

Choice of fluid in acute illness: what should be given? An international consensus[‡]

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Editor's key points

- The authors explore the rationale for the selection of i.v. fluids.
- They conclude that there is little evidence of superiority for any i.v. fluid.
- They note that the chloride content of i.v. fluids may have an important bearing.

Fluid management during critical illness is a dynamic process that may be conceptualized as occurring in **four phases: rescue, optimization, stabilization, and de-escalation (mobilization)**. The selection and administration of resuscitation fluids is one component of this complex physiological sequence directed at restoring depleted intravascular volume. Presently, the selection of i.v. fluid is usually dictated more by local practice patterns than by evidence. The **debate on fluid choice** has primarily focused on evaluating outcome differences between 'crystalloids vs colloids'. More recently, however, there is interest in examining outcome differences based on the **chloride content** of crystalloid solutions. **New insights into the conventional Starling model** of microvascular fluid exchange may **explain** that the **efficacy of colloids** in restoring and maintaining depleted intravascular volume **is only moderately better** than **crystalloids**. A number of investigator-initiated, high-quality, randomized controlled trials have demonstrated that **modest improvements in short-term physiological endpoints with colloids** have **not** translated into **better** patient-centred outcomes. In addition, there is substantial evidence that certain types of fluids may **independently worsen** patient-centred outcomes. These include **hydroxyethyl starch** and **albumin** solutions in **selected** patient populations. There is **no evidence to support** the use of **other colloids**. The use of **balanced salt** solutions in preference to 0.9% saline is supported by the **absence of harm** in large observational studies. However, there is **no compelling randomized trial-based evidence demonstrating improved clinical outcomes with the use of balanced salt solutions compared with 0.9% saline at this time**.

Keywords: balanced salt solutions; colloids; crystalloids; fluid choice; isotonic saline

The clinical decision to administer i.v. fluids in acute illness is followed by decisions on the amount and type of fluid to be infused.^{1–2} Like any other drug used during acute illness, i.v. fluids have quantitative¹ and qualitative adverse effects,^{2–4} with the therapeutic index depending on the type of fluid and the clinical setting. Patterns of fluid selection are dependent on local practice patterns and marketing and not necessarily based on evidence.⁵ When compared with crystalloids, colloids have not been shown to improve patient-centred outcomes, yet they are widely used on the basis of theoretical advantages inferred from traditional physiological principles.⁶ However, the classic Starling

model is being revised in the light of new findings.⁷ Emerging evidence suggests that the choice of fluid should instead be guided by contextual patient-specific factors. Fluid management goals vary depending on the phase of acute illness and the focus is:

- to achieve and maintain adequate effective circulating volume during the rescue and optimization phases;
- to minimize complications during the stabilization phase; and,
- finally to restore a more normal fluid balance during de-escalation.

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Until direct evidence to the contrary is presented, balanced salt solutions appear to be a reasonable default choice in the initial rescue and optimization phases. In this paper, we briefly update physiological precepts, discuss what is known about fluid choice, present a network meta-analysis, and outline an agenda for future research.

Methods

The 12th Acute Dialysis Quality Initiative (ADQI) conference was convened in the light of recent developments in the field of i.v. fluids with the aim of clarifying and advancing understanding of fluid management during acute illness. This report is the result of a modified Delphi analysis performed by the ADQI XII working subgroup charged with appraising the published evidence on fluid choice. The Delphi method is detailed in the first paper in this series.⁸

Results

Based on the literature identified before the conference, and iterative discussions during and after the meeting, the following key questions were addressed:

- Q1. What physiological model(s) explain the disposition and effects of different fluid types?
- Q2. What is known about fluid choice in acute illness?
 - Is there evidence of harm or benefit associated with specific types?

- Q3. What does the totality of the evidence concerning fluid choice suggest when viewed as a network of studies?
- Q4. A priority for future research?

Discussion

Physiological models: role of the glycocalyx

Clinicians continue to categorize fluids as crystalloids or colloids.⁵⁻⁹ Crystalloids, which are sterile solutions containing electrolytes, glucose molecules (small solutes), or both, are thought to pass readily through capillary membranes expanding the extracellular (intravascular and interstitial) space. Colloids, which contain macromolecules suspended in sterile electrolyte solutions (for adequate tonicity), are expected to distribute largely within the intravascular space. According to Starling's original description, colloids may be expected to have about **three-fold** greater volume expansion efficacy than crystalloids.⁶ Perhaps influenced by this model, clinicians worldwide continue to use colloids during acute illness as confirmed by a recent poll conducted in the *New England Journal of Medicine*.¹⁰ However, there is at most only **modestly greater efficacy** for colloids (30–40%),¹¹ and this has **not** translated to **improved** patient-centred **outcomes**. A revised Starling model has been proposed,¹² recognizing that the endothelial **glycocalyx** located on the luminal side of healthy vasculature⁷ plays a vital role in maintaining vascular integrity.^{12 13} Concordant with empiric observations, this **revised model accounts** for the **reduced**

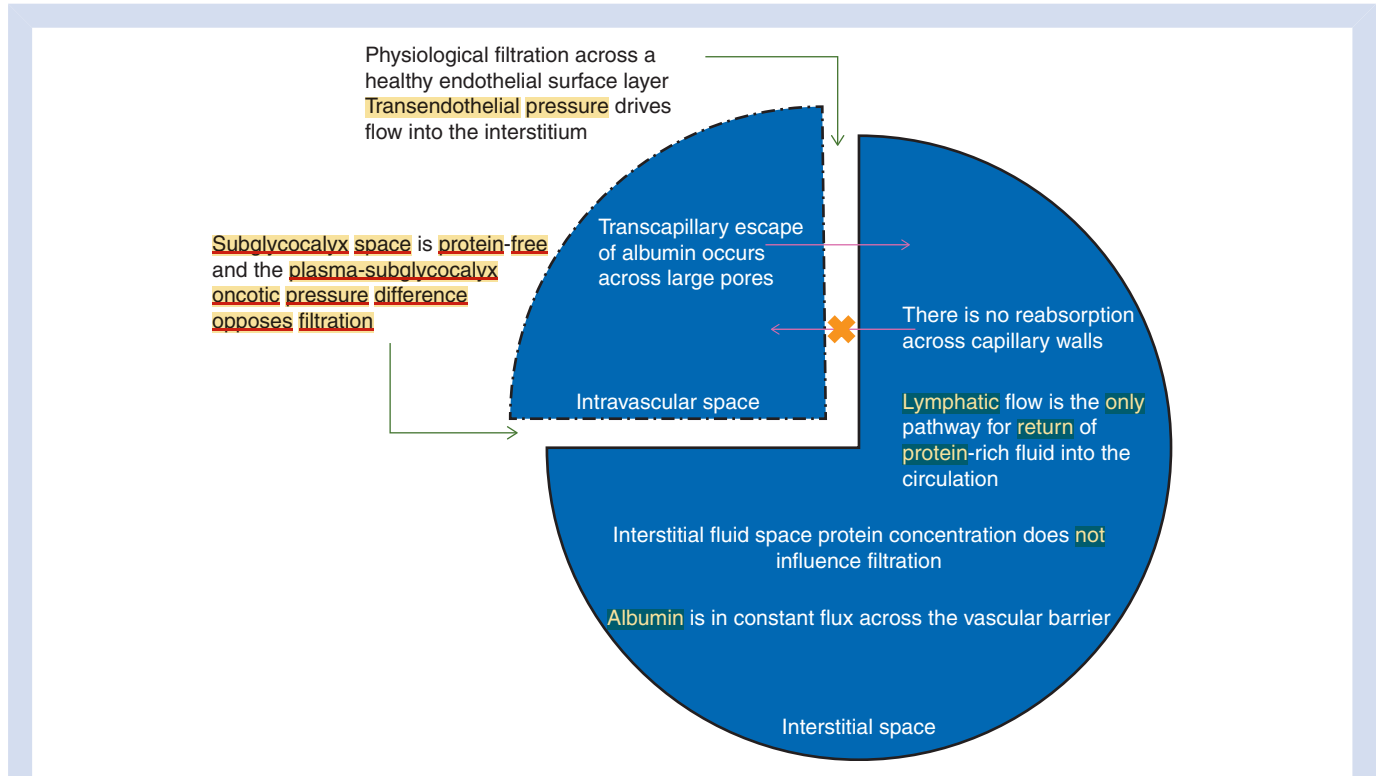


Fig 1 The revised Starling model in health. Key updates to the original model: overall filtration is much less than predicted by the original model as the important forces are the **transendothelial pressure difference** and the **plasma-subglycocalyx oncotic pressure difference**. Interstitial oncotic pressure is **not** a determinant of transvascular filtration. There is **no reabsorption of fluid** into the **intravascular** space from the interstitium.

filtration and lymph flow seen in most tissues at baseline (Fig. 1).¹⁴ Accordingly, crystalloid efficacy is expected to be equivalent to colloids when the vascular barrier is compromised, when capillary pressures are low, or both. In systemic inflammatory states such as surgery¹⁵ and sepsis,¹⁶ interstitial pressures decrease, and porosity increases as the integrity of the glycocalyx barrier is lost (Fig. 2).^{12–17} All resuscitation fluids can contribute to the formation of interstitial oedema and fluid balance may be more important than fluid type.¹⁸ Hence, the selection of specific fluids should be based on the understanding that differences in efficacy are modest, while differences in safety are significant (Table 1).

What is known about fluid choice?

Colloids

In large-scale randomized controlled trials (RCTs),^{23–20} short-term physiological gains associated with specific colloids have not translated into longer-term improvements in patient-centred outcomes. Accordingly, the goal is to minimize toxicity. Clinical context should determine choice in specific situations. Albumin is either not widely available or is expensive in most countries and the Saline versus Albumin Fluid Evaluation (SAFE) study specifically examined safety among nearly 7000 adults in the intensive care unit (ICU).²⁰ With respect to mortality or

the development of new organ failure, effects of resuscitation with 4% albumin were not significantly different from resuscitation with 0.9% saline. However, albumin therapy increased the risk of death in a prespecified subgroup with traumatic brain injury.⁴ Precise mechanisms are unclear, but the increase in intracranial pressure among patients in the albumin group may be related to the relatively hypotonic and hypo-osmolar nature of the 4% albumin. In contrast, resuscitation with albumin has been associated with a decrease in the adjusted risk of death among patients with severe sepsis. Contrary to recommendations in clinical guidelines,²¹ fluid boluses in the resuscitation of septic patients may have potential adverse effects and confer significant risks regardless of the fluid type. Mechanisms for harm related to the rate of administration are unclear but may involve a lack of compensatory neurohormonal responses.^{22–23}

The safety of hydroxyethyl starch (HES) has been under scrutiny for many years, with reviews noting increased risks, especially with older high molecular weight hyperoncotic HES.^{24–25} Modern tetrastarch (6% HES 130/~0.4) may have been considered preferable with faster plasma clearance (even with repeated administration).²⁶ However as seen in large investigator-initiated RCTs, risks of impaired kidney function with HES appear to be persistent, generic, and dose-dependent.²⁷ It is unclear if these results are generalizable to other semisynthetic colloids, like gelatin or polygeline

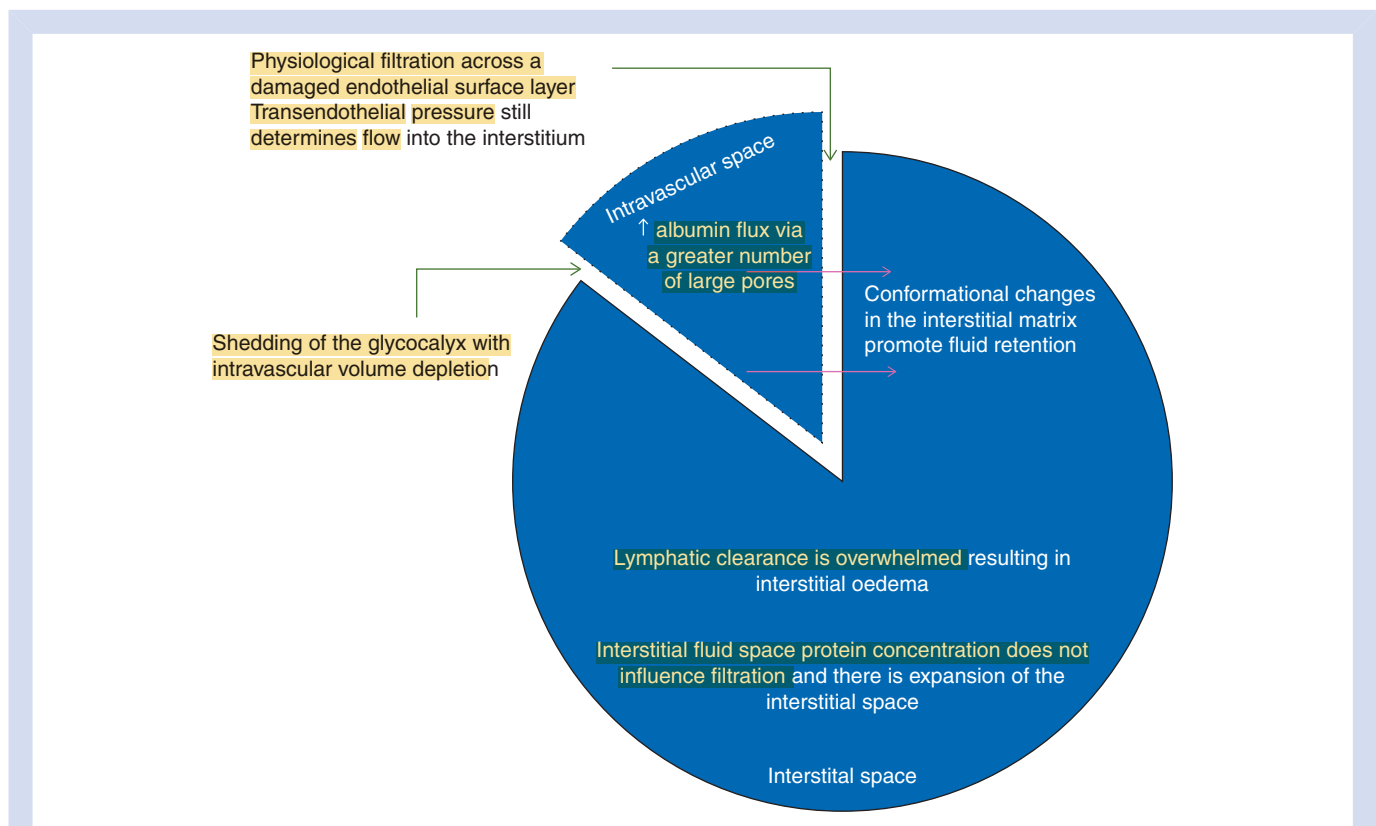


Fig 2 The revised Starling model during critical illness. During critical illness, loss of the glycocalyx, reduction in the effective circulating intravascular volume, and expansion of the interstitial space occur. Expansion of the interstitial space is shown as a relative increase in the proportion of extravascular fluid. Infusion of colloid solution increases the plasma volume, while infusion of crystalloid increases intravascular volume—filtration remains low in both cases when capillary pressures are low. Conversely, oedema occurs regardless of fluid type when capillary pressures are supranormal.

Table 1 Volume efficacy vs outcomes. Major crystalloid–colloid RCTs directly comparing albumin or modern starch solutions with corresponding control solutions are highlighted below. Differences in volume efficacy are modest and not consistent with differences in patient-centred outcomes. Differences in safety outcomes are significant

RCT, phase of resuscitation, fluids/ approaches compared	Primary study population, subpopulations, randomization and blinding	Volume efficacy, colloid:crystalloid ratio, time frame for comparison	Haemodynamic outcome, patient-centred outcome
SAFE , 'optimization phase', albumin vs saline ²⁰	Admitted to ICU, trauma and non-trauma, 1:1—blinded	Overall ratio: Alb:Sal—1:1.4; ratios on: day 1—1.3; day 2—1.6; day 3—1.3	No difference in MAP, small differences in CVP and HR, no difference in 28 day mortality
FEAST , 'resuscitation phase', bolus with albumin vs with saline vs no bolus ²³	Paediatrics patients with severe infections, with and without shock, 1:1:1—not blinded	Equivalent efficacy, over first 8 h, no bolus received 10 vs 40 ml kg ⁻¹ in the albumin and saline bolus groups (1:1)	Greater resolution of shock in bolus group but no difference in fluid type, greater relative risk of death with bolus vs no bolus (1.45), no difference in 48 h mortality for albumin vs saline
CHEST , 'optimization phase', HES vs saline ³	Admitted to ICU, six prespecified subgroups incl. kidney injury, sepsis, APACHE II scores, 1:1—blinded	Overall ratio: HES:Sal—1:1.2, over first 24 h, net fluid balance less positive in the HES group (clinically marginal difference)	Small differences in CVP and blood products; no difference in MAP, HR, no difference in 90 day mortality, increase in RRT with HES
6S , 'optimization phase', HES vs saline ²	Admitted to ICU, with severe sepsis, two prespecified subgroups: shock or kidney injury, 1:1—blinded	Equivalent, no difference in fluid balance over 3 days	Small increase in blood products received by HES group; no differences in circulatory variables over 24 h after randomization, increased risk with HES—relative risk death (1.17) and RRT (1.35)
CRYSTMAS , 'resuscitation phase', HES vs saline ²⁸	Severe sepsis, no large prespecified subgroups, 1:1—Blinded	Overall ratio 1:1.2, shorter time (2.5 h less) to reach haemodynamic stability over the first 12–24 h	20–30% less volume needed to reach haemodynamic stability (primary outcome), not adequately powered for patient-centred events (secondary outcomes)
CRISTAL , 'resuscitation phase', colloids vs crystalloids—no specific agents compared ²⁹	Admitted to ICU requiring resuscitation, sepsis, trauma, or hypovolaemic shock without sepsis or trauma, 1:1—not blinded	Overall ratio 1:1.5, over first week, significantly less colloid volume needed to achieve the same haemodynamic targets	First 24 h after randomization, mean arterial pressure, urinary output, weight, and chest X-ray scores were not significantly different. No difference in 28 day mortality; fewer deaths at 90 days, more ventilator-free and vasopressor-free days with colloids

preparations, as these have not been studied in high-quality RCTs. A recent observational study similarly raised concern about the risk of acute kidney injury with the use of gelatin.³⁰ In the light of current evidence, it is difficult to support the use of semisynthetic colloids during resuscitation in critically ill patients. The clinical use of HES solutions has been significantly restricted by regulatory authorities via warnings on the potential for adverse effects.

Crystalloids

Animal³¹ and human experiments^{32–36} have shown that infusions of moderate to large volumes of 0.9% saline can cause a hyperchloraemic acidosis and can also cause greater interstitial oedema than balanced crystalloids (which are similar to human plasma in their composition, strong ion difference, and do not produce hyperchloraemia and acidosis).³² Hyperchloraemia can cause renal vasoconstriction,³⁷ decreased renal artery flow velocity, blood flow, and cortical tissue perfusion,³² and reduced glomerular filtration rate,³⁸ leading to salt and water retention, when compared with balanced crystalloids. However, review of the literature fails to reveal a

single large randomized study showing 0.9% saline to be clinically superior to the more physiological balanced crystalloids. The absence of studies demonstrating better clinical outcomes with balanced crystalloids has led to the continued use of 0.9% saline in most areas of practice. Two early perioperative studies^{34, 39} and one in the resuscitation setting⁴⁰ suggested that the hyperchloraemic acidosis could be given a false pathological significance and could also exacerbate an acidosis resulting from an actual pathological state. In addition, two relatively small RCTs in humans comparing 0.9% saline with Ringer's lactate in the perioperative period showed that 0.9% saline caused more undesirable side-effects.^{41, 42} In the first study, involving patients undergoing abdominal aortic aneurysmorrhaphy, those receiving saline needed more packed red blood cells (780 vs 560 ml), platelets (392 vs 223 ml), and bicarbonate therapy (30 vs 4 ml).⁴² Postoperative pH was significantly lower and chloride concentration significantly higher in the saline group, but this hyperchloraemic acidosis did not result in an apparent change in outcome other than the requirement of larger amounts of bicarbonate to achieve predetermined measurements of base deficit and the use of larger amounts of blood products.⁴² The other study involving

patients undergoing renal transplantation had to be stopped prematurely because 19% of patients in the saline group had to be treated for hyperkalaemia and 31% for metabolic acidosis compared with none in those receiving Ringer's lactate.⁴¹ There was no statistically significant difference in postoperative renal function. As both these studies were relatively small, it is quite possible that the lack of difference in clinical outcome measures may represent a type II error. Three recent large observational studies^{43–45} have also suggested that the high chloride content of 0.9% saline may cause harm, especially to the kidney. Using a validated and quality assured database, evaluation of outcomes in 30 994 adult patients undergoing major open abdominal surgery showed that unadjusted in-hospital mortality (5.6% vs 2.9%) and the percentage of patients developing complications (33.7% vs 23%) were significantly greater in the 0.9% saline group when compared with the group receiving a balanced crystalloid.⁴³ Mortality differences ceased to be statistically significant after adjustment for confounding factors. Patients receiving 0.9% saline had significantly greater blood transfusion requirements, more infectious complications, and were more likely to require dialysis than those receiving balanced crystalloids. In another recent open-label prospective sequential study,⁴⁴ patients admitted consecutively to intensive care (30% of whom were admitted after elective surgery) received either traditional chloride-rich solutions (0.9% sodium chloride, 4% succinylated gelatin solution or 4% albumin solution, $n=760$) or chloride-restricted fluids (Hartmann's solution, Plasma-Lyte 148 or chloride-poor 20% albumin, $n=773$). After adjusting for confounding variables, the chloride-restricted group had decreased incidence of acute kidney injury [odds ratio 0.52 [95% confidence interval (CI) 0.37–0.75], $P<0.001$] and reduced use of renal replacement therapy (RRT) [odds ratio 0.52 (95% CI 0.33–0.81), $P=0.004$]. However, there were no differences in hospital mortality, hospital, or ICU length of stay.⁴⁴ A third study on 22 851 surgical patients with normal preoperative serum chloride concentration and renal function showed that the incidence of acute postoperative hyperchloraemia (serum chloride >110 mmol litre⁻¹) was 22%. Of the 4955 patients with hyperchloraemia after surgery, 4266 (85%) patients were propensity-matched with an equal number of patients who have normal serum chloride concentrations after operation. Patients with hyperchloraemia were found to be at increased risk of 30 day postoperative mortality [3.0% vs 1.9%; odds ratio 1.58 (95% CI 1.25–1.98)], have a longer median hospital stay, and were more likely to have postoperative renal dysfunction.⁴⁵ These large observational studies suggest that it may be time to reconsider the use of 0.9% saline as the default crystalloid of choice and restrict its use to specific situations (hypochloraemia and metabolic alkalosis).

What does the totality of the evidence suggest in network meta-analysis?

Previous dichotomous meta-analyses have focused on comparisons between specific crystalloids and colloids. This age-old 'crystalloid or colloid' question has now morphed into a

question of which fluids are superior when considering the totality of available choices and evidence. Conventional pairwise meta-analyses have not considered this problem. The issue is topical after the publication of two recent large randomized trials,^{2, 3} suggesting that HES may increase the incidence of renal failure among critically ill patients. A third open-label study did not find this suggestion of harm with colloids.²⁹ Furthermore, recent publications have drawn attention to the potential for saline to increase renal failure compared with the use of balanced salt solutions.^{45 46 47} We considered large trials of fluid choice as amenable to network meta-analysis. All trials in this network have at least one intervention in common and the goal is to allow clinicians to estimate the relative merits of interventions that may or may not have been contrasted against each other directly but can be considered simultaneously (Fig. 3). When different types of fluids have been compared in similar scenarios with common outcomes (e.g. mortality), network meta-analyses offer an opportunity to see and interpret the totality of evidence. Network meta-analysis has advantages over conventional pairwise meta-analysis, in that the technique borrows strength from indirect evidence to gain insight into treatment comparisons, and for estimation of comparative effects that have not been investigated head-to-head. By including observational studies with rigorous control for confounding variables, the evidence base is broadened. While pairwise comparisons aim to estimate direct treatment effects for each intervention relative to the control, network meta-analyses are designed to evaluate direct and indirect effects via comparisons of multiple interventions.

For our purposes, we combined the results of these 13 groups using REVMAN 5 software (Cochrane Collaboration,

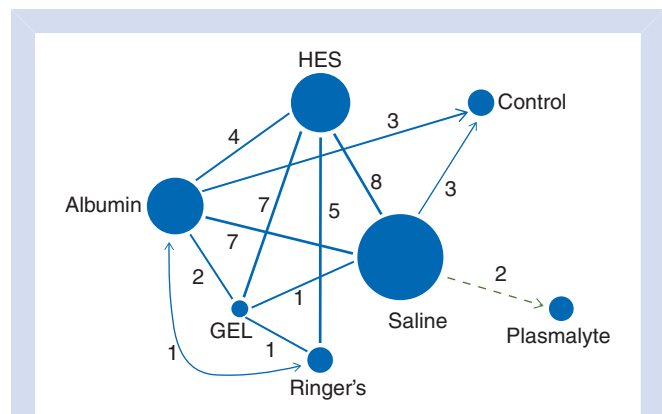


Fig 3 Network of studies evaluating 'fluid choice' in critical care. The network approach allows indirect comparisons in addition to the conventional direct comparisons. Each circle represents a particular type of fluid studied either in randomized or in observational comparisons. The size of the circle represents the number of patients who received that specific fluid across multiple trials. As shown, trials have typically compared saline with colloids (HES or albumin suspended in saline) but have not compared crystalloids with each other. Numbers adjacent to the lines represent studies performing direct pairwise comparisons, while arrows represent the direction of significant superiority in the network meta-analysis. Finally, the dotted line represents observational comparisons.

<http://ims.cochrane.org/revman>) and calculated the relative risk of mortality using the Mantel–Haenszel random effects model. During the conference, we were urged to delay our final analysis pending the publication of CRISTAL trial results.²⁹ CRISTAL did not prespecify a particular crystalloid–colloid comparison, leaving the decision to local preference. Strictly speaking, this does not represent a randomized choice; nevertheless, separate comparisons of each crystalloid to colloid were presented in the CRISTAL study report. Nine hundred and twenty-six patients received a synthetic colloid [645 HES, 281 a gelatin (GEL)], while 80 received albumin. The remaining population received more than one colloid. Although outside of the regular methodology for a meta-analysis, these were included in our analysis. We used the I^2 -statistic to quantify the degree of heterogeneity for each of the comparisons and assessed publication bias in each analysis using a standard Eggers plot.⁴⁸ The capacity to detect bias is limited when meta-analyses are based on small trials. The quality of each trial in the comparisons was assessed by (i) the method of randomization, (ii) allocation concealment, (iii) blinding, and (iv) intention-to-treat analyses. The risks of bias were rated as low, moderate, high, and very high. We arbitrarily decided not to report comparisons where there were less than three trials assessing <200 patients. Thus, we have not reported comparisons of GEL vs saline (1 trial, 24 patients), GEL vs Ringer's (1 trial, 100 patients), GEL vs Albumin (2 trials, 124 patients), or Albumin vs Ringer's (1 trial, 100 patients). The remaining nine comparisons are summarized in Table 2. With the exception of the HES vs GEL and HES vs Albumin, each comparison reflects data on more than 2000 patients. The comparisons had generally low heterogeneity; the comparison between HES and albumin had the highest heterogeneity ($I^2=26\%$). The randomized trials are of generally high quality, and the network trials had internal consistency. In each comparison, there is low to moderate risk of publication bias.

In this analysis of a heterogeneous critical care population, there is **no signal of overall superiority of crystalloid vs colloid**, nor did this analysis suggest that any specific type of fluid was clearly superior. The inclusion of the FEAST trial²³ suggests that bolus of both crystalloid and colloid increased mortality compared with simple triage measures, that is, **the rate of**

administration may have greater effects on outcomes rather than fluid type. In a sensitivity analysis that considered the incidence of RRT, fewer trials could be included because of sparse reporting. The SAFE trial²⁰ reported the median number of days on RRT as a secondary outcome measure, not as a simple dichotomous variable and did not find a difference in RRT. The two comparisons of HES (with saline^{28 51 68} and Ringer's)^{2 25 59} showed an increased incidence of RRT (RR 1.24, 95% CI 1.04–1.48) and mortality (RR 1.4, 95% CI 1.07–1.84). The HES vs Ringer's comparison has one-sixth the number of patients (1363 vs 7242) and was associated with moderate heterogeneity (36%). Specific consideration of the crystalloid observational trials^{44 45} showed more RRT with saline than Plasma-Lyte[®] (RR 1.6, 95% CI 1.15–2.21). Thus, this network shows that the greatest risk of RRT is conferred by HES, the least risk by balanced salt solutions, and both albumin and saline have approximately the same risk of necessitating RRT. Recent editorials have discussed these apparent benefits of balanced salt solutions but only in pairwise comparisons relative to isotonic saline.^{46 47} A further sensitivity analysis, using mortality as an outcome, **compared crystalloids with colloids in the setting of severe sepsis.**^{2 23 25 28 61} This analysis included the sepsis subgroups from CHEST,³ SAFE,²⁰ and CRISTAL²⁹ and **found no difference in mortality** (RR 1.0, 95% CI 0.91–1.1). When limited to **trials assessing only HES, there was still no difference in mortality** (RR 0.96, 95% CI 0.86–1.08).

Limitations

A network meta-analysis must **conform to the PRISMA guidelines** (<http://www.prisma-statement.org/>). In our network presented here, there are several important limitations with respect to our methodology. First, because of time and financial constraints, we did not conduct a systematic search of our own as laid out by the PRISMA guidelines; we utilized trials that were defined in the bibliographies of several recent meta-analyses,^{11 69–71} and our own expertise in the field. It is important to note that we did not include any trials reported by Boldt and colleagues; many of these trials have been

Table 2 Studies within the network meta-analysis of fluid choice in critical care. Relative risks represent pooled direct and indirect treatment estimates when heterogeneity is limited. The risk of bias and confounding is qualified and has to be accounted for when interpreting effect estimates

Comparison	No. of studies	No. of patients	Crude mortality rate	Relative risk (95% CI)	Heterogeneity (I^2)	Risk of confounding	Risk of publication bias
Albumin vs saline ^{20 23 29 49 50}	5	12 696	18.2	0.99 (0.90–1.05)	5%	Low	Low
HES vs saline ^{29 51–58}	9	9211	18.9	0.99 (0.85–1.14)	26%	Low	Low
HES vs Ringer's ^{2 19 55–60}	7	2408	33.9	1.10 (0.97–1.25)	6%	Moderate	Low
HES vs Gel ^{58 61–66}	7	780	26.5	1.10 (0.91–1.35)	0%	Moderate	High
HES vs albumin ^{64–67}	4	212	28%	1.01 (0.66–1.52)	0%	Moderate	High
Albumin vs control ^{23 49 50}	3	2201	9%	1.4 (1.05–1.84)	0%	Low	Moderate
Saline vs control ^{23 49 50}	3	2195	9.1%	1.38 (1.06–1.81)	0%	Low	Moderate
Saline vs Plasmalyte ^{43 44}	2	5237	4.7%	1.04 (0.8–1.35)	0%	High	High
Saline vs Ringer ⁴⁵	1	8532	2.4%	1.6 (1.2–2.1)	NA	Very high	High

retracted and there is general concern about the validity of any report by this group. Secondly, since we were **unaware of any large randomized comparisons of saline with balanced salt solutions**, we included three recent large retrospective reports. Several small RCTs exist, but none was conclusive relative to differences in patient-centred outcomes (Table 3). The quality of these observational reports is good when judged by the STROBE statement guidelines (<http://www.strobe-statement.org>), but results need to be confirmed in large-scale randomized trials. Thirdly, most large trials considered a heterogeneous critical care population that includes trauma, head injury, sepsis, and cardiac surgery. This may be a major limitation since subanalyses of trials suggested that some fluids may be superior in certain specific disease states. For instance, the SAFE²⁰ trial reported no differences in outcomes when

considering the entire population; however, saline was clearly superior to albumin in the prespecified subgroup with traumatic brain injury followed for 24 months after operation.⁴ When the potential for significant effect modification exists across subpopulations, a single summary estimate of effects may be inappropriate. Similarly, if there is imbalance in the distribution of effect modifiers between different types of treatment comparisons (i.e. if the populations for the different direct comparisons are heterogeneous), indirect comparisons may be biased and the validity of network meta-analysis compromised. Finally, conceptual heterogeneity may exist since the volume context in which specific comparisons are being performed may vary considerably (i.e. effects may not be meta-analysable across the salvage, optimization, or maintenance phases of fluid management taken together).

Table 3 RCTs comparing chloride-restricted crystalloids vs 0.9% saline. The population, interventions being compared, and outcomes for each of the RCTs are presented. Studies have largely measured surrogate outcomes. There is no direct estimate of long-term important patient-centred outcomes. As can be seen from the size of the study population, there is significant potential for type II error. *Total patients receiving either intervention compared; excludes other intervention groups included in study

Study	Country	Study population	Study population size (total)	Interventions compared	Key endpoints
Chua and colleagues ⁷²	Australia	Adults with severe DKA	23	PlasmaLyte 148 vs 0.9% saline	ICU LOS, urine output
Hadimioglu and colleagues ⁷³	Turkey	Adults undergoing kidney transplantation	60*	PlasmaLyte vs 0.9% saline	Acute renal injury, serum creatinine, serum chloride, urine output
Hasman and colleagues ⁷⁴	Turkey	Adults with moderate or severe dehydration	60*	PlasmaLyte vs 0.9% saline	Serum chloride
Khajavi and colleagues ⁷⁵	Iran	Adults undergoing kidney transplantation	52	Ringer's lactate vs 0.9% saline	Serum creatinine, urine output
Kim and colleagues ⁷⁶	Korea	Adults undergoing kidney transplantation	60	PlasmaLyte vs 0.9% saline	Serum creatinine, serum chloride, urine output, transfusion volume
Mahajan and colleagues ⁷⁷	India	Children with severe dehydration	22	Ringer's lactate vs 0.9% saline	Mortality, hospital LOS, serum chloride
Mahler and colleagues ⁷⁸	USA	Adults with DKA	45	PlasmaLyte A vs 0.9% saline	Serum chloride
Modi and colleagues ⁷⁹	Saudi Arabia	Adults undergoing kidney transplantation	74	Ringer's lactate vs 0.9% saline	Serum chloride, serum creatinine
O'Malley and colleagues ⁴¹	USA	Adults undergoing renal transplantation	51	Ringer's lactate vs 0.9% saline	Acute renal injury, hospital LOS, hyperchloremia/metabolic acidosis, serum creatinine, serum chloride, urine output
Scheingraber and colleagues ³⁴	Germany	Adults undergoing elective abdominal gynaecologic surgery	24	Ringer's lactate vs 0.9% saline	Urine output
Takil and colleagues ⁸⁰	Turkey	Adult spinal surgery patients	30	Ringer's lactate vs 0.9% saline	Hospital LOS, ICU LOS, serum chloride, urine output, transfusion volume
Van Zyl and colleagues ⁸¹	South Africa	Adults with DKA	54	Ringer's lactate vs 0.9% saline	Hospital LOS, serum creatinine, serum chloride
Waters and colleagues ⁴²	USA	Adult patients undergoing aortic reconstructive surgery	66	Ringer's lactate vs 0.9% saline	Mortality, acute renal injury, hospital LOS, ICU LOS, mechanical ventilation time, serum creatinine, serum chloride, urine output, transfusion volume
Wu and colleagues ⁸²	USA	Adults with acute pancreatitis	40	Ringer's lactate vs 0.9% saline	Acute renal injury, hospital LOS
Young and colleagues ⁴⁰	USA	Adults with traumatic injury	65	PlasmaLyte A vs 0.9% saline	Mortality, acute renal injury, hospital LOS, ICU LOS, mechanical ventilation time, serum creatinine, serum chloride, urine output, transfusion volume

Table 4 Types and compositions of resuscitation fluids (from *N Engl J Med*, Myburgh JM, Mythen MG. *Resuscitation Fluid* 369:1246, Copyright © 2013 Massachusetts Medical Society. Reprinted with permission)

Variable	Human plasma	Colloids								Crystalloids			
		4% Albumin	Hydroxyethyl starch				4% succinylated modified F:luid gelatin	3.5% urea-linked gelatin	0.9% saline	Compounded sodium lactate	Balanced salt solution		
			10% (200/0.5)	6% (450/0.7)	6% (130/0.4)	6% (130/0.42)							
Trade name		Albumex	Hemohes	Hextend	Voluven	Volulyte	Venofundin	Tetraspan	Gelofusine	Haemaccel	Normal saline	Hartmann's or Ringer's lactate	PlasmaLyte
Colloid source		Human donor	Potato starch	Maize starch	Maize starch	Maize starch	Potato starch	Potato starch	Bovine gelatin	Bovine gelatin			
Osmolarity (mmol litre ⁻¹)	291	250	308	304	308	286	308	296	274	301	308	280.6	294
Sodium (mmol litre ⁻¹)	135–145	148	154	143	154	137	154	140	154	145	154	131	140
Potassium (mmol litre ⁻¹)	4.5–5.0			3.0		4.0		4.0		5.1		5.4	5.0
Calcium (mmol litre ⁻¹)	2.2–2.6			5.0				2.5		6.25		2.0	
Magnesium (mmol litre ⁻¹)	0.8–1.0			0.9		15		1.0					3.0
Chloride (mmol litre ⁻¹)	94–111	128	154	124	154	110	154	118	120	145	154	111	98
Acetate (mmol litre ⁻¹)						34		24					27
Lactate (mmol litre ⁻¹)	1–2			28								29	
Malate (mmol litre ⁻¹)								5					
Gluconate (mmol litre ⁻¹)													23
Bicarbonate (mmol litre ⁻¹)	23–27												
Octanoate (mmol litre ⁻¹)		6.4											

A priority for research

None of the currently used resuscitation fluids has been rigorously evaluated through multiphasic processes that are required for new medications. This was primarily due to the adoption into clinical practice of 'historical' fluids such as Ringer's/Hartmann's solutions, saline, and albumin. The need to develop alternative colloids to albumin led to the development of the semisynthetic colloid industry that produces HES and gelatin. These solutions (Table 4) are widely used in the absence of clear evidence of long-term safety. After concerns about the safety of albumin and HES, a number of high-quality RCTs were conducted in ICU patients to test the safety of specific colloids compared with the respective carrier solutions. These pragmatic, large-scale trials produced clear signals about the effects of albumin and HES on patient-centred outcomes such as mortality and clinically significant kidney injury.

From these trials, data emerged that fluid choice may directly affect patient-centred outcomes in selected patient populations such as severe sepsis and traumatic brain injury. It is probable that specific fluid types may also affect outcomes in patients who were not included in these large pragmatic trials such as hypovolaemic patients due to haemorrhage, burns, or major surgery or in specific syndromes such as dengue fever, obstetric use, or anaphylaxis. Caution is, therefore, required when applying the results of these pragmatic trials to specific patient populations. Despite emerging evidence of harm associated with chloride-rich crystalloids when compared with buffered/balanced solutions, no high-quality RCTs have been conducted. Furthermore, there is a compelling body of evidence that suggests that the cumulative dose of fluid administered to a patient over the duration of the admission may be more important in determining outcome than the type of fluid.

In order to determine the safety and efficacy of buffered solutions compared with saline and whether the dose or volumes of these fluids may have an independent effect on patient-centred outcomes, a novel fluid resuscitation study designed to address these two key questions is required. Minimization of bias is critical and standard measures of internal validity are paramount. Of these, allocation concealment through robust randomization and blinding of the study fluids is essential. For a comparison between two crystalloids, this is completely feasible. The primary outcome must be patient-centred (mortality, use of RRT, or disease-free survival) and determined at an interval relevant to the patient population—at least 3 months post-randomization. The patient population needs to have a substantive mortality rate (~15–20%) to determine a plausible absolute reduction in mortality (3–5%), which will require a sample size between 5000 and 7500 patients. Consequently, a pragmatic design is required to reflect the reality of practice within such a large cohort. In order to determine the efficacy of a 'restrictive' or 'conventional' fluid strategy, a factorial, cluster-randomized clinical trial can be designed, incorporating the fluid type study above. To ensure separation between the two fluid resuscitation strategies, participating centres would be randomly allocated to one of the two strategies, stratified by academic status. To ensure compliance with the respective

strategy, an education campaign would precede the trial to familiarize clinicians, address equipoise concerns, and to minimize protocol violations. This was a key factor in the success of the FEAST trial.²³ Thereafter, eligible patients would receive blinded solutions of study fluid for the duration of the index admission and all aspects of patient management would be left to the attending clinicians.

Ideally, such a trial would be conducted across all areas in the participating hospital where fluids are administered such as the emergency and operating theatres, ICU, and wards. However, this may not be practical in many centres, and therefore, the ICU remains the likely area to conduct such a trial. In order to ensure balance between strategies and study drug, an adaptive statistical design would be required, developed using prespecified metrics and models to maximize the efficiency of the trial. Clearly, no such trial has been conducted in fluid resuscitation research previously. It underscores the complexity of studying processes of care in heterogeneous and specific patient populations. Alternative trials such as observational, propensity scoring trials, aggregate and individual patient-data meta-analysis and network meta-analysis provide important adjuvant and hypothesis-generating results, but are invariably subject to confounding and selection bias. However, given that the administration of fluids is the most common intervention in critical care medicine, there is an obligation to conduct such a trial that would have a substantive impact on clinical practice.

Conclusion

Based on the current evidence, there is no clearly superior fluid in a heterogeneous population of critically ill patients (relative to mortality as the primary outcome). It would appear that HES does increase the need for RRT, but does not increase mortality. Specific fluids may be superior in certain settings, for example, saline in head injury and balanced fluids when there is risk of renal injury. Presently, balanced salt solutions may be a reasonable default choice.

Supplementary material

Supplementary material is available at *British Journal of Anaesthesia* online.

Authors' contributions

K.R. and P.T.M. were the co-primary authors responsible for the drafting and submission of the manuscript on behalf of the authors. All authors contributed to the literature review, consensus conference plenary, and group breakout discussions, figure and table development, and manuscript preparation and review.

Declaration of interest

D.N.L. has received unrestricted research funding, travel grants, and speaker's honoraria from Baxter Healthcare, Fresenius Kabi, and BBraun, and has served on advisory boards for Baxter Healthcare and AbbVie. D.N.L. is a member of the IV Fluids Guideline

Development Group for the National Institute of Health and Care Excellence (NICE) and he is a co-author of the GIFTASUP fluid guidelines. J.M.'s institution (the George Institute for Global Health, Sydney, Australia) has received travel expenses from Fresenius Kabi in relation to the development and conduct of an investigator-initiated randomized controlled trial (the Crystalloid vs. Hydroxyethyl Starch Trial). J.A.K. has received grant support from Baxter; and serves as a paid consultant for Baxter and Grifols. M.G.M. has received honoraria for speaking/consultation and/or travel expenses from Baxter, BBraun, Covidien, Fresenius-Kabi, Hospira, LidCo, and as a consultant to AQIX (startup company with a novel crystalloid solution—pre-clinical). He is a director of Medical Defence Technologies LLC ('Gastrostim' patented) and a co-Inventor of 'QUENCH' IP being exploited by UCL Business. M.G.M.'s chair at UCL is endowed by Smiths Medical Ltd and this company provides charitable donations to the department on an annual basis. Deltex Medical also provides unrestricted grant funds to M.G.M.'s department. M.G.M. is a member of the IV Fluids Guideline Development Group for the National Institute of Health and Care Clinical Excellence (NICE) and he is a co-author of the GIFTASUP fluid guidelines. A.D.S. has received grant support from Baxter Healthcare related to Plasmalyte; and serves as a paid consultant for Baxter and Grifols.

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