American Burn Association Clinical Practice Guidelines on Burn Shock Resuscitation

Robert Cartotto, MD, FRCS(C)[*,1], Laura S. Johnson MD, FACS, FCCP, FCCM[2], Alisa Savetamal MD FACS[3], David Greenhalgh MD, FACS[4], John C Kubasiak MD[5], Tam N. Pham MD[6], Julie A. Rizzo MD[7,8], Soman Sen MD[9], Emilia Main MI[10]

This Clinical Practice Guideline (CPG) addresses the topic of acute fluid resuscitation during the first 48 hours following a burn injury for adults with burns ≥20% of the total body surface area (%TBSA). The listed authors formed an investigation panel and developed clinically relevant PICO (Population, Intervention, Comparator, Outcome) questions. A systematic literature search returned 5978 titles related to this topic and after 3 levels of screening, 24 studies met criteria to address the PICO questions and were critically reviewed. We recommend that clinicians consider the use of human albumin solution, especially in patients with larger burns, to lower resuscitation volumes and improve urine output. We recommend initiating resuscitation based on providing 2 mL/kg/% TBSA burn in order to reduce resuscitation fluid volumes. We recommend selective monitoring of intra-abdominal and intraocular pressure during burn shock resuscitation. We make a weak recommendation for clinicians to consider the use of computer decision support software to guide fluid titration and lower resuscitation fluid volumes. We do not recommend the use of transpulmonary thermodilution-derived variables to guide burn shock resuscitation. We are unable to make any recommendations on the use of high-dose vitamin C (ascorbic acid), fresh frozen plasma (FFP), early continuous renal replacement therapy, or vasopressors as adjuncts during acute burn shock resuscitation. Mortality is an important outcome in burn shock resuscitation, but it was not formally included as a PICO outcome because the available scientific literature is missing studies of sufficient population size and quality to allow us to confidently make recommendations related to the outcome of survival at this time.

Key words: burns; shock; fluid resuscitation.

AMERICAN BURN ASSOCIATION CLINICAL PRACTICE GUIDELINES

In 2020, the American Burn Association (ABA) began a process to create new Clinical Practice Guidelines (CPGs). The ad hoc CPG committee developed a standardized, evidence-based process for CPG production, which is now in use by several Investigator Panels. An overarching goal will be to harmonize the new CPGs with the ABA Quality Registry and burn center verification standards. The authors of this guideline represent the Investigator Panel for the topic of acute burn shock resuscitation, and construction of this CPG was conducted between March 2022 and March 2023.

[1]Department of Surgery, Ross Tilley Burn Centre, Sunnybrook Heath Sciences Centre, University of Toronto, Canada [2]Department of Surgery, Walter L. Ingram Burn Center, Grady Memorial Hospital, Emory University, Atlanta, GA, USA[3]Department of Surgery, Connecticut Burn Center, Bridgeport Hospital, Bridgeport, CT, USA[4]Shriners Hospital for Children, Northern California, Sacramento, CA, USA[5]Department of Surgery, Loyola University Medical Center, Maywood, IL, USA[6]Department of Surgery, University of Washington Regional Burn Center, Harborview Medical Center, Seattle, WA, USA[7]Department of Trauma, Brooke Army Medical Center, Fort Sam Houston, San Antonio, TX, USA [8]Uniformed Services University of Health Sciences, Bethesda, MD, USA[9]Department of Surgery, Division of Burn Surgery, University of California, Davis, CA, USA [10]Sunnybrook Health Sciences Centre, Toronto, Canada.

[*]Address correspondence to R.C. (email: robert.cartotto@sunnybrook.ca)

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PURPOSE

The recommendations in this guideline are intended only to guide clinicians faced with any of the clinical questions we have addressed. These recommendations do not rigidly define the standard of care or best practice, they are not prescriptive, and they do not replace bedside clinical judgement and decision making by a clinician resuscitating a patient with an acute burn injury. The recommendations are based upon a systematic review of available literature with critical evaluation of only the studies meeting our clinical question criteria. Recommendations were based on the quality of and our confidence in the published evidence, and finally consideration of the values and preferences of clinicians and patients.

For this CPG, the term "acute fluid resuscitation" refers to the provision of intravenous fluid during the first 48 hours following an acute burn injury in an adult involving at least 20% of the total body surface area (%TBSA). We recognize that the definition of completion of acute fluid resuscitation is nebulous and that resuscitation may continue between 48 and 72 hours post burn in some cases. However, we defined the first 48 hours post injury as the resuscitation period, because almost all studies on acute fluid resuscitation examine only in

this period. The term "burn shock" refers to inadequate perfusion of organs and tissues which follows an acute burn ≥20% TBSA. This CPG does not apply to the resuscitation of other forms of shock that may occur after a burn injury, such as septic shock.

USERS

This CPG will be of most use to clinicians who provide acute care to patients with major burn injuries (ie, burns ≥20% TBSA). Most of the interventions or diagnostic procedures that we will consider in this CPG are carried out in the burn center. Therefore, the recommendations primarily will guide burn care personnel who work in burn centers. However, some material in this CPG will be of value to clinicians who initiate acute burn resuscitation in the Emergency Department.

CLINICAL PROBLEM AND SCIENTIFIC BACKGROUND

Readers of this guideline are encouraged to consult more detailed reviews of the pathophysiology of burn shock and clinical burn resuscitation.[1–3] This section is intended only to describe the relevant scientific background that informed our panel's selection of important clinical questions related to burn shock resuscitation.

Following an acute burn to more than 20% of the BSA, intravascular volume depletion, depressed cardiac output, and elevated systemic vascular resistance combine to compromise perfusion to organs and tissues. Although it has long been recognized that fluid resuscitation is necessary to reverse this process, the optimal methods of providing and monitoring fluid resuscitation remain uncertain. Insufficient resuscitation clearly will lead to organ failure and even death.[4,5] However, recognition of the phenomenon of "fluid creep"[6] over 2 decades ago has focused attention on the opposite problem: provision of excessive resuscitation fluid leads to increased morbidity and mortality in major burn patients.[7,8] Thus, while fluid resuscitation is necessary and life-saving, the intervention itself can cause harm. This paradox has generated numerous practical clinical problems and questions for clinicians about how to monitor and resuscitate acute burn patients.

Central to this conundrum are the simultaneous problems of intravascular volume depletion and formation of soft tissue and organ edema, which results predominantly from an increase in microvascular permeability not only in the burn wound but also in unburned tissues and organs.[9] Re-expansion of the contracted plasma volume with intravenous fluids necessarily worsens edema formation. Therefore, critical components of resuscitation that have been considered to obtain balance between under and over-provision of fluid include the choice of resuscitation formula, how clinicians respond and titrate fluids, the composition of resuscitation fluids and the use of agents to limit microvascular leak and loss of intravascular fluids.

While all burn resuscitation formulae are meant to guide only the initial rate of fluid infusion, the choice of formula may be important. Some studies suggest that use of the Modified Brooke formula or alternative approaches may adequately resuscitate patients while limiting resuscitation volumes compared to the widely-used Parkland Formula.[10–12]

Striking the right balance between adequate resuscitation and over-resuscitation may be influenced by how fluids are titrated. Both historically and currently, urinary output (UOP) has been the primary guide to the titration of resuscitation fluids. However, alternative approaches to titration based on the use of malperfusion markers (lactate and base deficit), or hemodynamic endpoints (central venous pressure, transpulmonary thermodilution-derived variables, or arterial waveform analysis)[13] or algorithm-based and computer supported decisions have been considered.[14,15] A key question is whether any of these approaches help to limit resuscitation volumes or improve fluid resuscitation outcomes, compared to using UOP alone.

The content of the resuscitation fluid is of paramount importance to the goal of adequately resuscitating the burn patient with the least amount of fluid. Virtually, all resuscitation formulae specify that colloids should be introduced at some point during resuscitation.[16] Human albumin and plasma are the major colloids of interest, and the question of when to optimally introduce a colloid remains unresolved. With respect to albumin, various heterogeneous randomized controlled trials (RCTs)[17–20] and a meta-analysis[21] of 3 of the RCTs[17–19] suggest that early addition of albumin reduces total resuscitation volumes. However, the effect of albumin use on patient outcomes is entirely uncertain. Two study level meta-analyses of the 4 RCTs[17–20] found no effect of albumin on mortality.[21,22] A different study level meta-analysis found a trend toward increased mortality with the addition of albumin.[23] One meta-analysis,[22] while recognizing substantial study heterogeneity and that other outcomes were not uniformly measured across all the RCTs, also found no effect of albumin on compartment syndrome development, renal function, or respiratory complications. The resurgence of interest in the use of human plasma during burn shock resuscitation has largely been driven by the emerging understanding of the role of endotheliopathy in burn shock and the experimental observation of plasma's restorative effect on the endothelial glycocalyx post burn injury.[24] Furthermore, modern forms of plasma such as pathogen-reduced plasma and lyophilized plasma have created new inroads into the use of plasma as a volume expander during acute burn resuscitation.[25,26] A variety of retrospective studies and one small RCT have which have investigated plasma resuscitation have found that the use of plasma reduced resuscitation volumes and edema.[27–31] As was the case with albumin, very little is known about plasma's effects on other outcomes. An alternative to using colloids to resuscitate while limiting fluids is to add high dose vitamin C (ascorbic acid) to the resuscitation fluid. Preclinical studies found that high doses of ascorbic acid, likely acting through its antioxidant and free-radical scavenging properties, dramatically reduced crystalloid resuscitation volumes and edema formation following experimental burns.[32–35] In humans, the infusion 66 mg/kg/hour of ascorbic acid has been examined in a small number of studies, with mixed findings with respect to the outcome of reduction in resuscitation fluid volumes.[36–39] Even less is known about other outcomes following the use of high-dose ascorbic acid, and some concerns have been raised about a possible association with oxalate nephropathy and development of AKI.[37,40,41]

Resuscitation failure may take various forms.[42] Chiefly, it is characterized by diminishing urinary output and worsening

hemodynamic instability despite provision of escalating volumes of resuscitation fluids, and with the onset of dangerous edema-related complications including pulmonary edema and compartmental syndromes of the abdomen, limbs, and orbit. Resuscitation de-escalation and rescue approaches, including the use of vasopressors,[43] early renal replacement therapy (by translating the high-dose hemofiltration approach employed in septic shock with AKI),[44] therapeutic plasma exchange[45] and even extra-corporeal support[46] are understudied topics where many clinical questions remain.

METHODS

The Investigator Panel for this CPG met virtually and communicated electronically between March 2022 and March 2023. Through a consensus discussion, and based on the preceding scientific background, clinically relevant questions pertaining to the topic of acute burn shock resuscitation were developed. All questions were then placed into a PICO format. *Population*: The patient population to which the question applies, *Intervention*: The therapeutic intervention(s) or diagnostic test of interest, *Comparator:* The alternative approach being compared to the intervention of interest, and *Outcome*: The outcome(s) of interest related to the intervention(s) being examined. The Panel considered outcomes that would be important to both clinicians and patients. Many outcomes were considered, including survival. Based on the aforementioned scientific background, the panel concluded that while mortality is important in evaluating the success of any fluid resuscitation strategy, the available studies are relatively small, heterogenous, and most were not randomized controlled trial, thus diminishing our assurance about including mortality as a formal PICO outcome. We anticipate that in future iterations of this guideline, that mortality will be included as an outcome, as larger ongoing RCTs are completed. The following 10 questions were created by the panel:

Question 1: Among adults with burns ≥20% TBSA, does the administration of albumin during the first 24 hours of fluid resuscitation, compared to using crystalloid fluid alone, (a) reduce total fluid resuscitation volume or total crystalloid resuscitation volume at 24 or 48 hours post burn, (b) increase urine output, or (c) decrease edema-related complications?

Question 2: Among adults with burns ≥20% TBSA should albumin be initiated early (<12 hours post burn) or late (after 12 hours post burn) during acute fluid resuscitation to (a) reduce total fluid resuscitation volume or total crystalloid resuscitation volume at 24 or 48 hours post burn, (b) increase urine output, or (c) decrease edema-related complications?

Question 3: Among adults with burns ≥20% TBSA, does starting acute fluid resuscitation with 2 mL/kg/%TBSA burn compared to starting with 4 mL/kg/%TBSA burn (a) reduce total fluid resuscitation volume or total crystalloid resuscitation volume at 24 or 48 hours post burn, (b) affect the development of acute kidney injury, or (c) reduce edema-related complications?

Question 4: Among adults with burns ≥20% TBSA, should fresh frozen plasma (FFP) be used during acute fluid resuscitation compared to using crystalloids alone to (a) reduce total fluid resuscitation volume or total crystalloid resuscitation volume at 24 or 48 hours post burn, (b) increase urine output, or (c) decrease edema-related complications?

Question 5: For adult patients with a ≥ 20% TBSA burn injury, does administration of high dose (66 mg/kg/hour) ascorbic acid (vitamin C), compared to not using high dose ascorbic acid, while providing crystalloids alone during acute fluid resuscitation (a) reduce total crystalloid resuscitation volume at 24 or 48 hours post burn, (b) increase urine output, or (c) decrease edema-related complications?

Question 6: Among adults with burns ≥20% TBSA, during acute fluid resuscitation should (a) CVP, (b) transpulmonary thermodilution (TPTD), or (c) stroke volume variation(SVV) or pulse pressure variation (PPV) from arterial waveform analysis be used to titrate resuscitation fluids, compared to using hourly urine output either alone or in conjunction with "conventional" endpoints such as heart rate, blood pressure, serum lactate, and arterial base deficit, to (a) reduce total fluid resuscitation volume or total crystalloid resuscitation volume at 24 or 48 hours post burn or (b) decrease edema-related complications?

Question 7: Among adults with burns ≥20% TBSA, should computerized decision support software (CDSS) compared to using hourly urine output alone be used to titrate acute resuscitation fluids to (a) reduce total fluid resuscitation volume or total crystalloid resuscitation volume at 24 or 48 hours post burn and (b) decrease edema-related complications?

Question 8: Among adult patients with ≥20% TBSA burn injury undergoing acute fluid resuscitation who require a vasopressor for hypotension, should norepinephrine or vasopressin be the first administered vasopressor to (a) reduce 28-day mortality and (b) reduce acute kidney injury?

Question 9: Among adults with burns ≥20% TBSA, during acute fluid resuscitation, should early continuous renal replacement therapy (CRRT) without fluid removal be initiated, compared to not initiating CRRT to (a) reduce total fluid resuscitation volume or total crystalloid resuscitation volume at 24 and 48 hours post burn and (b) decrease edema-related complications?

Question 10: Among adults with burns ≥20% TBSA, should (a) intra-abdominal pressure(IAP), (b) intra-ocular pressure (IOP), (c) serum lactate (L), or (d) arterial base deficit be monitored during the first 48 hours post burn compared to not monitoring IAP, IOP, L, and BD, to (a) reduce total fluid resuscitation volume or total crystalloid resuscitation volume at 24 or 48 hours post burn or (b) reduce the incidence of abdominal compartment syndrome, or (c) orbital compartment syndrome?

The outcome of "edema-related complications" was defined as follows: any of the following occurring within the first 48 hours post burn: abdominal compartment syndrome (ACS), elevated intra-abdominal pressure (IAP), limb (extremity) compartment syndrome, orbital compartment syndrome (OCS), elevated IOP, or pulmonary edema (radiologic or reduced PaO_2/FiO_2 ratio in first 48 hours).

SEARCH STRATEGY AND FINAL ARTICLE SELECTION

A systematic literature search strategy to address each question was developed by a professional medical librarian (E.M.). To

address the relevant interventions, 7 concepts were identified: acute fluid resuscitation, crystalloids, vitamin C, CRRT, variables (eg, central venous pressure, stroke volume, etc.), Computerized Decision Support Software, and vasopressors. Concepts for albumin, fresh frozen plasma, and colloids were considered; however, testing with a sample set of articles indicated significant overlap with the Acute Fluid Resuscitation concept. In addition, 200 unique results from these concepts were screened by the lead author (R.C.) and determined to be highly irrelevant; therefore, these concepts were not explicitly included in the search. Each included concept was combined with a *Burns* concept using the Boolean AND, then combined with the Boolean OR. The search was drafted in Ovid Medline, then translated to additional databases using appropriate subject headings and syntax. The final searches utilized the following databases: Ovid Medline, Ovid Embase, Ovid EBM Reviews: Cochrane Central Register of Controlled Trials, Ovid EBM Reviews: Cochrane Database of Systematic Reviews, and the Cumulative Index of Nursing and Allied Health Literature (CINAHL) via EBSCO. In each database except the Cochrane Database of Systematic Reviews, animal studies were excluded using a filter developed by the McGill University Health Centre,[47] and results were restricted to English language. Results were de-duplicated by an information specialist (E.M.) using EndNote X9 (Clarivate Analytics LCC) and the methods outlined by Bramer et al.[48] Searches were run from inception of the databases until May 17, 2022.

The search returned 9326 titles; 3342 were duplicates and were removed using the Bramer Method,[48] leaving 5984 titles which were uploaded and stored using Covidence (Melbourne, Australia) reference management software, that removed 6 further duplicates. The remaining 5978 titles and abstracts were independently screened and reviewed by 2 panel members (R.C. and L.J.). The 2 reviewers then met virtually and agreed that 5471 articles were irrelevant, and these were dropped. The screeners then re-reviewed the remaining 237 articles on which they had originally disagreed and by consensus eliminated a further 167 titles, leaving 70 articles selected for full text review (Figure 1). Three panel members (R.C., L.J., and A.S.) then read these articles independently and assessed whether the article should be critically reviewed and included in this CPG. To be included, 4 criteria needed to be met: (1) the study needed to involve adults with burns ≥20% TBSA who received acute fluid resuscitation, (2) there had to be a defined intervention or investigation as specified in our PICO questions, (3) there had to be a corresponding

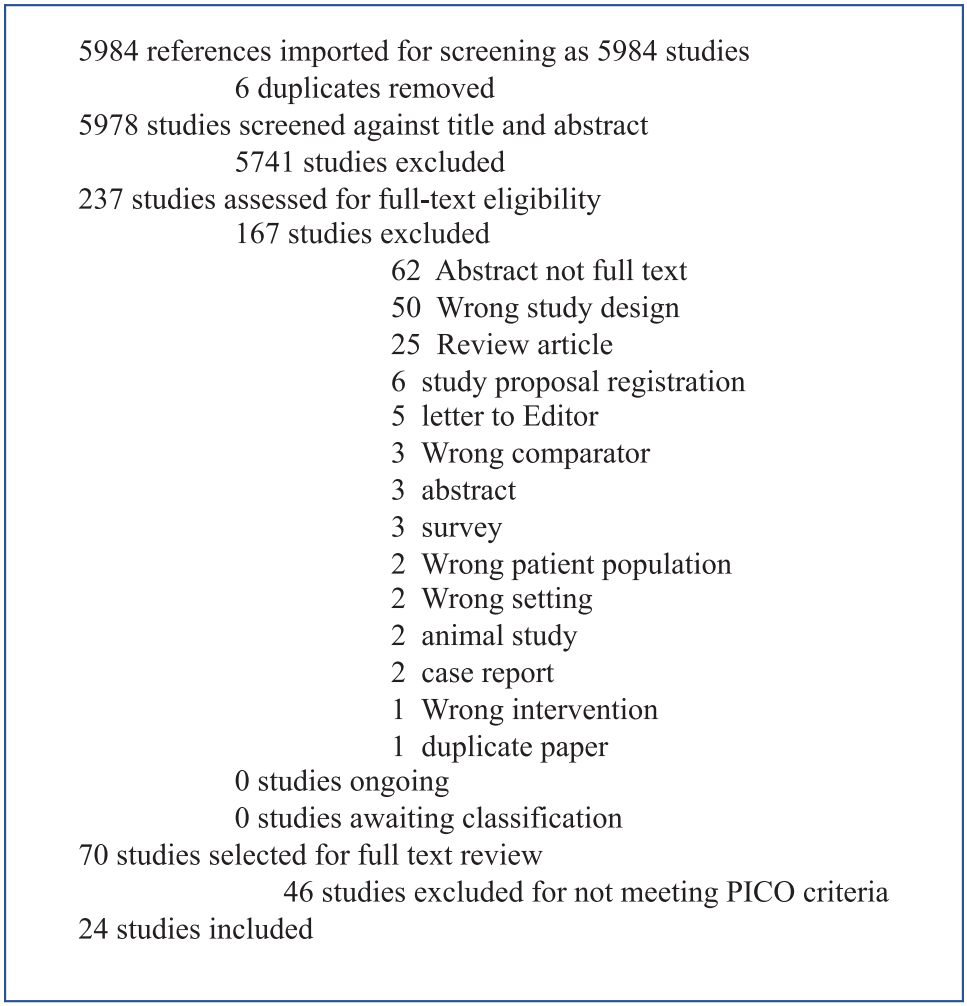

Figure 1. PRISMA flow to show how initial list of titles was reduced to the 24 articles selected for final critical review and inclusion.

comparator as defined in the PICO question, and (4) at least one of our defined PICO outcome measures had to be reported. The three panel members then met on December 12, 2022 and compared their individual observations and reached consensus on which studies to include. Unresolvable disagreements were settled by a vote. This process identified 24 studies for inclusion (Table 1).[10,17,19,20,29,31,36–38,49–63]

Finally, the 24 articles were critically reviewed and scored independently by 3 panel members (R.C., L.J., A.S.) using the method of Law et al.[64] These reviewers then met virtually on December 12, 2022, compared reviews, and reached consensus on the final score for each study (Table 2). We considered strength of evidence as high for a score of 12-14, moderate for a score of 9-11, and low for a score less than 9. The rationale for each of the final scoring decisions is included in Appendix 1. Authors were then assigned questions to draft a response and initial recommendation and then the panel met virtually on March 8, 2023 to finalize recommendations through a consensus discussion.

Question 1: *Among adults with burns ≥20% TBSA, does the administration of albumin during the first 24 hours of fluid resuscitation, compared to using crystalloid fluid alone, (a) reduce total fluid resuscitation volume or total crystalloid resuscitation volume at 24 or 48 hours post burn, (b) increase urine output, or (c) decrease edema-related complications?*

We identified several studies[17,19,20,50–54] which met our inclusion criteria and that compared use of albumin to crystalloid alone during the first 24 hours of resuscitation, and described at least one of our outcome measures (Table 1). These studies are extremely heterogeneous but can be broadly classified based on how albumin was administered. In one group of studies, albumin was started as a clinician-directed response to rescue patients that were receiving large amounts of crystalloids, and/or whose resuscitation was dete riorating.[49,50,52–54] In the other group of studies, albumin was administered as a predetermined resuscitation strategy.[17,19,20,51] The difference between these types of studies is important because in the rescue studies, patients administered albumin were generally sicker, had bigger and/or deeper burns, and were already receiving large amounts of crystalloids. All of these factors can then potentially influence our outcomes of interest.

With respect to the outcome of total crystalloid or resuscitation volumes at 24 or 48 hours, we can only consider the nonrescue studies, as these compared administration of albumin to crystalloid in patients who were similar at baseline. Two high-strength studies showed either a significant decrease in resuscitation volume[19] or a trend to lower resuscitation volume[20] with the use of albumin, compared to crystalloid alone. This effect was also observed in 2 low-strength studies.[17,51] Most of the rescue studies found that resuscitation volumes in patients receiving albumin were actually higher than when crystalloid alone was given.[49,52–54] However, in all cases, albumin was administered by clinician direction to patients with bigger and/or deeper burns or who were receiving very large amounts of crystalloid already. Although these rescue studies cannot directly answer the question regarding the outcome of resuscitation volumes, a highly important observation from three studies[50,52,53] was that the initiation of albumin rapidly lowered the in-to-out (I:O) ratio, suggesting that even in rescue situations, albumin appears to have a fluid-sparing effect. One moderate-strength rescue study found that despite having bigger and deeper burns, resuscitation volumes in albumin-treated patients were similar to those treated with crystalloid alone, inferring a volume-sparing effect.[50]

With respect to the outcome of UOP, one high strength study showed a tendency to higher UOP in the albumin treated patients.[19] Most studies did not directly examine or report this variable. However, one might infer that the rapid decline in the I:O ratio noted in 3 studies upon administering albumin[50,52,53] might be indicative of not only a fluid-sparing effect but also promotion of diuresis.

The outcome of edema-related complications was the most difficult to assess because most studies did not report these or used unreliable or unreproducible or surrogate measures of edema. We believe that in the absence of reporting compartment pressures or strict criteria and definitions for diagnosis of compartment syndrome, which outcomes such as performing a fasciotomy or abdominal decompression are operator-dependent, introduce a potential bias and are not reliable. One high-strength study where albumin was used in a predetermined fashion, and not for rescue, found that pulmonary edema significantly worsened over the first post burn week in albumin-treated patients, as assessed by measured lung water (using gas rebreathing) and evaluation of chest radiographs.[19] Considerations surrounding this finding are that it was assessed in only a subpopulation and not in all subjects, and the amount of free water and colloids given after 24 hours, development of sepsis, and mechanical ventilation were not quantified and may have differed between the colloid and crystalloid subjects. Interestingly, an earlier low-strength study by the same group[51] demonstrated no difference in lung water, and a high strength non-rescue study saw no respiratory compromise in patients receiving colloids compared to patients receiving crystalloid alone.[20] A study level meta-analysis found a lower odds of abdominal compartment syndrome (OR 0.19, 95%CI, 0.07-0.5), with albumin infusion,[22] but this analysis pooled data from heterogeneous studies, including randomized, non-randomized, rescue, and non-rescue studies.

We did not look at mortality as an outcome, because we recognized that the available studies comparing crystalloid to colloid in burn shock resuscitation are underpowered and too heterogeneous to confidently determine any relationship between colloid use and survival. Mortality is an important outcome, and this decision should not minimize its relevance. Similarly, it should not be inferred that reduction in resuscitation volume leads to lower or higher mortality. A useful analogy is seen with the use of the synthetic colloid hydroxyethyl starch (HES), which may reduce fluid volumes but which has adverse effects on renal function and survival.[65] In short, we need larger high-quality RCTs (eg, the ongoing ABRUPT 2 study, NCT04356859) to determine albumin's effect on the important outcome of survival.

Mortality outcomes in our selected studies for this question are shown in Table 1. Two random effects meta-analyses[21,22] pooled study level data from 4 RCTs[17–20] (one of which was not included in our final selection because the comparison included hypertonic lactated saline)[18] and found no effect of

Table 1. Study details.

Author	Design	Total *N*	Sample	PICO-relevant outcomes	Other relevant outcomes	Intervention and comparator	Results
Q1: Albumin vs. crystalloid							
Cochran 200749	Case control (controls matched for age and %TBSA burn)	202	ALB: *N* = 101, age 38 ± 21 years, %TBSA burn 42 ± 18, %FT burn 23 ± 16, INHI 51%* Control: *N* = 101, age 36 ± 21, %TBSA burn 40 ± 16, % FT burn 14 ± 21, INHI 18% **P* < .001 vs. control	Resuscitation volume* *a 24-hour volume was not specified. Volume was "required for resuscitation" until "maintenance rate achieved."	SIRS/sepsis ARDS mortality	ALB: 5% infusion 1:2 with LR within first 24 hours, at clinician's discretion if resuscitation volume exceeded Parkland for ≥ 2 consecutive hours, titrated to UOP, terminated when resuscitation at maintenance rate. Control: LR titrated to UOP	• Mean resuscitation volume at 53 ± 40 hours post burn was 9.4 ± 6.4 mL/kg/%TBSA burn in ALB vs. 6.4 ± 4.4 mL/kg/%TBSA burn at 36 ± 24 hours in control (*P* < .001) • No difference in SIRS/sepsis or mortality, ALB 3 times more likely to develop ARDS during hospitalization, but only INHI independently associated with ARDS. ALB associated with lower risk of mortality.
Comish 202150	Case control	91	Colloid: *N* = 30, age 44 ± 3 years, mean% TBSA burn 40*, mean % FT burn 16**, INHI 4% crystalloid: *N* = 61, age 45 ± 2 years, mean %TBSA burn 34, mean % FT burn 1, INHI 10% **P* = .047, ***P* = .005 vs. crystalloid	24-hour crystalloid resuscitation fluid volume Compartment syndrome	In to out ratio (IOR) LOS ICU LOS ARDS Mortality	Colloid: 25% albumin (0.1 mL/kg/%TBSA burn) started in first 24 hours for oliguria or unstable vital signs at clinician's discretion. Fluids titrated to UOP > 0.5 mL/kg/hour Crystalloid: LR only in first 24 hours, titrated to UOP > 0.5 mL/kg/hour Both groups received albumin after 24 hours	• 24 hours LR was 4.3 ± 1.8 mL/kg/%TBSA burn in colloid vs. 3.6 ± 1.2 in crystalloid (*P* = .129) • Compartment syndrome 3% in colloid vs. 0% in crystalloid (*P* = .33) • IOR reduced by 50% within 1 hour of starting 25% albumin. No differences in ARDS or mortality. LOS and ICU LOS significantly greater in colloid
Cooper 200620	Randomized controlled trial	42	Treatment: *N* = 19 age 36 (24-45) year, % TBSA burn 39 (32-53), %FT burn 15(0-43), INHI 63% Control: N=23, median Age 31 (25-39), %TBSA burn 32 (26-34), %FT burn 12 (0-20)	24-hour resuscitation fluids PaO_2/FiO_2 ratio (daily/14 days)	MODS Mechanical ventilation 28-day mortality	Treatment: 5% albumin Control: LR Fluids titrated in both groups to UOP > 0.5 mL/kg/hour and MAP > 70 mmHg	• Basal and resuscitation fluid in treatment were 1308 (480-1980) mL + 3355 (2588-9138) mL vs. 1500 (720-2450) + 6178 (3435-9481) in control (*P* = .42) • No differences in PaO_2: FiO_2 except on days 1 and 7 • No significant differences in MODS, duration ventilation or 28-day survival
Goodwin 198151	CC	24	Individual group characteristics not presented. Overall cohort (*N* = 24) mean age 27 (range 18-42) and mean % TBSA burn 47% (range 28%-79%)	Resuscitation volume Measured lung water		Colloid: 2.5% albumin in LR Crystalloid: LR Fluids titrated to UOP 30-50 mL/hour in both groups	• Colloid resuscitation volume 2.68 ± 1.18 mL/kg/%TBSA burn vs. crystalloid resuscitation volume 3.62 ± 1.24 mL/kg/%TBSA burn (*P* < .01) • No differences in lung water on PB days 0-7

Table 1. Continued

Author	Design	Total *N*	Sample	PICO-relevant outcomes	Other relevant outcomes	Intervention and comparator	Results
Goodwin 198319	RCT	79	Colloid: *N* = 40 age 28 ± 7, %TBSA burn 53 ± 17, no INHI Crystalloid: *N* = 39, age 28 ± 8 years, % TBSA burn 48 ± 12, no INHI	24-hour resuscitation fluids Radiographic pulmonary edema Measured lung water	Cardiac index EDVI	Colloid: 2.5% albumin in LR Crystalloid: LR Fluids estimated at 2 mL/kg/%TBSA burn and titrated to UOP 30-50 mL/hour in both groups	• 24 hours fluids: colloid 2.98 ± 1.1 mL/kg/%TBSA burn vs. crystalloid: 3.81 ± 1.48 mL/kg/%TBSA burn ($P < .01$) • Radiologic pulmonary edema first 7 days 20% in colloid vs. 4% in crystalloid • (*N* = 50) Lung water by day 7 significantly greater in colloid vs. crystalloid • (*N* = 29) EDVI and CI significantly higher between 12 and 24 hours in colloid vs. crystalloid.
Greenhalgh 202152 NB: This study also addressed Q2: early vs. late albumin.	CC (observational non-protocolized multicenter study)	379	Albumin *N* = 253, age 48 ± 16 y*, %TBSA burn 36(19.5)* *, %FT burn 15(26)**, 17.4% INHI Crystalloid: 43 ± 15 years, % TBSA burn 25 ± 11, %FT burn 0 (8), 3.2% INHI *$P < .003$ vs. crystalloid **$P < .001$ vs crystalloid	24-hour total fluid 24-hour UOP Fasciotomy for compartment syndrome at 48 hours ACS at 48 hours	In to out ratio (IOR) Duration ventilation In-hospital survival RRT in first 96 hours	Albumin: 5%, 25% or both in first 24 hours per center's resuscitation approach and clinician's discretion Crystalloid: LR only in first 24 hours per center's resuscitation approach and clinician's discretion	• Total 24 hours fluids: albumin: 5.2 ± 2.3 mL/kg/%TBSA vs. crystalloid: 3.7 ± 1.7 mL/kg/%TBSA burn • 24 hours UOP: albumin 0.8 ± 0.46 mL/kg/hours vs. 0.96 ± 0.57 mL/kg/hours crystalloid • Fasciotomy 3.6% in albumin vs. 0% in crystalloid. • ACS in first 48 hours: 0.8% in albumin vs. 0% in crystalloid • Immediate drop in IOR upon starting albumin • RRT, duration vent, and mortality all greater in albumin
Lawrence 201053	CC	52	Colloid (*N* = 26) age 42 ± 3 years, %TBSA burn 40 (23-87) * % FT burn 15 (0-76), 46% INHI Crystalloid (*N* = 26) 42 ± 3 years, % TBSA burn 28 (20-59), % FT burn (0-24), 27% INHI *$P = .005$ vs. crystalloid	Resuscitation volume* *a 24-hour volume was not specified. Volume was for resuscitation until UOP maintained at a calculated maintenance rate	In to out ratio (IOR) Mortality	Colloid: LR changed to 5% albumin in 1:2 ratio with LR in first 24 hours for high volume requirements or edema complications Crystalloid: LR only Both groups titrated to UOP goal 30-50 mL/hours, and completed when maintenance rate achieved.	• Colloid: 6.9 ± 3.1 mL/kg/%TBSA burn at median 37 hours PB crystalloid 4 ± 2 mL/kg/%TBSA burn at median 30 hours PB ($P < .001$) • Immediate drop in IOR upon starting albumin • No difference in mortality

Table 1. Continued

Author	Design	Total N	Sample	PICO-relevant outcomes	Other relevant outcomes	Intervention and comparator	Results
Park 201254	CC (historical control)	159	Preprotocol: $N = 98$ age 43 ± 18, % TBSA burn 39 ± 18, 42% INHI Postprotocol $N = 61$ age 41 ± 19 years, %TBSA burn 38 ± 18, 40% INHI	24-hour resuscitation fluids ACS requiring laparotomy PaO_2:FiO_2 ratio at 24 hours	Ventilator days Mortality	Preprotocol: LR at 4 mL/kg/%TBSA burn, titration not described + vasopressors at clinician's discretion Postprotocol: LR but at 12 hours, if 24-hour projected fluids are ≥ 6 mL/kg/%TBSA burn, LR changed to 5% albumin + possible additional colloids, eg, blood, hespan, FFP, (colloids used in 41% post protocol). Also vasopressin infusion started, titrated to BP, additional NE given for hypotension, IAP measured *q* 4 hours. Titration of fluid if UOP ≥ 1 mL/kg/hour.	• 24 hours fluids: preprotocol 4.6 ± 2.3 mL/kg/%TBSA burn vs 4.2 ± 1.7 mL/kg/%TBSA burn postprotocol (NS) • ACS with laparotomy 6% preprotocol vs. 0% postprotocol ($P < .05$). • PaO_2:FiO_2 ratio at 24 hours significantly higher in postprotocol • Significant reduction in ventilator days and mortality in postprotocol
Recinos 197517	RCT (pseudorandomized)	15	ADULT analysis (age 13-59) LR +ALB, $N = 9$, mean %TBSA burn 57% LR: $N = 6$ mean % TBSA burn 54%	24-hour fluid volume Edema complications		LR+ ALB: 2.3% albumin in LR LR: LR only No resuscitation formula used, fluids titrated in both groups to 30-50 mL/hours.	• 24 hours fluid volume: LR+ ALB: mean 2 (range 1.1-3.8) mL/kg/%TBSA burn vs. LR mean 2.9 (range) 1.7-4.9. ($P = .001$) • No edema complications in LR +ALB vs. 3 cases with complications in LR. Greater use of diuretics in LR than LR + ALB • No mortality difference
Q3: 2 mL/kg/%TBSA burn Vs. 4 mL/kg/%TBSA burn							
Chung 200910	CC	52	Modified Brooke $N = 31$, age 25 ± 5 years, %TBSA burn 55 ± 19, % FT burn 46 ± 22 4 % INHI Parkland: $N = 21$, age 25 ± 5, %TBSA burn 46 ± 17, % FT burn 39 ± 20, 29% INHI	Total 24-hour fluids 24-hour UOP admission PaO_2/FiO_2 ratio ACS (laparotomy-defined)	Ventilator-free days Mortality	Modified Brooke: Resuscitation initiated with LR based on 2 mL/kg/%TBSA burn Parkland: resuscitation initiated with LR based on 4 mL/kg/%TBSA burn Fluids titrated to 30-50 mL/hours UOP goal in both. Albumin allowed in both if 24-hour fluid projection at 12 hours PB exceeded 6 mL/kg/%TBSA burn	• 24 hours total fluids: modified Brooke: 3.8 ± 1.2 mL/kg/%TBSA burn vs. 5.9 ± 1.1 mL/kg/%TBSA burn ($P < .001$) • 24 hours UOP modified Brooke 1638 ± 477 mL vs. Parkland 1818 ± 455 mL (NS) • No mortality difference • No differences in PaO_2:FiO_2, vent free days, ACS, AKI, or mortality

Table 1. Continued

Author	Design	Total *N*	Sample	PICO-relevant outcomes	Other relevant outcomes	Intervention and comparator	Results
Saitoh 202155	RCT	36	Modified Brooke: *N* = 17, age 59 ± 20, %TBSA burn 39 (27-49), %FT burn 10 (1-31), INHI 24% Baxter: *N* =19, age 64 ± 22, %TBSA burn 30 (25-51), %FT burn 18 (0-23.5), INHI 21%	Resuscitation fluid volume at 24 hours AKI in first 48 hours ACS PaO_2:FiO_2 ratios to day 7	28-day and hospital survival	Modified Brooke: LR based on 2 mL/kg/%TBSA burn, fluid rate adjusted *q* 2 hours by one-third for goal UOP 0.5 mL/kg/hour. Baxter: LR based on 4 mL/kg/%TBSA burn, fluid rate adjusted *q* 2 hours at clinician's discretion "based on treatment policy of institution" for goal UOP 0.5 mL/kg/hours. Both groups received albumin and/or FFP in first 24 hours	• Fluid volume at 24 hours: Modified Brooke: 3.6 ± 1.1 mL/kg/hours vs. 4.59 ± 1.58 mL/kg/hour in Baxter (*P* = .05). • No differences in PaO_2:FiO_2 ratios, AKI in first 48 hours, ACS, or survival
Q4: FFP vs. crystalloid							
Du 199129	CC	30	LR: *N* = 10, age 39 ± 4 year, %TBSA burn 47 ± 4, % FT burn 23 ± 3 FFP, age 43 ± 4, % TBSA burn 44 ± 4, % FT burn 22 ± 4 HPT(hypertonic crystalloid): Age 34 ± 5 year, %TBSA burn 50 ± 4, % FT burn 25 ± 7	24-hour fluid volume 24-hour UOP Weight gain at 24 and 48 hours	Survival	LR: initiated at 4 mL/kg/%TBSA burn adjusted to UOP goal of 0.5 mL/kg/%TBSA burn FFP: basal LR at 84 mL/hour + FFP 75 mL/kg/36 hours, adjusted to UOP goal of 0.5 mL/kg/hour HPT: hypertonic sodium acetate initiated at 4 mL/kg/%TBSA burn, adjusted to UOP goal 0.5 mL/kg/hour	• 24-hour infusion volume: LR 4.8 ± 0.6 mL/kg/% TBSA burn, HPT: 3.16 ± 0.4 mL/kg/%TBSA burn, FFP: 2.7 ± 0.2 mL/kg/%TBSA burn (*P* < .01). • 24-hour UOP LR: 0.9 ± 0.1 mL/kg/hour HPT: 0.97 ± 0.15 mL/kg/hour, FFP: 0.7 ± 0.1 mL/kg/hour (NS) • % Weight gain by 48 h: LR: 14%, HPT 12%, FFP 4% (*P* < .01)
O'Mara 200531	RCT	31	Crystalloid *N* =15, age 46 ± 21, %TBSA burn 50 ± 12, % FT burn 28 ± 12, INHI 73% Plasma *N* = 16, age 45 ± 19, %TBSA burn 52 ± 12, % FT burn 29 ± 19, INHI 63%	24-hour fluid volume 24-hour UOP IAP weight gain	BD PAP Survival	Crystalloid: LR at 4 mL/kg/%TBSA burn titrated to achieve UOP 0.5-1 mL/kg/hour Plasma: Basal LR at 83 mL/hour + FFP at 75 mL/kg/24 hour titrated to achieve UOP 0.5-1 mL/kg/hour	• 24 hour fluid volume crystalloid 0.26 ± 0.12 L/kg (5 mL/kg/%TBSA burn) vs. 0.14 ± 0.1 L/kg (2.7 mL/kg/%TBSA burn) in plasma (*P* = .005). • 24-hour UOP crystalloid: 0.77 ± 0.21 mL/kg/hour vs. 0.76 ± 0.33 mL/kg/h (NS) • Peak and change in IAP and % weight gain significantly greater in crystalloid than plasma • Significantly greater correction of BD in plasma than crystalloid • PAP significantly higher in crystalloid • No survival difference

Table 1. Continued

Author	Design	Total *N*	Sample	PICO-relevant outcomes	Other relevant outcomes	Intervention and comparator	Results
Q5: High dose ascorbic acid vs. no ascorbic acid							
Flores 202256	CC (historical control)	75	HDAA: *N* =25, age 42 ± 13 y, %TBSA burn 52 ± 18*, INHI 24% Control: *N* = 50, age 47 ± 16 year, %TBSA burn 39 ± 16, INHI 32% *$P < .01$ vs. control	24-hour resuscitation fluids 24-hour UOP Compartment syndrome	72-hour fluids ARDS AKI EVLWI Mortality	HDAA: LR + vitamin C at 66 mg/kg/hour for 36 hours Control: LR only Both groups resuscitated to TPTD endpoints, both groups given "colloids" > 12 h if vasopressors required.	• 24-hour fluid 3.1 ± 0.9 mL/kg/%TBSA burn in HDAA Vs. 4.3 ± 1.5 mL/kg/%TBSA burn in control ($P < .05$) • UOP 1.5 ± 0.7 mL/kg/hour in HDAA vs. 1.2 ± 0.4 mL/kg/hour in control ($P = .13$) • Compartment syndrome 20% in HDAA vs. 24% in control ($P = .7$) • No differences in 72-hour fluids, EVLWI, ARDS, AKI, mortality
Kahn 201138	CC	33	Vitamin C: *N* = 17, 42 ± 16 yr %TBSA burn 45 ± 21, INHI 24% LR only: 50 ± 20 year, %TBSA burn 39 ± 15, INHI 25%	Resuscitation volume in first 24 hour Urine output in first 24 hour. Compartment syndrome ACS PaO_2:FiO_2 ratio	Renal failure Mortality	Vitamin C: LR + 66 mg/kg/hour Vitamin C continued to "approximately 24 h" LR only: LR Both groups titrated to UOP > 0.5 mL/kg/hour and "stable hemodynamics."	• 24-hour fluids: 5.3 ± 1 mL/kg/%TBSA burn in vitamin C vs. 7.1 ± 1 mL/kg/%TBSA burn in LR Only ($P < .05$). • UOP in 24 hours: 1.5 ± 0.4 mL/kg/hour in vitamin C vs. 1 ± 0.5 mL/kg/hour in LR Only ($P < .05$) • Fasciotomy 18% in vitamin C vs. 19% in LR Only. (NS) • ACS in 0 vitamin C vs. 6% in LR only (NS) • No differences in PaO_2/FiO_2 first 48 hours • No differences in mortality
Lin 201837	CC (age and burn size-matched controls)	80	HDAA: *N* =38, age 41 ± 15, %TBSA burn 47 21, ± 52%, INHI. Control *N* = 42, age 42 ± 17, %TBSA 43 ± 23, 36% INHI	Total resuscitation fluid at 24 hours Total 24-hour UOP Abdominal compartment syndrome	ARF requiring dialysis Ventilator days Mortality	HDAA: LR + Vitamin C at 66 mg/kg/h Control: LR Both groups titrated "based on Parkland formula."	• 24-hour fluids: HDAA 4.6 ± 2.6 mL/kg/%TBSA burn vs. 4.3 ± 2.5mL/kg/%TBSA burn in Control($P = .6$). • Median 24-hour UOP HDAA 1.1(0.9-1.6) mL/kg/hour vs. 0.81 (0.6-1) mL/kg/hour in control $P = .002$ • ACS in HDAA 5.2% vs. 2.3% in control • ARF/dialysis 23% in HDAA vs. 7% in control ($P = .06$), vitamin C independently associated with ARF/dialysis (OR 5.4, 1.1-26), no differences in ventilator days or mortality

Table 1. Continued

Author	Design	Total *N*	Sample	PICO-relevant outcomes	Other relevant outcomes	Intervention and comparator	Results
Tanaka 200036	RCT (pseudo-randomized)	37	Ascorbic acid: *N* = 19, age 40 ± 20 years, %TBSA burn 63 ± 26, %FT burn 51 ± 26, 79% INHI Control: *N* =18, age 49 ± 22, %TBSA burn 53 ± 17, % FT burn 40 ± 13, 67% INHI	Total resuscitation volume at 24 hours UOP at 24 hours Compartment syndrome PaO_2:FiO_2 0-96 hours PB	Duration ventilation Mortality	Ascorbic acid: 66 mg/kg/hour for the first 24 hours postburn. Control: LR alone Fluids titrated to "stable hemodynamic measurements" and UOP 0.5-1 cc/kg/%TBSA burn in both groups. Both groups received 5% albumin after 24 hours.	• 24 hours fluids: 3 ± 1.7 mL/kg/%TBSA burn in ascorbic acid vs. 5.5 ± 3.1 mL/kg/%TBSA burn in control ($P < .004$). • UOP in 24 hours: 1.3 ± 0.6 mL/kg/hour in ascorbic acid vs. 1.1 ± 0.3 mL/kg/hour in control (NS) • Fasciotomy 21% in ascorbic acid vs. 44% in control (NS) • PaO_2:FiO_2 ratios significantly higher in ascorbic acid from hours 18-96 • Ascorbic acid group had significantly less soft tissue edema, acute weight gain, and duration of ventilation
Q6: Semi-invasive monitoring vs. UOP and conventional parameters							
Aboelatta 201357	CC	30	Group I (TPTD): *N* = 15, age 30 ± 15 year, %TBSA burn 41 ± 11 Group II (control): *N* = 15, age 35 ± 11 years, %TBSA burn 39 ± 9	Average daily resuscitation fluid	Mortality	Group I (TPTD): LR initiated based on Parkland Formula, adjusted to achieve ITBVI > 800 mL/m^2, CI > 2.5 L/min/m^2, EVLWI > 10 mL/kg above normal range, additional vasopressors for hypotension or oliguria, 4% gelatin boluses after 24 hours to 72 hours for hypovolemia Group II (Control) LR initiated based on modified Parkland (3 mL/kg/%TBSA burn), adjusted to MAP > 60, UOP > 0.5 mL/kg/hour, lactate < 2 mmol/L, ScvO2 > 65%. Additional vasopressors for hypotension or oliguria, 4% gelatin boluses after 24 hours to 72 hours for hypovolemia	• Average 24 hours fluid volume (over first 72 hours): Group I (TPTD) 10 378 ± 3723 mL vs. group II (control): 5917 ± 1695 mL ($P < .001$) • No survival difference

Table 1. Continued

Author	Design	Total N	Sample	PICO-relevant outcomes	Other relevant outcomes	Intervention and comparator	Results
Chen 201758	CC	34	EGDT (early goal-directed therapy): $N = 13$, mean age 32 year, %TBSA burn 89 ± 4 CG (conventional group): $N = 21$, mean age 33 year, % TBSA burn 86 ± 6.	Fluid volume UOP PaO_2/FiO_2 ratio	Lactic acid Mortality	EGDT: 1:1 crystalloid: colloid, dopamine, and dobutamine titrated to GEDVI 650-800 mL/m^2, EVLWI 3-7 mL/kg, SVI 40-60 mL/m^2, SVRI 1200-1800 d·s·cm^{-5}·m^2, MAP > 65 mmHg, UOP ≥ 1 mL/kg/hour CG: Conventional monitoring and "traditional formula (First Affiliated Hospital of PLA General Hospital)"	• Fluid volume: EGDT: 3.29 ± 0.26 mL/kg/%TBSA burn vs. CG: 3.71 ± 0.3 mL/kg/%TBSA burn ($P < .05$) • UOP: EGDT: 0.83 ± 0.12 vs. CG: 0.85 ± 0.2 mL/kg/hour (NS) • PaO_2/FiO_2: EGDT: 381 ± 67 vs. CG: 329 ± 49 ($P < .05$) • Lactate: EGDT: 2 ± 0.6 mmol/L vs. CG: 3.9 ± 1.2 mmol/L ($P < .05$). • Mortality EGDT 8% vs. CG 14%
Foldi 200959	RCT	16	ITBVI: $N = 8$, age 59 (21-74), %TBSA burn 37 (27-58), %FT burn 36(27-55), INHI 75%. HUO (hourly urine output) $N = 8$, age 54 (20-70) year, % TBSA burn 38 (29-61), % FT burn 35 (26-58), INHI 88%	24 hours administered fluid 24 hours UOP	Lactic acid CI at 24 hours	ITBVI: resuscitation fluids titrated *q* 2 hours to achieve ITBVI 800-850 mL/m^2 HUO: resuscitation fluids titrated *q* 2 hours to achieve UOP 0.5-1 mL/kg/%TBSA burn. Resuscitation initiated with LR at 4 mL/kg/%TBSA burn in first 24 hours in both groups, LR + hydroxyethyl starch administered after 24 hours in both groups.	• 24 hours administered fluid: ITBVI: 5.5 (4.4-6.2) mL/kg/%TBSA burn vs. HUO: 4.3 ((4.2-5.2) ($P < .05$) • 24 hours UOP ITBVI: 1.1 (0.9-1.3 mL/kg/hour) vs. HUO 0.7 (0.5-1.1) mL/kg/hour ($P < .05$) • CI at 24 hours: ITBVI: 3.5 (3.2--3.9) vs. HUO: 2.9 (2.3-3.5) ($P < .05$) • No difference in lactate but more diminished oxidative stress on days 3-6 in ITBVI than HUO
Foldi 201060	RCT	30	ITBVI: $N = 15$, age 58 (22-75), %TBSA burn 44 (33-62), %FT burn 35(27-58), INHI 80%. HUO (hourly urine output) $N = 15$, age 56(23-65) year, % TBSA burn 42 (31-64), % FT burn 34 (28-56), INHI 87%	24 hours administered fluid 24 hours UOP ACS	Lactic acid CI at 24 hours Duration ventilation mortality	ITBVI: Resuscitation fluids titrated *q* 2 hours to achieve ITBVI 800-850 mL/m^2 HUO: resuscitation fluids titrated *q* 2 hours to achieve UOP 0.5-1 mL/kg/%TBSA burn. Resuscitation initiated with LR at 4 mL/kg/%TBSA burn in first 24 hours in both groups, LR + hydroxyethyl starch administered after 24 hours in both groups.	• 24 hours administered fluid: ITBVI: 5.4 (4.2-6.6) mL/kg/%TBSA burn vs. HUO: 4.5 (4.1-5.4) ($P < .05$) • 24 hours UOP ITBVI: 1.1 (0.9-1.3 mL/kg/hour) vs. HUO 0.8 (0.6-1.1) mL/kg/h ($P < .05$) • CI at 24 hours: ITBVI: 3.6 (3.3--3.9) vs. HUO: 2.8 (2.4-3.2) ($P < .05$) • No differences in lactate, ACS, duration ventilation, mortality.

Table 1. Continued

Author	Design	Total *N*	Sample	PICO-relevant outcomes	Other relevant outcomes	Intervention and comparator	Results
Holm 200461	RCT	50	TDD (transpulmonary thermodilution) *N* = 25, mean age 37 years, % TBSA burn 42%, INHI 44% Baxter: *N* = 25, mean age 45 years, % TBSA burn 42%, INHI 56%	24-hour fluid administered 24-hour UOP Lung water (EVLWI)	Lactic acid Cardiac index Renal failure requiring dialysis Mortality	TDD: LR initiated at 4 mL/kg/%TBSA burn, adjusted to achieve ITBVI > 800 mL/m^2, CI > 3.5 L/min/m^2, and EVLWI < 10 mL/kg above normal Baxter: LR initiated at 4 mL/kg/%TBSA burn, adjusted to achieve UOP > 0.5 mL/kg/hour, and MAP >70 mmHg and CVP > 6 mmHg Both groups received albumin ± hydroxyethyl starch after 24 hours.	• 24-hour fluids: TDD: 27 064 mL vs. Baxter: 16 232 (*P* = .001) • UOP at 24 hours: TDD 205 ± 127 mL/hours vs. Baxter: 123 ± 93 mL/hour (*P* = .01) • No differences in EVLWI to 48 hours. • CI significantly higher in TDD than Baxter only at 24 hours. • No differences in lactate, renal failure, mortality
Zhu 202162	CC	191	Study group *N* = 82, age 41 ± 12 years, % TBSA burn 55 ± 12, % FT burn 15 ± 7, INHI 48% Control group: *N* = 109, age 43 ± 12 years, % TBSA burn 53 ± 12, %FT burn 18 ± 7*, INHI 39% * *P* = .02 vs. study group	24-hour resuscitation fluid volume	AKI AEDS Survival	Study group: Fluids adjusted using "EDVI, ITBVI, CI, SVRI, and EVLWI" (no thresholds described) Control group: Fluids adjusted "according to HR, BP, urine volume, resp rate, and SpO2" (no thresholds described) Both groups resuscitated with 1.5 mL/kg/%TBSA burn +2000 mL in first 24 hours as 2:1 ratio of LR: Colloid (FFP or 5% albumin).	• 24-hour resuscitation fluid volume: Study group: 2.29 ± 0.4 mL/kg/%TBSA burn vs. control group: 2.59 ± 0.39 mL/kg/%TBSA burn (*P* < .001). • AKI higher in control (29%) vs. 16% in study group (*P* = .03). • No difference in ARDS, mortality

Table 1. Continued

Author	Design	Total *N*	Sample	PICO-relevant outcomes	Other relevant outcomes	Intervention and comparator	Results
Q7: Computerized Decision Support Software (CDSS) vs. UOP alone for titration of resuscitation							
Salinas 201163	CC	70	CDSS: *N* = 32, age 44 ± 16, % TBSA burn 39 ± 16, % FT burn 9 (0, 17), INHI 31 % Control: *N* = 38, age 50 ± 21, % TBSA burn 40 ± 19, % FT burn 12 (0, 41), INHI 29%	24-hour crystalloid volume	% of time UOP in target Vent-free days Mortality	CDSS: Hourly infusion rate recommended by CDSS to achieve target UOP 30-50 mL/hour; provider able to deviate from CDSS recommendation Control: Hourly infusion rate adjusted by provider for target UOP 30-50 mL/hour Both groups resuscitated with LR to achieve a target UOP of 30-50 mL/hour	• 24-hour total resuscitation fluid: CDSS: 4.2 ± 1.8 mL/kg/%TBSA burn vs. control 6.5 ± 4.1 mL/kg/%TBSA burn ($P <$ .05) • Hourly UOP in target range 31% in CDSS vs. 23% in control ($P <$ .05). • Vent-free days and mortality lower in CDSS ($P <$ .05)

All values shown as mean ± SD or median (IQR).
Abbreviations: ACS: abdominal compartment syndrome; AKI: acute kidney injury; ALB: albumin; ARF: acute renal failure; ARDS: acute respiratory distress syndrome; BD: base deficit; BP: blood pressure; CC: case control; CDSS: Computer Decision Support Software; CI: Cardiac Index; EDVI: End-Diastolic Volume Index; EVLWI: Extra Vascular Lung Water Index; FFP: fresh frozen plasma; FT: full thickness; GEDVI: Global End-Diastolic Volume Index; HDAA: high-dose ascorbic acid; IAP: intra-abdominal pressure; ICU LOS: intensive care unit length of stay; IOR: in-to-out ratio; INHI: inhalation injury; ITBVI: Intrathoracic Blood Volume Index; LOS: lengthy of stay; LR: lactated ringers solution; MAP: mean arterial pressure; MODS: multiple organ dysfunction syndrome; NE: norepinephrine; PAP: peak airway pressure; PaO_2/FiO_2: ratio of arterial partial pressure of oxygen to fractional inspired oxygen concentration; PB: post burn; RCT: randomized controlled trial; RRT: renal replacement therapy; SIRS: Systemic Inflammatory Response Syndrome; SVI: Stroke Volume Index; SVRI: Systemic Vascular Resistance Index; TBSA: total body surface area; TPTD: trans-pulmonary thermodilution; UOP: urine output.

albumin on mortality. This approach using pooled data from very heterogeneous studies has been criticized, and when an alternative fixed-effects model with these RCTs was used, albumin was actually shown to be associated with higher mortality.[23] A recent Cochrane Systematic Review of colloid versus crystalloid studies in critically ill patients (including burns) determined that it was unlikely that albumin or crystalloid use made any difference to mortality.[66]

We recommend that clinicians consider providing albumin in the first 24 hours of resuscitation to improve urinary output and to reduce the total volume of resuscitation fluids. The strength of this recommendation is greater for patients with larger burns, and weaker for patients with smaller burns. We also recommend administration of albumin in "rescue" situations where resuscitation is deteriorating despite receiving escalating amounts of crystalloids. We have low confidence in the strength of the limited available evidence to make any recommendations on the use of albumin to limit edema-related complications.

Question 2*: Among adults with burns ≥20% TBSA should albumin be initiated early (<12 hours post burn) or late (after 12 hours post burn) during acute fluid resuscitation to (a) reduce total fluid resuscitation volume or total crystalloid resuscitation volume at 24 or 48 hours post burn, (b) increase urine output, or (c) decrease edema-related complications?*

We identified only one study that met criteria for inclusion by addressing the PICO question of administering albumin "*early*" (<12 hours), compared to "*late*" (>12 hours).[52] The ABRUPT study provided essential observational data to inform the design of the ongoing ABRUPT-2 study (NCT04356859), but unfortunately, it provides only low-strength evidence to answer this question. Patients who received albumin <12 hours (N = 118) had significantly larger and deeper burns than those given albumin after 12 hours (N = 135). There was also a critical difference between these 2 groups: up to the point when albumin was started, those that received early albumin had been administered significantly more crystalloids and had a significantly higher in-to-out (I:O) ratio than those who were given albumin late. This creates a potential selection bias toward administering albumin earlier to patients with more extensive injuries who were rapidly consuming large volumes of crystalloids. Thus, this study cannot answer the question of early versus late albumin with respect to any of our specified outcomes. However, one finding using a linear mixed effect model did show a faster rate of decline in fluids if albumin is given compared to not giving it (point estimate −29.52, 95% CI, −24.21 to −34.83, $P <$ .001). Thus, one might hypothesize that the sooner albumin is administered, the faster the fluid infusion rate will decline, potentially leading to less fluid administration. This is theoretical, and no firm conclusions can be reached about the effects of earlier versus later albumin administration from the ABRUPT study.

Two studies provide additional information, but these were not included for critical review either because the population was not adult,[67] or there was no comparator.[68] A RCT in 46 pediatric patients with burns between 15% and 45% TBSA and no inhalation injury compared the intervention of giving a 4-hour infusion of 5% albumin once daily for 3 days starting at 8-12 hours post burn, with a control group that also received

Table 2. Scores from critical review using method of Law et al.[64]

			Sample			Outcomes			Intervention			Results					
Study	Study purpose	Literature review	Design	Size	Details	Justified	Reliable	Valid	Detailed description	Contamination	Co-intervention	Statistical significance	Analysis appropriate	Clinical importance	Dropouts reported	Conclusions appropriate	Total score
Abeoletta	1	1	CC	30	0.5	1	0.25	0.25	1	0	1	1	1	1	1	0.75	10.75
Chen	0.5	1	CC	34	0.5	1	0.25	0.25	0	0	0	1	1	0.5	1	0.5	7.5
Chung	1	1	CC	52	0.5	1	0.5	0.5	0.5	1	0	1	1	1	1	1	11
Cochran	1	1	CC	202	0.5	1	0.5	0.75	0.5	1	1	1	1	0.5	1	1	11.75
Comish	1	1	CC	91	1	0.5	0.5	0.5	0.5	1	0	1	0.5	0.5	1	0	9
Cooper	1	1	RCT	42	1	1	1	1	0.75	1	1	1	1	0.5	1	0.5	12.75
Du	1	1	CC	30	0.5	1	1	1	0.25	1	1	1	1	0.5	1	0.5	11.75
Flores	1	1	CC	75	0.75	1	0.75	0.75	1	1	0	1	1	0.5	1	1	11.75
Foldi 2009	1	1	RCT	16	1	1	1	1	1	1	1	1	1	0.25	1	0.5	12.75
Foldi	1	1	RCT	30	1	1	1	1	1	1	1	1	1	0.25	1	0.5	12.75
Goodwin	1	0.5	CC	24	0	0.75	0.5	0.5	0	1	1	1	1	0	1	0.5	8.75
Goodwin	1	1	RCT	79	1	1	1	1	0.75	1	1	1	1	1	1	0.25	13
Greenhalgh	1	1	CC	379	0	1	0.5	0.5	0	0	0	1	1	0.5	1	1	8.5
Holm	1	1	RCT	50	0.75	1	1	0.5	1	0.75	1	1	1	1	1	1	13
Kahn	1	1	CC	33	0.75	1	0.5	0.5	1	1	0	1	1	0.5	1	0.75	10.75
Lawrence	1	1	CC	52	0.5	1	0.5	0.5	0.75	1	1	1	1	0.75	1	0.75	11.75
Lin	1	1	CC	80	0.75	1	0.75	0.75	1	1	0	1	1	0.5	1	1	11.75
O'Mara	1	1	RCT	31	1	1	1	1	0.75	1	1	1	1	1	1	1	13.75
Park	1	1	CC	159	0.5	1	0.5	0.5	0.5	0	0	1	0.5	0.5	1	0.5	8.5
Recinos	1	1	RCT	15	0.25	1	0.5	0.5	0.25	1	0.5	0.25	0.25	0.5	1	0.5	8.5
Saitoh	1	1	RCT	36	0.75	0.75	0.75	0.75	1	1	0	1	1	0.5	1	1	11.5
Salinas	1	1	CC	70	0.5	1	1	1	0.5	1	0.5	1	1	1	1	1	12.5
Tanaka	1	1	RCT	37	1	1	0.75	0.75	1	1	1	1	1	1	1	1	13.5
Zhu	1	0	CC	191	0.5	1	0.5	0.5	0	0	0	1	1	0.5	1	0.5	7.5

the daily 4-hour albumin intervention but where the first dose was started after 24 hours.[67] Patients in the intervention group received significantly less crystalloid over the first 3 days and had significantly less "fluid creep," defined by subjective evaluation of edema in unburned tissue and presence of an associated problem (pulmonary congestion, cardiomegaly, effusion, deepening of burns, need for escharotomy or fasciotomy, abdominal compartment syndrome). A secondary analysis found that the intervention group had a shorter hospital length of stay, and that less "fluid creep" associated with the intervention led to a lower probability of developing an infection.[69] It is difficult to translate these findings to our question. The population involved children with a limited range of burn size and no inhalation injury, and the intervention was somewhat unusual in that most providers run continuous albumin infusions over longer periods of time, rather than as daily 4-hour doses. Nonetheless, the administration of a single "early" dose of albumin appears to have had an important effect. A particularly intriguing observation is that the early albumin patients had less pulmonary edema, whereas in Goodwin et al.'s RCT in adults[19] (albumin vs. crystalloid alone, discussed in question 1), more lung water was observed in patients in the albumin arm, where albumin had been started within 12 hours of injury. A retrospective study in adults with burns >20% TBSA including those with inhalation injury, examined a protocol where a 1:1 mixture or 20% albumin and LR was started within the first 8 hours post burn, then reducing the albumin concentration as resuscitation proceeded.[68] This protocol reduced the 24-hour resuscitation volume to 2.58 ml/kg/%TBSA; much less than the expected Parkland value of 4 ml/kg/%TBSA burn, but there was no control group where albumin was administered later to serve as a comparator.

In situations where albumin is part of the resuscitation plan, (ie, not a rescue situation), we are uncertain on whether to start albumin before or after 12 hours to reduce the volume of administered fluid, improve urine output, or decrease edema. Given the uncertainty around this question, the uncertainty about the undesirable outcome of pulmonary edema related to early albumin provision[19] and the overall importance of timing, we recommend that initiation of albumin any time in the first 12 hours preferably be considered in the context of a research study.

Question 3: *Among adults with burns ≥20% TBSA, does starting acute fluid resuscitation with 2 mL/kg/%TBSA burn compared to starting with 4 mL/kg/%TBSA burn (a) reduce total fluid resuscitation volume or total crystalloid resuscitation volume at 24 or 48 hours post burn, (b) affect the development of acute kidney injury, or (c) reduce edema-related complications?*

Numerous studies over the 2000s and 2010s brought to light the clinical implications of over-resuscitation and the reality of the "fluid creep" phenomenon.[6,8] The totality of these findings guided the American Burn Association to change from a resuscitation starting at 4ml/kg/%TBSA burn to a 2ml/kg/%TBSA burn in 2011 (ABLS Course Manual). The existing practice guidelines for acute fluid resuscitation recommend initiating crystalloids at 2 to 4 mL/kg/%TBSA burn.[70] All of these studies are a remarkable demonstration of the power of thoughtful retrospective observation on the ability to improve patient care. What remains lacking in the field is strong prospective data for the starting rate of 2ml/kg/%TBSA versus. 4ml/kg/%TBSA.

For this PICO question, 2 studies with moderate-strength evidence met criteria for inclusion and review.[10,55] The first study was a retrospective analysis of the military's experience in 52 cases with initiating crystalloids based on 2ml/kg/%TBSA (Modified Brooke formula) compared to starting with 4 mL/kg/%TBSA burn (Parkland formula).[10] Albumin was recommended if at 12 hours, the total fluids were projected to exceed 6 mL/kg/%TBSA by 24 hours. The study had several limitations, largely related to the retrospective design, and conduct under austere battlefield conditions in Afghanistan. These include (1) insufficient data for 58 of 105 patients meeting the inclusion criteria of being evacuated from combat operations with burns >20% TBSA, (2) a potential selection bias in favor of the Modified Brooke formula, because there was a tendency to use it in patients with bigger and deeper burns and those with more frequent associated injuries, whereas the Parkland formula was used proportionally more in burns under 40% TBSA and less in burns over 40% TBSA, (3) a risk of a performance bias as the Modified Brooke formula originated in the military, (4) although albumin was used similarly in both groups, there is potential for confounding due to this cointervention because albumin may have exerted more benefit in the more severely injured Modified Brooke resuscitations. FFP was also used in both groups in the first 24 hours, (5) all but one patient was male, limiting the generalization of the findings, and (6) the outcome of abdominal compartment syndrome was defined by decompressive laparotomy, which in the absence of documented abdominal pressures or other diagnostic criteria, is to some extent is an operator-dependent measure. The second study is a multicenter RCT of 39 adult burn patients which directly compared starting resuscitation with 2 mL/kg/% TBSA burn (Modified Brooke Formula) to starting with 4 mL/kg/%TBSA burn ("Baxter formula").[55] The study precluded the use of albumin during the first 6 hours of resuscitation, but both groups did receive albumin and/or FFP during the first 48 hours with a slight tendency to have administered more FFP to the Modified Brook group in the first 24 hours. There was also a small but relevant difference in titration approaches. In both groups, fluids were titrated to achieve a UOP of 0.5 mL/kg/hour, but in the Baxter group, this was done every 2 hours according to "the treatment policy of the facility," whereas in the Modified Brooke group, this was by a protocol of incremental one-third increases or decreases in the infusion rate. The study's limitations were (1) a small sample due to early termination resulting from slow enrollment before reaching the planned N of 50 patients, (2) cointervention with albumin and FFP with more FFP given in the 2 mL/kg/%TBSA group, (3) a risk of performance bias, as titration approaches appeared to be different between groups, and (4) criteria for the outcome of ACS were not defined and included ACS as late as 28 days; ACS during the acute resuscitation would be more relevant.

As was the case in question 1, we did not specify mortality as an outcome for this PICO question. Again, this only reflects the limited scope of the available investigations to answer this question, and not the importance of that outcome. Neither of our 2 included studies found any difference in mortality

between starting resuscitation with 2mL/kg/%TBSA burn versus 4 mL/kg/%TBSA burn, but as noted, both studies were small and underpowered to reliably assess this outcome.

With respect to the outcome of resuscitation volumes, both studies demonstrated that the 2 mL/kg/%TBSA burn approach reduced total fluid resuscitation volumes at 24 hours post burn (Table 1). Only the Saitoh study[55] reported fluids at 48 hours and found no significant difference in resuscitation volumes (5.52 ± 2.08 in the 2 mL/kg/%TBSA group compared to 6.90 ± 2.37 mL/kg/%TBSA in the 4 mL/kg/%TBSA group, $P = .078$). It is important to recognize that both studies may have had risks of selection and/or performance biases in favor of limiting fluids while using the Modified Brooke approach. Both studies are also subject to the potential confounding influence of administering colloids in the first 24 hours.

With respect to the outcome of AKI, both studies present data to suggest no differences in incidence of acute kidney injury between the 2 approaches. Chung et al.[10] show rates of AKI on arrival to the US Army Burn Center after evacuation from the battlefield at 19% in the 2 mL/kg/%TBSA group compared to 10% for the 4 mL/kg/%TBSA group ($P = .33$). An explicit statement of AKI definition was not provided. Saitoh et al. utilized KDIGO guidelines and presented findings at 24 and 48 hours with no differences between 2 mL/kg/%TBSA and 4 mL/kg/%TBSA.[55] Of interest was that in a subanalysis of patients with burns >40% TBSA, UOP tended to lag in the Modified Brooke approach in the first 8 hours of resuscitation, but eventually picked up by 24-48 hours.

Finally, with respect to the outcome of edema complications, neither study found any clinically meaningful differences in measures such as oxygenation or development of ACS. The available data are limited, and the outcomes as described were somewhat unreliable, because data regarding IAP, limb compartment syndrome, and ocular complications are not provided.

We recommend that clinicians consider starting acute fluid resuscitation using 2 mL/kg/%TBSA burn to reduce the total volume of resuscitation fluids. An important consideration is that in both studies that informed this recommendation,[10,55] colloids were coadministered in some patients. We also emphasize that this recommendation suggests only the initial fluid rate, and that titration based on the patient's response must follow. We are unable to make any recommendation on use of 2 mL/kg/%TBSA burn to reduce edema-related complications and we suggest that more research is needed to assess the effect of this approach on the development of AKI.

Question 4: *Among adults with burns ≥20% TBSA, should fresh frozen plasma (FFP) be used during acute fluid resuscitation compared to using crystalloids alone to (a) reduce total fluid resuscitation volume or total crystalloid resuscitation volume at 24 or 48 hours post burn, (b) increase urine output, or (c) decrease edema-related complications?*

For this question, our search identified 2 studies[29,31] which met our inclusion criteria of comparing fresh frozen plasma (FFP) to crystalloid alone and examined at least one of our defined outcomes. One investigation[29] was a moderate-strength case-control study, and one study was a high-strength randomized-controlled study.[31] Of note, these 2 studies contained common authors from the same institution.

Decreased fluid requirements are the main proposed benefit of FFP. Although the retrospective Du et al, study[29] is 30 years old and at risk of selection and performance bias, significantly decreased total infusion volumes at 24 hours were observed in the FFP cohort when compared to the crystalloid cohort. There was no difference in urine output at 24 hours between groups. Body weight gain was the only edema-related measurement taken in the study, which was significantly lower in the FFP cohort. Average weight gain in the FFP patients was only 20% and 28% of that gained by the crystalloid patients on post burn days 1 and 2, respectively, indicative of much less edema in the colloid-treated patients. However, no other edema-related morbidity outcomes were reported. In addition, the authors report no observation of early or late pulmonary complications in the FFP cohort. However, 2 of the 10 patients died in the FFP cohort. These patients were described as having "severe smoke inhalation injury." Considering the potential safety issue regarding FFP and Transfusion Related Acute Lung Injury (TRALI) to be discussed at the end of this section, this observation is relevant. It is conceivable that any pulmonary dysfunction related to these 2 deaths could have been related to TRALI (which was an unrecognized entity 30 years ago) rather than, or in combination with inhalation injury.

The RCT by O'Mara et al.[31] was a small but appropriately powered study which demonstrated significantly less fluid administered in the first 24 hours with improved physiologic parameters such as decreased peak inspiratory pressure (PiP), decreased intra-abdominal pressure and improved correction of base deficit with use of FFP compared to crystalloid alone. Urine output was similar between groups and over the standard target of 0.5 mL/kg/hour. Also at 24 hours, FFP resuscitation was associated with a lower peak intra-abdominal pressure (IAP) of 16.4 ± 7.4 compared to the crystalloid cohort at 32.5 ± 9.5. Both groups took over 68 hours to reach their peak IAP. There are no outcomes reported that relay whether a decreased PiP was associated with improved ventilation or oxygenation, but almost certainly this was related to lower intra-abdominal pressures. Similar to the Du et al. study, decreased weight gain was observed in the FFP cohort. Thus, less fluid translated to relatively objective improvements in edema-related outcomes such as weight gain, intra-abdominal pressures, and peak airway pressures.

There are 2 potential safety issues related to using FFP for acute burn shock resuscitation. The first is TRALI which continues to be the leading cause of transfusion-related death.[71] The incidence of TRALI and delayed TRALI is variable, and these syndromes are likely under-reported, but these dose-dependent events may occur in up to 3% and 25%, respectively, of critically ill patients who receive blood products.[72,73] The risk of TRALI during acute burn resuscitation with FFP is unknown and we are aware of only one report describing this.[30] The use of male-only donors for plasma products and possibly the use of pathogen reduced plasma through solvent-detergent (SD plasma) preparation[74] may help to reduce the risk of TRALI. The ongoing Plasma ResuscitatiOn WithOut Lung Injury (PROpOLIs) study NCT 04681638 will address much of this uncertainty. The second safety issue is the

risk of disease transmission from blood-borne pathogens. Fortunately, newer pathogen-reduced preparations of human plasma may prevent transmission of HIV, hepatitis B and C but not hepatitis A or some encapsulated viruses, or prion diseases.[74]

We recommend that fresh frozen plasma (FFP) be used in acute burn shock resuscitation only in the context of a research study. Currently, there is insufficient evidence to make a recommendation for FFP to affect any of our stated outcomes, but we believe there is a large potential for reducing uncertainty about the desirable and undesirable effects of FFP through further research.

Question 5**:** *For adult patients with a ≥ 20% TBSA burn injury, does administration of high dose (66 mg/kg/hour) ascorbic acid (vitamin C), compared to not using high dose ascorbic acid, while providing crystalloids alone during acute fluid resuscitation (a) reduce total crystalloid resuscitation volume at 24 or 48 hours post burn, (b) increase urine output, or (c) decrease edema-related complications?*

For this question, our search identified four studies[36–38,56] which met our inclusion criteria of comparing high-dose vitamin C (HDVC) at 66 mg/kg/hour to crystalloids alone, with examination of at least one of our defined outcomes. Three investigations were case-controlled retrospective studies of moderate strength,[37,38,56] while one study provided stronger evidence in the form of a pseudo-randomized controlled trial.[36]

Sparing of resuscitation fluids is the main purported benefit of HDVC. The retrospective studies found either no difference[37] or a significant reduction in 24-hour fluid resuscitation volumes.[38,56] Unfortunately, all 3 studies were confounded by the coadministration of colloids, without adequate description of whether this was controlled or similar between groups. The addition of colloids could have a significant effect on resuscitation fluid volume. In contrast, the study by Tanaka et al.[36] did show a significant reduction in 24-hour fluid volumes. While this study is weakened by a small sample size and risk of performance bias in fluid administration and titration between study arms due to its open-label and pseudo-randomized design, it provides the strongest evidence we have that HDVC has a fluid-sparing effect. It provides human validation of observations from preclinical animal studies.

It was recognized from preclinical studies that HDVC has a potent diuretic effect. All 4 of our included studies[36–38,56] reported increased urinary output when HDVC was administered (Table 1). One study which we did not include, because the comparator was a lower dose of ascorbic acid and not crystalloid alone[39] found a dose-dependent increase in UOP when higher doses (66 mg/kg/hour) of ascorbic acid were administered. The diuresis produced by HDVC has 2 consequences. The first is distortion of the hourly UOP as a titration endpoint. The second is the potential for dehydration due to the osmotic diuresis. Kahn et al. commented that several patients receiving HDVC had elevated hematocrits and signs of hypovolemia without decreased UOP in some cases, possibly a sign of dehydration from osmotic diuresis. These patients received additional FFP.[38] Patients in both the crystalloid and vitamin C arms in 2 of our included studies received 25% albumin[37] or "colloid"[56] potentially to counteract hypovolemia. A study of high-dose vitamin C (continuous infusion of 66 mg/kg/hour over 24 hours) versus low-dose vitamin C (single 3.5 gm infusion) allowed for "colloid" administration if resuscitation targets could not be met with fluid alone and had planned to stop the vitamin C infusion for hypotension or tachycardia as part of the protocol. (While no ascorbic acid infusions were stopped, the use of this safety feature raises the question of whether the investigators were anticipating hypovolemia effects related to the vitamin C infusion).[39]

Among our included studies, there were no differences in clinical outcomes with the use of HDVC compared to crystalloid alone (Table 1), except in the RCT by Tanaka et al.[36] That study demonstrated that the HDVC patients had less acute weight gain, less measured soft tissue edema, and possibly less pulmonary edema as measured by the surrogate markers of PaO_2/FiO_2 ratio over the first 96 hours and duration of mechanical ventilation.[36] Lin et al. observed the opposite: median ventilator days actually tended to be higher in the HDVC-treated patients than in controls (11 vs. 5 days, $P = .07$).[37]

Recently, a safety concern has been raised with respect to administration of HDVC. Oxaluria and deposition of calcium oxalate crystals in the renal tubules leading to nephropathy have been observed in both non-burn[75] and burn patients[40] receiving very high doses of ascorbic acid. Among our included studies, Lin et al. reported more frequent renal failure requiring dialysis in HDVC-treated patients compared to controls (23% vs. 7%, $P = .06$) with an independent association between HDVC with development of acute renal failure requiring dialysis (OR 5.4 95%CI, 1.1-26).[37] While not specified, it appears the dialysis occurred at any time during the hospitalization period, rather than during the resuscitation phase. Flores et al. reported no differences in AKI (KDIGO criteria) during the resuscitation phase.[56] Kahn et al. also reported no differences in renal function, but a definition or criteria for the diagnosis of AKI were not provided.[38] A retrospective study on early AKI following major burns identified an association with HDVC use during resuscitation (OR 5.5, 95% CI, 1.2-25.1).[41]

Finally, questions persist surrounding the dose of HDVC. While all our included studies provided 66 mg/kg/hour of ascorbic acid, only one study reported the total administered dose (170 gm).[56] Click or tap here to enter text. Of interest, Nagal et al.[39] observed that the use of HDVC (66 mg/kg/hour) compared to a 3.5 gm/day IV infusion produced significantly more diuresis (1.2 vs. 0.8 mL/kg/hour) but found no statistically significant or clinically relevant differences in 24-hour crystalloids, 24-hour or 24-72 hours total fluids, development of AKI or use of RRT, length of stay or mortality. A Japanese national database sample[76] compared patients who received either ≥10 gm ($n = 157$, median dose 50 gm) or ≥24 gm ($n = 127$, median dose 63 gm) of ascorbic acid in the first 48 hours with propensity score matched controls ($n = 628$ and $n = 508$, respectively). There were no differences in administered fluids or survival using the 24 gm threshold, but at the 10 gm threshold, the vitamin C patients received significantly more fluid at 24 and 72 hours, but paradoxically had significantly lower in-hospital mortality. Overall, it is not clear whether there is an optimal dose for vitamin C and whether such a dose might confer improvements in outcome. While not a study specifically on acute fluid resuscitation in

the first 48 hours, further understanding regarding dose and outcome may arise from the ongoing vitamin C in thermal injury (VICToRY) pilot trial (NCT04138394) which compares the effect of 200 mg IV ascorbic acid/kg/day for 96 hours to placebo, on the composite outcome of persistent organ dysfunction and all-cause mortality.

We are unable to form any recommendation for high-dose vitamin C (66 mg/kg/hour) to reduce total crystalloid resuscitation volumes, increase urine output, or decrease edema-related complications. While it appears that high-dose vitamin C promotes diuresis and may reduce resuscitation volumes, this is closely balanced by the trade-offs of distortion of urine output as a titration endpoint, possible dehydration from osmotic diuresis, uncertainty about dose, and the unknown risk of oxalate nephropathy.

Question 6: *Among adults with burns ≥20% TBSA, during acute fluid resuscitation should (a) CVP, (b) transpulmonary thermodilution (TPTD), or (c) stroke volume variation (SVV) or pulse pressure variation (PPV) from arterial waveform analysis be used to titrate resuscitation fluids, compared to using hourly urine output either alone or in conjunction with "conventional" endpoints such as heart rate, blood pressure, serum lactate, and arterial base deficit, to (a) reduce total fluid resuscitation volume or total crystalloid resuscitation volume at 24 or 48 hours post burn or (b) decrease edema-related complications?*

Fluid resuscitation in critical care has been augmented over the years with technology providing more insight into minute-to-minute patient physiology. For this question, we considered invasive or semi-invasive resuscitation monitoring adjuncts compared to either urine output alone (the gold standard for burn resuscitation) or urine output in conjunction with other more routinely available adjuncts. Six studies were identified that met inclusion criteria (Tables 1 and 2). Three were reported as randomized control studies,[59–61] all with high strength, while the other 3 were low to moderate strength case-control studies.[57,58,62]

Holm and colleagues compared use of the traditional Baxter formula (4 mL/kg/%TBSA) against transpulmonary thermodilution (double indicator, thermal, and dye).[61] They targeted intrathoracic blood volume index (ITBVI) cardiac index (CI) and extra-vascular lung water index (EVLWI). Control patient management was modified by use of central venous pressure and mean arterial pressure in addition to urine output. While fluid administration volumes were significantly higher in the invasive monitoring group, there were no differences in mechanical ventilation, acute renal failure, or multiple organ failure. No pulmonary edema was noted in either group. Two patients had catheter-related complications.

Foldi et al., in 2 high-strength studies,[59,60] evaluated intrathoracic blood volume index (ITBVI) obtained by TPTD versus hourly urine output. They also identified that more fluid was given in the invasive monitoring group (5.5 mL/kg %TBSA vs. 4.3 mL/kg/%TBSA) in the first 24 hours, but that when the resuscitation goal objective of ScvO2 of >70% was utilized as the endpoint of resuscitation, the same amount of fluid volume was required in both groups (6.1 mL/kg/%TBSA vs. 6.3 mL/kg/%TBSA). Interestingly, the time to achieving complete resuscitation was different between groups, 35 hours in the HUO group vs 28 hours in the ITBVI group. The multiorgan dysfunction score was significantly lower in the second 24 hours after presentation in the ITBVI group, but after 1 week, this difference appeared to resolve, and overall multiple organ failure during the stay was the same in both groups. Mortality, duration of mechanical ventilation, and incidence of sepsis were not different between groups, and neither group had any incidence of intra-abdominal compartment syndrome.

Retrospective data review by Zhu et al.[62] evaluated the utilization of Pulse index Continuous Cardiac Output (PiCCO) analysis. The study was rated at low-strength due to risks of performance bias, intervention contamination, and cointerventions. The control group was managed using standard fluid resuscitation and conventional monitoring, while the study group had additional data available from the PiCCO system. While overall resuscitation volumes were significantly different between the groups, this was driven by differences in colloid administration; crystalloid volumes were the same at both the 24 hours (1 mL/kg/%TBSA, a third lower than the stated Third Military Medical University, TMMU formula) and 48-hour mark (0.75 mL/kg/%TBSA, on target for the stated TMMU formula). They did identify that ARDS incidence was worse in the control group, and multivariate analysis suggested that PiCCO monitoring might decrease the incidence. In addition, length of stay was shorter in the monitored group, which they suggested was an outcome potentially related to fluid overload.

Chen and colleagues[58] used PiCCO to assess global end diastolic volume index (GEDVI), EVLWI, and systemic vascular resistance index (SVRI) in patients with massive burns (80% TBSA or greater). This study was also rated as low-strength evidence due to risks of selection and performance bias. Mean fluid volumes were lower when PiCCO was used (3.3 mL/kg/%TBSA vs. 3.7 mL/kg/%TBSA). They identified improvement in markers of oxygen delivery and improved gas exchange in the lung with the use of PiCCO, but no difference in renal end organ perfusion as measured by urine output. They were unable to comment on mortality differences and did not comment on local limb perfusion issues.

Aboelatta[57] looked at a cohort of patients using transpulmonary thermodilution (PiCCO) versus a modified Parkland formula of 3 mL/kg/TBSA and urine output with CVP. They definitively demonstrated higher fluid administration in the first 24 hours using PiCCO rather than conventional markers (5.4 mL/kg/%TBSA vs. 4.6 mL/kg/%TBSA), with higher UOP values (2.25-3.6 mL/kg/hour vs. 1.1-1.8 mL/kg/hour). Resuscitation in the PiCCO arm was stopped early given significant tissue edema; pulmonary edema and compartment syndrome occurrence were not recorded.

Overall, the data from the higher strength RCTs[59–61] and one moderate strength retrospective study[57] suggest equivalent to higher fluid resuscitation volumes with an invasive monitoring device-driven resuscitation. Edema complications were not significantly impacted by the use of a monitoring device. However, it is possible that by adjusting the physiologic target of the resuscitation[59,60] the duration of burn shock resuscitation might be shortened.

We do not recommend the use of transpulmonary thermodilution-derived variables (eg, ITBVI, GEDVI, CI, or EVLWI) to reduce total resuscitation fluid

volumes or decrease edema-related complications. Due to a paucity of evidence, we were unable to make any recommendation regarding use of SVV or PPV on either of these outcomes.

Question 7*: Among adults with burns ≥20% TBSA, should computerized decision support software (CDSS) compared to using hourly urine output alone be used to titrate acute resuscitation fluids to (a) reduce total fluid resuscitation volume or total crystalloid resuscitation volume at 24 or 48 hours post burn and (b) decrease edema-related complications?*

For this question, we found a single high-strength study[63] that met the inclusion criteria of comparing use of CDSS to not using CDSS. This study describes the validation of a computerized decision software system (CDSS) developed at the US Army Institute of Surgical Research (USAISR) and the University of Texas Medical Branch (UTMB). The CDSS was originally designed for combat casualties, with the anticipation that non-burn experienced providers would provide initial burn stabilization close to the point of injury and continue through transport to a definitive care facility. The bedside provider inputs the patient's weight, TBSA burn extent, time since injury, and fluids that had been administered prior to CDSS initiation. The provider then sets the initial fluid rate (based on available resuscitation formulae) as well as the urine output goal for each individual resuscitation. Every hour, the CDSS prompts manual input of urine output (UOP) for the last hour by the bedside clinician (most commonly a nurse). Using linear regression of UOP trend over the previous 3 hours, the CDSS provides the clinical team a recommendation for crystalloid rate over the next hour. This strategy is termed decision-support as the bedside clinician is free to accept or modify the fluid rate until check-in at the next hour. The CDSS also only makes a recommendation on crystalloid infusion rate, even though the provider can log data for all fluid types and routes administered (crystalloid, colloid, intravenous, enteral). Following its initial development, CDSS technology is now provided using an FDA-approved device used in many US burn centers under the trade name Burn Navigator.

Salinas and colleagues retrospectively evaluated the utility of CDSS in 32 adults with burns ≥ 20% undergoing acute fluid resuscitation with at least 24 hours of CDSS recommendations in the first 48 hours post burn at a single center compared to 38 historical control patients resuscitated through traditional/manual hourly urine output recording.[63] For the outcome of fluid resuscitation volumes, CDSS resuscitation resulted in 24-hour total resuscitation volume of 4.2 mL/kg/%TBSA burn which was significantly lower compared to 6.5 mL/kg/%TBSA burn for patients resuscitated by the traditional method. Notably, UOPs for CDSS patients were significantly more frequently within the set target UOP goals over the first 48 hours (31% vs. 23% of the time, respectively), highlighting the utility of CDSS in reducing hourly variations in fluid rates thanks to a "tighter" titration. Notwithstanding the risk of bias in this retrospective study that used historical controls, this is the only and strongest evidence available comparing CDSS to "usual titration" not using CDSS. Another limitation is that while at least 24 hours of recommendations were needed to be included in the intervention group, it is not clear how often the recommendations were followed. The discussion mentions that UOP rates within target were up to 20% higher "when providers followed the system recommendation."

Most recently, CDSS was evaluated in 5 burn US centers, combining retrospective data and prospectively obtained observational data.[77,78] This study was not included for critical review because no comparisons to not using CDSS were made. Across all 285 patients, clinicians agreed with the computer's recommended infusion rate, within ± 20 mL/hour, 72% of the time, but this ranged between 54% and 96% between centers. The mean 24-hour crystalloid volumes ranged across centers from 3.1 mL/kg/%TBSA burn to 4.5 mL/kg/%TBSA burn, while total administered 24-hour volume ranged from 3.5 to 5.3 mL/kg/%TBSA burn. This is lower than the average resuscitation volume of 5.2 mL/kg/%TBSA burn identified in a quantitative review of fluid resuscitation involving 3196 patients from 48 studies published over the past 30 years.[79] A total of 146 of the 285 patients followed the CDSS recommendations (defined as administering a fluid rate within ± 20 mL/h of the recommended rate, 83% of the time in the first 24 hours, ie, in 20 of the first 24 hourly decisions). In those that followed CDSS, the 24-hour crystalloid volume was 4 ± 1.6 mL/kg/%TBSA burn, and not significantly lower that the 4.1 ± 1.9 mL/kg/%TBSA burn administered to non-followers.[77] The interpretation of all fluid volumes, while using CDSS, should also consider that colloids were administered to some patients. While these were included in the reported total resuscitation volume, colloids may have a fluid sparing effect (see questions 1 and 4), and this potentially confounds the effect of CDSS titration on resuscitation volumes.

None of the existing studies has specifically or reliably evaluated edema-related outcomes. Salinas' 2011 study[63] reported secondary clinical outcomes, including an increased in number of ICU-free days, ventilator-free days, and lower mortality (29% vs. 44%, $P < .05$) with CDSS strategy. Given the mechanistic link between total fluid administration and edema formation, CDSS *may possibly* reduce edema-related complications, but this hypothesis remains to be proven, and no definitive conclusions on clinical outcomes can be made from the Salinas study.

The CDSS prospective observational trial recorded decompression procedures performed for both prophylactic and therapeutic purposes and found no differences in limb, abdominal, or orbital compartment syndromes between those that did or did not follow CDSS recommendations.[77,78]

We make a weak recommendation for clinicians to consider the use of CDSS to reduce total resuscitation fluid volumes, but we are unable to make any recommendation on use of CDSS to reduce edema-related complications. The panel was concerned about the potential for loss of frequent bedside clinical patient assessment and critical decision making by clinicians using CDSS. The benefit of CDSS probably, but not certainly, outweighs this undesirable effect.

Question 8**:** *Among adult patients with ≥20% TBSA burn injury undergoing acute fluid resuscitation who require a vasopressor for hypotension, should norepinephrine or vasopressin be the first administered vasopressor to (a) reduce 28-day mortality and (b) reduce acute kidney injury?*

For this question, our search did not find any studies which met our inclusion criteria of comparing norepinephrine and

vasopressin with the defined outcomes of lower 28-day mortality and a lower incidence of acute kidney injury.

Despite appropriate resuscitative volume administration, refractory vasoplegia can persist from systemic inflammation secondary to a severe (≥20% TBSA) burn injury causing hypotension.[80] In order to avoid the consequences of over-resuscitation, vasoactive agents are administered to optimize blood pressure. In an animal burn injury model, splanchnic blood vessels showed increased responsiveness to vasopressin compared to phenylephrine in the first 24 hours following burn injury.[81] During Operation Iraqi Freedom, the US military developed a resuscitative guideline in burn-injured military personnel undergoing resuscitation for burn shock to avoid consequences of over-resuscitation. In situations when the mean arterial pressure is ≤55 mm Hg, and urine output is inadequate, vasopressin (0.04 units/min) infusion is the first vasoactive agent initiated. If hypotension and inadequate urine output persists despite a central venous pressure of 8-10 mm Hg, then norepinephrine is added as a second agent.[82] In contrast, an international survey of intensivists, 80% of those surveyed would use norepinephrine, as the primary vasoactive agent during burn shock resuscitation.[83] A recent systemic review of the use of vasoactive agents during initial burn resuscitation found only 2 studies that addressed the potential harm and benefit of vasoactive agents during burn resuscitation.[84] One study is a retrospective review of 16 patients who received vasopressors. Norepinephrine was the first agent used in 15 of the patients, and phenylephrine was used first in one patient.[43] The other study is an abstract of a retrospective review of 20 patients in which vasopressors were administered during resuscitation. The vasopressor was not identified in the study.[84] In both reviews, older age was associated with initiation of vasopressors.

In the non-burn literature, there are studies comparing the efficacy and benefits of norepinephrine and vasopressin during resuscitation and shock. A double-blinded prospective randomized study of trauma patients undergoing resuscitation randomized adult patients to either placebo or vasopressin infusion. Vasopressin or placebo was initiated if the patient had a systolic blood pressure ≤90mm Hg. The patients in the vasopressin group required significantly less volume of fluid during the first 120 hours after admission.[85] A multicenter double-blind randomized control study compared 28-day mortality in patients with septic shock who treated with either vasopressin or norepinephrine. In this study of 778 patients, overall, there was no difference in 28-day mortality between the vasopressin (35.4%) and norepinephrine group (39.3%). There was a significant reduction in mortality in the less severe septic shock group for patients treated with vasopressin (26.5%) compared with those treated with norepinephrine (35.7%).[86] Another study of patients with septic shock randomized to either vasopressin or norepinephrine also showed no difference in mortality. However, surviving patients treated with vasopressin had significantly lower cytokine levels in the first 24 hours after infusion compared to the norepinephrine group.[87]

For the outcome of renal failure incidence, a multicenter randomized blinded study of 778 patients compared the incidence of acute kidney injury (28 day) during septic shock between patients treated with vasopressin versus patients treated with norepinephrine. The Risk Injury Failure Loss End Stage (RIFLE) criteria were used as the outcome measure. For patients in the Risk category, there was a lower incidence of progression to failure or loss for patients treated with vasopressin. Also, in the risk category, compared to the norepinephrine group, serum creatinine lowered over the study period in the vasopressin-treated patient. For the other RIFLE categories, there were no differences in progression to failure or loss or differences in serum creatinine.[88] Another large multicenter double-blind randomized study compared kidney failure-free days between patients with septic shock treated with vasopressin or vasopressin and hydrocortisone with patients treated with norepinephrine or norepinephrine and hydrocortisone. Kidney failure was defined as Acute Kidney Injury Network Stage 3. The study found that was no difference in kidney-free days between any of the groups; however, there were fewer patients requiring renal replacement therapy in the vasopressin groups.[89]

Due to the paucity of data about the benefit and risk of norepinephrine versus vasopressin, we cannot make a recommendation of which vasopressor to use during burn resuscitation.

Due to a complete absence of evidence, the panel is unable to form any recommendation on whether to start norepinephrine or vasopressin if a vasopressor is required.

Question 9*: Among adults with burns ≥20% TBSA, during acute fluid resuscitation, should early continuous renal replacement therapy (CRRT) without fluid removal be initiated, compared to not initiating CRRT to (a) reduce total fluid resuscitation volume or total crystalloid resuscitation volume at 24 and 48 hours post burn and (b) decrease edema-related complications?*

We did not identify any studies that compared early CRRT to not using early CRRT as an adjunct during acute burn shock resuscitation. Continuous venovenous hemofiltration (CVVH) allows for clearance by diffusion of solutes across the column's membrane. In this way, a convection process allows for removal of molecules based on the characteristics of the membrane. In most cases, this allows removal of water-soluble middle molecular weight proteins (5-50 kDa) such as cytokines.[90] A burn is known to have a profound inflammatory process mediated in part by a damage-associated molecular patterns (DAMPs) and pathogen-associated molecular patterns (PAMPs) and the resultant cytokine storm. Treatment methods to remove these mediators are promising conceptual approaches in the care of severely burned patients. In addition, the rate or "dose" of convection can be increased or decreased to the desired effect. Typical levels will approximate 20 mL/kg/hour, high-volume hemofiltration (HVHF) is typically described around 70-90 mL/kg/hour.[90] These approaches have been advocated in alternative inflammation-based disease processes such as ARDS, pancreatitis, and sepsis. The literature in these diseases does suggest a mortality benefit with HVHF (RR = 0.88, 95%CI, 0.81-0.95) The secondary outcomes suggest decreased level of plasma cytokines, with higher mean arterial pressures and decrease heart rates in the HVHF groups.[91] Data for CRRT-HVHF are more limited in burn care. We benefit from the work of the Randomized controlled Evaluation of High-Volume hemofiltration in adult burn patients with Septic shock and acUte kidney injury (RESCUE) investigators for their work on the use of

CVVH-HVHF.[44,92] The authors present promising results with HVHF decreasing vasopressor dependency index at 48 hours comparted to baseline, and a decreased multiple organs dysfunction syndrome score at 14 days. A limitation for the applicability of this study is all patients were past the first 48 hours of resuscitation, as such no statement to fluids needed or edema-related complications were presented. Additional work from the RESCUE Investigators provide further evidence for the safety of renal replacement therapy in burn[44] and suggest that CVVH as a preferred mode of therapy conveys a survival benefit for patients requiring vasopressors.

Despite the growing literature for the use of CVVH in burn injury, for this question, no articles were identified which met criteria for inclusion and review.

We are unable to form any recommendation regarding the use of early CRRT during acute burn shock resuscitation to reduce total resuscitation fluid volumes or decrease edema-related complications.

Question 10: *Among adults with burns ≥20% TBSA, should (a) intra-abdominal pressure(IAP), (b) Intra-ocular pressure (IOP), (c) serum lactate (L), or (d) arterial base deficit be monitored during the first 48 hours post-burn compared to not monitoring IAP, IOP, L, and BD, to (a) reduce total fluid resuscitation volume or total crystalloid resuscitation volume at 24 or 48 hours post burn or (b) reduce the incidence of abdominal compartment syndrome or (c) orbital compartment syndrome?*

We did not identify any studies that specifically compared routine monitoring of intra-abdominal or IOPs or serum lactate or arterial base deficit to not monitoring these parameters, in order to reduce burn resuscitation fluid volumes or the incidence of abdominal or orbital compartment syndromes.

High-volume crystalloid resuscitation of major burns may result in complications including intra-abdominal, orbital, and extremity compartment syndromes. Patients most at risk for these complications, of which abdominal compartment syndrome (ACS) is the most widely reported, generally have had aggressive fluid resuscitation. Suggested markers of high-volume fluid resuscitation requiring vigilance include the Ivy Index (250 mL/kg over 24 hours)[92] or the "runaway resuscitation" (6 mL/kg/TBSA over 24 hours).[93]

The optimal frequency of measuring either abdominal or ocular pressure is not defined. Diagnosis of ACS is aided by the finding of intra-abdominal pressure (IAP) greater than 20 mmHg with end-organ failure, measured by transducing urinary bladder pressure through an indwelling Foley catheter or with commercially available products.[94] The Abdominal Compartment Society (formerly the World Society of the Abdominal Compartment Syndrome, www.WSACS.com)[95] has developed an algorithm that recommends measuring abdominal pressures by urinary bladder pressure transduction every 4 to 6 hours in patients with IAP >12 mmHg, and at least every 4 hours in patients with an intra-abdominal pressure of >20 mmHg without new end organ dysfunction (www.WSACS.com).[96] There are no data specific to burn resuscitation, however, to recommend this frequency or to demonstrate the role of routine measurement in preventing abdominal compartment syndrome or in influencing the volume of resuscitation.

Diagnosis of orbital compartment syndrome, while often made clinically, can be augmented by use of ocular pressure monitoring. Normal IOP is less than 20 mmHg. Sullivan et al.[96] measured IOPs and found that major burn patients undergoing bilateral lateral canthotomy had maximal IOPs ranging from 54 to 90 mmHg while those who did not undergo canthotomy largely had peak IOPs of 23.5 mmHg or less. One recent retrospective analysis recommended monitoring IOP in a variety of scenarios: presence of deep periorbital burns, cumulative 24-hour fluids of 200 mL/kg, or presence of proptosis.[97] Another study identified large surface area burns, reaching the Ivy Index, and severe facial burns as potential risk factors for orbital compartment syndrome.[98] The optimal timing of IOP measurement and its role in preventing orbital compartment syndrome, however, remain unclear.

While hyperlactatemia during acute burn shock elevation confers a poor prognosis,[99,100] the use of the serum lactate level as a titratable endpoint during burn resuscitation is not well understood. Studies which have shown that resuscitation directed at improving the cardiac index is correlated with a decline in the serum lactate[101] lead us to infer that the opposite approach of resuscitating to lower the serum lactate would be associated with improving hemodynamic parameters. However, definition of the optimal use, timing, and frequency of lactate measurements during resuscitation remains elusive. Typically, lactate levels are used in combination with other endpoints like MAP and UOP, and we were unable to find any studies which specifically evaluated lactate as an endpoint compared to not using it. We encountered a similar problem with evaluating the arterial base deficit (BD) as a titration endpoint to affect any of our specified outcomes. Like the serum lactate level, persistent elevation of the BD during burn shock resuscitation is associated with worse outcomes.[99,102,103] The BD is a global but non-specific marker of acidemia, and it may not correlate with the serum lactate.[104] Once again, we found no studies that evaluated the BD compared to not using it during acute burn shock resuscitation.

We recommend selective monitoring of IAP and IOP but not routine monitoring in every resuscitation. For IAP monitoring, selective situations would include patients with massive burns, actual or projected 24-hour fluid volumes approaching 6 mL/kg/% TBSA burn or 250 mL/kg, or clinical evidence of evolving ACS. Some clinicians may wish to follow the WSACS guidelines as described earlier. For IOP monitoring, selective situations would include actual or projected 24-hour fluid volumes approaching 6 mL/kg/% TBSA burn or 250 mL/kg, presence of deep extensive periorbital burns regardless of the total burn size or fluid volume administered, or proptosis. The panel was unable to make a recommendation on routine serial measurement of the serum lactate (L) and arterial base deficit (BD) in all acute burn resuscitations to affect any of our defined outcomes. Serial monitoring of L and BD should be used selectively by clinicians.

OPPORTUNITIES FOR FURTHER RESEARCH

The investigator panel noted and was dismayed that many studies on acute fluid resuscitation lacked basic and relevant information on parameters such as full thickness burn size, presence of inhalation injury confirmed by bronchoscopy, pre-burn center fluid volumes, indexing of total resuscitation volumes at

24 and 48 hours based on mL/kg/% TBSA burn and mL/kg, reporting of 24 and 48-hour fluid volumes as total fluid, crystalloid component and colloid component, and urinary output indexed to mL/kg/h. The panel strongly recommends that these fundamental parameters be collected and reported in any future studies of acute fluid resuscitation. A few key areas were identified for further research in burn shock resuscitation (BSR):

- Studies on the use of FFP, and pathogen-reduced plasma, with direct comparison to human albumin solution in order to identify an optimal colloid for BSR. Unresolved safety issues must be examined related to colloid introduction during BSR including pulmonary edema and TRALI.
- Studies on the ideal timing of colloid introduction.
- Further studies on the utility, safety, and dose of high-dose Vitamin C during BSR. Unresolved questions on the issues of volume depletion related to osmotic diuresis, and risk of development of AKI must be addressed.
- Studies on optimal resuscitation strategies in specialized burn populations such as the obese, children, and the elderly.
- Studies to better define "failed" or "runaway" resuscitations.
- Studies to examine what role early CRRT might have during BSR.
- Studies to examine the use of PPV and SVV as "titratable endpoints" during BSR.

QUALITY AND PERFORMANCE MEASURES

An important additional goal of developing this CPG is to identify and suggest potential measures of quality and performance related to provision of BSR by burn centers. We base these recommended quality measures on our confidence in the available literature on BSR, as it relates to our selected clinical PICO questions. We emphasize that these recommended quality measures do not define standards or benchmarks that must be achieved to obtain reimbursement. Rather, they are intended for burn care programs to assess and improve their performance in the provision of BSR:

- The total fluid volume administered at 24 and 48 hours, indexed in mL/kg/%TBSA burn and mL/kg.
- Total fluid volume administered at 24 and 48 hours shown as crystalloid and colloid, also indexed as mL/kg/% TBSA burn.
- Average urinary output in the first 24 hours in mL/kg/hour
- Development of AKI in first 48 hours, using a unified definition, to be determined.
- Development of abdominal compartment syndrome, orbital compartment syndrome, and limb compartment syndrome in the first 48 hours, using unified definitions for each, to be determined.

SUPPLEMENTARY DATA

Supplementary data is available at *Journal of Burn Care & Research* online.

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