HUMAN ALBUMIN SOLUTIONS

D B L McClelland

Production of albumin and solutions available

Human albumin solutions for clinical use

	Human albumin (4·5 or 5%)	Human albumin (20%)	Plasma protein fraction (stable plasma protein solution)
Concentration of human albumin (g/l)	40-50	200	50
Albumin (as % total protein)	>96	>96	>85
Colloid osmotic pressure (mm Hg)	26-30	100-120	26-30
Sodium (mmol/l)	140-160	140-160*	140-160
Potassium (mmol/l)	<2	<10	<2
Stabilisers:			
Caprylate (nmol/l)	4	16	4
N-acetyl tryptophanate (mmol/l)	4	16	4
Typical dose units (others may be available from some suppliers)	250 or 500 ml	50 or 100 ml	250 or 500 ml

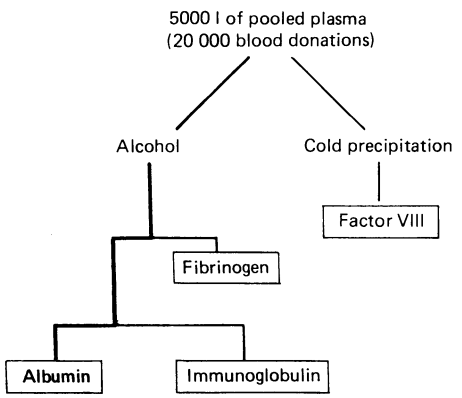
*In 20% albumin, the sodium content/g albumin is about a quarter of that in the other products.

Human albumin solutions were developed in the United States during the second world war to provide an alternative to blood or dried plasma for resuscitating military casualties. The method by which comparatively pure albumin solutions were produced from large quantities of pooled donor plasma by cold ethanol fractionation is still the basis for the production of almost all albumin products for clinical use. Albumin solutions contain no bactericide or antibiotic. The final product is sterilised by filtration and then heated for 10 hours at 59·5-60·5°C to inactivate any contaminating viruses. Before issue the bottles are held for at least two weeks at 30-32°C and examined for evidence of bacterial contamination. The rigorous application of these standards has contributed to the excellent safety record of albumin products.

Albumin solutions (stabilised plasma protein solution and plasma protein fraction) are available from the National Blood Transfusion Services, which have two manufacturing plants in the United Kingdom, and from commercial suppliers.

Physiological functions of albumin

Production of albumin solution from blood donor plasma



1 bottle of 5% albumin (20 g) requires the plasma that can be separated from four whole blood donations

Binding activity—Albumin, despite having a strong negative charge, binds both anions and cations—organic and inorganic—as well as uncharged material. Endogenous substances bound by albumin include long chain fatty acids, bilirubin, phospholipids, and other lipids including steroids and metallic cations like calcium and copper. Albumin also binds many drugs.

Colloid osmotic activity—Physiological concentrations of albumin (40-50 g/l in plasma) account for 60-80% of the normal plasma colloid osmotic pressure (26-28 mm Hg). Human albumin solutions (5%) have a similar colloid osmotic pressure to plasma, and 20% solutions are hyperoncotic.

Congenital albumin deficiency—This rare condition raises intriguing questions about the biological necessity for albumin. Affected subjects with albumin concentrations below 0·1 g/l may experience only mild (or no) oedema and have no obvious problems attributable to disordered transport functions. Compensatory increases in the concentrations of other plasma proteins are partly responsible for their lack of symptoms.

Therapeutic use of albumin solutions

Controlled clinical trials comparing crystalloid solutions and albumin in fluid replacement

Study No	Conditions studied	No of patients in each group	Average age of patients	Outcome
1	Elective aortic reconstruction	Ringer's solution 14 Albumin 15	58 58	Group receiving crystalloid required more fluid (average 11 litres) than those receiving albumin (6 litres). Pronounced fall in plasma colloid osmotic pressure in group receiving crystalloid but no difference between groups in pulmonary shunt or duration of ventilation. Two patients developed pulmonary oedema, both in group receiving albumin
2	Major trauma	Ringer's solution 84 Albumin 55	28 32	Three deaths in each group. Assisted ventilation needed in 4% of those receiving crystalloid and 14% of those receiving albumin. No significant changes in pulmonary function tests.
3	Major trauma (this report describes the patients from study No 2 who were shocked on admission)	Ringer's solution 22 Albumin 16	30	One death in each group. Two patients in each group needed assisted ventilation
4	Shock (mostly with sepsis)	Saline 8 Hydroxyethyl starch 9 Albumin 9	72 80 82	Group receiving crystalloid required 2-4 times more fluid, developed much lower plasma colloid osmotic pressure and 87% had radiological evidence of pulmonary oedema (22% in the two groups receiving colloid). Pulmonary gas exchange was similar in all groups. No difference in mortality
5	Shock and pulmonary insufficiency (radiological evidence with shunt >20%) most with sepsis	Ringer's solution 26 Albumin 20	51 44	Report only covers 48 hours of observation. Both groups showed improvement in intrapulmonary shunt. Greater improvement among those receiving albumin. No significant differences in other measurements of cardiorespiratory function

1 Virgilio RW, Rice CL, Smith DE, *et al.* Crystalloid vs. colloid resuscitation: is one better? *Surgery* 1979;**85**:129-39.
2 Lowe RJ, Moss GS, Jilek J, Levine HD. Crystalloid vs. colloid in the etiology of pulmonary failure after trauma: a randomised trial in man. *Surgery* 1977;**81**:676-83.
3 Moss GS, Lowe RJ, Jilek J, Levine HD. Colloid or crystalloid in the resuscitation of hemorrhagic shock: a controlled clinical trial. *Surgery* 1981;**89**:434-8.
4 Rackow EC, Falk JL, Fein A, *et al.* Fluid resuscitation in circulatory shock: a comparison of the cardiorespiratory effects of albumin, hetastarch, and saline solutions in patients with hypovolemic and septic shock. *Crit Care Med* 1983;**11**:839-50.
5 Metildi LA, Shackford SR, Virgilio RW, Peters RM. Crystalloid versus colloid in fluid resuscitation of patients with severe pulmonary insufficiency. *Surg Gynecol Obstet* 1984;**158**: 207-12.

- *Acute plasma volume replacement*

The choice of fluids in the management of acute hypovolaemia remains controversial because there have been no adequate controlled clinical trials comparing the outcome in patients resuscitated with albumin with that in patients resuscitated with other colloid solutions—for example, dextrans, gelatin, or hydroxyethyl starch. Controlled trials have, however, been done to compare the effects of albumin with those of isotonic saline in the resuscitation of patients with traumatic and septic shock, and also in patients undergoing major vascular operations who require large volumes of fluid replacement during the operation. The results of these trials indicate that—at least in younger patients—there is little difference in the effects of albumin and crystalloid solutions, provided that adequate volumes of crystalloid are given.

There has been concern that the reduction in colloid osmotic pressure caused by infusion of large volumes of crystalloid solutions would in turn induce pulmonary oedema by reducing the osmotic force that retains fluid in the pulmonary vessels. Albumin is widely distributed, however, two thirds being located in the extravascular space, and infused albumin is rapidly distributed across the capillary membrane even when permeability is normal. Thus infused albumin will increase albumin concentrations in extracellular fluid and may promote its retention in interstitial fluid. Studies in both humans and animals have shown greater increases in lung water when albumin was used for resuscitation.

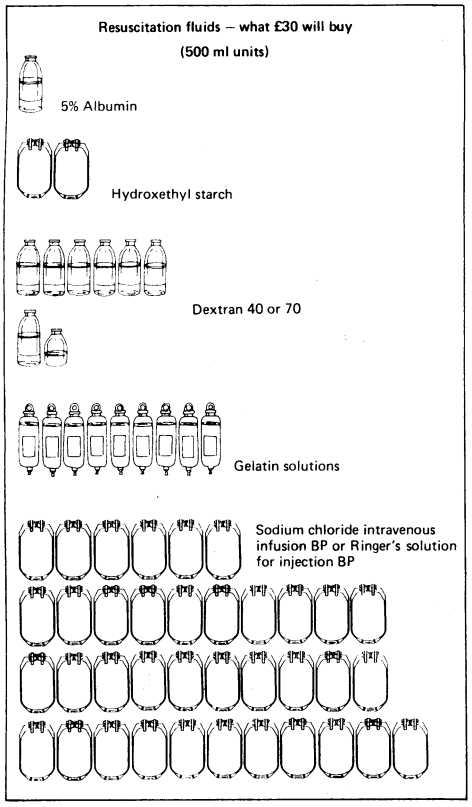
- Crystalloid solutions are safe and effective for resuscitation in traumatic and haemorrhagic shock, but many clinicians recommend a combination of crystalloid and colloid
- Colloid solutions maintain haemodynamic stability when vascular permeability is increased
- Albumin has no specific benefit over other colloid solutions and is much more expensive

Resuscitation with crystalloid requires larger volumes of fluid than resuscitation with colloid

Clinical studies in young and comparatively fit patients have shown that even pronounced reductions in colloid osmotic pressure do not impair pulmonary function. In older patients, however, there is some evidence that lung function may be compromised by excessive falls in colloid osmotic pressure, although it is not known whether this influences the eventual outcome.

Because of the necessity to use substantially larger volumes of fluid when resuscitating with crystalloid solutions, weight gain and oedema may result; these, however, clear quickly in patients with adequate renal function. Oedema may lead to tissue hypoxia, which could affect wound healing and may interfere with gut absorption and motility. Studies in postoperative patients who were routinely given albumin to maintain their plasma colloid osmotic pressure, however, did not show any clinical benefits.

Although debate continues about the precise indications for crystalloid or colloid in resuscitation, some guidelines can be suggested. When the primary deficit is of water or electrolytes, or both, crystalloid should be used initially; this has been proved to be effective in patients with haemorrhagic or traumatic shock. If more than a few litres are required, the addition of a colloid solution may be beneficial, especially if plasma colloid osmotic pressure is low. In conditions such as septic shock, the adult respiratory distress syndrome, and anaphylaxis (in which vascular permeability is increased) colloid solutions are useful in maintaining haemodynamic stability.



- *Replacement of plasma protein in burnt patients*

Burns cause a prolonged increase in microvascular permeability, resulting in large losses of fluid and protein; there is also a transient increase in permeability in healthy tissue. Protein loss is greatest during the first 8-12 hours, but as long as adequate perfusion is maintained the loss of plasma volume decreases after 18-24 hours. There are conflicting views about the use of albumin, some clinicians recommending that resuscitation should start with crystalloid solutions and that albumin should be given 8-12 hours later.

A randomised controlled trial in 79 burnt patients without inhalation injury compared resuscitation with Ringer's solution with that using Ringer's solution containing 2·5% albumin. Lung water remained unchanged in those receiving only Ringer's solution but progressively increased during the seven days of the study in the group who also received albumin, though several measurements of cardiac function were identical. The authors suggested that the addition of albumin to Ringer's solution might have a later adverse effect and concluded that crystalloid solutions were preferable in burnt patients.

- *Treatment of diuretic resistant oedema in hypoproteinaemic patients*

Hypoproteinaemia caused by an increased loss of plasma proteins through the kidneys or gut or by underproduction of proteins by the liver in chronic liver disease leads to oedema and contraction of the intravascular volume that triggers compensatory retention of salt and water. In those patients who do not respond to treatment with diuretics, infusion of 20% albumin followed by intravenous injection of a diuretic (such as frusemide) together with an aldosterone antagonist may produce a diuresis. Once the oedema has cleared, much smaller doses of diuretic are required to maintain than to initiate the diuresis.

Adverse reactions to albumin

Safety and cost of albumin and other colloid solutions for volume replacement

Product	Principal adverse reactions	Reported incidence and comments	Cost/500 ml (£)
5% Human albumin	Acute reactions of any kind	1/6600	25-35
	Severe or potentially life threatening acute reactions	1/30 000	
Dextran 70	Acute reactions of any kind	1/2200	4-5
	Severe or potentially life threatening acute reactions	1/4500 (reduced to 1/84 109 if Dextran 1 given before injection)	
	Interference with haemostasis	Because of this, dose restriction of 20 ml/kg/24 hours usually advised	
Modified fluid gelatin	Acute reactions of any kind	1/325	2-3
	Severe or potentially life threatening acute reactions	1/13 000	
Urea linked gelatin	Acute reactions of any kind	1/700	2-3
	Severe or potentially life threatening acute reactions	1/2000	
Hydroxyethyl starch	Acute reactions of any kind	1/1200	15-16
	Severe or potentially life threatening acute reactions	1/16 000	

Infusion of any of these fluids can cause circulatory overload in patients with pulmonary oedema.

Albumin products are safe. Even before screening of donors for hepatitis B was routine, the only rare incidents of transmission of hepatitis B by albumin resulted from defects in manufacturing. Bacterial contamination is also rare. Hypotension, sometimes severe, has been described, but this was related to the presence of prekallikrein activator in the batches concerned; assays to ensure low concentrations of prekallikrein activator are now part of quality control and such episodes are almost unknown.

Albumin should be given with caution to patients liable to develop left ventricular failure because each 100 ml of 20% albumin will produce a transient expansion of circulating fluid volume up to four times the volume being infused.

Inappropriate or unproved uses

Albumin should not be given for:

- Parenteral nutrition
- Management of chronic protein loss or impaired albumin production

A lot of albumin is prescribed for conditions that have not been described here, but its value in these conditions has not been proved. It should not be used as a source of parenteral nutrition because it is broken down slowly, contains few essential amino acids, and in large quantities may increase catabolism. In addition it has not been shown to be effective in managing chronic protein loss or chronically impaired albumin production.

Cost

Albumin is expensive

Albumin is expensive—for example, in the Royal Infirmary in Edinburgh the amount of 5% albumin supplied by the Blood Transfusion Service in 1987-8 would have cost about £340 000 if it had been bought, which would have added about 13% to the hospital pharmacy's budget of £2.6m. The use of albumin should be restricted to the indications for which it has been shown to be effective, and its use should be audited regularly.

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