The role of albumin in critical illness

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The last 25 yr have seen major advances in our understanding of albumin. We now know the amino acid sequences of bovine and human albumin, the complete gene sequence of human albumin, and the location of mutations in the gene sequence. During the 1990s, the heart-shaped crystalline structure of albumin has been described and a new protein, termed α-albumin (afamin), has been added to the albumin superfamily, which otherwise consists of serum albumin, vitamin D-binding protein and α-fetoprotein.74

The function of circulating albumin in critical illness is not fully understood. It may differ significantly from that in healthy subjects. A low serum albumin concentration in critical illness is associated with a poor outcome.2 11 66 Despite theoretical advantages for using human albumin solution as a plasma substitute, studies have shown that correcting hypoalbuminaemia has no impact on outcome in the critically ill.28 96 97

This review will examine the role of serum albumin in health and critical illness. It will also review aspects of the physiology of this protein that may be expected to lead to significant dysfunction in critical illness. Finally, the case for and against the use of exogenous albumin in the management of critically ill patients will be discussed.

Structure of albumin

In humans, albumin is the most abundant plasma protein, accounting for 55–60% of the measured serum protein.34 It consists of a single polypeptide chain of 585 amino acids with a molecular weight of 66 500 Da. The chain is characterized by having no carbohydrate moiety, a scarcity of tryptophan and methionine residues, and an abundance of charged residues, such as lysine, arginine, glutamic acid and aspartic acid.77 The mature, circulating molecule is arranged in a series of α-helices, folded and held by 17 disulphide bridges. The folding creates subdomains of three contiguous α-helices in parallel (Fig. 1). A pair of subdomains face each other to form domains. These can be seen as cylindrical structures with polar outer walls and a hydrophobic central core.23

The tertiary structure of human albumin crystal has been isolated by x-ray crystallography. It is seen as a heart-shaped molecule 80 × 30 Å.36 In solution, the shape is quite different. The three domains appear to be arranged in an ellipsoid pattern, giving the molecule low viscosity (Fig. 2).

The molecule is very flexible and changes shape readily with variations in environmental conditions and with binding of ligands.77 Despite this, albumin has a resilient structure and will regain shape easily, owing to the disulphide bridges, which provide strength, especially in physiological conditions.14 After their rupture, the molecule can re-establish these bridges and regain its structure. Denaturation occurs only with dramatic and non-physiological changes in temperature, pH and the ionic or chemical environment.

Albumin metabolism

The serum albumin concentration is a function of its rates of synthesis and degradation and its distribution between the intravascular and extravascular compartments. The total body albumin pool measures about 3.5–5.0 g kg⁻¹ body weight (250–300 g for a healthy 70 kg adult). The plasma compartment holds about 42% of this pool, the rest being in extravascular compartments. Some of this is tissue-bound and is therefore unavailable to the circulation. Each day, 120–145 g of albumin is lost into the extravascular space. Most of this is recovered back into the circulation by lymphatic drainage. Albumin is also lost into the intestinal tract (about 1 g each day), where digestion releases amino acids and peptides, which are reabsorbed. There is minimal urinary loss of albumin in healthy subjects. Of the 70 kg of albumin that passes through the kidneys each day, only a few grams pass through the glomerular membrane. Nearly all of this is reabsorbed, and urinary loss is usually no more than 10–20 mg day⁻¹.
The distribution of albumin between body compartments can be examined by injecting radiolabelled albumin into the venous circulation. A typical biexponential plot of log plasma concentration versus time shows a first-order process (Fig. 3). A two-compartment model can be constructed. There is a rapid phase of disappearance from the plasma over the first 2 days. This represents the transcapillary exchange rate of 4.5% h⁻¹, giving a distribution half-time of about 15 h. Then there is a slower exponential decay, representing the fractional degradation rate (FDR), of about 3.7% day⁻¹ with an elimination half-time of about 19 days. The FDR closely parallels the rate of synthesis in steady state (3.8% day⁻¹).

The extravascular pool is divided into exchangeable and remote components (Fig. 4). Significant locations of this large extravascular pool are listed in Table 1.

The mechanism of the escape of albumin into the extravascular compartment has come under review recently. Albumin must cross capillaries. Most organs in the body have continuous capillaries, but in some there are wide-open sinusoids (liver, bone marrow) or fenestrated capillaries (small intestine, pancreas, adrenal glands). Starling’s theory holds that the rate of escape depends on the permeability of the wall and hydrostatic and oncotic pressures on either side of the wall.⁵⁹ Half of the escaping albumin does so through the continuous capillaries, and there appears to be an active transport mechanism to facilitate this.⁶⁰ Albumin binds to a surface receptor called albonidin, which is widely distributed in many capillary beds, except in the brain.⁶¹,⁶² Bound albumin enters vesicles within the endothelial cell and is discharged on the interstitial side within 15 s. The rate of transfer is increased with the addition of long-chain fatty acids (LCFAs) to albumin, and with the cationization and glycosylation of the molecule.⁶³

Fig 2 The ellipsoid structure of albumin in solution.¹⁴

Fig 3 Decay pattern of labelled albumin versus time after i.v. injection of a tracer dose of ¹³¹I-labelled human serum albumin (thick line). Slope 1 (S1) is the transcapillary escape rate, which equals about 4.5% h⁻¹. Slope 2 (S2) is the fractional degradation rate, which is about 3.7% per hour. EV is the calculated increase in extravascular labelled albumin concentration. Note that the activity of extravascular albumin is greater than that of intravascular albumin from about day 3 onwards. This suggests that degradation occurs directly from the vascular compartment. Reproduced with permission from Peters, 1996.⁶⁶
**Synthesis**

In humans, albumin synthesis takes place only in the liver.\(^{56}\) Albumin is not stored by the liver but is secreted into the portal circulation as soon as it is manufactured. In healthy young adults, the rate of synthesis is 194 (SD 37) mg kg\(^{-1}\) day\(^{-1}\), or about 12–25 g of albumin per day.\(^{76}\) The rate of synthesis rate varies with nutritional and disease states. The liver can increase albumin synthesis to only 2–2.7 times normal because most of the liver’s synthetic machinery is already devoted to albumin at rest.\(^{76}\) The synthetic pathway is common to eukaryotes and is also used for synthesis of other proteins.\(^{52}\)

Albumin will be synthesized only in a suitable nutritional, hormonal and osmotic environment. The colloid osmotic pressure (COP) of the interstitial fluid bathing the hepatocyte is the most important regulator of albumin synthesis.\(^{70,85,107}\) Synthesis requires:

- mRNA for translation;
- an adequate supply of amino acids, activated by binding to tRNA;
- ribosomal machinery for assembly;
- energy in the form of ATP and/or GTP.

The mRNA concentration available for action on ribosomes is an important factor controlling the rate of albumin synthesis. Trauma and disease processes will affect the mRNA content.\(^{55,64}\) A reduction in albumin mRNA concentration, caused by a decrease in gene transcription, is seen in the acute-phase reaction mediated by cytokines, mainly interleukin-6 (IL-6) and tumour necrosis factor α (TNF-α).\(^{12,15,72}\) A decrease in gene transcription is also seen in hepatoma cells and in hepatocytes damaged with carbon tetrachloride.\(^{76}\)

The hormonal environment can affect the mRNA concentration. Insulin is required for adequate albumin synthesis. Diabetic subjects have a decreased synthetic rate, which improves with insulin infusion.\(^{20}\) Perfused livers of diabetic rats have a 50% decrease in gene transcription.\(^{55}\) Corticosteroids have complex effects on albumin synthesis. There is increased albumin synthesis with combinations of steroids and insulin, and of steroids with amino acids.\(^{30,76}\)

**Table 1** Distribution of extravascular albumin in the body.\(^{76}\)

<table>
<thead>
<tr>
<th>Organ</th>
<th>Fraction of body weight (%)</th>
<th>Fraction of total extravascular albumin (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td>18.0</td>
<td>41</td>
</tr>
<tr>
<td>Muscle</td>
<td>45.5</td>
<td>40</td>
</tr>
<tr>
<td>Gut</td>
<td>2.8</td>
<td>7</td>
</tr>
<tr>
<td>Liver</td>
<td>4.1</td>
<td>3</td>
</tr>
<tr>
<td>Subcutaneous, etc.</td>
<td>8</td>
<td>9</td>
</tr>
</tbody>
</table>

**Reduced albumin synthesis**

- Decreased gene transcription
- Trauma, sepsis (cytokines)
- Hepatic disease
- Diabetes
- Decreased growth hormone
- Decreased corticosteroids (in vivo)
- Fasting, especially protein depletion

Hydrocortisone and dexamethasone both increase gene transcription *in vitro*,\(^{65,67}\) but the overall *in vivo* effects are complex. Steroids also increase albumin catabolism. Growth hormone has been shown to stimulate gene transcription in cultured hepatocytes.\(^{41}\)

The rate of synthesis depends on nutritional intake, more so than for other hepatic proteins.\(^{56}\) Fasting reduces albumin production, but specifically omitting protein from the diet causes a greater reduction in synthesis. Early in protein deprivation, there is rapid disaggregation of free and bound polysomes, which can be reversed rapidly by refeeding the subject with amino acids.\(^{21}\) Two amino acids are particularly effective, tryptophan and ornithine.\(^{83}\) Ornithine, unlike tryptophan, is not incorporated into albumin. It is a product of the urea cycle and acts as a precursor of the polypeptide spermine. The increases in polysome aggregation and albumin synthesis with ornithine refeeding suggest that the urea cycle plays more of a role in protein metabolism than mere waste disposal.\(^{69}\) Protein deprivation for a longer time leads to a 50–60% decrease in the activity and concentration of the mRNA, presumably through increased breakdown, as gene transcription is not slowed in rats on a 0–4% protein diet.\(^{86}\)

Calories are important, however. There is a reduction in synthesis in starved rats, and polysomes will regaggregate with glucose feeding alone.\(^{80}\) Energy rather than the amino acid supply may be more important in determining polysome aggregation under normal circumstances.\(^{23}\)

**Table 2** Factors that modify albumin metabolism (see text for details)

Degradation

Total daily albumin degradation in a 70 kg adult is around 14 g day\(^{-1}\) or 5% of daily whole-body protein turnover. Albumin is broken down in most organs of the body. Muscle
and skin break down 40–60% of a dose of labelled albumin. The liver, despite its high rate of protein metabolism, degrades 15% or less of the total. The kidneys are responsible for about 10%, while another 10% leaks through the stomach wall into the gastrointestinal tract. The mechanism of breakdown involves uptake into endocytotic vesicles, which fuse with lysosomes in endothelial cells. This may involve binding to endothelial surface membrane scavenger receptors, called gp18 and gp30, which are widespread in the body tissues. They bind altered or denatured albumin, and it is likely that chemical modification of the circulating albumin is a signal for receptor-linked lysosomal degradation. It is also possible that modification prevents degradation. Binding of LCAFs to albumin seems to protect the molecule from breakdown. In analbuminemia, the LCAF/albumin ratio is increased and degradation is suppressed. The final breakdown products are free amino acids that add to the pools of amino acids within cells and in the plasma.

**Albumin and critical illness**

Critical illness alters the distribution of albumin between the intravascular and extravascular compartments. There are also changes in the rates of synthesis and degradation of the protein. The serum albumin concentration will decrease, often dramatically, from early in the course of a critical illness. It will not increase again until the recovery phase of the illness. The kinetics of albumin given i.v. will differ greatly between critically ill patients and healthy subjects. The implication of this, given the important functions albumin has in health, is that using exogenous albumin to increase the intravascular albumin concentration during critical illness is beneficial. But studies have failed to show any benefit of albumin over other colloidal therapies in adults.

The altered distribution in critical illness is related to an increase in capillary leakage. This occurs in sepsis and after major surgical stress. It involves dysfunction of the endothelial barrier, resulting in capillary leakage and loss of protein, inflammatory cells and large volumes of fluid into the interstitial space. The precise mediators of this capillary leakage are still being discovered and currently include:

- endotoxin from Gram-negative bacteria
- cytokines—TNF-α and IL-6
- arachidonic acid metabolites—leukotrienes and prostaglandins
- complement components C3a and C5a
- other vasoactive peptides—bradykinin, histamine
- chemokines—macrophage inflammatory protein 1α

The normal transcapillary escape rate for albumin increases by up to 300% in patients with septic shock, and by 100% after cardiac surgery. In septic patients, the transcapillary exchange rate may well improve with appropriate treatment. With increased flow of albumin across capillary membranes, there should be an increase in lymphatic return to the intravascular compartment. Studies of albumin kinetics during major surgery have shown a reduction in the flow rate of lymph and the albumin concentration in lymph. It is not known if this extends into the postoperative period. Measurement of total circulating and total exchangeable albumin pools shows a 30% reduction with major surgery, consistent with sequestration of albumin into non-exchangeable sites, such as wounds, the intestine and extra-abdominal sites.

The rate of albumin synthesis may be significantly altered in the critically ill. In the acute-phase response to trauma, inflammation or sepsis, there is an increase in the gene transcription rate for the positive acute-phase proteins such as C-reactive protein, and decreases in the rate of transcription of albumin mRNA and the synthesis of albumin. IL-6 and TNF-α both act to reduce gene transcription.

Induced inflammation in rats decreased the concentration of albumin mRNA and the rate of albumin synthesis, which reached a minimum by about 36 h and then began to rise again. A sustained inflammatory response in critical illness may lead to prolonged inhibition of albumin synthesis.

Catabolism of albumin may also be altered. The FDR is mass-dependent. That is, as the serum albumin concentration decreases, so does the FDR. Studies have shown a significantly shorter plasma half-life in hypoalbuminemic patients on total parenteral nutrition (9 days), but with a catabolic rate similar to normal. However, in situations of increased transcapillary albumin flux, an increase in the FDR has been observed. It is possible that the vascular endothelium has an important role in the degradation of albumin. In animal experiments, the tissues most actively involved in albumin catabolism are those with fenestrated or discontinuous capillaries. It may be that a high rate of tissue exposure in situations of increased capillary permeability may increase catabolism. However, studies of albumin extravasation in myxoeedema found that, while there was an increase in the extravascular pool of albumin, there was a decrease in the catabolic rate, implying tissue exposure and trapping of albumin, protecting it from degradation.

**Functions of albumin**

Albumin has extensively studied and well-established physiological functions in health. There are, however, few studies on the function of albumin in the critically ill.

**Oncotic pressure**

In healthy subjects, the role of albumin in the maintenance of normal COP is well recognized, but there appears to be little correlation between albumin and COP in the critically ill. In health, albumin contributes up to 80% of the normal COP of about 25 mmHg. This is because of its high
molecular weight and concentration in plasma. Albumin is present at a higher concentration than other plasma proteins, and though its molecular weight of 66.5 kDa is less than the average for serum globulins (about 147 kDa), it still has the greatest osmotic significance. This direct osmotic effect provides 60% of the oncotic pressure of albumin. The remaining 40% is a result of its negative charge, providing an attractive force for the intravascular retention of positively charged solute particles (the Gibbs–Donnan effect). Due to the large extravascular pool of albumin, its water-solubility and its negative charge, albumin also plays a significant role in the regulation of tissue fluid distribution.

Critically ill patients have a lowered serum COP. A sequential series of 200 critically ill patients had an mean COP of 19.1 mmHg. A lowered COP is associated with increased morbidity and mortality in critically ill patients. A serum COP of 15 mmHg was associated with a survival rate of 50%. Proponents of albumin supplementation argue that giving albumin will increase the COP and avoid potentially fatal complications such as pulmonary oedema, though the association with fatal progression of respiratory failure has not been substantiated by other studies. The pulmonary lymphatic system is capable of a sevenfold increase in flow rate in response to isobaric reduction in COP, to a level sufficient to induce massive peripheral oedema and ascites in baboons. There is evidence to suggest that the pulmonary dysfunction in critically ill, septic patients is independent of COP.

Binding of substances to albumin

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. Some general trends have emerged from binding studies. Most strongly bound are medium-sized hydrophobic organic anions, including long-chain fatty acids, bilirubin and haematin. Less hydrophobic and smaller substances can be bound specifically but with lower affinity, such as ascorbate and tryptophan. The chirality of the compound may be important: L-tryptophan is bound more strongly than D-tryptophan. Monovalent cations do not bind, but divalent cations do, namely calcium and magnesium. Albumin has a strong negative charge, but there is little correlation between the charge of the compound and the degree of binding to albumin. Acidic drugs tend to bind to other plasma proteins such as α1-acid glycoprotein whereas basic drugs tend to bind to albumin. There are exceptions, and drugs may bind to both.

Other endogenous compounds that bind to albumin include bile acids, eicosanoids, copper, zinc, folate and acutabolin. Albumin is also a secondary or tertiary carrier for some substances that have specific binding proteins, for example, steroids, including derivatives such as vitamin D and thyroxine. This can be clinically significant. Steroids have a low binding affinity for albumin but there is a large capacity owing to the high concentration of albumin. Thus a significant amount may be carried by albumin, and the lower binding affinity means that there is easy off-loading at target sites.

Drug-binding studies have traditionally been performed in vitro, measuring affinity and competition between ligands, at non-physiological temperature and with non-human albumin species. It is difficult to draw conclusions about in vivo binding from these studies. In recent years techniques such as DNA sequencing, fluorescence emission of ‘reporter’ compounds, which respond to the presence of ligands, x-ray diffraction and the isolation of functional fragments of albumin have given insight into the functional sites of binding.

Drug binding strongly affects the delivery of bound drug to tissue sites and the metabolism and elimination of the drug. The free serum concentration is the relevant factor in these processes. Highly bound drugs have only a small percentage of the total serum concentration in the free form. Other factors that are important in drug–albumin interactions and may be responsible for the wide interindividual variation seen include age (binding may decrease at the extremes); temperature, pH and ionic strength, which can affect the number of binding sites in vitro; and competition between drugs for binding sites.

Displacement of drugs from their binding sites by other drugs or by endogenous substances occurs and may alter the distribution, pharmacological action, metabolism and excretion of the displaced drug. There are a variety of binding sites on the albumin molecule. Sudlow et al. have classified drugs into two groups according to two broad binding sites, site I and site II. Site I appears to lie along the long loop of subdomain IIa, extending into the shorter loop. Many different drugs seem to bind here, including salicylates, warfarin, phenylbutazone, indometacin, digitoxin, furosemide, phenytoin, chloropropamide and some penicillins. Dyes such as sulfobromophthalein, iophen- oxate (a radio-opaque dye), methyl red, Evans blue and bromocresol green also bind here, as do endogenous compounds such as bilirubin.

Site II is a hydrophobic pocket of residues located in subdomain IIb. It is responsible for binding compounds such as L-tryptophan, thyroxine (which may also bind at site I), medium-chain fatty acids and chloride. Drugs that bind here include diazepam and other 2,3-benzodiazepines, non-steroidal anti-inflammatory agents that have ionized carboxyl groups (such as ibuprofen and naproxen) and clofibrate. Many other substances bind to various different sites on the albumin molecule.

There are many factors influencing drug–albumin interactions that become relevant in critically ill patients. Renal failure provides a good example of the mechanisms involved. The serum albumin concentration may be directly altered, due to increased loss of albumin through damaged glomeruli. Renal failure may influence drug binding to albumin. Possible mechanisms involved include changes in
pH$^{19}$ and the accumulation of compounds which compete with drugs for binding sites. Thus, there may be an increase in the free fraction of drugs in renal failure, resulting in an increased drug effect. We have compared cyclosporin (not bound to albumin) with tacrolimus (bound to albumin) in patients after liver transplantation who were given human albumin solution to maintain a serum albumin concentration of $>20$ g litre$^{-1}$ or a gelatin solution.$^{102}$ Patients given tacrolimus with the gelatin solution had a greater increase in their serum creatinine than all the other groups. The reason for this may be the greater free fraction of tacrolimus, causing nephrotoxicity. Reves and colleagues$^{82}$ showed that the onset of sleep in patients given midazolam was faster in those with a lower serum albumin concentration. We have shown that the rate of metabolism of midazolam by human liver microsomes is inversely proportional to the albumin concentration in the incubate, although the reverse occurred when human hepatocytes in long-term primary culture were used (unpublished observation, Park GA, Miller L).

Measurement of the free fraction of a drug such as midazolam in vivo is difficult. Patients with renal failure in an intensive care unit commonly require renal replacement therapy in the form of continuous venovenous haemofiltration. This uses a semipermeable membrane with a pore size of 45 000 Da. Substances of small molecular weight, such as midazolam, have a sieving coefficient of 1; they are freely filtered. The concentration in the filtrate will be the same as the free plasma concentration. Simultaneous measurement of blood and filtrate concentrations might allow the bound and free midazolam to be calculated (bound=total midazolam−free midazolam).

A thorough knowledge of the pharmacokinetic principles outlined above, and of possible drug interactions and displacement reactions, is vital for the management of critically ill patients. In many cases it is necessary to monitor the free serum concentrations of drugs to avoid toxicity.

**Metabolic function**

Apart from its vital role in transporting drugs and endogenous compounds, albumin is also involved in the inactivation of a small group of compounds.$^{76}$ Disulfiram is inactivated by binding with albumin. Members of the penem group of antibiotics bind irreversibly to albumin, through acetylation of an ε-lysine group close to the surface of the molecule in the region of Sudlow site 1.$^{75}$ The resulting complex may be clinically significant. Penicillin allergy has been linked to irreversible coupling of penicilloyl groups to these lysine groups. Coupling causes ‘bisalbuminaemia’, seen as a more rapidly moving albumin on an electrophoretic strip. This is associated with the appearance of antibodies to the drug–albumin complex (antipenicilloyl antibodies) in patients treated with penicillin.$^{53}$

Albumin is also involved in the metabolism of endogenous substances such as lipids and eicosanoids, because of the avidity with which these compounds bind to albumin. For instance, lipoprotein lipase activity in adipose tissue can be stimulated by the avidity with which fatty acids, freed from lipids in fat stores, bind to available albumin. Albumin can stabilize some eicosanoids during metabolism, such as prostaglandin $I_2$ and thromboxane $A_2$; it can increase the release of arachidonate from macrophages; and it seems to favour lipo-oxygenase over cyclo-oxygenase activity.$^{76}$

**Acid–base function**

The presence of many charged residues on the albumin molecule and the relative abundance of albumin in plasma mean that it can act as an effective plasma buffer.$^{23}$ At physiological pH, albumin has a net charge of negative 19. It is responsible for about half of the normal anion gap. A reduction in plasma protein concentration causes metabolic alkalosis. A decrease in serum albumin of 1 g dl$^{-1}$ may increase standard bicarbonate by 3.4 mmol litre$^{-1}$, produce a base excess of 3.7 mmol litre$^{-1}$ and reduce the anion gap by 3 mmol litre$^{-1}$. $^{58}$

**Antioxidant function**

Under physiological conditions, albumin may have significant antioxidant potential. It is involved in the scavenging of oxygen free radicals, which have been implicated in the pathogenesis of inflammatory diseases. Physiological solutions of human serum albumin have been shown to inhibit the production of oxygen free radicals by polymorphonuclear leukocytes.$^{37}$ This may be related to the abundance of sulphhydril (-SH) groups on the albumin molecule. These are important scavengers of oxidizing agents, such as hypochlorous acid (HOCI) formed from the enzyme myeloperoxidase, which is released by activated neutrophils.$^{38, 103}$ Other plasma substances, such as uric acid and ascorbic acid, are less important scavengers, but may be more important in extracellular fluids that have a low albumin concentration.$^{39}$ The implication of this is that hypoalbuminaemic patients have a reduced potential for oxygen radical scavenging. Serum from patients with rheumatoid arthritis shows decreased protection against α1-antiproteinase inactivation by HOCl and $H_2O_2$. $^{105}$ The situation in critically ill patients has not been investigated.

**Maintaining microvascular integrity**

It is possible that albumin has a role in limiting the leakage from capillary beds during stress-induced increases in capillary permeability.$^{22}$ Endothelial cells seem to be able to control the permeability properties of the capillary membrane, possibly by altering the nature and distribution of glycoproteins in the vessel wall. Albumin plays a part in this action, though the exact mechanism is not clear. It may involve the strong negative charge on the albumin molecule repelling other negatively charged molecules in the mem-
brane, or it may be a space-occupying function of the albumin molecule that reduces the size of channels. It is likely that only a small amount of albumin is necessary for this function. A direct protective function of albumin is suggested by the observation that albumin prevents apoptosis in cultured endothelial cells.\textsuperscript{110} Peak protection was seen at physiological concentrations of albumin.

It is also likely that other colloids are effective in preserving microvascular architecture.\textsuperscript{101} Medium molecular weight starches have been shown to produce higher reflection coefficients and less transcapillary leakage in animal studies, when compared with crystalloid, albumin and starches of smaller molecular weight. Human studies are needed, especially in the light of encouraging evidence of the beneficial effects of hydroxyethyl starch (HES) over albumin in terms of cardiorespiratory variables and splanchnic perfusion,\textsuperscript{9} which suggest attenuation of endothelial cell activation, and improved intravascular volume that is possibly caused by the plugging of capillary channels.

Albumin is the most important source of sulfhydryl groups in the circulation. Nitric oxide (NO) binds to these sulfhydryl groups to form a stable S-nitrosothiol group, and is thus protected from rapid degradation. The effects of albumin on the vasodilatory properties of NO have been studied \textit{in vitro}.\textsuperscript{46, 47} Albumin slowed the onset and reduced the maximal intensity of the vasodilatory response to NO. It is possible that albumin has a role in the modulation of vascular tone in different vascular beds, though there is no evidence for this.

\textbf{Anticoagulant effects}

Albumin has effects on blood coagulation. It seems to exert a heparin-like action, perhaps related to a similarity in the structures 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. There is a negative correlation between albumin concentration and the heparin requirement in patients undergoing haemodialysis.\textsuperscript{42} These investigations have shown a heparin-like activity of albumin, through enhancement of the neutralization of factor Xa by antithrombin III. They suggest that 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.\textsuperscript{43}

\textbf{Genetic mutations and analbuminaemia}

Around 100 variant forms of the albumin molecule have been described. These have been based on electrophoretic mobility studies. The locations of about 60\% of these genetic mutations are known. Besides haemoglobin, albumin has the greatest number of known variants. Only one variant has been shown to change the function of albumin. This is the form of albumin which has increased affinity for thyroxine, leading to the condition of familial dysalbuminaemic hyperthyroidism.\textsuperscript{72} Since the first report, in 1954, of a patient with no detectable albumin on electrophoretic studies, nearly 30 cases of analbuminaemia have been found.\textsuperscript{73} It is a rare condition and cases are widely dispersed. This would suggest that the cause is local gene mutation. The mutant gene in a family would be expressed only through intermarriage of its descendants, resulting in a homozygous individual. The albumin gene appears to be present, but mutations produce effects such as mRNA splicing errors, and early prevention of translation by premature stop codons.\textsuperscript{73}

The condition has baffled scientists convinced of the requirement of albumin for survival. There is some circulating albumin, probably owing to gene leakage, and cases are now defined as having a serum albumin concentration of <1 g litre\textsuperscript{−1}. This small amount of albumin seems to be sufficient for existence under normal conditions but, given a stressful environment, animal studies suggest that subsistence requires a higher circulating albumin concentration. Cases are not usually picked up until adulthood. The main pathological features are: peripheral oedema; lipodystrophy giving lower limb obesity; fatigue; and hyperlipidaemia, but without resultant atherosclerosis. Haemodynamic changes are minimal. There is a reduction in COP (16 vs 25 mmHg), a reduction in arterial pressure and a resultant increase in renin and aldosterone concentrations. The body seems to compensate by slowing the rate of degradation of the small amount of albumin present.\textsuperscript{73} Study of these individuals may give insight into the effects of hypoalbuminaemia in the critically ill.

\textbf{The prognostic value of serum albumin}

Serum albumin appears to be a reliable prognostic indicator in various contexts. A recent review suggests that serum albumin could be an independent predictor of mortality in a wide range of clinical and research settings.\textsuperscript{32} It reports an estimated increase in the odds of death from 24 to 56\% for each 2.5 g litre\textsuperscript{−1} decrease in serum albumin concentration over the range of studies reviewed. Large community-based studies have shown a link between low serum albumin and an increase in morbidity and mortality.\textsuperscript{25, 93} In one study, a serum albumin concentration of less than 34 g litre\textsuperscript{−1} was associated with a 30-day mortality rate of 24.6\%. This increased to 62\% if the serum albumin concentration was 20 g litre\textsuperscript{−1} or less.\textsuperscript{81}
The prognostic value of serum albumin extends to critically ill patients.\textsuperscript{2} 11 16 33 A low serum albumin concentration correlates with increased length of stay in the intensive care unit (ICU) and with complication rates, such as ventilator dependency and the development of new infection.\textsuperscript{66} The daily trend of serum albumin can be a useful tool in predicting the weaning capability of patients needing mechanical ventilation.\textsuperscript{88} Non-survivors of critical illness have lower serum albumin concentrations than survivors.\textsuperscript{33} 90 In one study, non-survivors had lower serum albumin concentrations on admission to the ICU, and their albumin concentrations decreased more rapidly in the first 24–48 h.\textsuperscript{59} The albumin concentration on admission was not a sensitive indicator of outcome, but the value at 24–48 h was as accurate as the APACHE II score in predicting mortality. The APACHE II system does not include serum albumin concentration as an independent predictor, and it has been found to be poorly predictive in hypoalbuminaemia.\textsuperscript{79} The APACHE III system does include serum albumin concentration, and it is more predictive of mortality in critical illness.\textsuperscript{50}

We have also shown a significant difference between serum albumin concentrations of non-survivors and survivors of prolonged critical illness. Patients who were in the ICU for 7 days or more and survived had higher mean serum albumin concentrations than non-survivors, and were able to recover to a higher mean serum albumin concentration than non-survivors.\textsuperscript{6} Significantly, there was no difference between the COPs of the two groups.

Similar results have been reported in other studies, in which serum albumin was used as a measure of the nutritional state of patients.\textsuperscript{11} 16 66 Some claim a benefit in supplementing total parenteral nutrition with albumin in terms of reducing in-hospital morbidity.\textsuperscript{13} 45 However, it is now accepted that serum albumin is not a reliable marker of nutritional status in critically ill patients.\textsuperscript{49}

\textbf{Intravenous albumin: use and abuse}

Albumin therapy has certain specific indications, but for volume therapy in critically ill patients no benefit over other colloidal therapies has been shown.\textsuperscript{96} 97 Stockwell and colleagues\textsuperscript{97} examined 475 intensive care patients randomized to receive either 4.5% human albumin solution or 3.5% polygeline (Haemaccel, Aventis, Marburg, Germany) for i.v. volume replacement during their stay in the ICU. Outcome measures were length of ICU stay and mortality. All patients received crystalloid solutions for basal fluid requirements, total parenteral nutrition if enteral nutrition was not possible, and blood products as required. Some patients in the gelatin group did receive concentrated albumin if they had profound hypoalbuminaemia that was felt to be contributing to peripheral and or pulmonary oedema. The authors point out that the clinical impact of this practice was minimal, the effect on the plasma albumin concentration was short-lived and the clinical course of the patients was not altered. The practice diminished during the study. There was no difference between the two groups in length of stay or mortality, a result that surprised the authors, who outlined several potential advantages of albumin in the critically ill. The same authors also looked at pathophysiological variables in the same patients.\textsuperscript{90} They found that patients in the gelatin group had lower mean serum albumin concentrations. When both groups were divided into survivors and non-survivors, albumin therapy maintained the serum albumin concentration in the survivors but not in the non-survivors. There was no difference between the groups in the incidence of pulmonary oedema or acute renal failure. These data are useful in confronting supposed indications for treating hypoalbuminaemia in critically ill patients. Despite improving the serum albumin concentration, there is no benefit in outcome for patients treated with albumin.

Another randomized controlled trial examined cardiorespiratory and circulatory variables in ICU patients treated with either human albumin therapy (HA) or HES.\textsuperscript{7} There was no significant difference between the two groups in the haemodynamic variables studied, though the cardiac index was higher in the HES group. Long-term infusion of HES compared with HA produced improved systemic haemodynamic variables, and specifically improved splanchnic perfusion. These authors also investigated the effects of both volume therapies on plasma concentrations of markers of the inflammatory response.\textsuperscript{8} They measured plasma concentrations of adhesion molecules, which are significantly increased during sepsis and indicate endothelial activation or damage. They found that in patients on long-term HES therapy the concentrations of adhesion molecules were unchanged or decreased, whereas in the HA group concentrations were increased, suggesting that the septic process continued or worsened in patients treated with albumin, whereas patients given HES got better, possibly because of improved microcirculatory haemodynamics.

Burnt patients are a specific group for whom albumin may have a beneficial role. In the first 24 h there is a marked increase in capillary permeability and transcapillary fluid shifts. It is argued that colloid infusion is unjustified in this situation, as it is inefficient in reducing fluid shift and may contribute to delayed pulmonary oedema.\textsuperscript{57} However, albumin is justified after 24 h in profoundly hypoalbuminaemic patients, as it favours the reabsorption of oedema.\textsuperscript{57} The Guidelines of the Consensus Conference in Paris have stated that albumin is not necessary for burns covering less than 15% of the body surface, but is essential from the start of treatment for patients with greater than 50% burns.\textsuperscript{87} Between these values, albumin is required but can be postponed for up to 24 h.

Another group who may benefit from albumin therapy are cirrhotic patients with ascites requiring paracentesis. Postparacentesis circulatory dysfunction, defined as an increase in plasma renin activity on the sixth day after paracentesis, is associated with increased morbidity and
mortality. Albumin was shown to be more effective than either dextran or polygeline in preventing this complication in 289 patients studied.\textsuperscript{30} Data discussed in the following section outline further groups of patients who may benefit from albumin.

Like any therapy, albumin has its side-effects. Injudicious use can lead to fluid overload, as plasma volume increases linearly with the dose of albumin. It may cause myocardial depression, perhaps related to the binding of calcium ions.\textsuperscript{24} Allergic reactions to albumin are rare but may occur, usually to contaminants in the solution or to polymers that form upon storage.\textsuperscript{29} Hypersensitivity reactions may be seen when certain drugs covalently bind to albumin; penicilloyl coupling has already been mentioned. Viral transmission is highly unlikely due to prolonged heat treatment during preparation.\textsuperscript{103} However, it is under renewed scrutiny after the decision to stop the pooling of British donated blood for manufacturing blood products, including human albumin solution, due to the theoretical risk of transmitting new variant Creutzfeld–Jakob disease.

Albumin is expensive. A 500 ml bottle of 4.5% human albumin solution costs up to 10 times as much as a 4% gelatin solution. Considering the amount of plasma expanders required in critically ill patients, the use of albumin represents a significant cost.

**Cochrane database meta-analysis**

The debate about the use of albumin in the critically ill has been stimulated by the publication of a meta-analysis in the *British Medical Journal.*\textsuperscript{17} The authors reviewed 32 randomized controlled trials, published between 1975 and 1998, in which albumin was used in the treatment of hypovolaemic, burnt or hypoalbuminaemic patients. The data suggested that the use of albumin in these groups resulted in six additional deaths per 100 patients. This message was widely broadcast by newspaper and television media, and there was a series of vigorous responses to this article from the medical fraternity. The controversy seems to have centred on the validity of the conclusions drawn from such a heterogeneous group of studies. The tool of meta-analysis is relatively new in statistical terms. In the current era of evidence-based medicine, clinicians are right to be wary of data re-examined by an alien tool. To change current clinical practice, evidence must be unequivocal and widely accepted. This systematic review did not present new data, and it is correct to criticize conclusions about mortality data from studies not using it as an outcome measure. However, the authors have clearly discussed the limitations of the review, acknowledging that the studies were small and there were few deaths. The choice of mortality as the outcome measure of the meta-analysis was based on the availability of the studies of data on death, and the measurement error and bias that may be associated with using pathophysiological outcomes. They point out that the studies examined represent the current licensed indications for albumin, which are the emergency management of shock, the treatment of burns, and conditions associated with hypoproteinaemia. They also acknowledge the possibility of publication bias threatening the validity of the meta-analysis, but are in a position to use sophisticated statistical analysis to justify their conclusions. Upon closer inspection, the actual conclusions of the review are that urgent attention needs to go into ‘a properly... conducted randomized controlled trial with mortality as the end point’ and in the meantime ‘a review of the licensed indications for albumin use’.\textsuperscript{17} A more detailed discussion can be found elsewhere.\textsuperscript{18}

Some of the responses to the review, published electronically, contained new data. Jones and colleagues suggested that capillary leakage may explain the increased mortality, and presented data showing that albumin leakage was greater in critically ill patients than in patients after major surgery, in whom it was in turn greater than patients with polycythaemia.\textsuperscript{104} Thus, infusion of albumin in the critically ill would not increase the intravascular albumin concentration, and would exacerbate interstitial oedema. Our preliminary data showing the toxicity of tacrolimus (FK506) in patients with a low concentration of albumin after liver transplantation represents a group that may benefit from maintaining a predetermined circulating concentration of albumin.\textsuperscript{102} Data from the Netherlands Cancer Institute have shown that patients with peritoneal cancer undergoing prolonged surgery might also benefit from albumin therapy.\textsuperscript{24}

Further electronic correspondence proposed explanations of why albumin might not work. It may be that the beneficial effects of albumin in the circulation, such as the binding of toxins, heavy metals and drugs, are detrimental outside of the circulation, given the increase in capillary permeability during critical illness.\textsuperscript{61} There may also be adverse immunological effects of albumin transfusion that could explain the increase in mortality suggested by the meta-analysis. More recently, the effects of albumin from different manufacturers and indeed different batches on adhesion molecules have been described.\textsuperscript{58}

**Conclusions**

Albumin has well-established and important functions in health. Its kinetic and dynamic properties are significantly altered in the critically ill. There is no significant correlation between serum albumin concentration and COP in these patients. Drug binding by albumin is important in critically ill patients, but the increased free fraction of drugs in patients with hypoalbuminaemia does not necessitate treating the decreased serum albumin concentration.

The choice of fluid for resuscitation in the critically ill remains contentious. Despite the fact that a low serum albumin concentration is an independent predictor of morbidity, there is no evidence to support the use of albumin to treat hypoalbuminaemia or hypovolaemia in
critically ill patients.4 28 81 96 97 Future research needs to address why the theoretical advantages of albumin are not borne out in clinical practice. This may identify patients in whom albumin is the volume expander of choice. In the wake of the highlighted meta-analysis, there is an urgent need for properly constructed trials in the critically ill.

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