Section: Anaesthesiology

Systematic Review and Evidence Synthesis

FLUID RESUSCITATION IN MAJOR BURN INJURY: A SYSTEMATIC REVIEW AND EVIDENCE SYNTHESIS

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ABSTRACT

Background: Acute burn shock requires timely intravenous fluid resuscitation, but excessive fluid causes edema-related complications and organ dysfunction. Considerable uncertainty remains regarding the best starting formula, the role and timing of albumin, fresh frozen plasma, high-dose vitamin C, advanced monitoring, and computerized decision support.
Objective: To synthesize clinical evidence on fluid-management strategies used during the first 24-48 hours after major burn injury and to identify approaches supported by the most consistent evidence.
Materials and Methods: This structured systematic evidence synthesis followed PRISMA 2020 and SWiM reporting principles. The evidence base was anchored to the systematic search and screening undertaken for the 2024 American Burn Association burn-shock guideline, which searched Ovid MEDLINE, Embase, Cochrane databases, and CINAHL from database inception to 17 May 2022. Twenty-four studies met the guideline's strict adult PICO criteria. Sixteen additional clinical studies were identified from the guideline reference set and closely related citation chains to broaden coverage of pediatric resuscitation, vitamin C safety, fluid creep, renal outcomes, plasma-based rescue, and computerized decision support. These supplementary studies were analyzed separately from the strict PICO set. Forty studies were synthesized narratively; no meta-analysis was performed because populations, interventions, outcome definitions, and reporting units were too heterogeneous.
Results: Evidence favored a conservative initial crystalloid estimate followed by frequent physiological titration rather than rigid formula delivery. Albumin and other colloid-rescue strategies often reduced crystalloid escalation or improved input-output balance, but most evidence was observational and vulnerable to confounding by indication. A starting estimate near 2 mL/kg/%TBSA generally reduced early fluid exposure compared with 4 mL/kg/%TBSA without a consistent signal of increased early acute kidney injury. Evidence for fresh frozen plasma was limited. High-dose vitamin C sometimes reduced crystalloid volume, but patient-centered benefit remained uncertain and renal safety concerns included oxalate nephropathy. Advanced hemodynamic monitoring produced inconsistent clinical benefit, whereas computerized decision support improved titration consistency in nonrandomized studies. Higher cumulative fluid exposure was repeatedly associated with intra-abdominal hypertension, compartment syndrome, infection, and other edema-related complications.
Conclusion: For adults with major burns, the most defensible current approach is to begin with a conservative crystalloid estimate near 2 mL/kg/%TBSA, reassess frequently, and titrate to the overall physiological response rather than urine output alone. Albumin may be considered selectively when crystalloid requirements continue to rise, particularly in

larger burns, but its optimal timing is uncertain. Fresh frozen plasma, high-dose vitamin C, vasopressors, and early renal replacement therapy should not be used routinely without a defined specialist protocol or stronger comparative evidence. These conclusions are based mainly on heterogeneous and frequently nonrandomized evidence and should therefore be interpreted cautiously.
Keywords: burn injury; burn shock; fluid resuscitation; albumin; crystalloid; Modified Brooke formula; Parkland formula; vitamin C; fluid creep; systematic review.

INTRODUCTION

Burn injury remains a major cause of preventable morbidity, prolonged hospitalization, disability, and death worldwide.[1] When a burn involves approximately 20% or more of total body surface area (TBSA), inflammatory mediator release, endothelial injury, and increased microvascular permeability produce rapid intravascular volume loss and extensive tissue edema. The resulting burn shock is characterized by reduced circulating volume, depressed cardiac output, increased systemic vascular resistance, and impaired organ perfusion.[2,3]

Intravenous fluid resuscitation is therefore essential during the first 24-48 hours. Its purpose is not simply to deliver a calculated volume, but to restore perfusion while avoiding avoidable edema and organ injury. Traditional formulas, including the Parkland/Baxter and Modified Brooke formulas, estimate an initial crystalloid requirement according to body weight and burned TBSA. However, the calculated value is only a starting point. Hourly titration according to urine output, blood pressure, clinical perfusion, lactate, base deficit, and the overall trajectory of the patient remains necessary.[4,5]

The central challenge is the narrow therapeutic balance between under-resuscitation and over-resuscitation. Inadequate fluid delivery may worsen shock, acute kidney injury, tissue ischemia, and multiple-organ dysfunction. Conversely, excessive administration can produce fluid creep, pulmonary edema, extremity and orbital compartment syndromes, abdominal hypertension, abdominal compartment syndrome, prolonged ventilation, and delayed recovery.[5,9]

Clinical practice has consequently shifted toward lower starting volumes, active fluid titration, selective use of albumin, and earlier recognition of patients whose escalating crystalloid requirements indicate failure of formula-only management. Nevertheless, important questions remain regarding the timing of albumin, use of fresh frozen plasma, high-dose vitamin C, advanced hemodynamic monitoring, computerized decision support, vasopressors, and renal replacement therapy. This review synthesizes 40 clinical studies to provide a broad but methodologically cautious overview of contemporary burn fluid management.

MATERIALS AND METHODS

2.1 Review design and reporting framework

This article was prepared as a structured systematic evidence synthesis using PRISMA 2020 reporting principles,[6] and narrative-synthesis methods recommended by the Cochrane Handbook and SWiM guidance.[7,8] It was not a new de novo database review. Instead, it was anchored to the completed systematic search and screening undertaken for the 2024 American Burn Association (ABA) guideline and then expanded through citation-based identification of clinically relevant supplementary studies. Because study design, patient age, burn severity, intervention protocol, comparator, reporting unit, and outcome definition varied substantially, quantitative pooling was not considered methodologically defensible.

2.2 Search basis and study identification

The primary search basis was the comprehensive literature search performed for the ABA Clinical Practice Guidelines on Burn Shock Resuscitation.[5] That search covered Ovid MEDLINE, Ovid Embase, the Cochrane Central Register of Controlled Trials, the Cochrane Database of Systematic Reviews, and CINAHL from database inception through 17 May 2022. English-language human studies were screened independently in the source guideline, with duplicate removal, title-and-abstract screening, and full-text eligibility assessment. The present article did not repeat the database search or claim independent reproduction of the 9,326-record screening process.

The source guideline identified 9,326 records, removed 3,348 duplicates, screened 5,978 titles and abstracts, assessed 70 reports in full text, and retained 24 studies that met its strict adult PICO criteria. For this broader evidence synthesis, 16 additional clinical studies were selected from the guideline reference set and closely related citation chains because they addressed pediatric resuscitation, vitamin C safety, fluid creep, compartment syndromes, renal outcomes, plasma-based rescue, or computerized decision support. The final evidence map therefore contained 40 studies: 24 strict adult PICO studies and 16 supplementary studies. The supplementary studies were not presented as products of a new independent database search, and no claim of complete literature capture beyond the source guideline search date was made.

2.3 eligibility criteria

Studies were eligible for the evidence map when they involved patients with acute thermal, scald, electrical, or chemical burns requiring intravenous resuscitation and evaluated a starting formula, fluid type, albumin or plasma strategy, vitamin C, goal-directed monitoring, computerized decision support, vasopressor exposure, renal adjunct, or a complication directly related to resuscitation volume. Randomized trials, prospective comparative studies, cohort studies, case-control studies, and clinically informative case series were included. Case series were retained only as supplementary safety or feasibility evidence and were not treated as comparative-effectiveness evidence. Animal studies, laboratory studies, narrative reviews, systematic reviews, editorials, and studies unrelated to acute fluid management were excluded from the primary clinical synthesis. No publication-year restriction was applied because historically important controlled studies predated 2000.

2.4 Outcomes

The primary outcomes were total fluid and crystalloid volume at 24 and 48 hours, urine output, acute kidney injury, organ dysfunction, mortality, and edema-related complications. Secondary outcomes included intra-abdominal pressure, abdominal compartment syndrome, pulmonary dysfunction, length of stay, infection, renal replacement therapy, adverse effects, and protocol adherence.

2.5 Data extraction and appraisal

For each study, the author, publication year, design, sample size when reported in the source evidence, intervention or exposure, comparator, outcomes, and principal methodological limitations were extracted. Randomized trials were appraised conceptually using RoB 2 domains; nonrandomized comparative studies were judged using ROBINS-I principles; cohort and case-control studies were considered using Newcastle-Ottawa/JBI domains; and uncontrolled case series were judged using the JBI case-series framework. The study-level judgments in Table 9 are preliminary because they were based on the information available in the source evidence set and article reports rather than duplicate independent full-text appraisal by two reviewers. A formal GRADE summary was not produced because no pooled analysis or uniform outcome extraction was available. The review was not prospectively registered.

Table 1: Evidence identification and selection

Stage	Number	Explanation
Records identified in the guideline search	9,326	Database records before duplicate removal
Duplicates removed	3,348	3,342 removed by the Bramer method and 6 additional duplicates removed in Covidence
Titles and abstracts screened	5,978	Independent screening by two reviewers in the source guideline
Reports assessed in full text	70	Selected after consensus screening
Studies meeting strict adult PICO criteria	24	Included in the 2024 ABA guideline
Supplementary clinical studies added	16	Broader evidence on pediatric care, safety, complications, renal outcomes and decision support
Studies synthesized in this review	40	Narrative synthesis; no quantitative pooling

Table 2: Characteristics of the 40 included clinical studies

Study	Year	Design	Sample	Intervention/comparator	Main outcomes	Key limitation
Recinos et al.	1975	RCT	15	Crystalloid vs colloid-containing solution	Fluid requirement; clinical response	Early randomized evidence; small sample
Jelenko et al.	1979	Prospective comparative	Not consistently reported	Hypertonic albumin-containing regimen	Hemodynamics; fluid need	Older protocol study
Goodwin et al.	1983	RCT	79	Crystalloid vs colloid	Hemodynamics; lung water	Randomized; limited contemporary applicability
Cooper et al.	2006	RCT	42	5% albumin vs lactated Ringer solution	24-h fluid; MODS; pulmonary outcomes	Small randomized trial
Ullmann et al.	2000	Observational	Not consistently reported	Haifa resuscitation formula	Formula performance; fluid adequacy	Single-center validation
Du et al.	1991	Comparative cohort	30	Different resuscitation regimens	Early weight gain; fluid accumulation	Small comparative study
Jones et al.	2015	Case series	Not consistently reported	Fresh frozen plasma-based protocol	Fluid volume; feasibility	No concurrent control
O'Mara et al.	2005	RCT	31	Crystalloid vs plasma/colloid-containing strategy	Intra-abdominal pressure; fluid volume	Randomized but small
Tanaka et al.	2000	RCT	37	High-dose vitamin C plus standard care	Crystalloid volume; urine output; edema	Key randomized vitamin C study
Lin et al.	2018	Retrospective cohort	80	High-dose vitamin C vs standard care	Fluid volume; AKI; mortality	Confounding possible
Kahn et al.	2011	Retrospective	33	High-dose ascorbic acid	Fluid requirement;	Small

		cohort		adjunct	safety	observational study
Nagal et al.	2020	Dose-comparison study	Not consistently reported	High- vs low-dose vitamin C	Safety; efficacy; pharmacodynamics	Dose heterogeneity
Buehner et al.	2016	Case series	Not consistently reported	Continuous high-dose vitamin C	Oxalate nephropathy	Safety signal only
Ho et al.	2021	Retrospective cohort	Not consistently reported	Early resuscitation exposures	Early AKI	Prognostic rather than direct intervention study
Adibfar et al.	2021	Retrospective cohort	Not consistently reported	Vasopressor use during resuscitation	Fluid volume; organ outcomes; mortality	Indication bias likely
Chung et al.	2017	Multicenter RCT	Not applicable to first 48 h	High-volume hemofiltration	Organ dysfunction; vasopressor dependency	Adjunctive evidence outside acute resuscitation window
Neff et al.	2010	Case series	Not consistently reported	Therapeutic plasma exchange	Hemodynamic rescue; survival	Rescue therapy; uncontrolled
Cochran et al.	2007	Matched case-control	202	Albumin rescue vs matched crystalloid controls	Fluid volume; ARDS; mortality	Adjusted observational evidence
Comish et al.	2021	Case-control	91	25% albumin rescue vs crystalloid	24-h crystalloid; perfusion; complications	Baseline severity imbalance
Greenhalgh et al. (ABRUPT)	2023	Prospective multicenter observational	379	Contemporary crystalloid and albumin practice	Fluid volume; practice variation	Large real-world cohort
Lawrence et al.	2010	Retrospective cohort	52	Colloid rescue	Fluid creep; resuscitation ratio	Historical-control limitations
Park et al.	2012	Retrospective cohort	159	Early albumin in difficult resuscitation	Fluid volume; mortality	Confounding by indication
Saitoh et al.	2021	Multicenter RCT	36	Modified Brooke 2 mL vs Baxter/Parkland 4 mL	24/48-h fluid; AKI; complications	Direct formula comparison; underpowered
Flores et al.	2022	Case-control	75	High-dose vitamin C	Fluid volume; renal outcomes; mortality	No clear clinical benefit
Abeoletta and Abdelsalam	2013	Case-control	30	TPTD-guided assessment	Volume overload; hemodynamic endpoints	Small monitoring study
Chen et al.	2017	Case-control	34	Early goal-directed therapy	Fluid volume; organ perfusion	Nonrandomized
Foldi et al.	2009	RCT	16	Alternative resuscitation methods	Oxidative stress biomarkers	Very small mechanistic trial
Foldi et al.	2010	RCT	30	Alternative resuscitation methods	Cytokines; adhesion molecules	Mechanistic outcomes
Holm et al.	2004	RCT	50	Invasive hemodynamic monitoring vs conventional guidance	Fluid volume; physiology	No consistent volume reduction
Zhu et al.	2021	Retrospective cohort	191	Pulse-contour cardiac-output guidance	Fluid volume; prognosis	Retrospective; potential selection bias
Salinas et al.	2011	Historical-control study	70	Computerized decision-support system	24-h fluid; target urine output	Lower fluid and tighter titration reported
Dittrich et al.	2016	Pediatric RCT	Not consistently reported	Early albumin plus crystalloid vs crystalloid	Fluid requirement; outcomes	Pediatric evidence; indirect for adult PICO
Blanco-Schweizer et al.	2020	Observational	Not consistently reported	Albumin using BET formula	Fluid control	Single-center observational study
Dittrich et al.	2020	Pediatric cohort	Not consistently reported	Fluid creep exposure	Infection; outcomes	Pediatric observational evidence
Nakajima et al.	2019	Nationwide retrospective cohort	Large database	High-dose vitamin C	Mortality; fluid volume	Propensity-based observational evidence
Rizzo et al.	2022	Prospective multicenter observational	Not consistently reported	Burn Navigator decision support	Fluid volume; effectiveness	No randomized comparator
Rizzo et al.	2023	Multicenter observational	285	Burn Navigator across five centers	Fluid volume; protocol adherence	Center-level heterogeneity
Chung et al.	2006	Retrospective	52	2 vs 4 mL/kg/%TBSA starting	Fluid volume; AKI	Combat setting;

		military cohort		strategy		historical comparison
Ivy et al.	2000	Prospective observational	Not consistently reported	IAP monitoring/high fluid exposure	IAH; ACS	Complication-focused evidence
Oda et al.	2006	Retrospective cohort	Not consistently reported	Higher vs lower resuscitation volume	Abdominal compartment syndrome	Dose-response observational evidence

Table 3: Distribution of studies by evidence category

Evidence category	Number	Studies
Albumin/colloid versus crystalloid or albumin rescue	11	Recinos; Goodwin; Cooper; Cochran; Comish; Greenhalgh; Lawrence; Park; Dittrich 2016; Blanco-Schweizer; Jelenko
Fresh frozen plasma or plasma exchange	3	Jones; O'Mara; Neff
Starting formula or protocol comparison	4	Ullmann; Du; Saitoh; Chung 2006
High-dose vitamin C	7	Tanaka; Lin; Kahn; Nagal; Buehner; Flores; Nakajima
Goal-directed or advanced hemodynamic monitoring	4	Abeoletta; Chen; Holm; Zhu
Computerized decision support	3	Salinas; Rizzo 2022; Rizzo 2023
Renal, vasopressor, and organ-complication evidence	3	Ho; Adibfar; Chung 2017
Fluid creep and mechanistic outcomes	3	Dittrich 2020; Foldi 2009; Foldi 2010
Compartment syndrome and pressure monitoring	2	Ivy; Oda

RESULTS

3.1 Overall characteristics of the evidence

The 40 studies covered more than four decades of burn-resuscitation research. The evidence included small randomized trials, matched case-control studies, retrospective cohorts, prospective multicenter observational studies, historical-control comparisons, pediatric studies, and uncontrolled rescue-therapy case series. Sample sizes ranged from fewer than 20 participants in mechanistic trials to several hundred patients in multicenter or database studies. Only a minority of studies were adequately powered randomized comparisons.

The most frequent outcome was fluid volume during the first 24 hours. Other commonly reported outcomes included urine output, acute kidney injury, intra-abdominal pressure, compartment syndrome, pulmonary dysfunction, organ dysfunction, mortality, and length of stay. Outcome definitions and units were inconsistent. Some studies reported mL/kg/%TBSA, others reported total liters, mL/kg, resuscitation ratios, or cumulative balance. This heterogeneity prevented valid meta-analysis.

3.2 Albumin and colloid strategies

Albumin was the most extensively studied adjunct. Randomized and observational studies generally suggested that albumin can reduce further crystalloid escalation or improve control of urine output in patients whose resuscitation is becoming difficult.[13,14,28-32] However, albumin recipients often had larger burns, greater full-thickness injury, inhalation injury, oliguria, or unstable vital signs before albumin was initiated. This creates strong confounding by indication.

Cochran et al. compared 101 albumin-treated patients with 101 matched controls. Albumin was introduced when fluid needs exceeded the expected formula. Although crude outcomes were difficult to interpret because albumin-treated patients were more severely injured, adjusted analysis suggested a lower mortality risk, while inhalation injury rather than albumin independently explained pulmonary complications.[28] Cooper et al. found no clear improvement in multiple-organ dysfunction with 5% albumin in a small randomized trial.[14] More recent rescue-colloid studies reported rapid improvement in input-to-output ratio and reduced crystalloid escalation, but no consistent reduction in mortality or major complications.[29-32]

The overall evidence therefore supports selective albumin use as a crystalloid-sparing rescue strategy rather than universal early administration. The optimal initiation time remains uncertain. The 2024 ABA guideline recommends considering human albumin, particularly in larger burns, to reduce resuscitation volume and improve urine output.[5]

3.3 Starting formula and initial crystalloid dose

The direct comparison between a 2 mL/kg/%TBSA starting approach and the traditional 4 mL/kg/%TBSA approach is clinically important. The military cohort reported lower fluid exposure after transition toward a 2 mL starting strategy.[48] Saitoh et al. directly compared Modified Brooke and Baxter/Parkland starting volumes in a small multicenter randomized trial and found lower 24-hour fluid administration with the 2 mL approach, without a consistent increase in early acute kidney injury.[33] At 48 hours, the difference was smaller and not statistically clear.

These findings support a lower starting rate followed by close hourly titration. They do not support rigid restriction. Patients with delayed presentation, inhalation injury, electrical injury, deep burns, or evolving shock may still require substantial fluid. The key practice change is to avoid automatically beginning at a high rate that increases

the risk of fluid creep before physiological response is assessed.

3.4 Fresh frozen plasma and plasma-based rescue

Fresh frozen plasma has been used in some institutional protocols to reduce crystalloid exposure and support oncotic pressure. O'Mara et al. reported lower intra-abdominal pressure with a colloid-containing strategy in a small randomized study.[18] The West Penn experience suggested feasibility of a plasma-based protocol, but the evidence was uncontrolled.[17] Therapeutic plasma exchange has been described for refractory burn shock, yet this remains rescue therapy supported by case-series evidence.[27] The available data are insufficient to establish routine efficacy or safety.

3.5 High-dose vitamin C

Tanaka et al. reported a marked reduction in crystalloid requirements with high-dose intravenous ascorbic acid in a randomized study of severely burned patients.[19] The intervention also produced high urine output, which may reflect osmotic diuresis and can complicate the use of urine output as a titration endpoint. Later retrospective studies did not consistently reproduce a meaningful improvement in mortality, acute kidney injury, or length of stay.[20,21,34,45]

Safety concerns are important. Continuous high-dose vitamin C has been associated with oxalate nephropathy.[23] Dose-comparison and observational studies have not established a single safe and effective regimen.[22,34,45] The evidence therefore suggests a possible crystalloid-sparing physiological effect but uncertain patient-centered benefit. Routine use cannot be recommended without stronger trials and careful renal monitoring.

3.6 Goal-directed monitoring and computerized decision support

Advanced hemodynamic monitoring has been investigated because urine output may lag behind changing intravascular conditions. Studies of transpulmonary thermodilution, invasive monitoring, early goal-directed therapy, and pulse-contour cardiac output produced inconsistent findings.[35,36,39,40] Some studies reported improved physiological assessment, but fluid volume was not consistently reduced, and invasive measurements did not reliably translate into fewer edema-related complications.

Computerized decision-support systems showed more consistent process benefits. Salinas et al. found lower 24-hour resuscitation volume and more time within urine-output targets when a computerized titration system was used rather than traditional manual adjustment.[41] Multicenter Burn Navigator studies demonstrated feasibility and improved protocol adherence, although between-center variation remained substantial.[46,47] Because these studies were not randomized, the certainty remains limited, but computerized support appears useful as an aid to frequent bedside titration rather than a replacement for clinical judgment.

3.7 Acute kidney injury, vasopressors, renal replacement therapy, and complications

Acute kidney injury is common after major burns and may result from shock, delayed resuscitation, nephrotoxic exposure, sepsis, abdominal hypertension, or excessive osmotic diuresis. Observational evidence did not show that a 2 mL starting formula increased early AKI compared with a 4 mL approach.[33,48] High-dose vitamin C studies produced mixed renal findings, and oxalate nephropathy remains a specific concern.[23,34,45]

Evidence on vasopressors during initial burn resuscitation is weak. Patients receiving vasopressors are usually older or more severely ill, making causal interpretation difficult.[25] High-volume hemofiltration has shown organ-support effects in septic burn patients with established AKI, but this evidence does not directly address prophylactic initiation during the first 48 hours.[26]

High fluid exposure was repeatedly associated with edema-related harm. Ivy et al. and Oda et al. linked large cumulative resuscitation volumes with intra-abdominal hypertension and abdominal compartment syndrome.[49,50] Pediatric evidence also associated fluid creep with infection.[44] These studies support selective pressure monitoring and early correction of runaway resuscitation.

Table 4: Summary of evidence by clinical outcome

Outcome	Overall finding	Confidence
24-h fluid volume	Lower starting formula, selective albumin rescue, some vitamin C studies, and decision support often reduced crystalloid exposure	Moderate direction; low certainty because of heterogeneity
Urine output	Albumin rescue and decision support may improve target achievement	Low to moderate
Acute kidney injury	No consistent difference between 2 and 4 mL starting strategies; vitamin C renal safety uncertain	Low
Mortality	Studies generally underpowered; observational albumin and vitamin C findings conflict	Very low
Compartment syndrome/abdominal hypertension	Higher cumulative fluid exposure consistently associated with greater risk	Moderate association
Multiple-organ dysfunction	No consistent benefit from albumin; renal support evidence relates mainly to later septic AKI	Low
Pulmonary outcomes	No reliable improvement from colloid;	Low

	severity and inhalation injury confound findings	
Protocol adherence	Computer decision support improves consistency of hourly titration	Low to moderate

Table 5: Risk-of-bias overview

Evidence group	Representative studies	Main concerns	Overall judgment
Randomized formula/solution trials	Recinos; Goodwin; Cooper; O'Mara; Tanaka; Saitoh; Holm; Foldi studies	Small samples, incomplete blinding, co-interventions, variable outcome definitions	Some concerns to high
Albumin rescue cohorts	Cochran; Comish; Lawrence; Park; Blanco-Schweizer	Confounding by indication, severity imbalance, historical controls	Serious
Vitamin C observational studies	Lin; Kahn; Flores; Nakajima	Dose variation, selection bias, inconsistent renal outcome definitions	Serious
Decision-support studies	Salinas; Rizzo studies	Historical or nonrandomized comparator, center effects	Moderate to serious
Complication cohorts	Ivy; Oda; Dittrich 2020; Ho	Exposure-outcome confounding, nonuniform definitions	Moderate to serious
Uncontrolled rescue therapy	Jones; Neff; Buehner	No comparator; strong selection bias	Critical for comparative efficacy

Table 6: Evidence-informed clinical implications

Clinical issue	Practical direction	Rationale
Initial crystalloid dose	Begin near 2 mL/kg/%TBSA for adults with major burns, then titrate hourly	Supported by guideline and limited direct comparative evidence
Urine-output target	Use urine output with blood pressure, perfusion, lactate/base deficit, and clinical trajectory	Urine output alone may be distorted by diuretics or vitamin C
Albumin	Consider selectively in larger burns or escalating crystalloid requirements	May reduce crystalloid escalation; timing uncertain
Fresh frozen plasma	Do not use routinely outside a protocol or research setting	Evidence limited and largely uncontrolled
High-dose vitamin C	Do not use routinely without specialist protocol and renal safety monitoring	Benefit uncertain; oxalate nephropathy risk
Advanced hemodynamic monitoring	Do not use transpulmonary thermodilution routinely solely to reduce fluid volume	No consistent clinical advantage
Computer decision support	May be considered to support frequent titration	Process benefits; low-certainty outcome evidence
Compartment monitoring	Measure intra-abdominal/intraocular pressure selectively in high-risk or runaway resuscitation	High fluid exposure linked to compartment syndromes

DISCUSSION

This synthesis shows that burn-resuscitation evidence is clinically broad but methodologically fragile. Many influential practices are supported by small randomized trials, retrospective comparisons, historical controls, or institutional protocols rather than by large pragmatic trials.[11-18,28-33] The most consistent message is therefore not that one formula or fluid is universally superior, but that excessive crystalloid exposure should be actively prevented through a conservative starting estimate, frequent reassessment, and timely correction of an escalating input-output imbalance.[5,9,31,33,48-50]

The shift from the traditional Parkland starting estimate of 4 mL/kg/%TBSA toward approximately 2 mL/kg/%TBSA is supported by lower early fluid exposure in the available comparative evidence.[33,48] This is clinically relevant because formula-based overestimation may contribute to fluid creep, tissue edema, intra-abdominal hypertension, and compartment syndromes.[9,31,49,50] However, a lower starting estimate must not become a rigid ceiling. It should serve as the initial rate from which bedside titration begins, with reassessment of urine output, blood pressure, perfusion, lactate or base deficit, and the patient's evolving clinical trajectory.[4,5]

Albumin occupies an intermediate position between physiological plausibility and secure comparative evidence. Several randomized and observational studies reported improved input-output balance or reduced crystalloid escalation after albumin or colloid administration.[13,14,28-32,42,43] Nevertheless, rescue albumin was usually started after conventional resuscitation had become difficult, so treated patients were often more severely injured and more unstable at baseline.[28-32] This confounding by indication limits causal interpretation and explains why selective albumin use is more defensible than routine universal administration. A sufficiently powered multicenter trial comparing protocolized early-selective albumin with protocolized crystalloid remains a priority.[5,10]

High-dose vitamin C illustrates the need to separate a reduction in fluid volume from improvement in patient-centered outcomes. The randomized study by Tanaka et al. reported lower crystalloid requirements, but later observational studies did not

consistently show better mortality, kidney outcomes, or length of stay.[19-22,34,45] Increased urine output may partly represent osmotic diuresis and can make urine-output-guided titration difficult. Reports of oxalate nephropathy further weaken confidence in routine use.[23] Future trials should standardize dose, renal surveillance, fluid endpoints, and clinically important outcomes before vitamin C is adopted as routine burn-resuscitation therapy.

Advanced monitoring technology has not consistently outperformed careful conventional assessment. Studies of transpulmonary thermodilution, invasive hemodynamic monitoring, early goal-directed therapy, and pulse-contour cardiac output produced mixed effects on fluid exposure and clinical outcomes.[35,36,39,40] Computerized decision support may be more useful because it addresses delayed or inconsistent hourly adjustment rather than attempting to replace clinical assessment. Salinas et al. and the multicenter Burn Navigator studies reported improved titration consistency and protocol adherence, although their nonrandomized designs and center effects limit certainty.[41,46,47] These systems should therefore support, rather than automate, bedside judgment.

A major limitation of the literature is inconsistent outcome reporting. Studies variously reported total liters, mL/kg, mL/kg/%TBSA, resuscitation ratios, cumulative balance, or physiological surrogates, which prevented defensible pooling.[5,30,33] Future studies should report pre-burn-center fluid, full-thickness burn percentage, inhalation injury, crystalloid and colloid components, total fluid at 24 and 48 hours, standardized urine-output measures, agreed acute-kidney-injury criteria, and precisely defined compartment syndromes. A burn-resuscitation core outcome set would substantially improve comparability and reduce selective reporting.

4.1 Strengths and limitations

The principal strength of this review is the transparent integration of the strict ABA guideline-eligible evidence with supplementary clinical studies covering safety, pediatrics, implementation, and complications.[5] The manuscript distinguishes randomized comparisons, observational effectiveness studies, complication cohorts, and uncontrolled rescue evidence rather than assigning them equal evidentiary weight. It also avoids unsupported pooled effect estimates and provides a study-level preliminary risk-of-bias table.

The principal limitation is that the 16 supplementary studies were identified through reference-set and citation-chain expansion rather than through a new independently documented database search. The article should therefore be read as a systematic evidence synthesis anchored to the ABA search, not as a fully updated de novo systematic review claiming complete capture through 2025. In addition, some older studies reported limited baseline and outcome data, study-level risk-of-bias judgments were not duplicated by two independent reviewers, and several interventions were assessed only in small or nonrandomized studies.[11-18,27,35-43] These limitations reduce certainty and preclude formal meta-analysis or definitive treatment ranking.

Table 7: Priority research gaps

Topic	Required study	Critical outcomes
Early selective albumin	Large multicenter RCT comparing protocolized albumin timing	Fluid volume, AKI, compartment syndromes, mortality
2 vs 4 mL starting formula	Adequately powered pragmatic RCT	24/48-h fluids, AKI, organ dysfunction, complications
Fresh frozen plasma	Comparative safety and efficacy trial	Fluid volume, transfusion reactions, thrombosis, organ outcomes
Vitamin C	Dose-finding placebo-controlled RCT with renal surveillance	Fluid volume, AKI, oxalate, organ dysfunction, mortality
Decision support	Cluster-randomized or stepped-wedge multicenter study	Protocol adherence, fluid exposure, complications
Standardized reporting	Consensus core outcome set	Comparable units and definitions across studies
Pediatric resuscitation	Dedicated multicenter pediatric trials	Age-specific fluid, glucose, renal and edema outcomes

Table 8: Evidence provenance and role in the synthesis

Evidence component	Extent	Purpose	Interpretive rule
Strict ABA adult PICO evidence	24 studies	Direct evidence used by the 2024 ABA guideline	Primary evidence for adult clinical recommendations
Supplementary comparative evidence	Studies added from the guideline reference set/citation chains	Pediatric, safety, implementation, renal, plasma and complication evidence	Interpreted separately because eligibility differed from the strict adult PICO
Uncontrolled case-series evidence	Jones; Neff; Buehner	Feasibility, rescue therapy or adverse-event signals	Not used to establish comparative efficacy
Quantitative synthesis	Not performed	Substantial clinical and statistical heterogeneity	No pooled effect estimates, heterogeneity statistics or pooled GRADE ratings reported

Table 9: Preliminary study-level risk-of-bias assessment

Study	Design	Appraisal framework	Main risk-of-bias concerns	Preliminary judgment
Recinos et al. (1975)	RCT	RoB 2	Very small sample; limited reporting of randomization and blinding; older care context	High
Jelenko et al. (1979)	Prospective comparative	ROBINS-I	Nonrandomized allocation; older protocol; incomplete baseline reporting	Serious
Goodwin et al. (1983)	RCT	RoB 2	Limited blinding; small trial; older co-interventions	Some concerns
Cooper et al. (2006)	RCT	RoB 2	Small sample; limited power; possible co-intervention imbalance	Some concerns
Ullmann et al. (2000)	Observational validation	JBI/NOS	Single center; no concurrent comparator; selection bias	Serious
Du et al. (1991)	Comparative cohort	ROBINS-I	Small sample; nonrandomized regimens; confounding	Serious
Jones et al. (2015)	Case series	JBI case series	No concurrent control; institutional protocol; selective reporting	Critical for efficacy
O'Mara et al. (2005)	RCT	RoB 2	Small sample; limited blinding; outcome-specific power uncertain	Some concerns
Tanaka et al. (2000)	RCT	RoB 2	Small sample; urine output affected by osmotic diuresis; limited patient-centered outcomes	Some concerns
Lin et al. (2018)	Retrospective cohort	ROBINS-I	Confounding by treatment selection; retrospective outcome definitions	Serious
Kahn et al. (2011)	Retrospective cohort	ROBINS-I	Small cohort; historical comparison; selection bias	Serious
Nagal et al. (2020)	Dose-comparison study	ROBINS-I	Dose heterogeneity; limited sample; unclear allocation process	Serious
Buehner et al. (2016)	Case series	JBI case series	Adverse-event case series without denominator or comparator	Critical for efficacy
Ho et al. (2021)	Retrospective cohort	NOS/JBI	Exposure-outcome confounding; prognostic rather than intervention design	Moderate to serious
Adibfar et al. (2021)	Retrospective cohort	ROBINS-I	Strong confounding by indication for vasopressor use	Serious
Chung et al. (2017)	Multicenter RCT	RoB 2	Addresses septic AKI rather than initial resuscitation; indirectness	Some concerns/indirect
Neff et al. (2010)	Case series	JBI case series	Rescue therapy; no control group; extreme selection bias	Critical for efficacy
Cochran et al. (2007)	Matched case-control	ROBINS-I	Residual confounding despite matching; albumin given to sicker patients	Serious
Comish et al. (2021)	Case-control	ROBINS-I	Baseline severity imbalance; nonrandomized rescue protocol	Serious
Greenhalgh et al. (2023)	Prospective multicenter observational	ROBINS-I	Practice variation; nonrandomized albumin use; center effects	Moderate to serious
Lawrence et al. (2010)	Retrospective cohort	ROBINS-I	Historical controls; protocol-era effects; confounding	Serious
Park et al. (2012)	Retrospective cohort	ROBINS-I	Confounding by indication; retrospective treatment selection	Serious
Saitoh et al. (2021)	Multicenter RCT	RoB 2	Small and underpowered; open-label intervention	Some concerns
Flores et al. (2022)	Case-control	ROBINS-I	Nonrandomized exposure; residual confounding; dose variation	Serious
Abeoletta and Abdelsalam (2013)	Case-control	ROBINS-I	Small sample; monitoring selection; surrogate outcomes	Serious
Chen et al. (2017)	Case-control	ROBINS-I	Nonrandomized; small sample; possible co-intervention differences	Serious
Foldi et al. (2009)	RCT	RoB 2	Very small mechanistic study; surrogate outcomes	High
Foldi et al. (2010)	RCT	RoB 2	Small mechanistic study; surrogate outcomes; limited clinical relevance	High
Holm et al. (2004)	RCT	RoB 2	Small open-label trial; invasive monitoring co-interventions	Some concerns
Zhu et al. (2021)	Retrospective cohort	ROBINS-I	Selection bias; residual confounding; center-specific practice	Serious
Salinas et al. (2011)	Historical-control study	ROBINS-I	Historical comparator; secular trends; implementation bias	Serious
Dittrich et al. (2016)	Pediatric RCT	RoB 2	Small pediatric trial; indirectness for adult recommendations	Some concerns/indirect
Blanco-Schweizer et al. (2020)	Observational	ROBINS-I	Single center; no randomized comparator; protocol selection	Serious
Dittrich et al. (2020)	Pediatric cohort	NOS/JBI	Exposure-outcome confounding; pediatric indirectness	Moderate to serious
Nakajima et al. (2019)	Nationwide retrospective cohort	ROBINS-I	Administrative-data limitations; residual confounding despite adjustment	Moderate to serious
Rizzo et al. (2022)	Prospective	ROBINS-I	No randomized comparator; center and	Moderate to serious

	multicenter observational		implementation effects	
Rizzo et al. (2023)	Multicenter observational	ROBINS-I	Center heterogeneity; nonrandomized protocol use	Moderate to serious
Chung et al. (2006)	Retrospective military cohort	ROBINS-I	Historical comparison; combat setting; changing co-interventions	Serious
Ivy et al. (2000)	Prospective observational	NOS/JBI	Complication-focused design; confounding by burn severity and fluid exposure	Moderate to serious
Oda et al. (2006)	Retrospective cohort	NOS/JBI	Dose-response confounding; retrospective outcome ascertainment	Moderate to serious

Note: These judgments are preliminary and should be confirmed through duplicate independent full-text appraisal before submission. "Critical for efficacy" indicates that an uncontrolled case series may inform feasibility or safety but cannot establish comparative effectiveness.

CONCLUSION

Fluid resuscitation is life-saving but can itself cause harm when fluid is delivered without frequent reassessment. For adults with major burns, current evidence supports beginning with a conservative crystalloid estimate near 2 mL/kg/%TBSA and titrating to the patient's overall physiological response rather than automatically delivering a fixed high volume.[5,33,48] Albumin may be considered when crystalloid requirements continue to rise, particularly in larger burns, but its optimal timing remains uncertain.[5,28-32] Fresh frozen plasma and high-dose vitamin C should not be routine because comparative evidence is limited and safety concerns remain.[17-23,34,45] Advanced hemodynamic monitoring has not consistently improved fluid efficiency, whereas computerized decision support may improve titration consistency.[35,36,39-41,46,47] Selective monitoring for compartment syndromes is important in patients with high cumulative fluid exposure.[49,50] These conclusions remain provisional because much of the evidence is heterogeneous, small, or observational.

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