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## Choice of fluid for critically ill patients: An overview of specific situations

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### Introduction

Fluids are one of the most common medications used in the intensive care unit (ICU) and the operating theatre (OR). The optimal use of fluid involves optimal decision to administer fluids, optimal type and volume [1]. Under-resuscitation is associated with a risk of hypovolemia, low oxygen delivery, and organ failure. Indications and volume of fluids remain a matter of debate. Often perceived as routine intervention, administration of fluids without rigorous clinical decision and monitoring targets to adverse effects. Over-resuscitation is now being increasingly recognised as associated with poor outcome, a risk of fluid overload, compartment syndromes, and organ failure [2]. The growing interest in balanced solutions (i.e. fluid solutions with electrolyte composition closed to the plasma and not enriched in sodium chloride) has not only enabled refinement of the use of crystalloid solutions and their consequences on the acid-base status but also on patient-centred outcomes, such as the risk of acute kidney injury (AKI) or death [3]. Among colloids, the use of hydroxyethyl starches (HES) has been rather restricted after signals of harmful effects in ICU patients, particularly those with sepsis, and a higher risk of AKI and risk of death [4]. The results of the last study also clarify the use of colloids

in the perioperative setting with no benefits of HES use and a signal of higher AKI risk [5]. Finally, the use of the natural colloid—albumin—remains debatable, particularly for sepsis and burn patients [6,7]. In this review, we discuss the physiological and pathophysiological aspects of different types of fluids available, along with the most recent evidence of their impact on the outcome of both ICU and high-risk surgical patients in accordance with the underlying reason for fluid administration.

## **Septic patients**

Four major changes in fluid therapy practices for sepsis patients in the ICU have been observed over the previous decade: systematic monitoring to prevent fluid overload, suspension of synthetic colloids use, restriction of use of a chloride-rich solution, and the controversial use of albumin.

### **1. Deleterious effects of fluid overload**

Fluid therapy is the first line of symptomatic hemodynamic management during septic shock [8]. Approximately two-thirds of patients are fluid-responsive in the early phase of septic shock [9]. After fluid challenge, fluid infusion is indicated as long as cardiac output or stroke volume continue to improve [8–10]. Therefore, haemodynamic monitoring is of particular importance in detecting hypovolemia as well as in avoiding undue fluid administration. The absence of an increase (< 15%) in cardiac output (or surrogates) after a fluid bolus (250 to 500 mL over 10 to 30 minutes) must lead to a cessation of fluid infusion [10]. The mini-fluid challenge (100 mL over 1 minute) or the passive leg raising (PLR) test can help to rapidly and non-invasively (transthoracic echocardiography) evaluate fluid responsiveness while avoiding unnecessary volume expansion [11–14].

In large randomised controlled trials (RCTs), the total volume of fluids administered during the early phase (six hours) of septic shock was found to significantly decrease over time: from 6000 ml in 2001 [15] to 2000 mL in 2015 [16–19]. During the same period, the mortality of septic shock patients decreased from 30% to 25%, thereby suggesting that a mean volume of 2000 mL (30 mL/kg in adults) is sufficient for a majority of patients in the early phase of septic shock. In an RCT conducted in a developing country with reduced healthcare resources (no intensive care and no available haemodynamic monitoring device), the administration of 2000 mL (usual care) of crystalloids during the first six hours was associated with 33% mortality *versus* 48% in the protocol group, which received 3500 mL ( $p < 0.001$ ) [20]. The analysis of a large database suggests that the administration of over 5000 mL during the first ICU day is associated with increased mortality and higher costs [21]. Beyond the infused fluid volume, cumulative fluid balance is also of importance. A positive fluid balance on the third ICU day is associated with increased mortality, thereby indicating that fluid overload risk persists after the first ICU day, which indicates the requirement of strictly monitoring fluid administration after the early phase and being careful of every gram of sodium and chloride administered to the patient [22]. Recent cohort studies suggest that fluid infusion (30 mL/kg) is mainly effective when administered in the first two hours, particularly in the first 30 minutes of septic shock [9,23,24]. After the second hour of shock, the necessity of fluid infusion is probably a marker or refractory shock rather than relative hypovolaemia; therefore, it is associated with mortality [9].

In summary, fluid infusion is mainly effective in the first two hours of septic shock. A volume of 2000 mL (30 mL/kg) is generally efficient in restoring blood volume during sepsis. Beyond this threshold, careful monitoring is recommended to detect remaining fluid responder patients and avoid undue fluid infusion. During the first day of septic shock, fluid infusion must not exceed 5000 mL, and fluid balance must ideally remain below 10% of baseline body weight.

## **2. Synthetic colloids use in sepsis**

Theoretically, colloids offer a larger and longer volume expansion than crystalloids and could therefore lead to faster haemodynamic stabilisation. This assertion has not been confirmed by literature, and synthetic colloid use among ICU patients has dramatically decreased. Negative results and harmful side-effects, including AKI, reported in large RCTs published from 2008 to 2013, explain the decreased use of synthetic colloids. In the field of sepsis, the “6S” trial indicated an increased mortality associated with HES use, mainly mediated through AKI [25]. Conversely, in other large RCTs—such as CHEST [26] or CRYSTMAS trials [27]—the increased mortality associated with HES use was not observed and deleterious effects on renal function were unclear, both in septic and non-septic populations. One RCT had controversial results: the CRYSTAL study is the more recent (2013), a large RCT that compared synthetic colloids (both gelatins and HES) in 2857 ICU patients with acute circulatory failure [28]. In this study, over 50% of patients were in septic shock; the study indicated a non-significant difference of mortality at 28 days (primary objective) but a significant decrease in mortality at day 90 (secondary objective) in the colloid group. Despite these controversial results, meta-analysis failed to show any clinical superiority of synthetic colloids over isotonic crystalloids and some of these suggest potential renal damage associated with synthetic colloid use [29–32]. Therefore, several national and international guidelines recommend that synthetic colloids must not be used for sepsis patients, particularly HES [8,33,34]. Further, restricting HES use in sepsis and critically ill patients was also confirmed in 2014 by the European Medical Agency. A possible suspension of HES from the market is currently being studied by the European Medical Agency [4]. If such a suspension raises legitimate controversies, particularly in perioperative and emergency medicine [35,36], HES use is not recommended for sepsis or ICU patients.

Gelatins are the second class of synthetic colloids available for ICU patients. In the 20% of ICU patients who received synthetic colloids in 2014, gelatins have been used in half of the cases [37]. It could be postulated that, considering the potential side effects of HES during sepsis, gelatins could replace HES in this indication as they are less toxic. However, there is no evidence to support the use of gelatins during sepsis. All synthetic colloids (dextrans, colloids, HES) induce vacuolisation of epithelial tubular cells and subsequent kidney function impairment. Currently available literature does not support the use of gelatins during sepsis, particularly to replace HES [38–40].

In summary, HES are counter-indicated for resuscitation of patients with sepsis or those in septic shock, and no data are available to support the use of gelatins in this setting.

## **3. Crystalloids, chloride accumulation, and sepsis**

Historically, isotonic saline is the most widely used crystalloid solution for ICU patients. However, its use has dramatically decreased over the previous decade, from 70% (2007) to 30% (2014) of ICU patients requiring fluid therapy, due to an increasing amount of literature revealing the deleterious effects of chloride accumulation [41]. Chloride accumulation has been suggested from the early 1900s onwards [42]. In humans, the administration of 5000 ml of saline is associated with constant metabolic acidosis, low plasma bicarbonate, and high chloride plasma concentration, all of which are not observed with Lactate Ringer (LR) or Ringer acetate. Due to a chloride concentration of 154 mmol/L (*versus* 130 mmol/L in LR), saline induces a significant increase in plasma chloride. Crystalloids with low chloride concentration (close to plasma concentration) are called balanced solutions. Lactate ringer is the most widely used balanced solution [43]. According to the Stewart model, excess chloride induces strong ion gap reduction, thereby leading to metabolic acidosis with a normal anion gap. A large retrospective study (6730 patients) suggested that saline use was associated with greater hyperchloremia and higher mortality as compared with a balanced solution administered during septic shock [44]. Thus far, there are three RCTs that compare balanced crystalloids and saline. The SPLIT RCT trial revealed that in non-severe ICU patients, a mean saline volume of 2500 mL was not associated with excess mortality, renal impairment, or acidosis. This result suggests that 2000–2500 mL of saline infusion is a safe volume that does not expose a patient to hyperchloremic acidosis. Beyond 2500 mL of infused saline, if additional crystalloid infusion is mandatory, a balanced solution is preferred. In a large trial conducted among over 15,000 ICU patients, hyperchloremic acidosis was associated with a significant increase in deleterious renal effects, mortality, and the need for renal replacement therapy [45]. In a comparable study published by the same group conducted in over 15,000 non-ICU patients admitted to emergency, no effect on mortality or hospital length of stay was reported (principal objective); however, a significant increase on renal effects was demonstrated (secondary objective) [46]. Further, the plasma chloride concentration associated with chloride acidosis and related complications appears to be 107 to 110 mmol/L in these studies. In addition, a post-hoc analysis of the ICU patient study focusing on septic patients indicated higher mortality in patients treated with saline compared with those treated with balanced crystalloids [47].

In summary, hyperchloremic acidosis is a frequent and potentially severe complication associated with saline, particularly when the infused volume exceeds 2500 mL. Beyond this, the use of a balanced solution is preferable, particularly for septic patients. In addition, the monitoring of chloride concentration during fluid resuscitation with the objective of keeping it within physiological ranges appears pragmatic even if not directly demonstrated.

#### **4. Albumin therapy and sepsis**

Albumin has several theoretical physiological properties that are particularly interesting for septic patients, such as a plasma-expanding capacity, a microcirculatory perfusion improvement, and a protective effect on glycocalyx [48] with anti-oxidant and anti-inflammatory effects. The integrity of glycocalyx determines optimal microcirculation and vascular permeability. In experimental ischemia-reperfusion models, albumin prevents the loss of glycocalyx [49] and improves microcirculation [50]; however, its beneficial effect on humans remains debatable. In addition to these theoretical protective properties, albumin has long been studied for its

expanding features in septic patients. Indeed, theoretically, 20% albumin increases oncotic pressure and promotes an influx of water into the vascular space, the haemodynamic effect and duration depend on albumin ability to remain intravascular [48]. Thus, the efficacy and safety of albumin in the resuscitation of septic patients was assessed in a few large RCTs and several meta-analyses have also clarified its usefulness in such a clinical situation.

A first RCT, the double-blind SAFE study, showed that fluid replacement with 4% albumin or saline for intravascular-fluid resuscitation during a 28-day ICU stay did not change the outcomes among ICU patients on day 28 [51]. However, in the subgroup of patients with severe sepsis, the mortality rate was lower in the albumin group, even when albumin levels were above 25 g/L [52]. Ten years later, the multicentre ALBIOS study randomised 1818 patients with severe sepsis or septic shock to receive either crystalloids alone or crystalloids associated with 20% albumin [53]. Here again, both the safety and efficacy of the use of human albumin during sepsis were reported. The main findings were a significant improvement in haemodynamic variables but no difference in mortality at 28 days and 90 days, number of organ dysfunctions, duration of being in the ICU or length of hospital stay. However, a post-hoc analysis compared patients with septic shock and those without at the time of randomisation (1121 *versus* 660); authors reported a significant survival advantage for patients who received crystalloid *versus* 20% albumin (RR = 0.87; 95% CI, 0.77 to 0.99) [53]. In this study, 20% albumin administration was guided according to albuminaemia with a minimal target of 30 g/L, with a daily albumin administration until ICU discharge or 28 days after randomisation.

Several systematic reviews and meta-analysis also explored evidence to use albumin in fluid resuscitation for patients with sepsis or those in septic shock [54,55]. Conclusions are variable, but two of them included studies in which reliability has been questioned [54,55]. For the other two, in patients with sepsis and in comparison with crystalloids, albumin did not improve mortality at days 28 and 90 [56,57]. Interestingly, in subgroup analysis according to severity, for both meta-analyses, mortality was significantly decreased in the albumin group for patients with septic shock. Nonetheless, Jiang et al. reported a lack of robustness to show a 10% decrease in mortality [56].

Thus, according to the results of RCTs and meta-analysis, the latest international guidelines for management of sepsis and septic shock published by the Surviving Sepsis Campaign suggest *“using albumin in addition to crystalloids for initial resuscitation and subsequent intravascular volume replacement in patients with sepsis and septic shock when patients require substantial amount of crystalloids”*, as a weak recommendation, with low-quality evidence [8]. Although the definition of *“substantial amounts”* is not provided in the guidelines, albuminaemia could help to guide its use.

In summary, due to conflicting results, no recommendation can be made for the use of albumin in septic patients.

### **Patients with acute kidney injury**

Fluid volume in general and the type of fluid in particular have a significant impact on renal outcome for the patients, particularly those already having AKI. First, fluid overload has been reported as an independent risk factor of AKI in both septic and non-septic critically ill patients, particularly when fluid balance exceeds 10% of

baseline body weight [58–60]. Therefore, reasoned vascular filling must be performed, fairly extensively in the first few hours of septic shock but quickly based on the dynamic criteria of the need for filling in order to avoid excesses [61,62]. On the other hand, it is necessary to have a rather restrictive filling attitude in perioperative management without, however, falling into excess, as latest studies reveal that an excessively restrictive attitude can also lead to a higher risk of renal failure [63]. Once the problem of fluid volume has been resolved, it is important to know what type of fluid must be used to preserve renal function, particularly in patients with already existing AKI.

Let us eliminate from the basis the HES, which has been banned in the ICU for a few years after the decision of the European Medical Agency and the Federal Drug Agency to prohibit its use in light of large number of RCTs, revealing excess mortality or increased renal failure in patients treated with HES *versus* crystalloids [64,65]. This leaves crystalloids and albumin.

First, albumin has shown no particular deleterious effects on renal function [51,52]; although it does not appear to be recommended but it may be used for patients with hypoalbuminaemia associated with hypovolemia. Unlike synthetic colloids, no nephrotoxicity was reported in a large number of RCTs that explored fluid challenge with albumin. In contrast, among ICU patients, 20% albumin would significantly decrease the occurrence of AKI and death of patients with AKI [66]. Indeed, the optimisation of albuminaemia is likely to protect renal function with an anti-inflammatory and antioxidant effect and would reduce drug nephrotoxicity (e.g. aminoglycosides) [48].

Finally, for the choice of crystalloid, the pathophysiology of AKI must be taken into account to avoid inducing or aggravating renal impairment or metabolic disorders [67]. Indeed, AKI leads to metabolic acidosis—particularly due to hyperchloremia and hyponatremia—and causes a decrease in the strong ion difference (SID) as well as hyperphosphatemia associated with hyperkaliaemia due to a decrease in urinary excretion on the one hand, and an outflow of potassium from the cells as a result of acidosis on the other [68]. Thus, taking into account these elements, it is necessary to favour fluids that are low in chloride and high in sodium and, therefore, to use balanced fluids and avoid saline. The fear of administering balanced solutions to AKI patients with high potassium plasma concentrations due to their containing 4 or 5 mmol/L of potassium is not justified. Indeed, it is not possible to worsen hyperkaliaemia by administering a solution containing a chloride concentration lower than the plasma one. Moreover, studies have shown—particularly in kidney transplant patients—that saline increased kaliaemia more than LR [69].

Even in non-AKI patients, fluids with a high chloride content can potentially have negative effects on the kidneys, particularly through the vasoconstrictive effect of chloride on the afferent arterioles [70]. Thus, in healthy volunteers, hyperchloremia induced by 2000 mL saline infusion decreases renal blood flow as compared to Plasma-Lyte®, thereby suggesting a vascular mechanism for chloride-induced renal impairment [67,71]. Finally, although the first large studies comparing saline *versus* balanced crystalloids revealed contradictory results on the possible deleterious effect of chloride on renal function [72–74], the last two RCTs that involved over 15,000 patients each clearly showed a better renal outcome in patients receiving balanced crystalloids *versus* saline [45,75].

In summary, chloride-poor balanced fluids are preferred in critically ill patients who are at risk of developing an AKI as well as in patients who already have an AKI. HES are prohibited and albumin might be reserved for patients with severe hypoalbuminaemia (<20 g/L).

### **Burn patients**

Burn injury is associated with early and profound hypovolaemia due to the capillary leak syndrome followed by systemic inflammatory response syndrome with a subsequent hyperdynamic state [76,77]. Haemodynamic management has long been identified as a key factor impacting a burn patient's outcome. Further, under and/or late fluid overload has been associated with an increased risk of death and organ failures [78]. Burn patients require a large quantity of crystalloids. Historically, balanced solutions (i.e. LR or Hartmann solutions) have been used due to the risk of hypernatremia and hyperchloremia with the use of saline. Other balanced solutions were scarcely explored in this population. On the other hand, the use of large amounts of crystalloid infusion also exposed the patient to the risk of organ failure (i.e. pulmonary oedema, AKI, and intra-abdominal hypertension), which negatively impacts the outcome. While various formulae (e.g. the Parkland formula) have been proposed to predict the amount of fluid to be administered, a general consensus is now to tailor fluid needs based on haemodynamic monitoring, avoiding both under- and over-resuscitation [79].

Further, the use of albumin during the first 24 hours of burn resuscitation is controversial. In a meta-analysis, the use of albumin in the first 24 hours was not associated with increased survival in severely burned patients. Nonetheless, significant statistical heterogeneity was present and after the exclusion of two studies at high risk of bias, albumin infusion was associated with reduced mortality (odds ratio (CI95%) = 0.34 (0.19–0.58) ( $p < 0.001$ )) and with decreased occurrence of the compartment syndrome (pooled odds ratio (CI 95%) = 0.19 (0.07–0.50) ( $p < 0.001$ )) [80]. In a multi-centre non-blinded controlled trial in patients with a total body surface area > 20%, Cooper et al. observed no significant difference in organ failures between the group receiving 5% albumin and the control group [81]. In a before-after study, Park et al. observed that the use of 5% albumin in the first 24 hours (*versus* LR and a synthetic colloid) was associated with lower mortality, lower use of vasopressors, lower duration of mechanical ventilation, and lower ventilator-associated pneumonia incidence [82]. In a retrospective observational study, Lawrence et al. observed that 5% albumin administration was associated with a reduction in crystalloid requirements [76–78,83]. However, albumin remains widely used among burn specialists [84]. There is a need for adequately powered, multi-centre randomised controlled trials to address the question of albumin administration on difficult outcomes in burn patients.

In summary, albumin could be used for fluid resuscitation in severe burn patients (> 30% of total cutaneous surface) after the sixth hour.

### **Trauma patients**

Haemorrhagic shock is the main cause of early death in trauma patients. Restricted volume replacement during initial trauma resuscitation is feasible and may prove efficient in terms of both morbidity (e.g. duration of hospital stay) and survival [85,86]. Based on these observations, the European guidelines for the management

of major bleeding and coagulopathy following trauma have recently strongly recommended to limit volume replacement during initial trauma resuscitation [87].

It is also important to consider the choice of fluid for resuscitation. Since the vascular endothelium is supposed to remain intact in trauma patients, colloids have long been the fluids of choice for the treatment of haemorrhagic shock. Notably, an exploratory study of trauma patients monitored with pulmonary artery catheter confirmed that colloids increased volaemia and cardiac output more significantly than crystalloids [88]. However, in the RCTs comparing colloids and crystalloids, the subgroup analyses of trauma patients did not reveal any reduction of patient outcomes, including 28-day or 90-day mortality [28] or transfusion requirements [89]. Thus, isotonic crystalloid solutions rather than colloids are recommended for the initial resuscitation of bleeding trauma patients [87]. Among crystalloid solutions, the respective roles of balanced solutions and saline is yet controversial for the resuscitation of haemorrhagic shock. In an RCT on adult trauma patients who required blood transfusion within 60 min of arrival, infusion of Plasma-Lyte® yielded better acid-base status and less hyperchloremia 24 hours after injury as compared to resuscitation with saline [90]. Taking into account all these results, the use of balanced solutions is promising for the resuscitation of trauma patients; however, the impact on outcomes has not yet been thoroughly investigated [91].

Favourable hemodynamic effects of colloids, notably HES, can be important in the most severe haemorrhagic shocks. The safety concern with the use of HES in septic shock is probably lower for trauma patients. Indeed, the use of HES was not associated with renal effects or clinically significant coagulopathy in trauma patients. The debate regarding intravascular volume expansion with hypertonic saline has not been concluded yet. In an RCT, patients allocated to hypertonic solutions (NaCl 3% or 7.5%) received approximately half the amount of fluids than those who received LR within the first hour of resuscitation, but this difference disappeared within 24 h. Moreover, side effects (e.g. arrhythmia, hypernatremia) were more common in patients who received 7.5% hypertonic saline. However, clinicians must be aware that trauma patient outcomes are not improved by the use of colloids or hypertonic solution [92].

In summary, crystalloids are recommended for first-line use in trauma patients who require fluid resuscitation. The role of HES appears marginal and future studies are required to determine the effectiveness of the use of hypertonic solutions.

### **Brain injury patients**

Fluid resuscitation is an integral part of the management of patients with brain injuries—traumatic brain injury (TBI), subarachnoid haemorrhage (SAH), arterial ischemic stroke (AIS), and intracerebral haemorrhage (ICH). The choice of fluid influences osmolarity and oncotic pressure, which has a direct impact on the brain. The type of fluid is of major importance in three cases: 1/ general fluid management, 2/ hyperosmolar fluid to prevent or treat intracranial hypertension, and 3/ fluid therapy for prevention or treatment of delayed cerebral ischemia (DCI) [93]. Here, we intend to address the issues that arise for general fluid management.

For general fluid maintenance in brain-injured patients, glucose-containing hypotonic solutions or other

hypotonic solutions (osmolality < 290 mOsm/L) must be avoided, at least in the acute phase, because of the effect of hyponatremia and hypo-osmolality on cerebral swelling. Data from the Prospective Observational Multicentre Major Trauma transfusion (PROMMTT) study of patients who received pre-hospital LR or saline were analysed [94]. Patients with TBI (n = 308) and who received LR had higher adjusted mortality than patients who received saline (hazard ratio [HR] 1.78, confidence interval [CI] 1.04-3.04,  $p = 0.035$ ).

Hyperchloremia and its possible side effects are a subject of debate [73,74], and clinicians may legitimately ask whether it is better to select saline or balanced solutions for patients with brain injury. However, existing literature only provides low-quality evidence. For TBI patients, a double-blind RCT (n = 41) reported that, compared to saline, balanced crystalloids reduced hyperchloremic acidosis without worsening intracranial pressure [95]. For patients with SAH, an RCT (n = 36) compared the use of saline to balanced crystalloid (Isofundine®) in the first 48 h after injury [96]. Both studies reported an increase in hyperchloremia, hyperosmolality, and positive fluid balance (> 1500 mL) with saline. The use of balanced crystalloids did not lead to increased hyponatremia or hypo-osmolality. However, because neither neurologic outcomes nor mortality have been tested in a large cohort, it remains difficult to provide recommendations. It is reasonable to recommend the use of first-line saline in patients with brain injury, but balanced crystalloids must be used in cases that require large fluid administration. It must be noted that in the two existing studies, HES was used for both patient groups. As reported above, for the last five years, regulatory authorities in the US and EU have limited the use of HES in septic, burn, or critically ill patients. Few studies have compared colloids with saline for patients with brain injury. A retrospective study in patients with SAH (n = 276) compared patients who received HES 6% and/or HES 10% with patients who received only saline [97]. No association was found between the incidence of AKI and HES. Using propensity scores, in patients with SAH (n = 123), the administration of colloids (plasma, dextran, starch, and/or albumin) and a positive fluid balance were associated with worse NIHSS and modified Rankin scales [98], without impact on DCI. Moreover, another study that pooled data on patients with SAH from two RCTs revealed an association between higher cumulative daily doses (4% succinylated gelatine or 6% pentastarch) and worse results on the six-month Glasgow Outcome Scale (GOS) (adjusted OR 2.53 (95% CI 1.13–5.68)). However, higher cumulative daily doses of saline were associated with better GOS (adjusted OR 0.27 (95% CI 0.11-0.67)). Associations between colloid and saline with GOS at six months were also dose-related [99]. Unfortunately, there have been only a few investigations of colloid infusion in TBI. Indeed, only one retrospective study that used a multivariate model to investigate severe TBI patients (n = 171) reported no association between cumulative pentastarch exposure and mortality [100]. Consequently, it is currently difficult to use colloids in patients with brain injury, either for fluid maintenance or for fluid resuscitation. Other studies have compared the use of albumin, a natural colloid, with the use of saline in patients with AIS, TBI, and SAH; in addition, experimental studies have reported encouraging results with the use of 25% albumin in patients with AIS. A randomised multi-centre efficacy trial (Albumin in Acute Stroke (ALIAS)) found no significant difference in the 90-day favourable outcome between patients with AIS who were administered 25% albumin and those who were administered saline within 5 hours (albumin, 44.1%; saline, 44.2%; risk ratio 0.96; 95% CI 0.84–1.10 with adjustment for baseline NIHSS score and thrombolysis stratum) [101]. The pilot trial of this prospective single-centre observational study in patients with AIS (n = 82) reported

better patient outcomes (modified Rankin Scale or NIHSS) at three months with high-dose albumin compared with lower doses (RR 1.81; 95% CI 1.11-2.94) [102]. The subgroup analysis of the SAFE study for TBI patients who underwent fluid resuscitation found higher mortality rates at 24 months when 4% albumin was used than when saline was used (33.2% vs. 20.4%) (RR 1.63; 95% CI, 1.17 to 2.26;  $p = 0.003$ ) [103]. Moreover, this result was more pronounced for patients with severe TBI (mortality rate: 41.8% vs. 22.2%, RR 1.88; 95% CI 1.31–2.70;  $p < 0.001$ ) than for patients with moderate TBI (16% vs. 21.6%, RR 0.74; 95% CI 0.31–1.79;  $p = 0.50$ ). A study that employed propensity scores to test whether hypervolemia and hypertension (catecholamine and/or albumin administration) during the DCI period would be associated with outcomes ( $n = 5400$ ) found that hypervolemia therapy (increased normalized fluid volume) and albumin administration during the DCI period were associated with a lower mortality rate and better awareness at discharge [104]. Finally, a small retrospective study reported that patients with SAH who received albumin ( $n = 37$ ) had better GOS scores at three months as compared to patients who received saline [105]. Thus, albumin must be avoided in TBI patients and cannot be recommended in other patients with brain injury because the evidence of a beneficial effect is limited.

Further, in patients with brain injury, the infusion of hypertonic fluids for fluid resuscitation is appealing because it restores cerebral perfusion, decreases cerebral oedema, and modulates inflammatory response. In the comparison of saline and LR solutions, all studies that included patients with TBI found no significant difference in mortality at 6 months, 30 days or GOS at 6 months, 30 days or at hospital discharge [106–108]. However, strategies of continuous infusion of hypertonic saline solutions, which induce sustained hyperosmolarity, have been associated with a lower risk of intracranial hypertension and a reduction of in-ICU mortality (OR 1.42, 95%CI 1.04–1.95,  $p = 0.03$ ) [109].

In summary, a multi-modal approach must be employed to optimize fluid therapy in patients with brain injury; however, hypo-osmolar therapy must be avoided.

### **Brain death and organ donors**

Brain-dead patients frequently exhibit arterial hypotension caused by the association of decreased sympathetic tone and hypovolemia. The latter results from diabetes insipidus, leading to massive losses of fluids and electrolytes. The management of heart-beating brain-dead organ donors follows guidelines that aim to optimize the quality of harvested organs. These guidelines recommend the use of crystalloids and colloids to treat hypovolemia [110]. HES represent the only colloids evaluated in this indication. Cittanova et al. reported that the use of an “old” HES (Elohes®), compared with gelatin, was associated with a worse renal function after kidney transplantation [111]. However, the long-term follow-up of these patients did not find any difference between HES and Gelatin [112]. Subsequently, several authors have reported conflicting results. This discrepancy could be explained by the use of a “modern” HES with a smaller molecular weight or smaller volumes of colloids [113,114]. The negative effects of HES on delayed graft function appeared to be associated with a volume higher than 1500 mL [114]. Currently, the debate on the use of HES in the context of organ donation seems out-of-date.

With regard to the type of crystalloids, the current debate is the choice of saline vs. balanced solutions. This debate cannot be applied to the context of brain-dead organ donor management, as no study has compared them in this context. However, a study evaluated the association of hyperchloremia (a frequent side effect of saline) on patient outcome after kidney transplantation [115] and found that the function of grafted kidneys did not differ between hyperchloremic and normochloremic donors.

In summary, the fluid management of brain-dead patients must be based on crystalloid infusion. In addition, owing to the lack of studies that compared different crystalloids, saline or balanced solutions can be used indifferently.

### **Paediatric patients**

Problems related to differences in volume expansion efficiency, the adverse effects of various solutions, and the role of balanced solutions are also the subject of various controversies in paediatrics, based on a much less extensive literature than that related to adults. The key messages remain the need to monitor and individualise fluid therapy. Fluid overload is associated with an increased morbidity and mortality in paediatrics [116]. Infancy and early childhood are characterised by heterogeneous haemodynamic profiles with important physiological features that are known to optimise hemodynamic parameters—increased sensitivity to water loss, limited blood volume, different thoraco-pulmonary and vascular compliances—as compared to adults. The years of middle childhood are probably similar to adolescence and early adulthood, although this population is rarely studied in adult literature. Maintaining optimal blood volume is one of the priority objectives in paediatric intensive care, where blood volume variations can be significant and frequent but occasionally underestimated. It is essential to select those children who will actually benefit from volume expansion before prescribing it. Thus, it is recommended, as in adults, to use predictive tests to evaluate the expected response to fluid therapy [117]. Only dynamic tests take advantage of heart-lung interactions and can reversibly vary ventricular loading conditions and detect a cardiac output improvement. However, even if they are less well-validated in children, predictive performance during fluid therapy of the respiratory variability of the systolic ejection volume or these derivatives (like aortic velocity peak) can be retained under certain controlled ventilation settings [118].

The current availability of numerous synthetic colloids reflects the challenge of specifying their respective indications, particularly since there is little data available for children, and the choice of solutions is based more on experience and concepts. Therefore, it appears interesting to consider the physiological features and solutions available to identify a strategy in accordance with specific clinical situations. Overall, it appears that the indications for albumin are gradually decreasing. A recent meta-analysis that includes paediatric studies does not suggest that it is superior to other solutions [92]. The American College of Critical Care Medicine (ACCM) recommends that saline or 5% albumin is preferred (in accordance with the results of the various meta-analyses) [118]. With regard to HES, the European Medical Agency has decided to contraindicate their use in paediatric intensive care despite the absence of studies on their renal or haematological toxicity compared with other fluid resuscitation. Nevertheless, a meta-analysis performed in the context of the OR did

not find an increased risk of renal or haematological toxicity with HES in children [119]. Synthetic colloids used in a rational manner, by limiting their dosage and targeting their indication, could find their place. Saline remains the most commonly used crystalloid and is recommended as a first-line solution in paediatric ICU patients. The use of balanced crystalloids, as opposed to saline, would limit the occurrence of hyperchloraemic acidosis. An increasing amount of literature suggests the deleterious effects of chloride accumulation [120]. However, the beneficial effect of balanced crystalloids has yet to be demonstrated in paediatrics [121].

In summary, it is important to distinguish the fluid replacement during the early phase of initial care from the fluid therapy during the ICU stay. Fluid infusion must be titrated from 5 to 10 mL/kg, carefully monitored for detecting remaining fluid responder patients. However, several controversies remain with regard to the modalities of fluid therapy in paediatric ICU patients. Nevertheless, it is essential to develop a fluid replacement strategy by considering the indications and the pathology as well as the available solutions, taking into account their possible adverse effects.

### **Conclusion**

Both hypovolaemia and overfilling are deleterious to critically ill patients and, therefore, vascular filling must be reasoned and supported by clinical and biological data as well as by dynamic criteria for fluid responsiveness and accurate haemodynamic monitoring. The choice of fluid is highly dependent on the clinical situation of the patient; however, overall, balanced crystalloids must be the first-line fluid of choice rather than saline except in specific situations (e.g. hypochloraemic alkalosis and brain injury), where HES are prohibited and albumin remains indicated for patients with proven severe hypoalbuminaemia.

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