

REVIEW

Fluid management in acute lung injury and ARDS

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Abstract - Acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) continue to be major causes of morbidity and mortality in the ICU due to a lack of specific, effective therapy. Affecting approximately 200,000 people every year in the United States alone, patients with this syndrome often require extensive ICU and hospital care. This leads to enormous utilization of healthcare resources and significant expenditures, and ultimately leaves survivors with a reduced quality of life. ALI/ARDS is a disease of altered capillary permeability characterized by significant fluid imbalances and oncotic pressure changes. Although investigations directed at these abnormalities may improve patient-centred outcomes, fluid management in ALI/ARDS continues to be a source of great controversy. In this article, we discuss fluid balance and the colloid osmotic pressure gradients in ALI/ARDS, followed by a review of the prognostic implications of increasing extravascular lung water. We conclude with contemporary approaches to optimizing therapy in this condition, including the role of albumin and diuretic therapy.

Keywords - Acute lung injury, ARDS, hypoproteinaemia, extravascular lung water, intravenous fluids, colloids

Introduction

Acute lung injury (ALI) and its severe form, acute respiratory distress syndrome (ARDS), continue to be significant challenges to the critical care physician. A common condition in the ICU and occurring in as many as 10% of critically ill patients and 25% of mechanically ventilated patients, ALI/ARDS is a clinically devastating and life-threatening syndrome [1]. In the United States, ALI is estimated to occur in approximately 200,000 people each year, at the rate of 86 per 100,000 inhabitants per year [2]. Mortality with ALI/ARDS varies with the underlying cause, and is still in excess of 40% in many cases, in addition to being an important cause of pulmonary and non-pulmonary morbidity in patients who survive hospitalization [3]. Even during hospitalization, patients with ALI/ARDS often require weeks of intensive hospital care, and account for an estimated \$5 billion per year in direct healthcare expenditures in the United States alone [4]. Thus, optimizing management to improve outcomes is of great clinical importance.

First described in 1967 [5], ARDS is characterized by the onset of clinically significant hypoxaemia, diffuse bilateral pulmonary infiltrates, and the absence of increased hydrostatic or cardiac filling pressures. The first American-European Consensus Conference on ARDS [6] introduced the term “acute lung injury” into the lexicon in an attempt to ensure the definition includes less severely ill patients, the majority of whom will progress to meeting the more severe ARDS definition. Regardless of nomenclature, the Consensus Conference definition emphasized that patients with ALI or ARDS develop increased microvascular permeability with extravasation of fluid and protein into the alveoli [3,6]. Although alveolocapillary

barrier dysfunction primarily causes the pulmonary oedema seen in this disease, reduced colloid osmotic pressure (COP) may contribute to the generation and persistence of pulmonary oedema [7,8]. In fact, hypoproteinaemia is one of the strongest predictors in the development of ALI/ARDS and subsequent clinical outcomes among patients with sepsis [8]. Fluid balance and oncotic pressure alterations have been shown to improve respiratory physiology, and a fluid-restrictive strategy has been associated with improved outcomes in critically ill patients [9-11]. Because of the similarity between ALI and ARDS, which exist together on a spectrum of respiratory dysfunction, I will hereafter refer to them together as ALI/ARDS, except in circumstances where it is important to specify the condition (either ALI or ARDS).

Supportive therapies have shown promise for reducing the duration of mechanical ventilation and improving survival, but no effective therapies directed at the pathophysiology of ALI/ARDS have been found. In this article, we discuss fluid balance and COP in ALI/ARDS, with strategies to optimize therapy in this disease.

Starling's Law

Fluid transport cannot be discussed without first discussing Starling's Law. Formulated in 1896 by physiologist Ernest Starling, this law describes the factors that influence fluid transport across a semipermeable membrane such as the capillary wall [12]. The balance of forces affecting fluid flux across the lung is quantified by the Starling Equation (see below and Figure 1):

$$Q_t = K_f [(P_c - P_i) - \sigma (\pi_c - \pi_i)]$$

Where Q_t is the net fluid movement between compartments, K_f is the capillary filtration coefficient, P_c is the capillary hydrostatic pressure, P_i is the interstitial hydrostatic pressure, σ is the reflection

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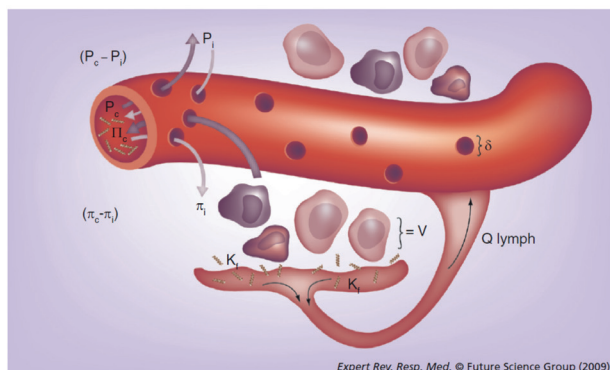
coefficient, π_c is the colloid osmotic pressure, and π_i is the interstitial oncotic pressure.

The first half of Starling's Law represents the hydrostatic pressure gradient, which normally favours translocation of fluid across the membrane and out of the vasculature. The second half represents the COP gradient across the capillary wall. The relative influence of COP on fluid flux is modulated by the oncotic reflection coefficient, which represents permeability of the vasculature to oncologically active substances such as plasma proteins. Oedema forms when Starling's forces are imbalanced, and there are three oedema-protective mechanisms that oppose further oedema formation when this process begins: 1) increases in interstitial hydrostatic pressure, 2) reductions in interstitial oncotic pressure, and 3) increases in capillary oncotic pressure. A fourth component not originally described by Starling is lymphatic flow, which may increase by nearly 10 times to prevent the accumulation of pulmonary oedema.

Hydrostatic forces in ALI/ARDS

Hydrostatic pressure is a key contributor to the formation of oedema and exerts an exaggerated effect in states of increased capillary permeability, a characteristic feature in ALI/ARDS. Animal studies have shown that pulmonary oedema does not accumulate until left atrial pressure exceeds the protective mechanisms of the lung to prevent oedema formation [13]. For hydrostatic forms of oedema, once hydrostatic pressure exceeds the oedema-protective mechanisms, pulmonary oedema begins to form in compliant regions of the lung. With continued oedema formation, pulmonary interstitium becomes congested and lymphatic flow is maximized before ultimately resulting in alveolar flooding. Whether this pattern of fluid accumulation is true in ALI/ARDS is uncertain, given that interstitial oedema may egress from both pulmonary capillaries and small arteries (and potentially venules). This is also confounded by uncertain and variable contributions from surfactant availability and function, as well as lung perfusion and ventilation.

Figure 1



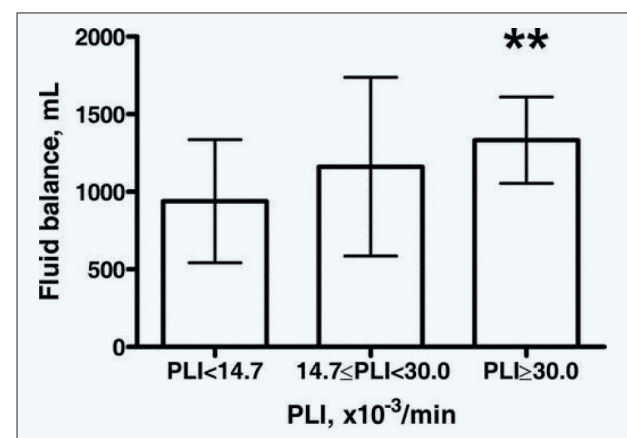
Graphic depiction of the forces described by Ernest Starling that affect fluid flux across a semipermeable membrane, such as in acute lung injury or acute respiratory distress syndrome. [Taken from Cribbs and Martin, Expert Review Respir Med 2009.]

Efforts have been made to distinguish ALI/ARDS from hydrostatic pulmonary oedema by either measuring pulmonary vascular resistance or. In fact, the Consensus Conference definition for ALI/ARDS focuses on the clinical manifestations of ARDS and excludes hydrostatic contributions, for its third component is a PCWP < 18 mmHg [6,13]. However, this measurement has been much debated with the realization that exceeding a PCWP of 18 mmHg does not preclude a diagnosis of ALI. Indeed, PCWP has been shown to intermittently exceed 18 mmHg in more than 80% of patients enrolled in a large-scale ARDS trial [14], while a recent large randomized controlled trial noted that approximately one-third of ALI patients had PCWP > 18 mmHg within hours of diagnosis [11]. Some studies have shown that a much higher percentage of ALI patients have an elevated PCWP at some point during their course [15].

Osmotic forces in ALI

Based on Starling's equation, a reduced oncotic pressure gradient between intravascular space and interstitium (i.e. in states of hypoproteinaemia) can promote oedema formation even at lower hydrostatic pressures, and may significantly contribute to increased extravascular lung water (EVLW) in patients with ALI/ARDS [13,16-18]. Serum total protein is a major determinant of COP, and animal models show us that a given decrease in COP causes a doubling of fluid flux from capillary to interstitium compared to a similar magnitude increase in hydrostatic pressure [17,19]. In a classic experiment, Guyton firmly established that low oncotic pressure is an important factor for the development of oedema when hydrostatic pressure is elevated [20]. Although permeability modifies the effect of COP on transvascular fluid flux as expected from Starling's Law, more recent evidence shows that COP remains influential even in

Figure 2



Fluid balance in groups of critically ill patients: those with normal lung permeability (left bar), those with moderate permeability abnormalities and acute lung injury (middle bar), and those with severe permeability defects and acute respiratory distress syndrome (right bar). [Taken from Aman et al., reference no. 23.]

states of altered vascular permeability, such as sepsis and ALI/ARDS [21,22]. These concepts are clinically relevant in critically ill patients who frequently suffer from reductions of COP secondary to their catabolic state and/or excessive crystalloid administration.

Hypoproteinaemia has been shown to be a risk factor for the development of ALI/ARDS. In a retrospective analysis of patients with severe sepsis at risk for developing ALI/ARDS, Mangialardi and colleagues showed that the initial serum total protein (STP) level and changes in STP level were the most highly significant variables in predicting the development of ARDS [8]. The incidence of ARDS was 22% among normoproteinaemic patients (STP > 6.0 g/dL) compared with 41% and 45% in patients with borderline (STP 5.0 g/dL – 6.0 g/dL) or severe (STP < 5.0 g/dL) hypoproteinaemia respectively ($p=0.0006$) [8]. In addition, reduction in STP (defined as less than 6.0 g/dL) was also highly predictive of positive fluid balance, fewer ventilator-free days (8.0 vs 17.6 days, severe hypoproteinaemia vs normoproteinaemia respectively, $p=0.001$), and mortality (severe (45%) or borderline (48%) hypoproteinaemia vs 14% in normoproteinaemic patients, $p=0.03$) [8], reflecting the greater prevalence of ARDS in the low-protein group. Moreover, 10 of the 14 patients with normal initial STP experienced rapid pulmonary recovery, evidenced by either extubation or $\text{PaO}_2/\text{F}_i\text{O}_2$ ratios > 200 within two days of study entry, and all 10 of these patients survived [8]. This convincingly demonstrated a strong association between hypoproteinaemia and ARDS, although not necessarily a causal relationship. Separate observational studies of patients with clinically evident pulmonary oedema have shown that the pulmonary leak index is higher and serum protein levels are lower in ARDS patients than in cardiogenic pulmonary oedema patients, suggesting that STP levels may help establish the cause of pulmonary oedema [7,23]. Similar studies have also emphasized the relationship between capillary permeability, fluid balance, and ALI/ARDS [23] (see Figure 2). The association between hypoproteinaemia

and the development of ARDS suggests that the oncotic pressure gradient may have important pathophysiologic and prognostic implications in this disease. Potential treatment strategies will be discussed later.

Fluid balance in critically ill patients

Fluid balance before ALI/ARDS

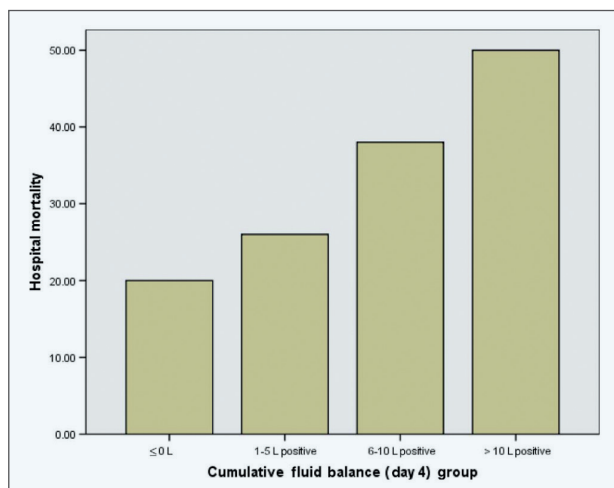
Fluid resuscitation is one of the most common interventions in the early management of critically ill patients, particularly among patients with septic shock where early goal-directed therapy may be employed. Recently, an observational cohort study from 198 European ICUs reported that patients who subsequently developed ALI/ARDS received more fluids during the first four days of their ICU stay compared to patients who did not develop ALI/ARDS, thus making positive fluid balance associated with the development of ALI/ARDS [24]. Furthermore, non-survivors of ALI/ARDS had a higher mean fluid balance, a longer mean ICU stay, and a higher cumulative fluid balance compared to survivors. Higher mean fluid balance was an independent predictor of mortality. As may be expected considering the ebb and flow phenomena of sepsis, the early application of goal-directed therapy and later application of fluid restriction appears to produce the best outcomes for these patients [25].

Prognostic value of extravascular lung water

Fluid balance is one component of pulmonary oedema, and the pathologic accumulation of pulmonary oedema can be quantified as extravascular lung water (EVLW). Although pulmonary oedema can be assessed by oxygenation indexes and chest radiographic techniques, EVLW has been shown to be more sensitive than these measurements [26,27], and the currently available clinical measures of EVLW correlate well with clinical and gravimetric indices of pulmonary oedema [28-31]. In addition, EVLW measurements have prognostic potential in ARDS patients. Previous studies estimating EVLW in states of respiratory failure and/or ARDS had conflicting outcomes [32,33], but recent studies where EVLW was adjusted to lung volume (or ideal body weight, rather than actual body weight) have found EVLW to be a significant predictor of mortality [30,34]. Among the largest studies to date, in 373 critically ill patients (including 193 patients with septic shock and 49 with ARDS), EVLW was significantly higher in ARDS compared to all other patients (median 14.9 mL/kg vs 11.9 mL/kg respectively, $p < 0.05$) [35]. In addition, EVLW was higher in non-survivors compared to survivors (median 14.3 mL/kg vs 10.2 mL/kg respectively, $p < 0.001$), correlating directly with survival and otherwise predicting the clinical prognosis.

Prospective studies have also shown similar results. In a prospective cohort study, ARDS patients with high EVLW were found to have poorer cumulative mean oxygenation ($\text{PaO}_2/\text{F}_i\text{O}_2$ ratio 135 ± 60 vs 197 ± 107 mmHg, $p=0.001$) and lung injury score (2.8 ± 1.1 vs 2.1 ± 0.7 , $p=0.002$) [29]. Interestingly, 4 out of 15 patients with severe sepsis who fulfilled the clinical Consensus Conference criteria for ARDS maintained a low EVLW and had a better 28-day survival than did ARDS patients with high EVLW (100% vs 36%, $p=0.03$) [29]. Similarly, in patients with septic shock EVLW correlated with markers of acute lung injury, and in non-survivors EVLW and

Figure 3



Hospital mortality by cumulative fluid balance in patients with ALI/ARDS.
[Taken from Rosenberg et al., reference no. 39.]

permeability indices were significantly increased at day 3 ($p < 0.05$) [36]. Similar prognostic findings have now been reported in children as well [37]. EVLW has been reported to be a more powerful independent predictor of in-hospital survival than other predictors (e.g. development of ARDS, lung injury score, APACHE II) with an adjusted odds ratio of 6.21 ($p=0.01$; 95% CI, 1.05-1.44) in patients with severe sepsis [38], a syndrome from which approximately 40% of patients develop ARDS [35].

As already mentioned, EVLW measurements were historically indexed to the actual body weight (ActBW) of the patient despite a lack of physiological rationale or clinical validation. As more than half of ARDS patients are overweight, recent studies have discussed the implications of calculating EVLW based on height [30,34]. Phillips et al. compared the relationship between EVLW indexed to predicted body weight (PBW, calculated from height) to that indexed to actual body weight in 19 patients with sepsis-induced ARDS [34]. They found that not only was EVLW indexed to PBW higher in non-survivors compared to survivors (20.6 ± 4.6 vs 11.6 ± 1.9 mL/kg, $p=0.002$), but that a three-day average of PBW-indexed EVLW > 16 mL/kg predicted death with a 100% specificity and 86% sensitivity [34]. More recently, in a prospective observational cohort of 30 patients, when indexed to ActBW, mean EVLW was greater in ARDS patients compared to non-ARDS sepsis patients (12.7 vs 7.8, $p < 0.0001$), however 7 out of 30 (23%) ARDS patients had normal EVLW (< 10 mL/kg) throughout the study [30]. When indexed to PBW, mean EVLW increased for both ARDS and non-ARDS sepsis patients by an average of 2.0 ± 4.1 mL/kg when indexed to PBW [30]. In addition, EVLW measurements correlated with the severity of lung injury and oxygenation, which was statistically greater when EVLW was adjusted to PBW ($p < 0.0001$). Increased EVLW is a feature of early ARDS and has prognostic implications in these patients, correlating with lung injury severity and predicting survival.

Fluid management in ALI/ARDS

Fluid management is a complex issue, and one of the most challenging aspects of patient care. It has long been known that

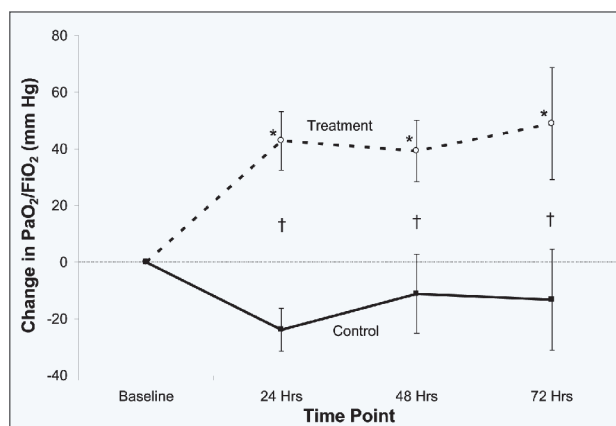
critically ill patients have difficulty maintaining fluid balance, an effect exacerbated by reductions in colloid pressure gradient. There is a significant amount of evidence suggesting benefits from either reductions in hydrostatic pressure or increases in oncotic pressure for patients with ALI/ARDS [39] (see Figure 3).

Fluid restriction in ALI/ARDS

Fluid restriction has been shown to improve clinical outcomes in several studies. Humphrey and his colleagues retrospectively analysed the survival and ICU length of stay in 40 ARDS patients to determine if a management strategy of lowering PCWP was associated with improved clinical outcomes [40]. They found a statistically significant increase in survival in those patients who had at least a 25% reduction in PCWP (75% vs 29%, $p < 0.02$), and although there was a trend in shorter ICU length of stay (8.9 ± 8 vs 14.8 ± 11.4 days), this result was not statistically significant [40].

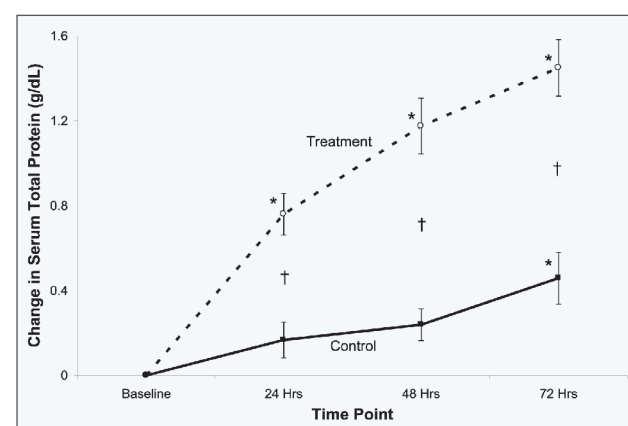
Since then, other prospective studies have shown similar results. Mitchell et al. performed a prospective randomized trial to evaluate whether fluid management could affect EVLW, time on mechanical ventilation, and time in the ICU [10]. They randomized 101 critically ill patients, where 52 patients were randomized to an EVLW management group using a protocol based on bedside indicator-dilution measurements of EVLW while the other 49 patients were managed based on PCWP [10]. They found that the study groups were managed differently, as evidenced by cumulative input-output of 2,239 +/- 3,695 ml (median = 1,600 ml) in the PCWP group versus 142 +/- 3,632 ml (median = 754 ml) in the EVLW group ($p=0.001$) [10]. EVLW decreased significantly and ventilator days and ICU days were significantly shorter only in patients from the EVLW group. No clinically significant adverse effect occurred as a result of following the EVLW group algorithm [10]. Most recently, ARDS network investigators conducted a large multi-centre trial, randomizing 1,000 patients, to compare central venous catheter (CVC) versus pulmonary artery catheter (PAC) and fluid-liberal versus fluid-conservative strategies [11]. The investigators found that a fluid-

Figure 4a



Changes in oxygenation for ALI/ARDS patients treated with the combination of albumin and furosemide (treatment) compared to furosemide alone (control).

Figure 4b



Changes in serum total protein (STP) in ALI/ARDS patients treated with the combination of albumin and furosemide (treatment) compared to furosemide alone (control). [Taken from Martin et al., reference no. 9.]

conservative strategy resulted in a nearly even fluid balance over seven days, while a fluid-liberal strategy resulted in an accumulation of fluid of almost one litre per day, similar to fluid balances seen in previous National Institutes of Health ARDS Network trials when fluid management was not controlled. Although there was no difference in mortality, the fluid-conservative strategy was associated with a significant improvement in lung function, specifically improved oxygenation and lung injury score, lower plateau pressures, and 2.5 more days alive and free of mechanical ventilation (14.6 ± 0.5 vs 12.1 ± 0.5 ventilator-free days; $P=0.0002$) and ICU-free days (13.4 ± 0.4 vs 11.2 ± 0.4 ; $P=0.0003$) to day 28, without increasing non-pulmonary organ dysfunction. These studies suggest that for those who can tolerate such an approach, adapting a more conservative fluid-management strategy better serves patients with ALI/ARDS.

Which fluid to use?

Although it is increasingly clear that a fluid-conservative approach is superior in patients with ALI/ARDS, there is a great deal of controversy over *which* intravenous fluid to use in these patients – crystalloids or colloids – particularly with fluid resuscitation. Colloid solutions generate protein or COP, and although they have theoretical advantages according to Starling's Law as we have mentioned above, appropriate indications for either crystalloids or colloids have been debated for decades [41]. Conflicting data have arisen from meta-analyses about colloid use in critically ill patients; colloids have a variety of different molecular weights, pharmacodynamics, pharmacokinetics, and different side-effect profiles [42].

Albumin is the most abundant protein in human plasma, exerting 75% to 80% of the normal COP [42,43]. It consists of three pharmacologically active substances: water, NaCl, and albumin. Albumin has a number of important biochemical properties that would be clinically relevant in critically ill patients. Albumin not only regulates fluid distribution between intra- and extravascular compartments, but it can also bind and transport an array of ligands including fatty acids, nitric oxide, and drugs [44].

Endogenous albumin is an important regulator of endothelial barrier permeability to large molecules [45]. It reduces microvascular permeability [45,46] and inhibits endothelial cell apoptosis [47], both functions favouring retention of fluid in the vasculature.

Although hypoalbuminaemia has shown to be a dose-dependent, independent predictor of poor outcome in acutely ill patients [48], whether hypoalbuminaemia directly contributes to poor outcomes or is merely a marker for further upstream pathologic processes is still a subject of contention. Dubois et al. randomized 100 hypoproteinaemic critically ill patients to receive 300 mL of 20% albumin solution on day 1, then 200 mL/day versus no albumin at all, and evaluated organ dysfunction (as assessed by sequential organ failure assessment (SOFA) score from day 1 to day 7). They found that organ function improved in the albumin group ($p=0.03$), mainly due to respiratory, cardiovascular, and central nervous system components [49]. Mean daily fluid gain was almost three times higher in the control group than in albumin group ($p=0.04$), maybe secondary to the effects of albumin on COP [49]. As mentioned earlier, it is clear that varying concentrations of albumin have different effects on COP, and ultimately on morbidity and mortality.

Vincent and his colleagues found that in trials with moderate-dose albumin (greater than 25%) in the control group, the relative risk was greater than 1 for nearly all comparisons, suggesting a biphasic dose-response relationship between albumin and morbidity [50].

Hydroxyethyl starch

An early randomized trial in patients with sepsis compared hydroxyethyl starch (HES) and gelatin and found an increased frequency of acute kidney injury, oliguria, and peak serum creatinine levels in the patients who received HES [51]. More recently, a large multi-centre randomized controlled trial of severe sepsis patients found a significantly greater incidence of renal failure (34.9% vs 22.8%, $p=0.002$) with more frequent need for renal replacement therapy (18.3% vs 9.2%) and a trend toward higher 90-day mortality among patients who received HES compared to Ringer's lactate (41% vs 33.9%, $p=0.09$) [52]. In this study there was a dose-dependent effect of HES on both the need for renal replacement therapy and rate of death at 90 days ($p < 0.001$ and $p=0.001$ respectively) [52], suggesting that this formulation of HES should not be used in patients with sepsis.

Albumin

The Saline versus Albumin Fluid Evaluation (SAFE) Study was a multi-centre randomized trial that compared 4% albumin and 0.9% normal saline in patients requiring fluid resuscitation. In the enrolled patients, there was no difference in 28-day all-cause mortality rate, organ dysfunction, duration of mechanical ventilation, ICU, or hospital length of stay [53]. Although there was no difference in mortality in the subgroup of patients with ARDS treated with albumin versus saline ($p=0.74$) [53], there was a modest reduction in mortality noted in the sepsis subgroup. This was reported recently as a separate post-hoc analysis, with an adjusted odds ratio for mortality of 0.71 (95% CI 0.52 – 0.97, $p=0.03$), suggesting that the use of albumin at this concentration in patients with sepsis – a major risk factor for developing ALI/ARDS – may improve survival.

Combination therapy with colloids and diuretics for ALI/ARDS

With evidence showing us that elevated hydrostatic pressures, fluid retention, and weight gain are associated with mortality in ARDS [54,55], clinical trials that further investigate reductions in hydrostatic pressure and colloid supplementation are essential, and may improve outcomes in ALI/ARDS.

Our group has conducted two studies evaluating the effect of diuretic therapy in patients with ALI or ARDS. In our initial study, 37 hypoproteinaemic patients with ALI were randomized into a double-blind trial of protocolized albumin replacement and continuous infusion of furosemide versus double placebo [56]. Acute improvements in oxygenation were observed in the treatment group at 24 hours without improvement in lung mechanics, but improvements in haemodynamics in the treatment group were associated with marked diuresis and weight loss over five days. There was no statistically significant difference in overall outcome, although there were favourable trends toward reduction in ventilator time, ICU, and hospital length of stay [56]. This was the first prospective trial that randomized ALI/ARDS patients to therapeutic regimen defined by diuretic therapy.

To further understand the implications for active reductions in hydrostatic pressure focusing on colloid supplementation, we conducted a trial with 40 patients randomized to either furosemide with albumin (treatment group) or furosemide with placebo (control group) [9]. ALI patients treated with a combination of albumin and furosemide had significantly greater improvements in oxygenation and COP (see Figures 4a and 4b) compared to those patients receiving furosemide alone [9]. Furthermore, the addition of albumin to furosemide therapy promoted diuresis while reducing hypotension and shock from furosemide monotherapy (net intake/output at day 3 was -5480 mL vs -1490 mL, $p < 0.01$) compared to those patients receiving furosemide alone. Moreover, patients in the treatment group had lower SOFA scores and an increased number of shock-free and ventilator-free days [9].

These data suggest that albumin is a critical component of this regimen, for both maintenance of haemodynamic stability and improved oxygenation, but the exact mechanism of improved oxygenation along with the timing of colloid/diuretic administration still remains uncertain. Kuper and his colleagues examined the short-term physiological changes produced by administration of hyperoncotic albumin alone, followed by albumin plus furosemide in two prospective non-randomized interventional case series in hypoalbuminaemic patients with severe sepsis-induced ARDS [57]. In the initial study with only 20% albumin, they found that oxygenation significantly improved at 30 minutes and 120 minutes, but declined to baseline by 4 hours [57]. The second series showed that oxygenation improved at 5 minutes, but decreased to baseline by 30 minutes [57].

Other colloids have been evaluated as resuscitative agents in addition to albumin. Bulger and colleagues conducted a double-blind randomized controlled trial in 209 patients with blunt trauma and hypovolaemic shock [58]. Patients were randomized to receive either a 250 mL bolus of 7.5% hypertonic saline and 6% dextran 70 versus 250 mL of lactated Ringer's solution (LRS), followed by additional LRS if necessary during transport. The study was

stopped due to expected futility when intent-to-treat analysis demonstrated no significant difference in ARDS-free survival at 28 days, the primary endpoint [58].

Conclusion

It is clear that fluid balance is among the most important issues in critically ill patients. With Starling's discovery, we have learned that many factors influence fluid transport across membranes and that the balance between hydrostatic and osmotic forces influences oedema formation, amplified in states of capillary permeability such as ALI/ARDS. Most recently, we have learned about the ebb and flow of fluid balance in critically ill patients, and that early fluid resuscitation is a critical component of optimal care. However, later management requires a conservative fluid approach or even active fluid removal. Fluid balance must be actively managed to reduce respiratory complications and a prolonged duration of mechanical ventilation, which can further lead to infectious complications and prolonged ICU and hospital lengths of stay with greater resource consumption. Whether early goal-directed fluid therapy may prevent ALI/ARDS remains to be determined, while in established ALI/ARDS a fluid-conservative approach is the minimum requirement. Further study is necessary to determine whether more aggressive fluid approaches – such as a decidedly *negative* fluid balance or fluid removal via ultrafiltration – can be achieved in broad groups of ALI/ARDS patients (such as those in shock), and if this more aggressive approach is superior to a simple fluid-conservative approach. Furthermore, whether the addition of a colloid to standard diuretic therapy will improve outcomes for ALI/ARDS patients remains to be determined by large clinical trials.

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