Fluid resuscitation in paediatric burns: how do we get it right? A systematic review of the evidence

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ABSTRACT

Background Optimal fluid resuscitation in children with major burns is crucial to prevent or minimise burn shock and prevent complications of over-resuscitation.
Objectives To identify studies using endpoints to guide fluid resuscitation in children with burns, review the range of reported endpoint targets and assess whether there is evidence that targeted endpoints impact on outcome.
Design Systematic review.
Methods Medline, Embase, Cinahl and the Cochrane Central Register of Controlled Trials databases were searched with no restrictions on study design or date. Search terms combined burns, fluid resuscitation, endpoints, goal-directed therapy and related synonyms. Studies reporting primary data regarding children with burns (<16 years) and targeting fluid resuscitation endpoints were included. Data were extracted using a proforma and the results were narratively reviewed.
Results Following screening of 777 unique references, 7 studies fulfilled the inclusion criteria. Four studies were exclusively paediatric. Six studies used urine output (UO) as the primary endpoint. Of these, one set a minimum UO threshold, while the remainder targeted a range from 0.5–1.0 mL/kg/hour to 2–3 mL/kg/hour. No studies compared different UO targets. Heterogeneous study protocols and outcomes precluded comparison between the UO targets. One study targeted invasive haemodynamic variables, but this did not significantly affect patient outcome.
Conclusions Few studies have researched resuscitation endpoints for children with burns. Those that have done so have investigated heterogeneous endpoints and endpoint targets. There is a need for future randomised controlled trials to identify optimal endpoints with which to target fluid resuscitation in children with burns.

What is already known on this topic?

► Optimal fluid resuscitation in children with burns is challenging.
► While initial fluid therapy in burns is often estimated, ongoing fluid resuscitation must be titrated according to response.
► A variety of resuscitation endpoints in adults with burns have been studied.

What this study adds?

► There is a paucity of evidence for goal-directed fluid resuscitation in children with burns.
► Endpoint targets for fluid resuscitation in children with burns show considerable heterogeneity.
► Further research is required to identify which endpoints and target ranges improve patient outcome.

INTRODUCTION

Optimal fluid resuscitation in children with severe burns is a key determinant of survival. It can minimise or prevent the hypovolaemic and distributive shock that develops from thermal injury, and limit complications related to over-resuscitation.[1 2] Accurate quantification of burn depth and affected total body surface area (TBSA) can be difficult. Furthermore, accurate estimation of fluid requirements in burn patients is challenging, partly because they are a heterogeneous patient group with varying burn size, depth and aetiology. Traumatic and inhalation injuries also affect fluid requirements, as does burn mechanism.[3 4] Children have a greater surface area to weight ratio than adults and have greater relative insensible and burn-related fluid losses.[5 6] The smaller circulating volume in children compared with adults requires a greater degree of accuracy when replacing fluids.

The challenge of resuscitating children with burns is compounded by the affected anatomical site and the extent of burn injury as these may impair monitoring methods. Furthermore, the majority of paediatric burns occur in low-income and middle-income countries, where provision of healthcare can be limited.[7 8]

Under-resuscitation of patients with burns leads to organ hypoperfusion, which can lead to organ failure and increased burn depth, and ultimately increased scar formation.[9] Over-resuscitation also confers additional morbidity and mortality through complications including pulmonary and cerebral oedema, compartment syndrome, and increased burn depth and scarring, but for reasons of oedema rather than poor perfusion.[10–12] Such excess fluid administration and associated complications have been shown to be increasingly common, and they are exacerbated by the tendency of medical staff to overprescribe fluids, described by Pruitt as 'fluid creep'.[10 12] Increased opiate doses in patients with burns ('opioid creep') have been postulated to be partly responsible for 'fluid creep'. The reasons for this are thought to relate to increased fluid administration to treat hypotension seen as a side effect of opiate use.[13 14]

Fluid requirements are estimated by the use of established formulae incorporating burn size and

patient weight. The Parkland formula remains the most widely used guide to initial fluid requirements and is recommended by the Emergency Management of the Severe Burn guidelines, although various modifications and alternative formulae exist.[15][16] While the goal of resuscitation is to ensure adequate end-organ perfusion and oxygenation, identifying when this has been achieved in burn patients is difficult. Urine output (UO), vital signs (heart rate, blood pressure) and clinical examination are used to titrate fluid resuscitation. However, tachycardia secondary to a burn-induced hypermetabolic state and stress-related antidiuretic hormone (ADH) release affecting UO, impact on this assessment.[16][17] As burn injury and secondary fluid shifts are dynamic in nature, fluid resuscitation must be titrated to clinical response. There is no consensus about which endpoints and targets should be used to guide fluid titration. Dries and Waxman[18] found poor correlation between UO, vital signs and invasive haemodynamic parameters, including cardiac index (CI), pulmonary artery occlusion pressure and calculated oxygen transport variables, obtained by pulmonary artery catheterisation (PAC). Finally, while oliguria may suggest impaired renal perfusion, it may also represent a physiologically normal ADH response to injury. 'Adequate' UO also does not exclude impaired end-organ perfusion.

Various resuscitation endpoints in adults with burns have been investigated, including intrathoracic blood volume, base excess, lactate, tissue oxygenation, cardiac contractility and filling on echocardiography and gastric tonometry.[19] Recent systematic and non-systematic reviews investigated the evidence for endpoint monitoring to guide fluid resuscitation in predominantly adult burn patients.[19][20] A review of the evidence for resuscitation endpoints in paediatric burn patients has not been reported to date.

The objectives of this systematic review were to (1) describe the methods of endpoint monitoring for fluid resuscitation in children younger than 16 years of age with burns; (2) review the range of reported endpoint targets; and (3) assess whether there is evidence that targeted endpoints in children with burns impact on outcome.

METHODS
Search strategy
The review protocol is registered on the PROSPERO database (reference: PROSPERO 2017: CRD42017045739).

Study eligibility criteria were predefined to identify relevant studies. Studies were eligible if they were (1) a full-text article reporting a study in which treatment for burn injury was investigated, (2) published in a peer-reviewed journal, (3) included children aged <16 years and (4) reported that fluid resuscitation endpoints were used to guide fluid titration. No restrictions were placed on publication date or study design. Studies not published in the English language were excluded. Endpoints were defined as indices that define a measured outcome of treatment or a specific physiological goal.[21] We refer to the desired numerical endpoint value/range as the endpoint target (at which the physiological variable should be maintained). We included studies that investigated endpoints as their primary aim, and those that investigated potential endpoints while routine care was provided, if this also included targeted endpoints.

Four electronic bibliographic databases were searched in January 2017 to identify relevant citations: Medline, Embase, Cinahl and the Cochrane Central Register of Controlled Trials. Search terms were developed to identify synonyms of burns, fluid resuscitation and endpoint/goal monitoring. Terms within each group were combined using OR, and groups of terms were combined using the AND function. Search terms were applied to titles, abstracts and keywords to increase search sensitivity. Search strategies are detailed in online supplementary appendix 1.

Screening of studies
Duplicate studies were removed and studies were screened using the inclusion and exclusion criteria (table 1) applied in a hierarchical manner. One author applied the inclusion and exclusion criteria to all titles and abstracts. The full-text article was reviewed for those that were retained and the same criteria applied. A second author reviewed 20% of citations at both stages. Disagreements were resolved through discussion. Inter-rater reliability for applying the screening criteria was found to be acceptable at each stage (titles and abstracts (n=154): 72.6% for inclusion; full text (n=24): 75% for inclusion and 100% for reason for exclusion). Where studies included both paediatric (<16 years of age) and adult participants, the study was included if at least one-third of the participants were paediatric. Where it was not clear if children were included, we contacted the authors for clarification. Studies were excluded if no response was received.

Data extraction
A standardised data extraction form was developed, piloted and used to extract data. Data extracted were (1) demographics:

Table 1 Inclusion and exclusion criteria

	Inclusion	Exclusion
Design	Randomised controlled trials. Controlled trials. Cohort studies. Observational studies. Case series.	Studies not written in English. Abstract only.
Participants	<16 years. Adult studies including participants <16 years old. Burns ≥10% total body surface area.	Studies not specifically about burns. Not about human participants. Studies without any paediatric (<16 years) participants. Adult and paediatric studies with less than one-third paediatric participants.
Intervention	Fluid resuscitation guided by monitored endpoints.	Studies not providing primary data investigating fluid resuscitation. Studies not conducted in the clinical setting. Studies not about fluid resuscitation endpoints.
Comparison	All comparators considered.	

Exclusion refers to the hierarchy of exclusion criteria for documenting the primary reason each paper was excluded.

Table 2 Characteristics of included studies

Study	Country	Aims	Design	Population, n, mean age±SD (age range)	%TBSA, mean±SD (range)
Faraklas et al[22] (2011)	USA	To assess if adding colloid (human albumin solution (HAS)) to resuscitation fluids in a paediatric population, who are showing signs of complications or reduced urine output during resuscitation, results in a reduction in the fluid input/output (I/O) ratio.	Retrospective observational.	Mixed (≤18 years), n=53 (29 crystalloid only, 24 also received HAS), NR (range 0.9–17)	Crystalloid group: 19.5 (15–62) HAS group: 28.5 (15–81)
Greenhalgh et al[23] (1995)	USA	To determine whether maintaining serum albumin levels in burned paediatric patients had any effect on morbidity and mortality.	Prospective randomised trial.	Mixed (<19 years), n=70 (36 low albumin group, 34 high albumin group), 6.3±0.6	45.9±2.2 (21–91)
Kraft et al[24] (2013)	USA	To determine that the use of the PiCCO system and consecutively adjusted fluid management has positive impact on the hospital course, morbidity and mortality in severely burned children.	Cohort (historical control).	'Paediatric'—but not defined TTD group n=76: 9.1±0.6 Control group n=76: 7.7 ±0.6	Control: 62.2±2.5 TTD: 64.0±2.3
Luo et al[25] (2009)	China	To examine the effectiveness of the TMMU protocol for modern fluid resuscitation in burn patients.	Prospective observational.	Mixed, n=71 (25 children), 2.73±2.05 (range 0.75–8) of paediatric group	38.73±8.46 (of paediatric group)
Müller Dittrich et al[26] (2016)	Brazil	To compare early versus delayed 5% albumin solution resuscitation in children with burns in terms of clinical outcome and response.	RCT	Paediatric, n=46 Early albumin (n=23): 37 m (IQR 22–53) Delayed albumin (n=23): 31 m (IQR 12–64)	Early albumin: 16 (IQR 15–18) Delayed albumin: 17 (IQR 15–22)
Okabayashi et al[27] (2001)	Japan	To identify if using burn depth in addition to burn size and body weight when calculating fluid requirements promotes more accurate estimation of fluid resuscitation requirements.*	Retrospective observational.	Paediatric, n=49 Lung injury: nil (4.9±3.9), mild-moderate (3.9±3.5), severe (4.8±3.9)	Lung injury: nil (41.4±18.7), mild-moderate (73.4±17.1), severe (67.2±16.6)
O'Neill[28] (1982)	USA	To assess the fluid resuscitation requirements of children with burns.	Prospective observational.	Paediatric, n=40, 5.8 (range 0.5–12)	45.4 (range 15–95)

Aims reported verbatim. Ages reported as available from published data.
Mixed: refers to a mixed adult and paediatric study population.
*Where aim not directly stated, apparent aim described.
HAS, human albumin solution; NR, not reported; PiCCO, pulse contour cardiac output; RCT, randomised controlled trial; TBSA, total body surface area; TTD, transpulmonary thermodilution; TMMU, Third Military Medical University.

paediatric/mixed sample, sample size, mean age, age range, gender and burn characteristics (size (TBSA), depth, burn cause); (2) aims, study design and intervention/s tested; (3) fluid regimen used; (4) endpoints monitored; (5) numerical endpoint targets; (6) techniques/devices for endpoint monitoring; and (7) outcomes relating to fluid resuscitation. Data were extracted by one researcher and all extracted data were verified by a second researcher. Disagreements were resolved through discussion. Risk of bias was not assessed since this review aimed to describe and document methods rather than assess the effectiveness of endpoints in achieving accurate fluid resuscitation.

Analysis and synthesis

Due to the heterogeneity of study designs, methods used and endpoints monitored across the included studies, a narrative synthesis of the studies was performed. Study characteristics and results are shown in tables 2 and 3.[22–28]

RESULTS

The combined database searches identified 1246 relevant articles, of which 469 were duplicates. Of the 777 titles and abstracts reviewed, 108 full-text articles were retained for further screening. Seven studies met the inclusion criteria (figure 1; n=359).[22–28]

Study characteristics and patient demographics

The seven studies that met the inclusion criteria were published between 1982 and 2016 (table 2).[22–28] Four studies were

undertaken in the USA,[22–24 28] with other studies carried out in Japan (n=1),[27] Brazil (n=1)[26] and China (n=1).[25] One randomised controlled trial,[26] one cohort study,[24] one prospective randomised study,[23] two prospective observational studies[25 28] and two retrospective observational studies[22 27] were identified.

Four studies were exclusively paediatric.[24 26 28] Three studies included both adult and paediatric participants.[22 23 25] Of this latter group, only one study carried out a subanalysis of the paediatric data.[25]

Three of the four paediatric studies had small sample sizes (n=40–49).[26–28] Two studies aimed to examine the effect of a specific resuscitation endpoint and compared this with a control endpoint.[23 24]

Endpoints

The majority of studies (n=6; 86%) used UO as the primary endpoint for fluid resuscitation (table 3).[22 23 25–28] One of these studies also compared targeting high versus low serum albumin.[23] One study used invasive haemodynamic monitoring to guide fluid resuscitation (transpulmonary thermodilution (TTD) parameters including intrathoracic blood volume, cardiac index (CI) and extravascular lung water) and compared this with conventional therapy (targeting UO).[24]

Targets

There was variability in the endpoint targets between studies targeting UO (table 3). Only one study set a minimum UO

Table 3 Monitoring methods, resuscitation endpoints and results of included studies

Study	Fluid regimen	Endpoints	Target parameters	Results
Faraklas et al[22] (2011)	Parkland	UO.	1–2 mL/kg/hour.	Fluid intake to urine output ratio significantly greater in the HAS group but fell after colloid administration to similar levels as the crystalloid group.
Greenhalgh et al[23] (1995)	Parkland	UO. High albumin. Low albumin.	0.5–1.0 mL/kg/hour. 2.5–3.5 g/dL. >1.5 g/dL.	Similar fluid resuscitation requirements (4.84 vs 4.91 mL/kg/%TBSA) for low versus high albumin groups; high albumin target group received 20 times more HAS than low albumin group. No difference in complication rates or mortality between groups.
Kraft et al[24] (2013)	Galveston	Control group. TTD (PiCCO) measurements: CI. EVLWI. ITBVI.	NR. 3–5 mL/m2/min. 3–7 mL/kg. 850–1000 mL/m².	Significantly higher fluid intake in the control group ('conventional resuscitation') versus the PiCCO group at similar UO. Cardiac and renal organ scores significantly lower in the PiCCO group. No significant difference regarding clinical outcome.
Luo et al[25] (2009)	TMMU	UO. HR. BP.	0.5–1.0 mL/kg/hour. <2 SD above age-specific norm. <2 SD below age-specific norm.	Average fluid intake within the first 24 hours was equal to that predicted by the TMMU formula but between 24 and 48 hours, approximately 25% more fluid than predicted was required.
Müller Dittrich et al[26] (2016)	Modified Parkland	UO. Early versus delayed albumin.	1–2 mL/kg/hour.	Early albumin group received approximately 32% less fluid on day 1 and 45% overall by day 3 compared with delayed albumin infusion. They also had a shorter hospital stay and experienced fewer complications of fluid overload.
Okabayashi et al[27] (2001)	5–7 mL/kg/%TBSA	UO.	2–3 mL/kg/hour.	Fluid requirements in 'massively burned children' might better be estimated by taking burn depth into account, as well as total burn size (%TBSA).
O'Neill[28] (1982)	Modified Brooke	UO.	>1 mL/kg/hour.	Apparent linear relationship of %TBSA and fluid requirement for 'adequate resuscitation'. Additional fluid required if inhalation injury present (non-linear).

CI, cardiac index; BP, blood pressure; EVLWI, extravascular lung water index; HAS, human albumin solution; HR, heart rate; ITBVI, intrathoracic blood volume index; NR, not reported; PiCCO, pulse contour cardiac output; TBSA, total body surface area; TMMU, Third Military Medical University; TTD, transpulmonary thermodilution; UO, urine output.

target (>1 mL/kg/hour).[28] In studies targeting a UO range, the target range varied from 0.5–1.0 mL/kg/hour to 2–3 mL/kg/hour.[22 23 25–27] Three studies reported a protocolised response

1246 articles identified in search

469 Duplicates removed

777 Titles and Abstracts screened

669 Did not meet inclusion criteria

108 Full text articles screened

101 studies excluded:
15 Abstract only
18 No primary data
37 No paediatric participants
5 No meaningful number of paediatric participants
18 Not about fluid resuscitation endpoints
7 Unclear if any children, no author response
1 Not written in English

7 studies included

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram.

to UO outside the target range.[22 25 26] No studies compared different UO targets. One study reported target mean arterial blood pressure (<2 SD below age-specific normal) and heart rate (<2 SD above age-specific normal).[25]

Only one study targeted invasively derived haemodynamic variables.[24] TTD and targeted normal physiological ranges were used to guide fluid and inotrope therapy.[24] Endpoints and 'conventional monitoring' for the historical control group were not reported.[24]

Outcomes of targeting endpoints

The heterogeneity of study type, endpoint targets and small sample sizes precluded a meta-analysis. Of the three studies including adults and children,[22 23 25] subanalysis of paediatric data was reported in one study.[25] In the remaining two studies, participants up to 18 years of age were included, but it was not clear how many children (<16 years) were included.[22 23]

Three targeted endpoints were identified: UO (with vital signs), albumin and invasive haemodynamic variables. For studies targeting UO, heterogeneous study protocols and measured outcomes precluded outcome comparison between UO targets. Greenhalgh et al[23] did not find evidence to suggest that targeting a high albumin level affected outcome. Müller-Dittrich et al[26] found that administering 5% albumin solution early, alongside targeted UO, reduced fluid requirements, subsequent oedema and duration of hospital stay. Finally, the targeting of invasive haemodynamic variables by Kraft et al[24] in comparison with their usual practice showed that significantly less fluid was administered in this group compared with controls. There was a trend towards reduced mortality in the invasively monitored and targeted group, but this was not statistically significant.[24]
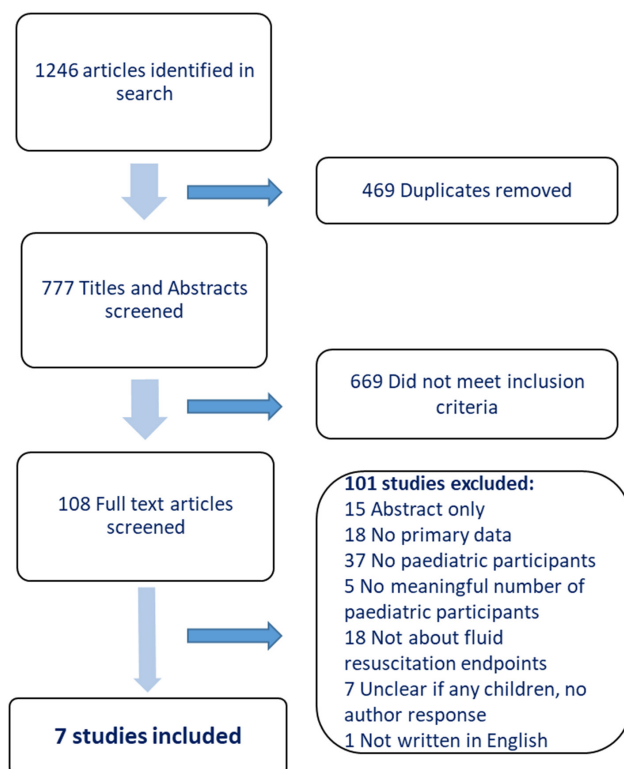
DISCUSSION

Achieving optimal fluid resuscitation in children with major burns presents a complex challenge to clinicians. We aimed to identify and describe the evidence for resuscitation endpoints to guide such therapy.

Only four exclusively paediatric studies were identified.[24 26–28] Two studies with predominant paediatric populations also studied young adults up to 18 years old, but the results were not disaggregated.[22 23] One study investigated a mixed adult and paediatric population where paediatric and adult data were subanalysed.[24] We identified three endpoints that have been targeted to guide fluid resuscitation in paediatric burn care research: (1) UO with vital signs (comprising heart rate and blood pressure); (2) invasive haemodynamic parameters; and (3) albumin levels. In the adult literature additional endpoints investigated include echocardiography and gastric tonometry.[19 20]

UO was the endpoint most frequently used to guide fluid resuscitation, but there was variation in UO targets between studies. This is likely to result from the lack of evidence to suggest the optimal UO for children with significant burns. The evidence for targeting invasive haemodynamic parameters is also limited given that only one study was identified using this method for guiding fluid resuscitation in paediatric burns compared with standard care.[24]

Biochemical parameters including lactate and base excess have been observed in predominantly adult studies as potential endpoints.[29 30] The authors found observational evidence that early trends in lactate and base excess are predictors of morbidity and mortality. There is some evidence to suggest that these endpoints are more representative of burn size than suboptimal resuscitation and may therefore have limitations if considered in isolation.[31] Targeting such parameters as resuscitation endpoints has not been studied in paediatric patients.

Studies targeting UO did not compare different targets, and comparison of outcomes between studies with different UO targets is not appropriate given differing study protocols and patient heterogeneity. Maintaining a high UO, achieved with fluid administration, has been shown to contribute to fluid creep.[32 33] Down-titration of the fluid infusion rate should occur when the upper UO range has been reached. Clinician response to UO outside the target range should be protocolised to minimise variation in practice and allow for outcome comparison between studies. There is some evidence to suggest that early albumin administration in addition to targeting UO is beneficial, but further research is needed.[26]

With regard to invasive haemodynamic monitoring, pulmonary artery catheterss are no longer commonly used in paediatric intensive care due to the risk to benefit ratio. TTD methods can provide haemodynamic variables which are less invasive,[34 35] and TTD has been found to be feasible in children with burns.[35] There are conflicting findings as to whether use of invasive haemodynamic monitoring to target physiologically 'normal' parameters results in more or less fluid being administered. While the study identified in this review found that less fluid was administered when invasive monitoring is used compared with controls,[24] a mixed adult and paediatric study comparing invasive, goal-directed, monitoring-guided fluid therapy with standard care found significantly more fluid was given in the invasive group.[36] Neither study found that targeting invasive haemodynamic variables significantly affected outcome when compared with standard care where UO was targeted.

When invasive haemodynamic variables are targeted, there is conflicting evidence in the adult literature as to whether targeting hyperdynamic or (permissive) hypovolaemic values is optimal.[37 38] While one study found that targeting hypovolaemic parameters resulted in the administration of less fluid without an increase in the complication rate,[37] another targeted hyperdynamic parameters, with administration of more fluid and reported reduced end-organ failure and improved survival.[38]

A variety of potential resuscitation endpoints exist that reflect global, regional or organ-specific perfusion, but all are impacted on by physiological response to burn injury. This systematic review did not identify evidence to suggest that one endpoint or target is superior to another. The outcome data were not robust enough to draw conclusions on the clinical effectiveness of targeted endpoints, and the heterogeneous nature of the studies identified precluded a meta-analysis.

This systematic review is the first to consider the current state of research in relation to endpoint monitoring in paediatric burn patients. While similar methods of endpoint monitoring to that used in adults may be useful, a number of modalities present challenges in children, particularly TTD as its use is not currently widespread in paediatric intensive care. Furthermore, it cannot be assumed that endpoint targets in adults are appropriate for children.

The studies identified have limitations which preclude quantitative conclusions being drawn. There were only seven studies identified, and relatively small sample sizes (four exclusively paediatric studies, n=287) may have prevented detection of intervention effects. Data analysis was not disaggregated in studies which included young adult and paediatric participants. To have omitted such studies would have resulted in loss of paediatric data, but their inclusion limits extrapolation of study findings to a paediatric population of <16 years old.

CONCLUSIONS

The evidence for endpoint monitoring to guide fluid resuscitation in children with burns is limited. Of the three endpoints (UO with vital signs, serum albumin and invasive haemodynamics) that have been targeted in this population, there is considerable heterogeneity between studies with regard to endpoint targets. While it remains clear that fluid resuscitation must be tailored to the clinical situation, there is not sufficient evidence to identify which endpoints and targets optimise outcome. Focusing on a single endpoint in isolation is unlikely to be helpful as each has limitations. A composite 'endpoint bundle' is likely to be more efficacious. There is a need for randomised multicentre paediatric studies with predetermined endpoints and protocolised fluid administration strategies comparing clinically significant standardised outcome measures.

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