Commentary

# Debate: Albumin administration should be avoided in the critically ill

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## Abstract

The benefit of albumin administration in the critically ill patient is unproven. Epidemiological evidence suggests that there is an increase in death among patients with burns, hypoalbuminaemia, and hypotension treated with human albumin solution (HAS). In critical illness, hypoalbuminaemia is a result of transcapillary leak, decreased synthesis, large volume body fluid losses and dilution caused by fluid resuscitation. When treating patients with hypoalbuminaemia, efforts must be centred around correction of the underlying disorder rather than reversal of hypoalbuminaemia. Problems with using albumin arise because it is an expensive blood product, and can result in systemic changes that include cardiovascular, haematological, renal, pulmonary, and immunological effects.

**Keywords:** albumin, critical illness

## Introduction

Any benefit for the use of albumin in the adult, critically ill patient is unproven. A low serum albumin concentration in critical illness is known to be associated with a poor outcome [1–4], but correcting hypoalbuminaemia has no impact on outcome in the critically ill. There is epidemiological evidence to suggest that there is an increase in death among patients who are treated with HAS for burns, hypoalbuminaemia and hypotension [5] by up to 6%. The published evidence does not support the use of albumin rather than other agents for volume replacement. We have not used HAS in 98% of our critically ill patients, because of its lack of efficacy and high costs. We believe that there is no role for routine use of albumin in the critically ill patient.

## Role of albumin in critical illness

Some of the functions of albumin include the following: transport; volume expansion and maintenance of colloid oncotic pressure; and scavenging of free radicals.

Unlike synthetic colloids albumin binds reversibly with drugs, hormones, bilirubin and metal ions, among other substances, and so affects their metabolism in the critically ill patient with hypoalbuminaemia [6,7]. Calcium also binds to albumin. Administration of albumin has been shown to result in a decrease in ionic calcium, which could result in myocardial depression [8].

In the intact vascular compartment, HAS has, in common with other colloids, the potential to produce significant volume expansion and has a half-life of 16 h. Serum albumin provides up to 65–75% of the normal colloid oncotic pressure, with globulins and fibrinogen accounting for most of the rest [9–11]. In disease the serum concentration of albumin correlates poorly with colloid oncotic pressure [12]. The concentration of albumin decreases, often dramatically, from early in the course of a critical illness. It does not increase again until the recovery phase of the illness.

HAS = human albumin solution; HES = hydroxyethyl starch.

We retrospectively studied the changes in serum albumin and oncotic pressure between survivors and nonsurvivors of prolonged critical illness [13]. The oncotic pressure varied little between or within either group of patients. There was no relationship between death and oncotic pressure.

Albumin has been shown [14] to be scavenger of free radicals, but this function has not been shown to be of relevance in clinical studies in humans with critical illness.

## Causes of hypoalbuminaemia in critical illness

Hypoalbuminaemia reflects morbidity, and predicts mortality and duration of intensive care unit stay in critically ill patients [1]. Increasing a low serum concentration of albumin, however, does not change the morbidity or mortality in the critically ill [5].

Hypoalbuminaemia may result from the following: transcapillary leak; decreased synthesis; large volume body fluid losses; and dilution due to fluid resuscitation.

The use of albumin for the treatment of hypovolaemia is centred around the argument that albumin will remain in the intravascular space. In the critically ill there is often an inflammatory response that results in capillary leakage and loss of protein (including albumin), inflammatory cells and large volumes of fluid into the interstitial space.

The increased vascular permeability is a major cause of hypoalbuminaemia in disease and injury [15–17]. In a healthy adult albumin is drained by the lymphatics. In illness albumin in the interstitium draws fluid into this space, impairing re-expansion of the intravascular space and increasing tissue oedema [18]. This could result in tissue hypoxia, which may be a contributory cause of multiorgan failure [19,20]. In critically ill patients hypoalbuminaemia is a reflection of the severity of the underlying disease.

The rate of albumin synthesis is also significantly decreased in the critically ill. The acute-phase response to trauma, inflammation or sepsis results in an increase in the gene transcription rates for the positive acute-phase proteins such as C-reactive protein, and a decrease in the rates of albumin mRNA transcription and thus synthesis [21,22]. A sustained inflammatory response in critical illness may lead to prolonged inhibition of albumin synthesis. Interleukin-6 and tumour necrosis factor-$\alpha$ both act to reduce gene transcription [23,24]. Inflammation, induced by turpentine, in rats decreased the albumin mRNA concentration and synthetic rate, which reached a minimum by about 36 h and then began to increase again [25,26].

## Analbuminaemia

There are some healthy humans who are analbuminaemic (essentially total lack of albumin). They have less than 1 g/l albumin in their circulation. They have a surprising paucity of symptoms, possibly because increases in other constituents of plasma such as globulins and lipids counter the lack of albumin. The half-life of the small amount of albumin present increases from 19 days to between 38 and 115 days [9].

## Problems associated with albumin administration

There are several potential problems associated with the administration of this substance, and are discussed below.

### Blood products

The use of any blood product is potentially harmful. Although HAS is pasteurized to reduce the risk of infection, human immunodeficiency virus contamination of a pooled source can be missed at the time of screening. This is because of the window period of seroconversion in donors who have these diseases. It has been suggested [27–29] that estimates of the risk of plasma being sourced from such a pool within the USA vary from one in five pools for hepatitis B virus, to one in 39 for human immunodeficiency virus, although this risk is being reduced with improved testing. Interestingly, the pool from which albumin is sourced for use in UK is from the USA. This change in source of albumin occurred after the suspicion that UK blood products are potentially contaminated with prion proteins.

Biological products are not pure. They contain constituents other than what is on the label. Albumin solution is allowed to be green because of its bilirubin content. There are large differences in the quality of albumin preparations. The presence of oligomers/polymers, endotoxins, haem compounds, prekallikrein, bradykinin and other albumin-bound proteins could alter the quality of albumin, and even result in anaphylaxis. Up to 10% of albumin solutions may be constituted by high-molecular-weight substances. This means that 1 g polymers/aggregates can be infused in a patient receiving 50 ml of 20% albumin [30,31].

### Correction of hypovolaemia and fluid overload

Albumin continues to be used in hypovolaemia by its proponents. One advantage of hypertonic albumin is said to be its ability to increase the intravascular volume by drawing in interstitial fluid from the extravascular compartment. This is limited, however, because in most critically ill patients there is an increased capillary leakage and extravasation of albumin into the interstitium [15–17].

For volume therapy in critically ill patients, no benefit over other colloidal therapies has been shown. Stockwell *et al* [32] examined 475 critically ill patients who were randomly allocated to receive either 4.5% HAS or 3.5% polygeline (Haemaccel, Hoechst UK) for intravenous volume replacement during their stay in the intensive care unit. There was no difference between the groups in the

incidence of pulmonary oedema or acute renal failure. That study showed no benefit in outcome for patients treated with albumin.

With rapid administration of albumin there is up to a four-fold increase in volume retention, which can result in fluid overload, especially pulmonary oedema. Maintenance of the plasma oncotic pressure by albumin blunts the natriuretic response to sodium loading. Infusion of albumin also results in water and sodium retention, which is described below.

**Pulmonary compromise**

An increase in extravascular lung water is seen after lung contusion, sepsis and cardiac failure. The pulmonary lymphatics have a limited ability to remove large volumes of fluid from the interstitium, making it more vulnerable to oedema than other tissues. Evidence [33] suggests that the pulmonary dysfunction in critically ill, septic patients is independent of colloid osmotic pressure. Change in pulmonary capillary permeability is thought to be the primary determinant of interstitial fluid accumulation in the lung after trauma [8]. Leaking of albumin into the interstitium increases the colloid oncotic pressure in this space, and may worsen conditions, such as acute respiratory distress syndrome.

The detrimental effects of albumin on the lung may be related to several factors, including hypervolaemia secondary to antinatriuresis and antidiuresis, and reversed oncotic pressure secondary to increased extravascular pulmonary albumin. Patients treated with albumin for severe hypovolaemia were shown [19] to have a greater dependence on respiratory support, and higher fraction of inspired oxygen:arterial oxygen tension ratios compared with the group who were not treated with albumin.

There is a potential for harm from the accumulation of albumin macroaggregates in the interstitium of the lung, especially among patients with smoke injury. Patients treated with colloids for burns have a greater lung water retention, at day 7 after injury [34].

**Albumin and the microcirculation**

Boldt *et al* [35] examined cardiorespiratory and circulatory variables in critically ill patients treated with either human albumin or hydroxyethyl starch (HES). There was no significant difference between the two groups in the haemodynamic variables studied, although cardiac index was higher in the HES group. Long-term infusion of HES compared with albumin produced improved systemic haemodynamic variables, and specifically improved splanchnic perfusion.

Those investigators also investigated the effects of both volume therapies on plasma concentrations of markers for the inflammatory response [36]. They measured plasma concentrations of adhesion molecules, which are significantly increased during sepsis and indicate endothelial activation or damage. They found that concentrations of adhesion molecules were unchanged or decreased in patients on long-term HES therapy, but in the albumin-treated group concentrations were increased. This suggests that the inflammatory process continued or worsened in patients treated with albumin, whereas patients given HES got better, possibly because of improved microcirculatory haemodynamics.

**Renal impairment**

Albumin causes plasma expansion and increases renal plasma flow, but paradoxically decreases glomerular filtration rate [37]. The mechanism for this decrease in glomerular filtration rate is also unknown. A possible mechanism is the decrease in clearance of albumin polymers as a result of already impaired renal function seen in serious illness. More specifically, albumin macroaggregates could impede glomerular filtration. In addition, the infusion of albumin can result in impaired sodium and water excretion, and worsen renal failure. A proposed mechanism is that albumin increases the oncotic pressure within the peritubular vessels, causing a decrease in sodium and water excretion [38,39].

Albumin was thought to increase the diuretic effect of frusemide. Akcicek *et al* [40] showed that albumin does not potentiate the natriuresis of frusemide. Albumin is thought to bind to frusemide in the renal tubule, inactivating it. Because this is the site of action of frusemide, there is a reduction in its diuretic effect [40].

**Immune system**

Adverse effects such as urticaria, fever and chills can occur with albumin administration, suggesting an immune response [8]. The transfusion of allogeneic blood or blood products results in substantial and clinically significant changes in recipient immune function. Although the main problem is transfusion of white blood cells, large pools of allogeneic albumin could affect host immunity [41,42].

Albumin therapy lowers the concentration of immunoglobulins in the blood and causes a reduced response to tetanus toxoid [43]. More studies need to be done to look into recipient immune response after fluid transfusion.

**Haemostasis**

Albumin affects blood coagulation. This was noted because there was a negative correlation between albumin concentrations and heparin requirements in patients undergoing haemodialysis. It seems to exert a heparin-like action, perhaps related to a similarity in structure of the two molecules. Heparin has negatively charged sulphate groups that bind to positively charged groups on antithrombin III, thus exerting an anticoagulant effect. Serum albumin has many negatively charged groups.

Albumin enhances the neutralization of factor Xa by antithrombin III.

The hypercoagulable state seen in the nephrotic syndrome may, in part, be explained by the accompanying hypoalbuminaemia. This may also be related to the lack of the inhibitory effect of albumin on platelet aggregation. Such an inhibitory effect is both dependent on, and independent of the cyclo-oxygenase system [44].

#### Drug elimination

The structure of the albumin molecule is such that it can incorporate many different substances. It is a flexible molecule, and bound compounds can be buried within the structure. Many drugs, hormones and metals are bound to albumin in the intravascular compartment. This binding is potentially useful in the intravascular compartment. In patients who are hypoalbuminaemic, excess toxicity of highly albumin-bound drugs is known to occur. With extravasation of albumin into tissue this function of albumin binding could upset the concentration of these substances at their effector sites, affecting their function and possibly enhancing toxicity and contributing to mortality [45–47].

#### Increased mortality (Cochrane database)

In a meta-analysis of published trials the Cochrane collaborative group has shown that there is no clinical benefit for albumin in the critically ill. They also show evidence that the risk of death in patients given albumin was 6% higher than that with other colloids [5].

#### Cost

Albumin is an expensive product. Compared with a 4% gelatin solution, a 500 ml bottle of 4.5% albumin costs up to 10 times as much. Considering the amount of plasma expanders required in critically ill patients, the use of albumin represents a significant cost. Significant financial benefit without clinical risk has been shown [48] by using a protocol in which crystalloids are the primary agent of choice in haemodialysis-induced hypotension. The use of albumin has declined in the UK primarily because of its expense and the availability of other colloids that are equally effective [49]. As a result of the decline in albumin use, the plasma products industry has launched a £1.4 million international programme to promote albumin, despite official advice to restrict its use [50,51].

## Guidelines from expert committees

The albumin expert working party for the Committee on Safety of Medicines in the UK looked at the individual trials in the Cochrane report that compared colloids with crystalloids, and concluded that the weighted relative risks for mortality in these trials were as follows: 1.43 for albumin versus crystalloids; 1.26 for dextrans versus crystalloids; and 0.96 for other colloids versus crystalloids [52]. They warn that special care is needed in illnesses that may affect the capillary integrity. They also state that the mechanism of death with albumin might be fluid overload. Because the inflammatory response is common in most causes of critical illness, and this causes capillary leakiness, their recommendation would suggest that it should be avoided.

The therapeutic indications allowed by the Committee on Safety of Medicines for 4.5% albumin include restoration and maintenance of circulating blood volume where volume deficiency has been shown and use of colloids is appropriate. For 20% albumin this should include where electrolyte or fluid load is contraindicated.

A Consortium of hospitals in the USA has also issued guidelines for fluid resuscitation in haemorrhagic and non-haemorrhagic shock, hepatic resection, cardiac surgery and thermal injury [53]. They suggest stringent restrictions for the use of albumin in these situations, crystalloids being the fluids of choice. They also suggest that albumin should be avoided in the event of cerebral ischaemia, and nutritional intervention to correct hypoalbuminaemia.

## Conclusion

The use of albumin in the critically ill patient is not supported by scientific evidence. It is no more effective than other agents used in the treatment of hypovolaemia. It has detrimental systemic effects in the critically ill patient. Furthermore, treatment of hypoalbuminaemia has no significant benefit. Efforts should be concentrated on correcting the underlying cause of disease to reverse hypoalbuminaemia. The use of albumin may cause death.

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