

CHAPTER 3

ALBUMIN

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BACKGROUND

This chapter describes when and how to use the plasma protein product albumin and introduces therapeutic alternatives to albumin.

Serum albumin is the most abundant protein in the plasma. It has a molecular weight of approximately 67 kilodaltons with a low serum viscosity. It is a highly soluble molecule that is negatively charged overall but is capable of binding to both cations and anions.

Serum albumin is responsible for about 80% of the total plasma oncotic pressure (also known as colloid osmotic pressure). This pressure is important for maintaining appropriate levels of water in the circulatory system. Generally, one gram of albumin attracts 18 ml of water by its oncotic activity; thus, an infusion of 25 g of albumin expands the plasma volume by 450 ml.

Serum albumin is synthesized in the liver at a rate of approximately 16 g per day in a healthy adult. Several hormones can increase the body's ability to synthesize albumin, but malnutrition, stress, medications and aging may all decrease production. Serum albumin is lost at a rate of 12 g per 500 ml of blood lost; thus, in the setting of a four-unit hemorrhage, the albumin lost will be entirely replaced by normal synthesis in three days.

EFFICACY AND SAFETY OF ALBUMIN

Albumin purified from human plasma has been used as a therapeutic agent since the 1940s, despite ongoing controversy regarding its efficacy and safety compared with other colloids and crystalloids. Many research publications and systematic reviews have attempted to resolve this controversy.

Two meta-analyses in the late 1990s indicated that albumin use for the treatment of hypovolemia, burns, or hypoalbuminemia was associated with an increase in mortality.^{1, 2} However, the studies examined were small and involved heterogeneous patient populations.

In 2004, a large randomized controlled trial (RCT) in 6,997 Australian intensive care unit (ICU) patients undergoing fluid resuscitation, the Saline versus Albumin Fluid Evaluation (SAFE) trial, showed no difference in mortality

between 4% albumin and saline.³ There were also no significant differences between albumin and saline when days in ICU, days in hospital, days on a ventilator, or multi-organ failure were assessed. Since the SAFE trial found that albumin was neither helpful nor harmful, clinicians on both sides of the albumin argument have used this study to support their point of view. Subgroup analyses of the SAFE trial did not demonstrate benefit in the infusion of albumin in hypoalbuminemic patients.

A multinational RCT in 2013, the Colloids Versus Crystalloids for the Resuscitation of the Critically Ill (CRISTAL) trial, found no significant difference in 28 day mortality of ICU patients with hypovolemia who were treated with colloids (including albumin) versus crystalloids (relative risk, RR, 0.96; 95% confidence interval, CI, 0.88–1.04).⁴ In the Albumin Italian Outcome Sepsis (ALBIOS) study, the addition of albumin to crystalloid therapy in severe sepsis/septic shock did not alter 28 day mortality in 1,818 patients (RR 1.0; 95% CI 0.85–1.05).

A 2013 Cochrane systematic review showed again that albumin had no benefit or harm compared to crystalloids for fluid resuscitation in critically ill (trauma, burns and postoperative) patients; the pooled RR for death with albumin was 1.01 (95% CI 0.93–1.10).⁶ This review did find, however, that one type of colloid, hydroxyethyl starch (HES), may contribute to an increased risk of death (RR 1.10; 95% CI 1.02–1.19). In patients with liver dysfunction, a meta-analysis has shown a benefit for albumin following large-volume paracentesis; albumin treatment reduced postparacentesis circulatory dysfunction (odds ratio, OR, 0.39; 95% CI 0.27–0.55), hyponatremia (OR 0.58; 95% CI 0.39–0.87) and mortality (OR 0.64; 95% CI 0.41–0.98) relative to treatment with other colloids.⁷ Smaller prospective studies have also suggested the potential benefit of albumin in cirrhotic patients with spontaneous bacterial peritonitis,⁸ as well as in patients with hepatorenal syndrome in conjunction with terlipressin.^{9,10}

Side effects specific to albumin include a very rare risk of anaphylaxis. There have been no reports of human immunodeficiency virus (HIV), hepatitis or other viral transmission at the time of writing, but a theoretical risk of variant Creutzfeldt-Jakob disease (vCJD) transmission exists. There are some concerns for certain patient populations regarding the osmolality, sodium content, pH and the product stabilizers (caprylate, N-acetyltryptophanate and aluminum).^{11,12}

PRODUCT DESCRIPTION

Human albumin is prepared from donated plasma using a process called fractionation.

In Canada, albumin is supplied as a human-derived plasma protein product that is a sterile, latex-free solution with a physiologic pH and a sodium concentration of 130–160 mmol per litre. Stabilizers are present but preservatives are not commonly included. Viral inactivation processes occur during the fractionation process. Normal albumin solutions are clear, slightly viscous fluids that range in colour from almost colorless to pale yellow, amber or green. See Table 1 for a list of albumin preparations available through Canadian Blood Services.

Albumin is typically available in two concentrations: 5% and 25%. Five percent albumin is isosmotic with plasma but 25% albumin is hyperoncotic and is roughly equivalent to a plasma volume four- to five-fold higher than the infused volume. Therefore, 25% albumin is the product of choice if the patient has an oncotic deficit, whereas 5% albumin is used for therapeutic plasmapheresis or conditions associated with volume deficit alone.

Table 1: Albumin preparations available through Canadian Blood Services*

Product name	Vial sizes	Supplier	Storage	Stabilizers and buffers	pH and sodium (Na)
Plasbumin / Albumin 5%	50 ml, 250 ml	Grifols	2 to 30°C	Sodium caprylate, acetyltryptophan, sodium carbonate	Na content = 145 mEq/L
Plasbumin / Albumin 25%	100 ml				
Alburex 5%	250 ml, 500 ml	CSL Behring	2 to 30°C	Sodium caprylate, acetyltryptophan, sodium carbonate	pH range = 6.4–7.4
					Na content = 3.2 mg/ml
Alburex 25%	50 ml, 100 ml				

*For ongoing updates, please refer to the complete table of plasma protein products at blood.ca.

INDICATIONS

In 1995, the University Hospital Consortium in the United States developed the first consensus statement on indications for albumin use.¹³ Many jurisdictions still use these indications, but based on recent systematic reviews including those discussed above, some newer guidelines limit the use of this product to volume replacement in hypovolemic shock.

Two Canadian (British Columbia and Ontario) recommendations are published on the respective provincial websites.^{14, 15} These recommendations differ slightly but agree that albumin would generally be indicated in the following situations:

25% albumin preparations:

- Patients with liver disease and bacterial peritonitis;
- Large volume (>5 litre) paracentesis in cirrhotic patients;
- Hepatorenal syndrome type 1.

5% albumin preparations:

- Therapeutic plasma exchange;
- Thermal injury involving >50% total body surface area, if unresponsive to crystalloid.

There is no strong evidence to support the use of albumin in the following:

- Cardiac surgery;
- Volume resuscitation for hypovolemia;
- Cerebral ischemia / hypovolemic brain injury;
- Hypoalbuminemia;
- Hypotension during dialysis therapy.

CONTRAINDICATIONS

Albumin is contraindicated in:

- Patients who would not tolerate a rapid increase in circulating blood volume.
- Patients with a history of an allergic reaction to albumin.

DOSE AND ADMINISTRATION

The volume and rate of infusion should be determined by the clinical situation. However, the infusion rates for 5% albumin solutions should not exceed 5 ml per minute whereas the rate for 25% albumin, because of its hyperosmotic nature, should not exceed 1-2 ml per minute. Monitoring of patients for circulatory overload and hyperhydration is recommended with 25% albumin infusions. Suggested albumin doses are indicated in Table 2.

Table 2: Suggested doses for indicated uses of 25% albumin.⁸

Indication	Dose
Large volume paracentesis > 5 litres in cirrhotic patients	6-8 g of albumin per litre of fluid removed
Spontaneous bacterial peritonitis (non-malignant)	Day 1: 1.5 g/kg Day 3: 1 g/kg
Hepatorenal syndrome type 1 (acute onset)*	Day 1: 1 g/kg Days 2-14: 100-200 ml/day
*administered with vasoactive agents (e.g. terlipressin)	

Infusion is through a standard vented intravenous (IV) set. Albumin is compatible with standard electrolyte and carbohydrate IV solutions such as normal saline, Ringer’s lactate, PlasmaLyte and D5W, but should not be co-infused with solutions containing alcohol or protein hydrolysates. Albumin must not be diluted with hypotonic solutions such as sterile water for injection, as it may lead to severe hemolysis.

Once opened, the vial of albumin should be discarded if not infused within four hours.

STORAGE AND TRANSPORTATION

See Table 1 for storage temperatures for the various albumin preparations available through Canadian Blood Services. The shelf life ranges from two to five years depending on the manufacturing process. An expiry date is stated on each package and the expiration date of each unit should be checked prior to administration.

The product should not be administered if it is expired or if:

- the solution has been frozen or otherwise stored under inappropriate conditions;

- the solution is turbid or contains particulate material (e.g. glass or cork); or
- the solution vials are damaged.

ALTERNATIVES TO ALBUMIN

Alternatives to albumin therapy include other colloid solutions and crystalloids. Generally, plasma volume-expanding therapeutic agents used clinically can be classified into three broad categories:

- crystalloid
- colloid (e.g. albumin)
- hypertonic solutions (as alternatives to 25% albumin).

The most common crystalloids in clinical use are normal saline, PlasmaLyte and Ringer's lactate. The advantages of crystalloid therapy over most colloid solutions include decreased expense, increased urine output and a simpler chemical structure that is easily metabolized and excreted. The disadvantages of crystalloids are primarily seen in situations requiring large volumes for clinical resuscitation, which may lead to peripheral and pulmonary edema, and a potential for hyperchloremia in patients with renal dysfunction.

Colloids differ from crystalloids in that they have an increased ability to hold water in the intravascular compartment. If there is normal membrane permeability, colloids do not enter interstitial or intracellular compartments and may preferentially increase plasma volume. In addition to albumin, colloids currently available in Canada for therapeutic use include:

- Dextrans (D40, D70)
- Gelatins (haemaccel)
- Hydroxyethyl starches (HESs) (Volulyte , Voluven and Hextend)

Potential disadvantages with colloid therapy include:

- cost, with colloids significantly more expensive than crystalloids;
- decreased recipient hemoglobin concentration following infusion;
- dilution of plasma proteins including coagulation factors; and
- circulatory overload.

Although other colloids such as HES products are cheaper than albumin, they may be associated with increased side effects.¹⁶ In 2013, a Health Canada advisory was issued advising clinicians that increased mortality, renal injury and liver failure have been associated with the use of HES solutions and that HES solutions are now contraindicated in patients with sepsis, severe liver disease or renal impairment with oliguria and anuria, not related to hypovolemia.¹⁷

CONTINUING PROFESSIONAL DEVELOPMENT CREDITS

Fellows and health-care professionals who participate in the Canadian Royal College's Maintenance of Certification (MOC) program can claim the reading of the [*Clinical Guide to Transfusion*](#) as a continuing professional

development (CPD) activity under [Section 2: Self-learning credit](#). The reading of one chapter is equivalent to **two credits**.

Medical laboratory technologists who participate in the Canadian Society for Medical Laboratory Science's [Professional Enhancement Program](#) (PEP) can claim the reading of the [Clinical Guide to Transfusion](#) as a non-verified activity.

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If you have questions about the *Clinical Guide to Transfusion* or suggestions for improvement, please contact us through the [Feedback form](#).

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