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Controversies in fluid therapy: Type, dose and toxicity

Robert C McDermid, Karthik Raghunathan, Adam Romanovsky, Andrew D Shaw, Sean M Bagshaw

Robert C McDermid, Adam Romanovsky, Sean M Bagshaw, Division of Critical Care Medicine, Faculty of Medicine and Dentistry, University of Alberta, Edmonton, AB T6G2B7, Canada
Karthik Raghunathan, Andrew D Shaw, Department of Anesthesiology, Duke University Medical Center/Durham VAMC, Durham, NC 90484, United States
Andrew D Shaw, Department of Critical Care Medicine, Duke University Medical Center/Durham VAMC, Durham, NC 90484, United States
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Supported by Canada Research Chair in Critical Care Nephrology; Clinical Investigator Award from Alberta Innovates-Health Solutions to Bagshaw MS
Correspondence to: Dr. Sean M Bagshaw, Division of Critical Care Medicine, Faculty of Medicine and Dentistry, University of Alberta, 3C1.12 Walter C. Mackenzie Centre, 8440-122 ST NW, Edmonton, AB T6G2B7, Canada. bagshaw@ualberta.ca
Telephone: +1-780-4076755 Fax: +1-780-4071228
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Abstract

Fluid therapy is perhaps the most common intervention received by acutely ill hospitalized patients; however, a number of critical questions on the efficacy and safety of the type and dose remain. In this review, recent insights derived from randomized trials in terms of fluid type, dose and toxicity are discussed. We contend that the prescription of fluid therapy is context-specific and that any fluid can be harmful if administered inappropriately. When contrasting "crystalloid *vs* colloid", differences in efficacy are modest but differences in safety are significant. Differences in chloride load and strong ion difference across solutions appear to be clinically important. Phases of fluid therapy in acutely ill patients are recognized, including acute resuscitation, maintaining homeostasis, and recovery phases. Quantitative toxicity (fluid overload) is associated with adverse outcomes and can be mitigated when fluid therapy based on functional hemodynamic parameters that predict volume responsiveness and minimization of non-essential fluid. Qualitative toxicity (fluid type), in particular for iatrogenic acute kidney injury and metabolic acidosis, remain a concern for synthetic colloids and isotonic saline, respectively. Physiologically balanced crystalloids may be the "default" fluid for acutely ill patients and the role for colloids, in particular hydroxyethyl starch, is increasingly unclear. We contend the prescription of fluid therapy is analogous to the prescription of any drug used in critically ill patients.

Key words: Fluid therapy; Resuscitation; Critical illness; Peri-operative; Toxicity; Saline; Crystalloid; Colloid

Core tip: Fluid therapy is exceedingly common in acutely ill patients; however, numerous questions on the efficacy and safety of fluid therapy in terms of the type and dose remain. Fluid therapy prescription is context-specific and any fluid type can be harmful if administered inappropriately. When considering crystalloids versus colloids, differences in efficacy are modest but the risk of kidney toxicity and bleeding complications with hydroxyethyl starch appear more significant. The differences in chloride load across crystalloid solutions appears to have physiologic and clinically important effects, in particular for contributing to hyperchloremic metabolic acidosis, kidney injury and greater utilization of renal replacement therapy associated with 0.9% saline. Fluid therapy should be viewed as analogous to the prescription of any drug in acutely ill patients.

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INTRODUCTION

Intravenous (*iv*) fluid therapy is one of the most common interventions administered to acutely hospitalized patients; however, a number of fundamental questions about its efficacy and safety remain.

The origins of the administration of *iv* fluids for acute resuscitation date back to the cholera epidemic of the early 19th century, when Dr. Thomas A Latta first administered a warmed *iv* solution of "two drachams of muriate, two scruples of carbonate of soda to sixty ounces of water" to combat the profound dehydration in six patients hospitalized at the Leith Infirmary in Scotland[1]. With this non-sterile hypotonic solution, he was able to spare a few moribund patients from refractory hypovolemic shock. Impressive volumes of fluid (over 12 liters in some cases) were required to restore hemodynamics, and as described resulted in "...an immediate return of the pulse, and improvement in the respiration… [and in] the appearance of the patient [were] the immediate effects". Yet, even in 1832, an editorial subsequently published in the *Lancet* commented that "...the mass of the profession is unable to decide; and thus, instead of any uniform mode of treatment, every town and village has its different system or systems..." and that "...a suitable clinical investigation is required to resolve between such conflicting authorities…"[2]. As such, after nearly two centuries of advancements in the modern medicine, this editorial seemed to be remarkably familiar in many respects to our current state of knowledge regarding the optimal prescription of fluid therapy for acutely ill patients.

Fluid used in acute resuscitation should be viewed in the same context as any other drug administered to patients. Their prescription is certainly analogous to how drugs are prescribed (Table 1). This is relevant when considering that the vast majority of hospitalized acutely ill patients, including children, will receive *iv* fluid therapy, usually as some combination of crystalloids, colloids and/or blood products.

However, data have supported the notion that the form of fluid therapy prescribed is largely dependent on where medical care is provided (*i.e.,* country, region, hospital, care unit) and on the specialty of the clinician (*i.e.,* surgical, medical, anesthesia, emergency)[3,4]. There is wide variation in clinical practice with respect to the type and dose of fluid prescribed[3]. This variation in practice has historically been derived from a general lack of clarity in the literature on the principles of optimal fluid prescription (*i.e.,* efficacy and safety)-the idea of prescribing fluid therapy for "the right patient, at the right time, and in the right context". In the last few years, a number of large high-quality randomized trials have reported on the efficacy and safety intravenous fluid therapy for acute resuscitation in the critically ill[4-6]. These data are beginning to provide clarity to long-standing debates regarding fluid type and dose, during and following acute resuscitation and to better inform clinical practice to improve patient outcomes[7]. In this review, we discuss recent relevant evidence related to the type and dose of fluid therapy used in the resuscitation of critically ill patients.

Table 1 Overview of the analogy of prescribing fluid therapy and prescribing a drug

Steps for prescribing a drug	Prescribing an oral hypoglycemic medication	Prescribing fluid therapy
Define the clinical problem	Diabetes mellitus	Hypovolemia or other fluid responsive state
Specify the therapeutic objective	Lower blood glucose	Restore absolute/ relative fluid deficit
Verify the suitability of the drug	Class of oral hypoglycemic agent	Crystalloid, colloid or blood product
Write a prescription to start the drug	Order written by MD, verified and dispensed by pharmacy	Order written by MD, verified by pharmacy, blood bank or RN, administered by RN
Monitor therapeutic response of the drug	Blood glucose or hemoglobin A1C, evidence of adverse effect/ toxicity	Monitor hemodynamic profile and end-organ perfusion, evidence of dose-response toxicity
Write an order to discontinue	Order written by MD, verified by pharmacy	Order written by MD, administered by RN

Adapted from Raghunathan *et al*[58].

DOSE OF FLUID THERAPY

As aforementioned, *iv* fluid therapy is one of the most common and certainly may be one of the most important initial interventions in the resuscitation of acute ill patients. A key concept for dosing fluid therapy in critically ill patients is to actively address ongoing losses coupled with constant reassessment of need for further hemodynamic support. The routine practice of providing "maintenance" or replacement of unmeasured fluid deficits such as "third space losses" for most patients is questionable and often contributes unnecessary fluid accumulation. The optimal target endpoints for fluid therapy during resuscitation remain controversial. Recent data suggest static metrics of resuscitation, such as thresholds in central venous pressure (CVP), as currently recommended by the Surviving Sepsis Campaign[8], may not accurately correlate with restoration of intravascular volume and improvement in tissue oxygen delivery and may be associated with worse outcome[9]. Additional measures such as achieving a normalized central venous oxygen saturation (> 65%-70%) and rapid serum lactate clearance (> 20% in 2 h) in response to fluid resuscitation (± additional hemodynamic support) have been recommended and correlate with improve outcome, both of these endpoints also have important caveats to consider[9,10]. Rather, functional hemodynamic measures such as stroke volume variation, pulse pressure variation[11], bedside ultrasonic interrogation of cardiac output or respiratory variation in inferior vena cava diameter and additional novel dynamic metrics such changes in cardiac output associated with passive leg raising, changes in end-tidal CO_2 and end-expiratory endotracheal tube occlusion can better predict the hemodynamic response to fluid loading[12-15]. These

dynamic measures are superior to blood pressure, CVP, and urine output targets. Importantly, critically ill patients are heterogeneous and may vary considerably with respect to baseline susceptibilities, admission diagnoses and response to fluid loading. When conventional blood pressure or urine output targets are used to guide fluid loading in critically ill patients, often large doses of fluids are administered, and in these circumstances, colloids such as hydroxyethyl starch (HES) are associated with toxicity[7]. The use of fluid boluses in critically ill patients without integrating functional hemodynamic parameters may be associated with cardiovascular decompensation and worse outcome[5]. These observations would strongly support the need for individualized resuscitation goals that integrate functional hemodynamic measures rather than use of generic resuscitation endpoints.

TYPE OF FLUID THERAPY

For a given dose of fluid administered, toxicity may depend on the type and composition of fluid being administered and on patient susceptibilities and physiology. Both patient-specific and context-specific differences should be considered when selecting the type of fluid therapy to be administered.

The debate regarding the relative risks and benefits of colloid and crystalloid solutions has raged on for years. Although various forms of crystalloid solutions have been used in humans since the 1830s, it was approximately 100 years more before the technology to isolate albumin from serum was available. In World War Ⅱ, fractionated bovine albumin was first used on the battlefield as a resuscitation fluid. Synthetic colloids such as HES and gelatins have until recently been considered reasonable alternatives to albumin, due to their theoretical advantages such as mitigating the infectious risks of human blood products, improving blood rheology and microvascular flow, and modulating neutrophil aggregation. The choice of fluid type; however, has largely been a matter of individual clinician preference rather than being specifically directed by high-quality data from clinical trials.

In 1998, the crystalloid/colloid controversy came to a head with the publication of a systematic review that suggested that the use of human albumin was associated with one additional death for every 17 patients treated[16]. Despite this review having methodological misgivings, a political firestorm ensued when the Cochrane Injuries Group urged politicians to "take action" six weeks before the article was published by the *BMJ*. Unfortunately, the lay media reported the findings prior to peer review and publication, resulting in statistically-questionable, poorly-supported inflammatory news headlines such as "300 die as health chiefs dither"[17]. The director of the United Kingdom Cochrane Center went so far as to suggest that he would sue any doctor who gave him an infusion of albumin[15,16].

Due to this ongoing narrative, interest in the patterns of clinical use of crystalloid and colloid solutions for fluid resuscitation in the intensive care unit (ICU) has increased. An international study of 391 ICUs across 25 countries observed that colloid therapy was the primary fluid used in 48% of instances for acute resuscitation, whereas crystalloid and blood products were used in 33% and 28% of instances, respectively[3]. However, the variation in the type of fluid administered was six-fold different between countries. These data suggested that local factors, such as "unit protocols" and commercial marketing played an important role in guiding clinicians' choice of fluid type for resuscitation. These data also recommended better evidence in the form of high-quality randomized trials were needed along with appropriate mechanisms to translate new knowledge from such data into bedside practice.

Several studies have repeated provided a physiological rationale for the preferential use of a colloid (with an emphasis on HES) over crystalloid therapy for resuscitation in septic shock and other in states of acute stress such as peri-operatively. HES solutions have been shown to attenuate the acute inflammatory response[18-21], mitigate endothelial barrier dysfunction and vascular leak[18,22], and preserve intestinal barrier function[17]. Small clinical trials have suggested superiority of HES solutions for resuscitation of the microcirculation in sepsis[22]. Small randomized clinical trials have also shown that early fluid resuscitation with HES solutions results in more rapid hemodynamic stabilization and shock reversal (*i.e.,* greater efficacy) compared with crystalloids, and require significantly less fluid to restore intravascular volume[23,24].

Several more recent randomized trials have specifically evaluated the "colloid/crystalloid" hypothesis for fluid resuscitation in critically ill patients. The SAFE[25] (4% albumin in 0.9% saline *vs* 0.9% saline), CHEST[6] (6% HES in 0.9% saline *vs* 0.9% saline) and 6S[7] (6% HES in Ringer's acetate *vs* Ringer's acetate) trials were specifically designed to evaluate the effectiveness of colloids against corresponding crystalloids. These trials have shown that the efficacy of volume expansion of colloids over crystalloids (*i.e.,* the ability to increase plasma volume) is greater for colloids (ratio 1.2-1.4:1 for crystalloid:colloid about 20%-40% enhanced effect with colloids); however, less than conventional teaching and evidence generated in experimental models[5-7,25]. This may be accounted for by the collapse of the classical "Starling model" based understanding of fluid movement across capillary membranes in critically ill states, where vascular endothelia is disrupted and hydrostatic (*i.e.,* systemic venous hypertension/endothelial injury) and oncotic (*i.e.,* hypoproteinemia) forces are deranged. Moreover, this also highlights that these issues are dynamic during the coarse of critical illness and that variable fluid types are expected to have heterogeneous effects that will depend upon: (1) the relative chloride load (*i.e.,* strong ion difference); (2) the presence of colloid (*i.e.,* HES or albumin); and (3) the underlying/evolving severity in patients pathophysiology.

The ideal electrolyte solution is yet undiscovered; however, for resuscitation may be one that reasonably parallels the plasma (chloride) and has a strong ion difference that is greater than zero (0.9% saline) but less

Table 2 Summary of studies comparing isotonic saline to balanced crystalloid solutions

Study	Design	Population	Solutions	Outcome
McFarlane *et al*[59]	RCT	Elective hepatobiliary/ pancreatic surgery	0.9% saline *vs* PL-148	Iatrogenic metabolic acidosis with 0.9% saline
Wilkes *et al*[47]	RCT	Major abdominal surgery	0.9% saline *vs* Hartmann's (in HES)	Iatrogenic metabolic acidosis with 0.9% saline
O'Malley *et al*[48]	RCT	Kidney transplant recipients	0.9% saline *vs* RL	Iatrogenic metabolic acidosis and hyperkalemia with 0.9% saline
Yunos *et al*[56]	Prospective before-and-after	Critically ill patients	Chloride-rich *vs* chloride-poor fluid strategy	More acidosis with chloride-rich; more alkalosis and reduced cost with chloride-poor
Chowdbury *et al*[26]	RCT (cross-over)	Healthy volunteers	0.9% saline *vs* PL-148 (2 L infusion)	↑ Δ [Cl⁻]; ↑ Strong ion difference; ↓ RBF; ↑ weight gain; ↑ extravascular volume; ↑ time to micturation
Chua *et al*[49]	Retrospective	Critically ill with DKA	0.9% saline *vs* PL-148	More rapid resolution of acidosis with PL-148
Shaw *et al*[55]	Retrospective	Major abdominal surgery	0.9% saline *vs* PL-148	↑ Major infection; ↑ composite of complications; ↑ blood transfusions; and ↑ RRT with 0.9% saline
Yunos *et al*[57]	Prospective before-and-after	Critically ill patients	Chloride-rich *vs* chloride-poor fluid strategy	↑ AKI (KDIGO stage Ⅱ / Ⅲ); ↑ RRT with chloride-rich strategy

Adapted from Raghunathan *et al*[58]. RCT: Randomized clinical trial; 0.9% saline: Normal saline; PL: Plasmalyte; RL: Ringers lactate; RBF: Renal blood flow; DKA: Diabetic ketoacidosis; AKI: Acute kidney injury; HES: Hydroxyethyl starch; RRT: Renal replacement therapy; KDIGO: Kidney disease improving global outcomes; FO: Fluid overload; FB: Fluid balance.

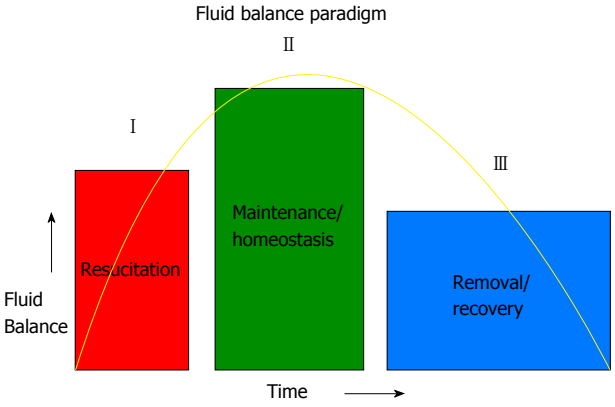

Figure 1 Fluid balance paradigm. The management of fluid therapy in critical illness can be conceptually viewed across three broad phases differentiated according to clinical status of the patient. During the "resuscitation" phase, the goal is restoration of effective intra-vascular volume, organ perfusion and tissue oxygenation. Fluid accumulation and a positive fluid balance may be expected. During the maintenance phase, the goal is maintenance of intravascular volume homeostasis. The broad aim here would be to mitigate excessive fluid accumulation and prevent unnecessary fluid loading. During the recovery phase, passive and/or active fluid removal would correspond to organ recovery.

than plasma during resuscitation[26]. Clinically important outcomes differ when comparing physiologically balanced crystalloids with isotonic saline solution. In the past year, a study at a single ICU[27] and another in patients undergoing major abdominal surgery[28], compared outcomes based on "chloride load". Consistent with earlier preclinical and human studies[25-28], chloride restriction was found to be beneficial (Table 2). However, even large volume resuscitation with balanced crystalloid solutions is capable of inducing mild metabolic acidosis due to hemodilution of weak acids and relative changes in strong ion difference. The challenges with many balanced crystalloid solutions is that they contain small concentrations of calcium and additional electrolytes that theoretically increase the risk for precipitation or clot formation during co-administration with citrated blood products when compared with saline. However, 0.9% saline is non-physiologic and the high (chloride) and a lower strong ion difference compared to plasma (0.9% saline: 0 mmol/L *vs* plasma: 40 mmol/L), directly contributes to iatrogenic hyperchloremic metabolic acidosis. Indeed, the use of balanced crystalloid resuscitation in patients with diabetic ketoacidosis, despite the added (potassium) content [(K^+) 5.0 mmol/L], was associated with more rapid correction of base deficit when compared to 0.9% saline[49]. Recent data have also clearly shown high (chloride) solutions contribute to renal vasoconstriction, decreased glomerular filtration, greater interstitial fluid accumulation[29-34] along with increased risk of acute kidney injury (AKI) and utilization of renal replacement therapy (RRT)[35].

A CONCEPTUAL FRAMEWORK FOR FLUID MANAGEMENT

A novel conceptual framework for fluid management in critical illness introduces the idea of interrelated phases of fluid management differentiated according to the clinical status of the patient with evolving goals for fluid need[33] (Figure 1). The model proposed for the epidemiology of fluid balance in AKI may be extended across the spectrum of critical illness with caveats: (1) In the initial phase of acute resuscitation-the objective is restoration of effective circulating blood volume, organ perfusion and tissue oxygenation. Fluid accumulation and a positive fluid balance may be expected; (2) In the second phase of resuscitation-the goal is maintenance of intravascular volume homeostasis. The objective during this phase is to prevent excessive fluid accumulation and avoid unnecessary fluid loading; and (3) In the final stage, the objective centers around fluid removal and the concept of active "de-resuscitation" corresponding to a state of physiologic stabilization, organ injury recovery and convalescence. During this phase, unnecessary fluid accumulation may contribute to secondary organ injury and adverse events.

Table 3 Studies in critically ill patients describing the association with fluid overload and worse outcome

Study	Design	Population	Exposures	Outcomes
Pediatric Studies				
Goldstein *et al*[33]	Retrospective	Pediatric critically ill starting CRRT	% FO	↑ % FO associated with ↑ mortality
Foland *et al*[60]	Retrospective	Pediatric critically ill starting CRRT	% FO	↑ % FO associated with ↑ organ dysfunction + mortality
Sutherland *et al*[31]	Retrospective	Pediatric critically ill starting CRRT	% FO	↑ % FO associated with ↑ mortality
Arikan *et al*[30]	Retrospective	Pediatric critically ill starting CRRT	% FO	↑ % FO associated with ↓ lung function
Adult Studies				
Payen *et al*[61]	Post-hoc prospective	Adult critically ill septic patients	FB	↑ FB associated with ↑ mortality
Murphy *et al*[62]	Retrospective	Adult critically ill ALI patients	AIFR + CLFM	↑ Survival for ↑ AIFR + ↑ CLFM
Bouchard *et al*[63]	Post-hoc prospective	Adult critically ill AKI patients	% FO > 10%	↑ FB associated with ↑ mortality
Wiedemann *et al*[36]	RCT	Adult critically ill with ALI	Conservative *vs* liberal fluid management strategy	↑ MV-free days; ↑ ICU-free days with conservative strategy
Fulop *et al*[64]	Retrospective	Adult critically ill starting CRRT	VRWG	↑ VRWG associated with ↑ mortality
Boyd *et al*[65]	Post-hoc analysis from VASST	Adult critically ill septic patients	Quartiles of FB + CVP at 12 h and 4 d	↑ FB at 12 h and 4 d associated with ↑ mortality; CVP < 8 at 12 h ↓ mortality
Grams *et al*[66]	Post-hoc FACCT	Adult critically ill with ALI + AKI	FB + diuretics	↑ FB associated with ↑ mortality
Heung *et al*[67]	Retrospective	Adult critically ill starting CRRT	% FO	↑ % FO associated with ↓ kidney recovery
Bellomo *et al*[68]	Post-hoc RENAL	Adult critically ill with AKI	FB	↑ FB associated with ↑ mortality

Adapted from Raghunathan *et al*[58]. ALI: Acute lung injury; AIFR: Adequate initial fluid resuscitation; CLFM: Conservative late fluid management; VRWG: Volume-related weight gain; AKI: Acute kidney injury; CVP: Central venous pressure; ICU: Intensive care unit; RCT: Randomized clinical trial.

Numerous studies in peri-operative and critical care settings support this concept of "ebb and flow" in fluid loading, fluid accumulation and removal. Indeed, these phases of resuscitation likely exist on a continuum and the observed variability in fluid balance is understood to be a dynamic process, does not necessarily follow a fixed temporal pattern or time scale and is likely highly individualized. For example, in septic patients with acute lung injury, the balance between early goal-directed therapy aimed at adequate initial fluid resuscitation coupled with downstream diuretic use and "de-resuscitation" (*i.e.,* conservative late fluid management) can improve outcomes[37,38]. Similarly in pediatric septic shock, outcome improved with early appropriate fluid therapy[39]. Such phasic need for fluid and then need for active fluid removal has also been demonstrated in peri-operative settings[40]. Inappropriate fluid therapy, regardless of fluid type, may disrupt compensatory mechanisms and worsen outcome[5].

QUANTITATIVE TOXICITY

Fluid therapy is a critical aspect of initial acute resuscitation in critically ill patients. Following the acute resuscitative phase (*i.e.,* achievement of immediate resuscitation goals and after hemodynamic stabilization), excessive fluid accumulation has been associated with worse clinical outcome, across a range in clinical settings, particularly in AKI[37] (Table 3). In patients with sepsis-associated AKI, continued fluid loading in the setting of apparent optimal systemic hemodynamics was shown not to improve kidney function, but worsen lung function and oxygenation[30]. Similar observational data in critically ill adults with sepsis-associated AKI has found fluid accumulation to be a predictor of 60-d mortality (HR = 1.21/L per 24 h, 95%CI: 1.13-1.28, $P < 0.001$)[37]. Additionally, although the FACCT trial did not demonstrate a mortality difference between a liberal and a more conservative fluid management strategy in the setting of acute lung injury, the conservative strategy was associated with improved lung function, reduced length of stay in ICU and a trend for lower utilization of RRT[36]. Increasing severity of fluid accumulation among both pediatric and adult patients with AKI at the time of initiation of RRT has been associated with higher mortality and reduced likelihood of recovery of kidney function[42-45]. For each 1% increase in percentage fluid overload (% FO, as calculated below) at RRT initiation, risk of death increased by 3%[31]. % FO = [(total fluid in-total fluid out)/admission body weight × 100].

Failure to appreciate these phases of fluid management following resuscitation may underscore the observed phenomenon of "fluid creep", first identified in the burn literature in response to the overwhelming enthusiasm for aggressive and sustained fluid resuscitation[29,32]. These observations highlight the importance of monitoring fluid balance in critical illness, in particular after the initial phase of resuscitation, where obligatory fluid intake (*i.e.,* medications, nutrition, blood products) may greatly exceed output (*i.e.,* relative oliguria), leading to rapid fluid accumulation[34]. In these circumstances, there should be effort to minimize or avoid all non-essential fluid administration. However, data on fluid accumulation in critically ill patients is almost entirely post-hoc, associative and not causal. Very few prospective interventional studies, with the exception of the FACCT trial and selected studies of conservative peri-operative fluid regimens have informed on the optimal fluid management strategies for critically ill patients and evaluated their association with organ function, adverse events, and survival[35,36]. This represents an important knowledge gap in our understanding of how to optimally manage-

Table 4 Summary of randomized trials of hydroxyethyl starch resuscitation in severe sepsis/septic shock and kidney outcomes

Ref.	RCT type	*n* (HES/CON)	Population (*n*)	HES fluid	Control fluid	Kidney parameters	RRT (OR; 95%CI)
Schortgen *et al*[50]	Multi-centre	129 (65/64)	Severe sepsis/ septic shock	6% (200/0.62)	3% gelatin	↑ AKI ↑ oliguria, ↑ peak SCr	1.20 (0.5-2.9)
Molnár *et al*[69]	Single centre	30 (15/15)	Septic shock	6% (200/0.60)	3% gelatin	NR	NR
McIntyre *et al*[70]	Multi-centre	40 (21/19)	Septic shock	6% (200/0.50)	0.9% NS	No difference	3.00 (0.3-31.6)
Brunkhorst *et al*[42]	Multi-centre	537 (262/275)	Severe sepsis/ septic shock	10% (200/0.5)	RL	↑ AKI	1.95 (1.3-2.9)
Guidet *et al*[23]	Multi-centre	196 (100/96)	Severe sepsis/ septic shock	6% (130/0.4)	0.9% NS	No difference	NR
Perner *et al*[6]	Multi-centre	798 (398/400)	Severe sepsis/ septic shock	6% (130/0.42)	Ringer's acetate	↑ AKI	1.35 (1.01-1.8)
Myburgh *et al*[5]	Multi-centre	7000 (3315/3336)	Sepsis (27.4%) (1921/7000)	6% (130/0.4)	0.9% NS	↑ RRT	1.21 (1.00-1.45)

RCT: Randomized clinical trial; HES: Hydroxyethyl starch; CON: Control; NS: Normal saline; RL: Ringer's lactate; AKI: Acute kidney injury; RRT: Renal replacement therapy; NR: Not report.

ment fluid beyond the initial resuscitation for acutely ill patients.

QUALITATIVE TOXICITY

Colloid solutions

The saline *vs* albumin fluid evaluation (SAFE) trial, in which nearly 7000 critically ill patients were randomized to either 4% human albumin or saline for resuscitation was the first large scale high-quality trial to show no overall difference in mortality, ICU length of stay, need for mechanical ventilation or RRT, or hospital length of stay. However, subgroup analyses founds trends for higher mortality in trauma patients, predominantly with head injury (OR = 1.36, $P = 0.06$) and lower mortality in sepsis (OR = 0.87, $P = 0.09$)[37]. Subsequently, a post-hoc longer-term follow-up study of patients enrolled in the SAFE trial who had suffered traumatic brain injury was performed, confirming the initial trends to suggest a higher mortality in head-injured patients receiving albumin (OR = 1.88, $P < 0.001$)[38].

While HES solutions, including newer starches, appear equally or more efficacious (*vs* older starches or crystalloids in certain situations) for restoration of intravascular volume in acute resuscitation, data continues to accumulate to suggest harm in critical illness (Table 4). Small clinical trials have suggested HES solutions are also superior for resuscitation of the microcirculation in sepsis and contribute to more rapid hemodynamic stabilization and shock reversal, and require significantly less fluid to restore intravascular volume. There has been suggestion of an improved safety profile for HES solutions with a lower molecular weight and lower degree of molar substitution, in terms of bleeding complications and AKI; however, these findings have been inconsistent. Prior to VISEP, 6S and CHEST, the literature had largely been dominated by small lower quality randomized trials that precluded a clear appraisal of potential survival benefit and the risk of toxicity[39,40]. In addition, wide scale retractions have followed reporting of fraud in research evaluating the safety of HES[41,46]. Accrued data from large randomized trials have now raised serious concerns about potential for dose-associated kidney toxic effects of HES[5,6,42,43]. Experimental data have shown even newer generation HES solutions can still accumulate in tissues within hours of administration, including in the liver, kidney, lung, spleen and lymph nodes[69]. In the VISEP trial, pentastarch (10% HES 200/0.5) was compared to Ringer's lactate for fluid resuscitation in ICU[42]. The trial was stopped early due to the increased incidence of AKI (34.9% *vs* 22.8%, $P = 0.001$) and a trend towards increased mortality (41% *vs* 33.8%, $P = 0.09$). These results were corroborated in the CHEST and 6S trials[5,6]. The CHEST trial evaluated the use of Voluven® (6% HES 130/0.4 in 0.9% saline) compared to 0.9% saline for acute resuscitation in ICU[5]. While there was no difference in mortality, there was an increase in the utilization of RRT (7.0% *vs* 5.8%, $P = 0.04$) in those receiving HES. In the 6S trial, Tetraspan® (6% HES 130/0.42 in Ringer's acetate) was compared to Ringer's lactate for acute resuscitation in severe sepsis[7]. Both the incidence of AKI (22% *vs* 16%, $P = 0.04$), and mortality (51% *vs* 43% at 90 d, $P = 0.03$) were significantly higher with HES. These data imply an increased risk for harm associated with HES solutions and have lead the European Society of Intensive Care Medicine to recommend against the use of HES in patients with severe sepsis or those at risk for AKI and has further suggested a moratorium on the use of HES except in the context of a clinical trial[49]. In addition, the United States Food and Drug Administration has recently issued black Boxed warning against their use in critically ill patients due to the increased risk of AKI and death[44]. However, there remains continued controversy on whether the use of HES in recent randomized trials was appropriate, such as only being used early and in limited volumes for the acute resuscitation of critically ill hypovolemic patients[45].

All HES solutions are carried in crystalloid. In the 6S trial, both arms received balanced crystalloid solution (*i.e.,* Ringer's acetate); whereas in the CHEST trial, both groups received 0.9% saline. It is biologically plausible there may be considerable interaction between the ad-

verse effects of HES and the chloride-rich 0.9% saline. When considering high chloride load is associated with adverse effects and worse outcome, it is therefore plausible that the harm associated with HES is exaggerated when used with 0.9% saline compared with a balanced crystalloid carrier.

In the 6S trial[6], patients were less likely to achieve shock reversal (*i.e.,* failure to clear lactate); whereas, in the CHEST trial[5], shock was reversed (*i.e.*, lactate cleared) with less total fluid administered in the HES group. These data imply that while HES may be more efficacious for shock resolution when compared to crystalloid; if there is delayed or failure to reverse shock, there may be greater toxicity and harm associated with HES; and this hazard may not be immediately apparent (*i.e.,* risk of harm is delayed several days to weeks).

The use of hyperoncotic colloid solutions for acute resuscitation remains controversial. In a large multi-centre European study of 822 critically ill adults with shock receiving fluid resuscitation, use of hypertonic natural and synthetic colloids was associated with a several fold increased risk for AKI and death[50]. A recent systematic review found divergent findings for use of hyperoncotic colloids for resuscitation and subsequent risk of AKI[51]. In this meta-analysis of 7 trials including 1220 patients, hyperoncotic albumin was associated with reduced risk (OR = 0.24, $P < 0.001$); whereas hyperoncotic HES solutions were associated with increased risk for AKI (OR = 1.92; 95%CI: 1.31-2.81, $P < 0.001$). These data seem to further infer the kidney toxicity may be a class effect associated with HES solutions.

Crystalloid solutions

The *iv* solution used in 1832 by Dr Thomas Latta for the treatment of cholera would today be considered a balanced salt solution: 134 mmol/L Na^+, 118 mmol/L Cl^-, 16 mmol/L HCO_3^-[52]. Surprisingly, it was not until 1888 that a reference to *normal* or *physiologic saline* is found in the medical literature, and not until 1896 that 0.9% saline is described[53,54]. Despite the fact that 0.9% sodium chloride is not isotonic to serum, it is believed that *in vitro* experiments comparing the freezing points of various solutions to serum led to the belief that this solution was "physiologic". Perhaps it was for simplicities' sake that solutions containing mixtures of anions were avoided in favor of the addition of table salt to water.

However, data are accumulating to suggest chloride-rich solutions are problematic. As aforementioned, the high (chloride) and a lower strong ion difference compared to plasma (0.9% saline: 0 mmol/L *vs* plasma: 40 mmol/L), directly contribute to iatrogenic hyperchloremic metabolic acidosis, which may mask, simulate and/or precipitate adverse effects[55,56]. In a randomized crossover trial of healthy volunteers, renal blood flow and renal cortical perfusion decreased significantly following the bolus administration of 2 L of 0.9% saline compared to plasma-lyte 148[30]. The use of chloride-rich solutions in critically ill patients is not only associated with increased costs and laboratory utilization[57], but also increased incidence of AKI and RRT utilization[27].

These observations are supported from a recent interrogation of the Premier perspective comparative database of patients undergoing elective or emergent open general surgical operations evaluating the rate of adverse events associated with receiving either balanced or isotonic saline solutions on the day of surgery[28]. In this study, patients who received exclusively a calcium-free balanced salt solution (plasma-Lyte A or plasma-Lyte 148) were matched on a 3:1 basis with those receiving exclusively 0.9% saline. Although there were no statistically significant differences between the two groups at baseline, the differences in outcome were dramatic: significantly fewer postoperative infections ($P = 0.006$), less dialysis ($P < 0.001$), fewer blood transfusions ($P < 0.001$), fewer electrolyte disturbances ($P = 0.046$), fewer acidosis investigations ($P < 0.001$) and interventions ($P = 0.02$) were all associated with the use of balanced salt solutions compared with 0.9% saline. While these data are not a randomized comparison of balanced *vs* 0.9% saline solutions, randomized trials are ongoing.

CONCLUSION

Despite its ubiquitous use in critical care, further carefully performed, transparent research on fluid resuscitation in critical illness is desperately needed. Context appears to be crucial when prescribing fluid and any fluid can be harmful if dosed incorrectly. Differences in immediate efficacy between crystalloid and colloid solutions are modest at best, but the differences in longer-term safety appear more significant. Qualitative toxicity for colloids (even with newer lower molecular weight, less substituted HES solutions) and isotonic saline remain a concern. The observed differences in chloride load and strong ion difference in the various crystalloid solutions appear to be clinically important. We contend that physiologically balanced crystalloids may be the best "default" fluid for acutely ill patients, and that the role of colloids is unclear. Optimal dosing of any resuscitation fluid mandates an understanding the dynamic nature of fluid resuscitation, and future investigations will hopefully allow for the development of better tools to guide therapy.

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