

REVIEW ARTICLES

Fluid resuscitation management in patients with burns: update

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Abstract

Since 1968, when Baxter and Shires developed the Parkland formula, little progress has been made in the field of fluid therapy for burn resuscitation, despite advances in haemodynamic monitoring, establishment of the 'goal-directed therapy' concept, and the development of new colloid and crystalloid solutions. Burn patients receive a larger amount of fluids in the first hours than any other trauma patients. Initial resuscitation is based on crystalloids because of the increased capillary permeability occurring during the first 24 h. After that time, some colloids, but not all, are accepted. Since the emergence of the Pharmacovigilance Risk Assessment Committee alert from the European Medicines Agency concerning hydroxyethyl starches, solutions containing this component are not recommended for burns. But the question is: what do we really know about fluid resuscitation in burns? To provide an answer, we carried out a non-systematic review to clarify how to quantify the amount of fluids needed, what the current evidence says about the available solutions, and which solution is the most appropriate for burn patients based on the available knowledge.

Key words: burns; colloids; crystalloid solutions; fluid therapy; thermodilution

Fluid and electrolyte treatment for burn resuscitation began in 1921 when Underhill¹ studied the victims of the Rialto Theatre fire in New Haven and found that blister fluid has a composition similar to plasma. In 1942, Cope and Moore² developed the burn oedema concept and introduced the body-weight burn budget formula. Other charts were then developed: the Wallace rule of nines,³ the rule of the hand, and the one currently considered the most exact, the Lund and Browder Chart.⁴ Finally, in 1968, Baxter and Shires^{5–6} developed the Parkland formula, the one most widely used today for initial fluid resuscitation in burn patients.⁷ In accordance with the indications of the Advanced Burn Life Support programme of the American Burn Association, this formula now stipulates 2–4 ml of Ringer's lactate (RL) solution per kilogram of weight per percentage of burned body surface area in adults. It is intended to be adapted to vascular permeability changes to avoid fluid excess (the phenomenon known as 'fluid creep'),^{8–10} and the amount has to be corrected according to the urinary output,^{5–8–11} which ultimately leads to

substantial variability in the quantity of fluids administered. Sometimes this process is imprecise because the body surface area calculations are not always reliable (e.g. in obese patients).

After all these years of studying burn patient pathophysiology and outcomes, it is now clear that prompt fluid resuscitation is essential for survival in these patients.¹² Since the implementation of efficient, dynamic fluid replacement, fewer patients die in the first 24–48 h.¹³ It is a priority to maintain intravascular volume and organ perfusion despite the oedema caused by intense fluid resuscitation.^{13–14} When resuscitation is suboptimal, burn depth increases and the shock period is longer, leading to greater mortality.¹² However, can we be sure that resuscitation is done properly?

We found it surprising that despite advances in haemodynamic monitoring and establishment of the 'goal-directed fluid therapy' concept, many burn units still base their resuscitation practice on a formula created 40 yr ago.^{7–15} In 1991, Dries and Waxman¹⁶ had already suggested that resuscitation based only

on the urinary output and vital signs might be suboptimal. It is also surprising that after the recent emergence of studies on hydroxyethyl starches (HES), burn patients have been included alongside septic patients as those in whom starch administration should be avoided, even though none of the studies on which these recommendations were based included patients with major burns. These considerations prompted us to undertake the present review.

The aim of this review concerning initial fluid resuscitation in burn patients was to provide an overview of the current data regarding two key questions: what is the best way to determine the amount of fluids a burn patient needs, and what are the optimal fluids to use in this patient population? The reasons why burn patients require large amounts of fluids in the initial resuscitation is not a subject of this review, because the pathophysiological changes occurring are extensive and would require a review in themselves.

Methods

To provide answers to the proposed questions, we carried out a two-phase bibliographic search of articles published since 2000, the time when the scientific community focused renewed interest on fluid therapy, new concepts such as goal-directed therapy appeared, some products such as the previous generation starches were no longer available, and the Boldt retraction occurred.^{17 18}

First, we identified related clinical practice guidelines, systematic reviews, and other critical syntheses of documents in the scientific literature, such as health technology evaluation reports. In this first phase, we consulted the electronic database MEDLINE, using PubMed and the Cochrane Database of Systematic Reviews. The search strategy included the following terms: burn, burn resuscitation, fluid therapy, colloids, gelatins, crystalloids, hydroxyethyl starch, albumin, isotonic and hypertonic solutions, saline, Ringer's solution, Ringer's lactate, Ringer's acetate (RA), monitoring, haemodynamic monitoring, goal-directed therapy, lactate, base deficit, burn metabolic parameters, lactate clearance, systematic, review, randomized controlled trial, controlled clinical trial, and meta-analysis.

In the second phase, we specifically searched individual studies, prioritizing randomized controlled trials, but also including observational studies, retrieved from MEDLINE. Only studies carried out in adults and reported in articles written in English, French, or Spanish were selected. The research was carried out in November 2014, and articles retracted up to that date were excluded. The GRADE criteria¹⁹ were used to evaluate the scientific quality of the studies selected.

During the period reviewed, 13 studies were published on goal-directed therapy in burn patients, and 11 of them are included in this review.^{15 20–29} One study performed in paediatric patients and another written in a language other than the three specified above were excluded.

Regarding crystalloids, we reviewed 42 articles, two of which were included.^{30 31} The remaining articles were excluded for the following reasons: 17 did not meet the search criteria, four were reviews, eight were written in other languages, five were protocols, guidelines, descriptions of daily clinical practice, or surveys, two were carried out in paediatric patients, and four were experimental animal studies.

In relation to hydroxyethyl starches, we first analysed the studies carried out with last-generation starches that later prompted the recommendations not to use these substances in burn patients,^{32–35} and then performed a search on HES use for burn resuscitation. Two articles investigating HES in burn

patients were included,^{36 37} whereas seven non-systematic reviews, nine articles that did not meet the search criteria, three that included critically ill patients, and four in other languages were excluded.

Eighteen articles were found on albumin use in burn patients, and four were included in the present review.^{38–41} We excluded three non-systematic reviews, two articles focusing on hypoalbuminaemia that did not deal with initial replacement therapy, one in paediatric patients, one in animals, one experimental study, four that were protocols, guidelines, or descriptions of daily clinical practice, and one deemed to have a high risk of bias. This last study⁴² was based on information from a database in which albumin administration was recorded as a 'special procedure'. The study assumed that patients who were not given albumin had received only crystalloids; the potential use of other colloids was not considered. Furthermore, fluid therapy did not seem to follow an established protocol; hence, it is likely that the more severely ill patients who did not respond to crystalloids were those given albumin treatment.

Fluid therapy for burns

Determining the initial amount of fluid therapy a burn patient needs

Burn patients receive a larger amount of fluids in the first 24 h than any other trauma patients because of the pathophysiological mechanisms occurring in the injury. Burn shock is a combination of hypovolaemic shock and cell shock, characterized by specific microvascular and haemodynamic changes. In addition to the local lesion, the burn stimulates the release of inflammatory mediators that induce an intense systemic inflammatory response, producing an increase in vascular permeability in both the healthy and the affected tissue. The increased permeability provokes an outpouring of fluids from the intravascular space to the interstitial space, giving rise to oedema, hypovolaemia, and haemoconcentration. These changes, together with increased vascular resistance and the decreased cardiac contractility produced by tumour necrosis factor and interleukin-1 release, can trigger a state of shock, depending on the magnitude of the lesions. The amount of inhalation injury also has an effect on the clinical course, fluid requirements, and the patient's prognosis (Fig. 1). The main objective of fluid administration in thermal trauma is to preserve and restore tissue perfusion and prevent ischaemia, but resuscitation is complicated by the oedema and transvascular displacement of fluids characteristic of this condition.^{12–14}

Given that the amount of fluids to be administered is directly proportional to the severity of the injuries, patients with major burns are the most difficult to manage. There are several published definitions of major burn based on the burn surface area (BSA), the amount of smoke inhalation, the patient's age and co-morbidities, and whether or not it is an electrical injury. It was Baxter⁴³ who first showed that patients with >30% BSA experience a systemic transmembrane potential decline in both burned and unburned cells. In our unit, major burns are considered to be those involving a BSA of at least 20%, because strict i.v. resuscitation is needed in such patients.⁴⁴ The correct choice of fluid therapy is extremely important in major burns because incorrect replacement can lead to a series of deleterious effects, as discussed below.

Initial resuscitation is based on crystalloids.^{5 6} Although it has been shown that these solutions have a smaller volume expansion effect than colloids,⁴⁵ because of the increased capillary

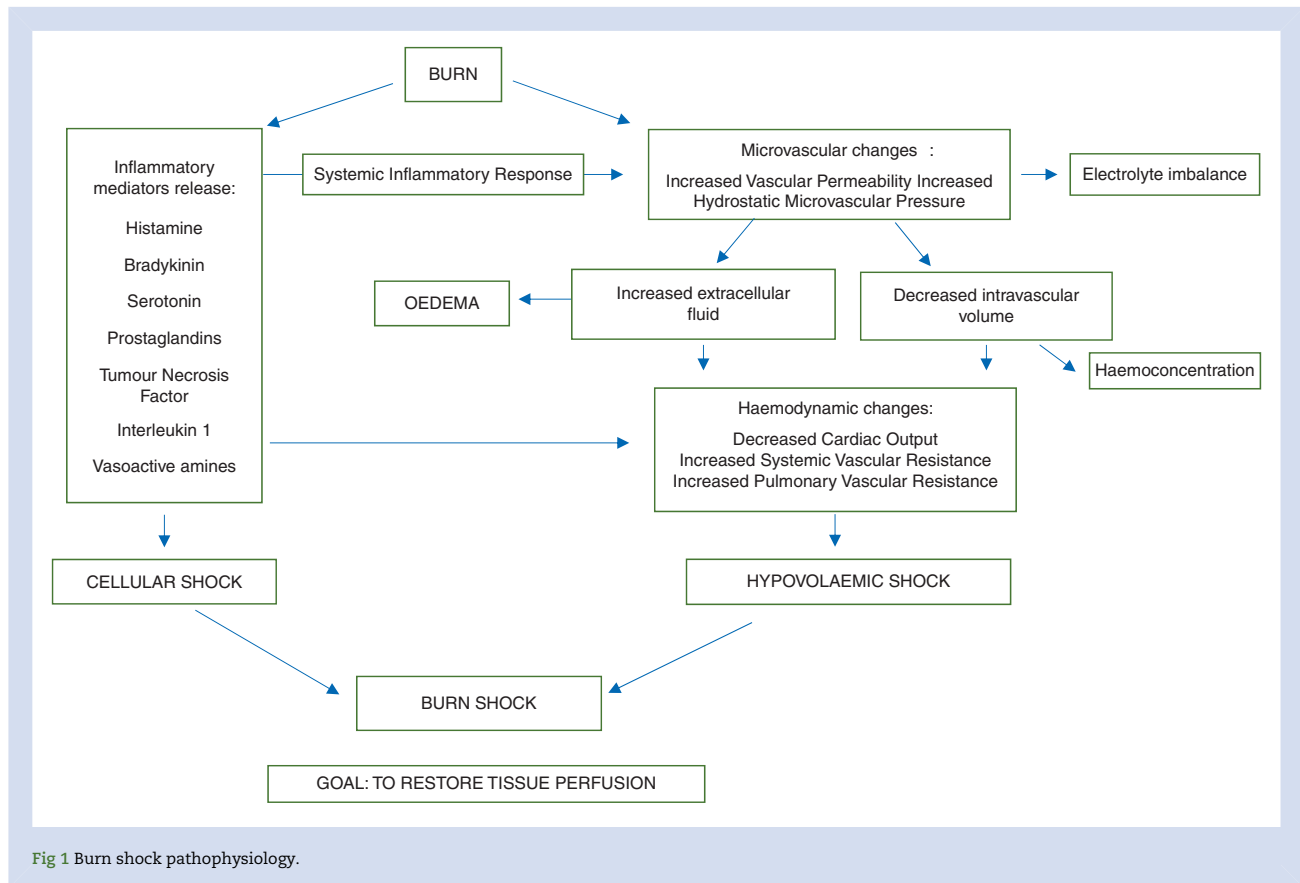


Fig 1 Burn shock pathophysiology.

permeability occurring during the first 24 h, colloids will pass to the extravascular space, exert an oncotic effect, and cause a paradoxical augmentation of what is commonly called the third space.⁴⁶ Although recent studies claim that the increased permeability starts at 2 h postburn and lasts for 5 h,⁴⁷ the use of colloids in burn patients remains controversial.

Goal-directed fluid therapy

Goal-directed fluid therapy has been an important concept in initial fluid resuscitation for major burns since publication of the retrospective study by Dries and Waxman¹⁶ in 1991. These authors observed that the vital signs and urinary output showed little variation after fluid replacement, whereas significant changes were seen in the parameters measured by pulmonary artery catheterization (PAC). These findings led to the conclusion that fluid resuscitation guided by the vital signs may be inadequate.¹⁶

Since that time, cardiac output has been considered one of the most important measures to guide volume therapy, but only 8% of burn units base their initial resuscitation plan on this parameter because PAC is needed for its measurement.¹⁵ However, during the last 15 yr, several articles have reported on a new volume monitoring and replacement approach for goal-directed fluid resuscitation based on transpulmonary thermodilution (TTD) and arterial pressure wave analysis, which are less invasive than PAC (Table 1).

But, are these new techniques applicable to burn resuscitation? Have they been validated in burn patients? Which parameters should we use as end points? And do they improve the outcomes?

As a result of the huge temperature changes and associated hypothermia burn patients experience, the applicability of thermodilution methods remained uncertain in this population until a publication in 2005 provided results supporting their use. In a prospective study including 50 patients with more than 25% BSA burns and receiving mechanical ventilation, 750 measurements were carried out. The study concluded that variability was <10% for the cardiac output, intrathoracic blood volume (ITBV), and total blood volume, and between 9.5 and 12.9% for the extravascular lung water (EVLW). In addition, there was no correlation between body temperature and the reproducibility of the measurements.²⁰

Two observational studies have compared the measures obtained by PAC and TTD,^{15 21} and another has compared transoesophageal echocardiography (TEE), TTD, and PAC.²² The first, carried out in 23 burn patients, compared the cardiac output values and concluded that although output measured by TTD was slightly higher, the difference was not important for clinical practice.¹⁵ The second study, performed in 14 patients, validated the parameters stroke volume index and systemic vascular resistance index for normal and low cardiac output using TTD, and reported a good correlation with measures obtained by conventional PAC.²¹

In 2009, Bak and colleagues²² published a study evaluating haemodynamic variables measured by TEE, TTD, and PAC during initial resuscitation according to the Parkland formula. The authors reported no significant differences between the various methods. They also found that the left ventricular end-systolic, left ventricular end-diastolic, and global end-diastolic volume indexes are suboptimal 12 h after burn injury and normalize at 24 h.

Table 1 Goal-directed therapy studies in major burns. BP, blood pressure; BSA, burned surface area; CI, cardiac index; CO, cardiac output; EVLW, extravascular lung water; GEDVI, global end-diastolic volume index; HOU, hourly urinary output; HR, heart rate; ITBV, intrathoracic blood volume index; LiDCO, lithium dilution cardiac output; LVED, left ventricular end-diastolic; LVES, left ventricular end-systolic; MAP, mean arterial pressure; MODS, multiple organ dysfunction score; PAC, pulmonary artery catheter; ScvO₂, central venous oxygen saturation; SVI, stroke volume index; SVRI, systemic vascular resistance index; TEE, transoesophageal echocardiography; TTD, transpulmonary thermodilution; UO, urinary output

Study	Design	Interventions compared	Objective	Results
Holm and colleagues ²³	Prospective Observational 21 patients Mean BSA 40 (20–67)%	The TTD technique was used for haemodynamic monitoring of 21 patients	Detect possible differences in the early haemodynamic and oxygen transport profile after thermal injury of survivors vs non-survivors	Survivors were found to have a significantly higher CI and oxygen delivery rate during the early postburn period. Initial serum lactate concentrations and the ability to clear them were significantly associated with survival. Blood pressure and HR were not significantly different. All patients received significantly higher volumes of crystalloids than predicted with the Baxter formula
Holm and colleagues ²⁴	Prospective Observational 24 patients BSA 20–85%	Correlation of filling pressure obtained by PAC vs ITBV by CO, and oxygen delivery	Evaluate the clinical utility of the ITBV as an end point for fluid resuscitation	The ITBV was significantly correlated with changes in CI and oxygen transport rate. Significantly larger volumes of crystalloids than predicted with the Parkland formula were administered. Extravascular lung water remained normal
Holm and colleagues ¹⁵	Prospective Observational 23 patients BSA 20–85%	218 CO measurements made in the first 72 h postburn with the PAC and the TTD technique	Study the agreement between CO measurements with the PAC vs TTD technique	Cardiac output derived from TTD was higher than from PAC. For clinical purposes, the difference was unimportant
Küntscher and colleagues ²¹	Prospective technique comparison 14 patients Average BSA 49.6%	Comparing PAC vs TTD (113 measurements with each system) for assessment of CI, SVI, and SVRI	Validate the TTD for assessment of CI, SVI, and SVRI	Good correlation between the two methods for CI, SVI, and SVRI in states of low to normal CO. The correlation was poor for cardiac indices >5.5
Küntscher and colleagues ²⁵	Prospective technique comparison 18 patients Average BSA 46.3%	Comparing ITBV and EVLW obtained from a single-indicator dilution vs data measured by double-indicator dilution	Validate the single-indicator dilution technique for ITBV and EVLW	The SD was higher than the mean value, and precision for estimated values for ITBV was poor
Holm and colleagues ²⁰	Prospective Observational 50 patients BSA >25%	250 triple measurements of ITBV, CO, total blood volume, and EVLW performed in the first 48 h postburn	Evaluate the influence of burn-induced hypothermia on the reproducibility of arterial thermodilution measurements	Variation correlation was <10% for CO, ITBV, and total blood volume; and slightly higher for EVLW. No correlation was found between body core temperature and reproducibility
Bak and colleagues ²²	Prospective Observational 10 patients BSA >20%	Haemodynamic changes measured with TEE, PAC, and TTD	Evaluate the haemodynamic changes at 12, 24, and 36 h postburn in patients treated with the Parkland formula	Oxygen transport variables, heart rate, MAP, and left ventricular fractional area did not change significantly. LVES, LVED, and GEDVI increased from subnormal values at 12 h to normal values at 24 h postburn. The EVLW and ITBV were increased 23 h after the burn

Continued

Table 1 Continued

Study	Design	Interventions compared	Objective	Results
Holm and colleagues ²⁶	Prospective randomized study 50 patients BSA >20%	Fluid resuscitation guided by TTD goal-directed therapy (n=25) and standard Baxter formula (n=25)	Compare goal-directed therapy by thermomodulation vs standard Baxter formula	Fluid administration and UO were significantly higher in the TTD group. Increased UO did not protect from renal failure. There were no significant differences in preload and CO. Subnormal values for ITBV and total blood volume were found in both groups
Csontos and colleagues ²⁷	Prospective randomized study 24 patients Median BSA 43 (30–63)%	Fluid resuscitation guided by HOU (n=12) or by ITBV (n=12)	Compare the effect of the two resuscitation regimens on MODS and Scv _O ₂ in the first 3 days	The Scv _O ₂ was significantly lower in the HOU group in the first 24 h. MODS was significantly higher in the ITBV group at 48 and 72 h
Aboelatta and Abdelsalam ²⁸	Prospective randomized study 30 patients BSA 25–60%	Fluid resuscitation guided by TTD (n=15) and by the Parkland formula (n=15)	Estimate and monitor fluid resuscitation using the TTD system in comparison with the Parkland regimen	Fluid administration in the first 72 h was significantly higher in the TTD group and was associated with tissue oedema. It was difficult or even impossible to achieve goals of normovolaemia and CO normalization during the early postburn period. Heart rate and MAP were lower in the TTD group
Tokarik and colleagues ²⁹	Prospective randomized study 21 patients BSA 10–75%	Fluid resuscitation guided by Baxter/Parkland formula (n=10) and by LiDCO monitoring (n=11)	Optimize volume resuscitation during burn shock using pulse contour analysis combined with intravascular volume monitoring by UO	Lower crystalloid consumption in the first 24 h postburn was recorded in the LiDCO group

Furthermore, both the EVLW and the ITBV are increased 23 h after burn injury.

With regard to TEE, only two additional studies were published in burn patients during the period of the present review, one describing the results of the measurements and their relationship with cardiac output⁴⁸ and the other using TEE as a diagnostic technique in burn patients with bacteraemia or hypotension.⁴⁹ Although TEE seemed to be a safe and minimally invasive technique in these reports, further studies are needed to validate its use for initial resuscitation in these patients.

Several authors have focused on determining which parameters should be used for guiding major burn resuscitation. In an observational study carried out in 2000, Holm and colleagues²³ reported that the cardiac index and oxygen delivery evaluated during the first hours were useful for this purpose in major burn survivors. Nonetheless, the findings did not suffice to indicate that these parameters should be the end points used.

During the same year, Holm and colleagues²⁴ published another observational study, including 24 patients in whom the ITBV was evaluated as a resuscitation end point. The authors concluded that patients received more fluids based on this parameter than would be estimated by the Parkland formula, with no differences in the EVLW. The ITBV increase improved the oxygen delivery and showed a good relationship with oxygen delivery and the cardiac index.

Küntschler and colleagues²⁵ undertook an observational study, in which ITBV and EVLW measurements obtained using single- and double-indicator dilution techniques were compared. The authors concluded that the single-indicator dilution technique was not accurate enough to assess ITBV and EVLW in burn shock.

Four prospective randomized studies, three using TTD^{26–28} and one using LiDCO[®] haemodynamic monitoring,²⁹ have compared the results of initial resuscitation performed according to the Parkland/Baxter formula with those of goal-directed therapy based on preload parameters.

The first of these, by Holm and colleagues²⁶ and including 50 patients, found that initial fluid administration was higher in the TTD group with resuscitation based on the ITBV. Urinary output was also higher, but there were no significant differences between the groups regarding renal failure. No relationship was found between the EVLW and the volume infused, and there were no significant differences in preload, cardiac output, morbidity, or mortality.

Csontos and colleagues²⁷ compared the multiple organ dysfunction score (MODS) and central venous oxygen saturation (Scv_O₂) values during the first 3 days postburn between patients treated according to the Parkland formula and those whose treatment was based on the ITBV measured by TTD. Fluid infusion was greater in the ITBV group during the first day, and the Scv_O₂ was found to be higher. In the Parkland group, the MODS score was higher at 48 and 72 h, and the usual haemodynamic parameters (urinary output and central venous pressure) showed no correlation with Scv_O₂ or any other haemodynamic parameter.

In 2013, Aboelatta and Abdelsalam²⁸ conducted a clinical trial with 30 patients and compared initial resuscitation using the Parkland formula vs TTD-guided resuscitation. The goals were ITBV >800 ml m⁻² and cardiac index >3.5 litre min m⁻², with limited fluid administration in patients with EVLW >10 ml kg⁻¹. The TTD group received a larger amount of fluids during the first 72 h, and urinary output was higher, but the mean arterial pressure and heart rate were lower in this group. There were no differences in central venous pressure, hospital stay, or mortality. Of note, the

authors highlighted the difficulty or even impossibility of achieving normovolaemia parameters in the first 24 h postburn and suggested the possibility of redefining them for this type of patient.

Curiously, also in 2013, Tokarik and colleagues²⁹ published the only study whose results were incongruent with those reported previously. It was a clinical trial including 21 patients that compared initial resuscitation according to the Parkland formula with resuscitation guided by preload dynamic parameters measured by the LiDCO[®] system. This is the only study in which the amount of crystalloid infusion during the first 24 h was lower in the goal-directed therapy group, but there were no significant differences between the groups in the total volume of resuscitation solution used or in the remaining study parameters. Of note, the monitoring device was different from that used in the previous studies, and it has not been validated in burn patients.

After reviewing these results, it seems reasonable to say that TTD has a role in burn resuscitation, while keeping in mind that the available studies included small samples, and the results were obtained in a short time and were based on haemodynamic parameters. Until now, the true effect of this approach on patient survival has not been reported. Multicentre studies with large samples and strict methodology are needed to achieve a good level of evidence for TTD use in these patients.

The studies described suggest that burn patients are likely to require more intensive resuscitation than the amount they receive based on the modified Parkland formula, particularly in the first 24 h, in order to improve the preload parameters, cardiac index, ScvO₂, and oxygen delivery. Normovolaemia may not be the main goal to achieve, although it seems that the EVLW is not affected by greater fluid administration in the first hours.

It is a fact that most centres providing initial care to burn patients are not equipped with the resources needed to guide resuscitation by goal-directed therapy techniques, and to date, these methods have not shown survival benefits relative to use of the Parkland formula. But it is also true that rigorous studies with large patient samples will further elucidate the initial pathophysiology of burn patients and enable development of formulas that are better adapted to their real needs.

Certain metabolic variables have been specifically investigated in burn patients. Lactate concentrations, the lactate/pyruvate ratio, the base deficit, and even microalbuminuria have shown prognostic value, and some of these parameters may be of use to guide the quality of initial resuscitation. Nonetheless, although these variables show value for this purpose, the results using current measurement methods are not immediately available; hence, they are not considered as useful as the real-time markers obtained by monitoring.^{50–52}

What fluids should be used in initial resuscitation?

Crystalloids

During the last few years, several studies have been published on crystalloid-based fluid therapy in various types of patients. Balanced solutions have been shown to be superior to unbalanced crystalloids (evidence level 1B).⁵³

Multiple adverse effects have been described with the use of saline solution, and several studies have reported problems associated with RL use in critically ill patients and others without burn injuries.^{31 54–59} But can these results be extrapolated to burn patients?

The literature is limited regarding what type of crystalloid is most appropriate for burns. By definition, the Parkland formula is performed with RL, which is why this has been the fluid of choice in burns.⁷ Only two observational studies were found comparing different types of crystalloids in burn patients, and only one of them compared two balanced isotonic solutions (Table 2).

In 2006, Oda and colleagues³⁰ studied a cohort of 36 burn patients with >40% BSA burns and no severe smoke inhalation injury. The authors' objective was to analyse the development of abdominal compartment syndrome and its relationship with initial fluid administration. Based on the fact that hypertonic serum reduces fluid requirements, the authors designed a study comparing initial resuscitation with RL vs hypertonic lactated saline, with urinary output at 0.5 ml kg⁻¹ h⁻¹. Patients given lactated saline received a significantly smaller amount of fluids than those given RL. Furthermore, peak abdominal pressure and peak inspiratory pressure at 24 h were lower in the saline group. Only 14% of patients receiving lactated saline developed abdominal compartment syndrome as opposed to 50% in the RL group.

A study by Gille and colleagues³¹ in 2013 provides interesting results, but it has a retrospective–prospective observational design, and the quality of the evidence is low. The authors compared initial resuscitation with RL (retrospective n=40) or RA (prospective n=40). Patients receiving RA had an initial trend to lower Sequential Organ Failure Assessment (SOFA) scores, which were significantly lower on days 3–6. There were no differences in the amount of crystalloids infused, but the RA group required a smaller amount of colloids, packed red blood cells, and plasma infusion. Lactate concentrations were increased in the RL group on days 1–3. Ringer's acetate was associated with a higher incidence of thrombocytosis, but no thrombotic events were described. The duration of hospital stay and days on mechanical ventilation were lower in the RA group. There were no significant differences in mortality.

Taking into account that balanced solutions have already proved superior for fluid replacement, RA would seem to be the most suitable option for large replacements. Nonetheless, although this solution has shown a favourable profile in trauma patients, the related evidence in burn patients is limited. Further studies comparing RL with RA for initial resuscitation are needed. Hypertonic solutions may also have a place in burn resuscitation. The Cochrane systematic reviews,⁶⁰ guidelines from the USA,⁴⁴ and other reviews^{11 61 62} have evaluated their efficacy in burn patients, but up to now there is no clear evidence in favour or against them, and additional studies are required to define the correct doses and timing.

Colloids

Colloids are controversial in burn management, even more so after the recent warning issued by various drug control agencies contraindicating the use of HES in burn patients.⁶³ Colloids are fluids that contain macromolecules, and they have a greater expansion effect than crystalloids.⁴⁵ They can have natural (plasma and albumin) or synthetic (HES and gelatine) components.

Gelatins are now the synthetic colloid used in burns, being the only available option after the HES warning,⁶³ but their expansion capacity is inferior to that of HES, and their effect ceases 1 h after administration.⁶⁴ Two meta-analyses^{65 66} published in 2012 concluded that gelatins have no advantages over crystalloids,⁶⁶ and as of today, their safety cannot be confirmed.⁶⁵ There are no studies ensuring their safety in burn patients.

Table 2 Crystalloid studies in major burns. ACS, abdominal compartment syndrome; BSA, burn surface area; HLS, hypertonic lactated serum; HUO, hourly urinary output; IAP, intra-abdominal pressure; RA, Ringer's acetate; RL, Ringer's lactate; SOFA, sequential organ failure assessment

Study	Design	Interventions compared	Objective	Results
Oda and colleagues ³⁰	Observational, cohort 36 burn patients BSA >40%	Development of ACS in burn patients resuscitated with HLS vs RL	Determine the effects of HLS on IAP in patients with severe burn injury	Resuscitation with HLS could reduce the risk of secondary ACS with lower fluid load in burn shock patients
Gille and colleagues ³¹	Observational, case-control, retrospective (RL), and prospective (RA) 80 burn patients BSA 20–70%	Fluid resuscitation with RL (n=40) vs RA (n=40) guided by the Parkland formula and adjusted to maintain HUO (0.5–1.0 ml kg ⁻¹ h ⁻¹)	Compare clinical outcome in patients resuscitated with RL vs RA	In comparison with RL solution, the study showed lower SOFA scores for RA solution

Several reviews have concluded that HES use is associated with a higher risk of mortality and kidney injury compared with other resuscitation solutions in septic patients, and burn patients have been included within this group.^{67, 68} Some of the studies leading to the HES alert have been reviewed and criticized for being methodologically questionable.^{69–72} Others were carried out with first- and second-generation starches, which are no longer used for this purpose.^{73, 74} Their adverse effects are well recognized, and they are not included in the present review.

We analysed the 6S,³² CRYSTMAS,³³ CHEST,³⁴ and CRISTAL³⁵ studies, which were the basis for the alert that HES should not be used in burn resuscitation. Surprisingly, patients with major burns were excluded from three of these studies,^{32, 34, 35} and in one study no information was provided in this respect.³³ The analysis of these studies is summarized in Table 3.

A systematic review and meta-analysis conducted by Zarychanski and colleagues⁶⁷ included 38 clinical trials in critically ill patients published up to October 2012, comparing the use of HES vs crystalloids, albumin, or gelatine and assessing the relationships with acute kidney injury and mortality. Most trials were classified as having a high or unclear risk of bias. After excluding the retracted studies, HES was associated with higher mortality rates, more prevalent renal failure, and higher requirements for renal replacement therapy. Two of the studies were carried out in burn patients, but one was written in Chinese⁷⁵ and the other used HES 200/0.6,⁷⁶ a previous-generation starch. Hence, both were excluded from the present review.

The Cochrane review⁶⁸ of 2010, updated in 2013, included 42 studies with good methodological quality, in which HES was compared with any other fluid therapy for hypovolaemia treatment. A significant increase in renal failure and renal replacement therapy was observed in the HES group. Burn patients were not excluded, but a separate analysis in this population was not provided.

The only study investigating third-generation HES in major burns was a randomized clinical trial including 48 patients, carried out by Béchir and colleagues³⁶ in 2013. Mixed resuscitation therapy (HES plus RL) was compared with crystalloids alone (RL). The aim was to calculate the total volume infused within the first 72 h and determine the safety profile. No differences were found in the mortality rate, volume administered, or renal damage between the groups (Table 4).

Concerning natural colloids, fresh frozen plasma has classically been used as a plasma expander, but the high associated cost and risk of disease transmission have limited its use mainly to coagulation disorders⁷⁷ (Table 4).

In 2005, O'Mara and colleagues³⁷ reported a prospective randomized study in 31 burn patients, comparing RL resuscitation with RL plus fresh frozen plasma. A larger volume was needed in the crystalloid alone group, and there was a greater increase in intra-abdominal pressure. In addition, a correlation was found between the amount of liquid infused and intra-abdominal pressure. These findings are consistent with those reported by Ivy and colleagues,⁷⁸ who described intra-abdominal hypertension and abdominal compartment syndrome in major burns. Nonetheless, the sample size was small; hence, larger studies are needed to evaluate the efficacy of fresh frozen plasma in preventing compartment syndrome.

The use of albumin for fluid resuscitation in critically ill patients has been questioned since 1998, when the Cochrane⁷⁹ review concluded that albumin may be associated with higher mortality. Since then, several studies, such as SAFE,^{80–82} ALBIOS,⁸³ and the review by Hartog and colleagues,⁸⁴ have shown favourable results, except in traumatic brain injury. The Surviving Sepsis Campaign,⁸⁵ published in 2013, recommends albumin in patients

Table 3 Colloid studies upon which the recommendations were based. AKI, acute kidney injury; BSA, burn surface area; HES, hydroxyethyl starch; ICU, intensive care unit; RRT, renal replacement therapy; RIFLE, risk injury failure loss or end stage kidney disease

Study	Design	Interventions compared	Objective	Results
Perner and colleagues ³² (6S)	Prospective randomized parallel-group 798 septic patients Patients with BSA >10% were excluded	Fluid resuscitation with Ringer's acetate (n=400) vs HES 6% (130/0.42; n= 398)	Evaluate increased risk of death or end-stage kidney failure at 90 days after randomization	Patients assigned to fluid resuscitation with HES had an increased risk of death at day 90 and were more likely to require renal replacement therapy compared with those receiving Ringer's acetate
Guidet and colleagues ³³ (CRYSTMAS)	Prospective randomized 196 septic patients. No information about burn patients included	Fluid resuscitation with HES 6% (130/0.4; n=100) vs saline 0.9% (n=96)	Evaluate the amount of fluid required to achieve haemodynamic stabilization, explore efficacy of both fluids, RIFLE score, and length of stay	Less fluid intake in HES group for haemodynamic stabilization. No differences in mortality or AKI
Myburgh and colleagues ³⁴ (CHEST)	Prospective randomized, parallel-group 7000 critical patients. Burns were considered an exclusion criterion	Fluid resuscitation with sodium chloride 0.9% (n=3500) vs HES 6% (130/0.4; n=3500)	Evaluate safety and efficacy of HES 6% in saline 0.9% compared with saline 0.9% alone for fluid resuscitation in a heterogeneous ICU population	No significant difference in 90 day mortality. Increased risk of RRT in HES group
Annane and colleagues ³⁵ (CRISTAL)	Prospective randomized 2857 patients with hypovolaemic shock. Patients with BSA >20% were excluded	Fluid resuscitation in ICU with colloids (n=1414) or crystalloids (n=1443)	Evaluate 28 and 90 day mortality. Survival days, need for RRT, mechanical ventilation, or vasopressor therapy	No differences in 28 day mortality. At 90 days, lower mortality in patients receiving colloids

Table 4 Colloid studies in major burns. ACS, abdominal compartment syndrome; AKI, acute kidney injury; BSA, burn surface area; FFP, fresh frozen plasma; HES, hydroxyethyl starch; IAP, intra-abdominal pressure; MODS, multiple organ dysfunction score; RL, Ringer's lactate; VAP, ventilator-associated pneumonia

Study	Design	Interventions compared	Objective	Results
Bécher and colleagues ³⁶	Prospective, randomized 48 burn patients BSA >15%	Fluid resuscitation with RL (n=24) vs HES 6% 130/0.4; n=24)	Evaluate safety and infused volume in the first 72 h	No differences in mortality rate, AKI risk, or volume infused
O'Mara and colleagues ³⁷	Prospective, randomized 31 burn patients BSA >25% plus inhalation injury or BSA >40%	Fluid resuscitation with crystalloid (n=15) vs resuscitation combining crystalloid and FFP (n=16)	Establish whether IAP in the plasma-resuscitated group is lower than in the RL- resuscitated group, considering that less volume is administered	There was a higher IAP increase in the crystalloid group (26.5 vs 10.6 mm Hg). Greater fluid volume was required in crystalloid resuscitation (0.26 vs 0.21 litre kg ⁻¹). A correlation between the volume infused and IAP was observed in both groups
Cooper and colleagues ³⁸	Prospective trial with stratified block randomization 42 burn patients BSA >20%	Fluid resuscitation with RL (n=23) vs 5% human albumin plus RL (n=19) by protocol	Investigate the effect of human albumin 5% during the first 14 days of treatment, measuring the worst MODS	In an intention-to-treat analysis, there was no significant difference between the treatment and control group in the lowest MODS from day 0 to day 14
Cochran and colleagues ³⁹	Retrospective, observational 202 burn patients BSA ≥20%	Fluid resuscitation with crystalloid (n=101) vs fluid resuscitation with crystalloid plus albumin (n=101)	Compare outcomes in patients who did and did not receive albumin during resuscitation	On multivariate analysis, albumin was a protective factor for mortality
Lawrence and colleagues ⁴⁰	Retrospective, observational 52 burn patients BSA ≥20%	Fluid resuscitation with crystalloid (n=26) vs fluid resuscitation with crystalloid plus albumin supplementation (n=26)	Evaluate the effect of adding albumin to the resuscitation solution on fluid creep and the resuscitation ratios	Added albumin improved the resuscitation ratios, reduced the hourly fluid requirement, and improved fluid creep
Park and colleagues ⁴¹	Retrospective, observational, prospective 159 burn patients BSA >20%	Fluid resuscitation with RL during the first 24 h and colloids later if necessary vs albumin 5% since inclusion if fluid requirements were >6 ml kg ⁻¹ h ⁻¹ at 12 h postburn	Investigate whether use of 5% albumin and vasopressors decreased fluid resuscitation- related complications and burn mortality	Mechanical ventilation days, VAP, and patients requiring open laparotomy for ACS management were lower in the albumin group. Ventilated patients receiving albumin had higher arterial partial pressure of O ₂ /fractional inspired O ₂ ratios at 24 h. Mortality in the albumin group was significantly lower (10 vs 26%)

unresponsive to crystalloid resuscitation, with a 2C level of evidence. However, burn patients are generally excluded from these studies or are not analysed as a subgroup. We retrieved four relatively recent studies specific to these patients.

In 2006, Cooper and colleagues³⁸ carried out a multicentre randomized clinical trial with 42 burn patients comparing fluid resuscitation with RL vs RL plus albumin. The BSA and inhalation injuries were more severe in the albumin group. Although the differences between arms were not significant in themselves, the expected mortality was 18.6% in the albumin group and 9.4% in the controls ($P=0.06$), and no adjustment was made for this imbalance. In the intention-to-treat analysis, there were no significant differences between the groups for the primary outcome, lowest MODS from day 0 to day 14, or mortality at day 28, but the authors mentioned that their study was underpowered for both these outcomes.

In 2007, Cochran and colleagues³⁹ conducted a study in patients with $\geq 20\%$ BSA burns, comparing those who received albumin because of increased fluid requirements with a cohort comparable for age and burn injury who did not require albumin administration. On multivariate analysis, albumin administration was found to be a protective factor for mortality.

In 2010, Lawrence and colleagues⁴⁰ performed a retrospective observational study in burn patients with $\geq 20\%$ BSA and reported that albumin use in patients receiving a volume of crystalloids above the amount estimated by the Parkland formula resulted in reductions in the mean resuscitation ratio and the hourly fluid requirements.

An observational retrospective-prospective study published by Park and colleagues⁴¹ in 2012 compared burn patients treated with RL and a synthetic colloid vs those treated with albumin. Mortality, days on mechanical ventilation, mechanical ventilation-associated pneumonia, and laparotomy for abdominal compartment syndrome were significantly lower in the albumin group. The study was limited partly by its prospective-retrospective design. No randomization or blinding was specified, implying a high risk of bias.

The latest study published on albumin in burn resuscitation was a meta-analysis carried out by Navickis and colleagues⁸⁶ in 2014, including randomized and non-randomized clinical trials. After exclusion of two studies with a high risk of bias, albumin was found to be associated with a lower incidence of compartment syndrome and lower mortality.

After concluding this review and in agreement with the opinions of others,^{70 87} we believe it is reasonable to say that the studies motivating the HES alert, which did not include burn patients, may not have been an entirely appropriate basis for the warning in this population. The small number of studies investigating colloids in burn patients do not reflect an increase in acute kidney injury or mortality. Furthermore, none of the HES studies prompting the alert was done with balanced HES, and chloride is known to be associated with renal injury.⁵⁸ Gelatins have not shown superiority over crystalloids, and their safety is uncertain. Both albumin and plasma could be a good option for burn patients, although the available data on plasma use are limited. Multicentre studies focused on colloid use should be carried out in this specific population.

Conclusions

Suboptimal fluid resuscitation in burn patients leads to greater burn depth and extension of the shock period, which usually takes place in the first 24–48 h. According to the results of goal-directed therapy studies, the amount of fluid given in the first

24 h should be somewhat higher than that estimated by the Parkland formula.

Major burn resuscitation should ideally be performed according to goal-directed therapy with thermodilution methods because they are less invasive than PAC and have been well validated in burns. Some studies have shown an improvement in the cardiac index, $ScvO_2$, oxygen delivery, and MODS when resuscitation is based on TTD and taking the ITBV and EVLW as end points; nonetheless, the optimal parameters remain to be defined.

The initial resuscitation fluid should be a balanced crystalloid. Colloids seem inappropriate during the first hours because of the patient's increased capillary permeability. Ringer's acetate seems to protect the electrolytic balance in large replacements, and it may be the crystalloid of choice for initial resuscitation in burn patients.

Although there are reports of poorer outcomes in septic patients with the use of HES, the current scientific evidence does not suffice to support a specific contraindication for HES use in burn patients. As was the practice in many burn units, we formerly used HES after the first 24 h when it was needed and we did not have the impression that outcomes were worse in our patients, but this is a subjective evaluation.

Gelatins have not shown superiority over crystalloids in their expansion capacity, and their safety is still uncertain.

Hypertonic solutions, albumin, and plasma have been associated with lower volume requirements for initial resuscitation, lower intra-abdominal pressure, and a lower incidence of compartment syndrome; hence, these solutions could have a place in burn resuscitation, but additional evidence is needed to support their use.

Multicentre randomized controlled trials on fluid resuscitation in major burns are still needed to define the best fluid therapy in this population. Data are lacking on the optimal end points for TTD, the difference between initial resuscitation with Ringer's lactate or Ringer's acetate, the proper timing to initiate colloids, and the comparative performance of the different natural and synthetic colloids in burn patients.

Authors' contributions

Study design: P.G., G.U., N.M., L.A., M.J.C.

Study conduct: P.G., M.J.C.

Data analysis: P.G., G.U., N.M., L.A.

Final approval of the contents: J.P.B.

Wrote the manuscript and approved the final manuscript: P.G., G.U., N.M., L.A., M.J.C.

Reviewed the final version: P.G., M.J.C.

Declaration of interest

None declared.

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