Methylprednisolone Versus Intravenous Immunoglobulins in Children with Paediatric Inflammatory Multisystem Syndrome Temporally Associated with SARS-CoV-2: A Randomised Multicentre Trial

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**Abstract**

**Background:** The emergence of Paediatric Inflammatory Multisystem Syndrome temporally associated with SARS-CoV-2 (PIMS-TS) led to widespread use of anti-inflammatory treatments in the absence of randomised controlled trials (RCT). We aimed to determine the effectiveness of intravenous methylprednisolone compared with intravenous immunoglobulins (IVIG) on length of hospital stay in children with PIMS-TS.

**Methods:** Open-label, multicentre two-arm RCT conducted at ten Swiss hospitals in children <18 years hospitalized with PIMS-TS. Patients were randomized 1:1 to intravenous methylprednisolone (10 mg/kg/day for three days) or IVIG (2 g/kg as a single dose). The primary outcome was length of hospital stay censored at day 28, death, or discharge. Secondary outcomes included proportion and duration of organ support. Analyses were intention-to-treat (ITT). Trial registration: SNCTP000004720, NCT 04826588.

**Findings:** Between May 21, 2021, and April 15, 2022, 75 patients with a median age of 9∙1 years [IQR 6∙2, 12∙2] were included in the ITT allocated to methylprednisolone (n=37) versus IVIG (n=38). The median length of hospital stay was 6∙0 days [IQR 4∙0 to 8∙0] in the methylprednisolone and 6∙0 days [IQR 5∙0 to 8∙8] in the IVIG arm (estimated effect size -0∙037 of the log10 transformed times, 95% CI [-0∙13, 0∙065], p 0∙42). Fewer patients on methylprednisolone (n=10, 27∙0%) required respiratory support compared to IVIG (n=21, 55∙%, p 0∙025). Need and duration of inotropes, ICU admission, post-baseline cardiac events, and major bleeding and thrombotic events were not significantly different between the study arms.

**Interpretation:** In this RCT, treatment with methylprednisolone in children with PIMS-TS did not significantly affect the length of hospital stay compared to IVIG. In addition, methylprednisolone was associated with lower requirement for respiratory support.

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**Putting research into context:**

**Evidence before this study**

The emergence of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic was followed by clusters of children presenting with a new inflammatory disease labelled Paediatric Inflammatory Multisystem Syndrome temporally associated with SARS-CoV-2 (PIMS-TS), or Multisystem Inflammatory Syndrome in children associated with COVID-19 (MIS-C). In the absence of evidence based on randomised controlled trials (RCT), clinical practice has been guided by expert opinion and consensus guidelines. In a PubMed search using the terms (“intravenous immunoglobulins” OR “methylprednisolone” OR “trial”) AND ("Paediatric multisystem inflammatory disease, COVID-19 related" OR "Paediatric Inflammatory Multisystem Syndrome") for studies published between April 1, 2020, and October 31, 2022, with no language restrictions, no study was identified reporting on results of randomised comparison of anti-inflammatory treatments for children with PIMS-TS. Five larger observational studies of patients with PIMS-TS were found, which analysed effectiveness of glucocorticoids, IVIG, or IVIG combined with glucocorticoids. IVIG in combination with glucocorticoids versus IVIG alone showed similar or superior effectiveness in relation to a range of outcomes including measures of inflammation, requirement for respiratory support, vasopressor treatment, and hospital length of stay.

**Added value of this study**

This is the first reported RCT comparing the two most commonly used anti-inflammatory treatments in children diagnosed with PIMS-TS. In this RCT, treatment with intravenous methylprednisolone once daily over three days compared to IVIG was associated with similar length of hospital stay. Bayesian analyses for the primary outcome of length of stay, and secondary analyses on need for respiratory support indicated moderate benefit associated with methylprednisolone. These findings are supported by the observational Best Available Treatment Study (BATS), which did not find evidence for differences in recovery for glucocorticoids alone, compared to IVIG alone.

**Implications of all the available evidence**

Due to the small sample size of this trial, independent confirmation from larger interventional trials, including the UK RECOVERY trial with subsequent meta-analysis, is needed. In addition, long-term follow-up of these cohorts to investigate the incidence of persistent cardiac anomalies, in particular coronary artery aneurysms, is required. Given the limited availability of IVIG around the globe, our findings add evidence that intravenous methylprednisolone could be an acceptable first-line treatment in children with PIMS-TS in addition to supportive care, being more affordable and more widely available globally than IVIG.

**Introduction**

The emergence of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic across the globe was followed in April 2020 by clusters of children presenting with a new inflammatory disease, characterized by fever, multisystem involvement and elevated inflammation parameters with similarities to Kawasaki Disease (KD)1-3. This entity has been labelled Paediatric Inflammatory Multisystem Syndrome temporally associated with SARS-CoV-2 (PIMS-TS), or Multisystem Inflammatory Syndrome in children associated with COVID-19 (MIS-C).. Disease criteria, including confirmed or suspected infection with SARS-CoV-2 and increased inflammation parameters, in the presence of mucocutaneous, circulatory, respiratory, or neurological symptoms, supported clinicians in making a diagnosis of PIMS-TS enabling therapeutic management. Although some early reports observed recovery in patients without immunomodulatory treatment4, it became common practice to treat patients as the disease was considered severe with many affected requiring admission to the Paediatric Intensive Care Unit (PICU) for cardiovascular and respiratory support5-7. In the absence of randomised controlled trials (RCTs), PIMS-TS management has been guided by expert opinion and consensus guidelines, and inference from KD trials, rather than PIMS-TS specific evidence. These recommend the use of intravenous glucocorticoids and intravenous immunoglobulins (IVIG) as mainstays of initial therapy, with consideration for biologic disease modifying anti-rheumatic drugs (bDMARDs), namely anakinra, tocilizumab or infliximab, in more severe or refractory cases8-11.

Up to now, there remains uncertainty about the effectiveness of glucocorticoid monotherapy as the initial treatment approach in PIMS-TS. Observational data indicate that while both treatment with IVIG monotherapy as well as IVIG in combination with glucocorticoids are effective in PIMS-TS, glucocorticoids alone compared to IVIG monotherapy may result in similar recovery12-15. As the availability of IVIG is limited especially for clinicians in low- and middle-income countries, a randomised comparison of anti-inflammatory treatments for children with PIMS-TS is urgently needed. The Swissped RECOVERY trial aimed at assessing the effectiveness of intravenous methylprednisolone versus IVIG in hospitalized children with PIMS-TS.

**Methods and analysis**

*Study design*

Swissped RECOVERY is an investigator-initiated randomized multicentre open-label two-arm trial in children and adolescents hospitalized with PIMS-TS conducted at ten paediatric hospitals in Switzerland. Patients with PIMS-TS diagnosed in line with the Swiss PIMS-TS guidelines which apply the RCPCH case definition8,16 were recruited in emergency departments (EDs), wards, and PICUs of hospitals in Aarau, Basel, Bern, Bellinzona, Fribourg, Geneva, Lausanne, Lucerne, St. Gallen, and Zurich. The design of Swissped RECOVERY was informed by a trial on children with PIMS-TS in the UK (NCT04381936, https://www.recoverytrial.net/files/recovery-paediatric-sap-v1-1.pdf)17, which was conducted within the Randomised Evaluation of COVID-19 Therapy trial (https://www.recoverytrial.net/RECOVERY, NCT04381936). In the UK RECOVERY trial, “no treatment” was defined as the standard of care arm. In contrast, in the Swissped RECOVERY trial treatment with IVIG was defined as standard of care, as withholding any anti-inflammatory treatment was considered unethical due to observational evidence of effectiveness of anti-inflammatory treatment, and lack of equipoise for any compared to no treatment12-14. The study was approved by the lead ethics committee (Ethics Committee Northwest/Central Switzerland; EKNZ, Project ID: 2021-00362; **Supplementary Appendix eMethods 1**), and other responsible ethics committees in Switzerland. The trial was registered on the Swiss National Clinical Trials Portal (SNCTP000004720) and clinicaltrial.gov (NCT 04826588) before commencement. An independent Data Monitoring Committee (DMC) monitored trial safety and evaluated the need for early trial termination (**Supplementary Appendix eMethods 2)**. The study protocol was published before completion of recruitment18.

*Patients*

Children aged <18 years with a clinical diagnosis of PIMS-TS admitted to hospital were eligible if the treating physician considered that the patient required intravenous anti-inflammatory treatment. The presumptive diagnosis of PIMS-TS was based following case definitions (i) age <18 years, (ii) fever and laboratory inflammation and single/multiorgan dysfunction, (iii) microbiologically proven or putative COVID-19 contact (iv) exclusion of any other probable disease (**Supplementary Appendix eMethods 3)**8. Patients were excluded if the treating clinician identified either (i) a medical history that may put the patient at significant risk in case of study participation, (ii) a specific contra-indication to one of the treatment arms, or (iii) clinical indication that a specific treatment arm had to be administered. Furthermore, neonates with a corrected gestational age of ≤44 weeks were excluded. Prospective written informed consent from parents (and by patients if aged ≥14 years) was required. In instances where timely informed consent was not achievable, a deferred consent approach was used, in which written consent from the parents/guardians and patients was obtained after enrolment19.

*Randomisation and masking*

Study patients were randomized 1:1 to intravenous methylprednisolone or IVIG by online randomisation through the electronic data capture system REDCapTM hosted by the University Children’s Hospital Basel20. The computer-generated randomisation list used random permuted blocks of 30 patients without stratification by site. No masking was performed, aligned with an open-label pragmatic trial design, and due to the logistic challenges associated with blinding IVIG and methylprednisolone.

*Procedures*

After randomisation, the trial treatment was prescribed by the treating clinician or a dedicated trial member to be administered without delay through a peripheral or central venous access line. Patients received either intravenous methylprednisolone 10 mg/kg/dose (maximum dose 1000 mg per day) once daily for three days (no tapering thereafter) or IVIG 2 g/kg/dose (maximum dose 100 g) as a single dose given as a slow infusion in line with the institutional standard operating procedures (infusion duration 12 hours ± 4 hours). The methylprednisolone dose as well as the IVIG dose were aligned with the UK RECOVERY trial. The study protocol did not mandate other management procedures such as organ support, fluids, anticoagulation, or antimicrobial use which could be delivered as per local practice. Treating clinicians could administer additional anti-inflammatory treatment not intended in the protocol when they considered it to be indicated. The study protocol recommended, however, to observe patients for at least 24 hours after starting the randomised treatment before considering additional anti-inflammatory treatment. All non-randomised anti-inflammatory treatments were considered intercurrent events (ICEs) including treatment with anakinra, additional use of oral glucocorticoids, as well as doses of the randomised treatment not intended in the protocol, fewer doses of the randomised treatment as intended in the protocol, administration of IVIG in the methylprednisolone arm and vice versa. ICEs were reviewed by a blinded endpoint review committee. Data on vital signs, organ function and support, laboratory parameters, additional specific examinations such as electrocardiograms, echocardiograms, and administered treatments were prospectively collected on days 0, 1, 2, 3, 4-5, 6-7, and 8-14 or until discharge.

*Outcomes*

The primary outcome was the length of hospital stay, defined as the time in days from hospital admission to discharge or death, with censoring at 28 days. Time from randomization to discharge was also assessed. Secondary outcomes included all-cause mortality; proportion of patients needing organ support, operationalized as respiratory support (i.e. invasive ventilation, continuous positive airway pressure (CPAP), biphasic positive airway pressure (BIPAP), high and low flow supplemental oxygen), inotropes, renal replacement, and extracorporeal membrane oxygenation; as well as duration of organ support; and proportion of patients with cardiac pathologies, defined as coronary artery enlargement (Z-score ≥2), left ventricular ejection fraction <55%, and/or arrhythmia at any time after randomisation. Pre-defined safety outcomes (major bleeding, and/or thrombotic events) and severe adverse events (SAEs) likely to be related to the study treatment were recorded.

*Statistical analysis*

The statistical analysis plan (SAP) was defined *a priori* (Version 1.3, 17.5.22, **Supplementary Material SAP**), following, wherever possible, the online available SAP defined for the UK-based trial17. The primary analysis, performed using data from the intention-to-treat (ITT) study population, compared the log-transformed time from admission to discharge (death or censoring) of the two arms using a two-sided t-test. For the period of the trial, it was estimated that approximately 50 and 120 children could be recruited. According to expert opinion, approximately 80 children in total were estimated. With this in mind the estimated target sample size of 80 patients (two groups of 40) would have 80% power to detect a difference in length of stay of 2∙5 days between the trial arms, assuming a two-sided 5% statistical significance level.

Baseline (randomisation) and follow-up patient characteristics were summarized using the number (percentage) for categorical variables and the median (inter-quartile range [IQR]) for continuous variables. Summary statistic comparisons between groups were performed using the chi-square test for categorical variables, and the Wilcoxon test for continuous variables (unless stated otherwise). Kaplan-Meier plots compared time from admission to discharge between the trial arms with the log-rank test used to test for differences. Furthermore, uni- and multivariable Cox Proportional Hazards models were fitted and adjusted for treatment arm, sex, age (in years) and body mass index (BMI). For binary outcomes, uni- and multivariable logistic regression models investigated the same baseline risk factors.

To enable consolidation and comparison with the pediatric UK RECOVERY trial17, a Bayesian analysis of the primary outcome was performed (**Supplementary Appendix eMethods 4**). In brief, we compared the two treatment arms by considering the difference between the respective mean of the posterior time to discharge distribution (and associated 95% credibility intervals). If the probability that the mean of the methylprednisolone arm was less than that on the IVIG arm was at least 95%, then this would signify a “very strong signal of benefit”. A probability between 80% and 95% would be interpreted as a “strong signal”, while a probability of 70% to 80% would constitute a “moderate” positive signal. A probability of 30% or less would be taken as a signal for “harm”. Differences in length of stay were also investigated according to age category, ethnicity, gender, PICU admission (at baseline and at any time) and phenotype (PIMS-TS with shock, KD-like PIMS-TS, undifferenciated PIMS-TS)18. Furthermore, the longitudinal trajectory of biomarkers was plotted.

All analyses were based on the complete case data only. For frequentist statistics, a p-value of less than 5% was considered statistically significant. The trial statistician was fully blinded up to database closure, and thereafter to the specific treatment arms for the primary analysis. The analysis was performed using the statistical software R (version 3∙6∙1)21 and OpenBUGS for the Bayesian analysis22.

*Role of the funding sources*

The funders of the study had no role in the trial design, data collection, data analysis, data interpretation or writing of the manuscript and the decision to submit.

**Results**

*Patients*

During the eleven months of trial (first-patient-in May 21, 2021, last-patient-in April 15, 2022) a total of 127 PIMS-TS patients were assessed for eligibility, of whom 76 were enrolled, provided informed consent and were randomly allocated to either the methylprednisolone (n=37) or the IVIG arm (n=39; **figure 1, Supplementary Appendix eTable S1**). Parents of one patient withdrew consent before the initiation of treatment, leaving 75 patients in the ITT study population. All 37 (100%) patients in the methylprednisolone arm included in the ITT study population received methylprednisolone, 37 of the 38 (97%) patients in the ITT population received IVIG. No children died during the study, with discharge time administratively censored at 28 days for only one patient. The study population had a median age of 9∙1 years [IQR 6∙2, 12∙2] and 19 (25∙%) were female (**table 1**). An underlying chronic disease was present in 8 (11∙%) children. At baseline, 72 (96∙0%) patients reported fever (≥38° Celsius ≥24 hours) in the past 7 days, and the majority presented with lymphopenia, increased inflammatory parameters, and elevated NT-proBNP (**table 1, Supplementary Appendix eTable S2**). At baseline, clinical symptoms of respiratory distress were similar between patients randomised to the two arms. Almost all patients (n=70, 93∙0%) were randomized within a day of admission, with four patients randomized within 2 days and one patient within 6 days.

*Primary outcome*

The median time from admission to discharge was 6∙0 days [IQR 4∙0, 8∙0] for the methylprednisolone and 6∙0 days [IQR 5∙0, 8∙8] for the IVIG arm (**table 2, figure 2A, Supplementary Appendix eFigure S1)**. There was no significant difference in the log10 transformed mean times between the two trial arms(p 0∙42).The between-group difference in admission to discharge estimated from the Bayesian posterior distribution model was of a similar magnitude (mean difference -0∙68 with IVIG having longer times, 95% credible interval [-2∙3, 1∙0], **figure 2B**), but indicated a “moderate benefit” in favour of the methylprednisolone arm (80%, 95% credible interval [-0 ∙12%, 100%], **table 2**). There was no difference between the treatment groups from unadjusted survival models (hazard ratio (HR) 0∙87, 95% confidence interval (CI) [0 ∙63, 1∙2], p 0∙41, **Supplementary Appendix eFigure S2 and eTable S3).**

*Secondary outcomes*

Fewer patients on methylprednisolone needed respiratory support at any time (n=10, 27∙0%) compared to IVIG (n=21, 55∙%, p 0∙025) and this trend continued post-randomisation (n=3; 8∙% versus n=11; 29∙%; p 0∙040; **table 2, figure 2D)**. Duration of respiratory support, treatment with and duration of inotropes were not different between the study groups (**table 2** and **figure 2A**). Post-baseline, 70 echocardiographic examinations were performed in 35 patients randomised to IVIG, and 74 in 35 patients randomised to methylprednisolone. Nine (24∙%) patients randomized to IVIG had a decreased ejection fraction <55% compared to five (14∙%) patients randomised to methylprednisolone (p 0∙52) (**table 2**). No patient needed extracorporeal membrane oxygenation or renal replacement therapy. Multivariable logistic regression adjusted for sex, age and BMI indicated that being treated with IVIG was an independent risk factor for post-baseline need for respiratory support (adjusted odds ratio (aOR), 5∙0, 95% CI [1∙9, 13], p 0∙030**, Figure 2D, Supplementary Appendix eTable S4**).

*Subgroup and posthoc exploratory analyses*

Twenty (27∙%) cases of PIMS-TS were categorized as PIMS-TS shock, 31 (41∙%) as KD-like PIMS-TS, and 24 (32∙0%) as undifferentiated PIMS-TS. In subgroup analyses, the median time to discharge was shorter in patients with KD-like PIMS-TS randomised to methylprednisolone (5∙0 days [IQR 4∙0, 6∙0]) compared to those randomised to IVIG (6∙5 days [IQR 5∙8, 9∙3], p 0∙035 [not adjusted for multiple testing]), with no treatment difference for the other phenotypes, and for the other predefined subgroup analyses (**Supplementary Appendix eTable S5, Supplementary Appendix eFigure S1).** Exploratory analyses of the trajectories for inflammation markers CRP, leukocytes, and neutrophils and other laboratory markers did not reveal major differences between patients in the IVIG versus those in the methylprednisolone arm (**Supplementary Appendix eFigure S3)**.

*Protocol deviations and adverse events*

In total, 76 ICEs were reported in 41 patients mainly due to additional not randomised anti-inflammatory treatment (**Supplementary Appendix eTable S5**). In the methylprednisolone arm, 24 (65∙%) patients had ICEs, of which 11 (30∙%) were related to taking IVIG and 10 (27∙0%) were related to tapering glucocorticoids. In the IVIG arm 17 (45∙%) patients had ICEs, of which 12 (32∙%) were related to taking methylprednisolone. **Figure 3** shows ICEs and per protocol treatment after randomisation until day six. There was no statistically significant difference between the two arms in terms of ICEs (p 0∙45, **Supplementary Appendix eTable S5).** Similarly, in a pre-defined per protocol analysis (ie “while on treatment strategy” for ICEs) of the primary endpoint, there was no difference between the arms (p 0∙4, **Supplementary Appendix eTable S5).**

Only one patient (3∙%) in the IVIG arm had a thrombotic event (**table 2**). During the trial period, seven (9∙%) patients had seven SAEs (**Supplementary Appendix eTable S6**). None of the SAEs were definitively related to the treatment intervention. Of three possibly related SAEs, two (hyperglycaemia and agitation/lethargy) were reported in the methylprednisolone arm, and one (hypotensive shock) was reported in the IVIG arm.

**Discussion**

In this open-label RCT comparing intravenous methylprednisolone treatment with IVIG in children with PIMS-TS, both treatments were comparable in terms of length of hospital stay. In a pre-planned Bayesian analysis, there was moderate benefit for the primary outcome associated with methylprednisolone treatment. In addition, PIMS-TS patients randomized to methylprednisolone required respiratory support less often at any time compared to patients randomized to IVIG. We did not observe significant differences in other secondary outcomes, including cardiac events such as coronary artery enlargement, within the 28 days` follow-up period.

In Swissped RECOVERY, the analysed patients with PIMS-TS had in general similar clinical and laboratory characteristics but lower proportions of patients admitted to PICU compared to previously published cohorts12-14,23,24. Since the first wave of the pandemic, rates of PICU admission in children with PIMS-TS decreased and IVIG, glucocorticoids, and anti-platelet medications emerged as the predominant treatments25. Six large observational studies have assessed effectiveness of glucocorticoid monotherapy, IVIG or IVIG plus glucocorticoids12-15,24,26. Son et al.13 compared 103 propensity-matched patients treated with IVIG plus glucocorticoids with 103 patients treated with IVIG alone. Initial treatment with glucocorticoids and IVIG was associated with lower risk of the composite outcome of cardiovascular dysfunction on or after day 2 than IVIG (17% versus 31%, risk ratio, 0∙56; 95% CI 0∙34 to 0∙94). Patients treated with IVIG plus glucocorticoids had a lower risk of additional anti-inflammatory treatment. Ouldali et al.12 compared 64 PIMS-TS patients treated with IVIG with 32 propensity-matched patients treated with IVIG plus methylprednisolone. The latter treatment was associated with lower risk of ongoing fever (OR 0∙25; 95% CI, 0∙09 to 0∙70), reduced use of additional anti-inflammatory treatment, and shorter PICU stay. McArdle et al.14 analysed 614 PIMS-TS patients (246 were treated with IVIG, 208 with IVIG and glucocorticoids, and 99 with glucocorticoids). The receipt of inotropic support or mechanical ventilation on day 2 or later or death was observed in 56 patients receiving IVIG plus glucocorticoids (adjusted OR for the comparison with IVIG alone, 0∙77; 95% CI, 0∙33 to 1∙82) and in 17 patients who received glucocorticoid monotherapy (adjusted OR, 0∙54; 95% CI, 0∙22 to 1∙33). The adjusted likelihoods to reduce disease severity were similar in the two treatment groups, as compared with to IVIG alone indicating similar recovery patterns14. Villacis-Nunez et al.15 assessed failure of initial therapy for 69 children receiving glucocorticoid monotherapy, 31 receiving IVIG alone, and 115 receiving glucocorticoids plus IVIG. After propensity score weighting, initial treatment failure was comparable between the patients in the glucocorticoid and the patients in the IVIG plus glucocorticoid group. Patients in the IVIG plus glucocorticoid group had a longer median inpatient stay compared with the glucocorticoid group (6 versus 5 days; p 0∙001). Harthan et al.24 compared 153 (43%) patients receiving IVIG and glucocorticoids, 33 (9%) patients with IVIG monotherapy, 43 (12%) patients with glucocorticoids, and 127 (36%) receiving neither IVIG nor glucocorticoids. Combination therapy was associated with shorter ICU length of stay. However, when comparing hospital length of stay between these groups in mixed linear regression analyses, no significant difference was observed after adjusting for confounding variables. Bagri et al. showed in their propensity score matched analysis that patients treated with glucocorticoids (n=45) versus IVIG combined with glucocorticoids (n=84) did not differ in relation to the need of inotropes and/or respiratory support two days and later after treatment initiation26.

Altogether, the available observational data supports our findings and suggests that glucocorticoid treatment is comparable to IVIG in patients with PIMS-TS. In our trial, this finding was consistent across all three *a priori* defined PIMS-TS phenotypes, including the KD-like group, but the respective subgroup sizes were too small to permit firm conclusions. Importantly, our study was unable not address whether IVIG or methylprednisolone are superior to no immunomodulatory treatment, as, when designing the study, clinicians considered it unethical to withhold treatment for patients with PIMS-TS. There remains a need for further research as IVIG has been widely used in PIMS-TS due to clinical overlap to KD. In KD IVIG is recommended as first-line treatment, although evidence particularly for long-term effects is limited4. Considering the lack of paediatric data forcing compassionate use of drugs27,28 in general, and the magnified relevance of this during the pandemic, our study provides urgently needed data on best treatments to a unique paediatric rare disease. Adverse events were rare compare to previous reports29. For some outcomes, such as need of respiratory support, the data from our trial suggest that treatment with glucocorticoids may be better than IVIG alone. Treatment with IVIG can be associated fluid overload particularly in children with decreased cardiac function, which potentially could account for the higher respiratory support requirements in our study.

Direct comparison of the observed treatment effects in different PIMS-TS studies is not only hampered by variable treatment protocols and variable outcome definitions, but also by considerable contamination with anti-inflammatory treatments. In the BATS study14, such were administered in 136 of 552 patients (25%) in the three treatment groups by day 2 and 238 patients (43%) received additional treatment at any time. Among the patients in the propensity score matched sample who received IVIG monotherapy in the Overcoming COVID-19 study13, 74 patients (72%) receiving an additional anti-inflammatory treatment and among those receiving IVIG and glucocorticoids 41 patients (39%) received additional anti-inflammatory treatment. In Swissped RECOVERY, ICEs were reported more commonly in the patients randomised to methylprednisolone compared to IVIG. This difference might be explained due to glucocorticoid tapering aligned with the Swiss PIMS-TS guidelines8, which was not prescribed in the trial protocol.

The results of two further RCTs investigating optimal anti-inflammatory treatment in PIMS-TS are being awaited, including the UK RECOVERY trial (NCT04381936) and the US MISTIC trial (NCT04898231). The UK RECOVERY trial investigated in children with PIMS-TS a two-stage randomisation with methylprednisolone, IVIG, and no anti-inflammatory treatment as first randomisation, and anakinra, tocilizumab, and no anti-inflammatory treatment as second randomisation. The US MISTIC study aims to randomize 180 patients to methylprednisolone, anakinra, and infliximab if IVIG monotherapy is considered clinically insufficient.

Several limitations of the Swissped RECOVERY study need to be stated. First, numbers of eligible patients with PIMS-TS declined considerably during the emergence of the omicron variant by spring 2022, leading to termination of the trial at 76 (out of 80 targeted) patients. The sample size was not powered to permit robust conclusions on secondary outcomes and subgroup analyses. Second, a number of exclusions occurred due to clinicians considering one of the treatments unsuitable before proceeding to possible enrolment or preferring a combination of IVIG and glucocorticoids. We were not allowed to analyse whether clinical characteristics of patients without consent differed from enrolled patients. Third, study treatments in this pragmatic trial were open label with the potential for bias, especially in relation to ICEs and therefore a second randomisation stage to additional rescue anti-inflammatory treatment might have been beneficial. Fourth, aligned with the UK RECOVERY study, the primary outcome of length of hospital stay included pre-randomization hospital stay and may be further affected by conditions not related to disease severity. However, this outcome was chosen as length of hospital stay represents a patient-centred, objective measure strongly related to health-care costs. Fifth, we have not collected data on fluid balance. Finally, the follow-up period was limited to discharge or a maximum of 28 days. Further follow-up is required to delineate the full long-term impact associated with the studied interventions.

In conclusion, in this RCT on children with PIMS-TS, treatment with methylprednisolone resulted in comparable length of hospital stay compared to IVIG, but was associated with lower requirement for respiratory support. Intravenous methylprednisolone could be an acceptable first line treatment for children with PIMS-TS, being considerably more affordable and more widely available globally than IVIG30.

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**Contributors:**

The study design originated from the publicly available U.K. RECOVERY Trial protocol which was conceived by lead investigators Professors Martin Landray and Peter Horby, University of Oxford. LJS and JB designed this study, oversaw study setup, conduct, analyses setup, contributed to the first draft, approved the final version, and take responsibility for the accuracy of reported findings. TW and NS contributed to study design, setup, conduct, analyses setup, and contributed to the first draft, and approved the final version. CS is the data manager for Swissped RECOVERY. AA wrote the statistical analysis plan and performed the final analyses. AA and CS contributed to study conduct, and approved the final version. MCA, DGNB, GBR, MB, SG, HK, MHP, JT, FV, PZ performed patient recruitment, data collection, contributed to manuscript writing and approved the final version.

**Declaration of interests:**

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**Data sharing:**

**Data availability:** Deidentified participant data will be shared upon reasonable request unless the request is conflicting with ongoing or planned analyses. Requests need to be addressed to the corresponding author at luregn.schlapbach@kispi.uzh.ch and will require approval by the Swissped RECOVERY steering group.

**How to access data:** Who can access the data: Researchers with an approved proposed use, approved by appropriate institutional review boards and the Swissped RECOVERY Steering Committee. Types of analyses: An approved specified purpose. Mechanisms of data availability: With a signed data access agreement. How to access data: Deidentified participant data will be shared upon reasonable request unless the request is conflicting with ongoing or planned analyses. Requests need to be addressed to the corresponding author at luregn.schlapbach@kispi.uzh.ch

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**References**

1. Riphagen S, Gomez X, Gonzalez-Martinez C, Wilkinson N, Theocharis P. Hyperinflammatory shock in children during COVID-19 pandemic. *Lancet* 2020; **395**(10237): 1607-8.

2. Levin M. Childhood Multisystem Inflammatory Syndrome - A New Challenge in the Pandemic. *N Engl J Med* 2020; **383**(4): 393-5.

3. 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): 259-69.

4. Davies P, Lillie J, Prayle A, et al. Association Between Treatments and Short-Term Biochemical Improvements and Clinical Outcomes in Post-Severe Acute Respiratory Syndrome Coronavirus-2 Inflammatory Syndrome. *Pediatr Crit Care Med* 2021; **22**(5): e285-e93.

5. Davies P, Evans C, Kanthimathinathan HK, et al. Intensive care admissions of children with paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS) in the UK: a multicentre observational study. *Lancet Child Adolesc Health* 2020; **4**(9): 669-77.

6. Williams V, Dash N, Suthar R, et al. Clinicolaboratory Profile, Treatment, Intensive Care Needs, and Outcome of Pediatric Inflammatory Multisystem Syndrome Temporally Associated with SARS-CoV-2: A Systematic Review and Meta-analysis. *J Pediatr Intensive Care* 2022; **11**(1): 1-12.

7. Angurana SK, Awasthi P, Thakur A, et al. Intensive Care Needs and Short-Term Outcome of Multisystem Inflammatory Syndrome in Children (MIS-C): Experience from North India. *J Trop Pediatr* 2021; **67**(3).

8. Schlapbach LJ, Andre MC, Grazioli S, et al. Best Practice Recommendations for the Diagnosis and Management of Children With Pediatric Inflammatory Multisystem Syndrome Temporally Associated With SARS-CoV-2 (PIMS-TS; Multisystem Inflammatory Syndrome in Children, MIS-C) in Switzerland. *Front Pediatr* 2021; **9**: 667507.

9. Cattalini M, Taddio A, Bracaglia C, et al. Childhood multisystem inflammatory syndrome associated with COVID-19 (MIS-C): a diagnostic and treatment guidance from the Rheumatology Study Group of the Italian Society of Pediatrics. *Ital J Pediatr* 2021; **47**(1): 24.

10. 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* 2021; **5**(2): 133-41.

11. 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 3. *Arthritis Rheumatol* 2022; **74**(4): e1-e20.

12. Ouldali N, Toubiana J, Antona D, et al. Association of Intravenous Immunoglobulins Plus Methylprednisolone vs Immunoglobulins Alone With Course of Fever in Multisystem Inflammatory Syndrome in Children. *JAMA* 2021; **325**(9): 855-64.

13. Son MBF, Murray N, Friedman K, et al. Multisystem Inflammatory Syndrome in Children - Initial Therapy and Outcomes. *N Engl J Med* 2021; **385**(1): 23-34.

14. McArdle AJ, Vito O, Patel H, et al. Treatment of Multisystem Inflammatory Syndrome in Children. *N Engl J Med* 2021; **385**(1): 11-22.

15. Villacis-Nunez DS, Jones K, Jabbar A, et al. Short-term Outcomes of Corticosteroid Monotherapy in Multisystem Inflammatory Syndrome in Children. *JAMA Pediatr* 2022; **176**(6): 576-84.

16. Guidance: Paediatric Multisystem Inflammatory Syndrome Temporally Associated With COVID-19. RCPCH (2020). Available online at: <https://www.rcpch.ac.uk/resources/paediatric-multisystem-inflammatory-syndrome-temporally-associated-covid-19-pims-guidance> (last access 02.2022)

17. Jaki T. Statistical Analysis Plan: Paediatric multisystem inflammatory syndrome population. Version 1.1. Date 31 August 2021. *UK Recovery Trial, Protocol Version: 161 (08 July 2021), 2021* [*https://wwwrecoverytrialnet/files/recovery-paediatric-sap-v1-1pdf*](https://wwwrecoverytrialnet/files/recovery-paediatric-sap-v1-1pdf).

18. Welzel T, Schobi N, Andre MC, et al. Multicenter Randomized Trial of Methylprednisolone vs. Intravenous Immunoglobulins to Treat the Pediatric Inflammatory Multisystem Syndrome-Temporally Associated With SARS-CoV-2 (PIMS-TS): Protocol of the Swissped RECOVERY Trial. *Front Pediatr* 2022; **10**: 905046.

19. Woolfall K, Frith L, Gamble C, et al. How parents and practitioners experience research without prior consent (deferred consent) for emergency research involving children with life threatening conditions: a mixed method study. *BMJ Open* 2015; **5**(9): e008522.

20. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform* 2009; **42**(2): 377-81.

21. Team RC. R: A Language and Environment for Statistical Computing 2019. <https://www.R-project.org/>.

22. Lunn DJ TA, Best N, Spiegelhalter D. . WinBUGS — a Bayesian modelling framework: concepts, structure, and extensibility. *Statistics and Computing* 2000; **10**: 325-37.

23. Feldstein LR, Tenforde MW, Friedman KG, et al. Characteristics and Outcomes of US Children and Adolescents With Multisystem Inflammatory Syndrome in Children (MIS-C) Compared With Severe Acute COVID-19. *JAMA* 2021; **325**(11): 1074-87.

24. Harthan AA, Nadiger M, McGarvey JS, et al. Early combination therapy with immunoglobulin and steroids is associated with shorter ICU length of stay in Multisystem Inflammatory Syndrome in Children (MIS-C) associated with COVID-19: A retrospective cohort analysis from 28 U.S. Hospitals. *Pharmacotherapy* 2022; **42**(7): 529-39.

25. Abrams JY, Belay ED, Godfred-Cato S, et al. Trends in Treatments for Multisystem Inflammatory Syndrome in Children (MIS-C), United States, February 2020 - July 2021. *Clin Infect Dis* 2022; **75**(7): 1201-9.

26. Bagri NK, Khan M, Pandey RM, Lodha R, Kabra SK, group M-Cs. Initial Immunomodulation and Outcome of Children with Multisystem Inflammatory Syndrome Related to COVID-19: A Multisite Study from India. *Indian J Pediatr* 2022; **89**(12): 1236-42.

27. Larcher V, Caplan A, Brierley J. COVID-19, children, clinical trials and compassion: The ethical case for using innovative or compassionate treatments. *Acta Paediatr* 2022; **111**(2): 363-7.

28. Hwang TJ, Randolph AG, Bourgeois FT. Inclusion of Children in Clinical Trials of Treatments for Coronavirus Disease 2019 (COVID-19). *JAMA Pediatrics* 2020.

29. Dain AS, Raffini L, Whitworth H. Thrombotic events in critically ill children with coronavirus disease 2019 or multisystem inflammatory syndrome in children. *Curr Opin Pediatr* 2022; **34**(3): 261-7.

30. Organization WH. Multisystem inflammatory syndrome in children (MIS-C) with COVID-19. 2021. <https://app.magicapp.org/#/guideline/j1WBYn> (accessed October 22nd 2022).

**Figure legends**

**Figure 1. Study flow chart.** PIMS-TS *Paediatric Inflammatory Multisystem Syndrome temporally associated with SARS-CoV-2,* ITT *intention to treat*

**Figure 2. Forest plots of estimated effect sizes for the primary and secondary endpoints.** Estimated effect sizes are shown for primary and secondary endpoints in unadjusted analyses (panel A), Bayesian analyses for the primary endpoint (panel B), as well as adjusted analyses for the primary endpoint (panel C) and for the secondary endpoint respiratory support at any time (panel D). Note: The effect sizes in panel A are evaluated on the log10 scale (since we log before performing the t-test), the Bayesian analysis is on the original scale (panel B). MP *intravenous methylprednisolone,* IVIG *intravenous immunoglobulin G, HR hazard ratio, OR odds ratio, CI confidence interval.*

**Figure 3: Sankey Diagram of intercurrent events in study patients until day six.** Overview of intercurrent events (ICEs) is shown in study patients randomised to the intravenous immunoglobulin G (IVIG; dark blue) or methylprednisolone (MP, light blue) arm until day 6. ICEs are defined as non per protocol anti-inflammatory treatments (such as additional anti-inflammatory treatment, more doses of the randomised treatment, IVIG in the methylprednisolone arm and vice versa). Day 0 was defined as day of randomisation where the patient received MP or IVIG. For all patients with ICEs, the different ICEs after randomisation are shown over the time (Day 0 to 6). Each day subsumes the ICEs occurring in a 24-hours period. IVIG *intravenous immunoglobulin G;* MP *methylprednisolone,* oral CS *oral glucocorticoids,* ANA *Anakinra,* NH *not hospitalized anymore,* NT *no treatment but hospitalized*