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High-dose intravenous immunoglobulin versus albumin 4% in paediatric toxic shock syndrome: a randomised controlled feasibility study

Aurélie Portefaix ,[1,2] Carole Dhelens,[3] Morgan Recher,[4,5] Fleur Cour-Andlauer,[6] Jérôme Naudin,[7] Guillaume Mortamet ,[8] Nicolas Joram,[9] Pierre Tissières,[10,11] Tiphanie Ginhoux,[1] Behrouz Kassai,[1,12] Florent Boutitie,[13] Delphine Maucort-Boulch,[13] Etienne Javouhey[14,15]

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For numbered affiliations see end of article.

Correspondence to
Dr Aurélie Portefaix;
aurelie.portefaix@chu-lyon.fr

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ABSTRACT

Purpose Toxic shock syndrome (TSS) is a rare disease responsible for significant morbidity and mortality. Intravenous immunoglobulin (IG) therapy in paediatric TSS could improve shock and organ failure, but more consistent efficacy and safety data are needed. Our objective was to determine whether a randomised clinical trial (RCT) assessing intravenous IG in TSS in children is feasible.

Methods We performed a multicentre, feasibility, double-blind RCT assessing efficacy of high-dose intravenous IG versus albumin 4% (control group) within the first 12 hours of shock onset. Included patients were aged above 1 month and below 18 years with suspected TSS and septic shock. Feasibility was assessed by measuring inclusion rate, protocol compliance and missing data regarding death and the Pediatric Logistic Organ Dysfunction-2 (PELOD-2) Score. Other secondary clinical outcomes were evaluated during hospital stay, at 60 day and 1 year.

Results 28 patients, admitted in 6 paediatric intensive care units during 36 consecutive months and followed for 1 year, received the allocated treatment: 13 in intravenous IG group, 15 in control group. The median age was 10.6 years and the sex ratio was 1. Inclusion rate was above 50%, protocol deviations were below 30% and missing data regarding death and PELOD-2 Score below 10%. No difference concerning secondary clinical outcomes between groups was observed, and more adverse events were reported in the control group.

Conclusion It seems to be feasible to conduct an RCT assessing intravenous IG efficacy and safety in paediatric TSS but must be realised internationally, with choice of a clinically relevant endpoint and a specific design in order to be realistic.

Trial registration number NCT02219165.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Toxic shock syndrome (TSS) is a rare disease responsible for significant morbidity and mortality.
⇒ Intravenous immunoglobulin (IG) in paediatric TSS could improve shock and organ failure.
⇒ Data are needed to evaluate efficacy and safety of IGs, but randomised clinical trial seem to be very difficult to conduct in this indication.

WHAT THIS STUDY ADDS

⇒ A randomised paediatric clinical trial is feasible in TSS.
⇒ Intravenous IG seems to be safe in paediatric TSS treatment.
⇒ An international trial is needed to assess efficacy of IG.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ For this rare disease, alternative design such as pragmatic study or single-arm design trial with an external formalised comparison cohort must be discussed.
⇒ An international trial is incontestably required to meet the inclusion target.
⇒ We described for the first time 1-year follow-up of children with TSS.

BACKGROUND

Toxic shock syndrome (TSS) is responsible for significant morbidity and mortality, with a fatality rate that could reach 28% in children with streptococcal TSS.[1–6] In TSS, superantigen-related toxins are produced by bacteria, foremost among them *Staphylococcus aureus* and *Streptococcus pyogenes*,[7 8] but also viruses.

The Surviving Sepsis Campaign Guidelines advise against the routine use of intravenous immunoglobulins (IGs) in TSS children with streptococcal aetiology.[9] Many intensivists declared having used intravenous IG for TSS management,[10] while their efficacy is questionable. Pathophysiology of TSS in children differs from adults: (1) immunological response varies with age, (2) the alterations of innate immunity in response to sepsis are more pronounced in children compared with adults[11] and (3) clinical and biological presentations are different.[12] By blocking superantigenic activity and owning anti-inflammatory and immunomodulatory properties, intravenous IG could decrease the initial inflammatory storm of TSS, thus limiting shock intensity and organ failure.[7 8 13 14]

In adults, one randomised controlled trial (RCT) stopped early due to lack of recruitment[15] reported a 3.6-fold higher mortality rate in the placebo group. A second RCT that enrolled less than 50%

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TSS patients reported inconclusive results on mortality or organ failure and physical functioning.[16] A recent literature review, however, mixing adult and paediatric data, suggested intravenous IG efficacy.[17] Ig M-enriched immunoglobulin (IgGAM) could be an alternative to intravenous IG as it has been reported to improve survival in adult septic shock.[16 18 19] Data on the use of IgGAM in children with TSS are scarce. Cryoprecipitate has also been proposed in septic shock without significant effect.[20] The last surviving sepsis campaign guidelines do not suggest its use in adults.[21]

Because the evidence on intravenous IG is expensive with limited supply, and its benefit-risk balance in children with TSS[1] stems from observational studies,[22–24] as underlined by the Center for Disease Control and Prevention (CDC) and the Infectious Diseases Society of America,[9 25] conducting an RCT seems justified.

Before launching such an RCT, we conducted a pilot study to assess its feasibility.

MATERIAL AND METHODS

We performed a multicentre, feasibility, double-blind RCT (1:1) comparing: high-dose intravenous IG versus albumin 4%. The trial, registered in https://www.clinicaltrials.gov (NCT02219165), was sponsored by the Hospices Civils of Lyon (HCL). The Clinical Investigation Center (INSERM 1407), coordinated the trial and collected all data.

Five amendments to the protocol were necessary (electronic supplemental material (ESM) online supplemental table 1).

We planned to recruit 30 patients with suspected TSS and septic shock over 24 months, admitted within 9 French paediatric intensive care units (PICUs).

Inclusion criteria were age above 1 month and below 18 years and admission to PICU for shock resistant to fluid resuscitation defined according to Goldstein criteria,[26] associated with a strong suspicion of staphylococcal or streptococcal infection (box 1).

Non-inclusion criteria were the first signs of shock appeared more than 24 hours before admission, hypersensitivity to one of the treatment components or to homologous IG, known hyperprolinaemia, immunodeficiency, ongoing immunosuppressive therapy, Kawasaki disease (KD), absence of health insurance.

At admission, the physician checked inclusion criteria and proposed trial participation to the parents of eligible patients. After their parents' consent, patients were randomised within 24 hours after diagnosis and 12 hours after admission or first signs of shock onset if appeared after admission.

Box 1 Toxic shock syndrome (TSS) definition by CDC criteria

Strong suspicion of staphylococcal or streptococcal infections defined as least one of these criteria:

TSS as defined by CDC criteria.

⇒ Group A streptococcal necrotising fasciitis (positive strep test).

⇒ Varicella with infected lesions and rash or positive strep test.

⇒ Erythrodermic rash with menstrual period or parapneumonic pleural effusion with erythrodermic rash.

⇒ Positive strep test in pleural fluid or erythrodermic rash and biological fluids positive to *Streptococcus A* or *Staphylococcus aureus*.

Randomisation was centralised using an Interactive Web Response System (IWRS), stratified by centre and balanced by block. Intravenous IG was PRIVIGEN 100 mg/mL, provided by CSL Behring AG, France. The comparator was albumin 4% (VIALEBEX, LFB, France). Both drugs were supplied in 100 mL numbered vials in the same size and packaging. To blind colours of the contents (pale yellow for intravenous IG vs darker yellow for albumin 4%), a specific tamper-evident overpack of vials was developed with Faubel pharma services. This allowed solution clarity to be checked before administration and ensured sanitary traceability, without revealing the drug nature. IMPs were double-blind packaged, labelled and delivered to each centre by the FRIPHARM (HCL).

Following international recommendations on the management of sepsis and TSS (Surviving Sepsis Campaign and CDC), all patients received sepsis shock treatment and first-line antibiotics (association of penicillin and clindamycin or linezolid to limit toxin production[23]). After randomisation, patients received a single injection of high-dose intravenous IG (1.5–2 g/kg) or albumin 4% at equivalent volume (0.8 g/kg dose). The IWRS assigned 1 numbered vial per 5 kg of weight whether the patient was in the intravenous IG or the control group.

Clinical and biological data were collected from admission to day 5 and data were collected at discharge. Clinical outcomes were assessed at 60 days and 1 year, including the Pediatric Glasgow Outcome Scale Extended (Gos-E-Peds).[27]

The primary outcome was to determine the feasibility of a blind RCT with two arms (intravenous IG and albumin 4%) in TSS children.

Feasibility indicators were:

- Eligibility: inclusion rate, screened patients, eligible patients, non-included patients (and reasons when possible).
- Protocol deviations: compliance with protocol design, including patients not meeting all eligibility criteria, unblinding process and non-compliance with treatment schedule.
- Practical feasibility: human resources required (time spent to include patients, to complete e-case report form (e-CRF), to perform trial-related exams).

The trial was deemed feasible if inclusion rate among eligible patients was between 40% and 50%; the protocol deviations were below 30% and missing data regarding death and Pediatric Logistic Organ Dysfunction-2 (PELOD-2) Score were below 10%.

Secondary outcomes were PELOD-2 Score evolution during the first 5 days; intrahospital, 60-day and 1-year mortality; clinical and biological evolution during PICU stay and TSS management; functional outcome at 1 year; adverse events (AEs) and severe AEs (SAEs).

A data safety and monitoring board (DSMB), comprising two PICU physicians and one methodologist, was implemented to ensure participants' safety by giving recommendations throughout the study.

Statistical analysis

Since it is a feasibility study and few data are available to assess a measurable outcome such as the PELOD-2 Score in TSS children, no sample size calculation was performed. Sample sizes were extrapolated based on the recruitment capacity of each centre over 1 year. No interim analysis was planned.

Continuous variables are reported as medians (quartiles 1–3) or means (SD) and compared between treatment groups using the Wilcoxon rank-sum test. Categorical variables are reported

Table 1 Initial characteristics of the 30 patients included in the trial

	Overall population N=30	Control group N=15	intravenous IG group N=15
Age, years, median (Q1–Q3)	10.6 (4–14.1)	13.1 (4–14.1)	7.1 (3.1–13.0)
Weight, kg, median (Q1–Q3)	35.0 (17–50)	48.0 (7.8–56)	35.0 (15–40)
Sex, female, N (%)	15 (50)	9 (60)	6 (40)
PELOD-2 Score, median (Q1–Q3)	6 (4–8)	6 (4–7)	6 (5–9)
PIM-3, median (Q1–Q3)	3.5 (1.9–939)	3.2 (1.5–39.0)	4.8 (2.2–51.3)
Age-adjusted hypotension, N (%)	18 (60)	8 (53.3)	10 (66.7)
Fever>38.5°C, N* (%)	7 (41)	2 (33)	5 (45.5)
Vomiting, N (%)	17 (57)	7 (47)	10 (67)
Diarrhoea, N (%)	17 (57)	8 (53)	9 (60)
Neurological injury, N (%)	9 (30)	3 (20)	6 (40)
Muscular injury, N (%)	13 (43)	5 (33)	8 (53)
Cutaneous signs			
Desquamation, N (%)	1 (3)	1 (7)	0 (0)
Rash, N (%)	25 (83)	13 (87)	12 (80)
Skin necrosis, N (%)	2 (7)	1 (7)	1 (7)
Mucosal lesion, N (%)	13 (43)	6 (40)	7 (47)
Minimum leucocyte count (G/L), median (Q1–Q3)	10.8 (8.1–14.1)	11.11 (8.11–16.1)	10.6 (6.6–12.7)
Minimum lymphocyte count (G/L), median (Q1–Q3) (N=17)	0.4 (0.2–0.7)	0.44 (0.2–1.3)	0.44 (0.3–0.7)
Minimum platelet value (G/L), median (Q1–Q3)	109.5 (84–143)	96 (74–155)	115 (94–143)
Disseminated intravascular coagulation, N (%)	11 (37)	7 (47)	4 (27)
Liver alterations†, N (%)	24 (80)	11 (73)	13 (87)
Maximum creatinine value (µmol/L), median (Q1–Q3)	99 (53–150)	115 (39–147)	79 (53–184)
Maximum PCT value (µg/mL), median (Q1–Q3) (N=25)	75 (54–122)	71 (60–100)	88 (50–300)
Maximum lactate value (mmol/L), median (Q1–Q3)	2.8 (2.3–40)	2.8 (2.3–3.6)	3.4 (2.4–4.3)
Maximum CK value (UI/L), median (Q1–Q3) (N=21)	353 (129–1283)	336 (67–775)	387 (295–1283)

*N=26.
†Liver alterations were defined as: aspartate aminotransferase>3N or alanine aminotransferase>3N according to normal values for age or prothrombin ratio (PR)<70%
CK, creatine kinase; IG, immunoglobulin; PCT, procalcitonin; PELOD-2, Pediatric Logistic Organ Dysfunction-2; PIM 3, Pediatric Index of Mortality-3.

as frequencies and percentages and compared using Fisher's exact test. All tests were two-sided and all p values were considered significant if below 0.05. Statistical analysis was performed using SAS V.9.4 in a Windows environment.

RESULTS

A total of 30 patients were recruited in 6 French PICUs between 8 January 2015 and 19 March 2018 and followed-up until 15 March 2019 (last visit of last patient).

The median age was 10.6 years (4.0–14.1) and the sex ratio was 1. In total, 18 patients (60%) had age-adjusted hypotension at admission. Table 1 displays baseline demographics and clinical characteristics. 10 patients (7 in the control group, 3 in the intravenous IG group) had a streptococcal infection and 17 patients (7 in the control group, 10 in the intravenous IG group) had a staphylococcal infection. Among the latest, no bacteria were identified for three children, but they had TSS clinical presentation according to CDC definition and were considered staphylococcal infections (ESM online supplemental table 1). Three patients were infected by other bacteria, and thus wrongly included.

Protocol feasibility

Figure 1 shows the trial flowchart. In total, 75 patients (0.3 %) were assessed for eligibility, including 26 who did not meet inclusion criteria: 13 did not present shock criteria, 5 were in refractory shock at admission, 3 did not meet all CDC criteria for TSS, 2 had acquired immunodeficiency, 1 was younger than 1 month and 2 were not included for administrative reasons. Among the 49 eligible patients, 19 (39%) were not included (5 parents declined, 6 patients were 'missed' by clinician team, 6 patients were not included for organisation issues including 3 for lack of treatment available and for 2 patients, both parents were not present). Overall, 30 patients were randomised to receive intravenous IG (15 patients) or albumin 4% (15 patients). Randomisation arm was respected for all the patients.

In total, 28 patients (93%) received the allocated treatment at the prespecified dosage: 13 in the intravenous IG group as 1 patient was transferred to another hospital for extracorporeal membrane oxygenation procedure before treatment administration and another developed adverse reaction after the first administration, versus 15 in the control group.

Seven patients (23%) were treated more than 12 hours (but less than 24 hours) after admission. Median time between admission and randomisation was 6.18 hours (1.1–47.9).

No call to the unblinding centre was made to break the blind. Despite the different colour and market packaging of both drugs and the absence of opaque tubing use for administration, nobody discovered the treatment arm.

In total, 73% of day 60 visits were made during the schedule planned. One patient withdrew consent and two were lost to follow-up.

Time needed to fill-in the e-CRF was satisfactory for 100% of the investigators who responded.

Following DSMB recommendations, an addendum was made to change fluid bolus volume (>30 mL/kg for >12 years and >40 mL/kg for <12 years) for eligibility criteria. The DSMB did not require any protocol modification during the study but

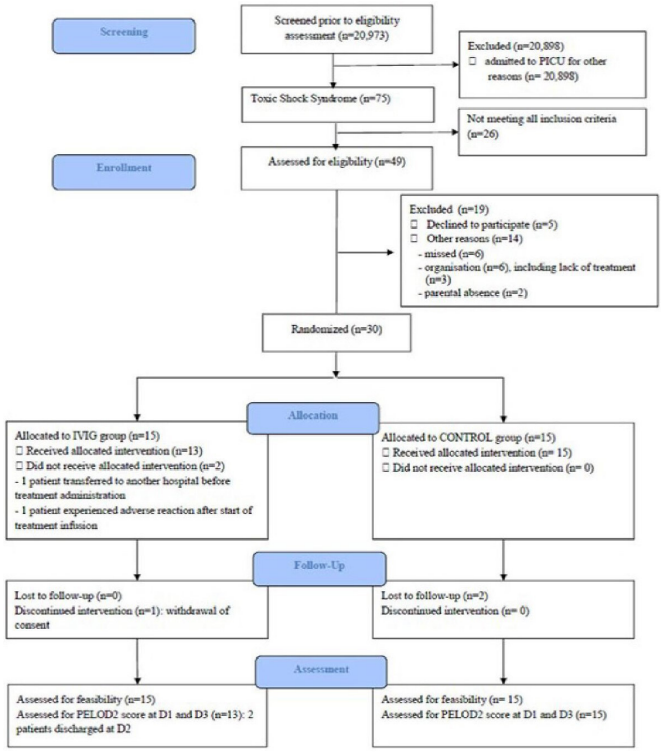

Figure 1 Flow chart of the trial. The control group consists of patients treated with albumin 4%. IVIG, intravenous immunoglobulin; PICU, paediatric intensive care unit.

recommended conducting a European study to ensure recruitment for the next study.

Inclusion rate was therefore above 50%, protocol deviations were below 30% (mostly for treatment administration time and missing data regarding death) and PELOD-2 Score below 10% (table 2), meaning that this feasibility trial was successful.

Clinical and biological outcomes

The PELOD-2 Score variation (figure 2), PELOD-2 scores (ESM online supplemental figure 1) and the haemodynamic parameters (ESM online supplemental table 2 and online supplemental figure 2) were similar between groups. At day 4, no patient needed vasopressor support in the intravenous IG group versus one in the control group. All patients received antibiotic therapies: clindamycin and β-lactam for 29 and clindamycin alone for 1. No patient died during the trial. The inflammatory response and biological data evolution are described in ESM online supplemental table 4. We observed no difference between groups for GOS-E-Peds Score at 1 year, figure 3, ventilation duration, PICU length and total hospital stays (ESM online supplemental table 5). The GOS-E-Peds Score at 1 year was good for 11 and 12 patients, respectively, in the control (14 patients assessed) and intravenous IG group (15 patients assessed).

In total, 14 patients (93%) in the control group and 10 (67%) in the intravenous IG group presented at least 1 AE; the most frequent ones being skin abnormalities and infection (ESM online supplemental figure 3). 11 SAEs were declared in the control group and 3 in the intravenous IG group, including 1 necrotising fasciitis. One intravenous IG treatment was stopped due to hypersensitivity reaction. Safety data appear to be favourable to the use of intravenous IG and albumin 4% in TSS children.

DISCUSSION

Our trial is the first RCT in the field of paediatric TSS. It demonstrates the feasibility of an RCT comparing intravenous IG with albumin 4% in PICUs, a crucial step before considering a larger study.

Randomisation was performed in a timely manner, with the clinical staff being blind to group allocation. Acceptability of the trial process by parents/legal guardians was high: only five parents refused their child's participation. Inclusion rate and parental protocol adherence were adequate with less than 30% protocol deviations, indicating that the protocol was acceptable for families and clinicians. Randomisation does not seem to be an issue for paediatricians. A survey conducted by the European Society of Pediatric and Neonatal Intensive Care showed that only one-quarter of paediatricians are reluctant to randomise (personal data). In addition, rescue IG administration was allowed in our study and was not used.

Nevertheless, our trial revealed some limitations to conduct such an RCT. The investigators highlighted the difficulties to perform children's inclusion simultaneously to their urgent care management. Particular attention should be paid to minimise the trial constraints. Moreover, although the a priori defined feasibility criteria were met, the time needed to achieve inclusion was more than two times the expected time. Trial inclusion and duration are the main obstacles identified by this feasibility trial.

Table 2 Criteria of feasibility of the trial

	Protocol defining cut-off (%)	Result (N=30)	Status
Inclusion rate among eligible patients	50	61	Successful
Protocol deviation	30		Successful
Not meeting inclusion criteria, N (%)		2 (7)	
Unblinding, N (%)		0 (0)	
Respect of treatment allocation			
► Non-compliance*, N (%)		2 (7)	
► Delay for treatment administration>12 hours, N (%)		7 (23)	
Missing data	10		Successful
PELOD-2, N (%)		0 (0)	
Death†, N (%)		3 (10)	

Cut-off were defined in the protocol of the trial.
*Compliance is defined as a high dose of immunoglobulins (between 1.5 and 2 g/kg).
†Three patients dropped out prematurely (one refusal and two lost to follow-up); however, data regarding the vital status of one of them was known (refusal), even if not recorded in the case report form.

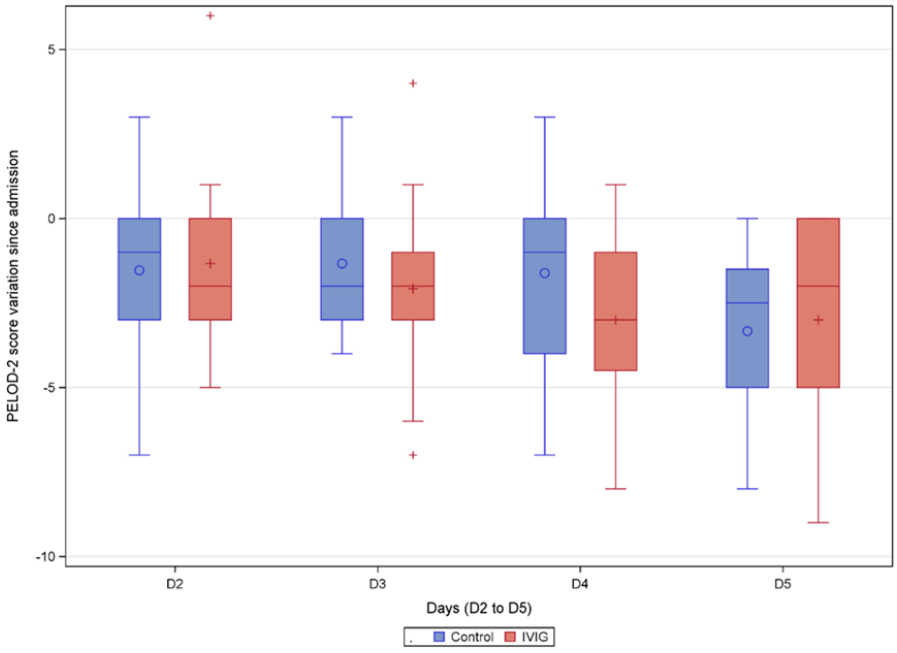

Figure 2 Evolution of Pediatric Logistic Organ Dysfunction-2 (PELOD-2) Score variation during the first 5 days according to treatment group. The control group (blue boxes) consists of patients treated with albumin 4%. The intravenous immunoglobulin (IVIG) group (red boxes) consists of patients treated with Intravenous Immunoglobulin.

TSS is very rare, representing less than 0.3% of the patients admitted to PICUs. We probably failed to estimate the true potential recruitment rate as we enrolled 30 patients over 36 months in 6 centres instead of 30 patients initially expected over 24 months. Noteworthy, thanks to information campaigns and the widespread use of clindamycin,[28] the incidence of menstrual TSS decreased during the trial period, making recruitment more difficult. Furthermore, the number of streptococcal infections was low, especially in the intravenous IG group whereas it is likely that efficacy of intravenous IG is probably easier to demonstrate in streptococcal TSS as they are more severe, with more organ dysfunction and higher mortality rate. An international multicentre trial is therefore required.

Selecting the most clinically relevant endpoint constitutes another challenge for the next RCT. PELOD-2 Score is well validated to predict mortality, widely used in French and European

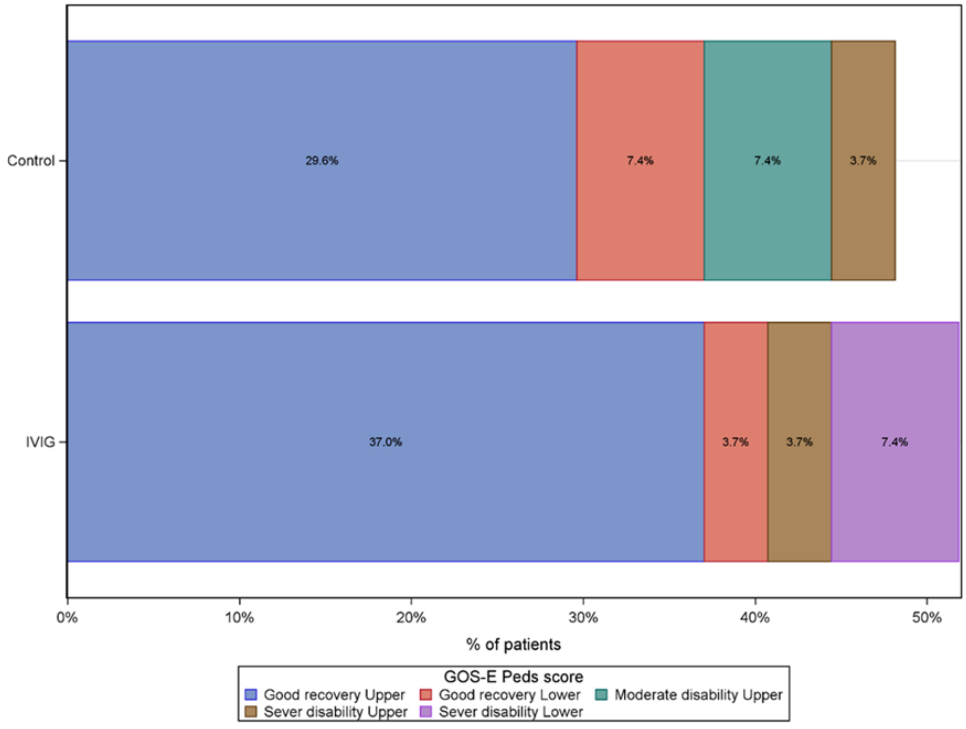

Figure 3 Pediatric Glasgow Outcome Scale Extended (GOS-E-Peds) at 1 year in each allocated group. The control group consists of patients treated with albumin 4%. The intravenous Immunoglobulin (IVIG) group (red boxes) consists of patients treated with intravenous immunoglobulin

PICUs[29] and easy to complete. With PELOD-2 Score variation as primary outcome, the number of patients needed is 72 in each arm (ESM online supplemental table 6). PELOD-2 is the best score to discriminate outcomes here,[30] but its variation is difficult to interpret in clinical practice and is not sensitive enough. It would be preferable to use a primary outcome with better clinical relevance and easier interpretation, such as the new or progressive multiple organ dysfunction syndrome (NP-MODS), already used in paediatric RCTs.[31] Unfortunately, for a NP-MODS incidence of 26% and an RR of 0.6, we need to include 318 patients per group. Other scores, such as GOS-E-Peds,[27] initially validated as a score used after traumatic brain injury, assess long-term outcomes and may be pertinent for our next trial. To demonstrate a difference of 10% on the Gos-E-Peds between both groups, we need to include 477 patients per group. With the experience of IGHN (paediatric toxic shock syndrome) study, including more than 200 patients is not a realistic hypothesis in terms of recruitment and funding. For 144 inclusions in 15 European centres, we would need to include nearly 5 patients per year per centre for 2 years; which is feasible. Time to resolution of organ dysfunction is a relevant outcome, whatever the aetiology of shock.

To be pragmatic, intravenous IG is considered for any shock with cutaneous rash (KD, TSS and multisystem inflammatory syndrome in children related to SARS-CoV-2 infection (MIS-C)). A study focusing on these patients could be an alternative. MIS-C and TSS have clinical and biological similarities but differ on V-beta expansion in T cells.[32] A larger trial, including all paediatric shock with rash (without confirmed KD), would be closer to practice, justified by the suggested efficacy of intravenous IG and IgGAM on mortality in adult septic shock,[19] and would improve assessment of the safety, such as renal impairment.[33] However, their aetiologies differ, and the number of subjects needed would be larger.

Finally, to compare more than two treatments, a platform trial could be performed.[34] However, there are so far, only a few potential treatments to be compared using this type of design.

Creating a European comprehensive registry can be the first step to make an external cohort, used to compare with the single-arm trial.[35]

CONCLUSION

A double-blind RCT is feasible to evaluate intravenous IG versus albumin 4% efficacy in paediatric TSS. The choice of inclusion criteria should be as close as possible to patients' usual management. Recruitment potential is less than expected and the most relevant endpoints have to be strictly selected, but an RCT design is always preferable to prove efficacy. An international trial is incontestably needed to meet the inclusion target.

Author affiliations
[1]Clinical Investigation Center, Hospices Civils de Lyon, Lyon Bron, France
[2]EMET LBBE, Université Claude Bernard Lyon 1, Villeurbanne, France
[3]Pharmacie FRIPHARM, Hospices Civils de Lyon, Lyon, Auvergne-Rhône-Alpes, France
[4]Services de Réanimation Pédiatrique, CHU Lille, F59000-Lille, France
[5]METRICS, Universite Lille Nord de France, Villeneuve-d'Ascq, Hauts-de-France, France
[6]Réanimation Pédiatrique, Centre Hospitalier Universitaire de Lyon, Bron, France
[7]Service de Réanimation Pédiatrique, Hôpital Universitaire Robert-Debré, Paris, Île-de-France, France
[8]Pediatric Intensive Care Unit, Necker Hospital, Paris, France
[9]Réanimation Pédiatrique, CHU Nantes, Nantes, Pays de la Loire, France
[10]Paediatric Intensive Care Unit, Hospital Bicetre, Le Kremlin-Bicetre, Île-de-France, France
[11]Institute for Integrative Cell Biology, Gif-sur-Yvette, Île-de-France, France
[12]Université Lyon 1, CNRS, UMR 5558, Laboratoire de Biométrie et Biologie Evolutive, Villeurbanne, France
[13]Biostatistics, Hospices Civils de Lyon, Lyon, Auvergne-Rhône-Alpes, France
[14]Hospices Civils de Lyon, Lyon, Auvergne-Rhône-Alpes, France
[15]EA 7426 Joint Research Unit HCL-bioMérieux, Université Claude Bernard Lyon 1, Villeurbanne, Auvergne-Rhône-Alpes, France

X Aurélie Portefaix @AureliPortefaix

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Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by French Southeast IV Ethics Committee (2014-017 B) in May 2014 and the French National Agency for Medicines and Health Products Safety in July 2014. A written informed consent from at least one parent/legal representative and oral agreement from the other one was required. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. The data that support the findings of this study are available from the corresponding author and the sponsor of this trial, the Hospices Civils de Lyon, on reasonable request.

ORCID iDs
Aurélie Portefaix http://orcid.org/0000-0003-4981-821X
Guillaume Mortamet http://orcid.org/0000-0003-2145-5330

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