Intravenous fluid therapy in critically ill adults

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Abstract | Intravenous fluid therapy is one of the most common interventions in acutely ill patients. Each day, over 20% of patients in intensive care units (ICUs) receive intravenous fluid resuscitation, and more than 30% receive fluid resuscitation during their first day in the ICU. Virtually all hospitalized patients receive intravenous fluid to maintain hydration and as diluents for drug administration. Until recently, the amount and type of fluids administered were based on a theory described over 100 years ago, much of which is inconsistent with current physiological data and emerging knowledge. Despite their widespread use, various fluids for intravenous administration have entered clinical practice without a robust evaluation of their safety and efficacy. High-quality, investigator-initiated studies have revealed that some of these fluids have unacceptable toxicity; as a result, several have been withdrawn from the market (while others, controversially, are still in use). The belief that dehydration and hypovolaemia can cause or worsen kidney and other vital organ injury has resulted in liberal approaches to fluid therapy and the view that fluid overload and tissue oedema are 'normal' during critical illness; this is quite possibly harming patients. Increasing evidence indicates that restrictive fluid strategies might improve outcomes.

The use of intravenous fluid to resuscitate hypovolaemic patients has been part of medical practice for at least 185 years — dating from the use of hypotonic saline solution with added sodium bicarbonate (effectively a buffered salt solution) for intravenous fluid resuscitation during the 1832 cholera epidemic in London[1–3]. In his published anecdotal reports of Thomas Latta's use of this treatment, Robert Lewin noted that "injecting a weak saline solution into the veins of the patient [had] the most wonderful and satisfactory effect…"[4]. Another contemporary physician reported that in cholera asphyxia, the blood was acidic and had "lost a large proportion of its water, a great proportion of its neutral saline … of the free alkali contained in healthy serum, not a particle remains…"[1]. Despite these early reports, the effectiveness of intravenous fluid therapy was disputed by many contemporary authorities, and it did not enter routine practice for another 100 years. Now, however, intravenous fluid therapy has become one of the most common interventions administered to patients treated in emergency settings, operating theatres and intensive care units (ICUs).

Shock can be defined as a generalized maldistribution of blood flow resulting in inadequate tissue perfusion, which presents most frequently as systemic arterial hypotension. Shock is one of the most common presenting syndromes in critically ill patients and can be categorized as hypovolaemic (inadequate intravascular volume), cardiogenic (cardiac pump failure), obstructive (circulatory flow restriction, for example, due to pulmonary embolus or atrial myxoma) or distributive (vascular hyporesponsiveness due to sepsis or other systemic inflammatory states, such as burns). Regardless of the underlying aetiology, the clinician's first response when faced with a hypotensive patient is almost invariably to administer a bolus of intravenous fluid. The choice of which fluid to administer, the timing and the amount have long been sources of controversy, which has persisted owing to a quite astonishing lack of robust outcome data. As a result, fluid resuscitation practices are highly variable around the world, particularly with regard to indications for fluid boluses, methods of administration and assessment of response[5].

Adoption of crystalloid fluids, such as normal saline, Ringer's lactate and Hartmann's solution, occurred following demonstrations that they did not cause acute haemolysis or other acute toxicity[6]. Proprietary fluids also received marketing authorization and regulatory approval based on little evidence outside small, methodologically unsound and short-term studies or even based on similarity to an already licensed fluid. For example, 6% hydroxyethyl starch (HES) 450/0.7 was approved by the US Food and Drug Administration (FDA) in 1972 on the basis of noncontrolled observations in

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Key points

- Intravenous fluid administration is one of the most common interventions in acute and critical care medicine, but much of the physiological theory on which practice has been based is flawed.
- Intravenous fluids were established in clinical practice and licensed for use without robust investigation of their efficacy or safety, although large, high-quality, investigator-initiated trials have now provided such data.
- Crystalloid fluids should be used for first-line therapy; in most patients, buffered salt solutions seem to offer benefits over normal saline.
- Albumin administration might be beneficial in patients with sepsis, cirrhosis or infections, but albumin in hypotonic carrier fluid is contraindicated in patients with acute traumatic brain injury.
- Synthetic colloids, notably hydroxyethyl starch and gelatins, should not be used owing to their unacceptable safety profiles and lack of proven benefits over crystalloids.
- Strategies that restrict fluid administration might reduce morbidity and mortality, but larger trials are still needed to confirm these promising initial data.

223 patients and studies in 92 healthy adults. The period of observation ranged from 60 min to 48 h, efficacy was demonstrated by changes in blood volume and vital signs, and safety was determined by the absence of local or systemic toxic effects and an absence of observed adverse reactions. Approval of additional isotonic HES preparations (for example, 6% HES 130/0.4 was approved in 2007) was based on small noninferiority studies, in which the comparators included 6% HES 450/0.7 — which even then was already known to be nephrotoxic. Eventually, high-quality, publicly funded, investigator-initiated, randomized controlled trials (RCTs) confirmed that all HES solutions were nephrotoxic and that their use was associated with an increased risk of death in specific high-risk populations[7–10]. The evidence used to approve other intravenous fluids (such as albumin and crystalloid solutions) was no more robust; much of the impetus came from the need to treat battle casualties during major wars of the 20th century. Safe blood transfusion followed the identification of blood groups[11] in 1900, and by 1907 that information was widespread[12]. Blood transfusion programmes were established in many countries, and stored blood was used by both sides during the Spanish Civil War (1936–1939)[12]. Liquid and dried plasma were used for volume expansion during the Second World War (1939–1945), and the first widespread use of human albumin solution for fluid resuscitation occurred following the 1941 attack on Pearl Harbor[12]. Human albumin was licensed by the FDA shortly thereafter, at a time when the FDA did not require data from controlled toxicological or pharmacological studies. Thus, crystalloid and colloid fluid resuscitation solutions that are still in common use today entered clinical practice without robust evaluation of their efficacy and safety or comparative studies.

In this narrative Review, we provide an overview of current theories of human physiology relating to intravenous fluid therapy. In relation to critically ill adults, we discuss the mechanisms by which hypovolaemia and fluid overload affect the kidney and the balance of risks and harms of different strategies for fluid management, including the type and amount of fluid. We highlight

Hypovolaemia
A state characterized by the loss of an effective intravascular volume.

Tonicity
The capability of a solution to exert osmotic pressure across a cellular membrane.

the renal effects of these strategies as well as non-renal outcomes of importance to patients.

The rationale for fluid therapy

In an international survey of fluid resuscitation practices conducted in 391 ICUs and published in 2007, the most common reason given for administering resuscitation fluid was impaired tissue perfusion or low measured cardiac output (the indication for 44% of fluid resuscitation episodes)[13]. The next most common indication, which accounted for 35% of fluid resuscitation episodes, was abnormal vital signs (blood pressure, heart rate, urine output or central venous pressure) in the absence of evidence of impaired tissue perfusion[13]. When the survey was repeated in 2014, impaired tissue perfusion or low measured cardiac output was the indication in 61% of fluid resuscitation episodes, whereas abnormal vital signs in the absence of evidence of impaired tissue perfusion accounted for another 25% of fluid resuscitation episodes[14], suggesting that clinical practice had moved away from the administration of fluid to treat abnormal vital signs in patients without impaired tissue perfusion. Two other similar studies were conducted in Europe in 2013: an observational study of French practice and an international study by the European Society of Intensive Care Medicine. Both studies found that hypotension, low urine output, tachycardia, skin mottling and hyperlactataemia were the most frequent triggers for fluid bolus administration[5,15]. In 2015, the results of a survey of ICU clinicians in the USA showed that low blood pressure, urine output and central venous pressure were the most common prompts for administration of resuscitation fluid[16].

Although the primary (and many clinicians would argue the only) reason to give a patient a fluid challenge is to effect a clinically meaningful increase in stroke volume, no universally agreed upon or recommended triggers currently exist for the administration of resuscitation fluid. Appropriate triggers are likely to vary between patients and even in the same patient at different times. The clinical course of circulatory shock has been proposed to consist of four phases: salvage, optimization, stabilization and de-escalation[17], each of which has different goals for fluid therapy (FIG. 1). This model has achieved a degree of popularity. However, fluid therapy will also be influenced by the patient's primary pathology, life goals and preferences in relation to aggressive medical therapy, as well as by their response to treatment. Ideally, fluid therapy, similar to other medical therapies, should be tailored to the needs of the individual patient.

Physiology of fluid resuscitation

Fluid resuscitation is a fundamental intervention in patients with symptomatic hypovolaemia. Compensatory responses to hypovolaemia include integrated and sympathetically mediated catecholamine and hormonal responses that aim to defend tonicity and thereby produce an effective circulating blood volume[17,18]. Baroreceptor-mediated, catecholamine-induced venoconstriction acts on the venous capacitance system to increase venous return and maintain cardiac output[19,20]. In addition, activation of the renin–angiotensin–aldosterone
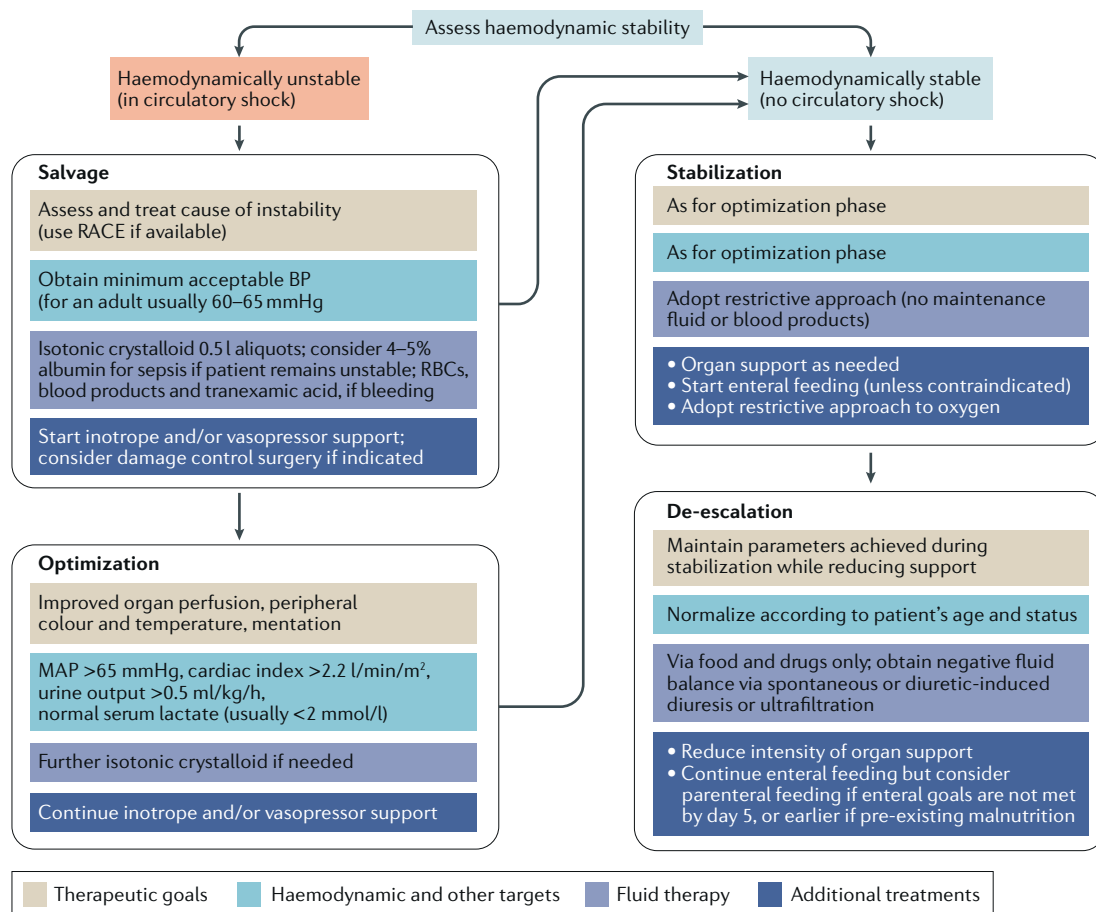
Fig. 1 | **Fluid management of the critically ill patient.** Fluid management differs in the four phases of shock: salvage, optimization, stabilization and de-escalation. Administration of fluid boluses is appropriate in the salvage and optimization phases, but each bolus should be followed by reassessment of the need for ongoing fluid administration. In haemodynamically unstable patients, inotropic and/or vasopressor agents should be started at the same time as fluid resuscitation to correct intravascular volume depletion. Once haemodynamic stabilization has been achieved, fluid should be administered primarily in or with food, and preferably by the enteral route. Most critically ill patients also receive fluid in the form of drug infusions. The obligatory fluid needed for administration of food and drugs often satisfies the patient's basal requirements and makes routine administration of so-called maintenance fluids unnecessary. Most critically ill patients develop salt and water overload during stabilization, which is addressed in the de-escalation phase. Recovering critically ill patients with adequate renal function and fluid excretion undergo spontaneous diuresis. If spontaneous diuresis is insufficient, excess fluid is removed by drug-induced diuresis or ultrafiltration. Therapeutic goals should take into account the patient's primary pathology, underlying life goals, preferences regarding aggressive medical therapy and response to treatment. Ideally, fluid therapy, like other medical therapies, should be tailored to the needs of the individual patient. BP, blood pressure; MAP, mean arterial pressure; RACE, rapid assessment by cardiac echocardiography; RBC, red blood cell.

and adrenocorticoid systems produces an antidiuretic response to retain water. Hypovolaemic shock occurs when intravascular volume loss exceeds the capacity of these compensatory mechanisms, resulting in the compromise of vital organ perfusion. The principal aim of administering resuscitation fluids is to restore and maintain intravascular volume at near-physiological levels, enabling the cause of hypovolaemia to be identified and treated. Concomitant treatment with vasoactive agents (primarily catecholamine infusions) augments endogenous neurohormonal responses and completes a multimodal resuscitation strategy[18,21,22].

Hypovolaemia can be caused by acute haemorrhage or the loss of other body fluids, commonly from the upper and lower gastrointestinal tract (via diarrhoea,

vomiting or fistulae), the urinary tract or skin (most notably in patients with severe burns). Inflammatory states occurring in sepsis and after burns, major surgery or trauma can produce a mixed picture of distributive and hypovolaemic shock. In sepsis and after burn injury, hypovolaemia results from extravascular fluid loss due to increased vascular permeability, whereas in trauma and major surgery, hypovolaemia is caused by uncorrected blood loss. Tissue injury and repair cause an inflammatory response that, in critically ill patients, can result in distributive shock. Differentiating between these mechanisms of shock and identifying the predominant factors in mixed shock states can be challenging but is necessary to determine the appropriate treatment strategy[23] (FIGS 2,3).
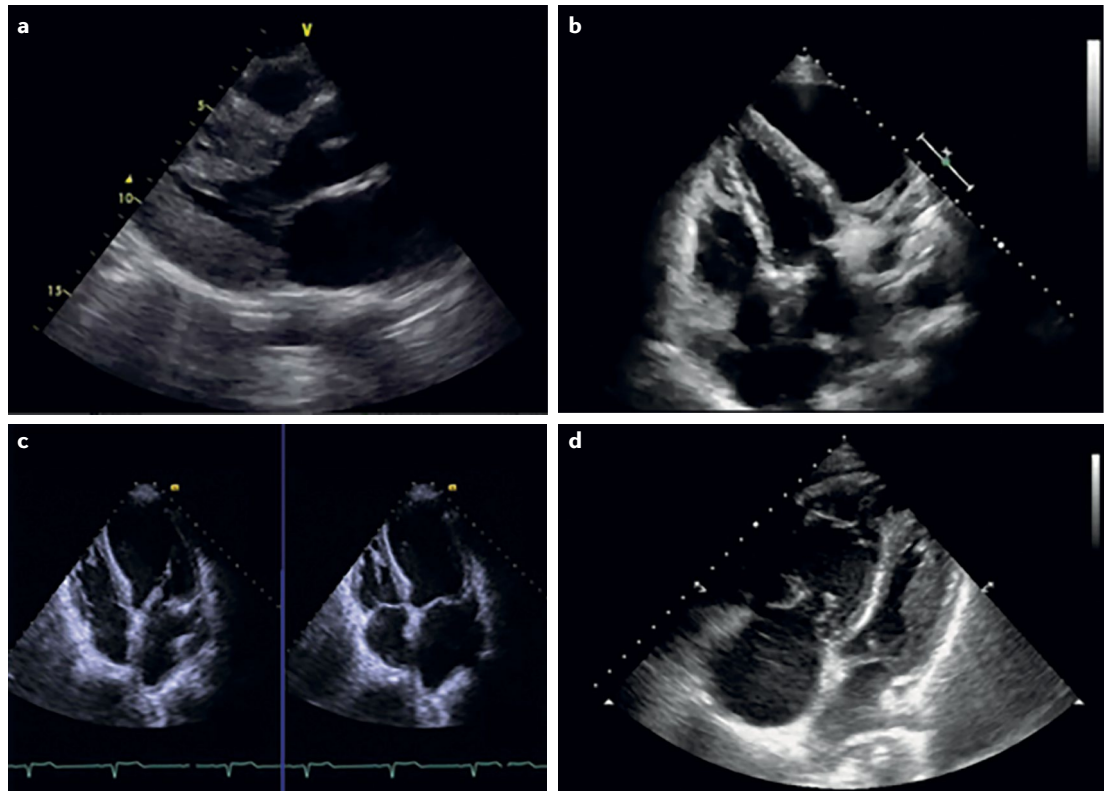
Fig. 2 | **Transthoracic echocardiography images of patients with shock.** Rapid differentiation of the cause of shock is greatly facilitated by bedside echocardiographic evaluations, such as rapid assessment by cardiac echocardiography (RACE), which can quickly demonstrate signs of hypovolaemia. **a** | 'Kissing' ventricular walls. **b** | Pericardial effusions causing tamponade. **c** | Dilated and poorly contracting left ventricle in a patient with cardiogenic shock (left image, diastole; right image, systole). **d** | Dilated right atrium and right ventricle and compressed, empty left ventricle caused by a massive pulmonary embolism. Images courtesy of K. Yastrebov, The St George Hospital, Australia and J. Wilkinson, Northampton General Hospital, UK.

The classic Starling model

During the past 75 years, most clinicians based their fluid administration practices on a physiological theory developed by Ernest Starling and others (FIG. 4). According to this model, fluid leaves the vasculature at the arterial end of the capillary bed (where the hydrostatic pressure gradient exceeds the osmotic pressure gradient) and re-enters at the venous end of the capillary bed (where, as a result of prior fluid loss, hydrostatic pressure will be lower and osmotic pressure higher). However, much of this theory is inconsistent with data from clinical trials and with our emerging understanding of the role of the endothelial glycocalyx layer, discussed below. In particular, the long-held beliefs that fluid re-enters the circulation in the post-capillary venous bed and that this fluid resorption can be augmented by the administration of fluids that increase colloid osmotic pressure have now been discounted[24].

The revised Starling model

Starling's original model was based on his observation that when isotonic saline was injected into the tissue of the hindlimb of a dog, blood perfused through the limb became haemodiluted, implying that the saline was absorbed into the vasculature[25]. However, when serum rather than saline was injected, the fluid was not absorbed[25]. As experimental and measurement techniques evolved, this model of fluid flux was superseded, and an alternative model, which can be explained by knowledge of the structure and function of the endothelial glycocalyx and which is consistent with the results of clinical trials, now prevails[26].

The endothelial glycocalyx layer is the key determinant of membrane permeability, represented by the reflection coefficient σ in the Starling equations (FIG. 4). This layer is a web of membrane-bound glycoproteins and associated proteoglycans found on the luminal side of vascular endothelial cells. The glycocalyx consists of an inner, dense matrix layer with membrane-attached glycoproteins up to 200–300 nm thick, which forms the primary selective barrier to plasma macromolecules. An outer, less dense layer extends one or more micrometres into the vessel lumen, forming a microstructure that supports red blood cell movement. The sub-glycocalyx space produces a colloid oncotic pressure that is the principal determinant of transcapillary fluid flow. Fluid from the interstitial space enters the circulation through a small number of large pores, but the primary route by which interstitial fluid returns to the circulation is as lymph. Both the endothelial and glycocalyx barriers are modulated by inflammatory mediators, endothelial stabilizing agents and physical forces on the vascular wall. The biology of the endothelial glycocalyx layer remains incompletely understood, although new and emerging
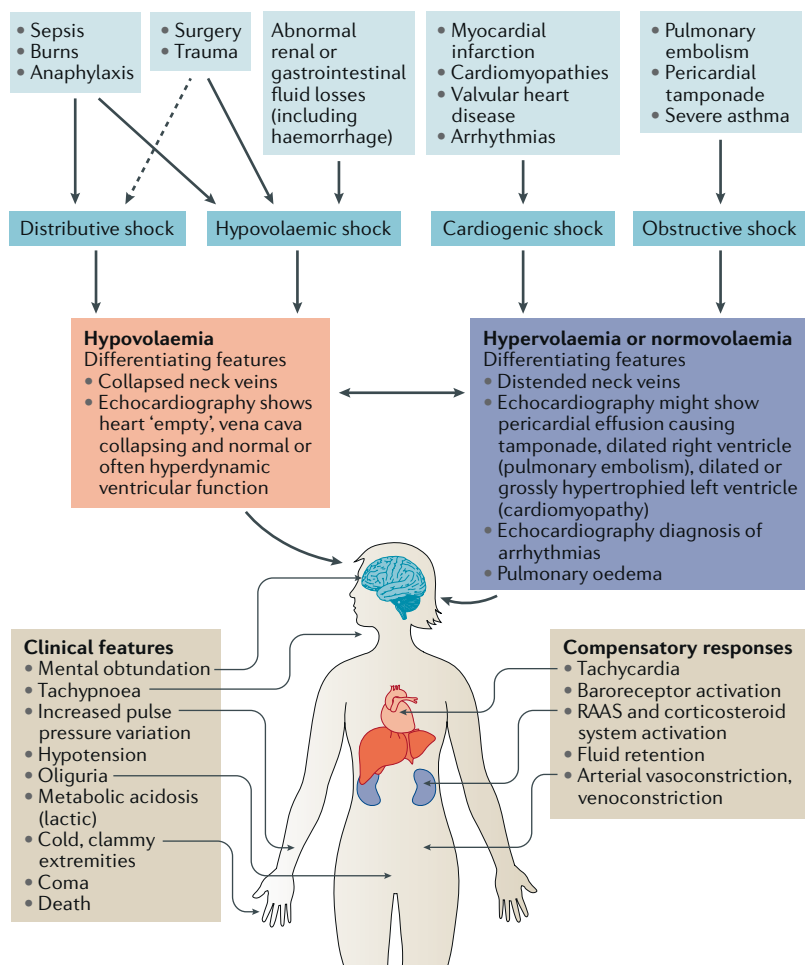
Fig. 3 | **Causes, classification and compensatory responses to shock.** Shock can be caused by any pathological process that leads to intravascular volume loss, pathological vasodilatation, myocardial dysfunction or obstruction of either venous return (as occurs in severe asthma) or ventricular outflow. Shock can be categorized as distributive (septic), hypovolaemic, cardiogenic or obstructive. Shock can also present a mixed picture; for example, in sepsis, burns and anaphylaxis, increased vascular permeability leads to loss of intravascular volume and hypovolaemic shock, while at the same time, pathological vasodilatation produces distributive shock. The compensatory responses to all forms of shock are similar. The cause of shock might be obvious (as in patients with trauma or massive haemorrhage) or unclear (unresuscitated septic shock is often clinically indistinguishable from hypovolaemic shock). RAAS, renin–angiotensin–aldosterone system.

research is highlighting the important roles of mediators, such as sphingosine-1-phosphate and angiopoietin 2, in regulating the glycocalyx structure and vascular permeability in health and disease[27,28]. The structure and function of the endothelial glycocalyx layer vary in different vascular beds and under differing physiological and pathological conditions[24,29]. For example, damage to the glycocalyx, as occurs in localized or systemic inflammatory conditions, leads to fluid extravasation. The permeability of the endothelial glycocalyx layer (and thereby the potential to develop interstitial oedema) also varies substantially between organ systems.

The clinical implications of the revised Starling theory are that the volume-sparing effect of colloid resuscitation fluids is much less than previously thought, and this is particularly true in the presence of local or systemic inflammation. These new observations provide the physiological basis to reappraise the efficacy of different resuscitation fluids in critically ill patients, in whom conditions such as sepsis, trauma and major surgery are associated with loss of endothelial glycocalyx structure and function (FIG. 4).

Fluids for intravenous administration

Although some clinical conditions mandate the use of specific resuscitation fluids (such as blood transfusion for acute haemorrhage), local habits and practice, along with pragmatic considerations (including financial), have largely driven clinicians' choice and use of proprietary resuscitation fluids.
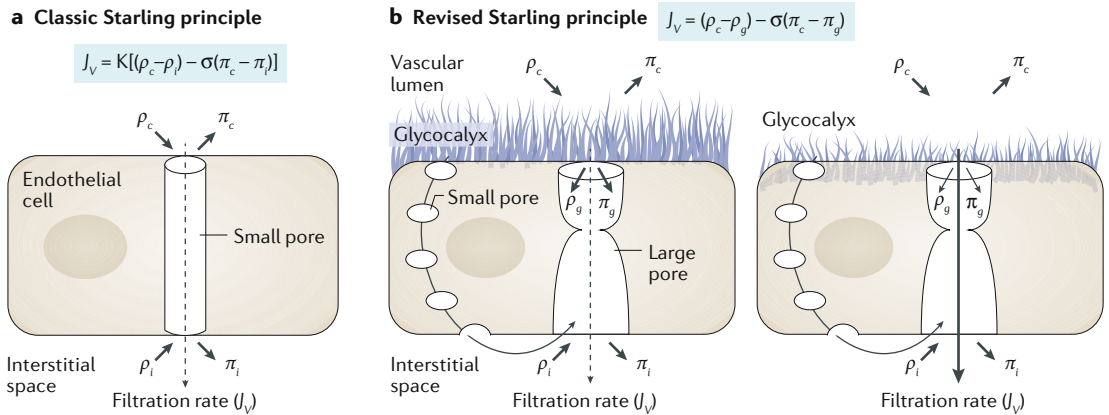
Fluids have classically been categorized as crystalloid or colloid, terms introduced by Thomas Graham (Professor of Chemistry, University College London, 1836–1855) long before intravenous fluids were widely used in clinical practice[30]. Crystalloid was used to describe solutions such as salt, sugar and urea that could be crystallized with ease. By contrast, colloid (derived from the Greek word for glue) was used to describe non-crystallizable solutions (such as those containing gelatin, gum, egg albumen, starch and dextrin) that formed gummy masses when evaporated to dryness, diffused with extreme slowness and would not pass through animal membranes. The chemical composition and comments on the risks and benefits of some commonly used intravenous fluids are given in TABLES 1 and 2.

Crystalloids

Crystalloids are now commonly defined as solutions of ions that are capable of passing through semipermeable membranes. They are less expensive than colloids and are the most commonly used fluids worldwide. They also have a long shelf life and are commonly commercially available in 500 ml or 1 l biocompatible, sterile polymer containers.

With the exception of pure glucose solutions, crystalloids contain sodium, chloride and other anions that determine their tonicity relative to extracellular fluid. These physicochemical properties are important determinants of both the efficacy of the fluid for vascular volume expansion and its potential for toxicity. Traditional physiological theory holds that the distribution of infused crystalloids within intracellular and extracellular compartments (including plasma) is determined by its sodium concentration.

When infused, crystalloids with a sodium concentration close to that of intravascular fluid (140 mmol/l) produce a transient increase in intravascular volume before equilibrating with the extracellular fluid. Crystalloids can be used either as resuscitation fluids (to increase or maintain intravascular volume) or as maintenance fluids (to maintain hydration and basic electrolyte balance) in persons unable to tolerate enteral administration of fluid. The crystalloids most commonly used for fluid resuscitation are normal saline and buffered or balanced salt solutions. Although the terms balanced and buffered are used interchangeably in the literature, for the purposes of this article, we refer to all such solutions as buffered.

a Classic Starling principle

$$J_V = K[(\rho_c - \rho_i) - \sigma(\pi_c - \pi_i)]$$

b Revised Starling principle $\quad J_V = (\rho_c - \rho_g) - \sigma(\pi_c - \pi_g)$

Fig. 4 | **The Starling principle of fluid transport across capillary membranes. a** | According to the classic Starling model, fluid leaves the vasculature at the arterial end of the capillary bed, where the hydrostatic pressure gradient driving the fluid out exceeds the osmotic pressure gradient (the pressure retaining fluid within the vascular lumen). Fluid re-enters the vessel from the interstitium at the venous end, where hydrostatic pressure is lower and osmotic pressure is higher owing to fluid loss as blood transitions through the capillary bed. This classic model is now considered flawed and has been superseded by the revised Starling principle. **b** | The revised Starling principle is depicted under physiological conditions (intact glycocalyx, left panel) and pathological conditions (damaged glycocalyx, right panel). The endothelial glycocalyx is a web of membrane-bound glycoproteins and proteoglycans on the luminal side of vascular endothelial cells that forms the primary selective barrier to plasma macromolecules. An outer, less dense layer that extends one or more micrometres into the vessel lumen forms a microstructure that supports red blood cell movement. The sub-glycocalyx space produces a colloid oncotic pressure that is the principal determinant of transcapillary fluid flow. Fluid from the interstitial space enters the vasculature through a small number of large pores, but the primary route by which fluid returns to the circulation is as lymph. The structure and function of the endothelial glycocalyx vary in different vascular beds and under differing physiological and pathological conditions. The integrity or 'leakiness' of the glycocalyx (and thereby the potential for fluid loss into the interstitium and to develop interstitial oedema) varies substantially between organ systems and in localized or systemic inflammatory conditions, during which the structural integrity of the glycocalyx is damaged. Classic model: J_v, fluid flux across the capillary membranes; K, filtration coefficient; ρ_c, capillary hydrostatic pressure; ρ_i, hydrostatic pressure in the interstitium outside the capillary; π_c, capillary osmotic pressure; π_i, interstitial osmotic pressure; σ, capillary wall permeability. Revised model: π_g, oncotic pressure in the sub-glycocalyx space; ρ_g, hydrostatic pressure of the thin layer of interstitial fluid in the sub-glycocalyx space. Arrow and line weights represent relative changes in effect and direction.

Strong ion difference
Strong ions are cations and anions that exist as dissociated charged particles at physiological pH. The strong ion difference of a solution is the difference between the sums of concentrations of strong cations and strong ions. In plasma, the strong ion difference is (Na^+ + K^+ + Ca^{2+} + Mg^{2+}) − (Cl^- − [other strong anions]) and is normally around 40 mEq/l.

Patient-centred outcomes
Outcomes that measure how a patient feels, functions or survives.

Normal saline. Normal saline (0.9% sodium chloride) is an isotonic crystalloid and traditionally the most commonly prescribed crystalloid solution worldwide[13]. It is also the crystalloid vehicle for many colloid solutions, including preparations of human albumin, gelatins and HES. As sodium and chloride are present in equal concentrations (each 154 mmol/l), the strong ion difference is zero, and rapid administration of a large volume will cause hyperchloraemic metabolic acidosis. Adverse effects attributed to this metabolic acidosis, particularly in animal models, include impaired renal and splanchnic function, hypotension and coagulopathy[31–35]. Observational studies have reported that intravenous administration of normal saline is associated with an increased risk of surgical complications, acute kidney injury (AKI) and death compared with administration of crystalloids that have lower chloride concentrations[36,37]. Chloride-rich solutions might also activate tubuloglomerular feedback[38], induce afferent arteriolar vasoconstriction and decrease the glomerular filtration rate (GFR)[32]. However, these adverse outcomes have not been consistently observed in the few RCTs published to date[39–41]. Given that much of the evidence supporting this claim is derived from observational studies in perioperative medicine and considering the inherent risk of

residual confounding in such studies, this evidence must be considered inconclusive[42].

Normal saline is recommended as a first-line resuscitation fluid for patients who are hypovolaemic owing to upper gastrointestinal fluid losses resulting in hypochloraemic metabolic alkalosis and traditionally for patients with diabetic ketoacidosis, although these recommendations have not been tested in trials that had adequate sample sizes to detect differences in patient-centred outcomes. Crystalloid (and colloid) fluid resuscitation is currently out of favour in patients with both blunt and penetrating trauma[43]. In this population, the adoption of damage control resuscitation, which involves acceptance of a low arterial blood pressure, occurred following publication of the results of a seminal pseudo-randomized trial[44] in which this technique was associated with reduced mortality. In patients with traumatic brain injury (TBI), normal saline is preferred to albumin because albumin use results in significantly higher mortality[45]. Animal models suggest that the increased mortality is related to the hypotonicity of the carrier fluid rather than the albumin per se[46]. Taken together, these findings also offer support for the use of normal saline rather than crystalloid solutions with lower tonicity, although it is worth noting that prehospital resuscitation with

Table 1 | **Composition of commonly used crystalloid intravenous fluids**

Solution	Characteristics and composition (per litre)	Comments
Normal (0.9%) saline	• Osmolarity 308 mOsm/l (calculated) • Osmolality 286 mOsm/kg (measured) • pH 5.0 • Na^+ 154 mmol; Cl^- 154 mmol	• Traditionally the most commonly used intravenous fluid • Rapid, high-volume infusion causes hyperchloraemic metabolic acidosis • High Cl^- load might be associated with AKI • Fluid of choice in patients with acute TBI
Sodium lactate (Hartmann's solution)	• Osmolarity: 280.6 mOsm/l (calculated) • Osmolality: 254 mOsm/kg (measured) • pH 5.0–7.0 • Na^+ 131 mmol, K^+ 5.4 mmol, Cl^- 111 mmol, Ca^{2+} 2.0 mmol and lactate 29 mmol	• Buffered salt solutions in which chloride is replaced with other anions to reduce Cl^- load • Reduced or absent propensity to cause hyperchloraemia compared with normal saline • Rapid or high volume infusion can result in metabolic alkalosis • Might be less likely than normal saline to cause AKI • Perioperative use might be associated with reduced postoperative complications • Most current evidence is from observational studies or non-blinded trials • Large-scale multicentre blinded trials comparing PlasmaLyte 148 with normal saline in critically ill patients are underway in Brazil, Australia and New Zealand • As individual buffered salt solutions have varying compositions, considering them as a 'class' of fluid (such that the effects resulting from use of one fluid can be attributed to others or to all) is unwise
Ringer's lactate	• Osmolarity: 273 mOsm/l (calculated) • Osmolality: 273 mOsm/kg (measured) • pH 6.5 • Na^+ 130 mmol, K^+ 4 mmol, Cl^- 109 mmol, Ca^{2+} 2.7 mmol and lactate 28 mmol	
Ringer's acetate	• Osmolarity: 304 mOsm/l (calculated) • Osmolality: 254 mOsm/kg (measured) • pH 4.6–5.4 • Na^+ 140 mmol, K^+ 4 mmol, Cl^- 127 mmol, Ca^{2+} 2.5 mmol, acetate 24 mmol, malate 5.0 mmol and Mg^{2+} 1.0 mmol	
PlasmaLyte 148	• Osmolarity: 294 mOsm/l (calculated) • Osmolality: 271 mOsm/kg (measured) • pH 4.0–6.5 • Na^+ 140 mmol, K^+ 5 mmol, Cl^- 98 mmol, acetate 27 mmol, gluconate 23 mmol and Mg^{2+} 1.5 mmol	
PlasmaLyte A	• Osmolarity: 294 mOsm/l (calculated) • Osmolality: NK • pH 7.4 • Na^+ 140 mmol, K^+ 5 mmol, Cl^- 98 mmol, acetate 27 mmol, gluconate 23 mmol and Mg^{2+} 1.5 mmol	

AKI, acute kidney injury; NK, not known; TBI, traumatic brain injury.

hypertonic saline has not proved beneficial in patients with TBI[47].

Buffered salt solutions. Concerns about the possible adverse effects associated with the high chloride content of normal saline have resulted in increased use of buffered crystalloids. In these solutions, the chloride concentration is reduced by substituting other anions, with the goal of achieving a chemical composition close to that of extracellular fluid. The predominant anions in extracellular fluid are chloride and bicarbonate, but bicarbonate-containing solutions are unstable in plastic polymer containers; alternative anions, such as lactate, acetate, gluconate and malate, are used instead[48]. The choice of substituted anion is governed by the desired physicochemical properties, pharmacokinetics and commercial considerations. In particular, the selected anions should be nontoxic, rapidly and efficiently metabolized, preferably unaffected by the presence of hepatic and/or renal dysfunction, and should have a pH that does not cause haemolysis or endothelial damage[48]. For example, lactate can be used in patients without severe liver dysfunction because it undergoes gluconeogenesis and enters the Krebs cycle via acetyl coenzyme A. Acetate

is also rapidly metabolized, including via extrahepatic pathways, making it theoretically attractive for use in patients with liver damage or dysfunction. One caveat is that the use of acetate in haemodialysis solutions has been associated with hypotension, myocardial dysfunction and metabolic disturbances. Citrate, although used in dialysis fluids, is not a component of buffered crystalloid solutions, presumably because of concerns about its calcium-chelating ability. In addition to the chloride-substituting anion, buffered solutions might contain cations other than sodium (for example, potassium, calcium and magnesium) in concentrations close to those in human extracellular fluid.

Some buffered salt solutions are relatively hypotonic — that is, they have a lower sodium concentration than extracellular fluid. Excessive administration of such buffered salt solutions can result in hyperlactataemia, metabolic alkalosis, hypotonicity (for compounds containing sodium lactate) and cardiotoxicity (for compounds containing acetate). If solutions containing calcium are co-administered with citrated red blood cells, microthrombi can form during administration. Hypotonic crystalloids are contraindicated in patients with acute brain injury because of their theoretical potential to cause or worsen cerebral oedema.

Damage control resuscitation
A systematic approach to the management of severe trauma that involves haemostatic resuscitation, including permissive hypotension to limit non-blood-product fluid resuscitation, which can worsen the coagulopathy of trauma. Might also incorporate damage control surgery, which prioritizes management of the metabolic derangement of ongoing bleeding over the need for definitive surgery.

Table 2 | **Composition of commonly used colloid intravenous fluids**

Solution	Characteristics and composition (per litre)	Comments
Albumin 4%	• Osmolarity: 250 mOsm/l (calculated) • Osmolality: 260 mOsm/kg (measured) • pH 6.7–7.3 • Na^+ 140 mmol, Cl^- 128 mmol and octanoate 6.4 mmol	• Product of blood fractionation, consequent theoretical risk of disease transmission • Expensive compared with crystalloid solutions and artificial colloids • Volume-sparing effect (1 l estimated to be equivalent to 1.4 l of saline) • Contraindicated in acute TBI • Recommended in patients with sepsis who are not stabilized with crystalloid • Beneficial in patients with cirrhosis and infection
Albumin 5%	• Osmolarity: 309 mOsm/l (calculated) • Osmolality: 309 mOsm/kg (measured) • pH 6.4–7.4 • Na^+ 130–160 mmol, K^+ <2 mmol, Cl^- ~130 mmol, sodium caprylate 4 mmol and sodium N-acetyl tryptophanate 4 mmol	
Albumin 20%	• Osmolarity: 130 mOsm/l (calculated) • Osmolality: 130 mOsm/kg (measured) • pH 6.7–7.3 • Na^+ 48–100 mmol and octanoate 32 mmol	• Lower Na^+ and Cl^- loads per gram of albumin than with 4% or 5% albumin • When added to crystalloid (to maintain serum albumin ≥30 g/l), it did not improve outcomes in adults with sepsis; possible beneficial effect in patients with septic shock
Albumin 25%	• Osmolarity: 312 mOsm/l (calculated) • Osmolality: 312 mOsm/kg (measured) • pH 6.4–7.4 • Na^+ 130–160 mmol, K^+ <1 mmol, Cl^- ~130 mmol, sodium caprylate 4 mmol and sodium N-acetyl tryptophanate 4 mmol	
6% HES (130/0.4) in normal saline	• Osmolarity: 308 mOsm/l (calculated) • Osmolality: 304 mOsm/kg (measured) • pH 4.0–5.5 • Na^+ 154 mmol and Cl^- 154 mmol	• Volume-sparing effect similar to that of 4% albumin • Nephrotoxic: compared with saline, increased serum creatinine levels and risk of AKI requiring RRT in critically ill patients
6% HES (130/0.4) in buffered salt solution	• Osmolarity: 286 mOsm/l (calculated) • Osmolality: 283 mOsm/kg (measured) • pH 5.7–5.5 • Na^+ 137 mmol, K^+ 4 mmol, Cl^- 110 mmol, acetate 34 mmol and Mg^{2+} 1.5 mmol	
6% HES (130/0.42) in Ringer's acetate	• Osmolarity: 296 mOsm/l (calculated) • Osmolality: NK • pH 5.6–6.4 • Na^+ 140 mmol, K^+ 4 mmol, Cl^- 118 mmol, Ca^{2+} 2.5 mmol, acetate 24 mmol, malate 5 mmol and Mg^{2+} 1.0 mmol	• Nephrotoxic: compared with Ringer's acetate, increased risk of AKI requiring RRT and increased risk of death in critically ill patients with sepsis and septic shock
Succinylated gelatin 4%	• Osmolarity: 274 mOsm/l (calculated) • Osmolality: NK • pH 7.4 • Na^+ 154 mmol and Cl^- 120 mmol	• Not studied in large-scale randomized controlled trials • Risk of life-threatening anaphylaxis • Increased risk of AKI in observational studies
Polygeline 3.5%	• Osmolarity: 301 mOsm/l (calculated) • Osmolality: NK • pH 7.3 • Na^+ 145 mmol, K^+ 5.1 mmol, Cl^- 145 mmol and Ca^{2+} 6.25 mmol	

AKI, acute kidney injury; HES, hydroxyethyl starch; NK, not known; RRT, renal replacement therapy; TBI, traumatic brain injury.

Colloid solutions

Commercially available colloid solutions are suspensions of large plasma-derived or semisynthetic molecules that cannot pass through intact semipermeable membranes. The duration of intravascular expansion produced by specific colloids varies and is dependent on the rate of metabolism and clearance of the constituent molecules. Generally, the intravascular volume expansion achieved by plasma derivatives (4–6 h) is longer than that produced by semisynthetic colloids (1–4 h), although actual durations vary substantially between patients.

The theoretical advantage of colloids over crystalloids is that a reduced fluid volume is needed to produce the same intravascular volume expansion, suggesting that colloid use would result in reduced interstitial oedema. Traditional teaching, based on the original Starling equation[38], is that 3 l of isotonic crystalloid produces the same intravascular expansion as 1 l of colloid[49]. Often referred to as the 3:1 rule, this so-called volume-sparing effect has been the basis for advocating the use of colloids in fluid resuscitation, particularly in high-risk patients, such as those with major trauma, sepsis or burns. However, the evidence from high-quality, blinded RCTs comparing the safety and efficacy of proprietary colloid and crystalloid solutions consistently shows a far more modest volume-sparing effect, with intravascular expansion ratios of around 1:1.4, for colloids versus crystalloids[7–9,50]. Treatment with colloid solutions might also reduce net filtration pressure by increasing oncotic pressure, which could also lead to a decrease in GFR; however, the clinical relevance of this effect is unclear[51–53].

Human albumin. Of the available colloids, human albumin was traditionally regarded as the most physiologically appropriate fluid resuscitation solution and, following the development of blood fractionation, was widely used during the Second World War[54]. However, the high cost of albumin, the need to distribute it in glass containers and concerns about the possibility of disease transmission with blood-derived products decreased its popularity once alternative semisynthetic colloids became available.

Under physiological conditions, albumin is the predominant protein in plasma and the principal determinant of plasma colloid osmotic pressure. The normal biological half-life of albumin is 15 days. Endogenous plasma albumin has many physiological functions, including acting as a buffer molecule, an important carrier for both endogenous and exogenous molecules, and the main extracellular antioxidant. Human albumin is commercially available as heat-treated 4–5% albumin iso-oncotic preparations and as concentrated (generally 20% or 25% albumin) hyperoncotic preparations, which contain a lower proportion of sodium than do the 4–5% solutions.

Overall, the use of either albumin or saline for fluid resuscitation produces similar outcomes in ICU populations. In the Saline Versus Albumin Fluid Evaluation (SAFE) trial[50], 6,997 patients from 16 ICUs in Australia and New Zealand were randomly assigned to receive fluid resuscitation with either 4% albumin or normal saline. Overall, all-cause mortality at 28 days was the same in both groups, although different effects were seen in some subgroups of patients (see below). The study reported organ-specific effects of albumin and saline using the Sequential Organ Failure Assessment (SOFA) score, which (similar to the risk, injury, failure, loss of renal function and end-stage renal disease (ESRD) (RIFLE) and Kidney Disease: Improving Global Outcomes (KDIGO) criteria) uses urine output and serum creatinine concentration to assess AKI. The researchers found no difference between the albumin and normal saline groups in the renal component of their SOFA scores or in the proportion of patients treated with renal replacement therapy (RRT). Therefore, current evidence from high-quality RCTs indicates that, compared with saline, albumin does not reduce mortality in mixed populations of medical and surgical ICU patients[50], including those who have hypoalbuminaemia on presentation to the ICU[55], and, importantly, it does not increase the risk of AKI. In the SAFE study, patients with severe TBI assigned to resuscitation with 4% albumin in a slightly hypotonic carrier fluid had significantly increased mortality owing to the development of intracranial hypertension, making this preparation of albumin specifically contraindicated in this population[45,56].

In patients with sepsis, the evidence is equivocal regarding whether albumin administration, either for fluid resuscitation or to maintain serum albumin concentration, is associated with reduced mortality[50,51,55]. In post hoc adjusted analyses of the SAFE study data, resuscitation with albumin rather than saline might have reduced mortality[57]. The use of hyperoncotic (20–25%) albumin for resuscitation and to maintain

serum albumin concentration was evaluated in the Albumin Italian Outcome in Sepsis (ALBIOS) trial[51]. In this open-label RCT, 1,818 critically ill patients with sepsis and septic shock were randomly assigned to receive 20% albumin and crystalloid solution or crystalloid solution alone; albumin supplementation aimed to achieve and maintain a target serum albumin concentration ≥30 g/l. The ALBIOS investigators reported no between-group differences in the proportion of patients treated with RRT or in overall mortality. A post hoc analysis found reduced mortality in the subgroup of patients with septic shock[51].

Two fairly small randomized trials ($n = 126$ and $n = 110$, respectively) conducted in patients with cirrhosis and either spontaneous bacterial peritonitis or other bacterial infections showed that adding concentrated albumin to antibiotic therapy reduced the risk of renal failure and death[58,59]. In two small RCTs, hypoproteinaemic patients with acute lung injury treated with furosemide were randomly assigned in a 1:1 ratio to receive concentrated albumin or normal saline. The albumin-treated patients had improved oxygenation and other measures of organ dysfunction, but both trials were too small and their follow-up too short to draw definitive conclusions about the potential benefits of concentrated albumin in this population[60,61].

Thus, current evidence suggests that, overall, albumin is equivalent to saline for fluid resuscitation of critically ill patients but could have beneficial effects in patients with sepsis and those with spontaneous bacterial peritonitis or other bacterial infections. Iso-oncotic albumin (4% or 5%) in hypotonic carrier fluid is contraindicated in patients with acute TBI.

Hydroxyethyl starch. HES solutions, which are produced by hydroxyethyl substitution of amylopectin obtained from sorghum, maize or potatoes, are the most commonly used semisynthetic colloids worldwide[13]. HES solutions are supplied in saline or buffered salt solutions in 500 ml biocompatible plastic polymer containers.

HES solutions are differentiated by their concentration (g/100 ml, expressed as a percentage), their average molecular mass and the degree of molar substitution, defined as the fraction of glucose units that are hydroxyethylated. For example, a HES solution with a concentration of 10 g/100 ml, an average molecular mass of 200 kDa and 6 hydroxyethyl groups per 10 glucose residues is designated as 10% HES (200/0.6). The pattern of hydroxyethyl substitution also influences the susceptibility of HES molecules to hydrolysis by nonspecific amylases in the blood. A high degree of molar substitution and increased substitution at carbon 2 (C2) rather than carbon 6 (C6) of the glucose molecule (that is, an increased C2:C6 ratio) protects against enzymatic breakdown, thereby prolonging the duration of plasma volume expansion and increasing the potential for HES to accumulate in the reticuloendothelial system.

Older, hyperoncotic HES preparations, such as 10% pentastarch, have a high molecular mass (>200 kDa) and a high degree of molar substitution (>0.6). The use of such 10% HES (200/0.6) solutions is associated with an increased risk of AKI, increased use of RRT, pruritus and

Iso-oncotic
A solution having a colloid osmotic pressure similar to that of plasma.

Hyperoncotic
A solution having a colloid osmotic pressure higher than that of plasma.

coagulopathy[7,10]. In response to these findings, manufacturers produced and marketed less-concentrated HES solutions with lower molecular mass, such as 6% HES with a molecular mass of 130 kDa and molar substitution of around 0.4 (designated 6% HES (130/0.4) and 6% HES (130/0.42), respectively). These newer HES formulations have been widely used for fluid resuscitation, particularly in patients undergoing general anaesthesia for major surgery and in patients with trauma and sepsis. Unfortunately, these second-generation HES solutions seem to be equally nephrotoxic[62]. Synthetic colloids, notably HES solutions, are a known cause of osmotic nephrosis (which is characterized by vacuolization, swelling and colloid accumulation in tubular cells)[63,64], and their propensity to cause AKI has now also been proved. Large, high-quality, blinded RCTs have demonstrated a dose-dependent adverse effect of 6% HES (130/0.42) in Ringer's acetate on the risk of death and need for RRT in patients with severe sepsis and septic shock, as well as an increased use of RRT in a general population of ICU patients who received 6% HES (130/0.4) in saline[8,9]. Meta-analyses of pooled data have consistently shown substantial increases in the risk of death and use of RRT in patients receiving HES solutions[65], and HES-related nephrotoxicity is also apparent in kidneys transplanted from donors who had received HES solutions[66].

In an open-label trial that compared colloids and crystalloids, in which the treating clinicians were free to choose the specific fluid (and many of them selected HES as the colloid solution), some secondary outcomes favoured the use of colloids[67]. Although some reports have interpreted the results of this trial as supporting the use of HES solutions for specific indications[68], the totality of the available evidence indicates that HES solutions carry unacceptable risks of toxicity and do not confer any benefit over crystalloids. Moreover, HES administration offers no discernible benefits relating to mortality or other patient-related outcomes[65]. As a result, regulatory authorities, such as the FDA and European Medicines Agency (EMA), placed restrictions on the use of HES in high-risk patients[69,70]. In 2013, the EMA requested that drug-utilization studies should be performed to verify clinicians' adherence to these restrictions. The results of these studies showed that HES was being used contrary to the restrictions; as a result, the EMA has recommended withdrawal of marketing authorization for the use of HES solutions in critically ill patients and those with sepsis or burn injuries across the European Union[71].

Gelatin. Gelatin is prepared by hydrolysis of bovine or porcine collagen. The most commonly available preparations are succinylated gelatin and urea-linked gelatin–polygeline, both of which have a long shelf life. They are supplied in saline in 500 ml biocompatible plastic polymer containers. Gelatin has a relatively low molecular mass (30–35 kDa) and expands plasma volume for only 1–2 h, after which it is metabolized and excreted via the kidney.

The use of gelatin-based fluids is associated with an increased risk of AKI, owing to the accumulation of gelatin in the reticuloendothelial system[72], and they can also cause life-threatening anaphylaxis[73]. Indeed, artificial colloid solutions containing gelatin exhibit many of the same toxicities as HES solutions[74]. For example, animals treated with either gelatin or HES solutions demonstrated similar capillary dilatation, injury to the basement membrane of epithelial cells, tubular vacuolation and increased cell death. Moreover, although both groups of treated animals showed increased interstitial oedema and loss of the proximal tubular cell brush border as well as increased serum levels of urea and creatinine, these changes were even greater in animals receiving gelatin than in those receiving HES[63]. No large-scale trials have compared the efficacy and safety of gelatins with those of other resuscitation fluids, and their role as resuscitation fluids has not been clearly defined. As for HES solutions, in the absence of any data suggesting a benefit of gelatin solutions over crystalloids, their continued use is difficult to justify[75].

Fluid physiology in renal disease

Renal disease, either acute or chronic, can have clinically important effects on fluid physiology. In patients with oligoanuric AKI, the most important of these effects on fluid physiology relate to the accumulation of fluid or the diminished ability to excrete excess fluid. In patients with chronic kidney disease (CKD) or marked proteinuria, fluid accumulation can cause peripheral and pulmonary oedema[76]. Fluid retention also contributes greatly to systemic hypertension and has consequent adverse effects on cardiac function, notably diastolic dysfunction. These changes contribute to the development of cardiorenal syndrome[77], in which fluid retention aggravates hypertension, oedema and cardiac dysfunction, and cardiac dysfunction aggravates fluid retention. The resultant episodes of acute heart failure or acute decompensation of chronic heart failure are, in turn, associated with episodes of acute-on-chronic renal dysfunction with consequent progressive loss of glomerular filtration capacity[78]. In addition, uraemia itself seems to contribute to cardiac dysfunction, further exacerbating the consequences of fluid accumulation.

In such patients, diuretic therapy can maintain fluid balance up to a point but might fail to prevent fluid overload. Once CKD has progressed to ESRD, the only way to control the patient's fluid status and prevent fluid accumulation is through fluid intake restriction and, when that proves inadequate, fluid removal via RRT or dialysis[79]. This situation inevitably exposes the patient to oscillations between variable (and occasionally clinically relevant) fluid overload and fluid depletion and hypotension during intermittent haemodialysis. Use of peritoneal dialysis attenuates such swings in volume status.

Similarly, patients with AKI are commonly unable to excrete fluid normally, which makes them susceptible to fluid overload. Moreover, in many conditions that cause AKI (particularly sepsis and septic shock), rapid, high-volume fluid resuscitation has been widely advocated and used as a first-line treatment. Once AKI is severe, diuretic therapy is ineffective[80], and fluid balance can be maintained only by RRT. Once RRT is in use, fluid removal and fluid management are possible through net ultrafiltration, but fluid management must be tailored

to the individual patient. Often, competing clinical and biochemical factors require consideration, including the individual patient's haemodynamic stability, gas exchange, and control of solute and potassium levels and the acid–base balance. The optimal approach to fluid management in patients with AKI remains controversial, as, to date, restrictive and liberal fluid approaches have not been directly compared in RCTs. In the absence of such data, the persistent dogma worldwide is that vigorous fluid removal or restriction risks hypovolaemia that would be injurious to the kidneys of patients with or at high risk of AKI. However, an increasing body of evidence suggests that injudicious use of intravenous fluid therapy also carries risks to both patient and their kidneys[81] and that such risks relate both to fluid overload and to the adverse effects of some fluid types on renal function (TABLES 3,4).

Fluid volume and overload

The traditional management paradigm for patients with AKI or at risk of AKI involves high-volume fluid resuscitation. Typically, fluid is initially given as a bolus (for example, updated sepsis guidelines recommend 30 ml/kg in the first hour of treatment[82]) followed by infusion. This practice persists because oliguria is one of the top three triggers for fluid bolus therapy, and the subsequent changes in urine output are then commonly used to assess response to this therapy[5,83,84]. However, whether receiving fluid bolus therapy (versus receiving a reduced amount or no fluid, with or without vasoactive drug therapy) leads to different renal outcomes in patients with oliguria is unknown. What is known is that the administration of fluid to oliguric patients at risk of AKI commonly leads to fluid accumulation, which might be injurious to the kidney. In healthy individuals, the administration of 2 l of crystalloid fluid infused over 60 min increases kidney volume, which implies the development of renal oedema[85]. As the kidney is an encapsulated organ, such oedema could lead to increased resistance to venous return and contribute to renal ischaemia[86–92].

The above considerations raise the question of whether a conservative approach to fluid therapy, combined where necessary with inotropic or vasoconstrictor support to maintain organ perfusion and renal filtration pressure, might improve the outcomes of these patients. In support of a conservative approach, the results of the pilot Conservative Versus Liberal Approach to Fluid Therapy of Septic Shock in Intensive Care (CLASSIC) trial[93] showed that AKI occurred less often in patients with septic shock who were randomly assigned to a restrictive fluid strategy. In this trial, the median volume of resuscitation fluid given in the fluid restriction group was 500 ml compared with 2,200 ml in the standard care group. Similar findings were reported in a study of patients with acute lung injury, in whom the mean cumulative fluid balance during the first 7 days was −136 ml in the restrictive strategy group and +6,692 ml in the liberal strategy group[94]. The aggregated data from three large trials of early goal-directed therapy (EGDT), which mandates the use of aggressive fluid therapy in patients who present to emergency departments with

septic shock, found no beneficial effect of EGDT on mortality or organ function, including renal function[95]. In the FEAST trial[96], conducted in African children, no differences in outcomes were demonstrated between the groups of children given albumin and those given saline fluid boluses. However, reduced mortality was observed in children from whom fluid boluses (both albumin and saline) were withheld. A trial in Zambia reported that patients randomly assigned to EGDT (who received a median of 3.5 l of resuscitation fluid during the first 6 h of their treatment) had increased mortality compared with patients assigned to usual care (who received a median of 2.0 l resuscitation fluid during the same time period)[97]. Collectively, these trials call into question the assumption that liberal use of high-volume fluid resuscitation is beneficial, particularly in patients with septic shock, the most common cause of AKI in critically ill patients[98].

Contrary evidence comes from a randomized trial published in 2018, in which 3,000 patients were randomly assigned to a restrictive or liberal fluid strategy during and after major abdominal surgery[99]. During and up to 24 h after surgery, patients in the liberal and restrictive groups received a median of 6.1 l and 3.7 l of intravenous fluid, respectively. Patients assigned to liberal fluid therapy had lower rates of AKI and surgical site infections, and fewer were treated with RRT[99]. These data indicate that evidence from trials in critically ill patients, particularly those with sepsis, should not be extrapolated to guide perioperative management and vice versa.

Although the mechanisms through which a liberal fluid strategy might result in poor outcomes remain to be elucidated, the current theory holds that the administration of large amounts of sodium and chloride is the probable culprit. Rapidly administered, high-volume fluid therapy remains common in clinical practice, owing to the fear that AKI could result from untreated hypovolaemia. Currently, however, this practice is neither supported nor refuted by convincing clinical trial data.

Fluid type

The type of fluid given to patients with renal injury or at risk of renal injury can affect both organ function and patient outcome[100]. The effects of HES, albumin and gelatin have already been discussed above; in this section, we focus on comparisons of the two most commonly administered fluids, normal saline and buffered solutions, in critically ill patients.

Much of the evidence supporting the use of buffered solutions rather than normal saline has come from observational studies in perioperative medicine[36]. Evidence from cluster-randomized studies in critically ill patients is steadily accumulating but not yet totally conclusive. In a pilot study with a double crossover, cluster-randomized design, PlasmaLyte 148 (TABLE 1) was compared with normal saline in a population of 2,278 patients admitted to four ICUs in New Zealand[39]. The results indicated no differences between the groups in the effect of the two fluids on RIFLE-defined or KDIGO-defined AKI or in the use of RRT. However, this

Table 3 | **Trials comparing different fluids (in chronological order)**

Population	Treatment arms	Outcomes	Results	Implications for clinical practice	Refs
52 brain-dead kidney donors (France, 1996)	6% HES (200/0.62) to maximum of 33 ml/kg then gelatin if needed versus gelatin only	SCr during the first 10 days and proportion of transplant recipients treated with haemodialysis or haemofiltration during the first 8 days	SCr and treatment with haemodialysis or haemofiltration increased in recipients of donors resuscitated with HES; three renal biopsy specimens in the HES group had osmotic nephrosis-like lesions in the tubules	Supports contention that HES is nephrotoxic; HES should not be used in potential kidney donors	66
129 adults with severe sepsis or septic shock in three ICUs (France, 2001)	6% HES (200/0.6) versus 3% fluid-modified gelatin	AKI (doubling of SCr or need for RRT)	AKI increased in HES group	HES should not be given to adults with sepsis	10
SAFE: 6,997 adults in mixed medical, surgical and specialty ICUs (Australia and New Zealand, 2004)	4% albumin while in ICU until 28 days after enrolment versus normal saline (for same indications)	28-day all-cause mortality	No difference in 28-day mortality; albumin associated with increased mortality in patients with TBI	Overall, albumin and saline produce equivalent outcomes, but saline is less expensive and thus preferred; albumin should be avoided in patients with TBI	50
VISEP: 537 adults with sepsis (Germany, 2008)	10% HES (200/0.5) while in ICU versus modified Ringer's lactate (for same indications)	28-day mortality and mean SOFA score	No difference in 28-day mortality or mean SOFA score; HES associated with increased rates of AKI and RRT	HES 200/0.5 should not be given to adults with sepsis	7
CHEST: 7,000 adults in mixed medical, surgical and specialty ICUs (Australia and New Zealand, 2012)	6% HES (130/0.4) to maximum of 50 ml/kg daily then normal saline while in ICU until 90 days after enrolment versus normal saline (for same indications)	90-day all-cause mortality	No difference in 90-day mortality; HES associated with increased use of RRT and increased SCr; no beneficial effect of HES on patient-centred outcomes	Supports contention that HES is nephrotoxic; HES should not be given to patients in the ICU	9
6S: 804 patients with severe sepsis in ICUs (Denmark, Norway, Finland and Iceland, 2012)	6% HES (130/0.42) to maximum of 33 ml/kg daily then Ringer's acetate while in ICU until 90 days after enrolment versus Ringer's acetate only	Composite outcome: death or ESRD at 90 days after randomization, need for RRT	HES associated with increased risk of composite outcome and with increased proportion of patients requiring RRT	HES should not be given to adults with sepsis; HES still linked to adverse outcomes despite use of 'safer' formulation	8
CRISTAL: 2,857 patients with acute hypovolaemia admitted to ICUs (France, North Africa, Belgium and Canada, 2013)	Colloid solution versus crystalloid solution (exact agent used chosen by treating clinician)	28-day mortality	No difference in 28-day mortality; secondary outcomes (measures of organ dysfunction and 90-day mortality) favoured colloids	This is the only large study suggesting that colloids offer benefits over crystalloids; the non-blinded nature of the study increases the risk of bias but the totality of evidence favours crystalloids over colloids	67
ALBIOS: 1,818 patients with severe sepsis in ICUs (Italy, 2014)	Crystalloid plus 20% albumin to maintain serum albumin concentration ≥30 g/l versus crystalloid alone	28-day all-cause mortality	No difference in 28-day mortality; albumin administration associated with reduced mortality in patients with septic shock only	Albumin administration does not reduce mortality in patients with sepsis; a possible benefit in patients with septic shock is considered preliminary or hypothesis-generating	51
SPLIT: 2,278 patients admitted to ICUs requiring crystalloid fluid therapy (New Zealand, 2015)	Buffered crystalloid (PlasmaLyte 148) versus normal saline	Proportion of patients with AKI (doubling of SCr or baseline SCr 3.96 mg/dl with an increase of 0.5 mg/dl)	No difference in incidence of AKI	Cluster crossover trial conducted as pilot study; high proportion of elective surgical patients and relatively small volumes of study fluids used; however, provides justification for larger phase III randomized trial in higher risk population	39
SALT-ED: 13,347 adults treated with crystalloid in a single emergency department, hospitalized outside ICU (USA, 2018)	Buffered crystalloid (PlasmaLyte A or Ringer's lactate) versus normal saline	Hospital-free days (days alive after discharge before day 28)	No difference in hospital-free days; lower incidence of MAKE30 in buffered crystalloid group	Open-label, multiple-cluster crossover single-centre randomized trial; suggests that adverse kidney events are less common with buffered crystalloid than with saline	40

Table 3 (cont.) | **Trials comparing different fluids**

Population	Treatment arms	Outcomes	Results	Implications for clinical practice	Refs
SMART: 15,802 adults treated with crystalloid in ICUs at a single centre (USA, 2018)	Buffered crystalloid (PlasmaLyte A or Ringer's lactate) versus normal saline	MAKE30	Reduced incidence of MAKE30 in buffered crystalloid group (NNT 99); reduced in-hospital mortality in buffered crystalloid group ($P = 0.06$)	Open-label, multiple-cluster crossover randomized single-centre trial; suggests that adverse kidney events are less common with buffered crystalloid than with saline	[41]

AKI, acute kidney injury; ESRD, end-stage renal disease; HES, hydroxyethyl starch; ICU, intensive care unit; MAKE30, major adverse kidney events (a composite outcome of death from any cause, new renal replacement therapy (RRT) or persistent renal dysfunction defined as doubling of serum creatinine level (SCr) from baseline) at 30 days; NNT, number needed to treat; SOFA, sequential organ failure assessment; TBI, traumatic brain injury.

pilot study had limited statistical power and does not provide definitive evidence about the possible benefits or harms of buffered solutions compared with saline[101,102].

The strongest evidence to date comes from two open-label, multiple-crossover, cluster-randomized trials conducted simultaneously at one academic centre in the USA[40,41]. The Saline Against Lactated Ringer's or PlasmaLyte in the Emergency Department (SALT-ED) trial[40] compared normal saline with two buffered crystalloids (either lactated Ringer's solution or PlasmaLyte A, chosen by the treating clinician) in the treatment of all patients in the emergency department who were subsequently admitted to hospital wards other than the ICU[40]. The design of the trial required the entire emergency department to alternate between buffered solutions and normal saline for successive periods of 1 month. During the months when only buffered fluids were used, the treating clinicians were free to choose either lactated Ringer's solution or PlasmaLyte A. The primary outcome, hospital-free days (defined as days alive after hospital discharge before day 28), did not differ between the groups, although the secondary outcome, major adverse kidney events (MAKE, a composite of death, dialysis or doubling of baseline creatinine concentration) censored at 30 days — the so-called MAKE30 — favoured the use of buffered solutions. This benefit was most marked in the patients who had the poorest renal function at randomization[40].

The Isotonic Solutions and Major Adverse Renal Events Trial (SMART)[41], conducted by the same investigators, also compared saline with buffered crystalloids (lactated Ringer's solution or PlasmaLyte A, chosen at the clinicians' discretion) in an open-label, multiple-crossover, cluster-randomized design. The participants comprised patients admitted to all five ICUs at the same institution. The allocation of individual ICUs to the use of either buffered solutions or normal saline was again performed on a monthly basis, and the fluids used in the medical, surgical and trauma ICUs (which admitted most patients from the emergency department) were the same as those used in the emergency department during that same month. Although the participants received only small volumes of the allocated fluids (a median of 1 l buffered solution versus 1.02 l normal saline) during the period from ICU admission to the earlier of hospital discharge or 30 days, the primary outcome (MAKE30) occurred more frequently in the patients who received normal saline[41]. The effect of fluid type on MAKE30 incidence was also examined in a number of prespecified subgroups; the effect was strongest in patients with sepsis, although the test for heterogeneity fell just short of the traditional level of statistical significance.

The two trials were well conducted, transparently reported and followed the prespecified treatment protocol and statistical analysis plan[103]. They employed some novel methods, most notably allocating patients to subgroups and collecting all trial data via electronic health records rather than the traditional approach of using dedicated data collectors. These methods were evaluated in separate preparatory studies, instead of performing traditional trial monitoring or verification of the data within the trials[104,105]. Although these two trials provide the strongest evidence to date favouring buffered salt solutions over normal saline, a number of caveats should be borne in mind. The trials were open-label and conducted at a single centre, and the results of such trials have often been refuted when repeated in multicentre trials[106–109]. Another important factor is that the most robust outcome measures for open-label trials are those that are not subject to ascertainment bias. The MAKE30 outcome measure, although it does include mortality (a patient-centred outcome), also includes initiation of RRT, which, in an open-label design, might be heavily biased by clinicians' perceptions that normal saline is nephrotoxic. The third component of the composite outcome was a doubling of the serum creatinine concentration from a known or calculated baseline level. The investigators used the lowest recorded serum creatinine level in the preceding 12 months as the baseline value; validity would have been improved if they had instead used the last value available before randomization. The most robust reported outcome, mortality at day 60, did not differ significantly between the groups: 11.7% for patients assigned to buffered solutions versus 12.4% for those assigned to normal saline; RR 0.94, 95% CI 0.87–1.02). These and other caveats were noted in an editorial accompanying the publication of the trials, which concluded that although the results might inform thinking on the choice of intravenous fluids, they did not provide unequivocal evidence to guide clinical practice[110].

Interpretation of the SMART[41] and SALT-ED[40] trial data will be facilitated when the results of two currently ongoing large multicentre blinded RCTs comparing PlasmaLyte 148 with normal saline in ICU patients are published. The BaSICS study[111] aims to recruit 11,000 ICU

Table 4 | **Trials comparing fluid versus no fluid or different amounts of fluid (in chronological order)**

Population	Treatment arms	Outcomes	Results	Implications for clinical practice	Refs
126 patients with cirrhosis and SBP from a single centre (Spain, 1999)	Intravenous cefotaxime plus fixed-dose albumin versus intravenous cefotaxime alone	Development of renal impairment or mortality	Mortality and incidence of renal impairment were both reduced in patients who received albumin	Administration of albumin improved outcomes, but results could not inform whether this effect was specific to albumin or would also have occurred had another fluid been administered	58
FACCT: 1,000 patients with acute lung injury or ARDS (USA, 2006)	Conservative versus liberal fluid strategy	60-day mortality	No difference in mortality; conservative fluid strategy improved oxygenation and lung injury scores and increased the number of ventilator-free days and non-ICU days alive	Results support the use of a conservative fluid management strategy in patients with acute lung injury	94
FEAST: 3,141 children with febrile illness and impaired perfusion (Kenya, Uganda and Tanzania, 2011)	Fluid boluses of 5% albumin or normal saline versus no fluid bolus	48-h mortality	Fluid boluses increased mortality; no difference in mortality between saline and albumin boluses	In resource-poor settings, avoid fluid boluses in critically ill children with impaired perfusion; implications for high-income countries are unclear	96
110 patients with cirrhosis and infections other than SBP (Spain, 2012)	Antibiotics plus fixed-dose albumin versus antibiotics alone	Survival at 3 months	No difference between groups	Small trial that does not provide evidence for administration of albumin to patients with cirrhosis and infection	59
CLASSIC: 152 adults with septic shock treated in ICUs (Denmark, 2016)	Restrictive versus liberal (standard care) approaches to resuscitation fluid administration	Amount of resuscitation fluid given in first 5 days and during entire ICU stay	Significantly less fluid was given to the restrictive group; secondary outcomes (ischaemic events, worsening of AKI and death) favoured the restrictive approach; statistically significant result observed for worsening of AKI	Study supports feasibility and biological rationale for a large trial of fluid restriction in patients with septic shock; mortality and renal function should be major outcome measures	93
212 adults with septic shock presenting to emergency department (Zambia, 2017)	Early resuscitation protocol versus usual care	In-hospital mortality	Early resuscitation protocol increased in-hospital mortality; patients in the protocol group received more fluid, and more patients received vasopressors than in the usual care group	Administration of more fluid and vasopressor agents might not always be beneficial in patients with septic shock; further research in such settings is urgently needed; implications for high-income countries are unclear	97
RELIEF: 3,000 adults undergoing major abdominal surgery (Australia, 2018)	Restrictive versus liberal (standard care) fluid administration	Disability-free survival at 1 year	No difference in disability-free survival, but AKI, surgical site infections and treatment with RRT were all reduced in patients assigned to liberal fluid administration	Restrictive fluid approach might be harmful in adults undergoing major abdominal surgery	99

AKI, acute kidney injury; ARDS, acute respiratory distress syndrome; ICU, intensive care unit; RRT, renal replacement therapy; SBP, spontaneous bacterial peritonitis.

patients in Brazil, and the PLUS study[112] aims to recruit 8,800 ICU patients in Australia and New Zealand. Both trials target populations of patients with more severe illness than the SMART participants, and both have landmark mortality at 90 days as their primary outcome measure. Pending the results of these trials, a degree of uncertainty remains over the relative benefits or harms of normal saline and buffered salt solutions in critically ill patients, both overall and in specific subgroups. Outside RCTs, clinicians might reasonably prefer buffered salt solutions over isotonic saline, although calls to abandon the use of normal saline could prove premature[113].

Interpretation of trial data

A major challenge in determining whether a given amount of fluid or a particular type of fluid is beneficial or injurious to the kidney relates to our limited ability to assess renal injury or benefit. Ideally, outcome measures should be patient-centred, but the only truly patient-centred measure of kidney injury is treatment with RRT, which is a relatively uncommon event. In large blinded trials conducted in a general population of ICU patients receiving resuscitation fluids, the proportion of patients newly treated with RRT is around 6–7%[9,50], whereas in trial populations consisting of patients with sepsis or septic shock, this proportion might be around 20%[8]. Thus, treatment with RRT is unsuitable for use as an outcome measure in phase II trials or pilot investigations. Treatment with RRT might be used as an outcome measure in phase III trials, albeit with similar limitations, unless the signal for benefit or harm is very strong or the trial is very large.

To increase sensitivity and maintain clinical relevance, the severity of AKI (as defined by RIFLE[114] and KDIGO[115] criteria or other scoring systems) has been widely used as an outcome measure, although these scores were originally designed as prognostic tools in patients with renal dysfunction or ESRD. The RIFLE and KDIGO criteria

both rely on two measures: serum creatinine concentration and urine output. Rapid fluid resuscitation might dilute serum creatinine[116,117], and urine output might be increased by osmotic diuresis even as patients are developing AKI[9]. This effect can produce misleading or distorted outcomes in clinical research, particularly when threshold values are used (as they are in AKI scoring systems). This issue was evident in the Crystalloid Versus Hydroxyethyl Starch Trial (CHEST)[9]: in patients assessed as falling within the RIFLE categories R (risk) and I (injury), measures of AKI based on creatinine favoured normal saline, whereas measures of AKI based on urine output favoured HES. For patients in RIFLE category F (failure), both measures favoured normal saline.

Competing risk, defined as the occurrence of an event that prevents observation of the outcome being studied, is a recognized and ever-present methodological challenge in critical care trials. The most common competing risk in critically ill patients is death, which prevents a patient from being treated with RRT and/or might prevent the recording of a peak creatinine concentration above a relevant threshold, if, for example, an anuric patient dies before creatinine accumulation has occurred. Attempts to compensate for such difficulties include the increasing use of competing risk analyses in statistical analysis plans and the use of composite outcome measures, such as MAKE. MAKE can be measured over different periods of observation, commonly 30 days or 90 days, resulting in the variants MAKE30 and MAKE90, respectively. However, an approach that considers death and a doubling of serum creatinine level to be equivalent components of a composite outcome measure seems intuitively flawed. Several biomarkers of renal injury have emerged over the past decade (notably neutrophil gelatinase-associated lipocalin and the cell cycle arrest biomarkers). However, their value as surrogates for clinically relevant or patient-centred outcomes remains untested[118].

With the improvements in survival of patients with sepsis and other forms of critical illness, the health-related quality of life of survivors takes on increasing importance[119]. No consensus has yet been reached on the best way to assess health-related quality of life in the context of clinical trials. Multicomponent generic scoring systems (such as the Short-Form 36 or Euro-QOL 5) are often used, as the sequelae of critical illness include physical, neuropsychiatric and cognitive impairments[120]. However, as in other areas of medical research, whether the outcomes of interest to researchers are similarly important to patients is unclear. Initiatives such as Core Outcome Measures in Effectiveness Trials (COMET)[121] seek to address these uncertainties and to encourage appropriate and standardized outcome reporting.

Conclusions

Despite the administration of intravenous fluids to critically ill patients being a near-universal intervention, the available evidence base guiding their safe and appropriate use is scarce and derived mainly from academically driven, investigator-initiated trials (TABLES 3,4). These trials have proved that HES, the most frequently administered colloid solution, has an unacceptable safety profile and offers no benefits other than a clinically unimportant volume-sparing effect. Several unresolved questions remain, including whether buffered solutions are definitely better than normal saline and whether critical care clinicians should adopt a restrictive approach to fluid administration, either in general or in selected subgroups of patients. Finally, whether fluid resuscitation approaches should be different in resource-poor settings (where the majority of the world's population lives and where advanced organ support might not be available) remains to be addressed.

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