Supplemental Material: Hryciw *et al.* Intravenous Albumin for Mitigating Hypotension and Augmenting Ultrafiltration during Kidney Replacement Therapy. *CJASN* 2020 doi: 10.2215/CJN.09670620

Contents

Additional Details Regarding Albumin Physiology in Patients on Kidney Replacement Therapy.

New Insights Related to Starling Forces and the Endothelial Glycocalyx

Though a transient fluid resorption of approximately 0.5 L may occur during an acute hypotensive episode, in the steady-state, contrary to the historical understanding based on Starling forces, recent research suggests that there is actually no absorption of fluid from the interstitial space via capillaries, with few exceptions (including the kidneys) (1, 2) (i.e. all resorption of fluid that passes out of the capillary due to relatively high hydrostatic pressure within the capillary compared to the extravascular space is returned by the lymphatic drainage rather than some being returned through resorption across the end-capillary due to higher oncotic pressure in the end-capillary relative to the extravascular space). The endothelial glycocalyx, an intricate network of proteoglycans (PGs) and associated glycosaminoglycans lining the vascular endothelial lumen, has been shown to play a significant role in this new model of vascular permeability regulation and microcirculation (3, 4). The glycocalyx consists of proteins that create an osmotic barrier that opposes outward movement of fluid (5).

In both critically ill patients with dialysis requiring acute kidney injury (AKI) and those on maintenance hemodialysis (HD), serum albumin may redistribute into the interstitial space more rapidly due to breakdown of the endothelial glycocalyx, as is illustrated in Figure 2 (main text). This has been confirmed experimentally whereby retention of albumin within the vasculature and its effects on volume expansion has been shown to differ between healthy controls and hospitalized patients. In one study comparing controls to septic individuals, infusion of 200 mL 20% albumin was shown to induce maximum volume expansion at approximately 30 minutes in both groups (6). However, the degree of maximal volume expansion in healthy individuals compared to those with sepsis differed, estimated at 500 mL and 430 mL respectively when calculated from hematocrit changes over time. The degree of albumin retention within the intravascular space was also reduced in septicemia, where intravenous albumin retention was 10% less in this group at 4 hours (6). This divergence from the theoretical effects of albumin in the hospital setting is presumably secondary to disruption of the endothelial barrier in sick patients, which allows albumin to move more rapidly into the interstitial space (7, 8). Following this movement, not all albumin remains sequestered in the interstitial space and large amounts of albumin may be lost due to small bowel losses in the context of gut hypoperfusion (9).

Poor patient outcomes have been associated with breakdown of the endothelial glycocalyx in the setting of critical illness, such as sepsis (10). Shedding of this endothelial glycocalyx is mediated by several factors, including hypotension, inflammation, oxidative stress and the activation of proteases that breakdown the connections between the glycocalyx and endothelial cells (11, 12). The impact of albumin on this vascular barrier in the setting of acute illness is an emerging area of interest in the literature. Matrix metalloproteinase (MMP) mediated cleavage appears to be one such mechanism with a role in glycocalyx breakdown. Interestingly, serum protein depletion has been identified to amplify endothelial glycocalyx shedding, unrelated to osmotic pressure. Proteins, such as albumin, are felt to protect against MMP degradation of the endothelial glycocalyx through transportation of protein bound substances that inhibit MMP (13). There is evidence in animal studies that use of human albumin restores or protects the thickness of the glycocalyx to a greater extent than that of normal saline or Ringer's lactate (14, 15). Prevention or reduction in vascular in vascular permeability through maintenance of the endothelial glycocalyx would theoretically help preserve intravascular volume and reduce the risk of hemodynamic instability in the setting of critical illness and KRT.

The endothelial glycocalyx also plays an important role in the regulation of microvascular

perfusion (16). In maintenance hemodialysis (HD) patients, Vlhau and colleagues (2012) (17) noted a perturbation in the microvascular circulation of HD patients compared to healthy controls. This was felt to be directly related to dysfunction in the endothelial glycocalyx based on techniques used to detect changes in the glycocalyx dimension and also higher serum levels of glycocalyx constituents (i.e. hyaluronan and syndecan-1) that suggests shedding into the blood (17). They proposed that this dysfunction in the glycocalyx barrier leads to exposure of the underlying endothelium, contributing to the endothelial dysfunction and vascular pathology that burdens maintenance HD patients. Furthermore, it is well known that microvascular perfusion is a key player in tissue hypoxia and that microvascular dysfunction serves an important pathological role in critical illness (18). Changes in microvascular circulation and dysfunction have been shown to be relatively independent from gross hemodynamic parameters and are associated with worse outcomes in critical care (18-21). Animal models of critical illness have shown that infusion of serum albumin (both iso-oncotic and hyper-oncotic solutions) improves microcirculatory parameters, such as increased density of perfused vessels as well as reduced blood-flow heterogeneity in comparison to normal saline (22). However, whether colloids improve microvascular perfusion to a greater extent than saline in the clinical setting remains unknown, and thus far evidence has been conflicting (21).

Antioxidant & Anti-Inflammatory Role of Albumin

In addition to its other functions, human albumin has been shown to modulate oxidative stress and inflammation. Oxidative stress is known to play a pivotal role in critical illness, as well as in the breakdown and dysfunction of the glycocalyx barrier that can lead to interstitial edema (12, 23-25). In-vitro studies have demonstrated significant anti-oxidant effects on human cell lines (epithelial, lymphocytic and fibroblast) after incubation with human albumin (26). Another potential effect of albumin may be the direct inhibition of heparin binding-protein which is a mediator of increased endothelial cell permeability and kidney cell inflammation (27). It has been hypothesized that the antioxidant properties of albumin may, in part, explain both the beneficial and conflicting evidence for intravenous albumin in the literature (28). Human albumin, released by the liver into the bloodstream, has multiple ligands that enable it to bind transition metals, preventing reactions that lead to free radical formation. Furthermore, albumin exerts antioxidant properties by binding bilirubin, homocysteine and lipids (29). Endogenous albumin also primarily exists in a reduced form, allowing it to scavenge free radicals and maintain the plasma redox state (28). Commercial human albumin solutions contain heterogenous modifications of albumin that result from the isolation process and storage methods, with significant variability between products, including differences in redox states, potential anti-oxidant properties and molecular binding capacity (30). From this standpoint, it has been suggested that these alterations in human albumin products could result in differences in clinical outcomes from what would be expected based on endogenous albumin physiology (28, 31).

There is little research in the hospital setting regarding the antioxidant and anti-inflammatory nature of albumin. A statistically significant reduction in various inflammatory makers was identified in IDH-prone HD patients routinely treated with infusion of 200 ml 20% albumin, though whether this was a direct effect of albumin versus a reduction in tissue ischemia-reperfusion from low blood pressure is not known (32). Furthermore, in animal models, resuscitation with albumin solutions was the least inflammatory of commonly administered fluids (33). Studies have also suggested that hypoalbuminemia, inflammation and oxidative stress are biologically linked in patients with renal failure (34). In recent literature, it has been shown that the mortality risk associated with hypoalbuminemia in maintenance HD patients may only be increased when accompanied by inflammation, marked by elevated CRP (35). Patients on HD

with hypoalbuminemia but normal inflammatory measures were not at increased risk of death compared to controls (35). It remains unknown whether low serum albumin is directly implicated in patient complications, such as IDH in HD patients, or is instead only an indirect marker of inflammation and poor outcomes. Regardless, it seems likely that inflammation, hypoalbuminemia and endothelial glycocalyx dysfunction are interconnected, and the presence of any individual component may predispose patients to hemodynamic instability during dialysis**.**

Conclusion

Overall, the new paradigm of limited reabsorption at the level of capillary, regulated by the endothelial glycocalyx, highlights some of the controversy and potential trade-offs with respect to the use of intravenous albumin. Although albumin does seem to result in greater volume expansion than crystalloid, this may not be a clinically important difference and overall is poorly studied in the maintenance HD population – a population where fluid balance is a significant focus of management. Other possible benefits of albumin, such as anti-inflammatory effects and repair or maintenance of the endothelial barrier, could defend against third-spacing and loss of effective arterial blood volume, though disruption of the glycocalyx is also associated with increased loss of albumin into the interstitial space (Figure 2 main text).

Supplemental Table 1. Albumin formulations available in the United States and Canada

Brand (Manufacturer)	Concentration	Chemistry	pH	Approximate Cost (USD)
USA				
Albuked (Kedrion Biopharm)	5%	Sodium 145 mEq/L	pH 6.4 – 7.4	$0.23 per mL
	25%			$0.15 - 1.15 per mL
Albuminar (CSL Behring LLC)	5%	Sodium 130 - 160 mEq/L	pH 6.9 +/- 0.5	$0.41 - 43 per mL
	25%			$2.05 - $2.15 per mL
Albuminex (Bio Products Laboratory)	5%	Sodium 130-160 mEq/L	pH not specified	$0.31 - $0.34 per mL
	25%			$1.56 - $1.68 per mL
AlbuRx (CSL Behring LLC)	5%	Sodium 140 mEq/L	pH ~ 7	$0.39 – $0.41 per mL
	25%			$1.97 - $2.07 per mL
Albutein (Grifols Therapeutics LLC)	5%	Sodium 130-150 mEq/L	pH 7.0 +/- 0.3	$0.21 - $0.87 per mL
	25%			$1.06 - $1.91 per mL
Buminate (Baxter)	5%	Sodium 145 +/- 15 mEq/L	Physiological pH	$0.47 - 49 per mL
	25%			$2.08 - $6.13 per mL
Flexbumin (Baxter)	5%	Sodium 145 +/- 15 mEq/L	Physiological pH	$0.28 per mL
	25%			$1.30 - $1.40 per mL
Kedbumin (Kedrion Biopharma)	25%	Sodium 130 – 160 mEq/L	pH 6.4. – 7.4	$1.07 per mL
Canada				
Alburex (CSL Behring LLC)	5%	Sodium 139 mEq/L	pH 6.4-7.4	$0.12 - $0.24 per mL
	25%			$0.60 - $0.65 per mL
Plasbumin (Grifols Therapeutics LLC)*	5%	Sodium 130-160 mEq/L	pH 6.4-7.4	$0.25 – 0.87 per mL
	25%			$1.11 – 1.86 per mL

*Available in the USA & Canada
USD, United States Dollars

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