Transfusion Medicine and Hemotherapy

Transfus Med Hemother 2009;36:399–407

5 Human Albumin

KARGER

Fax +49 761 4 52 07 14
Information@Karger.de
www.karger.com

Accessible online at:
www.karger.com/tmh

5.1 Preparation

Human albumin is prepared from human pool plasma by alcoholic precipitation [12]. For pathogen inactivation albumin is pasteurized for at least 10 h at 60 °C (see also European Pharmacopoeia).

5.1.1 Quality Criteria

Human albumin solutions for transfusion are obtained from human plasma proteins as sterile preparations which, according to the monograph 'Human Albumin Solutions' of the European Pharmacopoeia, must contain a minimum of 95% albumin. Aside from human albumin, preparations currently available have a sodium concentration between 87 and 160 mmol/l and a potassium concentration below 2 mmol/l. Because of variable electrolyte concentrations contained in albumin preparations, it is required to monitor the balance of water and electrolyte, especially when administering large amounts. Up to 3.2 g/l sodium octanoat and up to 4.29 g/l acetyltryptophan are added as stabilizers. All albumin preparations currently available contain less than 200 µg/l of aluminum.

Albumin solutions do not contain isoagglutinins or blood group substances and can thus be administered independent of the recipient's blood group. They do not contain oxygen carriers, coagulation factors, or antibodies. Based on the manufacturing process and the pathogen inactivation involved, albumin preparations are considered to carry no risk of transmitting infections.

5.2 Active Constituents

Human albumin solutions are manufactured as two preparations, namely as isooncotic (5%) or as hyperoncotic (20–25%) infusion solutions. The effective component is human albumin with a molecular weight of around 66 kDa consisting of 584 amino acids of known sequence. Albumin preparations intended for clinical use may contain monomers along with dimers and, in small amounts, polymers of albumin. According to the European Pharmacopoeia, a maximum content of 10% polymers and aggregates is permitted.

5.3 Physiological Properties and Function

The reference concentration of albumin in plasma ranges between 33 and 52 g/l. Albumin is synthesized exclusively in the liver. The normal rate of albumin synthesis is approximately 0.2 g/kg body weight/day. Extravascular colloid osmotic pressure (COP) in the liver is considered to be the factor regulating synthesis. Albumin synthesis may be suppressed by an exogenous supply of substances affecting COP, i.e. natural or synthetic colloids [36]. A lasting increase in albumin concentration can only be achieved by suitable nutrition therapy.

Under physiological conditions a steady state exists between albumin synthesis and metabolism. The amount of albumin metabolized daily is proportional to the plasma concentration, i.e. a fixed percentage of approximately 10% of plasma albumin content is metabolized per day [29, 31]. Its half-life changes inversely proportionately to the plasma albumin concentration; i.e. a decreased albumin content results in increasing its half-life, whereas increasing albumin concentrations cause the metabolic rate to increase by up to 50%.

The distribution of albumin in the human body is adequately described by a two-compartment model where about 40% is taken up by the intravascular and 60% by the extravascular space [29, 36, 47]. The balance between plasma and interstitial space is established at varying rates with respect to the two subcompartments of the extravascular albumin pool [57]. The total exchange rate between intra- and extravascular volume amounts to approximately 5% of the intravascular albumin content per hour (so-called transcapillary escape rate). The transcapillary escape rate of albumin is increased in arterial hypertension, myxedema, burns, liver cirrhosis and diabetic microangiopathy [38, 39].

The physiological function of albumin can be summarized as follows:

– volume effect (colloid oncotic effect),
– transport function.

Volume effect (colloid osmotic pressure (COP)): Albumin has a high capacity for binding water (approximately 18 ml/g), an intravasal residence time of approximately 4 h presupposing physiological capillary permeability [57] as well as an in vivo half-life of approximately 18–21 days [29, 31, 57]. At equal concentrations the oncotic (colloid osmotic) effect of albumin is about 2.5 times greater than that of globulins which have an average molecular weight of around 170 kDa [28]. Although albumin comprises only about 50–60% of the total protein content of plasma, it is responsible for about 80% of intravascular COP.

Transport function: Because of its high net charge albumin possesses excellent binding capacities, among other things for water, calcium, sodium and trace elements. Albumin is also an important transport protein for fatty acids, bilirubin and hormones as well as for many drugs. Although these transport qualities are of physiological and pharmacological importance, no therapeutic indication is documented for administering human albumin to improve the transport function.

5.4 Storage, Shelf Life, Packaging Sizes

Human albumin preparations can be stored at room temperature, although storage temperature for human albumin solutions should not exceed 25 °C according to expert information

(Summary of Product Characteristics). Therefore it is not possible to administer pre-warmed solutions.

The European Pharmacopoeia merely requires storage conditions under protection from light.

Human albumin solutions can be administered by a peripheral or central venous line and are well tolerated. No daily maximum permissible dose is specified for human albumin. It is available as 5% or 20% solution in ampoules or infusion bottles. Therefore no rapid supply ('pressure infusion') is possible with human albumin to rapidly compensate for acute volume loss.

5.5 Indications

Clinical application of albumin derives from its physiological functions. Possible areas of application are:
- hypovolemia,
- hypoalbuminemia,
- other areas of application (e.g. transport function).

5.5.1 Acute Volume Replacement

Albumin is the protein with the highest concentration in plasma and is the main factor responsible for maintaining COP. To achieve a normalization or an increase of COP was therefore considered as one possible indication for the administration of albumin solutions. However, this can also be achieved in a similar manner by using synthetic colloids.

A meta-analysis of the 'Cochrane Injuries Group Albumin Reviewers' published in 1998 has led to a negative assessment regarding the use of human albumin [51]. The use of albumin was associated with an increased absolute risk of mortality in critically ill patients (one extra death for every 17 patients treated with albumin). The authors concluded that the continued use of human albumin should be challenged. Another meta-analysis investigated the effect of albumin administration on mortality when compared with other plasma substitutes [61]. The analysis included volume substitution in surgery/trauma (27 trials), burns (4 trials), neonates (6 trials), in patients with ascites (5 trials), in those with hypoalbuminemia (5 trials) as well as in other non-specified indications (8 trials). A total of 55 trials with a total of 3,504 patients were investigated, and none of the attributes analyzed ('outcome', 'mortality') showed a significant difference between the treated groups, not even between subgroups. In contrast to the meta-analysis of the 'Cochrane Injuries Group Albumin Reviewers' of 1998, albumin administration was not associated with excess mortality, but there was also no benefit regarding survival (mortality) when comparing albumin with other volume substitutes (e.g. synthetic colloids).

Note: In cases where administration of human albumin in treating hypovolemia showed no benefit when compared with alternative volume substitution, a 'non-recommendation' was made based on the fact that it is impossible to perform a rapid infusion ('pressure infusion') of human albumin stored at room temperature. According to the individual level of recommendation, it may be reasonable in particular cases to pursue a deviating course of treatment.

5.5.1.1 Acute Volume Replacement in the Perioperative Phase

Neither benefit nor harm was shown when using human albumin for increased hemodynamic stability in the perioperative phase, as compared to a crystalloid or any other colloid volume substitute [5, 6, 57, 61].

Human albumin should not be used as substitute in hypovolemia or for increased hemodynamic stability of adult patients in the perioperative phase.	**2 A**

5.5.1.2 Acute Volume Replacement in Intensive-Care Patients

The largest trial currently available (approximately 7,000 patients), using a prospective, randomized, double-blind design, compared volume substitution in intensive-care patients by administering either crystalloid substitutes or human albumin 4% (SAFE Study [18]). No significant beneficial effect of human albumin was determined regarding either morbidity and mortality or days spent in ICU or in hospital.

According to the Guideline for Diagnosis and Therapy of Sepsis [44], it is not recommended to administer human albumin for volume replacement, also in critically ill patients with severe sepsis and septic shock.

Human albumin is not recommended as substitute in hypovolemia or for increased hemodynamic stability of adult intensive-care patients.	**1 A**

5.5.1.3 Acute Volume Replacement in Burn Patients

Trauma caused by burning is viewed as a potential indication for administration of albumin solutions, however, not during the first 24 h after burning. In this context, preference is given to crystalloid solutions as volume replacement [7].

The administration of human albumin for increased hemodynamic stability of burn patients is not recommended during the first 24 h. In the further course of treatment administration of human albumin may be reasonable.	**2 B**

5.5.1.4 Acute Volume Replacement in Trauma Patients

In trauma patients with (severe) hypovolemia, no rapid compensation is possible using human albumin (pressure infusion not possible). No benefit regarding survival is documented when compared to other volume substitutes.

In patients with traumatic brain injury a post hoc follow-up analysis of data from the SAFE Study [18] showed a significantly increased mortality for the group treated with human albumin as opposed to the non-albumin group [48].

The administration of human albumin for increased hemodynamic stability of patients with traumatic brain injury is not recommended.	**2 B**

5.5.1.5 Acute Volume Replacement in Pregnant Women

There are hardly any reports on any kind of volume substitution (including human albumin) in pregnant women. Severe hypovolemia during the first months of a pregnancy (e.g. in the context of surgical intervention) is a possible indication for albumin administration. In contrast, administration of modern synthetic volume substitutes is an established procedure in clinics to correct hypovolemia during delivery (e.g. during cesarean delivery).

In pregnant women human albumin could be administered in cases of severe hypovolemia during early pregnancy.	**2 C**
It is not recommended to administer human albumin exclusively for volume substitution in the course of a cesarean delivery.	**2 C**

5.5.1.6 Acute Volume Replacement in Cardiac Surgery

Human albumin is considered to be indicated for volume replacement in cardiac surgery. In particular, the risk of excessive bleeding when administering older synthetic colloids (dextran, older hydroxyethyl starch (HES) preparations) is seen as the rationale for the application of human albumin [3, 9, 13, 27] since no relevant substance-specific alterations regarding coagulation have been reported for human albumin use. The majority of the studies reporting benefits when using human albumin solutions in the context of cardiac surgery originate from the USA. However, no modern synthetic colloids with few adverse reactions are available there. Therefore the results of a retrospective analysis of data that reported a lower incidence of mortality in cardiac surgery patients when using human albumin [52] must be interpreted with caution because no specifics were given for the volume substitutes used as an alternative. In a meta-analysis published in 2001, Wilkes and co-workers [62] compared the risk of postoperative bleeding following administration of older HES preparations (with either high or medium molecular weight (Mw) and a high degree of substitution (MS)) in the context of cardiac surgery. Human albumin and HES were administered as volume replacement prior to and after cardiopulmonary bypass (CPB), respectively, and also as constituents of the priming fluid of the extracorporeal circuit (heart-and-lung machine). In nine trials involving 354 patients the effects of a first-generation starch (Mw 450 kDa, MS 0.7) and albumin were compared. Postoperative blood loss was significantly lower in patients exposed to albumin than in those exposed to HES. If in contrast a more modern synthetic colloid solution was administered (Mw 200 kDa, MS 0.5; 8 trials involving 299 patients), there was no longer a statistically significant difference in comparison to albumin under the conditions of the systematic meta-analysis.

In cardiac surgery patients the administration of human albumin for compensation of hypovolemia and for increased hemodynamic stability is not recommended.	**1 A**

5.5.1.7 Acute Volume Replacement in Patients with Bleeding Disorder and Patients with Manifest Bleeding due to Coagulopathy

In patients with altered coagulation (e.g. polytrauma, patients with septicemia) or in patients in whom coagulation disorders are anticipated (e.g. cardiac surgery patients with extracorporeal circulation) the application of albumin is possible since no substance-specific alterations regarding coagulation have been reported for human albumin use. However, in such situations other volume substitutes have also been administered without seriously altered coagulation function. Similarly the administration of large doses of albumin or other volume substitutes leads to hypocoagulopathy due to dilution.

In patients who are at risk of bleeding the administration of albumin for volume replacement is not recommended.	**2 C**

5.5.1.8 Acute Volume Replacement in Hepatic Surgery (e.g. Liver Transplantation)

Compensation of hypovolemia in patients undergoing major liver surgery or liver transplantation has long been considered an indication for human albumin therapy. Meanwhile patients in such situations have also successfully been treated with synthetic colloids, but large-scale prospective trials are lacking [8]. There is also a lack of unambiguous data (controlled, randomized, comparative trials investigating modern synthetic volume substitutes) regarding the significance of substitution by albumin in major liver surgery, e.g. of extended hepatocellular carcinoma.

In cases of liver transplantation the administration of human albumin or synthetic colloids is recommended for volume replacement, subject to the therapy strategy of the particular hepatic surgery center.	**2 C**

5.5.1.9 Acute Volume Replacement in Children

For a long time, administration of human albumin and stored serum has been the treatment of choice regarding volume substitution in children. Meanwhile safe and effective volume substitution in children is also possible by using crystalloid or modern colloid solutions [4, 11, 24, 53, 58]. In general, there are only few publications reporting experiences with the application of albumin or different volume substitutes in neonates, premature infants, and children under the age of 12 months. However, some studies showed that in neonates and pediatric patients human albumin that is administered for increased hemodynamic stability can be replaced by other volume substitutes [4, 11, 53, 58].

Routine application of human albumin for volume replacement in children is not recommended.	**2 A**

5.5.1.10 Acute Volume Replacement in Therapeutical Plasmapheresis

Administration of human albumin is indicated for volume replacement with albumin in therapeutic plasmapheresis. However, there are no large comparative trials involving other substances for volume replacement that would document a benefit.

Human albumin could be administered in order to balance volume withdrawal in plasmapheresis.	**2 C**

5.5.2 Therapy of Hypoalbuminemia

5.5.2.1 Physiology/Pathophysiology

Compensation of hypoalbuminemia is considered to be an essential indication for administration especially of highly concentrated albumin preparations. In human plasma albumin concentration ranges around 3.5–4.5 g/dl and amounts to approximately 60% of the total plasma proteins (6–8 g/dl). Around 30–40% of the replaceable albumin pool is located in the plasma compartment (approximately 120 g in around 3 l of plasma volume) [25]. Concentration in the tissue spaces is considerably lower (approximately 1.4 g/dl; approximately 160 g in 10–12 l of interstitial volume). Under normal conditions the liver produces around 200 mg/kg/day in albumin, corresponding to around 15 g/day in a man weighing 70 kg. The foremost factor in monitoring the production of albumin is apparently COP in the region of the extravascular space of the liver. In sepsis, infection, trauma, or mental strain the albumin level decreases (approximately 1–1.5 g/dl during 3–7 days). Albumin synthesis is also reduced under these circumstances, but with a half-life of around 20 days this cannot explain the rapid drop in serum albumin concentration. The most significant cause of the reduced albumin level is apparently redistribution and/or catabolism. Particularly in patients with sepsis an increased vascular permeability (capillary leak) plays an important role in developing hypoalbuminemia [19].

Following transfusion of human albumin, its distribution within the extravascular compartment is complete after 7–10 days. Approximately 10% of transfused albumin migrates from the intravascular space within 2 h [38], 75% of transfused albumin is distributed into the extravascular space after 2 days [25]. In particular clinical pictures (e.g. in sepsis) this distribution process happens far more rapidly. In this connection capillary permeability of albumin can increase 13-fold compared to its normal level [10].

5.5.2.2 Therapy of Hypoalbuminemia in Intensive-Care Patients

Hypoalbuminemia is a predictor of increased mortality and morbidity [29, 31]. Compensation of hypoalbuminemia however showed no benefit regarding morbidity and mortality in comparison to an untreated control group. This was shown for adults as well as for children in meta-analyses [26, 61].

It is not settled yet which albumin level can be considered to be still tolerable and whether there is a 'critical' threshold value in hypoalbuminemia below which an administration of albumin is beneficial.

Two prospective randomized studies were able to show that in hypoalbuminemia with levels of <31 g/l or total protein concentrations of <60 g/l albumin administration significantly improved organ function (respiratory, cardiovascular and central nervous system function). Also a better tolerance to enteral feeding, an improved oxygenation in acute pulmonary failure, and a less positive fluid balance were achieved [14, 30]. Both studies however failed to use for comparison another substance which also increases COP. Furthermore, both studies enrolled only small numbers of patients; therefore, they are not comparable with the available meta-analyses enrolling hundreds of patients.

Transfusion of human albumin to balance a state of hypoalbuminemia in critically ill patients is not recommended.	**2 A**

Since a beneficial effect of albumin replacement in critically ill patients with sepsis or those with severe multiorgan failure cannot be completely ruled out, it might be reasonable to follow a deviating course of treatment in individual cases [60].

5.5.2.3 Therapy of Hypoalbuminemia in Undernutrition, Malnutrition and Enteropathies / Malabsorption Syndrome

In clinical practice no benefit is shown for the administration of albumin in undernutrition, malnutrition and enteropathies / malabsorption syndrome. Because of the composition of amino acids with a low ratio of some essential amino acids

(tryptophan, methionine, isoleucine) as well as its long biological half-life of around 19–21 days, albumin is principally unsuitable for parenteral nutrition.

Administration of albumin in undernutrition, malnutrition, enteropathies and malabsorption syndrome is not recommended.	**1 C+**

5.5.2.4 Therapy of Hypoalbuminemia in Liver Cirrhosis

In cirrhotic patients with ascites there is some evidence that albumin transfusion leads to a reduction in morbidity and mortality [21, 56]. However, as an individual parameter, hypoalbuminemia per se is no confirmed indication for substitution in patients with established liver cirrhosis and ascites. The decision on whether volume replacement or albumin substitution are necessary depends on the degree of severity of liver cirrhosis as well as the extent of the hemodynamic, hormonal and immunological deficits.

Three clinical situations are described below where transfusion with human albumin as volume replacement or an albumin substitution may be indicated:

– spontaneous bacterial peritonitis (SBP),
– hepatorenal syndrome (HRS),
– post paracentesis.

5.5.2.4.1 Spontaneous Bacterial Peritonitis

According to the Guideline by the American Association for the Study of Liver Diseases (AASLD), SBP is defined by the detection of neutrophil granulocytes (>250/mm^3 of ascites) in the absence of an intra-abdominal source of infection [45]. A single randomized controlled trial involving patients with ascites and SBP investigated the administration of cefotaxime plus albumin (1.5 g/kg body weight at the time of SBP diagnosis (day 1) and 1 g/kg body weight on day 3) and compared this to treatment with cefotaxime alone without plasma volume expansion [56]. In this connection the incidence of renal impairment could be prevented by the additional use of albumin, and the mortality rate at 3 months was significantly improved. However, the trial has methodological flaws because the control group did not receive adequately controlled fluid replacement.

In patients with chronic liver failure (e.g. in the context of liver cirrhosis) and drainage of ascitic fluid attention shall be paid to an adequate volume replacement.	**1 C+**

However, a subgroup analysis of the data of the above-mentioned trial showed that the incidence of renal impairment following SBP was almost exclusively in patients with elevated creatinine levels at the time of SBP diagnosis and serum bilirubin levels of at least 4 mg/dl [56]. A randomized unblinded pilot study involving 10 patients compared the administration of 20% albumin for 6 h and the administration of HES 200/0.5 for 18 h regarding the prevention of hemodynamic and renal complications in patients with SBP [17]. There were fewer incidences of renal complications in the human albumin group in comparison with the HES group (3 vs. 5 patients).

Administration of albumin (1.5 g/kg body weight on day 1 and 1 g/kg body weight on day 3) could be carried out in patients with liver cirrhosis and SBP as well as elevated serum bilirubin levels (>4 mg/dl) and renal impairment.	**2 C**

5.5.2.4.2 Hepatorenal Syndrome

In patients with HRS (definition according to [50]) vasoconstrictors are used. In the majority of the trials performed on the treatment of an HRS, vasoconstrictors were in each case combined with albumin [2, 15, 34, 55]. In a prospective, non-randomized study patients receiving terlipressin combined with albumin (1 g/kg body weight on day 1 and 20–40 g albumin/day on consecutive days with a central venous pressure of ≤18 mm Hg) were compared with patients receiving terlipressin alone [37]. A considerably increased rate of complete response was found under albumin therapy. However, this trial has methodological flaws in that after the enrolment of 13 patients the protocol (terlipressin plus albumin) was modified: only subsequently, non-randomized, the other patients were treated with terlipressin alone.

In patients with liver cirrhosis and HRS the treatment with vasoconstrictors should be combined with albumin therapy.	**1 B**

5.5.2.4.3 Post Paracentesis

Following paracentesis with drainage of ascitic fluid, i.e. post paracentesis, without volume compensation after puncture, there is the risk of developing a so-called post paracentesis syndrome (PPS). PPS is defined as circulatory dysfunction accompanied by activation of the renin-angiotensin-aldosterone system (increase by >50% of the pre-treatment value to a level >4 ng/ml/h on day 6 post paracentesis) [22].

The incidence of PPS is associated with impaired renal function, a concomitant considerably higher risk of developing renal failure and an overall increased mortality [23, 32]. To prevent PPS, volume substitution shall therefore be performed after each total paracentesis (i.e. drainage of the total volume of ascites) [32, 33].

Regarding the selection of plasma expanders for the prevention of PPS, there are randomized clinical trials comparing albumin (6–8 g/l of ascitic fluid) with dextran 70 [16, 23, 41], polygeline [23, 35, 49], dextran 40 [20] and HES [1]. Partly the trials showed considerable differences regarding volume and number of paracenteses performed, the degree of severity of liver disease, the length of follow-up, and the definition of

clinical complications. So far, a meta-analysis of this issue is only available in the form of an abstract. There were no significant differences between the individual groups regarding mortality and incidence of clinical complications.

Regarding the question of whether the volume of ascitic fluid evacuated played a role in indicating the type of plasma expander therapy, there is only one case-control trial (without incidence of PPS if the volume of ascitic fluid evacuated was <5 l and without plasma expander therapy) [40]. There is also one randomized controlled trial comparing albumin and saline (3.5%) therapy after paracentesis [54]. The latter trial found a higher incidence of PPS in the total number of patients when 3.5% saline was used (170 ml/l of ascitic fluid and transfusion rate of 1 l/h), but not in a subpopulation for whom less than 6 l of ascitic fluid were evacuated. According to a consensus guideline, this evidence is not strong enough to deny plasma expander therapy to those patients in whom less than 6 l of ascitic fluid were evacuated. In this case it is recommended to use synthetic plasma expanders [33].

Following total paracentesis and a volume of ascitic fluid ≥6 l, plasma expander therapy with albumin (6–8 g/l of ascitic fluid) should be performed.	**2 A**
Following paracentesis and a volume of ascitic fluid evacuated of <6 l, saline (3.5%) should be administered alone or, alternatively, synthetic plasma expander or albumin (6–8 g/l of ascitic fluid) should be used for substitution.	**2 A**

A randomized unblinded clinical trial involving patients with liver cirrhosis and first-onset ascites compared a standard therapy according to a consensus guideline [33] with and without administration of human albumin (25 g/week in the first year and 25 g every 2 weeks thereafter) [46]. It was found that the albumin-treated group had a significantly greater cumulative survival rate. However, this trial was not placebo-controlled and represented a continuation of a previous trial with a different primary endpoint [21].

In patients with cirrhosis and first-onset ascites albumin therapy at regular intervals could be beneficial.	**2 C**

5.5.2.5 Therapy of Hypoalbuminemia in Nephrotic Syndrome
In nephrotic syndrome, albumin is lost via the kidneys. Compensation of the resulting hypoalbuminemia is not reasonable because the transfused albumin is soon eliminated again to the greatest extent.

In cases of nephrotic syndrome the administration of human albumin is not recommended.	**1 C+**

5.5.3 Other Applications of Albumin

In addition to increasing COP and the volume-stabilizing effect associated with this, numerous other features are assigned to albumin that exceed its function for volume substitution [42, 43].

5.5.3.1 Albumin Improving Transport Capacity for Drugs
Albumin serves as a transport protein for many substances (e.g. bilirubin, drugs). It is doubtful whether in the case of hypoalbuminemia there may also be an increase in the 'free' unbound (biologically active) fraction of drugs (e.g. coumarin derivatives). Since an increase in the free fraction of a substance is most often followed by a more rapid metabolism or an increased elimination of this substance, no critical increase in the concentration of the free substance in plasma is to be anticipated in case of low levels of albumin. There is no risk of acute toxic effects resulting from hypoalbuminemia because of rapid migration of the unbound fraction of drugs from the intravascular to the extravascular space, so that a (low-level) balance is reached. In addition, apparently binding sites for drugs are lost in the production process of human albumin solutions.

Administration of human albumin to improve the transport capacity for drugs is not recommended.	**2 C**

5.5.3.2 Albumin as Free Radical Scavenger and for Binding Toxic Substances
Physiologically, albumin is assumed to serve as free radical scavenger and is able to bind toxic substances (e.g. free fatty acids). Therefore, albumin seems to be indicated in particular in patients with sepsis because toxic oxygen radicals play a role in pathogenesis and maintenance of sepsis [43]. Allegedly albumin can also bind toxins in large-scale burns. Therefore, albumin solutions could have a beneficial effect in these patients. However, to date there are no confirmed factual data on the benefit of human albumin therapy regarding morbidity or mortality in humans. It is uncertain whether human albumin preparations currently commercially available have the same (radical scavenger) properties as natural albumin or whether they are altered by the manufacturing process.

Administration of human albumin as free radical scavenger and for binding toxic substances, e.g. in patients with sepsis, is not recommended.	**1 C**

5.6 Adverse Reactions

No substance-specific clinically relevant alterations in the coagulation capacity nor alterations in organ function (e.g. renal function) due to albumin therapy have been reported. There

is also no risk of retention of albumin. Although albumin is prepared from pooled plasma, albumin preparations currently available are considered to be non-immunogenic due to the manufacturing process.

Investigating the safety of application of human albumin, Vincent et al. [59] showed that from 1990 to 1997 approximately 112 million units of human albumin were administered worldwide; while from 1998 to 2000 approximately 10^7 units of 40 g each were administered. Adverse reactions that were directly associated with albumin were an extremely rare event during this observation period.

A study compared approximately 7,000 critically ill patients who either received 4% human albumin or crystalloid solutions (SAFE study [18]). No serious adverse reactions were reported for the human albumin group in comparison to the crystalloid solution group.

5.7 Absolute and Relative Contraindications

The only substance-specific contraindication for albumin is an established allergy against human albumin (or rather against the dissolving agent). As any albumin infusion (e.g. to compensate hypovolemia) simultaneously causes increased intravascular volume, any hypervolemic state is to be considered a contraindication. Special caution is necessary in patients with severely restricted cardiac function. As is true for all volume substitutes, the following contraindications apply also to human albumin in general:

– congestive heart failure,
– pulmonary edema,
– hypocoagulopathy due to dilution.

5.8 Documentation

The product type, batch number and recipient of human albumin must be documented in writing in accordance with section 14 of the German Transfusion Act (Transfusionsgesetz; TFG).

5.9. References

1 Altman C, Bernard B, Roulot D, Vitte RL, Ink O: Randomized comparative multicenter study of hydroxyethyl starch versus albumin as a plasma expander in cirrhotic patients with tense ascites treated with paracentesis. Eur J Gastroenterol Hepatol 1998;10:5–10.

2 Angeli P, Violpin R, Gerunda G, et al: Reversal of type 1 hepatorenal syndrome with the administration of midodrine and octreotide. Hepatology 1999;29:1690–7.

3 Avorn J, Patel M, Levin R, Winkelmayer WC: Hetastarch and bleeding complications after coronary artery surgery. Chest 2003;124:1437–42.

4 Boldt J, Knothe C, Schindler E, Hammermann H, Dapper F, Hempelmann G: Volume replacement with hydroxyethyl starch solution in children. Br J Anaesth 1993;70:661–5.

5 Boldt J: Volumensubstitution in der perioperativen Phase unter besonderer Berücksichtigung der Kardiochirurgie. Infusionsther Transfusionsmed 1997;24:92–8.

6 Boldt J, Scholhorn T, Mayer J, Piper S, Suttner S: The value of an albumin-based intravascular volume replacement strategy in elderly patients undergoing major abdominal surgery. Anesth Analg 2006; 103:191–9.

7 Boldt J, Pabsdorf M: Fluid management in burn patients: Results from a European survey – more questions than answers. Burns 2008;34:328–38.

8 Cammu G, Troisi R, Cuomo O, de Hemptinne B, Di Florio E, Mortier E: Anaesthetic management and outcome in right-lobe living liver-donor surgery. Eur J Anaesthesiol 2002;19:93–8.

9 Canver CC, Nichols RD: Use of intraoperative hetastarch priming during coronary bypass. Chest 2000; 118:1616–20.

10 Chien S, Sinclair DG, Dellenback RJ, et al: Effect of endotoxin on capillary permeability to macromolecules. Am J Physiol 1964;207:518–22.

11 Chong Sung K, Kum Suk P, Mi Ja Y, Kyoung Ok K: Effects of intravascular volume therapy using hydroxyethyl starch (130/0.4) on post-operative bleeding and transfusion requirements in children undergoing cardiac surgery: a randomized clinical trial. Acta Anaesthesiol Scand 2006;50:108–11.

12 Cohn EJ, Oncley JL, Strong LE, Hughes WL Jr, et al: Chemical, clinical and immunologic studies on the products of human plasma fractionation. I. The characterization of the protein fractions of human plasma. J Clin Invest 1944;23:417.

13 Cope JT, Banks D, Mauney MC, et al: Intraoperative hetastarch infusion impairs hemostasis after cardiac surgery operations. Ann Thorac Surg 1997;63:78–82.

14 Dubois MJ, Orellana-Jimenez C, Melot C, et al: Albumin administration improves organ function in critically ill hypoalbuminemic patients: A prospective, randomized, controlled, pilot study. Crit Care Med 2006;34:2536–40.

15 Duvoux C, Zanditenas D, Hezode C, Chauvat A, Metreau J: Effects of noradrenalin and albumin in patients with type 1 hepatorenal syndrome: a pilot study. Hepatology 2002;36:374–80.

16 Fassio E, Terg R, Landeira G, et al: Paracentesis with dextran 70 vs. paracentesis with albumin in cirrhosis with tense ascites. Results of a randomized study. J Hepatol 1992;14:310–6.

17 Fernandez J, Monteagudo J, Bargallo X, et al: A randomized unblinded pilot study comparing albumin versus hydroxyethyl starch in spontaneous bacterial peritonitis. Hepatology 2005;42:627–34.

18 Finfer S, Bellomo R, Boyce N, French J, Myburgh J, Norton R; SAFE Study Investigators: A comparison of albumin and saline for fluid resuscitation in the intensive care unit. N Engl J Med 2004; 350:2247–56.

19 Fleck A, Raines G, Hawker F, et al: Increased vascular permeability. Major cause of hypoalbuminaemia in disease and injury. Lancet 1985;i:781–3.

20 Garcia-Compean D, Blanc P, Larrey D, et al: Treatment of cirrhotic tense ascites with Dextran-40 versus albumin associated with large volume paracentesis: a randomized controlled trial. Ann Hepatol 2002;1:29–35.

21 Gentilini P, Casini-Raggi V, Di Fiore G, et al: Albumin improves the response to diuretics in patients with cirrhosis and ascites: results of a randomized, controlled trial. J Hepatol 1999;30:639–45.

22 Gines P, Tito L, Arroyo V, et al: Randomized comparative study of therapeutic paracentesis with and without intravenous albumin in cirrhosis. Gastroenterology 1988;94:1493–502.

23 Gines A, Fernandez-Esparrach G, Monescillo A, et al: Randomized trial comparing albumin, dextran 70, and polygeline in cirrhotic patients with ascites treated by paracentesis. Gastroenterology 1996;111:1002–10.

24 Greenhalgh DG, Housinger TA, Kagan RJ, et al: Maintenance of serum albumin levels in pediatric burn patients: a prospective, randomized trial. J Trauma 1995;39:67–73.

25 Guthrie RD Jr, Hines C Jr: Use of intravenous albumin in the critically ill patient. Am Coll Gastroenterol 1991;86:255–63.

26 Jardine LA, Jenkins-Manning S, Davies MW: Albumin infusion for low serum albumin in preterm newborn infants. Cochrane Database Syst Rev 2004; 3:CD004208.

27 Knutson JE, Deering JA, Hall FW, et al: Does intraoperative hetastarch administration increase blood loss and transfusion requirements after cardiac surgery? Anesth Analg 2000;90:801–7.

28 Ladegaard-Pedersen HJ: Plasma volume and plasma colloid osmotic pressure. Scand J Clin Lab Invest 1969;23:153–8.

29 Margarson MP, Soni N: Serum albumin: touchstone or totem? Anaesthesia 1998;53:789–803.

30 Martin GS, Moss M, Wheeler AP, Mealer M, Morris JA, Bernard GR: A randomized, controlled trial of furosemide with or without albumin in hypoproteinemic patients with acute lung injury. Crit Care Med 2005;33:1681–7.
31 Mendez CM, McClainCJ, Marsano LS: Albumin therapy in clinical practice. Nutr Clin Pract 2005; 20:314–20.
32 Moore KP, Wong F, Gines P, et al: The management of ascites in cirrhosis: report on the consensus conference of the International Ascites Club. Hepatology 2003;38:258–66.
33 Moore KP, Aithal GP: Guidelines on the management of ascites in cirrhosis. Gut 2006;55(suppl VI):1–12.
34 Moreau R, Durand F, Poynard T, et al: Terlipressin in patients with cirrhosis and type 1 hepatorenal syndrome: a retrospective multicenter study. Gastroenterology 2002;122:923–30.
35 Moreau R, Valla DC, Durand-Zaleski I, et al: Comparison of outcome in patients with cirrhosis and ascites following treatment with albumin or a synthetic colloid: a randomised controlled pilot trail. Liver Int 2006;26:46–54.
36 Oratz M, Rothschild MA, Schreiber SS: Effect of dextran infusions on protein synthesis by hepatic microsomes. Am J Physiol 1970;218:1108–12.
37 Ortega R, Gines P, Uriz J, et al: Terlipressin therapy with and without albumin for patients with hepatorenal syndrome: results of a prospective, nonrandomized study. Hepatology 2002;36:941–8.
38 Parving HH, Rossing N: Simultaneous determination of the transcapillary escape rate of albumin and IgG in normal and long-term juvenile diabetic subjects. Scand J Clin Lab Invest 1973;32:239–44.
39 Parving HH, Ranek L, Lassen NA: Increased transcapillary escape rate of albumin in patients with cirrhosis of the liver. Scand J Clin Lab Invest 1977; 37:643–8.
40 Peltekian KM, Wong F, Liu PP, Logan AG, Sherman M, Blendis LM´: Cardiovascular, renal, and neurohumoral responses to single large-volume paracentesis in patients with cirrhosis and diuretic-resistant ascites. Am J Gastroenterol 1997; 92:394–9.
41 Planas R, Gines P, Arroyo V, et al; Dextran-70 versus albumin as plasma expanders in cirrhotic patients with tense ascites treated with total paracentesis. Results of a randomized study. Gastroenterology 1990;99:1736–44.
42 Qiao R, Siflinger-Birnboim A, Lum H, Tiruppathi C, Malik AB: Albumin and Ricinus communis agglutinin decrease endothelial permeability via interactions with matrix. Am J Physiol 1993;265: C439–46.
43 Quinlan GJ, Mumby S, Martin GS, Bernard GR, Gutteridge JM, Evans TW: Albumin influences total plasma antioxidant capacity favorably in patients with acute lung injury. Crit Care Med 2004; 32:755–9.
44 Reinhart K, Brunkhorst FM, Bone HG, et al: Diagnose und Therapie der Sepsis. S-2 Leitlinien der Deutschen Sepsis-Gesellschaft e.V. (DSG) und der Deutschen Interdisziplinären Vereinigung für Intensiv- und Notfallmedizin (DIVI). Intensivmedizin 2006;43:369–84.
45 Rimola A, Garcia-Tsao G, Navasa M, et al: Diagnosis, treatment and prophylaxis of spontaneous bacterial peritonitis: a consensus document. J Hepatol 2000;32:142–53.
46 Romanelli RG, La Villa G, Barletta G, et al: Long-term albumin infusion improves survival in patients with cirrhosis and ascites: an unblinded randomized trial. World J Gastroenterol 2006;12:1403–7.
47 Rossing N: Intra- und extravascular distribution of albumin and immunoglobulin in man. Lymphology 1978;11:138–42.
48 SAFE Study Investigators, Australian and New Zealand Intensive Care Society Clinical Trials Group, Australian Red Cross Blood Service, George Institute for International Health, Myburgh J, Cooper J, Finfer S, et al: Saline or albumin for fluid resuscitation in patients with traumatic brain injury. N Engl J Med 2007;357:874–84.
49 Salerno F, Badalamenti S, Lorenzano E, Moser P, Incerti P: Randomized comparative study of hemaccel vs. albumin infusion after total paracentesis in cirrhotic patients with refractory ascites. Hepatology 1991;13:707–13.
50 Salerno F, Gerbes A, Gines P, Wong F, Arroyo V: Diagnosis, prevention and treatment of hepatorenal syndrome in cirrhosis. Gut 2007;56:1310–8.
51 Schierhout G, Roberts I: Fluid resuscitation with colloid or crystalloid solutions in critically ill patients: a systematic review of randomised trials. BMJ 1998;316:961–4.
52 Sedrakyan A, Gondek K, Paltiel D, Elefteriades JA: Volume expansion with albumin decreases mortality after coronary artery bypass graft surgery. Chest 2003;123:1853–7.
53 So KW, Fok TF, Ng PC, Wong WW, Cheung KL: Randomised controlled trial of colloid or crystalloid in hypotensive preterm infants. Arch Dis Child Fetal Neonatal Ed 1997;76:F43–6.
54 Sola-Vera J, Minana J, Ricart E, et al: Randomized trial comparing albumin and saline in the prevention of paracentesis-induced circulatory dysfunction in cirrhotic patients with ascites. Hepatology 2003;37:1147–53.
55 Solanki P, Chawla A, Garg R, Gupta R, Jain M, Sarin SK: Beneficial effects of terlipressin in hepatorenal syndrome: a prospective, randomized placebo-controlled clinical trial. J Gastroenterol Hepatol 2003;18:152–6.
56 Sort P, Navasa M, Arroyo V, et al: Effects of intravenous albumin on renal impairment and mortality in patients with cirrhosis and spontaneous bacterial peritonitis. N Engl J Med 1999;342:403–9.
57 Standl T. Albumin; in Boldt J (Hrsg): Volumenersatztherapie. Stuttgart, Thieme, 2001, pp 39–61.
58 Stoddart PA, Rich P, Sury MRJ: A comparison of 4.5% human albumin solution and haemaccel in neonates undergoing major surgery. Paediatr Anaesth 1996;6:103–6.
59 Vincent JL, Wilkes MM, Navickis RJ: Safety of human albumin-serious adverse events reported worldwide in 1998–2000. Br J Anaesth 2003;91: 625–30.
60 Vincent JL: Resuscitation using albumin in critically ill patients: research in patients at high risk of complications is now needed. BMJ 2006;333:1029–30.
61 Wilkes MM, Navickis RJ: Patient survival after human albumin administration – a meta-analysis of randomized controlled trials. Ann Intern Med 2001;135:149–64.
62 Wilkes MM, Navickis RJ, Sibbald WJ: Albumin versus hydroxyethyl starch in cardiopulmonary bypass surgery: a meta-analysis of postoperative bleeding. Ann Thorac Surg 2001;72:527–33.