

REVIEW

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Dose and type of crystalloid fluid therapy in adult hospitalized patients

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Abstract

Objective: In this narrative review, an overview is given of the pros and cons of various crystalloid fluids used for infusion during initial resuscitation or maintenance phases in adult hospitalized patients. Special emphasis is given on dose, composition of fluids, presence of buffers (in balanced solutions) and electrolytes, according to recent literature. We also review the use of hypertonic solutions.

Methods: We extracted relevant clinical literature in English specifically examining patient-oriented outcomes related to fluid volume and type.

Results: A restrictive fluid therapy prevents complications seen with liberal, large-volume therapy, even though restrictive fluid loading with crystalloids may not demonstrate large hemodynamic effects in surgical or septic patients. Hypertonic solutions may serve the purpose of small volume resuscitation but carry the disadvantage of hypernatremia. Hypotonic solutions are contraindicated in (impending) cerebral edema, whereas hypertonic solutions are probably more helpful in ameliorating than in preventing this condition and improving outcome. Balanced solutions offer a better approach for plasma composition than unbalanced ones, and the evidence for benefits in patient morbidity and mortality is increasing, particularly by helping to prevent acute kidney injury.

Conclusions: Isotonic and hypertonic crystalloid fluids are the fluids of choice for resuscitation from hypovolemia and shock. The evidence that balanced solutions are superior to unbalanced ones is increasing. Hypertonic saline is effective in mannitol-refractory intracranial hypertension, whereas hypotonic solutions are contraindicated in this condition.

Keywords: Shock, Hypovolemia, Fluid resuscitation, Normal saline, Ringer's lactate, Hypertonic saline

Review

The debate on fluid treatment of the surgical and critically ill patient is ongoing, partly because of insufficient data, historical and geographical differences, and poor training [1-3]. This includes the type and amount of fluids to be given when a patient is considered to be hypovolemic with a low plasma volume, or in shock, with a low or normal plasma volume, and in need of fluids for resuscitation or subsequent maintenance treatment [2,4,5]. Furthermore, the composition, presence or absence of buffer (so-called balanced and unbalanced solutions, respectively) and the additions of certain electrolyte, such as a potassium, calcium and magnesium, are controversial issues.

This review aims to describe the place of various crystalloid fluids in the treatment of adult hospitalized patients, in a narrative manner for educational purposes, leading through various clinical conditions and considerations by evaluation of various studies. We first discuss normal fluid and electrolyte composition of the body, balances and doses of crystalloid fluids, before embarking upon a discussion of relative pros and cons, under various circumstances, of the variously composed crystalloid solutions currently available. We will not discuss any experimental animal-derived nor pediatric data and studies. We end with a discussion of specific electrolyte repletion.

Fluid and electrolyte balance of the body

Table 1 shows the daily fluid balance of a healthy 70 kg male adult with 45 l of total body water (60% of body weight) [6]. Daily requirements are 80 to 120 mEq sodium,

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Table 1 Water balance per 24 hour in a healthy 70 kg male adult

Intake		Output	
Liquids	1,400 ml	Urine	1,500 ml
Water in food	850 ml	Skin	500 ml
Water by oxidation	350 ml	Respiratory tract	400 ml
		Stool	200 ml
Total	2,600 ml	Total	2,600 ml

50 to 100 mEq potassium, 2 to 4 mEq calcium and 20 to 30 mEq magnesium. Fluid and electrolyte therapy aims to correct deficits, and maintain daily requirements and normal concentrations in body fluids (Table 2).

In hospitalized or critically ill patients, however, fluid and electrolyte requirements may be increased following fever, vomiting, diarrhea, blood/plasma loss (trauma and surgery) and polyuria. For fever, formulas are available to estimate insensible losses, which approach 10 ml/kg per 1°C rise in temperature above 37°C [7]. Careful analysis of fluid intake and output, as well as estimations of insensible losses, may then be necessary to correct derangements in fluid status of the patient. This assessment may also include obtaining a body weight on a daily basis, although the latter is confounded by food intake. In the intensive care unit (ICU), obtaining daily weight can be difficult and, although clinically relevant in several (renal) patient groups, can be poorly associated with fluid balances [7].

Assessing hypovolemia is hard in hospitalized patients and many methods, from simple physical to complex physiological, have been described. Hypovolemia is often, rightfully or erroneously, considered in case of hypotension, low filling pressures, low central or mixed venous hemoglobin oxygen saturation, or need of isotropic or vasopressor drugs, which are clinical triggers for fluid infusion, even though this may benefit the patient only in the presence of preload and fluid responsiveness, irrespective of circulating plasma volume. Fluid responsiveness is defined by an increase in stroke volume or cardiac output by a fluid challenge or, preferably, passive leg raising to increase venous return. Incorporation of this strategy into decision

making on fluid loading, even in a patient in shock, may help to prevent potentially harmful overhydration.

Although not beyond doubt, severe hypovolemia may include the interstitial and eventually even the intracellular space, and repletion of these volumes can be accomplished by intravenous fluid administration [8,9]. Hypovolemia and decreased organ perfusion leading to tissue hypoxia may lead to shock. Fluid losses otherwise always include plasma water constituents, including sodium, potassium and magnesium, and their anions, such as chloride and bicarbonate, and other electrolytes. Electrolyte losses thus accompany fluid losses, for instance perioperatively [8]. In addition, the postoperative state is characterized by non-osmotic release of vasopressin, and activation of the renin-angiotensin-aldosterone system and the hypothalamic-pituitary-adrenal axis, with release of hormones which promote renal retention of water and sodium, to compensate in part for extrarenal losses.

Repletion of lost plasma should ultimately include all components, to prevent electrolyte and acid-base derangements, even independently of hypovolemia- and shock-induced alterations in production and elimination of acids and shifts in electrolyte distributions between intra- and extravascular spaces. One should take into account the electrolyte status of a patient before choosing an optimal fluid type for resuscitation and maintaining euvolemia.

Treating hypovolemia and shock

In this section, we will discuss fluid doses and types from a 'crystalloid' perspective. Crystalloid fluid loading may decrease mortality in hypovolemic patients, for instance after hemorrhage [10], but the optimal type and dose of crystalloid fluids remains to be defined in a variety of clinical settings.

In contrast to crystalloids, colloids remain in the circulation and increase intravascular volume by raising colloid osmotic pressure. They therefore have a three- to fourfold greater (sustained) plasma volume expanding and hemodynamic effects compared to crystalloids, for a given infusion volume [5,11-16]. A ratio of 1:3 to 1:4 for colloids versus crystalloids to result in similar plasma volume

Table 2 Composition of bodily fluids

	Na ⁺ (mmol/l)	K ⁺ (mmol/l)	Ca ²⁺ (mmol/l)	Mg ²⁺ (mmol/l)	HCO ₃ (mmol/l)	Lactate (mmol/l)	Other buffer (mmol/l)	Cl ⁻ (mmol/l)	Organic acid (mmol/l)	Protein
Plasma	142	4	5	2	101	27	2	1	6	16
Plasma water	153	4.3	5.4	2.2	109	29	2.2	1	6.5	17
Interstitial water	139	4	5	2	114	31	2	1	7	1
Intracellular water	10	160	2	26	3	10	100	20		65

expansion may even hold true in conditions such as sepsis where increased permeability may limit intravascular retention of colloid substances, provided that similar hemodynamic endpoints associated with plasma volume expansion are reached [11,13,17-20]. Authors have suggested, however, that in daily practice only 10 to 40% more crystalloids than colloids are infused, and results in similar resuscitation goals and outcomes [4,6,21-26]. Hence, the three to fourfold increased requirements for crystalloids to replace a given plasma volume are probably somewhat overestimated in clinical practice and are likely to be less. In hemorrhaged volunteers, 100 to 200% of Ringer's acetate may suffice to replace lost blood [27]. However, in other studies only 20% of infusion volumes of crystalloids are retained intravascularly and more than 60% equilibrates with the extravascular space within minutes or is excreted by the kidney within hours after administration [13,15,28]. Albumin only saves about 40% of saline volume loading in the so-called SAFE study (a large Australian study to investigate safety of albumin solution in intensive care), together with a slightly higher central venous and arterial blood pressure, and lower heart rate [21].

Indeed, it is likely that the simpler the hemodynamic targets are, like static hydrostatic pressures, the less they reflect plasma volume, and the less strictly they are used to guide resuscitation, the lower is the anticipated volume difference between resuscitation fluid types [25]. This largely explains some of the seeming discrepancies noted above and, conversely, implies that the hemodynamic effects of crystalloids are much less than of roughly equal amounts of infused colloids. Otherwise, the greater the hypovolemia, the slower the clearance and longer the half life are of a given infused crystalloid fluid volume, as calculated from kinetics of hemoglobin concentrations [29]. Finally, accommodation by unstressed volume in compliant veins attenuates the plasma volume expanding effect of infusion fluids.

Although fluid therapy is essential in the treatment of shock and tissue hypoperfusion, overhydration and grossly positive fluid balances are, generally, considered harmful by contributing to organ dysfunction after sepsis, trauma or surgery, raising the question which fluid type and dose can optimize hemodynamics and volume status, with the lowest risk of fluid overloading [30-34]. Crystalloids do not seem inferior to colloids, that is increase mortality, in surgical and critically ill patients with hypovolemia or shock of various origins [5,11-16]. Some of excessively infused crystalloid fluids may be excreted by the kidneys, sometimes even more than colloid fluids, and thereby contribute to limit an increasing fluid balance over hours and days [15]. It is, however, also generally suggested that resuscitation with crystalloids results in a more positive fluid balance and risk for (pulmonary) edema formation than that with colloids, even

though the magnitude of this effect has probably also been overemphasized in the past [17,24-26,30].

The propensity of crystalloid fluids to increase pulmonary edema formation, even in face of increased pulmonary vascular permeability and edema (in sepsis) at baseline, has not been confirmed, provided that fluid loading was done in the steep (rather than the plateau) portion of cardiac and pulmonary vascular filling [35]. The tendency for pulmonary edema formation, as inferred from radiologic and gas exchange changes in other studies, can thus be explained in part by fluid loading in the plateau of cardiac filling (fluid unresponsiveness) and pulmonary vascular filling (pulmonary congestion), independent of fluid type [17,35]. During hypothermia after cardiac arrest, more isotonic crystalloids were needed as compared to starch and hypertonic saline, but this did not lead to cerebral edema [36]. Nevertheless, it cannot be denied that overzealous crystalloid fluid loading has somewhat greater tendency for development of peripheral edema (and compartment syndromes) than resuscitation with colloids, against similar hemodynamic targets, particularly after multiple trauma, and that this can be detrimental [16,34,37,38]. Table 3 summarizes the pros and cons of clinical use of (balanced or unbalanced) crystalloid fluids, related to fluid volumes.

Compared to isotonic crystalloids, relatively small volumes of hypertonic solutions may suffice in restoring euvolemia and hemodynamics without grossly expanding the interstitial space, in hypovolemia and shock [9,13,30]. Relatively small-volume hypertonic saline 3 to 7% (whether or not accompanied by colloid fluids) is commonly used in emergency medicine for patients with traumatic hemorrhage and/or severe traumatic brain injury [39-42]. Hypertonic solutions may require less volumes than isotonic crystalloids in maintaining hemodynamics, also perioperatively, but may not carry other advantages in that setting [43]. This type of solution exerts a rapid volume expanding effect, which is larger than that of isotonic solutions, and a positive inotropic effect without too much

Table 3 Pros and cons of (unbalanced) crystalloid fluids leading to under- or over-resuscitation in clinical practice

Too little	Too much
Tissue hypoxigenation	Tissue edema and hypoxigenation
Risk for acute kidney injury	Compartment syndromes and renal dysfunction
Lactate and unmeasured anion acidosis	Hyperchloremic metabolic acidosis and risk forhyponatremia
Gastrointestinal disturbances	Anastomotic leakage; diarrhea and other gastrointestinal disturbances
	Pulmonary edema; hepatic congestion and injury
	Prolonged mechanical ventilation

dilution of coagulation factors, and perhaps prevents, delays or ameliorates a detrimental increase in intracranial pressure [40]. By limiting volume needs, it may also prevent development of abdominal compartment syndrome, as compared to Ringer's lactate during resuscitation from burn injury [37]. The hypertonic solutions may also have anti-inflammatory properties [44,45]. Nevertheless, the formal large-scale clinical studies on the subject are inconclusive, as their use may not decrease morbidity or mortality [39-43].

Hypertonic lactate solutions are also available and, like other hypertonic solutions, may have positive inotropic effects on the heart [37,46]. Hypertonic saline 3 to 7% can also be regarded as osmotherapy when applied for reducing intracranial pressure, as a primary drug or when mannitol has failed, which is the more common application [40,47,48]. However, serum sodium levels above 160 mmol/l are unlikely to further decrease cerebral edema [47]. The treatment may be even more effective in controlling intracranial hypertension than mannitol, but may not improve outcomes [40,48]. Obviously, the major adverse effect is severe hypernatremia, which is sometimes hard to control. Conversely, hypotonic fluids should be avoided in the condition, carrying the risk of edema aggravation, whereas under-resuscitation and resultant hypotension are also associated with a worse outcome. Management thus requires a careful balance, helped by hemodynamic and intracranial pressure monitoring, between systemic hemodynamics and cerebral perfusion pressure.

Perioperative fluid therapy strategies: dose and targets

Dosing and guiding emergency or perioperative crystalloid fluid therapy is still surrounded by controversy. In spite of the less plasma volume expanding and hemodynamic effects of crystalloids versus colloids, for a given fluid infusion volume, a restricted (usually defined as <7 ml/kg/h) fluid policy has been suggested to result in less complications than a standard or more liberal fluid strategy, regardless of the principal type of solution used, in randomized studies in surgical patients [30,33,49-55]. The surgery may involve abdominal, pancreatic, colorectal, gall bladder, vascular, and hip and knee surgery, whereas definitions of policies for fluid amounts differ across studies [49-57]. The complications prevented may include anastomotic leaks, gastrointestinal disturbances with nausea and vomiting, infections, pulmonary complications, and others [53,56,58]. Indeed, many of these complications may result from overhydration, particularly by crystalloids, whereas fluid restriction often refers to limitation of crystalloids [22,30,49,57,59].

However, too restrictive fluid therapy may result in under-resuscitation and potentially associated adverse sequelae, again including gastrointestinal hypoperfusion,

anastomotic leaks, nausea, vomiting, and others, which can be prevented in part by more liberal (colloid or crystalloid) fluid loading [30,54,59-63]. Perioperative, goal-directed hemodynamic optimization by (mostly colloid, sometimes crystalloid) fluids may better reduce postoperative complications, because of dosing fluids to individual needs in the patient and by taking individual cardiac reserve into account, than either liberal or restrictive policies [2,4,22,52,53,61,64-66].

Hence, the debate on fluid volumes and hemodynamic targets is confounded by the type of fluid, with increasing doubts on the safety of synthetic colloids, at least in sepsis and perhaps not in trauma and surgery, thereby favoring crystalloids [25,67]. Also, the risk to benefit ratio of a fluid type may be determined by the severity of hypovolemia and shock during which it is infused. In any case, preoperative starvation commonly includes fluids and may contribute to postoperative hypovolemia [68], and authors have studied the effect of preoperative optimization with help of Ringer's lactate and found that this policy reduced postoperative morbidity [69]. In the emergency treatment of trauma, avoidance of overzealous crystalloid fluid therapy may also be associated with better outcomes [34].

Concluding this section, one should give crystalloid fluid challenges as a first choice on clinical grounds, for resuscitation from hypovolemia or shock, by utilizing rapid infusions of 500 to 1000 ml, provided that the patient is likely to be fluid responsive at baseline or indeed responds to fluids during loading. In the maintenance phase, measurable losses augmented by 1 l per day for insensible losses mostly result in infusion of about 2 to 2.5 l per day. For resuscitation and maintenance, special considerations obviously apply to brain injury, trauma and surgery, when restriction of fluids and electrolytes may be preferred to limit a positive fluid balance, and to cardiac failure and edema-forming states, when a negative fluid balance rather than maintaining the balance is aimed at.

Composition and clinical use of various crystalloid fluids

We will now discuss varying crystalloid fluid types and their properties. Normal or physiological saline was first described and applied in 1831, and since then 0.9% sodium chloride (NaCl) is the most widely used intravenous fluid in the hospital, in spite of doubts on its 'normal' or 'physiological' properties [70]. Adding lactate as a buffer to better resemble electrolyte composition of human plasma yields Ringer's lactated (or Hartmann's) solution, yet is still slightly hypotonic with the ability to lower serum osmolality [71]. Hypotonic solutions, including colloids (albumin) and crystalloids, may increase (the risk for) cerebral edema in traumatic brain injury, which seems determined in part by osmotic pressure, unless rapid

excretion of hypotonic urine maintains plasma osmolality [71,72]. Infusion of hypotonic dextrose 5% in water is thus also contraindicated in traumatic brain injury, if decreasing plasma osmolality [11]. The solution has a minimum effect on plasma volume and is therefore not a suitable resuscitation fluid either. Therefore, normal saline or isotonic balanced solutions should be preferred to treat hypovolemia in brain injury. Sodium bicarbonate is available in hypertonic solutions. Even though the benefit of treating metabolic (lactic) acidosis during ischemia and resuscitation is controversial, sodium bicarbonate is still widely used to ameliorate metabolic acidosis from various other origins and adjunctive treatment to keep the pH above 7.15 to 7.20 in high risk patients remains commonly recommended. Sodium bicarbonate is also used in the prevention of contrast nephropathy, although probably hardly more effective than prehydration with normal saline [73-75]. Conversely, infusion may not be harmless, and result in hypernatremia and overshoot alkalosis if (too much of) hypertonic solutions are used.

Commonly applied crystalloid solutions of osmolality, cationic and anionic composition are described in Table 4.

Chloride and balanced solutions

The chloride content of normal saline (0.9% NaCl), a so-called unbalanced solution, that is 154 mmol/l, is much higher than found in plasma (101 to 110 mmol/l) and higher than the so-called balanced solutions as (modified) Ringer's or Hartmann's, where some of the anions are buffering lactate, acetate, or gluconate instead of chloride [76]. The strong ion difference of these latter solutions is thus higher than that of saline (for example closer to that of plasma, 42 mEq/l). Even though the pH of these solutions may not differ much, their *in vivo*

effects on acid–base balance are profoundly different [77]. Indeed, saline infusion commonly leads to hyperchloremic metabolic acidosis and contributing to hyperkalemia, particularly when large volumes are infused, whereas infusion of balanced solutions does not carry this effect [76,78-86].

Although the use of saline may result in organ dysfunction (shown extensively in animal studies) and may contribute to gastrointestinal symptoms after surgery, the true detriments of hyperchloremic acidosis in clinical studies remain uncertain [76]. Furthermore, plasma dilution, by any type of infusion solution not containing bicarbonate (or precursor buffer anions), including dextrose 5% in water, decreases strong ion differences and thus blood pH [87].

However, Shaw *et al.*, in a large retrospective study, using propensity-matched samples, recently found that use of normal saline resulted in a higher mortality than using balanced solutions during and following surgery (5.6% versus 2.9%), preventing hyperchloremic metabolic acidosis as well [88]. In addition, the administration of balanced solutions was associated with less morbidity as shown by fewer days on the ventilator, less need for fluid, less need for transfusions, fewer major infections and less need for renal replacement therapy. This suggests that balanced solutions are favored to saline considering the risk of metabolic derangements as hyperchloremic metabolic acidosis and patient morbidity, and clinical course. However, the mechanisms of some of these effects in humans remain unclear and further research on effect on morbidity and mortality is needed [76,89].

Finally, we caution against the use of potassium-containing balanced solutions in anuric patients with renal insufficiency since the infused potassium cannot be excreted ultimately.

Table 4 Commonly applied crystalloid solutions: osmolality, cationic and anionic composition

	Osmolality (mOsm/kg)	pH	Na ⁺ (mmol/l)	K ⁺ (mmol/l)	Ca ²⁺ (mmol/l)	Mg ²⁺ (mmol/l)	HCO ₃ ⁻ (mmol/l)	Lactate (mmol/l)	Other buffer (mmol/l)	Cl ⁻ (mmol/l)
0.9% saline	308	5.5	154							154
Ringer's	309		147	4	5					156
Ringer's lactate	273	6.5	130	5.4	2.7		29			109
Ringer's lactate	273	6.5	130	5.4	2.7			29 ^a		
Hartmann's	280	6.5	131	5.4	2		29			112
Modified	290		145	4	2.5	1			24 [†]	127
Balanced	294	5.5	140	5		1.5			50 ^b	98
Fluids	299	5.5	140	10	5	3		8	47 ^a	103
1.4% Na bicarbonate	333	>7.0	167				167			
4.2% Na bicarbonate	1,000	>7.0	500				500			
8.4% Na bicarbonate	2,000	>7.0	1,000				1,000			
3% saline	1,026		513							513
7% saline	2,394		1,197							1,197

^aacetate, [†] with 5 mmol/l maleate, ^b27 mmol/l as acetate and 23 mmol/l as gluconate.

Lactate is reshuttled via the Cori cycle

Hepatic uptake results in gluconeogenesis, an energy costing process. Oxidation is the fate of 30 to 60% of infused lactate, even in septic and cardiogenic shock, thereby sparing other substrates [90]. Lactate may thus serve as a fuel for liver, and even heart and brain, particularly when other substrates are less available [46]. Infusion of (large quantities of) lactate-containing infusions may transiently and slightly elevate the serum lactate level (but do not decrease pH), particularly in case of liver dysfunction [46,91,92]. It may increase glucose levels in patients with poorly controlled diabetes mellitus or otherwise enhanced gluconeogenesis. Use of Ringer's lactate is safer and saves more lives than use of starch solutions, when compared in the resuscitation of septic shock [67].

Ringer's acetate solution closely resembles Ringer's lactate. Acetate, a component of Ringer's acetate and other solutions, is, similarly to lactate, not metabolically inert. It enters the tricarboxylic acid cycle and is combusted, thereby consuming oxygen by partly replacing other substrates. Indeed, when infused, about 90% is oxidized. Acetate as a buffer, so that, upon infusion, the bicarbonate concentration and pH rises, similarly as when equimolar bicarbonate is infused, in acidosis following diarrhea or renal insufficiency [93]. Also, acetate carries vasodilating and myocardial depressant properties, and may thus be harmful in patients with shock [94], although this has been denied in other studies [95,96]. In fact, it has recently been demonstrated that resuscitation from septic shock with Ringer's acetate results in greater survival than resuscitation with colloid, but this can be attributed to adverse effects of starches [25].

Renal effects

On the one hand, crystalloid solutions better preserve diuresis and renal function, and prevent need for renal replacement therapy than colloids in the critically ill [24], but not in healthy volunteers [15], probably by a fall in plasma colloid osmotic pressure promoting glomerular filtration. However, crystalloid fluid overloading *per se* may be associated with increased need for renal replacement therapy [16,76].

Recent evidence suggests that this may also depend on the type of crystalloid administered and the evidence for a renal protective effect of balanced (versus unbalanced) crystalloids is cumulating. Hypotonic Ringer's lactate infusion in healthy volunteers is more rapidly excreted via urine than normal saline (requiring hours), but this can be attributed in part to hypotonicity of the fluid rather than prevention of hyperchloremia, even though normochloremia may protect against a fall in measured renal (and gastric) blood flow associated with hyperchloremia [76,81,83,97]. Animal experiments indeed suggest that hyperchloremia may increase renal

vascular resistance and decrease blood flow following a direct renal vasoconstrictive effect by the chloride anion. Hadimioglu *et al.* compared in a randomized controlled trial balanced fluids with normal saline as intraoperative fluid replacement during renal transplant surgery, and showed that only saline decreased pH, bicarbonate and base excess [92]. This and other studies did not demonstrate a difference in the effects on renal function, but these studies may have been underpowered [84,92].

In contrast, a recent large sequential cohort study suggests that the use of a chloride-restricted fluid regimen of (modified) Ringer's lactate solution (versus chloride liberal and saline-based regimens) did not decrease mortality, but decreased acute kidney injury and need for renal replacement therapy [98]. In the study by Shaw *et al.*, mentioned above [88], administration of balanced solutions is associated with a reduction of need of renal replacement therapy after laparotomy from 4.8 to 1.0% ($P < 0.001$), even after adjustment for confounders. The incidence of tubular injury and acute kidney injury in sodiumbicarbonate-treated cardiac surgery patients may be lower than when equimolar saline is used [99,100]. However, the implications for hospitalized patients with risk factors for renal dysfunction still need to be firmly established.

Immune depression and coagulation

Another controversy relates to alleged immune effects of balanced versus unbalanced solutions [76]. It has been suggested that normal, unbalanced saline has proinflammatory properties, relating to neutrophil activation [44,101]. This may contribute to detrimental effects in trauma and sepsis resuscitation. Ringer's lactate may also be proinflammatory but it appeared that the D-lactate in racemic mixtures was largely responsible, so that its elimination abolished that effect [101,102]. Hypertonic saline has been claimed to have anti-inflammatory properties, but this is not beyond doubt either [101]. In contrast, the chloride anion has been suggested to impair coagulation [76,81]. However, saline and Ringer's lactate (-based colloid solutions) equally induced, *ex vivo*, a hypercoagulable state at 20 to 40% dilution of blood and decreased coagulability at 60% dilution [103,104].

Electrolyte solutions to treat electrolyte disorders

In hospitalized and surgical or critically ill patients, electrolyte disturbances are common [8,105]. Solutions are available to selectively supplement specific electrolyte deficits. Hypokalemic alkalosis is common and risk factors include use of diuretics, vomiting and diarrhea, and others, leading to chloride depletion. The condition may be accompanied by hypomagnesemia and may be a risk factor for cardiac depression, tissue hypoxxygenation and

rhythm disturbances. Correction of hypokalemia may be more successful by potassium supplementation when hypomagnesemia is simultaneously corrected. Potassium repletion can be accomplished by the oral and enteral route, if functioning, or otherwise by slow, intravenous administration of concentrated solutions at a maximum rate of 20 mEq/h, or higher if vitally indicated [106,107]. Infusion of potassium-containing balanced solutions may lead to dangerous hyperkalemia in the patient with renal insufficiency and anuria who cannot excrete the extra potassium load, although, on the other hand, prevention of acidosis may somewhat ameliorate a dangerous increase in serum potassium concentration [84,86,92,106].

Dysnatremia is often observed in the ICU setting and is associated with higher in-hospital mortality. Hypertonic saline is used in the urgent treatment, when indicated, of hyponatremia [108,109]. Glucose 5% is commonly used in the treatment of hypernatremia. For maintenance fluid therapy in the starving patient, the more complete and balanced solutions are more likely to maintain normal plasma electrolyte concentrations and acid–base balance than merely sodium-containing saline. To these fluids that resemble plasma but are not identical as far as their composition is concerned, glucose 5% can be added to meet some energy requirements too.

Hypocalcemia is also relatively frequent in postoperative and critically ill patients and may have adverse consequences [110]. It is likely that most critically ill patients are in a negative calcium balance, when immobilized, treated by citrate-based venovenous hemofiltration for acute kidney injury, and so on. A calcium deficit may lead to gradual bone loss. Hypocalcemia, even when adjusted for hypoalbuminemia, and resulting from a shift of extra- to intracellular calcium and hypovitaminosis D, may be associated with critical illness neuro- and myopathy [111]. Calcium is hard to include in (alkali) fluids, because it may easily become insoluble.

Continuous renal replacement therapy is a well known risk factor of hypophosphatemia in the critically ill. The latter may also be a feature of refeeding and hypophosphatemia is thus relatively frequently encountered in the critically ill patient (with and without renal failure) [111]. It may be associated with muscle weakness and prolonged need for mechanical ventilator support, and therefore requires prevention and correction with help of sodium-potassium-phosphate solutions, preferably via continuous infusions [112,113]. Currently, phosphate containing replacement fluids are available to prevent hypophosphatemia during continuous renal replacement therapy.

Conclusion

Crystalloid fluids are the fluids of choice for expanding and maintaining plasma volume in hospitalized patients

with hypovolemia or shock, although relatively large volumes have to be administered to increase circulating plasma volume and tissue oxygen delivery. Overzealous crystalloid administration increases the risk for fluid overload with hypernatremia, peripheral and pulmonary edema, and compartment syndromes. Hence, both under-resuscitation and overhydration should be avoided by careful monitoring. The evidence that balanced solutions are superior, particularly in helping to prevent acute kidney injury and when isotonic, to unbalanced ones is increasing. Hypotonic solutions are generally contraindicated in conditions with or at risk for cerebral edema. In the maintenance phase of non-oral fluid infusion, solutions which more resemble plasma water composition than normal saline are also to be recommended. We finally recommend serum sodium-guided treatment by hypertonic saline for mannitol-refractory cerebral edema and intracranial hypertension.

Abbreviations

Ca²⁺: Calcium; HCO₃: Bicarbonate; HP04: Phosphate; HSO₄: Hydrogen sulfate; ICU: Intensive care unit; K⁺: Potassium; Mg²⁺: Magnesium; Na: Sodium; SAFEstudy: Saline versus albuminfluid evaluation study.

Competing interests

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Authors' contributions

AS and ABJG brought about initial set-up, literature research and writing of the manuscript. CI provided comments and recommendations, and improved the quality and clarity of the manuscript. ABJG was the supervising author. All authors read and approved the final manuscript.

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