dtbn
DRUG AND THERAPEUTICS BULLETIN OF NAVARRE, SPAIN
YEAR 2023
VOL 31, Issue 3
www.dtb.navarra.es
@DTBNavarre.es

Bol Inf Farmacoter Navar. 2023;31 (3):1-26
https://doi.org/10.54095/BITN20233103EN

# Use of fluid therapy in clinical practice

INTRODUCTION The aim of fluid therapy is to increase intravascular volume, improve organ perfusion and oxygenation and/or maintain hydration. The composition, dose, rate, time and duration of fluid therapy are essential factors for its correct use. OBJECTIVE To help clinical staff to choose the most appropriate intravenous fluid therapy in different clinical situations. MATERIAL AND METHODS A search of systematic reviews and clinical trials comparing the use of any combination of crystalloids or colloids for any clinical condition was performed up until September 2023 in Cochrane Library, Epistemonikos, Web of Science and Pubmed. Additionally, Clinical practice guidelines were consulted. RESULTS AND CONCLUSIONS The use of intravenous fluid therapy must meet a need that cannot be met by oral administration and is not free from risk. No perfectly physiological intravenous solution is currently available. Intravenous solutions are classified into crystalloids and colloids. For the majority of indications, optimal intravenous fluid therapy is based on the use of crystalloids. The choice of fluid therapy must be personalised based on the patient's characteristics and prior medical history, the current clinical situation, the osmolality and association of hydroelectrolytic imbalances and the acid-base equilibrium. The use of synthetic colloids is subject to significant restrictions given their negative effects on health outcomes, mainly anaphylactic reactions. KEYWORDS Fluid therapy, crystalloids, colloids, Ringer solution, saline, balanced solution, albumin.

*The author declares no conflicts of interest related to this article.*

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## Introduction

Fluid therapy is a treatment administered by parenteral route using solutions of different compositions for four types of indications: a) resuscitation: replenishment of intravascular volume in the event of hypovolaemia; b) replenishment: correction of deficits that is not possible with oral administration only; c) maintenance: meeting daily water and electrolyte needs in patients unable to receive them orally; and d) substance transport: used as a solvent for drugs to be administered, or permeabilisation of parenteral administration[1]. The aim of intravenous fluid therapy is to increase intravascular volume, improve organ perfusion and oxygenation and/or maintain hydration.

Most of studies about the use of intravenous fluid therapy have been conducted in cases of emergency, resuscitation and surgery, although efficacy studies for less-critical situations have also been conducted.

The aim of this review is to present the main solutions used in intravenous fluid therapy, their main indications and contraindications, as well as the potential adverse effects associated with its use.

To that end, a literature search for systematic reviews and clinical trials has been performed up to September 2023 in Cochrane Library, Epistemonikos, Web of Science and Pubmed. Clinical practice guidelines have also been consulted to complete the information.

Determine the patient's history, current condition, electrolytes, weight and whether oral intake is possible before prescribing fluid therapy

## Types of fluid therapy

Intravenous solutions (Table 1) are classified, on the basis of their osmolality with regard to plasma, as: a) isotonic (similar osmolality to plasma); b) hypotonic (lower osmolality than plasma); or c) hypertonic (greater osmolality than plasma). Sodium is the electrolyte with the greatest influence on the osmolality of plasma and intravenous solutions, therefore, this classification often relates to a comparison of the sodium concentration. Despite being hyperosmolar, some salt-containing glucose/dextrose solutions (generally 5%) are considered to be isotonic given the rapid rate of glucose metabolism after infusion into the bloodstream[2]. This is due to the fact that osmotic pressure allows the passage of free water between solutions of different concentrations separated by a semi-permeable membrane. Oncotic pressure, in turn, is a type of osmotic pressure caused by the differing presence of proteins (mainly albumin) in two solutions separated by a semi-permeable membrane.

Intravenous solutions are also classified on the basis of their physical state (crystalloids or colloids). No perfectly physiological intravenous solution is currently available.

The bodily distribution of fluid therapy solutions (Figure 1) after intravenous infusion varies depending on the compound concerned. One hour after the infusion of 1000 mL of glucose serum 5%, saline 0.45%, saline 0.9% and albumin, 83 mL, 167 mL, 250 mL and 900 mL of fluid, respectively, remains in the intravascular space[3,4].

The total volume of fluid therapy used in Navarra has remained relatively unchanged in the past few years (Figure 2).

### Crystalloids

Crystalloid solutions composed low molecular weight ionic and non-ionic solutes, thus allowing them to readily pass through cell membranes.

The indications for crystalloids vary, including use as a pharmacological vehicle, maintenance of parenteral lines, supply of fluids and ions in situations of deficient intake, stimulation of diuresis, renal protection in the presence of nephrotoxic agents and facilitating tissue perfusion by elevating blood pressure (BP) in emergency situations[2].

**Figure 1.** Bodily distribution after infusion of one litre of fluid therapy. Adapted from Frost et al[3].

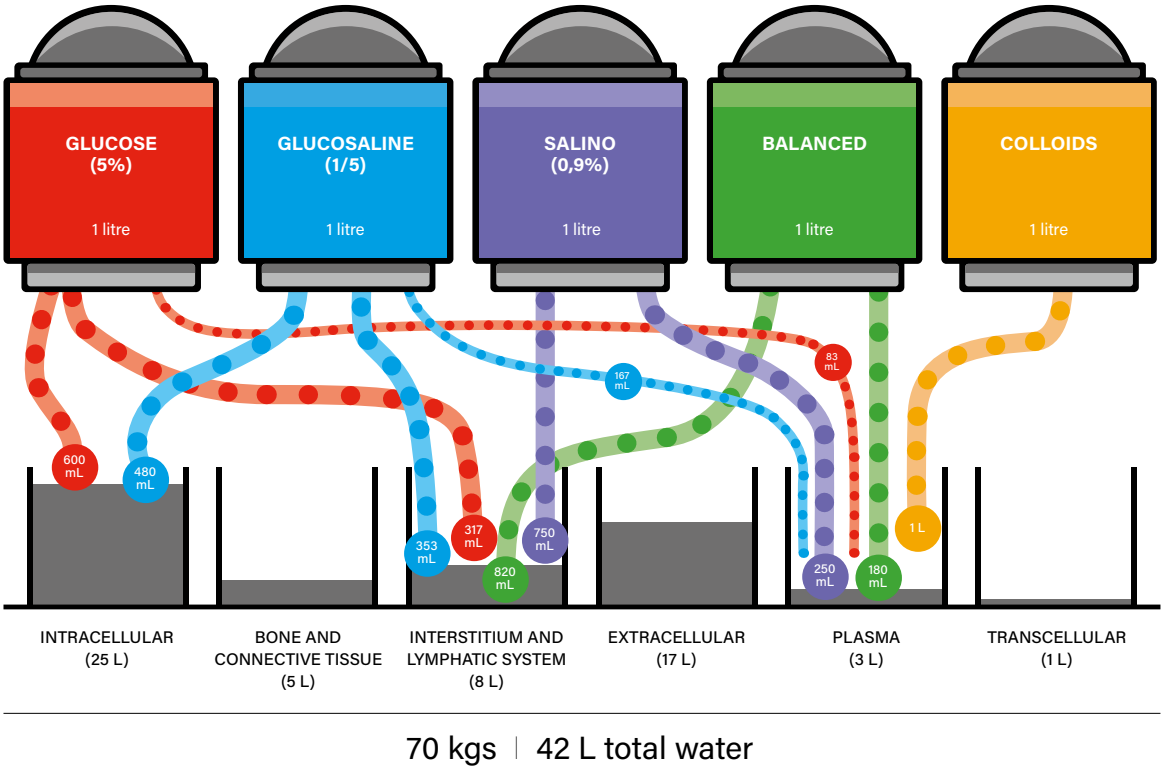
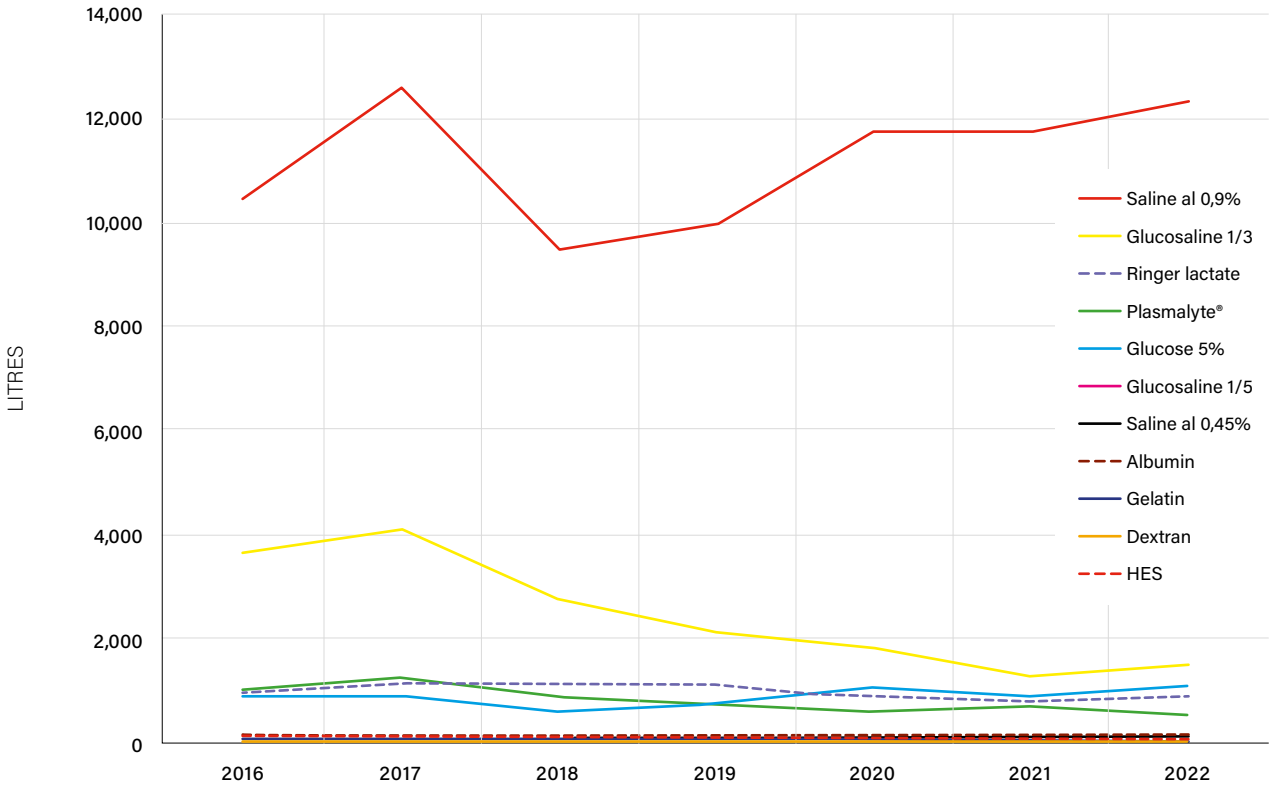



**Figure 2.** Use of fluid therapy in Navarra.



## Unbalanced crystalloids

Unbalanced crystalloids contain only different concentrations of sodium chloride or glucose, sometimes in combination with potassium.

The two sodium-containing solutions tha are used most frequently are physiological saline or normal saline (0.9%) and hypotonic saline (0.45%). Other formulations with higher concentrations (2%, 3%, 7.5%) are used in fluid therapy less often or are added in small volumes (12.5%, 20%) to compensate deficiencies.

Saline 0.9%, known as "normal saline" or "physiological saline" is neither normal nor physiological in comparison with plasma. Indeed, its osmolality (308 mOsm/L) differs markedly from that of plasma (275–285 mOsm/L). The quantity of sodium (154 mEq/L) is also not normal when compared with that of plasma (135–145 mEq/L) and the quantity of chloride (154 mEq/L) differs even more from that found in plasma (98–109 mEq/L)[5].

Glucose solutions (glucose sera) have different concentrations and are, therefore, useful for preventing endogenous catabolism and, despite being hyperosmolar, are considered to be hypotonic given their limited oncotic potential. Glucose sera are available in different formulations for different energy requirements (5%, 10%, 20%, 30%, 40%, 50% and 70% glucose).

Glucosaline solutions contain saline and glucose as solutes: 0.20% (1/5) NaCl, 0.33% (1/3) NaCl or 0.9% NaCl. The 0.2% and 0.33% solutions tend to produce hyponatraemia, whereas 0.9% glucosaline does not.

Prediluted solutions of potassium with different concentrations are available to minimise the risks associated with handling concentrated solutions[6].

## Balanced crystalloids

The so-called "balanced solutions" (Ringer, Ringer lactate/Hartmann solution, Ringer acetate, Plasmalyte®) are crystalloids with a similar osmolality and composition (sodium, potassium, chloride, calcium and magnesium) to human plasma. These solutions contain a lower quantity of chloride than unbalanced solutions as this is replaced by other anions (Table 1) that can readily be converted into bicarbonate. This allows a rapid access to bicarbonate while reducing the generation of chloride-related acidosis. Hence, these solutions are better able to maintain the acid/base equilibrium. In addition, their potassium content facilitates an increase in blood sodium levels due to transmembrane cation exchange via the Na+/K+ pump[7,8].

Since the creation of Ringer solution[9], its composition has undergone minor changes to obtain other compounds, such as Hartmann solution (incorporation of lactate) or Ringer acetate. Ringer lactate is hypotonic and contains a similar chloride concentration to plasma. The risk of lactate build-up is minimal given the quantity present and the form, namely the L-lactate isomer. However, it is contraindicated in liver failure as it is converted into pyruvate, before it can be converted into bicarbonate, via the Cori cycle.

Plasmalyte® A or 148 solution is an isotonic electrolyte solution containing acetate and gluconate that allows rapid conversion into bicarbonate in any tissue, whereas the conversion of lactate is dependent on hepatic or renal tissue[10]. It does not contain calcium or lactate, thus meaning that it is compatible with blood transfusions and limits the increase of blood lactate levels while also reducing the onset of acidosis, thus making it a useful fluid therapy in cases of mild or moderate acidosis. Its main effect is expansion of the extracellular space. Given that its main effect is, it should be used with care in cases of hypocalcaemia.

## Colloids

Colloids (from the Greek Kolas, "which can stick together") are solutions of molecules with a high molecular weight in a transporting crystalloid solution with a limited ability to cross a healthy semi-permeable capillary membrane[3]. The used colloids in medicine are proteins or polysaccharides in solution that can be used to increase or maintain the osmotic (oncotic) pressure in the intravascular compartment, such as albumin, dextran, gelatins, blood components such as plasma and platelets, and have the physical properties of a gel. They are unable to cross cell membranes and remain in the intravascular space[8].

Colloids can be of a natural type, for example plasma derivatives such as albumin (concentrations of 5–20%), or synthetic, which typically comprise polymers such as hydroxyethyl starch (HES) 6% (Voluven®, Isohes®, Elo-Hes® Expafusin®), dextran (Rheomacrodex®) or succinylated gelatins (Hemoce®, Gelafundin®, Gelaspan®, Fresegel®).

The main drawback of human albumin is its limited availability given that it is a blood component. Gelatins and dextran, in turn, present a high risk of anaphylaxis. In addition, gelatins have only a short half-life as they are eliminated via the kidneys in 2–3 hours[11].

**Table 1.** Main fluid therapy solutions. Source[2] and AEMPS[12-25]. ■ Balanced solutions.

| SOLUTION | SODIUM | POTASIUM | CHLORIDE (MMOL/L) | ACETATE | OTHERS | CALCIUM (mEq/L) | MAGNESIO (mEq/l) | GLUCOSA (gr) | OSMOLARIDAD TEÓRICA (MEDIDA) (mOsm/L) | PH |
|---|---|---|---|---|---|---|---|---|---|---|
| Plasma | 135-145 | 4.5-5.0 | 94-111 | 0.02-0.2 | | 2.2-2.6 | 0.8-1.0 | | 275-295 | 7.35-7.45 |
| Hypotonic | | | | | | | | | | |
| Glucose serum 5% | | | | | | | | 50 | 278 | 3.5-5.5 |
| Glucosaline 1/5 | 30,8 | | 30.8 | | | | | 47 | 320 | 3.5-6.5 |
| Glucosaline (1/3) | 51 | | 51 | | | | | 36 | 302 | 3.5-6 |
| Saline serum 0,45% | 77 | | 77 | | | | | | 154 | 4.5-7.0 |
| Ringer lactate | 130 | 5.4 | 111.7 | | Lactate 27.2 | 3.6 | | | 273 (256) | 5.0-7.0 |
| Hartmann solution | 130 | 5.4 | 112 | | Lactate 28 | 3.6 | | | 277 | 5.0-7.0 |
| Isotonic | | | | | | | | | | |
| Saline serum 0,9% | 154 | | 154 | | | | | | 308 (286) | 4.5-7.4 |
| Plasmalyte® | 140 | 5 | 98 | 27 | Gluconate 23 | | 3 | | 295 (271) | 7.4 (6.5-8) |
| Ringer acetate | 130 | 5 | 112 | 27 | | 1 | 1 | | 276 | |
| Succinylated gelatin (Gelaspan®, Hemoce®) | 151 | 4 | 103 | 24 | Succinylated gelatin 40 gr. | 1 | 1 | | 284 | 7.4 |
| Dextran 40 (Rheomacrodex 10%®) | 154 | 154 | | | Dextran 40 gr | | | | | 3.5-7.0 |
| 20% Albumin | 122 | < 2 | | | Albumin 192 gr. | | | | | |

The use of synthetic colloids increased significantly in the 1980s and 1990s. However, in 2021 the Food and Drug Administration recommended that HES should not be used in critical patients or those with kidney disease given the greater association of these compounds with episodes of death, kidney failure and haemorrhage[26]. In May 2022, the European Commission[27] banned the use of HES 6% (Voluven®, Isohes®, Volulyte®), with this decision becoming effective in Spain in December 2022[28].

The perfectly physiological intravenous solution does not exist.

## Dose and infusion rate

According to the various protocols and consensus documents studied, intravenous fluid therapy is an active part of the treatment for serious diseases. However, there is some degree of variability in its application in clinical practice as regards the indication, quantity and type.

For maintenance, an adult requires 1–1.25 mL/kg/h or 25–30 mL/kg water, 1 mEq/kg sodium, potassium and chloride and 50–100 g glucose per day29. During major surgery, fluid requirements may be as high as 3 mL/kg/h.

In paediatric patients, the Holliday–Segar formula is used to calculate maintenance fluid therapy needs. This formula proposes daily fluid requirements of 100 mL/kg/day for patients weighing less than 10 kg, 1000 mL, with an additional 50 mL per kg above 10 kg for patients weighing 10–20 kg, and 1500 mL, with an additional 20 mL per kg above 20 kg for patients weighing more than 20 kg[30]. Hypotonic solutions were used initially, although this led to situations of hyponatraemia and worsened the reputation of this formula. Although there is no scientific evidence available, the use of this formula with the correct choice of fluid therapy, based on the condition to be treated, is considered to be a correct approach in maintenance fluid therapy[2].

Situations of hypovolaemia, whether real or functional, have other requirements. The main challenge as regards the use of fluid therapy in shock is to use the smallest quantity needed to prevent tissue hypoxia due to a lack of volume while avoiding diastolic overload, which can lead to pulmonary and peripheral oedema[31].

Indirect systems, including blood pressure, heart rate and diuresis, have been used to calculate the volume of fluid therapy required in these situations. However, situations of shock may nevertheless arise with these parameters in range[32]. The concept of Goal Directed Therapy (GDT) began to be applied in 2001. This technique allows the use of fluid therapy (and vasopressors) to be guided by established targets and evaluated by monitoring based on haemodynamic parameters [blood pressure, central venous pressure (replaced due to mechanical and infectious risks), inferior vena cava collapsibility index, central venous oxygen saturation, stroke volume and cardiac output][33]. Serum infusions are performed if required (fluid challenge of 250–500 mL in 5–15 minutes) and the parameters re-evaluated[34,35]. In newborns, 10 mL/kg is administered in less than 10 minutes, whereas in older children and adolescents infusions of 20 mL/kg in less than 10 minutes are used[36]. There is some controversy as regards the scope of this technique and its inherent drawbacks given the variability and limited predictivity of the measurement methods[37]. Indeed, clinical trials and systematic reviews both in favour of[38-42] and against[33,43-45] this technique can be found in the literature.

Definitive guidelines for the administration and evaluation of the fluids test are yet to be defined. Indeed, not all patients respond to the infusion of fluids to obtain adequate cardiac performance, which allows optimal oxygen release in tissues. For those who do not respond, infusion of the loading dose (between 250 and 500 mL) is irreversible. As such, measures such as elevating the lower limbs (the effects of which can be detected in a few seconds or minutes by monitoring cardiac output) have been used to predict the response to the fluid load in both patients receiving mechanical ventilation or with spontaneous respiration[46].

The Parkland formula [4 mL x weight in kg x % total body surface area burned (TBSA)] is used in the event of major burns[47]. Although not free from controversy, this formula is still used provided the haemodynamic indicators are monitored on a regular basis[48].

## Selection criteria for fluid therapy in different clinical situations

### Hydroelectric and acid/base equilibrium imbalances

In cases of hypovolaemia, the main objective is to re-establish a volaemia that allows tissue perfusion and oxygenation to counteract the effects of the reduced extracellular volume. However, volume overload must be avoided, especially in patients with heart or kidney failure. In the event of a decrease in extracellular fluids due to vomiting, diarrhoea, bleeding or diabetic ketoacidosis, the use of isotonic solutions, such as 0.9% saline or Plasmalyte®, is beneficial initially. The cause can then be treated. Hypovolaemia is often associated with alterations to the hydroelectric balance[49].

#### Hyponatraemia

Hyponatraemia (generally chronic, lasting for more than 48 hours) is the main electrolytic imbalance found in clinical practice. It can appear acutely during the postoperative period, preparation for colonoscopy, after intense exercise or with the use of thiazides, intravenous cyclophosphamide or oxytocin. It is very important to determine the causes and clinical severity of hyponatraemia before commencing fluid therapy infusion. Hyponatraemia is commonly associated with the secretion of antidiuretic hormone or vasopressin (ADH), occasionally as an adequate response to insufficient effective intravascular volume, but also due to inadequate secretion (SIADH). The determination o ADH is not recommended as a confirmation of SIADH[50].

The most common causes of hypovolaemia-related hyponatraemia are renal loss due to the use of diuretics or a mineralocorticoid deficiency, or non-renal losses due to vomiting, diarrhoea, hyperhidrosis or third space (pancreatitis, intestinal obstruction, sepsis, muscle trauma). The most common causes of euvolaemia are SIADH, secondary adrenal failure, hypothyroidism or polydipsia. Similarly, the most common causes of hypovolaemia are advanced kidney failure and secondary hyperaldosteronism (cirrhosis, heart failure, nephrotic syndrome). However, the difficulty in measuring volaemic status on a daily basis means that algorithms based on it are impractical in clinical practice[51].

A simplified approach to the possible causal mechanism only requires the determination of urinary osmolality (Osmu) and the urinary sodium concentration ([Na]u) in a simple urine sample. If Osmu is 100 mOsm/kg or lower, the cause is likely to be excess water intake, whereas if Osmu is higher than 100 mOsm/kg and [Na]u is 30 mmol/L or lower, the cause may be loss of effective

arterial volume, such as in cases of secondary hyperaldosteronism (heart failure, liver cirrhosis or nephrotic syndrome), third-space loss or external losses (diarrhoea or vomiting). A [Na]u value higher than 30 mmol/L suggests a situation of euvolaemia or hypervolaemia, with a sensitivity of 94–100% and a specificity of 24–69% (depending on the lack or use of diuretics). In this scenario, the presence of SIADH should be evaluated initially, or the prior use of diuretics or the existence of kidney failure, as well as other circumstances[51].

An adult requires 1–2 mEqNa+/kg bw per day. One litre of saline 0.9% contains 9 g of salt, which represents 154 mEq Na+ (much higher than the daily requirement). Depending on the diagnosis and clinical severity, the infusion of more fluids should be avoided, or this should be restricted (chronic hyponatraemia with no severe symptoms or SIADH), use saline 0.9% or balanced crystalloids (0.5–1.0 mL/kg/h in the event of reduced circulating volume, with or without metabolic alkalosis) or hypertonic saline as a rapid infusion (2 mL/kg 150 mL in 20 min of saline 3% in the event of severe symptoms or acute hyponatraemia of more than 10 mEq/L with a decrease in serum sodium of more than 10 mEq/L). If hyponatraemia occurs jointly with hypokalaemia, recovery of sodium is accelerated with the recovery of potassium. In addition, an inappropriately fast recovery of hyponatraemia must be avoided given the risk of overload in cases of prior kidney or heart failure or the onset of central pontine myelinolysis. In such situations with hypokalaemia, saline 0.45% should be used rather than saline 0.9%[7,51].

A careful causal diagnosis, monitoring of serum sodium levels and the urgent use of hypertonic saline are critical measures, in their own scenario, for the management of hyponatraemia[51].

## Hypernatraemia

Severe hypernatraemia presents a much greater risk of death than hyponatraemia, and has a greater impact in women[52]. It generally occurs together with hypovolaemia via three main mechanisms: renal losses, loss of feeling thirsty or no water intake and insufficient fluid therapy[53].

Replenishment with glucose 5% or saline 0.45% is sufficient in hypovolaemic hypernatraemia with no haemodynamic instability. An aggressive reduction in sodium (<12 mEq/L/day) should be avoided in chronic hypernatraemia due to the risk of cerebral oedema. The change in serum sodium per litre of solution infused can be calculated using the following formula: (mmolNa+ infused – Na+ serum)/(total body water +1). Total body water by weight is 0.6 in children younger than 14 years, 0.6 and 0.5 in adult males and females, respectively, and 0.5 and 0.45 in elderly males and females, respectively. In the event of haemodynamic instability (hypotension, oligoanuria), saline 0.9% can be used initially to ensure tissue perfusion (0.45% if associated with hypokalaemia). Ringer lactate or Plasmalyte® are also good alternatives in the case of concomitant hypokalaemia[49]. Euvolaemic hypernatraemia (excessive sweating, central diabetes insipidus or nephrogenic diabetes) is treated with the replenishment of free water (glucose serum 5%).

## Hypokalaemia

This usually develops due to renal or digestive losses and is often accompanied by metabolic alkalosis. In these cases, solutions containing potassium chloride are indicated. However, in the event of metabolic acidosis (for example diarrhoea), the use of other salts such as potassium acetate is recommended.

In the event of concomitant hypovolaemia, the best option is to use potassium chloride together with Ringer lactate (in the absence of alkalosis) or saline 0.45% (instead of 0.9%) given the risk of an increase in sodium levels after the correction of potassium due to transmembrane cation exchange via the Na+/K+ pump.

Peripherally, the maximum concentration of potassium infused should be 60 mEq/L (optimally less than 40 mEq/L) and the maximum rate should be 20 mEq/h (optimally less than 10 mEq/h). Centrally, the maximum concentration should be 100 mEq/L and the maximum rate 40 mEq/h (optimally less than 20 mEq/h) for large fluid volumes. Heart monitoring should be implemented for rates higher than 10 mEq/h. A blood test should be performed every 24 h for infusions greater than 60 mEq/day. For optimal potassium correction, magnesium should be replenished first in the event of a deficiency thereof. The use of glucose solutions should be avoided in cases of severe hypokalaemia to limit associated insulin secretion, which facilitates the entry of potassium into cells[6].

## Hyperkalaemia

Hyperkalaemia is generally associated with the presence of severe kidney failure (GF < 20 mL/min), hypoaldosteronism (suspected for a urine potassium/creatinine ratio < 13 mmol/L), acidosis, uncontrolled diabetes mellitus or drug-related iatrogenesis (NSAID, ACEI, ARA II, digitalins). In such situations (in the absence of hyperglycaemia), the use of glucose solutions with insulin (glucose 5%-10%, glucosaline) to correct potassium levels may be combined with the use of isotonic (0.9%) or hypotonic saline (0.45%). In general, the use of balanced should be avoided in hypokalaemia given their potassium content[49].

## Metabolic acidosis

Situations of hypovolaemia with metabolic acidosis may occur after the presence of diarrhoea (intestinal loss of bicarbonate and compensating increase in chloride with a normal, hyperchloraemic anion-gap metabolic acidosis), loss of pancreatic or biliary secretions or kidney failure. In such situations, the fluid therapy of choice is Ringer lactate given the speed of correction of the acidosis as a result of the ability of lactate to be converted into bicarbonate, provided there is no contraindication for this therapy[54,55] (Table 3). It should be noted, however, that the rapid administration of chloride may favour the onset of hyperchloraemic acidosis[7].

In the case of acidosis resulting from diabetic ketoacidosis or trauma, the best option is a balanced crystalloid (Plasmalyte®) instead of saline 0.9% to prevent hyperchloraemia56. In the event of concomitant hypokalaemia, the best option is to use Ringer lactate (contains potassium), Plasmalyte® or hypotonic saline (0.45%) with potassium, instead of saline 0.9%, to prevent hypertonic infusion and the risk of hypernatraemia[51].

Maintenance perfusion in paediatric patients is calculated using the Holliday–Segar formula and is 25–30 mL/kg/d in adults.

There is a risk of metabolic acidosis, hyperchloraemia and kidney failure with high volumes of saline 0.9%.

**Table 2.** Fluid therapy recommended for hydroelectric and acid/base imbalances.

| CLINICAL SITUATION | COMMON CAUSES | RECOMMENDED FLUID THERAPY | RISKS |
|---|---|---|---|
| Hypovolaemia | Bleeding, diarrhoea, vomiting, diabetic ketoacidosis | Isotonic: Saline 0.9%, Plasmalyte® (concomitant ketoacidosis) | Volume overload |
| Metabolic acidosis | Kidney failure, diarrhoea, pancreatic or biliary loss, hypoaldosteronism, ketoacidosis | Ringer lactate or Plasmalyte® (concomitant severe metabolic acidosis, ketoacidosis or trauma-related acidosis) | Avoid saline 0.9% with concomitant acidosis and hyperchloraemia. Avoid Ringer lactate with concomitant lactic acidosis |
| Metabolic alkalosis | Vomiting, nasogastric tube aspiration, use of loop or thiazide diuretics | Saline 0.9% or saline 0.45% with potassium (concomitant hypokalaemia) | Avoid balanced crystalloids as they worsen alkalosis |
| Hyponatraemia | Renal losses (diuretics, adrenal failure), non-renal losses (vomiting, diuretic, hyperhidrosis, third-space) SIADH, secondary hypoaldosteronism (heart failure, cirrhosis, nephrotic syndrome) | Depending on scenario. Fluid restriction, emergency hypertonic saline, saline 0.9%, saline 0.45%, balanced crystalloids | Close monitoring of natraemic recovery. Less sodium or slower rate with concomitant hypokalaemia or risk of HF. Risk of central pontine myelinolysis if excess, risk of cerebral oedema if deficit. |
| Hypernatraemia | Renal losses, loss of thirst sensation or lack of access to water and insufficient fluid therapy | Glucose serum 5% or saline 0.45%. Balanced crystalloids with concomitant hypokalaemia | Avoid Ringer with concomitant lactic acidosis |
| Hypokalaemia | Renal or digestive losses | Saline 0.45% or balanced (avoid with concomitant alkalosis) with potassium chloride. Replenish magnesium | Avoid glucose solutions May be concomitant metabolic alkalosis (avoid balanced) Rule out hypomagnesaemia |
| Hyperkalaemia | Kidney failure or hypoaldosteronism | Glucose serum 5% with insulin Saline 0.45% | Avoid balanced solutions as they contain potassium |

### Metabolic alkalosis

In situations of metabolic alkalosis, fluid therapy may be necessary in the event of hypovolaemia caused by the presence of vomiting, nasogastric tube aspiration (loss of hydrogen ions) or the use of diuretics (loop or thiazides). In these cases, the best fluid therapy is saline 0.9% (tends to cause acidosis) or saline 0.45% with potassium in the event of concomitant hypokalaemia. Plasmalyte® and Ringer lactate are contraindicated in these situations given the tendency of bases to be converted into bicarbonate, thus worsening the alkalosis[49].

The evidence for selecting the optimal fluid therapy based on the condition is presented below in the form of tables and conclusions per section. Results from systematic reviews with meta-analyses are shown preferentially. In the secondary objectives column, the results with statistical significance supporting the intervention are highlighted in bold, and significant differences in favour of the comparator are underlined. To ensure better readability, we have presented the results by sub-group. Although the secondary objectives are presented given their obvious interest, numerical values are not provided as they are exploratory.

## Resuscitation

### Critical state

Studies performed on patients in a critical state, in general admitted to the ICU (preferably) or need for emergency resuscitation.

### Comparison between crystalloids

There is no evidence for a clinical difference between the use of balanced crystalloids or unbalanced solutions in patients in a critical state.

**Table 3.** Critical state. Comparison between crystalloid.

| REF. | INTERVENTION | COMPARATOR | RTC no. | No. PATIENTS | POPULATION | PRIMARY OBJECTIVES | DIFFERENCES (RR; 95% CI) | EVIDENCE QUALITY | I2 | SECONDARY OBJECTIVES |
|---|---|---|---|---|---|---|---|---|---|---|
| 2015[57] | <111 mEq Cl | >111 mEq Cl | 21 | 6,253 | ICU or PeriQx | Mortality | 1.13 (0,92- 1,39) | - | 0% | **AKF, hyperchloraemia, DFMV**, MA, |
| 2015[57] | <111 mEq Cl | >111 mEq Cl | 21 | 6,253 | ICU or perisurgery | AKF | 1.64 (1,27- 2,13) | - | 0% | Metabolic acidosis, RRT |
| 2018[58] | <111 mEq Cl | >111 mEq Cl | 21 | 3,710 | ICU or perisurgery | Mortality | 0.90 (0,69-1,17) | Low | 0% | AKF, TV, MS, DFMV, DV |
| 2018[58] | <111 mEq Cl | >111 mEq Cl | 22 | 3,724 | ICU or PeriQx | RRT | 1.12 (0.80-1.58) | Low | 0% | |
| 2019[59] | Balanced | SS 0.9% | 9 | 32,777 | ICU | Mortality | 0.94 (0.82- 1.07) | Very low | 0% | AKF, RRT |
| 2019[60] | Balanced | SS 0.9% | 14 | 19,664 | Critical state | Mortality | 0.91 (0.83- 1.01) | High | 0% | Abnormal clotting, TV |
| 2019[60] | Balanced | SS 0.9% | 9 | 18,701 | Critical state | AKF | 0.92 (0.84- 1.00) | Low | 0% | Organ dysfunction, pH and hyperchloraemia |
| 2019[61] | Balanced | SS 0.9% | 7 | 20,171 | Critical state | Mortality | 0.92 (0.85- 1.00) | - | - | **Higher pH, lower chloraemia** |
| 2019[61] | Balanced | SS 0.9% | 7 | 20,171 | Critical state | AKF ≥ 2 | 0.95 (0.88- 1.01) | - | - | RRT |
| 2019[62] | Balanced | SS 0.9% | 9 | 20,345 | Critical state | Mortality | 0.93 (0.86 - 1.01) | Moderate | 0% | RRT, AKF, AKF ≥ 2, MS |
| 2019[63] | SS 0,9% | Balanced | 8 | 20,684 | ICU | Mortality | OR 1.08 (1.00-1.17) | - | 0% | AKF |
| 2020[64] | Balanced | SS 0.9% | 6 | 31,116 | Critical state | Mortality | 0.86 (0.75- 0.99) | - | 82% | **AKF, RRT, MS, DFMV** |
| 2021[65] | Balanced | SS 0.9% | 6 | 19,049 | Critical state | MAKE 30 | 0.95 (0.88 - 1.01) | - | 0% | Mor 30, Mor H, Mor ICU, MS ICU, RRT, MS |
| 2022[66] | Balanced | SS 0.9% | 7 | 34,517 | Critical state | Mortality | 0.96 (0.92- 1.01) | - | 0% | |
| 2022[66] | Balanced | SS 0.9% | 7 | 24,593 | Critical state | AKF | 0.95( 0.90- 1.01) | | 0% | |
| 2022[66] | Balanced | SS 0.9% | 7 | 33,830 | Critical state | RRT | 0.93 (0.86- 1.02) | - | 19% | |

**AKF** Acute kidney failure. **DFMV** Days free from mechanical ventilation. **DV** Days with vasopressors. **ICU** Intensive care unit. **MA** Metabolic acidosis. **MAKE 30** combination of variables such as mortality, persistent kidney failure, or new RRT at 30 days. **mEq Cl** Milliequivalents of chlorine. **Mor 30** Mortality at 30 days. **Mor ICU** Mortality in ICU. **Mor H** Hospital mortality. **MS** Mean stay. **OR** Odds ratio. **PeriQx** Perioperative. **RL** Ringer lactate. **SS 0.9%** Saline 0.9%. **RCT** Randomised clinical trial. RRT Renal replacement therapy. **TV** Transfusion volume.

## Comparison between colloids

A systematic review of 69 studies (42 RCTs) involving 10,382 patients with acute critical disease, comparison of safety outcomes for different colloids. Albumin was found to be the safest colloid and HES the least safe for the variables acute kidney failure, bleeding and clotting abnormalities, and pruritus as main adverse events[67].

## Comparison between colloids and crystalloids

Intravenous colloids have not shown any benefit with respect to intravenous crystalloids in a population in a critical state.

## Hypovolaemia and hypovolaemic shock

Taken together, the data show that the use of colloids does not show any clinical improvement with respect to the use of crystalloids in cases of hypovolaemic shock or hypovolaemia. Adverse events are rarely considered.

**Table 4.** Critical state. Comparison between colloids and crystalloids.

| REF. | INTERVENTION | COMPARATOR | RTC no. | No. PATIENTS | POPULATION | PRIMARY OBJECTIVES | DIFFERENCES (RR; 95% CI) | EVIDENCE QUALITY | I2 | SECONDARY OBJECTIVES |
|---|---|---|---|---|---|---|---|---|---|---|
| 1998[68] | Colloids | Crystalloids | 9 | 1,315 | Critical state | Mortality | 1.19 (0.98- 1.45) | - | 12% | |
| 1998[69] | Albumin | Crystalloids | 3 | 163 | Critical Hypoalbuminemia | Mortality | 2.4 (1.11-5.19) | - | 2% | |
| 2004[70] | Albumin | Crystalloids | 19 | 7,576 | Critical state | Mortality | 1.02 (0.93- 1.11) | - | 0% | |
| 2011[71] | Albumin | Crystalloids | 12 | 757 | Critical Hypoalbuminemia | Mortality | 1.26 (0.84 -1.88) | - | 0% | |
| 2011[71] | Albumin | Crystalloids | 8 | 10,842 | Critical state | Mortality | 1.05 (0.95-1.16) | - | 0% | |
| 2013[72] | Albumin | Crystalloids | 24 | 9,920 | Critical state | Mortality | 1.01 (0.93- 1.10) | - | 15% | |
| 2004[70] | Dextran | Crystalloids | 9 | 834 | Critical state | Mortality | 1.24 (0.94-1.65) | - | 0% | |
| 2013[72] | Dextran | Crystalloids | 9 | 834 | Critical state | Mortality | 1.24 (0.94- 1.65) | - | 0% | |
| 2004[70] | Gelatine | Crystalloids | 7 | 346 | Critical state | Mortality | 0.54 (0.16-1.85) | - | 0% | |
| 2013[72] | Gelatine | Crystalloids | 11 | 506 | Critical state | Mortality | 0.91 (0.49- 1.72) | - | 0% | |

**CI** Confidence interval. **RCT** Randomised clinical trial. **RR** Relative risk.

**Table 5.** Hypovolaemic shock.

| REF. | INTERVENTION | COMPARATOR | RTC no. | No. PATIENTS | POPULATION | PRIMARY OBJECTIVES | DIFFERENCES (RR; 95% CI) | EVIDENCE QUALITY | I2 | SECONDARY OBJECTIVES |
|---|---|---|---|---|---|---|---|---|---|---|
| 2014[73] | SH 7,5% | Isotonic (0.9% SS or RL) | 6 | 1,254 | Hypovolaemic shock | Mortality | 0.96 (0.82-1.14) | – | 0% | Elevated BP |
| 2017[74] | SH 7,5% | 0.9% SS or RL | 12 | 2,932 | Hypovolaemic shock | Mortality | 0.96 (0.82-1.12) | – | 0% | |
| 2022[75] | Hypertonic | Isotonic (0.9% SS or RL) | 9 | 2,081 | Hypovolaemic shock | Mortality 30 days | 1.19 (0.97-1.45) | – | 48% | Mor 90, Mortality, AEs, MS |
| 2017[74] | Dextran | 0.9% SS or RL | 12 | 2,932 | Hypovolaemic shock | Mortality | 0.92 (0.80-1.06) | – | 0% | |
| 2019[76] | Dextran | Crystalloids | 19 | - | Hypovolaemic shock | Mortality | 1.02 (0.94-1.09) | – | 0% | |
| 2019[76] | Gelatine | Crystalloids | 3 | - | Hypovolaemic shock | Mortality | 1.19 (0.68-2.08) | – | 0% | Cardiac output |

**AE** Adverse Event. **AKF** Acute kidney failure. **BP** Blood pressure. **CI** Confidence interval. **HS** Hypertonic saline. **IV** Infusion volume. **Mor 90** 90-Day mortality. **MS** Mean stay. **RCT** Randomised clinical trial. **RL** Ringer lactate. **RR** Relative risk. **SS** Saline solution.

**Table 6.** Hypovolaemia.

| REF. | INTERVENTION | COMPARATOR | RTC no. | No. PATIENTS | POPULATION | PRIMARY OBJECTIVES | DIFFERENCES (RR; 95% CI) | EVIDENCE QUALITY | I2 | SECONDARY OBJECTIVES |
|---|---|---|---|---|---|---|---|---|---|---|
| 1998[69] | Albumin | Crystalloids | 13 | 534 | Hypovolaemia | Mortality | 1.46 (0.97-2.22) | - | 9% | |
| 2004[77] | Albumin | Crystalloids | 28 | 1,522 | Hypovolaemia | Mortality | 0.96 (0.75- 1.23) | - | 0% | |
| 2011[71] | Albumin | Crystalloids | 22 | 9,880 | Hypovolaemia | Mortality | 1.02 (0.92- 1.13) | - | 0% | |
| 2019[76] | Albumin | Crystalloids | 14 | - | Hypovolaemic shock | Mortality | 1.02 (0.96-1.10) | - | 0% | Cardiac output |
| 2010[78] | Hyperoncotic albumin | Hypo-oncotic albumin | 7 | 524 | Hypovolaemia | AKF | 0.24 (0.12-0.48) | - | 0% | Mortality |
| 2016[79] | Albumin or crystalloids | Gelatine | 16 | 2,525 | Hypovolaemia | Mortality | 1.15 (0.96-1.38) | Low | 0% | TV, AKF, anaphylaxis |

**ECA** Ensayo clínico aleatorizado. **IC** Intervalo de confianza. **IRA** Insuficiencia renal aguda. **RR** Riesgo relativo. **VT** Volumen de transfusión.

## Sepsis

### Comparison between crystalloids

The use of balanced crystalloid solutions is associated with a lower mortality than the use of unbalanced crystalloids in situations of severe sepsis Adverse events are rarely considered.

### Comparison between colloids and crystalloids

The use of colloids does not result in a clinical improvement with respect to the use of crystalloids in situation of severe sepsis. The European Society of Intensive Care Medicine recommends to avoid the use of HES-type colloids and gelatins in patients with severe sepsis[86]. Similarly, an international guideline for the management of sepsis and septic shock, which represents 25 international organisations, recommends the use of crystalloids in the reanimation of patients with sepsis and septic shock (strong recommendation, moderate evidence)[87]. Adverse events are rarely considered.

**Table 7.** Sepsis. Comparison between crystalloids.

| REF. | INTERVENTION | COMPARATOR | RTC no. | No. PATIENTS | POPULATION | PRIMARY OBJECTIVES | DIFFERENCES (RR; 95% CI) | EVIDENCE QUALITY | I2 | SECONDARY OBJECTIVES |
|---|---|---|---|---|---|---|---|---|---|---|
| 2014[80] | Balanced | S 0.9% | 10 | 6,664 | Severe sepsis | RRT | 0.85 (0.56-1.30) | Low | | |
| 2020[81] | Balanced | S 0.9% | 23 | 14,659 | Severe sepsis | Mortality | 0.84 (0.74-0.95) | Moderate | – | |
| 2020[81] | Balanced | S 0.9% | 11 | 10,569 | Severe sepsis | AKF | 0.98 (0.82-1.17) | Moderate | – | |

**AKF** Acute kidney failure. **CI** Confidence interval. **HR** Relative risk. **RCT** Randomised clinical trial. **RRT** Renal replacement therapy. **SS** Saline solution.

**Table 8.** Sepsis. Comparison between colloids and crystalloids.

| REF. | INTERVENTION | COMPARATOR | RTC no. | No. PATIENTS | POPULATION | PRIMARY OBJECTIVES | DIFFERENCES (RR; 95% CI) | EVIDENCE QUALITY | I2 | SECONDARY OBJECTIVES |
|---|---|---|---|---|---|---|---|---|---|---|
| 2014[80] | Albumin | Crystalloids | 10 | 6,664 | Severe sepsis | RRT | 1.04 (0,78-1,38) | Moderate | | |
| 2014[82] | Albumin | Crystalloids | 5 | 3,650 | Severe sepsis | Mortality 90 days | 0.88 (0.76-1.01) | - | 0% | Mor, Mor 30 Septic shock |
| 2014[83] | Albumin | Crystalloids | 11 | 6,741 | Severe sepsis | Mortality | 0.95 (0.87-1.04) | - | 5% | |
| 2016[84] | Dextran | Crystalloids | 10 | 2,501 | Severe sepsis | Mortality | 0.86 (0.71-1.03) | Moderate | 0% | |
| 2016[84] | Gelatin/Colloids | Crystalloids | 6 | 2,241 | Severe sepsis | Mortality | 0.90 (0.73-1.11) | Moderate | 40% | |
| 2018[85] | Albumin | Crystalloids | 6 | 3,088 | Severe sepsis | Mortality | 0.91 (0.83-1.00) | - | 0% | |

**AE** Adverse event. **AKF** Acute kidney failure. **CI** Confidence interval. **Mor 30** 30-Day mortality. **RCT** Randomised clinical trial. **RR** Relative risk. **SS** Saline.

## Major burns

According to the findings of the systematic reviews studied, which do not report the quality of the evidence, the use of albumin in patients with burns on more than 15% of their body surface area is associated with a higher mortality than the use of crystalloids. These findings are in agreement with those of the MAPAC (Mejora de la Adecuación de la Práctica Asistencial y Clínica [Improvement of the Adaptation of Clinical and Care Practices]) of the SNS-O [Navarra Health Service][92]. In these situations, the fluid therapy of choice is crystalloids, in agreement with the recommendations of the International Society for Burns Injuries (ISBI)[93]. Two randomised clinical trials present better indirect results with hypertonic saline or Plasmalyte® than with Ringer lactate. Adverse events are rarely considered.

## Trauma

A systematic review in severe trauma patients (including the use of HES) concluded that the use of dextran does not present differences in terms of mortality outcomes with respect to the use of crystalloids. There were also no difference between the use of hypertonic saline and isotonic saline, whether balanced or not. Adverse events are rarely considered.

**Table 9.** Major burns.

| REF. | INTERVENTION | COMPARATOR | RTC no. | No. PATIENTS | POPULATION | PRIMARY OBJECTIVES | DIFFERENCES (RR; 95% CI) | EVIDENCE QUALITY | I2 | SECONDARY OBJECTIVES |
|---|---|---|---|---|---|---|---|---|---|---|
| 1995*[88] | HS | RL | 1 | 213 | Burn patients | FV 24 h | MD: 3.94 vs 5.25 mL/kg/%BSA | - | - | |
| 2017[89] | Hyperosmotic | iso-osmotic | 6 | 294 | Burn patients | Mortality | 1.18 (0.60–2.34) | - | 0% | FV, diuresis 24 h, serum creatinine 24 h |
| 1998[69] | Albumin | Crystalloids | 8 | 507 | Burn patients | Mortality | 1.69 (1.26–2.267 | - | 1% | |
| 2011[71] | Albumin | Crystalloids | 4 | 205 | Burn patients | Mortality | 2.93 (1.28–6.72) | - | 0% | |
| 2017[90] | Albumin + RL | Crystalloids | 4 | 140 | Burn patients | Mortality | 1.60 (0.63–4.08) | - | 41% | |
| 2020*[91] | Plasmalyte® | RL | 1 | 28 | Burn patients | Base excess | MD: −0.9 vs −2.1 | - | - | Mortality, MS |

(*) RCT. **BSA** Body surface area. **CI** Confidence interval. **FV** Fluid volume. **HS** Hypertonic saline. **MD** Mean difference. **MS** Mean stay. **RCT** Randomised clinical trial. **RL** Ringer lactate. **RR** Relative risk.

**Table 10.** Trauma (including gunshot injuries).

| REF. | INTERVENCIÓN | COMPARADOR | Nº ECA | NÚMERO PACIENTES | POBLACIÓN | OBJETIVOS PRIMARIOS | DIFERENCIAS (RR; IC 95%) | CALIDAD EVIDENCIA | I2 | OBJETIVOS SECUNDARIOS |
|---|---|---|---|---|---|---|---|---|---|---|
| 2017[94] | Dextran | RL | 2 | 269 | Trauma | Mortality | 1.47 (0.30–7.18) | Low | 85% | AE, infection, multiorgan failure, MS |
| 2017[95] | SH | Isotonic | 5 | 1,162 | Trauma | Mortality | 1.02 (0.95-1.10) | - | 0% | |

**AE** Adverse event. **AKF** Acute kidney failure. **CI** Confidence interval. **HS** Hypertonic saline. **MS** Mean stay. **RCT** Randomised clinical trial. **RL** Ringer lactate. **RR** Relative risk.

# Surgery

## General surgery

### Comparison between crystalloids

In the case of non-cardiac surgery, the use of balanced crystalloids does not provide a clinical benefit compared with unbalanced solutions. Supplementation with crystalloids is associated with a reduction in postoperative nausea and vomiting compared with the standard dose. The quantity of evidence regarding the use of restrictive versus goal-oriented fluid therapy is very low, therefore no conclusions can be reached.

The NICE guideline recommends the use of crystalloids in perioperative adult care[101].

## Heart surgery

### Comparison between colloids and crystalloids

The use of gelatins does not show better health outcomes than the use of crystalloids in priming the extracorporeal circuit in heart surgery. The MAPAC recommends the use of crystalloids for circuit priming[92].

**Table 11.** General surgery. Comparison between crystalloids.

| REF. | INTERVENTION | COMPARATOR | RTC no. | No. PATIENTS | POPULATION | PRIMARY OBJECTIVES | DIFFERENCES (RR; 95% CI) | EVIDENCE QUALITY | I2 | SECONDARY OBJECTIVES |
|---|---|---|---|---|---|---|---|---|---|---|
| 2012[96] | Balanced | Unbalanced | 3 | 267 | Surgery | Mortality | 1.85 (0.37–9.33) | Moderate | 0% | **Lower pH**, TV |
| 2017[97] | Balanced | Unbalanced | 3 | 267 | Surgery | Mortality | 1.85 (0.37–9.33) | Low | 0% | **RRT, diuresis, change creatinine, postoperative creatinine, PCO2, postoperative NAVO**, BV, TV, platelet transfusion. |
| 2018[98] | Balanced | SS 0.9% | 8 | 871 | Surgery | pH PostQx | MD 0.06 (0.04–0.08) | Moderate | 82% | |
| 2019[99] | Crystalloid supplements | Standard dose | 18 | 1,766 | Surgery | Nausea PostQx | 0.62 (0.51–0.75) | Moderate | 57% | **Need for antiemetics, readmissions, AEs** |
| 2019[99] | Crystalloid supplements | Standard dose | 20 | 1,970 | Surgery | Vomiting PostQx | 0.50 (0.40–0.63) | Moderate | 40% | |
| 2019[100] | Restrictive (balance 0) | Goal-oriented | 5 | 484 | Surgery | Major complications | 1.61 (0.78–3.34) | Very low | 47% | **MS, surgical complications, AKF.** Non-surgical complications |
| 2019[100] | Restrictive (balance 0) | Target-oriented | 6 | 544 | Surgery | Mortality | DR 4.81 (1.38-16.84) | Very low | 0% | |

**AE** Adverse event. **AKF** Acute kidney failure. **BV** Bleeding volume. **CI** Confidence interval. **DR** Difference of risks. **MD** Mean difference. **MS** Mean stay. **PostQx** Postoperative. **RCT** Randomised clinical trial. **RR** Relative risk. **RRT** Renal replacement therapy. **SS** Saline solution. **TV** Transfusion volume.

**Table 12.** Heart surgery. Colloids versus crystalloids.

| REF. | INTERVENTION | COMPARATOR | RTC no. | No. PATIENTS | POPULATION | PRIMARY OBJECTIVES | DIFFERENCES (RR; 95% CI) | EVIDENCE QUALITY | I2 | SECONDARY OBJECTIVES |
|---|---|---|---|---|---|---|---|---|---|---|
| 2017[102] | Gelatin | Crystalloids | 3 | 44 | Heart surgery | Blood loss in 24 h | SMD –0.07 (–0.40, 0.26) | Low | 0% | |

**CI** Confidence interval. **RCT** Randomised clinical trial. **RR** Relative risk. **SDM** Standardized mean difference.

### Neurosurgery

In neurosurgical interventions, the use of hypertonic solutions, specifically hypertonic saline, is likely to result in better outcomes as regards the reduction in intracranial pressure, and probably also mortality, compared with other fluid therapy alternatives. Hypernatraemia is the main adverse event. As recommended by the MAPAC initiative and the European Society for Intensive Care Medicine (ESICM), the use of hypotonic solutions in this type of patient is not recommended given the risk of onset of cerebral oedema. Colloids, including albumin, are also not recommended[86,92].

## Internal Medicine

### Acute pancreatitis

A study of the evidence available provides contradictory results when comparing the use of aggressive hydration (bolus of 15–20 mL/kg plus 3 mL/kg/hour) (preferably with Ringer lactate) with standard hydration (10 mL/kg bolus and 1.5 mL/kg/hour) in situations of acute pancreatitis. There is moderate evidence that the use of aggressive hydration produces less multiorgan failure. The findings for mortality, adverse events, systemic inflammatory response syndrome (SIRS), mean stay, local complications, admission to ICU, risk of sepsis are contradictory in the reviews evaluated, which share a low quality rating. However, there is greater consensus regarding the use of Ringer lactate as first-line fluid therapy. In contrast, the use of an aggressive fluid therapy infusion strategy (mainly with Ringer lactate) in ERCP (endoscopic retrograde cholangiopancreatography) is associated with a lower risk of onset of pancreatitis, elevated amylase, or onset of abdominal pain in the absence of major adverse events. The benefit remains irrespective of whether hydration is performed before or started during the procedure.

**Table 13.** Neurosurgery.

| REF. | INTERVENTION | COMPARATOR | RTC no. | No. PATIENTS | POPULATION | PRIMARY OBJECTIVES | DIFFERENCES (RR; 95% CI) | EVIDENCE QUALITY | I2 | SECONDARY OBJECTIVES |
|---|---|---|---|---|---|---|---|---|---|---|
| 2015[103] | HS | Mannitol | 4 | 368 | Neurosurgery | Intraoperative brain relaxation | 2.25 (1.32–3.81) | - | 53% | VF |
| 2015[103] | HS | Mannitol | 4 | 149 | Neurosurgery | Intraoperative intracranial pressure | MD –2.51 (–3.09, –1.93)* | - | 29% | |
| 2016[104] | HS | Mannitol or SS 0.9% | 4 | 1,638 | Neurosurgery | Mortality | 0.96 (0.83–1.11) | - | 0% | MS, MS ICU, hypernatraemia, AE |
| 2016[104] | HS | Mannitol or SS 0.9% | 6 | 532 | Neurosurgery | Control intracranial pressure | WMD –0.39 (–3.78, 2.99) | - | 0% | |
| 2019[105] | HS | Mannitol | 11 | 418 | Neurosurgery | Maximum reduction in ICP | MD –0.16 (–0.59, 0.27) | - | 30% | Control ICP, osmolality level |
| 2020[81] | HS | Albumin | 4 | 1,970 | Neurosurgery | Mortality | 0.55 (0.35–0.87) | Very low | | |
| 2020[106] | HS | Mannitol | 2 | 85 | Neurosurgery | Mortality 6 months | 0.84 (0.46-1.55) | Very low | 0% | AEs not recorded |
| 2023[107] | Hypertonic (>308 mmosm) | Isotonic | 10 | 1,883 | Neurosurgery | Hospital mortality | 0.68 (0.54–0.85) | - | 0% | ICP, neurological outcome at 90 days, hypernatraemia, AKF |

(*) mmHg. **AE** Adverse event. **AKF** Acute kidney failure. **CI** Confidence interval. **FV** Fluid volume. **HES** Hydroxyethyl starch. **HS** Hypertonic saline. **ICP** Intracranial pressure. **ICU** Intensive care unit. **MD** Mean difference. **MS** Mean stay. **RCT** Randomised clinical trial. **RR** Relative risk. **SS** Saline solution. **WMD** Weighted mean difference.

**Table 14.** Acute pancreatitis and ERCP.

| REF. | INTERVENTION | COMPARATOR | RTC no. | No. PATIENTS | POPULATION | PRIMARY OBJECTIVES | DIFFERENCES (RR; 95% CI) | EVIDENCE QUALITY | I2 | SECONDARY OBJECTIVES |
|---|---|---|---|---|---|---|---|---|---|---|
| 2021[108] | RL | SS 0.9% | 4 | 248 | Acute pancreatitis | Moderate/ severe pancreatitis | 0.49 (0.25–0.97) | Low | 0% | **MS**, SIRS, **AE and local complications, admission to ICU** |
| 2021[109] | RL | SS 0.9% | 6 | 549 | Acute pancreatitis | Mortality | 0.73 (0.31-1.69) | - | 10% | **Admission to ICU**, mortality, SIRS at 24 h, respiratory distress, AKF, pancreatic necrosis |
| 2022[110] | Aggressive hydration | Standard hydration | 4 | 339 | Acute pancreatitis | Mortality | 2.88 (1.41–5.88) | Low | 0% | AE, Sepsis |
| 2022[111] | RL | SS 0.9% | 6 | 549 | Acute pancreatitis | SIRS | 0.59 (0.22–1.62) | - | 48% | **Admission to ICU**, mortality, moderate/ severe pancreatitis, pancreatic necrosis, multiorgan failure, nutritional support, invasive treatment |
| 2022[112] | Aggressive hydration | Standard hydration | 3 | 204 | Acute pancreatitis | Clinical improvement at 36 h | 1.33 (0.95–1.87) | Very low | 58% | **MS, abdominal pain** |
| 2022[112] | Aggressive hydration | Standard hydration | 5 | 370 | Acute pancreatitis | SIRS | 0.48 (0.31-0.72) | Low | 22% | |
| 2022[112] | Aggressive hydration | Standard hydration | 3 | 266 | Acute pancreatitis | Multiorgan dysfunction | 0.34 (0.13–0.91) | Moderate | 0% | |
| 2017[113] | Aggressive hydration | Standard hydration RL | 7 | 1,047 | ERCP | Pancreatitis | 0.46 (0.23–0.95) | Moderate | 46% | **Hyperamylasaemia, AE** |
| 2021[114] | Aggressive hydration | Standard hydration RL | 7 | 1,227 | ERCP | Pancreatitis | 0.41 (0.27-0.62) | - | 59% | **Hyperamylasaemia, abdominal pain** |
| 2022[115] | Aggressive hydration | Standard hydration RL | 10 | 2,200 | ERCP | Pancreatitis | 0.40 (0.26–0.63) | Moderate | 43% | **Hyperamylasaemia, abdominal pain**, fluid overload |

**AE** Adverse events. **AKF** Acute kidney failure. **ERCP** Endoscopic retrograde cholangiopancreatography. **IC** Confidence interval. **ICU** Intensive care unit. **MS** Mean stay. **RCT** Randomised clinical trial. **RL** Ringer lactate. **RR** Relative risk. **SIRS** Systemic inflammatory response syndrome. **SS** Saline solution.

## Diabetic ketoacidosis

In the event of diabetic ketoacidosis, balanced crystalloid solutions appear to allow faster recovery from ketoacidosis than saline 0.9%.

## Heart failure

In situations of decompensated heart failure, the combination of hypertonic saline (100–150 mL HS 1.7–4.6% in 30–60 minutes) with furosemide produces better outcomes in terms of mortality, hospital readmission due to heart failure, kidney function, weight loss and mean hospital stay than furosemide alone.

**Table 15.** Diabetic ketoacidosis.

| REF. | INTERVENTION | COMPARATOR | RTC no. | No. PATIENTS | POPULATION | PRIMARY OBJECTIVES | DIFFERENCES (RR; 95% CI) | EVIDENCE QUALITY | I2 | SECONDARY OBJECTIVES |
|---|---|---|---|---|---|---|---|---|---|---|
| 2021*[116] | Plasmalyte® | SS 0.9% | 1 | 90 | Diabetic ketoacidosis | Increase base excess 48 h | 3.93 (0.73–21.16) | | | **Significant at 24 h** |
| 2023*[117] | Plasmalyte® | SS 0.9% | 1 | 84 | Diabetic ketoacidosis | Admission to ICU | 0.73 (0.13–4.16) | | | |
| 2022[118] | Balanced | SS 0.9% | 3 | 316 | Diabetic ketoacidosis | Time to resolution | HR 1.46 (1.10–1.94) | Moderate | 12% | |

**(*) CI** Confidence interval. **HR** Hazard ratio. **ICU** Intensive care unit. **RCT** Randomised clinical trial. **RR** Relative risk. **SS** Saline solution

**Table 16.** Heart failure.

| REF. | INTERVENTION | COMPARATOR | RTC no. | No. PATIENTS | POPULATION | PRIMARY OBJECTIVES | DIFFERENCES (RR; 95% CI) | EVIDENCE QUALITY | I2 | SECONDARY OBJECTIVES |
|---|---|---|---|---|---|---|---|---|---|---|
| 2011[119] | HS+ Furosemide | Furosemide | 4 | 2,032 | Heart failure | Readmission due to aHF | 0.63 (0.44–0.90) | – | 72% | |
| 2014[120] | HS+ Furosemide | Furosemide | 5 | 2.064 | Heart failure | Mortality | 0.56 (0.41-0.76) | – | 43% | Readmission due to HF, MS, weight loss, improvement kidney function |
| 2015[120] | HS+ Furosemide | Furosemide | 5 | 2.064 | Heart failure | Mortality | 0.57 (0.44-0.74) | – | 65% | Readmission due to HF, MS, weight loss, improvement kidney function |
| 2021[121] | HS+ Furosemide | Furosemide | 6 | 2.298 | Heart failure | Mortality | 0.55 (0.46-0.67) | Moderada | 12% | MS, improvement kidney function, sodium increase, natriuresis, daily diuresis, weight loss |
| 2021[121] | HS+ Furosemide | Furosemide | 4 | 2.032 | Heart failure | Readmission due to aHF | 0.50 (0.33–0.76) | Moderada | 61% | |
| 2021[122] | HS+ Furosemide | Furosemide | 5 | 2.338 | Heart failure | Long-term mortality | 0.55 (0.47–0.65) | – | 0% | Readmission due to HF, MS, improvement kidney function, natriuresis, daily diuresis, weight loss |

**AE** Adverse event. **aHF** Acute heart failure. **AKF** Acute kidney failure. **CI** Confidence interval. **HS** Hypertonic saline. **ICU** Intensive care unit. **MS** Mean stay. **RCT** Randomised clinical trial. **RR** Relative risk.

## Cerebrovascular accident (CVA)

A single systematic review (2 of 12 studies performed with HES as comparator) did not find any improvement in terms of mortality outcome with the use of colloids compared with the use of crystalloids in the event of CVA.

## Acute respiratory distress

There is insufficient evidence to recommend the use of albumin rather than crystalloids in patients with acute respiratory distress. In a single systematic review involving a limited number of patients, the majority of benefits were for secondary variables.

**Table 17.** Cerebrovascular accident.

| REF. | INTERVENTION | COMPARATOR | RTC no. | No. PATIENTS | POPULATION | PRIMARY OBJECTIVES | DIFFERENCES (RR; 95% CI) | EVIDENCE QUALITY | I2 | SECONDARY OBJECTIVES |
|---|---|---|---|---|---|---|---|---|---|---|
| 2015[123] | Colloids | Crystalloids | 12 | 2,351 | CVA | Mortality | 1.02 (0.82–1.27) | Moderate | 24% | Pulmonary oedema |

**CI** Confidence interval. **RCT** Randomised clinical trial. **RR** Relative risk.

**Table 18.** Respiratory distress.

| REF. | INTERVENTION | COMPARATOR | RTC no. | No. PATIENTS | POPULATION | PRIMARY OBJECTIVES | DIFFERENCES (RR; 95% CI) | EVIDENCE QUALITY | I2 | SECONDARY OBJECTIVES |
|---|---|---|---|---|---|---|---|---|---|---|
| 2014[124] | Albumin | Crystalloids | 3 | 206 | Acute respiratory distress | Mortality | 0.89 (0.62–1.28) | – | 0% | AKF, RRT, MS ICU |
| 2014[124] | Albumin | Crystalloids | 3 | 206 | Acute respiratory distress | PaO2/FiO2 | WMD 56 mmHg; (47–66) | – | 0% | |

**AKF** Acute kidney failure. **CI** Confidence interval. **DMP** Weighted mean difference. **ICU** Intensive care unit. **MS** Mean stay. **RR** Relative risk. **RRT** Renal replacement therapy.

## Paediatrics

In light of the results obtained, the population studied in the systematic reviews analysed was diverse. In general, we can see a tendency to obtain better outcomes with balanced crystalloids versus saline 0.9% in severe disease or gastroenteritis-related dehydration; and with the use of isotonic serum (saline serum 0.9%, Hartmann solution) versus hypotonic solutions (glucose serum or glucosaline) as maintenance serum to prevent intrahospital hyponatraemia. A bolus infusion appears to be associated with better mortality outcomes in septic shock compared with no bolus.

### Risks and side effects

Generally speaking, excess intravenous fluid therapy is associated with a risk of positive balance, which can cause interstitial oedema, cardiac, pulmonary or intestinal dysfunction or dilutional coagulopathy and is a predictor for death at 60 days in patients with acute kidney failure or sepsis[134].

### Crystalloids

#### Unbalanced

The main risk of saline 0.9% arises due to the excess chlorine (1.5-times higher than in plasma), which facilitates the onset of metabolic acidosis in the absence of a buffer to counterbalance this effect. Hyperchloraemia can also cause kidney failure as a result of a reduction in renal flow rate and renal cortical perfusion 57,135,136. This response is most commonly observed after administration of more than 2.5 litres of saline 0.9% per day (35 mL/kg/d or 1.5 ml/kg/h approx.) in adult patients[48,134,137].

The infusion of hypotonic solutions, such as saline 0.45%, glucose serum or glucosaline, is associated with hyponatraemia[134].

The greatest risk with maintenance doses of hypotonic solutions, in turn, is the onset of hyponatraemia, especially in paediatric patients. The best option to minimise this is to use glucosaline solutions with a sodium concentration of 0.9%[2].

**Table 19.** Paediatric patients.

| REF. | INTERVENTION | COMPARATOR | RTC no. | No. PATIENTS | POPULATION | PRIMARY OBJECTIVES | DIFFERENCES (RR; 95% CI) | EVIDENCE QUALITY | I2 | SECONDARY OBJECTIVES |
|---|---|---|---|---|---|---|---|---|---|---|
| 2001[125] | Expansion volume | No expansion | 4 | 940 | Preterm | Mortality | 1.11 (0.88–1.40) | – | – | |
| 2005[126] | Crystalloids | Colloids | 2 | 30 | Neonatal polycythaemia | Short-term physiological effects | 1.36 (0.38–4.89) | Very low | 0% | |
| 2015[127] | Isotonic | Hypotonic | 10 | 1,006 | Hospitalisation | Hyponatraemia 48 h | 0.50 (0.40–0.62) | – | 0% | Severe hyponatraemia, hypernatraemia |
| 2019[128] | With dextrose | Without dextrose | 2 | 333 | Extra-hospital dehydration | Hospitalisation | 0.83 (0.62–1.10) | – | 0% | |
| 2021[129] | No bolus | Bolus | 7 | 5,337 | Septic shock | Mortality | 0.74 (0.62–0.88) | High | 0% | |
| 2022[130] | Rapid infusion | Slow infusion | 2 | 1.439 | Diabetic ketoacidosis | Resolution time | SMD 1.42 (0.28, 2.56) | Very low | 98% | |
| 2022[131] | Balanced | SS 0.9% | 3 | 162 | Critical state | Mean change in bicarbonate 24 h | MD 1.60 (0.04–3.16) | – | 59% | **RRT, DV, DFMV, MS, Mortality** |
| 2023[132] | Balanced | SS 0.9% | 2 | 90 | Acute diarrhoea with severe dehydration | Time in hospital | MD −0.35 (−0.6, −0.10) | Moderate | 0% | **Higher pH,** mortality, **bicarbonate level, risk of hypokalaemia** |
| 2023[133] | Crystalloid supplements | Standard regimen | 5 | 620 | Surgery | Postoperative vomiting | 0.56 (0.39–0.80) | High | 66% | **Need for antiemetics, NAVO** |

**AE** Adverse event. **CI** Confidence interval. **DFMV** Days free from mechanical ventilation. **DV** Days with vasopressors. **MS** Mean stay. **NAVO** Nausea and vomiting. **SMD** Standardized mean difference. **SS** Saline solution. **RCT** Randomised clinical trial. **RR** Relative risk. **RRT** Renal replacement therapy.

Glucose serum 5% is not suitable for treating hypovolaemia. After infusion, only 10% of the quantity infused remains in the intravascular space. It is useful for preventing endogenous catabolism and as an alternative to hypotonic solutions with risk of hyponatraemia, especially in children. Their adverse effects include the onset of hyponatraemia and hypokalaemia[134].

### Balanced

Stressful situations, such as those observed in hospitalised patients, induce the secretion of ADH, which makes the elimination of hypotonic solutions such as Hartmann solution, Ringer lactate or hypotonic salines more difficult and increases the risk of causing a positive fluid balance and states of hyponatraemia, which may affect up to 30% of such patients[2]. Indeed, SIADH is the leading cause of hyponatraemia and can be observed on situations of euvolaemia[138]. These hypotonic solutions should also be avoided in the event of cerebral oedema[139].

Solutions containing calcium (Ringer lactate or Hartmann solution) should not be mixed or administered concomitantly with bicarbonate or some drugs such as ceftriaxone given the risk of forming insoluble calcium salts and their precipitation[49,140,141].

Plasmalyte® and Ringer lactate have an overall alkalifying effect, therefore they should be used with caution in cases of hypocalcaemia, and their use should be avoided in cases of metabolic alkalosis, hypochloraemia and hyperkalaemia.

### Colloids

As mentioned above, the scientific evidence available led the European Commission to withdraw colloid solutions containing HES 6% (Voluven®, Isohes®, Volulyte®) from the market given the worst outcomes in terms of renal function, coagulopathy, bleeding and pruritus, with the risks associated with their use being greater than the benefit obtained[27,28]. Deposition in the skin is associated with the onset of pruritus as of the third week of infusion and this can persist for six months, or as long as 12–24 months, with severe or very severe intensity in up to 80% of patients who received them[142,143]. This was greater than observed for saline 0.9% in all cases[144,145]. Dextran and gelatins are associated with a greater risk of anaphylactic reactions compared with albumin (less risk for gelatins) (RR: 2.32; 95% CI: 1.21–4.45)[142].

A summary of indications and contraindications for the solutions used most commonly in fluid therapy can be found in the following table.

Solutions containing calcium (such as Ringer lactate) are contraindicated in combination with bicarbonate or ceftriaxone.

**Table 20.** Indications and contraindications for solutions commonly used in fluid therapy.

| FLUID THERAPY | INDICATIONS | CONTRAINDICATIONS |
|---|---|---|
| Glucose serum | Energy maintenance<br>Hyperkalaemia<br>Hypernatraemia | Hyponatraemia<br>Fluid maintenance<br>Hypokalaemia<br>Hyperlactacidaemia<br>Hyperglycaemia<br>Acute cerebrovascular accident |
| Glucosaline serum | Energy maintenance<br>Hyperkalaemia<br>Hypernatraemia<br>Postoperative | Fluid overload<br>Hyperglycaemia<br>Hyponatraemia (paediatric) |
| Saline serum 0.45% | Fluid maintenance<br>Hypernatraemia Postoperative<br>Hypokalaemia | Fluid overload |
| Saline serum 0.9% | Fluid maintenance<br>Hypovolaemia<br>Hyponatraemia<br>Metabolic alkalosis<br>Hypokalaemia<br>Acute cerebrovascular accident | Hyperchloraemic metabolic acidosis<br>Kidney failure<br>Fluid overload<br>Hypernatraemia<br>HBP<br>Hepatic cirrhosis |
| Hypertonic saline | Intracraneal disease<br>Heart failure with furosemide<br>Acute hyponatraemia | Hypernatraemia<br>Kidney failure<br>Hepatic cirrhosis |
| Ringer lactate | Surgery<br>Trauma<br>Diabetic ketoacidosis<br>Major burns<br>Acute pancreatitis | Severe metabolic alkalosis<br>Lactic acidosis<br>Severe hyperkalaemia<br>Risk of cerebral oedema<br>Co-administration with citrate<br>Co-administration with bicarbonate<br>Co-administration with ceftriaxone<br>Liver failure |
| Plasmalyte | Diabetic ketoacidosis<br>Lactic acidosis<br>Hypernatraemia hypokalaemia<br>Acute pancreatitis | Hyperkalaemia<br>Kidney failure<br>Heart block<br>Metabolic or respiratory alkalosis<br>Hypochlorhydria |
| Albumin | Hypovolaemia and major burns<br>(after infusion of crystalloids) | Severe heart failure<br>Severe anaemia<br>Simultaneous blood transfusion |
| Synthetic colloids | Haemorrhagic hypovolaemia<br>(after infusion of crystalloids) | Anaphylaxis<br>Pruritus |

## Conclusions

No perfectly physiological intravenous solution is currently available.

Saline 0.9%, known as "normal saline" or "physiological saline" is neither normal nor physiological in comparison with plasma.

The use of colloids does not show any clinical benefit with respect to crystalloids in situations of hypovolaemic shock or hypovolaemia, severe sepsis, severe trauma, heart surgery, respiratory distress or CVA.

The use of balanced crystalloid solutions rather than unbalanced crystalloids is associated with lower mortality in situations of severe sepsis, but not in other critical patients. Similarly, balanced solutions allow faster recovery than saline 0.9% in situations of diabetic ketoacidosis.

The fluid therapy of choice in major burn patients is crystalloids (hypertonic saline or Plasmalyte®). The use of albumin is associated with a higher mortality.

In the case of non-cardiac surgery, the use of balanced crystalloids does not provide a clinical benefit compared with unbalanced solutions. Supplementation with crystalloids is associated with a reduction in postoperative nausea and vomiting compared with the standard dose.

In neurosurgical interventions, the use of hypertonic solutions, specifically hypertonic saline, appears to lead to better outcomes as regards the reduction of intracranial pressure, and probably also mortality, than other fluid therapy alternatives.

In situations of acute pancreatitis and ERCP, the use of aggressive hydration, preferably with lactated Ringer's solution, leads to better health outcomes than standard hydration.

In situations of decompensated heart failure, the combination of hypertonic saline with furosemide leads to better outcomes than the use of furosemide alone.

In paediatric patients, the use of crystalloids is associated with better health outcomes in severe disease or dehydration than the use of unbalanced crystalloids. However, isotonic solutions (saline 0.9% or Hartmann) are preferred for maintenance to prevent intrahospital hyponatraemia. A bolus infusion appears to be associated with better mortality outcomes in septic shock compared with no bolus.

Fluid therapy is not risk-free, therefore the need for such therapy must be evaluated periodically.

In general, synthetic colloids are associated with a higher risk of anaphylactic reactions than albumin.

## References


1. Malbrain M, Langer T, Annane D, et al. Intravenous fluid therapy in the perioperative and critical care setting: Executive summary of the International Fluid Academy (IFA). *Ann Intensive Care*. May 24 2020;10(1):64. https://doi.org/10.1186/s13613-020-00679-3

2. Moritz ML, Ayus JC. Maintenance Intravenous Fluids in Acutely Ill Patients. *N Engl J Med*. Oct 2015;373(14):1350-60. https://doi.org/10.1056/NEJMra1412877

3. Frost P. Intravenous fluid therapy in adult inpatients. *Bmj*. Jan 6 2015;350:g7620. https://doi.org/10.1136/bmj.g7620

4. Tinawi M. New Trends in the Utilization of Intravenous Fluids. *Cureus*. Apr 21 2021;13(4):e14619. https://doi.org/10.7759/cureus.14619

5. Awad S, Allison SP, Lobo DN. Fluid and electrolyte balance: the impact of goal directed teaching. *Clin Nutr*. Jun 2008;27(3):473-8. https://doi.org/10.1016/j.clnu.2008.03.009

6. MSC. Recomendaciones para el Uso Seguro del Potasio Intravenoso. Madrid: Ministerio de Sanidad y Consumo; 2009.

7. Kaplan LJ, Kellum JA. Fluids, pH, ions and electrolytes. *Curr Opin Crit Care*. Aug 2010;16(4):323-31. https://doi.org/10.1097/MCC.0b013e32833c0957

8. Gordon D, Spiegel R. Fluid Resuscitation: History, Physiology, and Modern Fluid Resuscitation Strategies. *Emerg Med Clin North Am*. Nov 2020;38(4):783-793. https://doi.org/10.1016/j.emc.2020.06.004

9. Ringer S. A further Contribution regarding the influence of the different Constituents of the Blood on the Contraction of the Heart. *J Physiol*. Jan 1883;4(1):29-42.3. https://doi.org/10.1113/jphysiol.1883.sp000120

10. Rizoli S. PlasmaLyte. *J Trauma*. May 2011;70 (5 Suppl): S17-8. https://doi.org/10.1097/TA.0b013e31821a4d89

11. Ertmer C, Rehberg S, Van Aken H, Westphal M. Relevance of non-albumin colloids in intensive care medicine. *Best Pract Res Clin Anaesthesiol*. Jun 2009;23(2):193-212. https://doi.org/10.1016/j.bpa.2008.11.001

12. AEMPS. Agencia Española de Medicamentos y Productos Sanitarios. *Ficha Técnica*. APIROSERUM Glucosalino 1/5 https://cima.aemps.es/cima/dochtml/ft/49869/FT_49869.html Última consulta 12 de septiembre de 2023.

13. AEMPS. Agencia Española de Medicamentos y Productos Sanitarios.*Ficha Técnica*. Suero glucosalino isotónico (1/3) https://cima.aemps.es/cima/dochtml/ft/39858/FT_39858.html Última consulta 12 de septiembre de 2023.

14. AEMPS. Agencia Española de Medicamentos y Productos Sanitarios. *Ficha Técnica*. Suero salino 0,45% https://cima.aemps.es/cima/dochtml/ft/60916/FT_60916.html Última consulta 12 de septiembre de 2023.

15. AEMPS. Agencia Española de Medicamentos y Productos Sanitarios. *Ficha Técnica*. Suero salino 0,9% https://cima.aemps.es/cima/dochtml/ft/39005/FT_39005 Última consulta 12 de septiembre de 2023.

16. AEMPS. Agencia Española de Medicamentos y Productos Sanitarios. *Ficha Técnica*. Plasmalyte. https://cima.aemps.es/cima/dochtml/ft/67821/FT_67821.html Última consulta 12 de septiembre de 2023.

17. AEMPS. Agencia Española de Medicamentos y Productos Sanitarios. *Ficha Técnica* Gelatina succinada. https://cima.aemps.es/cima/dochtml/ft/76222/FT_76222.html Última consulta 12 de septiembre de 2023.

18. AEMPS. Agencia Española de Medicamentos y Productos Sanitarios. *Ficha Técnica V*oluven. https://cima.aemps.es/cima/dochtml/p/64001/P_64001.html Última consulta 12 de septiembre de 2023.

19. AEMPS. Agencia Española de Medicamentos y Productos Sanitarios. *Ficha Técnica Isohes 6%* https://cima.aemps.es/cima/dochtml/ft/68812/FT_68812.html Última consulta 12 de septiembre de 2023.

20. AEMPS. Productos Sanitarios Agencia Española de Medicamentos. *Ficha Técnica.* Ringer lactato. https://cima.aemps.es/cima/dochtml/ft/57281/FT_57281.html Última consulta 12 de septiembre de 2023.

21. AEMPS. Agencia Española de Medicamentos y Productos Sanitarios. *Ficha Técnica* Albúmina 20% https://cima.aemps.es/cima/dochtml/ft/71446/FT_71446.html Última consulta 12 de septiembre de 2023.

22. AEMPS. Agencia Española de Medicamentos y Productos Sanitarios. *Ficha Técnica*. Suero glucosado 5% https://cima.aemps.es/cima/dochtml/ft/39004/FT_39004.html Última visita 12 septiembre 2023.

23. AEMPS. Productos Sanitarios Agencia Española de Medicamentos. *Ficha Técnica* Dextrano 40 salino https://cima.aemps.es/cima/pdfs/es/ft/39627/39627_ft.pdf Última consulta 12 de septiembre de 2023.

24. Reddy S, Weinberg L, Young P. Crystalloid fluid therapy. *Crit Care*. Mar 15 2016;20:59 https://doi.org/10.1186/s13054-016-1217-5

25. AEMPS. Agencia Española de Medicamentos y Productos Sanitarios. *Ficha Técnica Solución Hartmann* https://cima.aemps.es/cima/dochtml/ft/39000/FT_39000.html Última consulta 12 de septiembre de 2023.

26. FDA. Labeling Changes on mortality, kidney injury, and excess bleeding with hydroxyethyl starch products. https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/labeling-changes-mortality-kidney-injury-and-excess-bleeding-hydroxyethyl-starch-products Consultado el 12 de septiembre de 2023. 2021.

27. Europea C. Decisión de ejecución de la Comisión de 24.5.2022 relativa a las autorizaciones de comercialización, en el marco del artículo 107 septdecies de la Directiva 2001/83/CE del Parlamento Europeo y del Consejo, de los medicamentos para uso humano que contienen la sustancia activa «hidroxietilalmidón (HEA), soluciones para perfusión», tras la evaluación de un estudio de seguridad posterior a la autorización. https://ec.europa.eu/health/documents/community-register/2022/20220524155341/dec_155341_es.pdf 2022.

28. AEMPS. Soluciones de hidroxietil-almidón: suspensión de comercialización en España el 15 de diciembre. https://www.aemps.gob.es/informa/soluciones-de-hidroxietil-almidon-suspension-de-comercializacion-en-espana-el-15-de-diciembre/ 2022.

29. NICE. National Institute for Health and Care Excellence (NICE) Surveillance report 2017 – Intravenous fluid therapy in adults in hospital (2013) NICE guideline CG174.

30. Holliday MA, Segar WE. The maintenance need for water in parenteral fluid therapy. *Pediatrics*. May 1957;19(5):823-32. https://www.nice.org.uk/guidance/cg174

31. Magder S. Volume and its relationship to cardiac output and venous return. *Crit Care*. Sep 10 2016;20(1):271. https://ccforum.biomedcentral.com/articles/10.1186/s13054-016-1438-7

32. Wo CC, Shoemaker WC, Appel PL, Bishop MH, Kram HB, Hardin E. Unreliability of blood pressure and heart rate to evaluate cardiac output in emergency resuscitation and critical illness. *Crit Care Med*. Feb 1993;21(2):218-23. https://doi.org/10.1097/00003246-199302000-00012

33. Rivers E, Nguyen B, Havstad S, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med*. Nov 8 2001;345(19):1368-77. https://doi.org/10.1056/NEJMoa010307

34. Messina A, Longhini F, Coppo C, et al. Use of the Fluid Challenge in Critically Ill Adult Patients: A Systematic Review. *Anesth Analg*. Nov 2017;125(5):1532-1543. https://doi.org/10.1213/ane.0000000000002103

35. Messina A, Calabrò L, Pugliese L, et al. Fluid challenge in critically ill patients receiving haemodynamic monitoring: a systematic review and comparison of two decades. *Crit Care*. Jun 21 2022;26(1):186. https://doi.org/10.1186/s13054-022-04056-3

36. National Clinical Guideline C. National Institute for Health and Care Excellence: Clinical Guidelines. *IV Fluids in Children: Intravenous Fluid Therapy in Children and Young People in Hospital*. National Institute for Health and Care Excellence (UK). Copyright © 2015 National Clinical Guideline Centre.; 2015. https://www.nice.org.uk/guidance/ng29

37. Cecconi M, De Backer D, Antonelli M, et al. Consensus on circulatory shock and hemodynamic monitoring. Task force of the European Society of Intensive Care Medicine. *Intensive Care Med*. Dec 2014;40(12):1795-815. https://doi.org/10.1007/s00134-014-3525-z

38. Messina A, Robba C, Calabrò L, et al. Association between perioperative fluid administration and postoperative outcomes: a 20-year systematic review and a meta-analysis of randomized goal-directed trials in major visceral/noncardiac surgery. *Crit Care*. Feb 1 2021;25(1):43. https://doi.org/10.1186/s13054-021-03464-1

39. Li X, Zhang Q, Zhu Y, et al. Effect of perioperative goal-directed fluid therapy on postoperative complications after thoracic surgery with one-lung ventilation: a systematic review and meta-analysis. *World J Surg Oncol*. Sep 18 2023;21(1):297. https://doi.org/10.1186/s12957-023-03169-5

40. Giglio M, Dalfino L, Puntillo F, Brienza N. Hemodynamic goal-directed therapy and postoperative kidney injury: an updated meta-analysis with trial sequential analysis. *Crit Care*. Jun 26 2019; 23 (1): 232. https://ccforum.biomedcentral.com/articles/10.1186/s13054-019-2516-4

41. Chong MA, Wang Y, Berbenetz NM, McConachie I. Does goal-directed haemodynamic and fluid therapy improve peri-operative outcomes?: A systematic review and meta-analysis. *Eur J Anaesthesiol*. Jul 2018; 35 (7): 469-483. https://doi.org/10.1097/eja.0000000000000778

42. Liu B, Ding X, Yang J. Effect of early goal directed therapy in the treatment of severe sepsis and/or septic shock. *Curr Med Res Opin*. Nov 2016;32(11):1773-1782. https://doi.org/10.1080/03007995.2016.1206872

43. Janssens U. [Early goal-directed therapy for septic shock : Systematic review and meta-analysis]. *Med Klin Intensivmed Notfmed*. Sep 2016;111(6):551-5. Frühe zielorientierte Therapie bei septischem Schock : Systematisches Review und Metaanalyse. https://doi.org/10.1007/s00063-015-0108-x

44. Mouncey PR, Osborn TM, Power GS, et al. Trial of early, goal-directed resuscitation for septic shock. *N Engl J Med*. Apr 2 2015;372(14):1301-11. https://doi.org/10.1056/NEJMoa1500896

45. Peake SL, Delaney A, Bailey M, et al. Goal-directed resuscitation for patients with early septic shock. *N Engl J Med*. Oct 16 2014;371(16):1496-506. https://doi.org/10.1056/NEJMoa1404380

46. Harris T, Coats TJ, Elwan MH. Fluid therapy in the emergency department: an expert practice review. *Emerg Med J*. Aug 2018; 35(8):511-515. https://doi.org/10.1136/emermed-2017-207245

47. Baxter CR, Shires T. Physiological response to crystalloid resuscitation of severe burns. *Ann N Y Acad Sci*. Aug 14 1968;150(3):874-94. https://doi.org/10.1111/j.1749-6632.1968.tb14738.x

48. Joannes-Boyau O, Roquilly A, Constantin JM, et al. Choice of fluid for critically ill patients: An overview of specific situations. *Anaesth Crit Care Pain Med*. Dec 2020;39(6):837-845. https://doi.org/10.1016/j.accpm.2020.10.003

49. Liamis G, Filippatos TD, Elisaf MS. Correction of hypovolemia with crystalloid fluids: Individualizing infusion therapy. *Postgrad Med*. May 2015;127(4):405-12. https://doi.org/10.1080/00325481.2015.1029421

50. Spasovski G, Vanholder R, Allolio B, et al. Clinical practice guideline on diagnosis and treatment of hyponatraemia. *Eur J Endocrinol*. Mar 2014;170(3):G1-47. https://doi.org/10.1530/eje-13-1020

51. Spasovski G, Vanholder R, Allolio B, et al. Clinical practice guideline on diagnosis and treatment of hyponatraemia. *Intensive Care Med*. Mar 2014;40(3):320-31. https://doi.org/10.1007/s00134-014-3210-2

52. Otterness K, Singer AJ, Thode HC, Peacock WF. Hyponatremia and hypernatremia in the emergency department: severity and outcomes. *Clin Exp Emerg Med*. Jan 30 2023; https://doi.org/10.15441/ceem.22.380

53. Hoorn EJ, Betjes MG, Weigel J, Zietse R. Hypernatraemia in critically ill patients: too little water and too much salt. *Nephrol Dial Transplant*. May 2008;23(5):1562-8. https://doi.org/10.1093/ndt/gfm831

54. Van Zyl DG, Rheeder P, Delport E. Fluid management in diabetic-acidosis-Ringer's lactate versus normal saline: a randomized controlled trial. *Qjm*. Apr 2012;105(4):337-43. https://doi.org/10.1093/qjmed/hcr226

55. Cieza JA, Hinostroza J, Huapaya JA, León CP. Sodium chloride 0.9% versus Lactated Ringer in the management of severely dehydrated patients with choleriform diarrhoea. *J Infect Dev Ctries*. Jul 15 2013;7(7):528-32. https://doi.org/10.3855/jidc.2531

56. Eisenhut M. Causes and effects of hyperchloremic acidosis. *Crit Care*. 2006: 413; author reply 413. vol. 3. https://ccforum.biomedcentral.com/articles/10.1186/cc4963

57. Krajewski ML, Raghunathan K, Paluszkiewicz SM, Schermer CR, Shaw AD. Meta-analysis of high- versus low-chloride content in perioperative and critical care fluid resuscitation. *Br J Surg*. Jan 2015;102(1):24-36. https://doi.org/10.1002/bjs.9651

58. Kawano-Dourado L, Zampieri FG, Azevedo LCP, et al. Low- Versus High-Chloride Content Intravenous Solutions for Critically Ill and Perioperative Adult Patients: A Systematic Review and Meta-analysis. *Anesth Analg*. Feb 2018;126(2):513-521. https://doi.org/10.1213/ane.0000000000002641

59. Zwager CL, Tuinman PR, de Grooth HJ, et al. Why physiology will continue to guide the choice between balanced crystalloids and normal saline: a systematic review and meta-analysis. *Crit Care*. Nov 21 2019;23(1):366. https://doi.org/10.1186/s13054-019-2658-4

60. Antequera Martín AM, Barea Mendoza JA, Muriel A, et al. Buffered solutions versus 0.9% saline for resuscitation in critically ill adults and children. *Cochrane Database Syst Rev*. Jul 19 2019;7(7):Cd012247. https://doi.org/10.1002/14651858.CD012247.pub2

61. Jackson CD, Patel SB, Haltom MB, et al. Choice of Intravenous Crystalloid Fluid and Mortality in Critically Ill Adult Patients. *South Med J*. Jul 2019;112(7):401-405. https://doi.org/10.14423/smj.0000000000000993

62. Liu C, Lu G, Wang D, et al. Balanced crystalloids versus normal saline for fluid resuscitation in critically ill patients: A systematic review and meta-analysis with trial sequential analysis. *Am J Emerg Med*. Nov 2019;37(11):2072-2078. https://doi.org/10.1016/j.ajem.2019.02.045

63. González-Castro A, Ortiz-Lasa M, Rodriguez-Borregan JC, et al. Meta-analysis of the effects of normal saline on mortality in intensive care. *Rev Esp Anestesiol Reanim (Engl Ed)*. Jan 2019;66(1):3-9. Metaanálisis de los efectos del suero salino en la mortalidad en cuidados intensivos. https://doi.org/10.1016/j.redar.2018.06.007

64. Hammond DA, Lam SW, Rech MA, et al. Balanced Crystalloids Versus Saline in Critically Ill Adults: A Systematic Review and Meta-analysis. *Ann Pharmacother*. Jan 2020;54(1):5-13. https://doi.org/10.1177/1060028019866420

65. Zhu Y, Guo N, Song M, et al. Balanced crystalloids versus saline in critically ill patients: The PRISMA study of a meta-analysis. *Medicine (Baltimore)*. Sep 24 2021;100(38):e27203. https://doi.org/10.1097/md.0000000000027203

66. Dong WH, Yan WQ, Song X, Zhou WQ, Chen Z. Fluid resuscitation with balanced crystalloids versus normal saline in critically ill patients: a systematic review and meta-analysis. *Scand J Trauma Resusc Emerg Med*. Apr 18 2022;30(1):28. https://doi.org/10.1186/s13049-022-01015-3

67. Groeneveld AB, Navickis RJ, Wilkes MM. Update on the comparative safety of colloids: a systematic review of clinical studies. *Ann Surg*. Mar 2011;253(3):470-83. https://doi.org/10.1097/SLA.0b013e318202ff00

68. Schierhout G, Roberts I. Fluid resuscitation with colloid or crystalloid solutions in critically ill patients: a systematic review of randomised trials. *Bmj*. Mar 28 1998;316(7136):961-4. https://doi.org/10.1136/bmj.316.7136.961

69. Reviewers. CIGA. Human albumin administration in critically ill patients: systematic review of randomised controlled trials. *Bmj*. Jul 25 1998;317(7153):235-40. https://doi.org/10.1136/bmj.317.7153.235

70. Roberts I, Alderson P, Bunn F, Chinnock P, Ker K, Schierhout G. Colloids versus crystalloids for fluid resuscitation in critically ill patients. *Cochrane Database Syst Rev*. Oct 18 2004;(4):Cd000567. https://doi.org/10.1002/14651858.CD000567.pub2

71. Roberts I, Blackhall K, Alderson P, Bunn F, Schierhout G. Human albumin solution for resuscitation and volume expansion in critically ill patients. *Cochrane Database Syst Rev*. Nov 9 2011; 2011 (11): Cd001208. https://doi.org/10.1002/14651858.CD001208.pub4

72. Perel P, Roberts I, Ker K. Colloids versus crystalloids for fluid resuscitation in critically ill patients. *Cochrane Database Syst Rev*. Feb 28 2013; (2): Cd000567. https://doi.org/10.1002/14651858.CD000567.pub6

73. Wang JW, Li JP, Song YL, et al. Hypertonic saline in the traumatic hypovolemic shock: meta-analysis. *J Surg Res*. Oct 2014;191(2):448-54. https://doi.org/10.1016/j.jss.2014.04.027

74. Wu MC, Liao TY, Lee EM, et al. Administration of Hypertonic Solutions for Hemorrhagic Shock: A Systematic Review and Meta-analysis of Clinical Trials. *Anesth Analg*. Nov 2017; 125 (5): 1549-1557. https://doi.org/10.1213/ane.0000000000002451

75. Safiejko K, Smereka J, Pruc M, et al. Efficacy and safety of hypertonic saline solutions fluid resuscitation on hypovolemic shock: A systematic review and meta-analysis of randomized controlled trials. *Cardiol J*. 2022; 29 (6): 966-977. https://doi.org/10.5603/CJ.a2020.0134

76. Martin GS, Bassett P. Crystalloids vs. colloids for fluid resuscitation in the Intensive Care Unit: A systematic review and meta-analysis. *J Crit Care*. Apr 2019; 50: 144-154. https://doi.org/10.1016/j.jcrc.2018.11.031

77. Vincent JL, Navickis RJ, Wilkes MM. Morbidity in hospitalized patients receiving human albumin: a meta-analysis of randomized, controlled trials. *Crit Care Med*. Oct 2004; 32 (10): 2029-38. https://doi.org/10.1097/01.ccm.0000142574.00425.e9

78. Wiedermann CJ, Dunzendorfer S, Gaioni LU, Zaraca F, Joannidis M. Hyperoncotic colloids and acute kidney injury: a meta-analysis of randomized trials. *Crit Care*. 2010;14(5):R191. https://doi.org/10.1186/cc9308

79. Moeller C, Fleischmann C, Thomas-Rueddel D, et al. How safe is gelatin? A systematic review and meta-analysis of gelatin-containing plasma expanders vs crystalloids and albumin. *J Crit Care*. Oct 2016;35:75-83. https://doi.org/10.1016/j.jcrc.2016.04.011

80. Rochwerg B, Alhazzani W, Sindi A, et al. Fluid resuscitation in sepsis: a systematic review and network meta-analysis. *Ann Intern Med*. Sep 2 2014; 161 (5): 347-55. https://doi.org/10.7326/m14-0178

81. Tseng CH, Chen TT, Wu MY, Chan MC, Shih MC, Tu YK. Resuscitation fluid types in sepsis, surgical, and trauma patients: a systematic review and sequential network meta-analyses. *Crit Care*. Dec 14 2020; 24 (1): 693. https://doi.org/10.1186/s13054-020-03419-y

82. Xu JY, Chen QH, Xie JF, et al. Comparison of the effects of albumin and crystalloid on mortality in adult patients with severe sepsis and septic shock: a meta-analysis of randomized clinical trials. *Crit Care*. Dec 15 2014;18(6):702. https://doi.org/10.1186/s13054-014-0702-y

83. Jiang L, Jiang S, Zhang M, Zheng Z, Ma Y. Albumin versus other fluids for fluid resuscitation in patients with sepsis: a meta-analysis. *PLoS One*. 2014; 9 (12): e114666. https://doi.org/10.1371/journal.pone.0114666

84. Qureshi SH, Rizvi SI, Patel NN, Murphy GJ. Meta-analysis of colloids versus crystalloids in critically ill, trauma and surgical patients. *Br J Surg*. Jan 2016; 103(1): 14-26. https://doi.org/10.1002/bjs.9943

85. Zou Y, Ma K, Xiong JB, Xi CH, Deng XJ. Comparison of the effects of albumin and crystalloid on mortality among patients with septic shock: systematic review with meta-analysis and trial sequential analysis. *Sao Paulo Med J*. Sep-Oct 2018; 136 (5): 421-432. https://doi.org/10.1590/1516-3180.2017.0285281017

86. Reinhart K, Perner A, Sprung CL, et al. Consensus statement of the ESICM task force on colloid volume therapy in critically ill patients. *Intensive Care Med*. Mar 2012; 38 (3): 368-83. https://doi.org/10.1007/s00134-012-2472-9

87. Rhodes A, Evans LE, Alhazzani W, et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. *Crit Care Med*. Mar 2017;45(3):486-552. https://doi.org/10.1097/ccm.0000000000002255

88. Huang PP, Stucky FS, Dimick AR, Treat RC, Bessey PQ, Rue LW. Hypertonic sodium resuscitation is associated with renal failure and death. *Ann Surg*. May 1995;221(5):543-54; discussion 554-7. https://doi.org/10.1097/00000658-199505000-00012

89. Kao Y, Loh EW, Hsu CC, et al. Fluid Resuscitation in Patients With Severe Burns: A Meta-analysis of Randomized Controlled Trials. *Acad Emerg Med*. Mar 2018; 25 (3): 320-329. https://doi.org/10.1111/acem.13333

90. Eljaiek R, Heylbroeck C, Dubois MJ. Albumin administration for fluid resuscitation in burn patients: A systematic review and meta-analysis. *Burns*. Feb 2017;43(1):17-24. https://doi.org/10.1016/j.burns.2016.08.001

91. Chaussard M, Dépret F, Saint-Aubin O, et al. Physiological response to fluid resuscitation with Ringer lactate versus Plasmalyte in critically ill burn patients. *J Appl Physiol (1985)*. Mar 1 2020; 128 (3): 709-714. https://doi.org/10.1152/japplphysiol.00859.2019

92. asistencial) MMdladlp. Informe. Uso de albúmina en distintas indicaciones. Vol. 1-Núm. 7 (2020) https://www.navarra.es/home_es/Temas/Portal+de+la+Salud/Profesionales/Documentacion+y+publicaciones/Publicaciones+tematicas/SIECI/Mapac/Informes/

93. ISBI Practice Guidelines for Burn Care, Part 2. *Burns*. Nov 2018; 44 (7): 1617-1706. https://doi.org/10.1016/j.burns.2018.09.012

94. de Crescenzo C, Gorouhi F, Salcedo ES, Galante JM. Prehospital hypertonic fluid resuscitation for trauma patients: A systematic review and meta-analysis. *J Trauma Acute Care Surg*. May 2017; 82 (5): 956-962. https://doi.org/10.1097/ta.0000000000001409

95. Blanchard IE, Ahmad A, Tang KL, et al. The effectiveness of prehospital hypertonic saline for hypotensive trauma patients: a systematic review and meta-analysis. *BMC Emerg Med*. Nov 28 2017;17(1):35. https://doi.org/10.1186/s12873-017-0146-1

96. Burdett E, Dushianthan A, Bennett-Guerrero E, et al. Perioperative buffered versus non-buffered fluid administration for surgery in adults. *Cochrane Database Syst Rev*. Dec 12 2012; 12: Cd004089. https://doi.org/10.1002/14651858.CD004089.pub2

97. Bampoe S, Odor PM, Dushianthan A, et al. Perioperative administration of buffered versus non-buffered crystalloid intravenous fluid to improve outcomes following adult surgical procedures. *Cochrane Database Syst Rev*. Sep 21 2017; 9 (9): Cd004089. https://doi.org/10.1002/14651858.CD004089.pub3

98. Huang L, Zhou X, Yu H. Balanced crystalloids vs 0.9% saline for adult patients undergoing non-renal surgery: A meta-analysis. *Int J Surg*. Mar 2018;51:1-9. https://doi.org/10.1016/j.ijsu.2018.01.003

99. Jewer JK, Wong MJ, Bird SJ, Habib AS, Parker R, George RB. Supplemental perioperative intravenous crystalloids for postoperative nausea and vomiting. *Cochrane Database Syst Rev*. Mar 29 2019; 3 (3): Cd012212. https://doi.org/10.1002/14651858.CD012212.pub2

100. Wrzosek A, Jakowicka-Wordliczek J, Zajaczkowska R, et al. Perioperative restrictive versus goal-directed fluid therapy for adults undergoing major non-cardiac surgery. *Cochrane Database Syst Rev*. Dec 12 2019; 12 (12): Cd012767. https://doi.org/10.1002/14651858.CD012767.pub2

101. National Institute for Health and Care Excellence: Guidelines. *Perioperative care in adults*. National Institute for Health and Care Excellence (NICE). Copyright © NICE 2020.; 2020. https://www.nice.org.uk/guidance/ng180

102. Ghijselings I, Himpe D, Rex S. Safety of gelatin solutions for the priming of cardiopulmonary bypass in cardiac surgery: a systematic review and meta-analysis. *Perfusion*. Jul 2017; 32 (5): 350-362. https://doi.org/10.1177/0267659116685418

103. Shao L, Hong F, Zou Y, Hao X, Hou H, Tian M. Hypertonic saline for brain relaxation and intracranial pressure in patients undergoing neurosurgical procedures: a meta-analysis of randomized controlled trials. *PLoS One*. 2015;10(1):e0117314. https://doi.org/10.1371/journal.pone.0117314

104. Berger-Pelleiter E, Émond M, Lauzier F, Shields JF, Turgeon AF. Hypertonic saline in severe traumatic brain injury: a systematic review and meta-analysis of randomized controlled trials. *Cjem*. Mar 2016;18(2):112-20. https://doi.org/10.1017/cem.2016.12

105. Gu J, Huang H, Huang Y, Sun H, Xu H. Hypertonic saline or mannitol for treating elevated intracranial pressure in traumatic brain injury: a meta-analysis of randomized controlled trials. *Neurosurg Rev*. Jun 2019;42(2):499-509. https://doi.org/10.1007/s10143-018-0991-8

106. Chen H, Song Z, Dennis JA. Hypertonic saline versus other intracranial pressure-lowering agents for people with acute traumatic brain injury. *Cochrane Database Syst Rev*. Jan 17 2020; 1 (1): Cd010904. https://doi.org/10.1002/14651858.CD010904.pub3

107. Hourmant Y, Huard D, Demeure Dit Latte D, et al. Effect of continuous infusion of hypertonic saline solution on survival of patients with brain injury: a systematic review and meta-analysis. *Anaesth Crit Care Pain Med*. Apr 2023;42(2):101177. https://doi.org/10.1016/j.accpm.2022.101177

108. Zhou S, Buitrago C, Foong A, et al. Comprehensive meta-analysis of randomized controlled trials of Lactated Ringer's versus Normal Saline for acute pancreatitis. *Pancreatology*. Dec 2021; 21 (8): 1405-1410. https://doi.org/10.1016/j.pan.2021.07.003

109. Aziz M, Ahmed Z, Weissman S, et al. Lactated Ringer's vs normal saline for acute pancreatitis: An updated systematic review and meta-analysis. *Pancreatology*. Oct 2021;21(7):1217-1223. https://doi.org/10.1016/j.pan.2021.06.002

110. Di Martino M, Van Laarhoven S, Ielpo B, et al. Systematic review and meta-analysis of fluid therapy protocols in acute pancreatitis: type, rate and route. *HPB (Oxford)*. Nov 2021; 23 (11): 1629-1638. https://doi.org/10.1016/j.hpb.2021.06.426

111. Vedantam S, Tehami N, de-Madaria E, Barkin JA, Amin S. Lactated Ringers Does Not Reduce SIRS in Acute Pancreatitis Compared to Normal Saline: An Updated Meta-Analysis. *Dig Dis Sci*. Jul 2022;67(7):3265-3274. https://doi.org/10.1007/s10620-021-07153-5

112. Wu D, Wan J, Xia L, Chen J, Zhu Y, Lu N. The Efficiency of Aggressive Hydration With Lactated Ringer Solution for the Prevention of Post-ERCP Pancreatitis: A Systematic Review and Meta-analysis. *J Clin Gastroenterol*. Sep 2017;51(8):e68-e76. https://doi.org/10.1097/mcg.0000000000000856

113. Zhang ZF, Duan ZJ, Wang LX, Zhao G, Deng WG. Aggressive Hydration With Lactated Ringer Solution in Prevention of Postendoscopic Retrograde Cholangiopancreatography Pancreatitis: A Meta-analysis of Randomized Controlled Trials. *J Clin Gastroenterol*. Mar 2017;51(3):e17-e26. https://doi.org/10.1097/mcg.0000000000000781

114. Wang RC, Jiang ZK, Xie YK, Chen JS. Aggressive hydration compared to standard hydration with lactated ringer's solution for prevention of post endoscopic retrograde cholangiopancreatography pancreatitis. *Surg Endosc*. Mar 2021; 35(3):1126-1137. https://doi.org/10.1007/s00464-020-07477-9

115. Wu F, She D, Ao Q, Zhang S, Li J. Aggressive intravenous hydration protocol of Lactated Ringer's solution benefits patients with mild acute pancreatitis: A meta-analysis of 5 randomized controlled trials. *Front Med (Lausanne)*. 2022;9:966824. https://doi.org/10.3389/fmed.2022.966824

116. Ramanan M, Attokaran A, Murray L, et al. Sodium chloride or Plasmalyte-148 evaluation in severe diabetic ketoacidosis (SCOPE-DKA): a cluster, crossover, randomized, controlled trial. *Intensive Care Med*. Nov 2021;47(11):1248-1257. https://doi.org/10.1007/s00134-021-06480-5

117. Attokaran AG, Ramanan M, Hunt L, et al. Sodium chloride or plasmalyte-148 for patients presenting to emergency departments with diabetic ketoacidosis: A nested cohort study within a multicentre, cluster, crossover, randomised, controlled trial. *Emerg Med Australas*. Aug 2023;35(4):657-663. https://doi.org/10.1111/1742-6723.14198

118. Catahay JA, Polintan ET, Casimiro M, et al. Balanced electrolyte solutions versus isotonic saline in adult patients with diabetic ketoacidosis: A systematic review and meta-analysis. *Heart Lung*. Jul-Aug 2022; 54: 74-79. https://doi.org/10.1016/j.hrtlng.2022.03.014

119. Gandhi S, Mosleh W, Myers RB. Hypertonic saline with furosemide for the treatment of acute congestive heart failure: a systematic review and meta-analysis. *Int J Cardiol*. May 1 2014;173(2):139-45. https://doi.org/10.1016/j.ijcard.2014.03.020

120. De Vecchis R, Esposito C, Ariano C, Cantatrione S. Hypertonic saline plus i.v. furosemide improve renal safety profile and clinical outcomes in acute decompensated heart failure: A meta-analysis of the literature. *Herz*. May 2015;40(3):423-35. https://doi.org/10.1007/s00059-013-4041-6

121. Liu C, Peng Z, Gao X, et al. Simultaneous Use of Hypertonic Saline and IV Furosemide for Fluid Overload: A Systematic Review and Meta-Analysis. *Crit Care Med*. Nov 1 2021; 49 (11): e1163-e1175. https://doi.org/10.1097/ccm.0000000000005174

122. Covic A, Copur S, Tapoi L, et al. Efficiency of Hypertonic Saline in the Management of Decompensated Heart Failure: A Systematic Review and Meta-Analysis of Clinical Studies. *Am J Cardiovasc Drugs*. May 2021; 21 (3): 331-347. https://doi.org/10.1007/s40256-020-00453-7

123. Visvanathan A, Dennis M, Whiteley W. Parenteral fluid regimens for improving functional outcome in people with acute stroke. *Cochrane Database Syst Rev*. Sep 1 2015; 2015 (9): Cd011138. https://doi.org/10.1002/14651858.CD011138.pub2

124. Uhlig C, Silva PL, Deckert S, Schmitt J, de Abreu MG. Albumin versus crystalloid solutions in patients with the acute respiratory distress syndrome: a systematic review and meta-analysis. *Crit Care*. Jan 9 2014; 18 (1): R10. https://doi.org/10.1186/cc13187

125. Osborn DA, Evans N. Early volume expansion for prevention of morbidity and mortality in very preterm infants. *Cochrane Database Syst Rev*. 2001; (4): Cd002055. https://doi.org/10.1002/14651858.cd002055

126. Dempsey EM, Barrington K. Crystalloid or colloid for partial exchange transfusion in neonatal polycythemia: a systematic review and meta-analysis. *Acta Paediatr*. Nov 2005; 94 (11): 1650-5. https://doi.org/10.1080/08035250500192748

127. Padua AP, Macaraya JR, Dans LF, Anacleto FE, Jr. Isotonic versus hypotonic saline solution for maintenance intravenous fluid therapy in children: a systematic review. *Pediatr Nephrol*. Jul 2015; 30 (7): 1163-72. https://doi.org/10.1007/s00467-014-3033-y

128. Grigsby A, Herron J, Hunter BR. Does the addition of dextrose to IV crystalloid therapy provide clinical benefit in acute dehydration? A systematic review and meta-analysis. *Cjem*. Sep 2019; 21 (5): 638-645. https://doi.org/10.1017/cem.2018.500

129. Yue J, Zheng R, Wei H, et al. Childhood Mortality After Fluid Bolus With Septic or Severe Infection Shock: A Systematic Review and Meta-Analysis. *Shock*. Aug 1 2021;56(2):158-166. https://doi.org/10.1097/shk.0000000000001657

130. Hamud AA, Mudawi K, Shamekh A, Kadri A, Powell C, Abdelgadir I. Diabetic ketoacidosis fluid management in children: systematic review and meta-analyses. *Arch Dis Child*. Nov 2022; 107 (11): 1023-1028. https://doi.org/10.1136/archdischild-2022-324042

131. Lehr AR, Rached-d'Astous S, Barrowman N, et al. Balanced Versus Unbalanced Fluid in Critically Ill Children: Systematic Review and Meta-Analysis. *Pediatr Crit Care Med*. Mar 1 2022; 23 (3): 181-191. https://doi.org/10.1097/pcc.0000000000002890

132. Florez ID, Sierra J, Pérez-Gaxiola G. Balanced crystalloid solutions versus 0.9% saline for treating acute diarrhoea and severe dehydration in children. *Cochrane Database Syst Rev*. May 17 2023; 5 (5): Cd013640. https://doi.org/10.1002/14651858.CD013640.pub2

133. Puri S, Bandyopadhyay A, Ashok V. Supplemental intraoperative crystalloids for pediatric postoperative nausea and vomiting-A systematic review and meta-analysis. *Paediatr Anaesth*. Jan 2023; 33 (1): 38-45. https://doi.org/10.1111/pan.14566

134. El Gkotmi N, Kosmeri C, Filippatos TD, Elisaf MS. Use of intravenous fluids/solutions: a narrative review. *Curr Med Res Opin*. Mar 2017;33(3):459-471. https://doi.org/10.1080/03007995.2016.1261819

135. Scheingraber S, Rehm M, Sehmisch C, Finsterer U. Rapid saline infusion produces hyperchloremic acidosis in patients undergoing gynecologic surgery. *Anesthesiology*. May 1999; 90 (5): 1265-70. https://doi.org/10.1097/00000542-199905000-00007

136. Chowdhury AH, Cox EF, Francis ST, Lobo DN. A randomized, controlled, double-blind crossover study on the effects of 2-L infusions of 0.9% saline and plasma-lyte® 148 on renal blood flow velocity and renal cortical tissue perfusion in healthy volunteers. *Ann Surg*. Jul 2012;256(1):18-24. https://doi.org/10.1097/SLA.0b013e318256be72

137. Orbegozo Cortés D, Rayo Bonor A, Vincent JL. Isotonic crystalloid solutions: a structured review of the literature. *Br J Anaesth*. Jun 2014; 112 (6): 968-81. https://doi.org/10.1093/bja/aeu047

138. Greenberg A, Verbalis JG, Amin AN, et al. Current treatment practice and outcomes. Report of the hyponatremia registry. *Kidney Int*. Jul 2015;88(1):167-77. https://doi.org/10.1038/ki.2015.4

139. Reddy S, Bailey M, Beasley R, et al. Effect of saline 0.9% or Plasma-Lyte 148 therapy on feeding intolerance in patients receiving nasogastric enteral nutrition. *Crit Care Resusc*. Sep 2016; 18 (3): 198-204. https://pubmed.ncbi.nlm.nih.gov/27604334/

140. Murney P. To mix or not to mix – compatibilities of parenteral drug solutions. 2008. p. 98-101. https://australianprescriber.tg.org.au/articles/to-mix-or-not-to-mix-compatibilities-of-parenteral-drug-solutions.html

141. AEMPS. Productos Sanitarios Agencia Española de Medicamentos. *Ficha Técnica.* Ringer lactato. https://cima.aemps.es/cima/dochtml/ft/57281/FT_57281.html Última consulta 12 de septiembre de 2023.

142. Barron ME, Wilkes MM, Navickis RJ. A systematic review of the comparative safety of colloids. *Arch Surg*. May 2004; 139 (5): 552-63. https://doi.org/10.1001/archsurg.139.5.552

143. Ständer S, Richter L, Osada N, Metze D. Hydroxyethyl starch-induced pruritus: clinical characteristics and influence of dose, molecular weight and substitution. *Acta Derm Venereol*. May 2014;94(3):282-7. https://doi.org/10.2340/00015555-1639

144. Myburgh JA, Finfer S, Bellomo R, et al. Hydroxyethyl starch or saline for fluid resuscitation in intensive care. *N Engl J Med*. Nov 15 2012; 367 (20): 1901-11. https://doi.org/10.1056/NEJMoa1209759

145. Guidet B, Martinet O, Boulain T, et al. Assessment of hemodynamic efficacy and safety of 6% hydroxyethylstarch 130/0.4 vs. 0.9% NaCl fluid replacement in patients with severe sepsis: the CRYSTMAS study. *Crit Care*. May 24 2012; 16(3): R94. https://doi.org/10.1186/cc11358

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