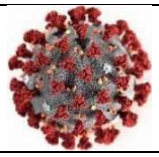
National COVID-19 Science Task Force (NCS-TF)



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Expert involved: Luregn Schlapbach and Christoph Berger 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)	**Date of response:** 22/01/2021
Contact person: ncs – Task Force contact: Nicolas Müller Main authors: Luregn Schlapbach, Head Pediatric Intensive Care Unit, University Children`s Hospital Zurich; phone 044 266 37 90; email: luregn.schlapbach@Kispi.uzh.ch (Lead PIMS-TS Working Group), Christoph Berger, Head Pediatric Infectious Diseases, University Children`s Hospital Zurich; phone 044 266 71 11; email: christoph.berger@Kispi.uzh.ch.	
Comment on planned updates:	

Paediatric Inflammatory Multisystem Syndrome Temporally Associated with SARS-CoV-2 (PIMS-TS; Multisystem Inflammatory Syndrome in Children, MIS-C) in Switzerland

Content

Summary

Background: Contrary to elderly adults, most pediatric COVID-19 infection occur asymptomatically, and severe disease in children has remained extremely rare. However, 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). PIMS likely results from a multifactorial post-infectious process where the host immune system mounts an excessive response to persistent viral antigens, possibly on the background of genetic predisposition. Children with PIMSs classically manifest, weeks after asymptomatic COVID-19 infection, a febrile disease often accompanied by gastrointenstinal symptoms and rash/conjunctivitis, showing similar features to atypical Kawasaki disease. Many children develop shock mimicking toxic shock syndrome, with vasoplegia and cardiac dysfunction as prominent features. Intensive care support for cardiovascular, and sometimes respiratory, CNS, and other organ dysfunction is frequently required.
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. Careful information of the public, and of clinicians caring for children is warranted, to ensure accurate and timely recognition of the relatively rare condition.

Current PIMS-TS situation in Switzerland:
In Switzerland, first cases of PIMS were treated in late spring 2020. In recent weeks, numbers of cases have increased substantially. To date, over 60 children have been diagnosed with PIMS, the majority requiring paediatric intensive care unit (PICU) admission. Most cases were observed subsequent to the beginning of the second wave of COVID-19 in Switzerland, predominantly in the past weeks. Our observations so far have been that albeit children with PIMS often show rapid progression and sometimes severe organ dysfunction, anti-inflammatory treatment and state-of-the art PICU support usually lead to a favourable outcome with full resolution (less is known on long-term outcomes). Although PIMS is a relatively rare disease, we anticipate that more PIMS cases will be observed in 2021 considering the current COVID-19 situation.

Aims and methodology of the Swiss PIMS-TS guidelines:
In order to standardize management in Switzerland, we aimed to develop best practice recommendations for the diagnosis and treatment of children with PIMS-TS.
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[1-3]. 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.

Endorsement status for the Swiss PIMS-TS guidelines, Version 1.0, date 30.12.2020
Subsequent to finalization of the guidelines, they underwent peer review in the relevant societies and were subsequently endorsed by all

- *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)*

The guidelines have been released on 30.12.2020 and are online available under http://transfer.imk.ch/f.php?h=1h3U-v2W&d=1

Relevance and impact:
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[4,5]. 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[6,7]. 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[8-10], 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[11], regular updates of the recommendations will be required.

Implications and recommendations for further research:
1. Dissemination of the guidelines through the societal webpages (SGI, SGP, PIGS) and networks will start after 30.12.2020.
1. A media release was drafted by Christoph Berger and Luregn Schlapbach aiming to carefully inform the public about the current state and need for the guidelines.
2. Considering the multiple uncertainties in relation to clinical phenotypes, long-term outcomes, and optimal management[11], and in the absence of randomized trials, evidence for best treatment is scarce for the diagnostic, anti-inflammatory, anti-infectious, and supportive measures which have been proposed[17,18]. The field is rapidly changing with reports being published on an almost weekly basis[19], hence revision and updates of the recommendations will be required regularly.
3. There is an urgent need to enrol children with PIMS-TS in clinical trials. The most advanced trial setup is the RECOVERY trial in the UK which is currently being updated to ensure key questions pertinent to PIMS-TS can be addressed (1. First line immunomodulative therapies IVIG vs high dose steroids vs standard care; 2. Second line biologicals). The lead of the working group, Luregn Schlapbach, is finalizing a proposal with the UK RECOVERY group to

enable a parallel Swiss study hub for a RCT testing anti-inflammatory interventions in PIMS-TS. Once ready, the proposal will be shared with the Swiss PIMS-TS working group to seek participation from different hospitals.

4. We foresee that a robust trial setup will be advantageous as well to ensure reliable capture of population-based data on PIMS-TS in Switzerland, and enable biospecimen collection on observational studies aiming to improve our understanding of mechanisms underlying PIMS-TS, such as rare host genomic variation.

Experts involved

The recommendations were led by Luregn Schlapbach (University Children`s Hospital Zurich) and Peter Rimensberger (University Hospital Geneva), in close collaboration with Christoph Berger and Christoph Aebi who are the BAG contact persons for paediatric specific aspects.

Representation of each of the university children`s hospitals includes experts in paediatric intensive care, infectious diseases, immunology/rheumatology, and haematology:

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, Arnaud 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

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