospitals, University of Geneva, Geneva, Switzerland
[13] Pediatric Immuno-Rheumatology of Western Switzerland, Department Women-Mother-Child, Lausanne University Hospital, Lausanne, and University Hospitals of Geneva, Geneva, Switzerland
[14] Division of Immunology and Children`s Research Center, University Children's Hospital Zurich, Zurich, Switzerland

[15] Pediatric Intensive Care Unit, University Hospital Lausanne, Lausanne, Switzer[16] Department of Rheumatology, University Children's Hospital Basel, Basel, Switzerland
[17] Faculty of Science and Medicine, University of Fribourg and Department of Paediatrics, Fribourg Hospital, Fribourg, Switzerland
[18] Infectious Diseases Research Group, Murdoch Children's Research Institute, Parkville, Australia

Corresponding author/contact:
Prof. Luregn Schlapbach, MD, PhD, FCICM
Head, Pediatric and Neonatal Intensive Care Unit
University Children's Hospital Zurich – Eleonore Foundation
Steinwiesstrasse 75
CH-8032 Zurich Switzerland
phone +41 44 266 71 11
email: luregn.schlapbach@kispi.uzh.ch

Key words: child; COVID-19; Kawasaki disease; multisystem inflammatory syndrome; MIS-C; pediatric multisystem inflammatory syndrome; PIMS; sepsis; septic shock

Conflict of interest statement: none declared.

Word count manuscript: 3494
Figures: 1
Tables: 3

Abstract

Background: Following the spread of the coronavirus disease 2019 (COVID-19) pandemic a new disease entity emerged, defined as Paediatric Inflammatory Multisystem Syndrome temporally associated with COVID-19 (PIMS-TS), or Multisystem Inflammatory Syndrome in Children (MIS-C). In the absence of trials, evidence for treatment remains scarce.
Purpose: To develop best practice recommendations for the diagnosis and treatment of children with PIMS-TS in Switzerland. It is acknowledged that the field is changing rapidly, and regular revisions in the coming months are pre-planned as evidence is increasing.
Methods: Consensus guidelines for best practice were established by a multidisciplinary group of Swiss paediatric clinicians with expertise in intensive care, immunology/rheumatology, infectious diseases, and haematology. Subsequent to literature review, four working groups established draft recommendations which were subsequently adapted in a modified Delphi process. Recommendations had to reach >80% agreement for acceptance.
Results: The group achieved agreement on 24 recommendations, which specify diagnostic approaches and interventions across anti-inflammatory, anti-infectious, and support therapies for children with suspected PIMS-TS. A management algorithm was derived to guide treatment depending on the phenotype of presentation, categorized into PIMS-TS with a) shock, b) Kawasaki-disease like and c) undifferentiated inflammatory presentation.
Conclusion: Using available literature and guidelines from international health authorities, the Swiss PIMS-TS recommendations represent best practice guidelines based on currently available knowledge to standardize treatment of children with suspected PIMS-TS in Switzerland. Given the absence of high-grade evidence, regular updates of the recommendations will be warranted, and participation of patients in trials should be encouraged.

Introduction

Subsequent to the first wave of the coronavirus disease 2019 (COVID-19) pandemic[1], clusters of children presenting with unusual multisystem inflammatory conditions emerged[2,3]. The clinical syndrome showed some heterogeneity with patients presenting either akin to toxic shock, Kawasaki-disease like or with undifferentiated inflammatory characteristics, in addition to evidence of current or past COVID-19 infection in the majority of cases[4,5]. Accordingly, this new disease entity has been called Paediatric Inflammatory Multisystem Syndrome temporally associated with COVID-19 (PIMS-TS) as per the Royal College of Paediatrics and Child Health case definition (RCPCH, https://www.rcpch.ac.uk/resources/guidance-paediatric-multisystem-inflammatory-syndrome-temporally-associated-covid-19-pims) and Multisystem Inflammatory Syndrome associated with COVID-19 (MIS-C) as per the Center for Disease Control (CDC, https://www.cdc.gov/mis-c/) and the WHO (World Health Organisation, https://www.who.int/publications/i/item/multisystem-inflammatory-syndrome-in-children-and-adolescents-with-covid-19).

While a number of studies have attempted to explain the underlying biological and genetic mechanisms of PIMS-TS, its pathophysiology and the observed variation in clinical presentation remains largely unknown[6-8]. It is currently assumed that a complex process involving SARS-CoV-2-specific antigen presentation to autoreactive T cells, superantigen-like viral structures, cross-reactive SARS-CoV-2-specific antibodies and unbalanced cytokine responses may initiate PIMS-TS in genetically predisposed children[9-13]. In other paediatric hyperinflammatory syndromes, such as Kawasaki disease (KD), macrophage activation syndrome (MAS), and hemophagocytic lymphohistiocytosis (HLH), timely initiation of anti-inflammatory therapy and immunosuppression can often reverse the hyper-inflammatory state and prevent or mitigate organ damage. Therefore, therapeutic immune modulation is widely used as a mainstay of PIMS-TS treatment with the aim to inhibit cytokine secretion and restore immune homeostasis. In addition, PIMS-TS patients may also show signs of vasculitis, endothelial damage, and thrombosis, hence antiplatelet and anticoagulation management in PIMS-TS represent important additional considerations[14].

In order to standardize management in Switzerland, we aimed to develop best practice recommendations for the diagnosis and treatment of children with PIMS-TS.

Methods

Subsequent to a call for Expressions of Interest, the Interest Group for Paediatric and Neonatal Intensive Care (IGPNI) of the Swiss Society of Intensive Care Medicine (SSICM) and the Paediatric Infectious Diseases Group Switzerland (PIGS) formed a working group on PIMS-TS. In total, 22 panellists across the fields of paediatric intensive care, infectious diseases, immunology and rheumatology, hematology and nursing composed the panel.

Four subgroups focused on the domains of i) disease criteria and diagnosis, ii) anti-inflammatory therapies, iii) anti-infective therapies, and iv) additional support therapies including coagulation management. Each subgroup performed a focused literature review on publications since the description of PIMS-TS in early 2020 until December 2020. In addition, we searched for available pathways, diagnostic and therapeutic recommendations from different international institutions[15-17]. Over a period of five weeks, weekly virtual meetings of the entire working group were held to develop and discuss the recommendations in a modified Delphi process. Finally, voting was performed by the entire panel for each recommendation using Survey Monkey. The threshold for recommendations was met if >80% of panellists voted for full agreement on an item.

Statement of uncertainty:

At present, professionals remain confronted with substantial uncertainties regarding clinical phenotypes, long-term outcomes, and optimal management[18]. In the absence of randomized trials, evidence for best treatment is minimal for the diagnostic, anti-inflammatory, anti-infectious, and supportive measures which have been proposed[6,19]. Recommendations therefore base primarily on expert opinion and similar recommendations in the United Kingdom. The field is rapidly changing with reports being published on an almost weekly basis[20], hence revision and updates of the recommendations will be required regularly.

Recommendations

Diagnosis

1. In Switzerland, the following case definition should be used:
Adapted RCPCH - case definition[21,22]

- Patient aged <18 years of age. Persistent fever + inflammation (elevated CRP and neutrophils, or lymphopaenia) + single or multiorgan dysfunction (shock, cardiac, respiratory, renal, gastrointestinal, neurological) + additional features (see **Table 1**). This may include children fulfilling full or partial criteria for Kawasaki disease (KD).
- Exclusion of any other probable cause, such as bacterial sepsis, staphylococcal/streptococcal shock syndromes, and viral infections associated with myocarditis. Waiting for these results should not delay seeking expert advice.
- Positive for current or recent SARS-CoV-2 infection by PCR, serology, or antigen test; or COVID-19 exposure within 4 weeks prior to the onset of symptoms. Waiting for these results should not delay seeking expert advice.

2. If a child fulfils the diagnostic criteria for PIMS-TS we recommend classifying these patients according to the presenting phenotype due to the implications for diagnostic workup and management:

- Shock-like presentation: signs of shock as per the Goldstein 2005 definition of cardiovascular failure[23] (**Appendix**)
- Kawasaki disease-like presentation: complete or incomplete with cardiac involvement, according to AHA[24]
- Undefined inflammatory presentation: persistent pyrexia with signs of PIMS-TS but not meeting shock criteria nor having cardiac involvement

Overall, PIMS-TS remains a rare condition and most children with SARS-CoV-2 infection will remain asymptomatic or will exhibit only mild symptoms[4,25]. Predominant clinical features include persistent fever and gastrointestinal symptoms, e.g. abdominal pain, vomiting or diarrhoea. Many patients may exhibit additional clinical features (**Table 1**). Cardiovascular impairment can be manifest at presentation or develop during admission[26,27]. Some patients show rapid clinical deterioration often characterized by a vasoplegic shock state requiring admission to intermediate or intensive care units (IMC/PICU).[4,28]

It is paramount to avoid anchoring bias given that PIMS-TS remains a rare condition[29], and in view of the fact that many children suffering from other disease during the pandemic may have concomitant

microbiological evidence of SARS-CoV-2 exposure. Other, more common differential diagnoses need to be considered, such as, but not restricted to:

- Invasive bacterial infection
- Sepsis
- Toxic shock syndrome (TSS)
- Staphylococcal Scalded Skin Syndrome (SSSS)
- Kawasaki disease (KD)
- Viral myocarditis/infection (EBV, CMV, adenovirus, enterovirus, HHV6)
- Serum sickness
- Acute appendicitis/acute surgical abdomen
- Gastroenteritis
- Macrophage activation syndrome (MAS) and hemophagocytic lymphohistiocytosis (HLH) (**Appendix**)
- Malignant diseases, e.g. acute leukaemia

Although the clinical presentation of PIMS-TS patients shares similarities with KD and TSS[4,25], patients with PIMS-TS have been reported to be older than KD patients and by definition lack microbial confirmation of a staphylococcal or streptococcal infection.
We recommend a staged diagnostic approach, starting with standard investigations for all children where PIMS-TS is suspected (**Table 2**), followed by more in-depth diagnostic work-up in children with evidence of severe disease, or those with diagnostic uncertainty. Early involvement of a paediatric multidisciplinary team (MDT) including intensive care, immunology, infectious diseases, rheumatology, cardiology, haematology and others (e.g. general surgery) should be considered. Diagnostic measures, including laboratory tests such as markers of inflammation and organ dysfunction, and imaging modalities such as echocardiography should be repeated sequentially depending on the presentation, disease severity, and evolution to guide escalation and de-escalation of therapy, and to rule out other diagnoses.

3. Patients who have been clinically well on regular wards with evidence of normal or recovering cardiac function, and who have been afebrile (<38 degrees) for 48 hours should be considered for discharge home after MDT review.

In general, we suggest performing a follow-up visit 1 to 2 weeks and 6 weeks after discharge which should encompass a multidisciplinary consultation. In children where cardiac involvement was diagnosed, consultation of cardiology is recommended before discharge to guide frequency of follow-up echocardiographic assessment, as cardiac function may not have fully normalized by the time of discharge.

Anti-inflammatory therapies

4. Therapeutic immune-modulation in PIMS-TS patients requires a multidisciplinary approach. Clinicians should re-evaluate the patient response and consider differential diagnoses at every step.

We recommend a MDT approach to guide initiation, escalation, and tapering of empiric immunomodulatory therapy, particularly because available evidence for such treatment is currently only based on observational reports. The panel recommends using a management algorithm (**Figure 1**) to guide the step-wise selection of the initial interventions. Dosing recommendations are provided in **Table 3** and were adapted from the Imperial College Healthcare NHS Trust PIMS-TS guideline (Prof. Elizabeth Whittaker, personal communication).

5. In patients with Kawasaki disease-like PIMS-TS, immunomodulation and management should follow established guidelines for Kawasaki disease.
6. In patients with PIMS-TS shock, we recommend using immunoglobulins (IVIG, 2 g/kg) as first line therapy.
7. In patients with PIMS-TS shock we recommend treatment with intravenous pulse high-dose methylprednisolone (10mg/kg to max 30 mg/kg q24h for 1-3 days, max. 1 g/day).
8. In non-shocked patients with PIMS-TS undefined inflammatory presentation clinicians should consider administration of immunoglobulins (IVIG, 2 g/kg).
9. In non-shocked patients with PIMS-TS (Kawasaki-like presentation or undefined inflammatory presentation) clinicians should consider administration of prednisolone (2 mg/kg q24h, max. 60 mg/day).
10. In all patients with confirmed PIMS-TS treated with steroids, steroids should be tapered over a period of 2-6 weeks depending on the clinical course and considering the clinical and biochemical (such as CRP, D-Dimer and ferritin levels) response.

For children with Kawasaki disease-like PIMS-TS, the panel recommends that established institutional or international guidelines such as the 2020 American College of Rheumatology guidelines[30] on Kawasaki disease-like PIMS-TS should be followed. In addition, both the European SHARE initiative[31] and the American Heart Association guidelines[24] provide guidance on KD.

We recommend, based on currently available reports and in line with other recommendations, to use intravenous immunoglobulin (IVIG) as the first line treatment in PIMS-TS patients presenting with shock, and to consider IVIG in PIMS-TS with undefined presentation. While IVIG should be usually administered as a single dose of 2g/kg (max. 100g/dose), clinicians should assess the cardiac and fluid status, particularly in patients in shock, as in some patients a slower administration become necessary.
While corticosteroids have often been used as adjuncts to IVIG[32], the specific indication, dosing, timing or type of glucocorticoids in PIMS-TS remains unknown. The panel considered that benefit versus harm justify pulse high-dose steroids for a duration of 1 to 3 days in PIMS-TS patients with shock, with an initial dose of 10mg/kg methylprednisolone (max 1g/day). Increasing the methylprednisolone dose to 30mg/kg q24h may be considered. PIMS-TS patients treated with pulse corticosteroids should receive gastric protection with proton-pump inhibitors.
Given potential side effects and the lack of data, we advise against the use of pulse steroids in PIMS-TS patients without shock but suggest to consider a lower dose therapy given intravenously and, subsequently, orally. While the optimal duration of steroid therapy in PIMS-TS remains unknown, the joint view of the panel is that decisions on steroid treatment duration should be guided by the clinical response (resolution of signs and symptoms), as well as by laboratory evidence of decreasing inflammation and improving organ function. A longer course of steroids of up to 6 weeks may contribute to prevent rebound inflammation.

A proportion of patients may not respond to initial treatment, and deterioration of the disease can be life-threatening. Refractory PIMS-TS is characterized by persistent fever and/or increase of inflammatory markers, worsening organ function, or increase in need of vasoactive drugs (measured by Vasoactive-Inotrope Score[33]) within 24 to 48 hours after start of treatment. Consideration of disease severity in particular in PICU patients, and assessing evidence of persistent or progressive (multi-) organ dysfunction is paramount to guide treatment escalation. Again, MDT assessment is recommended

and needs to take differential diagnoses into account at every step before escalating treatment, and should carefully evaluate risk-versus-benefit ratio of escalating immunomodulatory therapies. For example, PIMS-TS patients may develop secondary infections and immuno-suppressive treatment regimens may further impair the host defense against infection. The current list of biological drugs includes IL-1R (i.e. anakinra), and IL-6R (i.e. tocilizumab) and tumor necrosis factor (TNF) (infliximab) blocking agents (**Table 3**). In addition, clinicians may discuss administration of a second dose of IVIG, or pulse steroids.

11. In patients with PIMS-TS refractory to initial treatment with IVIG and steroids, and after exclusion of alternative causes by the multidisciplinary team, we suggest consideration for anakinra. We recommend starting at 2-3 mg/kg q12h s.c. (max. 100 mg/dose, total of 4-6 mg/kg/day). In case of clinical improvement, stopping of anakinra after 48 to 72 hours should be considered in the multidisciplinary team.
12. In patients with PIMS-TS where no clinical and biochemical improvement to anakinra treatment is observed within 24-48 hours, the multidisciplinary team should consider other targeted immunomodulation therapy with either tocilizumab or infliximab.
13. Clinical assessment and serial laboratory testing on measures of inflammation and organ dysfunction should guide escalation and duration of immunomodulation therapy treatment.

Despite its limited licensed indication, anakinra is increasingly chosen for off-label use in PIMS-TS patients[4,34-36]. Anakinra has been approved for subcutaneous administration, however continuous intravenous administration has been reported[37]. Its short half-life (4-6 hrs) (**Table 3**), allows for repeated re-assessment of the immunosuppressive regimen. We therefore suggest a short trial of IL-1R blockade in PICU-hospitalized PIMS-TS patients that have not responded within a period of 24 to 36 hours following administration of both IVIG and steroids. Anakinra dose increase in the absence of clinical improvement may be considered in the MDT. We suggest stopping anakinra after 48-72 hours without tapering in case of clinical improvement. There is no evidence to support routine serial cytokine level assessment to guide cytokine-targeted therapy (CTT).

Tocilizumab is an IL-6R blocking agent currently approved for the treatment of both systemic and polyarticular juvenile idiopathic arthritis in children above 2 years of age. Tocilizumab has also been used in children with PIMS-TS as IL-6 has been described to be one of the main drivers of the inflammatory cytokine storm in this disease entity. However, safety concerns exist as significant side effects have been described such as a reversible elevation of liver enzymes and an increased risk for bacterial and fungal infections (**Table 3**). Therefore, tocilizumab should be reserved for children with life-threatening PIMS-TS in whom anakinra has failed to show a clear benefit within 48 hours. Given the long half-life (150 hours) tocilizumab is usually given as a single intravenous dose.
The TNF-alpha blocking agent infliximab, classically used in children with various autoimmune inflammatory diseases has also been successfully used in children with KD. However, since infliximab increases the risk for secondary infections, and based on its long half-life (around 8 days, **Table 3**), infliximab should only be administered to patients with PIMS-TS who failed to respond to anakinra and as a single intravenous dose.

Anti-infective therapies

14. Based on the absence of evidence of remdesivir treatment for children with COVID-19 and the proposed post-infectious concept of PIMS-TS[38] we do not recommend the routine administration of remdesivir in PIMS-TS patients.
15. Children with suspected PIMS-TS and signs of shock or other organ dysfunction should be treated empirically with intravenous broad-spectrum antimicrobial therapy for bacterial sepsis.
16. In children with PIMS-TS receiving intravenous antimicrobial therapy, we recommend daily assessment (e.g., clinical, laboratory assessment) for de-escalation of antimicrobial therapy in consultation with infectious diseases specialists. Stopping of antimicrobial therapy should be considered depending on the clinical course, microbiological findings, and the presence of PIMS-TS diagnostic criteria, including evidence of recent or current SARS-CoV-2 infection by serology or PCR.

Remdesivir, a nucleoside analogue prodrug, has been approved for the treatment of COVID-19 in adults based on emerging evidence demonstrating the efficacy in shortening time to clinical recovery[39,40], however recent experience[39,41] has not confirmed these findings. The safety and effectiveness of remdesivir for treatment of COVID-19 in children has not yet been evaluated (studies are underway) outside case reports[42,43]. Hence the role of remdesivir in the management of PIMS-TS is uncertain, especially as PIMS-TS represents a post-infectious disorder rather than active SARS-CoV-2 infection. For these reasons the panel agreed that remdesivir should not be *routinely* used in children with PIMS-TS. However, PIMS-TS patients may be considered for the compassionate use of remdesivir on a case-by-case basis[25,44]. When remdesivir is used the FDA emergency use authorization instructions for the use of remdesivir in children >3.5 kg should be followed (https://www.fda.gov/media/137566/download).

Children with PIMS-TS initially often present with signs and symptoms that mimic those of septic shock and toxic shock syndrome[29] and neither clinical findings (fever, rash, abdominal symptoms), infection markers (CRP), nor other laboratory measures of inflammation may allow reliable discrimination[45,46]. Mortality in children with sepsis and septic shock increases as time to effective antimicrobial therapy increases[47,48]. All suspected PIMS-TS patients with clinical signs of sepsis should therefore receive prompt empiric intravenous antibiotics within one hour of presentation for those with shock, and within up to three hours for those without shock[49]. The choice of antibiotics should be based on local guidelines and taking into account age, epidemiology, and pre-existing medical conditions. Antibiotics should be stream-lined or stopped on the basis of the clinical course and microbiological culture results in discussion with the infectious diseases team.

Supportive measures

17. All PIMS-TS patients with shock or other organ dysfunction must be transferred to a centre with availability of specialized Paediatric Intensive Care Units, cardiology, infectious diseases, and immunology/rheumatology.
18. Haemodynamic, respiratory, and other organ support should follow established guidelines such as the Surviving Sepsis Campaign.
19. Extracorporeal Membrane Oxygenation should be considered in PIMS-TS with cardiac, respiratory, or cardiorespiratory failure refractory to conventional management as per established guidelines such as the Surviving Sepsis Campaign.

Many PIMS-TS patients do not show evidence of active viral infection and may be less likely to be infectious to healthcare workers. However, clinical staff should wear appropriate personal protective equipment[25] as per institutional guidelines. Children should be triaged, assessed and management in line with recommendations for management of fever in infants <36 months, Surviving Sepsis Campaign[47], and standard PALS resuscitation algorithms for critically ill children. As some children progress rapidly and may develop haemodynamic compromise, close monitoring and early referral to a tertiary centre for cardiac and PICU review is important.

20. In the absence of contraindications, we recommend starting prophylactic i.v. unfractionated heparin at a dose of 10 U/kg/h in PIMS-TS patients with shock. Conversion to low molecular weight heparin (LMWH, such as enoxaparin at a dose of 0.5 mg/kg q12hrs) after the first days should be considered, depending on renal function.
21. In any other PIMS-TS patient requiring intensive care admission, we recommend prophylactic heparin (at a dose of 10 U/kg/h) or low molecular weight heparin (LMWH, such as enoxaparin at a dose of 0.5 mg/kg s.c. q12hrs) depending on renal function.
22. For PIMS-TS patients not requiring PICU care, individual risk factors for thrombotic complications should be assessed to guide decisions on individualized anticoagulation therapy.
23. In patients with Kawasaki disease-like PIMS-TS, antiplatelet management should follow established guidelines for Kawasaki disease.
24. In PIMS-TS patients not showing Kawasaki disease-like presentation, treatment with low dose aspirin (5mg/kg daily) should be considered.

Given the increased risk of thromboembolic complications during acute PIMS-TS[14,50], the panel advised to use prophylactic anticoagulation in patients of higher severity requiring PICU admission. Starting with intravenous heparin before converting to LMWH (pending normal renal function) is suggested. In non PICU patients, the overall assessment of the individual risk profile should include well-established risk factors such as a previous history of venous thromboembolism or a first-degree relative with venous thromboembolism, the presence of a central line, post-pubertal age or estrogen therapy amongst other. In addition, obesity may increase risk for thromboembolic events in patients with SARS-CoV-2 infection or PIMS-TS. At the same time, clinicians should weigh benefit of antiplatelet and anticoagulation treatments against the individual risk for clinically relevant bleeding.
Similar to classical KD patients, children with PIMS-TS irrespective of the phenotype may be at risk for the development of coronary artery aneurysms. Hence it appears to be reasonable to consider low dose aspirin (5mg/kg) in addition to prophylactic anticoagulation in all critically ill patients with PIMS-TS.

Discussion

Within months of the COVID-19 pandemic spread, many countries across the globe have reported children presenting unwell with features of severe inflammation and multisystem disease[51,52]. Using available literature and guidelines from international institutions, the Swiss PIMS-TS recommendations represent best practice guidelines based on currently available knowledge to facilitate and standardize treatment of children with suspected PIMS-TS in Switzerland.

A number of limitations need to be considered. First, while the expert group includes specialists from the relevant disciplines, numbers of children with PIMS-TS during the first wave of COVID-19 in Switzerland were low, limiting experience in managing the disease[11,34]. However, the group assessed

institutional pathways from other health care systems and consulted world leading experts in the field during the process. Second, the literature review performed was not systematic but focussed. Third, to date there are no published results from randomized controlled trials in the field, and the evidence base for optimal PIMS-TS management remains minimal. Finally, recommendations were issued in the context of a well-resourced setting, where IVIG and biologicals are relatively easily available, and may not be applicable to resource limited settings. In relation to applying these guidelines, clinicians should be mindful of the risk of anchoring bias during the pandemic. Many children may test positive for COVID-19, not necessarily implying causality. The CDC, WHO and RCPCH case definitions of PIMS-TS bear a risk to overdiagnose an assumedly rare syndrome in children who suffer from other common infectious or inflammatory or conditions such as septic shock, or rarer conditions such as HLH.

In conclusion, it is imperative that children with PIMS-TS are enrolled in prospective trials where feasible[53-55], and that clinical data are collected and shared to improve our understanding of the disease and its best management. Given the absence of high-grade evidence[18], regular updates of the recommendations will be required.

Acknowledgements:
We thank Laura Chapuisat, Swiss Society of Intensive Care, for the administrative support during the project and voting. We thank Prof. Mike Levin, and Prof. Elizabeth Whittaker, Imperial College London, for their valuable advice.

Author contribution:
LJS and PCR designed and coordinated the work, wrote the first draft, and take responsibility for the content of the work. MCA, NS, SG, and NR led subgroups and wrote the first draft on their section. All other authors participated in literature review, voting, writing, and have seen and approved the final version.

References

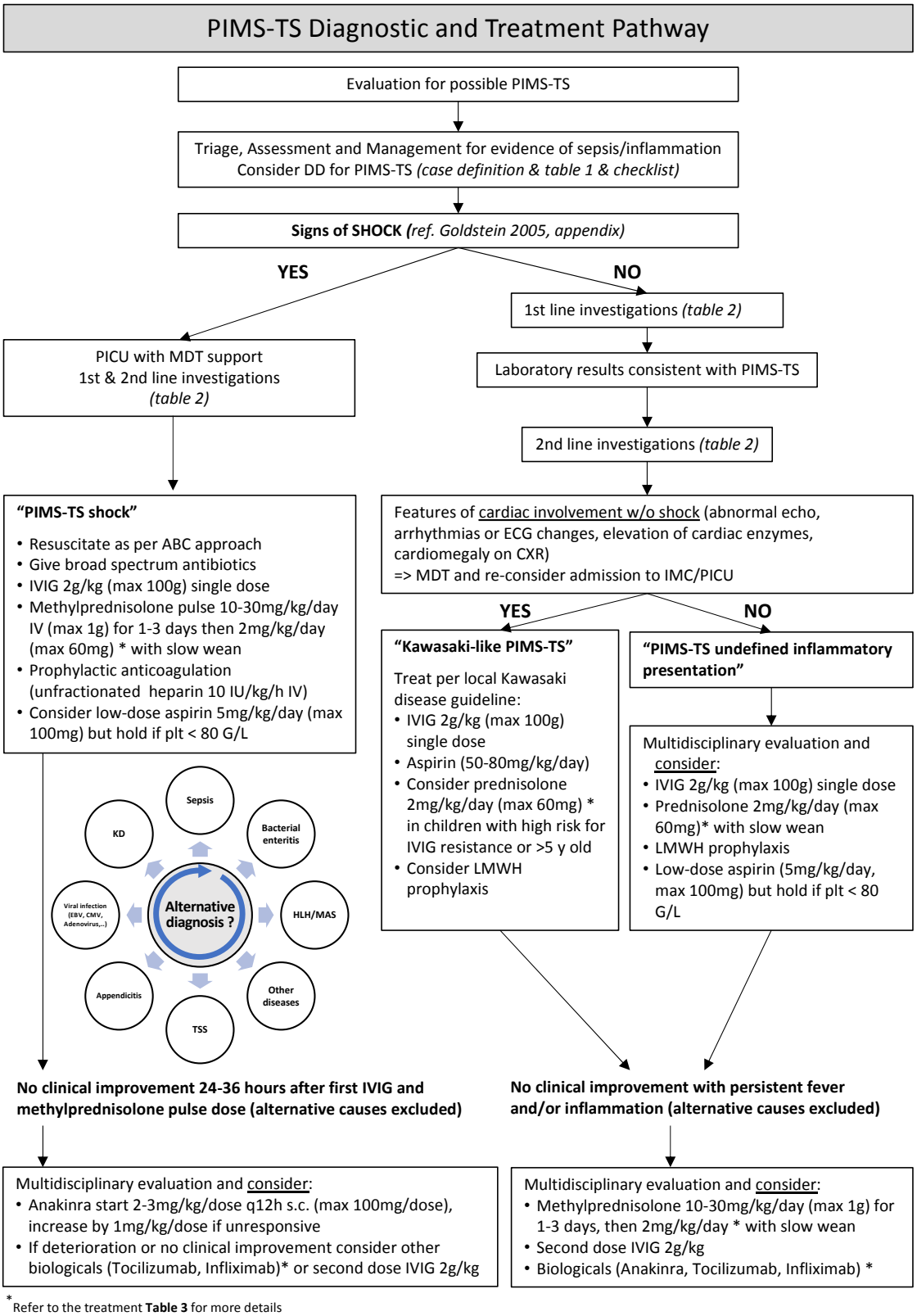
1. Berlin DA, Gulick RM, Martinez FJ. Severe Covid-19. *N Engl J Med.* 2020.
2. Levin M. Childhood Multisystem Inflammatory Syndrome - A New Challenge in the Pandemic. *N Engl J Med.* 2020;383(4):393-395.
3. Rimensberger PC, Kneyber MCJ, Deep A, et al. Caring for Critically Ill Children With Suspected or Proven Coronavirus Disease 2019 Infection: Recommendations by the Scientific Sections' Collaborative of the European Society of Pediatric and Neonatal Intensive Care. *Pediatr Crit Care Med.* 2020.
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;324(3):259-269.
5. Feldstein LR, Rose EB, Horwitz SM, et al. Multisystem Inflammatory Syndrome in U.S. Children and Adolescents. *New England Journal of Medicine.* 2020;383(4):334-346.
6. Carter MJ, Shankar-Hari M, Tibby SM. Paediatric Inflammatory Multisystem Syndrome Temporally-Associated with SARS-CoV-2 Infection: An Overview. *Intensive Care Med.* 2020.
7. Ahmed M, Advani S, Moreira A, et al. Multisystem inflammatory syndrome in children: A systematic review. *EClinicalMedicine.* 2020;26:100527.
8. Gruber CN, Patel RS, Trachtman R, et al. Mapping Systemic Inflammation and Antibody Responses in Multisystem Inflammatory Syndrome in Children (MIS-C). *Cell.* 2020;183(4):982-995.e914.
9. Carter MJ, Fish M, Jennings A, et al. Peripheral immunophenotypes in children with multisystem inflammatory syndrome associated with SARS-CoV-2 infection. *Nat Med.* 2020;26(11):1701-1707.
10. Lee PY, Day-Lewis M, Henderson LA, et al. Distinct clinical and immunological features of SARS–CoV-2–induced multisystem inflammatory syndrome in children. *Journal of Clinical Investigation.* 2020;130(11):5942-5950.
11. Grazioli S, Tavaglione F, Torriani G, et al. Immunological assessment of pediatric multisystem inflammatory syndrome related to COVID-19. *J Pediatric Infect Dis Soc.* 2020.
12. Consiglio CR, Cotugno N, Sardh F, et al. The Immunology of Multisystem Inflammatory Syndrome in Children with COVID-19. *Cell.* 2020;183(4):968-981.e967.
13. Rowley AH. Understanding SARS-CoV-2-related multisystem inflammatory syndrome in children. *Nature Reviews Immunology.* 2020;20(8):453-454.

14. Goldenberg NA, Sochet A, Albisetti M, et al. Consensus-based clinical recommendations and research priorities for anticoagulant thromboprophylaxis in children hospitalized for COVID-19-related illness. *J Thromb Haemost.* 2020;18(11):3099-3105.
15. Dove ML, Jaggi P, Kelleman M, et al. Multisystem Inflammatory Syndrome in Children: Survey of Protocols for Early Hospital Evaluation and Management. *J Pediatr.* 2020.
16. Harwood R, Allin B, Jones CE, 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. *The Lancet Child & Adolescent Health.* 2020.
17. Jonat B, Gorelik M, Boneparth A, et al. Multisystem Inflammatory Syndrome in Children Associated With Coronavirus Disease 2019 in a Children's Hospital in New York City: Patient Characteristics and an Institutional Protocol for Evaluation, Management, and Follow-Up. *Pediatr Crit Care Med.* 2020.
18. Davey Smith G, Blastland M, Munafò M. Covid-19's known unknowns. *BMJ.* 2020:m3979.
19. Nijman RG, De Guchtenaere A, Koletzko B, et al. Pediatric Inflammatory Multisystem Syndrome: Statement by the Pediatric Section of the European Society for Emergency Medicine and European Academy of Pediatrics. *Frontiers in pediatrics.* 2020;8:490. doi:10.3389/fped.2020.00490. Accessed 2020.
20. Pouletty M, Borocco C, Ouldali N, et al. Paediatric multisystem inflammatory syndrome temporally associated with SARS-CoV-2 mimicking Kawasaki disease (Kawa-COVID-19): a multicentre cohort. *Ann Rheum Dis.* 2020;79(8):999-1006.
21. Guidance: Paediatric multisystem inflammatory syndrome temporally associated with COVID-19. RCPCH. https://www.rcpch.ac.uk/sites/default/files/2020-05/COVID-19-Paediatric-multisystem-%20inflammatory%20syndrome-20200501.pdf. Published 2020. Updated 1st May 2020. Accessed 17th November 2020.
22. Multisystem Inflammatory Syndrome in Children (MIS-C) Interim Guidance. American Academy of Pediatrics. https://services.aap.org/en/pages/2019-novel-coronavirus-covid-19-infections/clinical-guidance/multisystem-inflammatory-syndrome-in-children-mis-c-interim-guidance/. Published 2020. Updated 1st September 2020. Accessed 17th November 2020.
23. Goldstein B, Giroir B, Randolph A. International pediatric sepsis consensus conference: definitions for sepsis and organ dysfunction in pediatrics. *Pediatr Crit Care Med.* 2005;6(1):2-8.
24. 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(17):e927-e999.
25. Harwood R, Allin B, Jones CE, 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.* 2020.
26. Alsaied T, Tremoulet AH, Burns JC, et al. Review of Cardiac Involvement in Multisystem Inflammatory Syndrome in Children. *Circulation.* 2020.
27. Valverde I, Singh Y, Sanchez-de-Toledo J, et al. Acute Cardiovascular Manifestations in 286 Children with Multisystem Inflammatory Syndrome Associated with COVID-19 Infection in Europe. *Circulation.* 2020.
28. White M, Tiesman B, Handforth J, Kenny J. Paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS): the Evelina Experience. *Arch Dis Child.* 2020;105(11):1025-1027.

29. Weiss SL, Peters MJ, Agus MSD, et al. Perspective of the Surviving Sepsis Campaign on the Management of Pediatric Sepsis in the Era of Coronavirus Disease 2019. *Pediatr Crit Care Med.* 2020.
30. Henderson LA, Canna SW, Friedman KG, et al. American College of Rheumatology Clinical Guidance for Multisystem Inflammatory Syndrome in Children Associated With SARS-CoV-2 and Hyperinflammation in Pediatric COVID-19: Version 1. *Arthritis Rheumatol.* 2020.
31. de Graeff N, Groot N, Ozen S, et al. European consensus-based recommendations for the diagnosis and treatment of Kawasaki disease - the SHARE initiative. *Rheumatology (Oxford).* 2019;58(4):672-682.
32. Belhadjer Z, Auriau J, Méot M, et al. Addition of Corticosteroids to Immunoglobulins Is Associated With Recovery of Cardiac Function in Multi-Inflammatory Syndrome in Children. *Circulation.* 2020;142(23):2282-2284.
33. Gaies MG, Gurney JG, Yen AH, et al. Vasoactive-inotropic score as a predictor of morbidity and mortality in infants after cardiopulmonary bypass. *Pediatr Crit Care Med.* 2010;11(2):234-238.
34. Fouriki A, Fougere Y, De Camaret C, et al. Case report: Anakinra treatment in children with Multisystem Inflammatory Syndrome following SARS-CoV-2 infection in Switzerland. *Front Pediatr.* 2020.
35. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ. COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet.* 2020;395(10229):1033-1034.
36. Mehta P, Cron RQ, Hartwell J, Manson JJ, Tattersall RS. Silencing the cytokine storm: the use of intravenous anakinra in haemophagocytic lymphohistiocytosis or macrophage activation syndrome. *Lancet Rheumatol.* 2020;2(6):e358-e367.
37. Galea J, Ogungbenro K, Hulme S, et al. Intravenous anakinra can achieve experimentally effective concentrations in the central nervous system within a therapeutic time window: results of a dose-ranging study. *J Cereb Blood Flow Metab.* 2011;31(2):439-447.
38. Diorio C, Henrickson SE, Vella LA, et al. Multisystem inflammatory syndrome in children and COVID-19 are distinct presentations of SARS-CoV-2. *J Clin Invest.* 2020;130(11):5967-5975.
39. Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the Treatment of Covid-19 - Final Report. *N Engl J Med.* 2020.
40. Rochwerg B, Agarwal A, Zeng L, et al. Remdesivir for severe covid-19: a clinical practice guideline. *Bmj.* 2020;370:m2924.
41. Wang Y, Zhang D, Du G, et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. *Lancet.* 2020;395(10236):1569-1578.
42. Orf K, Rogosic S, Dexter D, et al. Remdesivir during induction chemotherapy for newly diagnosed paediatric acute lymphoblastic leukaemia with concomitant SARS-CoV-2 infection. *Br J Haematol.* 2020;190(5):e274-e276.
43. Chiotos K, Hayes M, Kimberlin DW, et al. Multicenter interim guidance on use of antivirals for children with COVID-19/SARS-CoV-2. *J Pediatric Infect Dis Soc.* 2020.
44. Sanders JM, Monogue ML, Jodlowski TZ, Cutrell JB. Pharmacologic Treatments for Coronavirus Disease 2019 (COVID-19): A Review. *JAMA.* 2020;323(18):1824-1836.
45. Schlapbach LJ. Paediatric sepsis. *Curr Opin Infect Dis.* 2019;32(5):497-504.
46. Schlapbach LJ, Kissoon N. Defining Pediatric Sepsis. *JAMA Pediatr.* 2018;172(4):312-314.

47. Weiss SL, Peters MJ, Alhazzani W, et al. Surviving sepsis campaign international guidelines for the management of septic shock and sepsis-associated organ dysfunction in children. *Intensive Care Med.* 2020;46(Suppl 1):10-67.
48. Evans IVR, Phillips GS, Alpern ER, et al. Association Between the New York Sepsis Care Mandate and In-Hospital Mortality for Pediatric Sepsis. *JAMA.* 2018;320(4):358-367.
49. Weiss SL, Peters MJ, Alhazzani W, et al. Executive summary: surviving sepsis campaign international guidelines for the management of septic shock and sepsis-associated organ dysfunction in children. *Intensive Care Med.* 2020;46(Suppl 1):1-9.
50. Diorio C, McNerney KO, Lambert M, et al. Evidence of thrombotic microangiopathy in children with SARS-CoV-2 across the spectrum of clinical presentations. *Blood Adv.* 2020;4(23):6051-6063.
51. Antúnez-Montes OY, Escamilla MI, Figueroa-Uribe AF, et al. COVID-19 and Multisystem Inflammatory Syndrome in Latin American Children: A Multinational Study. *Pediatr Infect Dis J.* 2021;40(1):e1-e6.
52. García-Salido A, De Carlos Vicente JC, Belda Hofheinz S, et al. Severe manifestations of SARS-CoV-2 in children and adolescents: from COVID-19 pneumonia to multisystem inflammatory syndrome: a multicentre study in pediatric intensive care units in Spain. *Critical Care.* 2020;24(1).
53. Garcia-Prats AJ, Salazar-Austin N, Conway JH, et al. COVID-19 pharmacologic treatments for children: research priorities and approach to pediatric studies. *Clin Infect Dis.* 2020.
54. Goldman RD, Staubli G, Cotanda CP, et al. Factors associated with parents' willingness to enroll their children in trials for COVID-19 vaccination. *Hum Vaccin Immunother.* 2020:1-5.
55. Campbell JI, Ocwieja KE, Nakamura MM. A Call for Pediatric COVID-19 Clinical Trials. *Pediatrics.* 2020;146(2).

Figure 1: PIMS-TS Diagnostic and therapeutic algorithm.



*Refer to the treatment **Table 3** for more details

MDT: immunology, infectious diseases, respiratory medicine, rheumatology, cardiology, intensive care, general paediatrics, haematology (surgery, radiology, neurology); *consider expert opinion from another center*

Table 1. List of diagnostic criteria for PIMS-TS. Patients must be below 18 years and meet at least one criterion for each group, including i) presence of fever, ii) organ involvement, iii) laboratory evidence of inflammation, iv) microbiologically proven or putative COVID-19 contact, and v) exclusion of other causes.

Clinical features		
General	Criteria	
Required	Fever	O
Organ systems	Single or multi-organ involvement	
Gastrointestinal	Abdominal pain, diarrhoea, vomiting	O
	Abnormal liver function tests	O
	Colitis, ileitis, ascites	O
Cardiovascular	Hypotension, shock, oliguria	O
	Myocardial dysfunction, pericardial effusion	O
	Coronary artery dilatation	O
Respiratory	Cough, sore throat	O
	Oxygen requirement	O
	Patchy infiltrates, pleural effusion	O
Dermatologic	Conjunctivitis, periorbital swelling/redness	O
	Mucus membrane changes	O
	Rash	O
	Lymphadenopathy	O
	Swollen hands and feet	O
Neurologic	Headache, confusion, irritability, reduced level of consciousness	O
	Syncope	O
Abnormal laboratory findings indicating inflammation (any combination)		
Inflammatory markers	Elevated CRP / fibrinogen / D-Dimers / ferritin, hypoalbuminaemia, lymphopaenia, neutrophilia	O
Cardiac markers	Elevated Troponin / NT-pro-BNP	O
COVID-19 contact	Either confirmed or putative	O
Confirmed	Positive for current or recent SARS-CoV-2 infection by PCR, serology, or antigen test	O
Putative	COVID-19 exposure within the 4 weeks prior to the onset of symptoms	O
No alternative plausible diagnosis (microbial or inflammatory)		O

Table 2. Recommendations for diagnostic work-up in children evaluated for PIMS-TS.
Note: where possible, PIMS-TS patients should be enrolled in observational or interventional studies, which may include additional diagnostics.

Initial investigations in case of suspected PIMS-TS (according to disease severity)	Full blood count (FBC) C-reactive protein (CRP) Blood gas, lactate, glucose Urea, creatinine, electrolytes (U&E) Liver function tests (LFTs) Coagulation: INR, aPTT, Fibrinogen Blood cultures (always before starting antibiotics) Urine microscopy and culture NPA: respiratory panel, SARS-CoV-2 PCR Urine Lumbar puncture if clinically indicated
Second line investigations: (in addition to initial bloods) Desirable measures which should NOT delay seeking expert opinion or treatment	Erythrocyte sedimentation rate (ESR) Ferritin D-dimers Troponin NT-pro-BNP LDH CK Albumin Triglycerides Store serum and EDTA blood (before administration of IVIG) EBV/CMV/Adeno-/Enterovirus blood PCR SARS-CoV-2 serology 12-lead ECG and echokardiography Chest radiograph Abdominal ultrasound (if gastrointestinal symptoms) IL-10, IL-6, sCD25* * consider full HLH screen if suggestive features present (e.g. splenomegaly, fibrinogen normal or low; ferritin >2000): Perforin-, SAP- and XIAP-expression, NK cell degranulation and consider HLH-directed therapy (MDT)
Follow up investigations:	*Unstable patient (deteriorating or in PICU):* 12-24 hourly: FBC, CRP, U&E, LFTs, coagulation, ferritin; parameters that need to be repeated guided by clinical progress such as Troponin and NT-pro-BNP, echocardiography (in consultation with cardiology) *Stable patient with ongoing pyrexia:* 24-48 hourly: FBC, CRP U&E, LFTs, ferritin *as above Echocardiography 48 hourly (in consultation with cardiology) *Child improving +/- defervescence:* 48 hourly bloods or pre-discharge bloods: FBC, CRP, U&E, LFTS

	Echocardiography before discharge

*Children with evidence of cardiac involvement should be discussed with a tertiary centre for cardiology involvement and care in PICU should be considered.

Table 3. Anti-inflammatory therapies in patients with PIMS-TS. DISCLAIMER: Medication dosing and administration should be checked with the local hospital pharmacists and considering recent evidence updates. Where possible, PIMS-TS patients should be enrolled in interventional studies. Data were accessed from www.accessdata.fda.gov/, www.ema.europa.eu/, and the British Paediatric Allergy, Immunity, and Infection Group (Position Statement: Management of novel coronavirus (SARS-CoV-2) infection in paediatric patients in the UK and Ireland) and adapted from the Imperial College Healthcare NHS Trust PIMS-TS guideline for external use. MDT, multidisciplinary team; IVIG, intravenous immunoglobulins.

Class	Drug	Route	Dose	Duration	Comments and side effects
Blood products	**IVIG**	IV	2 g/kg (max 100g)	Infusion over 12 hours	*Side effects:* Aseptic meningitis, volume load, systemic inflammation, haemolytic anaemia, neutropenia. *Slower the rate or divide the dose over two days if signs of volume overload or severe cardiac dysfunction*
Corticosteroids	**Methylprednisolone**	IV	2 mg/kg daily (max 60 mg/day) ***or*** 10-30 mg/kg daily for 1-3 days (max 1 g/day)	1-3 days discuss in MDT	*Side effects:* Hyperglycaemia, hypertension, agitation
	Prednisolone	PO	1 mg/kg q12h ***or*** 2 mg/kg q24h	Up to 2-6 weeks	*Taper:* over 2-6 weeks
Biologicals	**Anakinra** (recombinant interleukin-1 receptor antagonist)	SC	start at 2-3 mg/kg q12 hours (max. 100mg/dose)	Discuss in MDT	*Escalation/taper:* MDT decision. IV administration possible under different dosing scheme. *Side effects:* neutropenia, leukopenia, thrombocytopenia, eosinophilia, headache, abdominal pain, nausea/vomiting, diarrhea, hepatitis, increased serum transaminases, hypersensitivity reactions, injection-site reactions, skin rash, arthralgia
	Tocilizumab (recombinant interleukin-6 receptor	IV	< 30kg: 12 mg/kg single dose (max 800mg) ≥ 30kg: 8 mg/kg single dose (max 800mg)	Discuss in MDT	*Escalation:* If no clinical improvement after initial dose, may repeat dose 8-12 hours after the initial dose after MDT discussion. *Side effects:* neutropenia, leukopenia, thrombocytopenia, anemia, pain, headache, dizziness, insomnia, demyelinating disorders, ulcerations, nausea, increased serum transaminases, liver impairment, increase in serum lipids, pancreatitis, hypertension, hypothyroidism, hypersensitivity reactions, Steven-Johnson-Syndrome, conjunctivitis, nephrolithiasis, injection-site reactions, rash
	Infliximab (chimeric tumour necrosis factor TNF α monoclonal antibody)	IV	5 mg/kg single dose	Discuss in MDT	*Side effects:* neutropenia, leukopenia/agranulocytosis, thrombocytopenia, anemia, pain, headache, dizziness, insomnia, demyelinating disorders, hypersensitivity reactions, injection-site reactions, skin rash

Appendix:

2005 International Pediatric Sepsis Definition Consensus Conference criteria for shock
(*as per Goldstein, B., et al. 2005 "International pediatric sepsis consensus conference: definitions for sepsis and organ dysfunction in pediatrics." Pediatr Crit Care Med 2005; 6(1): 2-8; with corrigenda in Gebara, B. M. et al. "Values for systolic blood pressure." Pediatr Crit Care Med 2005; 6(4): 500; author reply 500-501*).

Presence of the following despite appropriate intravenous fluid resuscitation:

- blood pressure <5th centile for age or systolic blood pressure <2 SD below normal for age

Age Group	***Systolic Blood Pressure (mmHg)***
0 days – 1 week	<59
1 week to 1 months	<79
1 months – 1 year	<75
1 – 5 years	<74
6-12 years	<83
13 - <18 years	<90

AND/OR

- need for vasoactive drugs to maintain blood pressure in normal range

AND/OR

- two of the following:
  - unexplained metabolic acidosis (base deficit >5.0 mEq/L)
  - arterial lactate >2 times upper limit of normal
  - oliguria (urine output <0.5 ml/kg/h)
  - capillary refill time >5 sec
  - core to peripheral temperature gap >3° Celsius

HLH diagnostic criteria:
(as per Pachlopnik Schmid J, Volkmer B, Ehl S: "Classification, clinical manifestation and diagnosis of HLH". Abla O. and Janka G. (eds.): Histiocytic Disorders. Springer Verlag, Stuttgart 2018; page 173 – 187. ISBN (online): 978-3-319-59632-7)

The diagnosis of HLH can be established if **(A)** and **(B)** are fulfilled

A. A molecular diagnosis consistent with HLH: disease-causing mutations in *PRF1*, *UNC13D*, *Munc18-2*, *STX11*, *RAB27A*, *LYST*, *SH2D1A*, or *BIRC4*

B. Five out of the eight criteria listed below are fulfilled:

1. Fever ≥ 38.5 °C
2. Splenomegaly (palpable below costal margin or increased size by imaging)
3. Cytopenia (affecting ≥ 2 out of the 3 lineages):
   Hemoglobin (<90 g/l; in newborns, <100 g/l)

Neutrophilic granulocytes (<1.0 G/l)
Platelet count (<100 G/l)
4. Hemophagocytosis (in the bone marrow or CSF)
5. Hyperferritinemia (≥ 500 µg/l)
6. Hypertriglyceridemia (fasting level, ≥ 3.0 mmol/l) or hypofibrinogenemia (≤ 1.5 g/l)
7. Elevated soluble CD25 (=soluble IL2 receptor, sIL2R) (≥ 2400 U/ml)
8. Decreased NK-cell cytotoxicity