The value of volume substitution in patients with septic and haemorrhagic shock with respect to the microcirculation

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Summary

After decades of ordinary scientific interest, fluid resuscitation of patients with septic and haemorrhagic shock took centre stage in intensive care research at the turn of the millennium. By that time, resuscitation fluids were the mainstay of haemodynamic stabilisation, avoidance of vasopressors and treatment of hypovolaemia in patients in shock, but were accompanied by adverse events such as excessive tissue oedema. With the spread of early goal-directed therapy research intensified and it was realised that type, volume and timing of resuscitation fluids might affect the course and outcome of critically ill patients. At the same time, the importance of microvascular blood flow as target of resuscitation was accepted.

Today, once-forbidden albumin is the recommended colloid in severe sepsis and septic shock, and the European Medical Agency is considering the removal of starch solutions from the European market because of an increased incidence of acute kidney injury and mortality. This is unprecedented, especially because the administration of low-molecular-weight starches seems to have advantages in indications other than sepsis, and because practices in fluid resuscitation have changed fundamentally since the negative starch studies. Crystalloids are still the mainstay of hypovolaemia treatment in critically ill patients, but awareness is increasing that electrolyte composition, strong ion gap, tonicity and the bicarbonate-substituting anion may have an effect on adverse effects and outcome. In haemorrhagic shock, the utilisation of crystalloids and colloids is retreating, and plasma and erythrocyte concentrates are gaining more importance in the resuscitation of the patient with acute bleeding. However, there are still influential voices warning against the liberal usage of plasma concentrates and erythrocytes in trauma and haemorrhagic shock.

This review describes the evidence relating to fluid resuscitation in sepsis, septic shock and massive haemorrhage. Beside the scientific evidence based on clinical trials, possible effects on the microcirculation and, therefore, organ function will be illustrated and areas of future research highlighted. The critical appraisal of the existing evidence should enable the reader to choose the optimal volume substitution for an individual patient.

Keywords: *shock, septic haemorrhagic shock, serum albumin microcirculation, physiopathology, hydroxyethyl starch, balanced crystalloids*

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Introduction

Hypovolaemia is an essential part of virtually all types of shock, sometimes even in cardiogenic shock. In haemorrhagic and hypovolaemic shock, an absolute volume deficit exists owing to absolute blood or fluid loss, whereas in septic and anaphylactic shock vasodilatation and extravasation of fluid cause relative hypovolaemia. Both relative and absolute hypovolaemia lead to decreased vascular filling and wall tension, and cardiac output [1]. The reduced cardiac output attenuates microvascular organ blood-flow, resulting in tissue hypoxia, anaerobic metabolism and acidosis [2]. Rapid fluid resuscitation is, therefore, a mainstay of the treatment of this common pathway of shock. In this respect, an ideal resuscitation fluid should normalise intravascular and cardiac filling and improve microvascular blood flow without propagating capillary permeability and impairing endothelial integrity [3].

Erythrocyte and plasma concentrates, colloids and crystalloids all normalise intravascular and cardiac filling to a greater or lesser extent and according to the timing of administration [4]. The effects of resuscitation fluid on the microcirculation of organs are critical for the volume expanding effect under different pathological conditions [3]. Under physiological conditions, fluid shift out of capillaries is a tightly regulated mechanism that depends upon endothelial cells, endothelial cell junctions and the endothelial glycocalyx [5]. The endothelial glycocalyx is a luminal network of membranous glycoproteins and proteoglycans of vessel-proportional thickness [6]. Under physiological conditions, the space between endothelial glycocalyx and endothelial cells is free of proteins and blood cells, preventing the escape of large amounts of plasma protein-containing fluid. Organ-specific gaps within the endothelial cell junctions constitute the pathways for trans-vascular fluid and protein exchange [7]. The classic Starling prin-

ciple assumes that hydrostatic pressure promotes leakage whereas oncotic pressure promotes the reabsorption of fluid along the length of microvascular blood vessels. The so-called revised Starling equation additionally considers the endothelial glycocalyx, stating that an intact glycocalyx prevents protein extravasation into the interstitial space independent of capillary pressure, and that the low oncotic pressure between glycocalyx and endothelial cells determines fluid exchange [7]. This implies that an increased plasma oncotic pressure will not promote reabsorption of interstitial fluid but rather counteract fluid extravasation, and that lymphatic vessels clear all interstitial fluids back into the venous system via the thoracic duct.

High venous pressure, therefore, increases oedema in two ways; on one hand, high venous outflow pressure transmits to intracapillary pressure promoting fluid extravasation and on the other side, a high central venous pressure hinders thoracic duct lymphatic drainage.

The microcirculatory blood flow provides oxygenation and nutrition to, and removes metabolic products from, the organs. In sepsis and haemorrhagic shock, the integrity of the microcirculation is severely abnormal due to the existing hypovolaemia, dysfunctional vascular tone, activated coagulation, increased leucocyte adherence and activation [8], and shedding of the glycocalyx. In 2002, de Backer and colleagues showed that the microcirculation in septic patients is severely disturbed and that nonsurvivors had less perfused small vessels than survivors [9]. The same group showed in a subsequent study that the microcirculation in nonsurvivors of septic shock did not improve, despite resolution of the clinical signs of shock [10]. The administration of fluid in shock states improves microvascular perfusion and increases capillary pressure (fig. 1). Unfortunately, the endothelial glycocalyx is disrupted by lipopolysaccharides [11] and other inflammatory conditions such as trauma [12] and ischaemia reperfusion [13], as a result of oxidative stress [4]. At the same time, sepsis increases endothelial permeability by a disassembling of intercellular junctions, promoting the extravasation of smaller proteins such as albumin [14, 15]. Finally, the inadequate administration of bolus fluid and hence hypervolaemia increase the level of atrial natriuretic peptide, causing enhanced shedding of the glycocalyx and alteration of the microcirculation [16]. This leaves a narrow path in fluid resuscitation of septic and haemorrhagic shock, with the recovery of microvascular flow by optimal capillary filling on the one hand and the exacerbation of fluid extravasation and tissue oedema by volume overloading on the other hand. Fluid extravasation and oedema alone may lead to pulmonary oedema [17], or abdominal compartment syndrome [18], and contribute to acute kidney injury (AKI) [19].

The objective of this review article is to discuss commonly used resuscitation fluids, to present the scientific evidence related to volume resuscitation in septic and haemorrhagic shock and to classify the different findings with respect to impact on the microcirculation.

Fluid replacement in septic patients

In 2001, the landmark paper of Rivers et al. [20] started a new approach to volume resuscitation in septic patients and intensive care medicine in general. In this single-centre randomised controlled trial, early goal-directed therapy entailing fluid resuscitation (according to central venous and mean arterial pressure), transfusions and inotropic support during the first 6 hours of therapy improved 30-day survival by 16%. Surprisingly, not much weight was given to the 24% increase in the numbers of patients receiving blood transfusions to improve central venous saturation with early goal-directed therapy, although the total amount of fluid was equal after 3 days. Because in this study the types of fluid used for early goal-directed therapy were not specified and there was a sceptical attitude to erythrocyte transfusions in intensive care in general [21], a decade of intense research to find the optimal volume of replacement fluid began. Although the concept of early goal-directed therapy has since been abandoned because its mortality benefit could not be confirmed in three large randomised trials [22–24] and two meta-analysis [25, 26], the search for the best type, volume and time of resuscitation fluid is still ongoing (table 1).

Recommendations for the application of resuscitation fluids in different types of shock are summarised in table 2.

Figure 1: Changes of the microcirculation under the tongue of a patient in shock with incident dark field (IDF) imaging (CytoCam-IDF, Braedius Medical, Huizen, The Netherlands). Panel A shows the normal microcirculation with normal flow in capillaries and venules. Panel B illustrates the different microcirculatory flow patterns during shock. Very few normally perfused (green lines) next to intermittently perfused (orange lines) vessels. Almost half of the vessels show no-flow (red lines), meaning that the blood cells do not move. Fluid resuscitation of shock aims to improve or normalise microvascular blood flow.
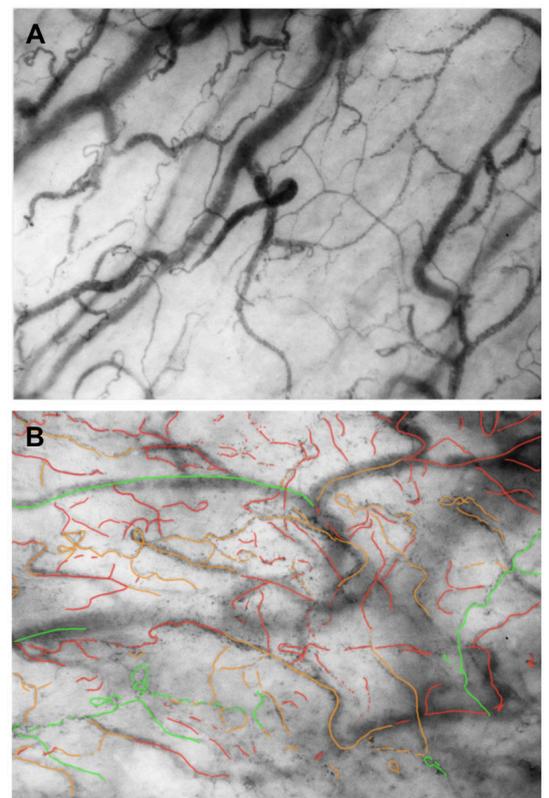
Albumin

At a first glance, albumin seems to be the ideal reference colloid. This small endogenous protein, synthesised in the liver, has antioxidant properties, transports electrolytes, drugs and hormones/cytokines, provides 80% of the plasma oncotic pressure and interacts with the endothelial glycocalyx [27]. Albumin continuously leaks into the interstitial space, where 40% of total body albumin is located, and is brought back to the circulation by lymphatic return. The normal plasma escape rate of albumin is 5% per hour, increases by at least 200% in patients with septic shock and returns to baseline after 2 days [28]. This is an obvious disadvantage of albumin administration in the very early phase of septic shock when capillary leak is substantial.

However, the latest guidelines from the Surviving Sepsis Campaign recommend albumin for fluid resuscitation in sepsis and septic shock patients who require substantial amounts of crystalloids (weak recommendation) [29]. The American College of Critical Care Medicine recommended 20 ml/kg fluid boluses of either isotonic crystalloids or 5% albumin (level 1C) for early fluid resuscitation in children and neonates with septic shock [30].

Following a Cochrane Review conducted in 1998 that suggested increased mortality associated with albumin use in critically ill patients [31], albumin infusion underwent a period of nearly total avoidance in intensive care. The albumin tide was turning in 2006 when a large blinded randomised controlled trial in almost 7000 patients compared

Table 1: Advantages and risks of preparations for volume resuscitation in septic and haemorrhagic shock.

	Molecular weight (kDa)	Osmolarity (mosm/l)	Chloride (mmol/l)	Advantages	Risks	Volume effect
Albumin	66	291	140	Human protein Transport capacities for proteins and drugs Antioxidant potential	Hyperoncotic preparations may increase risk for AKI Increased bleeding and mortality in haemorrhagic shock	Rapid microcirculatory plasma escape rate in septic shock
Modern semi-synthetic colloids	130	297-308	110–118	Improve micro-vascular blood flow Anti-inflammatory	In high doses increased risk of mortality Increased risk of AKI and renal replacement therapy Itching and rash	Volume effect longer than duration of infusion
Gelatines	30	284	103–120		Allergic reactions Increased risk of AKI and renal replacement therapy Insufficient data for mortality risk	Rapid degradation and temporary volume effect
Sodium chloride ("normal saline")		308	154	High osmolarity	Hyperchloraemic acidosis Decreased renal blood flow Rapid emergence of tissue oedema	Volume effect only during infusion
Balanced crystalloid solutions		273–294	98–112	Inert Comparable electrolyte composition to plasma	Rapid emergence of tissue oedema	Volume effect only during infusion
Pooled fresh frozen plasma	50–340	322	73–79	Coagulation factors Human proteins	Transfusion associated lung injury (very low risk with pooled preparations) Transfusion associated circulatory overload Low risk of infection	Good volume expanding effect and long intravascular stay

AKI = acute kidney injury

Table 2: Recommendations for the application of resuscitation fluids in different types of shock.

Type of shock		First Choice	Alternative	Comments
Hypovolaemic		Balanced crystalloids	Albumin	In patients with a high chloride loss (e.g., hyperemesis) NaCl 0.9% may be indicated.
Haemorrhagic	With apparent severe bleeding	Erythrocyte concentrates Plasma Thrombocytes	Balanced crystalloids	Albumin and all synthetic colloid solutions have the potential to increase bleeding, especially with large wound areas.
	Without apparent bleeding	Balanced crystalloids	Erythrocyte concentrates and plasma Albumin HES (130/0.4) or gelatines	Here applies the same as mentioned above.
	With traumatic brain injury	NaCl 0.9%	HES (130/0.4) or gelatines Erythrocyte concentrates and plasma	Hypo-oncotic albumin solutions may increase bleeding and mortality.
Septic		Balanced crystalloids	Albumin	Consider erythrocytes and plasma at low haematocrit and disturbed coagulation parameters. Synthetic colloids compromise kidney function and may increase mortality.
Anaphylactic		Balanced crystalloids	Albumin HES (130/0.4)	Fluid resuscitation only for correction of anaphylaxis-related relative hypovolaemia (usually 1–2 L crystalloids).
Cardiogenic		Balanced crystalloids	Albumin	In cardiogenic shock, small volume boluses may improve cardiac output due to correction of relative hypovolaemia. Especially in cases with preserved ejection fraction.
HES = hydroxylethyl starch				

4% albumin with 0.9% sodium chloride for fluid resuscitation in intensive care units (SAFE trial) [32]. The two heterogeneous groups of critically ill patients showed no difference in 28-day mortality, days on mechanical ventilation and renal replacement therapy (RRT), and length of intensive care and hospital stay. On the contrary, in the predefined subgroup of severely septic patients with complete baseline data (919/1218; 75.5%), the adjusted odds ratio for death with albumin versus saline was 0.71 (95% confidence interval [CI] 0.52–0.97) without increased renal or other organ impairment [33]. Despite a significantly higher mortality rate in the subgroup of traumatic brain injury patients resuscitated with hypo-oncotic albumin [34] and a relatively small fluid saving effect, the results of the SAFE trial corroborated the belief in the beneficial effects of colloids for resuscitation in severe sepsis and septic shock.

A prospective, multicentre open-label trial tested the potential of albumin replacement in severe sepsis and septic shock in 1818 patients randomised to receive either albumin and crystalloids or crystalloids alone [35]. This study targeted a serum albumin concentration of 30 g/l with the infusion of 3×100 ml of hyperoncotic albumin 20% per day. During the early phase of volume resuscitation, fluid administration in both groups was according to early goal-directed therapy guidelines. There was no difference in 28- and 90-day mortality or in the appearance and severity of organ dysfunction; however, a *post hoc* subgroup analysis showed a decreased mortality with albumin in patients with shock at enrolment (relative risk [RR] 0.87; 95% CI 0.77–0.99) [35]. The total fluid volume infused after 7 days was not different, although albumin administration resulted in faster haemodynamic stabilisation. A third randomised open-label multicentre study compared 3×100 ml albumin 20% daily with saline boluses in patients with septic shock [36]. This French trial (abstract only available) also showed faster circulatory stabilisation and no difference in mortality between the two groups.

Representative of the urgent wish for a safe and effective colloid are not fewer than eight meta-analyses for the use of albumin in patients with sepsis published between 2011 and 2014, based mainly on the results from the three studies described above [37]. The largest meta-analysis, by Patel et al. [38], included 16 prospective randomised clinical trials published between 1982 and 2014 with patients having sepsis of any severity who received albumin for volume resuscitation compared with a control fluid (crystalloid or colloid; n = 4190). Presenting an overall moderate quality of evidence, the analysis showed a similar risk of death for albumin groups and control fluid groups (RR 0.94; 95% CI 0.87–1.01). There was no indication of harm from albumin in patients with sepsis of any severity. Strong evidence of no difference was found in 3878 patients when albumin was compared with crystalloids only (RR 0.93; 95% CI 0.86–1.01). In contrast, Xu and colleagues found a decreased 90-day mortality with albumin compared with crystalloids for resuscitation in septic shock patients [39]. Overall, this meta-analysis of five studies comparing the effects of albumin with those of crystalloid or saline therapy on mortality exclusively in patients with severe sepsis (n = 3658) and septic shock (n = 2180) observed a trend toward reduced 90-day mortality in the albumin group.

In summary, it can be said that the application of human albumin for resuscitation in severe sepsis and septic shock is an option for supporting haemodynamic stabilisation in patients with high fluid requirements, without negative effects on survival. The significance of albumin in the very early phase of fluid resuscitation with marked capillary leakage and the impact on oedema generation needs further evaluation.

Semisynthetic colloid solutions

After the results of the Rivers study [20] and the almost significant improved survival of septic patients treated with albumin in the SAFE trial [32], semisynthetic colloid solutions (hydroxyethyl starch [HES], gelatines) were adopted as ideal resuscitation fluids for early goal-directed therapy. The allegedly reduced amount of resuscitation fluid with colloid solutions was thought to reduce the interstitial oedema accompanying high volume fluid therapy and lacked the high costs of albumin [40]. Initial concerns about the use of HES for volume resuscitation in severe sepsis appeared after two studies with HES solutions of higher molecular weight and grade of substitution (200 kD / 0.5–0.66). Both studies showed an increased risk of AKI and RRT but no difference in mortality compared with either gelatine 3% or Ringer's lactate [41, 42]. Specifically, the Volume Substitution and Insulin Therapy in Severe Sepsis (VISEP) trial was criticised because a substantial proportion of patients received more than the maximum recommended amount of hyperoncotic HES [42]. At about the same time as this unsettling result, new iso-oncotic HES solutions with a lower molecular weight and degree of substitution (130 / 0.4–0.42) were developed [4].

In 2012, three studies investigating these new HES solutions in a general intensive care population and in severe sepsis and septic shock were published. The multicentre double-blind Scandinavian 6S trial compared HES with Ringer's acetate for the therapy of severe sepsis and septic shock patients [43]. This study found a 17% increased relative risk of 90-day mortality (95% CI 1.01–1.36) for HES, without a difference in fluid volume administered. Interestingly, the mortality rates at 28 days and at 6 and 12 months were not significantly different between HES 130/0.4 and Ringer's acetate [44]. Despite a significant difference in short-term RRT, without an increased RRT-related mortality, the same number of patients had RRT for >5 days and an adjustment for AKI stage as covariate eliminated the significance of 90-day mortality [45]. Crystalloid versus Hydroxyethyl Starch Trial (CHEST), a randomised controlled double-blind trial (n = 7000, 1937 patients with sepsis) also found an increased risk for RRT with HES (130/ 0.4) as compared with sodium chloride 0.9% (RR 1.21, 95% CI 1.00–1.45) [46]. Ninety-day mortality did not differ between the groups and the patients receiving HES showed a decreased incidence of AKI assessed with the RIFLE criteria. The HES group received significantly less fluid during the first 4 days. A smaller French study compared HES 130/04 with sodium chloride for early fluid resuscitation and found that a significantly lower amount of HES was needed to achieve haemodynamic stability [47]. This study found no difference in mortality and renal failure in 196 patients with severe sepsis. The open-label, randomised controlled Colloids Versus Crystalloids for the Resuscitation of the Critically ill (CRISTAL) trial ran-

domised 2857 patients in shock to receive either colloid or crystalloid for the initial treatment of shock [48]. In this trial, the majority of patients received HES 130/0.4 as colloid or sodium chloride as crystalloid, and the colloid group required significant less resuscitation fluid. The primary endpoint of 28-day mortality was not different, although there was a small mortality benefit in favour of colloids after 90 days. No difference in the number of patients receiving RRT was observed [48].

A meta-analysis comparing only HES 140/03 with either crystalloids or albumin in sepsis found no overall increased mortality in 3546 patients. In the studies with low risk of bias (3016 patients), the relative risk of death with the use of HES was 1.11 (1.00–1.23 trial sequential analysis adjusted 95% CI 0.95–1.29) [49]. Patients receiving HES needed more RRT and showed a nonsignificant increase in the risk of AKI. Another meta-analysis comparing HES of different molecular weights, substitution and oncotic preparations with other resuscitation fluids in critically ill patients found an increased relative risk of mortality (1.09, 95% CI 1.02–1.17) and an increased risk for AKI (RR 1.27, 95% CI 1.09–1.47) and RRT (RR 1.32, 95% CI 1.15–1.50) [50]. Finally, a network meta-analysis examining the effect of different resuscitation fluids on mortality in sepsis showed with high confidence higher mortality with starches than with crystalloids [51]. Balanced crystalloids revealed with moderate confidence a lower mortality than low- and high molecular weight HES preparations.

Although gelatines are widely used semisynthetic colloids, there is a paucity of high-quality randomised controlled trials [40, 52]. In a prospective sequential fluid resuscitation analysis, gelatine 4% was an independent risk factor of AKI (OR 1.85, 95% CI 1.31–2.62) [53]. A recent meta-analysis of three studies comparing gelatine with crystalloids or albumin in 212 patients showed a 15% increased relative risk for mortality and a 35% increased risk for AKI in patients receiving gelatines [54]. Although these findings were not significant, they point to avoidance of gelatine use in septic patients.

Semisynthetic colloids, especially starches, should not be administered to patients with severe sepsis and septic shock because there is an increased risk for mortality and AKI when they are given in large amounts for volume resuscitation in critically ill septic patients. However, particularly the large, randomised controlled trials used high amounts of HES for more than 2 days partly in patients already fluid-resuscitated [42, 43, 46]. A recent meta-regression analysis of studies using HES 130/0.4 in septic patients suggested that the inappropriately high daily delta fluid balance is an important source of heterogeneity and was associated with mortality in these trials [55]. Studies using HES in the very early phase of sepsis resuscitation showed a decreased volume of fluid required in the HES group without an increased risk for mortality and AKI [47, 48]. The increased number blood products received, interpreted as to the detriment of HES [43, 46], could also be viewed as a sign of effectiveness, because haematocrit is more affected with a better plasma expanding capacity [56]. In the light of the increased mortality with higher amounts of fluid in patients with septic shock [57, 58], semisynthetic colloids and their influence on microvascular flow [59] in the initial phase of septic shock therapy deserve further investigation.

Crystalloid solutions

Crystalloids are the mainstay of volume resuscitation and maintenance in critically ill patients [29]. Crystalloids are classified as "balanced" and "unbalanced". Balanced crystalloids are characterised by a plasma-like strong ion gap (about 24 mmol/l) [4]. Sodium chloride (saline, NaCl), the most commonly used crystalloid worldwide, has a strong ion difference of zero and is therefore called "unbalanced" [40]. Administration of large amounts of saline results in a hyperchloraemic metabolic acidosis [1]. High plasma chloride concentrations increase inflammatory markers, induce coagulopathy and decrease renal blood flow [60, 61]. In sepsis studies, crystalloid solutions are mainly used as comparator fluids for semisynthetic colloids and albumin. Direct comparisons between different balanced crystalloids are rare. No trials have evaluated the differences between different buffered crystalloids or their side effects in critically ill patients, although there are theoretical reasons for preferring acetate- to lactate-buffered solutions. In fact, nearly every human cell type is able to metabolise acetate, whereas lactate increases with declining liver function, hampering the interpretation of serum lactate levels.

A prospective, open-label, sequential period study in a single intensive care unit in Australia compared sodium chloride with balanced electrolytes [62]. In this before and after study, patients who received almost entirely balanced infusions showed a significant decrease in the incidence of AKI (adjusted OR 0.52, CI 95% 0.37–0.75) and RRT (adjusted OR 0.53, CI 95% 0.33–0.81) compared with patients treated with normal saline during an earlier period. Two retrospective studies including patients with sepsis (n = 53,448) [63] and systemic inflammatory response syndrome (n = 109,836) [64] showed a reduced in-hospital mortality with balanced infusions, a finding that was proportional to the chloride load. Patients in the sepsis cohort showed no difference in AKI. Another retrospective study in septic patients found an increased mortality in patients with hyperchloraemia on admission, independent of base deficit, cumulative fluid balance and AKI [65]. A retrospective cohort study in more than 60,000 septic shock patients compared four groups of fluid resuscitation [66]. Patients receiving saline together with balanced electrolytes had a significantly lower mortality (17.7%) than saline 0.9% alone (20.2%), saline and colloids (24.2%), and all three categories together (19.2%). In contrast to this retrospective cohort studies, two prospective, cluster randomised, crossover trials (SALT and SPLIT) comparing more than 3000 intensive care patients to either crystalloids or sodium chloride 0.9% found no difference in mortality, AKI and RRT [67, 68]. In both studies, the amount of fluid infused was rather low and the group of sepsis patients small, so that a possible negative effect on kidney function was obscured. In the SALT trial, patients administered larger volumes of saline showed a significant increase in the composite of death, AKI and RRT [68]. A retrospective study of large volume resuscitation (60 ml/kg per day) showed a significantly increased crude rate of hyperchloraemic acidosis, AKI and hospital mortality with increased chloride load [69]. After adjustment for disease severity, total fluids and age, only mortality remained sig-

nificant with a 5.5% increased risk of death for each 100 mmol of administered chloride, or 11% for 2 L of sodium chloride 0.9%. Finally a recent cluster-randomised, multiple cross-over trial in 15,802 critically ill adults showed that primarily the administration of balanced fluids resulted in a lower rate of a composite outcome of death, AKI and initiation of RRT [70]. The separate analysis of the three outcomes did not reach significance. In the relatively small group of septic patients (n = 2936), the composite endpoint and the 30-day mortality were lower with balanced infusions [70].

Up-to-date randomised, controlled, double-blind trials comparing saline 0.9% with balanced crystalloids, or different crystalloid preparations are lacking. Nevertheless, the existing data seem to indicate an increased mortality risk with saline 0.9%, especially when administered in high amounts. Hyperchloraemic acidosis seems to outweigh the possible adverse effects of the slightly hypotonic balanced crystalloid solutions. The only exception may be traumatic brain injury, where hypotonic balanced solutions may increase brain oedema more than slightly hypertonic saline 0.9%.

Volume replacement in massive haemorrhage

Fluid resuscitation in uncontrolled haemorrhage aims to maintain adequate organ perfusion and tissue oxygen delivery in a system compromised by the physiological consequences of traumatic injury. However, fluid therapy is only one component of a complex haemodynamic resuscitation strategy in massively injured patients [71]. Additional therapeutic options, including the use of vasopressors, early surgical exploration with emphasis on damage control, angiographic embolisation of bleeding arteries and deliberate hypotension, are comparably important, especially in penetrating trauma [40, 72, 73]. For the latter, patients with traumatic brain injury or patients with or at risk of coronary artery or cerebrovascular disease are important exceptions.

Fluid resuscitation of trauma patients is an ongoing challenge with various recommendations regarding the use of crystalloids, colloids, blood products and clotting factor concentrates [72–77]. No ideal resuscitation fluid for trauma patients exists in clinical practice [40], and the debate about this is highly emotional [76, 77]. The choice of type of resuscitation fluid is mainly based on institutional practice and clinician's preferences, and rarely on physiological principles and study data. Further, regional variations, varying institutional protocols, availability and legal restrictions might relevantly influence the choice [74, 76].

However, there is accumulating evidence that the amount and type of fluid resuscitation might affect outcome in patients with massive haemorrhage similarly to patients with severe sepsis. Generally, it is suggested to restrict fluid administration in the prehospital period and in the emergency department [72]. Over-resuscitation with overzealous crystalloid administration leading to dilutional coagulopathy, hypothermia and potentially acidosis might further aggravate bleeding and coagulopathy [6, 16, 78].

Although their positive effect and advantage is not fully proven, crystalloids have an established role as inexpensive and widely available first-line resuscitation fluids in trauma [40]. Albeit the use of semisynthetic colloids in trauma patients is often perceived to be associated with improved haemodynamic stability, but with increased risk of coagulopathy and renal failure, a large meta-analysis could not show that one solution is relevantly safer or associated with improved survival [79, 80]. Similarly, the use of human albumin for fluid resuscitation did not improve outcome compared with crystalloid in a randomised study including nearly 7000 patients [32]. In a subgroup of patients with traumatic brain injury, the use of hypo-oncotic albumin 4% actually increased mortality [34].

The administration of colloids over a prolonged period of time and in dosages beyond any recommendations must be avoided. However, colloids might be better than crystalloids for replacing plasma deficits and avoiding acute intravascular hypovolaemia or for preventing tissue oedema [6, 76, 81]. Potentially, limited amounts of colloids in the initial resuscitation phase of haemodynamically unstable patients (fig. 2) might be beneficial, but should be continued with a "crystalloid" maintenance phase. The value of hyperosmolar saline solution is unclear [82], and the solution has been abandoned.

Use of blood products

During massive haemorrhage, there is a rapid loss of red blood cells and coagulation factors, in combination with hyperfibrinolysis resulting in acute trauma coagulopathy. In the case of massive haemorrhagic shock, the transfusion of red blood cells is often unavoidable to preserve a minimal haematocrit level. However, the infusion of crystalloids and colloids will lead to further dilutional anaemia and coagulopathy.

Plasma might be an ideal resuscitation fluid as it is protein-rich and contains coagulation factors. The endothelial glycocalyx might be better preserved with less fluid loss in the interstitium and potentially lead to less additional coagulopathic deterioration by administration of plasma products [16, 83]. However, this concept has only been proven in a rodent model of haemorrhagic shock [83]. Recent German guidelines stated that plasma is contraindicated for primary volume resuscitation (recommendation grade 1C) [84]. The clinical effectiveness of fresh frozen plasma to preserve or restore coagulation deficits has been questioned by a large meta-analysis [85]. Nonetheless, despite the questionable indication and clinical benefit of plasma, and although its use had not been studied in non-trauma settings and in septic shock, the use of plasma as a "supercolloid" has been advocated by some experts [4].

In the event of haemorrhagic shock, early transfusion of plasma and platelets together with red blood cell concentrates has been advocated [72] as part of a massive transfusion protocol (MTP) aiming to transfuse "whole blood". MTPs are also thought to prevent rather than reverse or treat trauma coagulopathy. MTPs with an approximate 1:1:1 ratio of blood components might be especially helpful in the early resuscitation phase before bleeding is controlled surgically. However, the value of MTPs has been evaluated only in retrospective analyses, most of which are associated with a relevant survivorship bias [86]. Further, even an MTP leads to relevant dilution of coagulation factors [87] and might be able to only partially limit rather than prevent further coagulopathy.

Finally, a recent study from Austria suggested that the early use of coagulation factor concentrates instead of the administration of plasma is feasible in the trauma setting and associated with less use of allogeneic blood products [88]. However, it is unclear whether such a regimen is associated with better outcome and lower morbidity and mortality.

Discussion

After 15 years of intense research, no fluid resuscitation panacea has been found and the optimal type and amount of fluid for the early volume replacement should be individualised for each patient and type of shock (table 1). A very recent Cochrane review stated with moderate evidence that fluid resuscitation with starches, albumin or fresh frozen plasma shows little or no difference in mortality compared with crystalloids in critically ill patients [89]. In current surviving sepsis guidelines [29], five out of six recommendations for fluid therapy are based on moderate- or low-quality evidence. The only strong recommendation with high-quality evidence is against the use of HES. Even this recommendation should be considered with caution, because the studies comparing HES 130/0.4 with crystalloids used rather high volumes of resuscitation fluid in patients already volume resuscitated [43, 46, 56]. The two studies testing starches in the very early course of shock did not find an increased mortality or a higher risk of AKI [47, 48]. Studies with an early administration of starch also found a volume-sparing effect in a ratio of 1.2 to 1.5 in favour of colloids, which is far below

the theoretical expected value of 3, and an effect that is not so obvious in studies using high amounts of fluid over >2 days [56]. A possible explanation for this weak volume expanding effect could be that the fluid requirement is context sensitive [3]. This means that after initial resuscitation of the microcirculation, further volume replacement increases tissue oedema disproportionately. The reason for this could be a direct transmission of the increased mean arterial pressure through the dilated resistance vessels to the capillaries, where the thinned out glycocalyx together with the increased number of endothelial gaps are unable to retain volume intravascularly. Ospina-Tascone and colleagues showed that infusion of either 1 L of Ringer's lactate or 400 ml of albumin 4% only increased the proportion of perfused small microcirculatory vessels during the first 24 hours of severe sepsis but not 48 hours after the diagnosis [59]. No relation to mean arterial pressure or cardiac index was found. The study also found a direct relationship between improved microvascular perfusion and decreased serum lactate [59]. Earliest evidence for the relevance of the administered volume came from a study of patients with acute respiratory distress syndrome, predominantly from pneumonia and sepsis, where a conservative fluid therapy improved lung function and decreased duration of mechanical ventilation [17]. In 2006, a European multicentre, observational cohort study in 1177 septic patients found a positive cumulative fluid balance as the only modifiable risk factor for death [90]. In the meantime, several retrospective cohort and prospective observational studies showed an association between higher positive flu-

Figure 2: Influence of fluid resuscitation on the sublingual microcirculation. Panel A shows the microcirculation of a patient in haemorrhagic shock. Most of the visible microvessels show are intermittently perfused (orange lines) or show no flow (red lines). Panel B shows the microcirculation of the same patient after resuscitation with on unit packed red cells. The amount of microvessels with intermittent flow differs markedly. Only very view vessel parts show a no flow phenomenon.
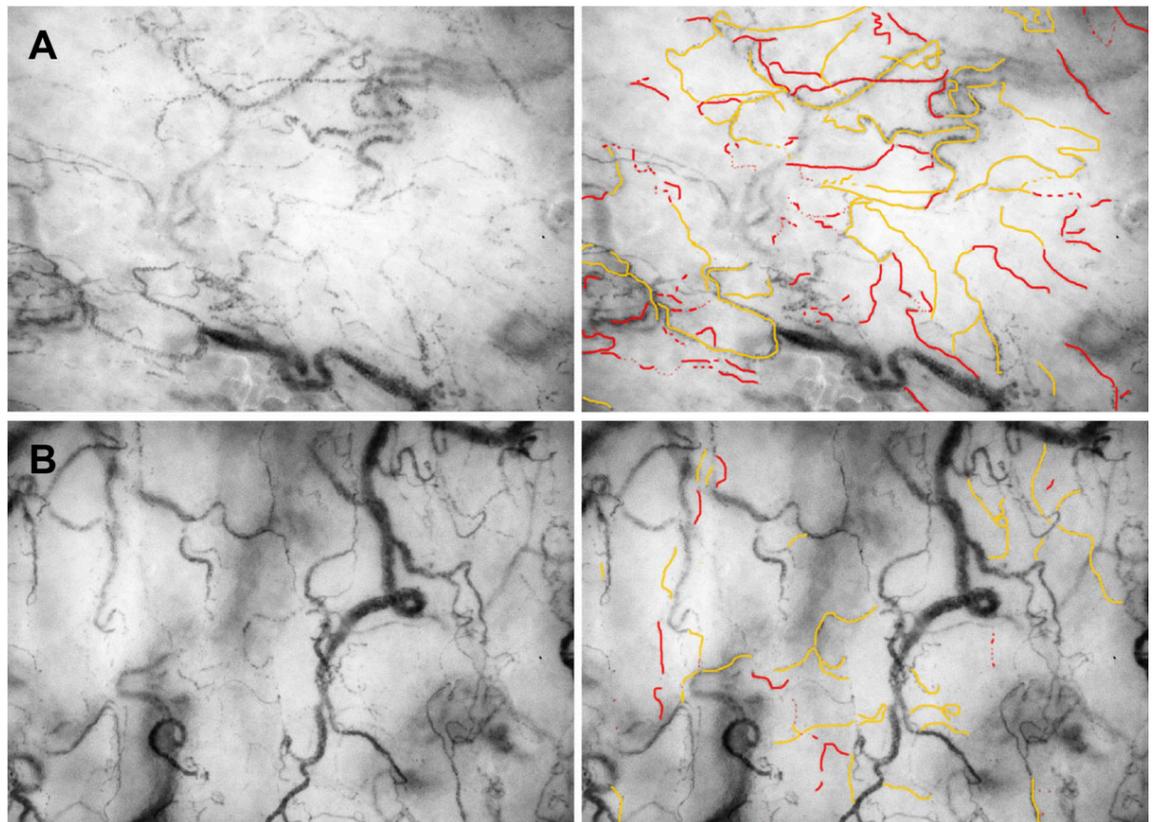
id balances from 24 hours to 8 days and mortality [91–93]. In two very recent retrospective analyses of patients with severe sepsis or septic shock, the administration of more than 5 litres of resuscitation fluid on day one or a higher cumulative fluid balance on day three was associated with an increased risk of death [58, 94]. A retrospective review of fluid use in the prospective, randomised, blinded Vasopressin in Septic Shock Trial (VASST) [95] showed that a more positive fluid balance after 12 hours and 4 days was associated with a higher risk of mortality [57]. A central venous pressure of more than 12 mm Hg in the first 12 hours of resuscitation was also associated with increased mortality. Increased central venous pressure increases microvascular outflow and capillary pressure, which also increases the extravasation of fluid to the interstitium [3]. The possible positive impact of modulating microvascular in- and outflow pressure to reduce capillary pressure and thereby fluid extravasation was shown by two studies. Jansen et al. used a treatment algorithm according to which they applied vasodilators to correct microcirculatory derangement to foster decreased blood lactate concentrations [96]. Together with a minimal increased fluid volume during the first 8 hours, this modulation of microvascular outflow pressure decreased ICU and in-hospital mortality. An increase of microvascular inflow pressure with a fixed dose of vasopressin (0.03 U/min) in addition to vasopressors decreased the relative risk of 90-day mortality in patients with less severe sepsis [95]. Norepinephrine increased cardiac preload and reduced preload dependency in septic shock patients [97]. The current surviving sepsis campaign guidelines recommend 30 ml/kg body weight administered during the first 3 hours of sepsis therapy, norepinephrine as the first line vasopressor and vasopressin (0.03 U/min) as the second line to increase mean arterial pressure.

Conclusion

Fifteen years of intensive research have not found the optimal resuscitation fluid, as relative uncertainty remains about type and amount of fluid. Balanced crystalloids seem to be more advantageous than normal saline. Iso-oncotic albumin should be used as a colloid since the liberal use of starches over days has shown an increased incidence of AKI, RRT and mortality. The role of plasma and red blood cell concentrates is still controversial. The classic haemodynamic targets, including mean arterial pressure, cardiac output, lactate and even dynamic tests (e.g., passive leg raising), alone may not be sufficient to guide fluid administration in patients with haemorrhagic and septic shock. Direct or indirect monitoring of microcirculation including skin mottling and turgor, central venous pressure and peripheral oedema, should be considered as well, as the microcirculation it the primary target of fluid therapy.

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