Transfusion Medicine and Hemotherapy

Clinical Information

Transfus Med Hemother 2016;43:223–232
DOI: 10.1159/000446043

Received: January 12, 2016
Accepted: January 12, 2016
Published online: May 3, 2016

Cross-Sectional Guidelines for Therapy with Blood Components and Plasma Derivatives: Chapter 5 Human Albumin – Revised

Executive Committee of the German Medical Association on the Recommendation of the Scientific Advisory Board

Summary

Chapter 5 'Human Albumin' that was suspended on January 10, 2011 has been completed and updated in the present version.

5 Human Albumin

5.1 Preparation

Human albumin is prepared from human pool plasma by alcoholic precipitation [15]. 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. Up to 19.3 mmol/l sodium octanoate and up to 17.4 mmol/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 hypooncotic (4%), isooncotic (5%) or hyperoncotic (20% or 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 contain monomers and may contain also dimers and, in small amounts, polymers of albumin. 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. 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 albumin synthesis. Albumin synthesis may be suppressed by an exogenous supply of substances affecting COP, i.e. natural or synthetic colloids [18]. A lasting normalization 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 [61, 65]. 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 neonatal Fc receptor FcRn (also called Brambell recep-

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tor) is responsible for this homeostatic regulation of albumin as well as for that of serum IgG, both of which have the longest half-life of all serum proteins with 19–23 days [9, 52]. It is a membrane molecule, similar to the MHC class I molecule, on endothelial and intestinal epithelium cells that binds human albumin and IgG at different positions, continuously taking them up into pinocytotic vesicles in order to protect both serum proteins from rapid degradation [72]. The pinocytotic vesicles containing albumin bound to FcRn are released either into the extravascular space through transcytosis or back into the circulation [4]. Because of the limited binding capacity of FcRn, the unbound amount of molecules increases with increasing serum concentration of albumin, and accordingly their catabolic rate, increases exponentially [51].

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 about 60% by the extravascular space [61, 73, 83]. The balance between plasma and interstitial space is established at varying rates with respect to the two subcompartments of the extravascular albumin pool [103]. 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 [74, 75].

The physiological function of albumin can be summarized as follows:
(1) volume effect (colloid oncotic effect),
(2) transport function.

Volume Effect (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 [103] as well as an in vivo half-life of approximately 18–21 days [61, 65, 103]. At equal concentrations the oncotic effect of albumin is about 2.5 times greater than that of globulins which have an average molecular weight of around 170 kDa [53]. 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, there is at best a reasonable therapeutic indication for administering HA for binding of bilirubin and thus reduction of the need for phototherapy and exchange transfusion in neonates with severe hyperbilirubinemia [45, 66, 96].

5.4 Storage, Shelf Life, Packaging Sizes

Human albumin preparations can be stored protected from light and at room temperature, although storage temperature for human albumin solutions should not exceed 25 °C. Therefore, it is not possible to administer pre-warmed solutions.

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. However, concentration and dose should be adjusted to the individual needs of the patient. It is licensed in Germany as 4%, 5%, 20% or 25% solutions in ampoules, polyethylene bags, or glass bottles.

5.5 Indications

Clinical application of albumin derives from its physiological functions. Possible areas of application are:
(1) hypovolemia,
(2) hypoalbuminemia,
(3) other areas of application.

5.5.1 Therapy of Hypovolemia

Possible areas of application of human albumin for the purpose of volume replacement are presented below, according to the respective specific underlying circumstances.

5.5.1.1 Acute Volume Replacement during the Perioperative Phase

There are three Cochrane analyses [10, 76, 113] and two systematic reviews [46, 110] on the application of albumin as volume replacement during the perioperative phase, investigating the effect of albumin as compared to a crystalloid or any other colloid volume substitute. Regarding mortality neither benefit nor harm was shown when using human albumin.

For the application of hyperoncotic albumin (20%), a benefit regarding morbidity (renal function, formation of gastrointestinal edema) was reported in one review [46].

- *Human albumin is not recommended as substitute in hypovolemia or for increased hemodynamic stability of adult patients in the perioperative phase, unless therapeutic alternatives have been exhausted* **(1 B)**.

5.5.1.2 Acute Volume Replacement in Intensive-Care Patients without Sepsis

For an assessment of using human albumin as substitute in hypovolemia or for hemodynamic stabilization of adult nonseptic intensive-care patients, the following references were incorporated in the evaluation: [14, 19, 24, 25, 28, 36, 56, 78, 81, 82, 93, 95, 104, 105, 109, 110, 112]. The meta-analyses of the Cochrane Collaboration [81, 82] are referred to in the following.

The consensus statement of the ESICM task force of 2012 [81] and the meta-analysis of the Cochrane Collaboration of 2011 [82]

show no benefit regarding mortality for the therapy using human albumin as compared to using crystalloid or colloid solutions.

- *Human albumin is not recommended as substitute in hypovolemia or for hemodynamic stabilization of adult nonseptic intensive-care patients, unless therapeutic alternatives have been exhausted* **(1 A)**.

5.5.1.3 Acute Volume Replacement in Intensive-Care Patients with Sepsis

The German S2k guideline of 2010 [86] recommends using albumin as volume substitute in patients with severe sepsis or septic shock as an expert recommendation. The guideline of the Surviving Sepsis Campaign of 2013 gives a very weak recommendation (2 C) for using human albumin in patients with severe sepsis or septic shock who continue to require infusions to maintain adequate mean arterial pressure [20]. Recent meta-analyses have reached diverging results: Delaney et al. [19] show a benefit for the use of albumin for hemodynamic stabilization of patients with sepsis (OR 0.82; 95% CI 0.67–1.0; p = 0.047). Two recently published prospective randomized trials showed no benefit regarding lower mortality for patients treated with albumin compared to patients treated with crystalloid solutions [5, 11].

Because of the ambiguous data situation [5, 19, 20, 86] on whether the treatment of patients with sepsis, severe sepsis, and septic shock with human albumin for hemodynamic stabilization is superior to that using other infusion solutions, no recommendation is given here.

5.5.1.4 Acute Volume Replacement in Burn Patients

Regarding the use of albumin and other colloid solutions for acute volume replacement in severely burned patients, several systematic reviews from the Cochrane database as well as randomized clinical trials show no effect on the mortality rate compared to treatment with crystalloid solutions [10, 42, 76, 82, 110].

- *The administration of human albumin for increased hemodynamic stability of burn patients is not recommended during the first 24 h* **(1 A)**.

Based on published data, the relevance of using albumin for long-term treatment in burn patients as substitute in hypoalbuminemia cannot be assessed conclusively [42, 110]. The prophylactic use of albumin for maintaining physiological serum albumin levels showed no effect on mortality or morbidity [34, 35, 49].

- *In the further course of treatment of burn patients administration of human albumin may be considered* **(2 B)**.

5.5.1.5 Acute Volume Replacement in Trauma Patients

Along with the S3-Guideline on Treatment of Patients with Severe and Multiple Injuries [88], the following publications have been included in the assessment of hemodynamic stabilization of trauma patients: [27, 32, 66, 95, 100]. In addition, data of a subgroup analysis of trauma patients enrolled in the SAFE trial are referred to for assessment [27].

Neither the S3-Guideline nor the meta-analysis of the Cochrane Collaboration of 2011 [82] showed a survival benefit for trauma patients treated with albumin (consistent results based on three prospective randomized trauma trials and one quasi-randomized trial).

This is supported by the fact that the mortality rate of the trauma patients enrolled in the SAFE trial and treated with albumin for hemodynamic stabilization tended to increase (13.6 vs. 10.0%; p = 0.06). In this trial hypooncotic human albumin (4%) was used that is not commonly used in Germany. Systematic reviews [27, 32, 95, 100] also consistently find no survival benefit for patients treated with albumin. However, the systematic reviews and meta-analyses by Groeneveld et al. [36], Heier et al. [43], Vincent et al. [110], and Wilkes et al. [115] did not strictly discriminate in group allocation between trauma and surgical patients; therefore, a bias cannot be ruled out in the end.

- *The administration of human albumin for increased hemodynamic stability of patients with traumatic injury is not recommended* **(1 B)**.

5.5.1.6 Acute Volume Replacement in Pregnant Women

There are only few reports on any kind of volume substitution (including human albumin) in pregnant women. Severe hypovolemia during pregnancy (e.g. in the context of surgical intervention) is a possible indication for albumin administration. There are hardly any data on albumin use for correcting hypovolemia during delivery (e.g. during Cesarean delivery) and for preventing hypotension in connection with performing a spinal anesthesia [16, 63]. In comparison, administration of synthetic colloid volume substitutes or crystalloid solutions is better documented in the literature [7, 16, 55]. In case synthetic colloids are contraindicated or the maximum limit of a colloid dose has been exceeded, albumin can be considered.

- *The administration of human albumin for volume replacement in the context of a Cesarean delivery is not recommended (2 C).*
- *The administration of human albumin for preventing hypotension during spinal anesthesia in the context of a Cesarean delivery is not recommended* **(2 B)**.

5.5.1.7 Volume Replacement in Cardiac Surgery

Regarding the correction of hypovolemia and for hemodynamic stabilization in cardiac surgery as well as for pump priming of the cardiopulmonary bypass, the S3-Guideline for Intensive Care in Cardiac Surgery Patients 'Hemodynamic Monitoring and Cardiovascular Circulation' [89] was incorporated in the evaluation, along with the following individual studies: [33, 75 99]. All of these investigated the effect of albumin- versus non-albumin-based priming of the cardiopulmonary bypass on the outcome of cardiac surgery patients, like decrease of platelets, weight gain, blood loss etc., whereas mortality was only considered in the analysis by Himpe [44].

The S3-Guideline for Intensive Care in Cardiac Surgery Patients recommends using synthetic colloid solutions as well as human al-

bumin solutions for hemodynamic stabilization even though no better outcome in patients has been demonstrated for human albumin (grade of evidence D, grade of recommendation 0). A significant benefit has been shown when using human albumin (4–5%) for pump priming of the cardiopulmonary bypass (reduced drop in platelets and lower blood loss; one study reported a lower mortality rate). Because of the date of the studies cited this usually concerned hydroxyethyl starch (HES) preparations with higher molecular weight which were compared with human albumin [44, 85, 114]. In a recent meta-analysis, also including HES preparations with lower molecular weight, the use of synthetic colloid solutions resulted in increased blood loss and a higher rate of reoperation and transfusion [69].

- *Human albumin solution (5%) can be used for correction of hypovolemia and for hemodynamic stabilization in cardiac surgery as well as for pump priming of the cardiopulmonary bypass* **(2 B)**.

5.5.1.8 Acute Volume Replacement in Patients with Risk of Bleeding and Patients with Manifest Bleeding due to Coagulopathy

In patients with altered coagulation (e.g. polytrauma, patients with sepsis, 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, the administration of large amounts of albumin can also cause a dilutional coagulopathy [116].

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

Patients undergoing hepatic surgery (including transplantation) frequently have previous liver damage possibly including a coagulation disorder. Additional coagulopathy occurs during the anhepatic and postreperfusion stages of liver transplantation. The main cause of this is assumed to be a rapidly increasing plasma level of the tissue-type plasminogen activator which is caused by lacking hepatic clearance on the one hand and by release from ischemically damaged endothelium of the donor liver on the other hand [22, 50, 77]. Coagulopathy may be aggravated by intraoperative hypothermia, hypocalcemia, and thrombocytopenia [37]. Accordingly, this group of patients is especially at risk during further compromise of hemostasis.

Large-scale prospective trials comparing various strategies of volume substitution in hepatic surgery are lacking. There is also a lack of unambiguous data from controlled, randomized trials investigating the significance of substitution by albumin in major liver surgery, e.g. of extended liver tumors. Thus the present data situation does not allow any further assessment of using human albumin for volume replacement in hepatic surgery.

5.5.1.10 Acute Volume Replacement in Neonates and Older Children

While the number of studies is limited, the effects of human albumin versus those of synthetic colloid solutions are comparable when used for perioperative volume replacement in neonates and older children [41, 102].

In hypotensive neonates the effects of human albumin versus those of synthetic colloid or crystalloid solutions are inconsistent [57, 59, 71]. In dehydrated neonates with enteritis, there is no benefit in using human albumin compared to isotonic saline [40].

No benefit has been shown when using human albumin in infants and older children with severe infections or septic shock [2, 60].

The use of human albumin in preterm neonates with hypoalbuminemia [47] and in neonate jaundice [66] also remains controversial. There is a need for further trials covering different age brackets to improve the data situation regarding therapeutic success and adverse effects [47].

- *The use of human albumin for volume replacement in preterm and term neonates as well as in older children cannot be assessed conclusively in comparison to other crystalloid and colloid solutions, and therefore* human albumin *should only be used if therapeutic alternatives have been exhausted* **(2 A)**.

5.5.1.11 Volume Replacement in Therapeutic 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 [54, 58, 64].

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

5.5.2 Therapy of Hypoalbuminemia

Albumin is the protein with the highest concentration in plasma and primarily responsible for maintaining the COP. Therefore normalization or increase of COP has been considered as a possible indication for administration of albumin solutions.

5.5.2.1 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 33–52 g/l and amounts to approximately 60% of the total plasma proteins (60–80 g/l). Around 30–40% of the replaceable albumin pool is located in the plasma compartment (approximately 120 g in around 3 l of plasma volume) [39]. Concentration in the tissue spaces is considerably lower (approximately 14 g/l; 160 g in 10–12 l of interstitial volume). Under normal conditions the liver produces around 0.2 g/kg body weight/day 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 10–15 g/l 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 [29].

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 [75], and 75% of transfused albumin is distributed into the extravascular space after 2 days [39]. 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 [13].

5.5.2.2 Therapy of Hypoalbuminemia in Intensive-Care Patients

Hypoalbuminemia is a predictor of increased mortality and morbidity [38, 109]. However, it has not been investigated comprehensively or documented well whether compensation of hypoalbuminemia shows benefits regarding morbidity or mortality compared to an expectant treatment. At present, due to an insufficient data situation, no answer is possible regarding any benefit on the outcome, particularly for infants [47].

For compensation of hypoalbuminemia in adult intensive-care patients the data situation is more substantial, although any assessment is doubtful because of the small group size in the trials included in the meta-analysis [115]. None of the four trials included could show a survival benefit for the patients treated with albumin, with groups of between 15 and 116 patients (184 of which received albumin and 173 of which were in the control group). The combined relative risk for death during the observation period was 1.59 (95% CI 0.91–2.78) to the disfavor of albumin.

Another meta-analysis of randomized clinical trials focusing on the morbidity endpoint arrives at a different assessment from the one above regarding the use of human albumin in children and adults. Complications (combined endpoint: one or more complications in a patient) tended to occur less frequently after application of human albumin, with an OR of 0.81 (95% CI 0.41–1.60) [109]. Even if focusing on randomized trials of adult patients who either received albumin in the context of parenteral nutrition or because of lowered levels of albumin in plasma, this tendency towards a lower rate of complications, also in another systematic review by the same authors [110], could be regarded as weak indication of a beneficial effect in individual cases and based on an underlying pathology. However, these results must be interpreted with utmost caution in view of the considerable heterogeneity of data, given the overall small group sizes (15–116 patients per group), a small total number of patients for each cohort analyzed (199 patients received albumin and 188 patients were in the control groups) as well as the quasi-retrospective approach (classification of the occurring complications) with an OR of 0.92 (95% CI 0.77–1.08). For the time being, on no account does this permit to draw the conclusion that it is generally recommended to use human albumin for preventing complications.

Moreover, it is doubtful which albumin level can still be considered to be tolerable and whether there is a 'critical' threshold in hypoalbuminemia starting from which there is a benefit in administering human albumin.

- *Human albumin shall not be used exclusively for compensating hypoalbuminemia in intensive-care patients without any additional indication* **(1 B)**.

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 and isoleucine) as well as its long biological half-life of around 19–21 days, albumin is principally unsuitable for parenteral nutrition [17, 67, 118].

- *Administration of human albumin in undernutrition, malnutrition, enteropathies and malabsorption syndrome shall not be given (1 B).*

5.5.2.4 Therapy of Hypoalbuminemia in Liver Cirrhosis

As an individual parameter, hypoalbuminemia per se is no confirmed indication for substitution in patients with established liver cirrhosis and ascites.

Three clinical situations are described below where transfusion with human albumin as volume replacement or an albumin substitution can be indicated:
(1) spontaneous bacterial peritonitis
(2) hepatorenal syndrome
(3) post paracentesis.

5.5.2.4.1 Spontaneous Bacterial Peritonitis

Even without sepsis, spontaneous bacterial peritonitis (SBP) can lead to an impaired circulatory function and end in a type 1 hepatorenal syndrome (HRS) with a high mortality rate. A single randomized controlled trial involving patients with SBP and simultaneously elevated levels of serum bilirubin and creatinine showed that patients developed type 1 HRS less frequently (10 vs. 30%) if they received human albumin in addition to their antibiotics therapy. The dose was 1.5 g/kg body weight at the time of SBP diagnosis (day 1) and 1 g/kg body weight on day 3 after SBP diagnosis. Particularly patients with serum bilirubin levels > 4 mg/dl and creatinine > 1 mg/dl profited from human albumin infusions [101]. In contrast toHES, albumin seems to improve circulatory function [26]. A meta-analysis showed that the incidence of renal impairment could be significantly lowered by the use of albumin, and the mortality rate was significantly improved. This effect has also been proven in patients with a serum bilirubin level < 4 mg/dl and normal levels of creatinine [23, 91].

- *Administration of human albumin (1.5 g/kg body weight on day 1 and 1 g/kg body weight on day 3) shall be carried out in patients with liver cirrhosis and SBP* **(1 B)**.

5.5.2.4.2 Hepatorenal Syndrome

The HRS is defined as renal failure in patients with advanced liver disease without evidence of a renal cause [6]. HRS is subdi-

vided into a rapidly progressing type 1 and type 2 with moderate renal impairment. Type 2 HRS can turn into type 1 HRS.

Various randomized controlled and partly blinded trials have investigated albumin alone and in combination with terlipressin. Most patients had type 1 HRS. In the treatment arm terlipressin + albumin, all trials showed a significant improvement of renal function and short-term survival. In contrast, infusion of albumin alone only rarely led to an improvement of renal function [62, 70, 92, 99]. Two meta-analyses reviewed the data of these reports and confirmed the results [33, 90].

Regarding dosage, the S3-guidelines recommend an albumin dose of 1 g/kg body weight (maximum 100 g) on day 1, followed by 20–40 g/day, and a terlipressin dose of 2–4 mg/day up to a maximum of 8–12 mg/day. The European guidelines give no dosage recommendation for albumin and for terlipressin 1 mg as bolus every 4–6 h up to a maximum of 2 mg every 4 h. The treatment should be continued for at least 3 days and for patients without decrease in serum creatinine for up to 14 days [23, 87].

There are fewer data on the therapy of type 2 HRS. The combination of terlipressin and albumin is effective in 60–70% of type 2 HRS patients. However, clinical benefit is not proven unambiguously.

There are insufficient data on other vasoconstrictors that were investigated for therapy of HRS or compared to terlipressin. Two randomized, non-blinded trials with low patient numbers (N = 22/40) suggested that noradrenaline might have an equivalent therapeutic effectiveness in treating HRS [3, 97]. The lack of large randomized controlled trials makes an unambiguous recommendation impossible.

- *In patients with liver cirrhosis and type 1 HRS the treatment with human albumin shall be combined with terlipressin* **(1 B)**.

5.5.2.4.3 Post-Paracentesis

A large-volume paracentesis in patients with liver cirrhosis can lead to circulatory alterations. This disorder, called post-paracentesis circulatory dysfunction in the literature, frequently leads to rapid ascites recurrence [98]. Also water retention develops with dilution hyponatremia, and the disorder can lead to a HRS [32]. In addition, there may be a further increase in the portal pressure by vasoconstrictive stimulation [84]. These pathological alterations increase the mortality rate in patients with liver cirrhosis [31].

In controlled trials administration of albumin to treat large-volume paracentesis (>5 l) led to an increased hemodynamic stability [31, 32, 80, 106]. Some randomized controlled trials compared albumin to synthetic colloids. Albumin was superior regarding prevention of post-paracentesis circulatory dysfunction. There was no survival benefit [31, 68, 100].

A meta-analysis involving 17 randomized trials (n = 1,225 patients) comparing albumin to synthetic colloids could demonstrate that administration of human albumin significantly lowered the mortality risk after large-volume paracentesis [8].

There are as yet no large randomized controlled trials investigating the effect of albumin, crystalloid solutions or synthetic volume replacement substances after paracentesis < 5 l. There are only data on patient subgroups from other trials. However, the patient numbers are very small, and the trials were not designed for these subgroups [31, 100].

Based on the trial data available, no unambiguous recommendation can be given. The S3-guidelines do not consider the use of albumin to be indicated and give no recommendation [87]. In case volume substitution using colloid solutions is indicated, the EASL guidelines recommend using albumin rather than synthetic colloids because the latter may have adverse effects on coagulation and renal function [23].

- *Following paracentesis with a volume of ascitic fluid ≥ 5 l, volume replacement with human albumin (6–8 g/l of ascitic fluid) shall be performed* **(1 A)**.

There are no large randomized controlled trials investigating the long-term effect of albumin in cirrhotic patients with the first occurrence of ascites. There are two small randomized trials comparing albumin in combination with diuretics versus diuretics alone [1, 30]. One of these trials demonstrated a benefit in the albumin group regarding hospital stay, a less frequent recurrence of ascites and lower rates of hospital readmission due to ascites [30]. The other trial reported also a lower mortality rate in the albumin group [1]. Another trial that admittedly involved only 13 patients could showed no benefit [12]. A retrospective trial investigating 19 patients perceived a benefit in albumin therapy to maintain diuresis in cirrhotic patients with contraindications against a transjugular intrahepatic portosystemic shunt [107].

It is not indicated to administer albumin regularly in the first occurrence of ascites in liver cirrhosis patients [87].

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 human albumin shall not be given* **(1 C+)**.

5.5.2.6 Therapy of Hypoalbuminemia in Premature Infants

Hypoalbuminemia is a frequent occurrence in preterm neonates because of reduced synthesis, increased catabolism, increased loss or distribution disorder between the intra- and extravascular space. Although there is no well-defined critical threshold, human albumin is frequently substituted. There is a lack of randomized double-blind trials. Efficacy and safety of human albumin replacement in preterm neonates with hypoalbuminemia are doubtful [47].

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 [21, 55].

5.5.3.1 Albumin in Patients with Ovarian Hyperstimulation Syndrome

Further potential indications concern the prevention and therapy of a severe ovarian hyperstimulation syndrome [117], despite the fact that the data situation is quite controversial and that two additional systematic reviews could prove no or at most a marginal effect on the incidence rate of ovarian hyperstimulation syndrome [48, 108]. Furthermore, deleterious effects (e.g. on the pregnancy rate) are discussed [48].

- *Human albumin can be used as a colloid volume substitute for the prevention and therapy of a severe ovarian hyperstimulation syndrome in those cases in which other interventions are contraindicated* **(2 B)**.

5.5.3.2 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 the 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. At present, no assessment is possible regarding the question whether albumin use is clinically beneficial in patients with hypoalbuminemia in view of the non-oncotic properties.

5.5.3.3 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 [79]. 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. The current AWMF guidelines regarding sepsis do not recommend using human albumin in this regard [86].

In severe cases of neonatal jaundice, human albumin therapy can contribute to a decrease of unconjugated serum bilirubin, together with phototherapy and exchange transfusion [66].

5.5.3.4 Albumin for Hemodilution in Neonates with Polycythemia

In neonatal polycythemia there is no difference in using human albumin and crystalloid solutions regarding a blood-thinning effect in the context of hemodilution.

5.6 Adverse Reactions

In general, human albumin is tolerated well. No substance-specific, clinically relevant alterations in the coagulation capacity or 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 plasma pooled from numerous donors, albumin preparations per se are considered to be non-immunogenic. Nevertheless, in rare cases slight reactions can occur after human albumin administration, like flush, urticaria, elevated temperature, and nausea. Generally, such reactions resolve rapidly after the infusion is administered more slowly or discontinued. In singular cases an anaphylactic shock can develop. In this case the infusion must be discontinued immediately and a suitable shock therapy started.

An investigation of the safety of human albumin application showed that in approximately 112 million units of human albumin administered worldwide adverse reactions directly associated with albumin were an extremely rare event [111]; from 1998 to 2000 alone approximately 10^7 units of 40 g each were administered.

A study compared approximately 7,000 critically ill patients who either received 4% human albumin or crystalloid solutions (SAFE study [27]). No serious adverse reactions were reported for the human albumin group in comparison to the crystalloid solution group.

Hyperoncotic albumin solutions as well as synthetic colloid solutions can cause renal failure in patients with shock [94]. Therefore, attention must be paid to sufficient hydration.

5.7 Absolute and Relative Contraindications

The only substance-specific contraindication for albumin is an established allergy against human albumin. 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:
(1) congestive heart failure,
(2) pulmonary edema,
(3) 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).

Appendix

The appendix is available at *http://content.karger.com/ProdukteDB/produkte.asp?doi=446043*.

References

1 Ahn HJ, Yang M, Gwak MS, et al: Coagulation and biochemical effects of balanced salt-based high molecular weight vs saline-based low molecular weight hydroxyethyl starch solutions during the anhepatic period of liver transplantation. Anaesthesia 2008;63:235–242.

2 Akech S, Ledermann H, Maitland K: Choice of fluids for resuscitation in children with severe infection and shock: systematic review. BMJ 2010;341:c4416.

3 Alessandria C, Ottobrelli A, Debernardi-Venon W, et al: Noradrenalin vs terlipressin in patients with hepatorenal syndrome: a prospective, randomized, unblinded, pilot study. J Hepatol 2007;47:499–505.

4 Andersen JT, Sandlie I: The versatile MHC class I-related FcRn protects IgG and albumin from degradation: Implications for development of new diagnostics and therapeutics. Drug Metab Pharmakokinet 2009;24:318–332.

5 Annane D, Siami S, Jaber S, et al; CRISTAL Investigators: Effects of fluid resuscitation with colloids vs crystalloids on mortality in critically ill patients presenting with hypovolemic shock. The CRISTAL randomized trial. JAMA 2013;310:1809–1817.

6 Arroyo V, Ginés P, Gerbes AL, et al: Definition and diagnostic criteria of refractory ascites and hepatorenal syndrome in cirrhosis. Hepatology 1996;23:164–176.

7 Banerjee A, Stocche RM, Angle P, Halpern SH: Preload or coload for spinal anesthesia for elective Cesarean delivery: a meta-analysis. Can J Anaesth 2010;57:24–31.

8 Bernardi M, Caraceni P, Navickis RJ, Wilkes MM: Albumin infusion in patients undergoing large-volume paracentesis: A meta-analysis of randomized trials. Hepatology 2012;55:1172–1181.

9 Brambell FW, Hemmings WA, Morris IG: A theoretical model of gamma-globulin catabolism. Nature 1964;203:1352–1354.

10 Bunn F, Trivedi D, Ashraf S: Colloid solutions for fluid resuscitation. Cochrane Database Syst Rev 2011;3:CD001319.

11 Caironi P, Tognoni G, Masson S, et al; for the ALBIOS Study Investigators: Albumin replacement in patients with severe sepsis or septic shock. N Engl J Med 2014;370:1412–1421.

12 Chalasani N, Gorski JC, Horlander JC Sr, Craven R, Hoen H, Maya J: Effects of albumin/furosemide mixtures on responses to furosemide in hypoalbuminemic patients. J Am Soc Nephrol 2001;12:1010–1016.

13 Chien S, Sinclair DG, Dellenback J, et al: Effect of endotoxin on capillary permeability to macromolecules. Am J Physiol 1964;207:518–522.

14 Cochrane Injuries Group Albumin Reviewers: Human albumin administration in critically ill patients: systematic review of randomised controlled trials. BMJ 1998;317:235–240.

15 Cohn EJ, Oncley JL, Strong LE, 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.

16 Cyna AM, Andrew M, Emmett RS, Middleton P, Simmons SW: Techniques for preventing hypotension during spinal anaesthesia for caesarean section. Cochrane Database Syst Rev 2006;4:CD002251.

17 D'Angio RG: Is there a role for albumin administration in nutrition support? Ann Pharmacother 1994;28:478–482.

18 de Jonge E, Levi M: Effects of different plasma substitutes on blood coagulation: a comparative review. Crit Care Med 2001;29:1261–1267.

19 Delaney AP, Dan A, McCaffrey J, Finfer S: The role of albumin as a resuscitation fluid for patients with sepsis: a systematic review and meta-analysis. Crit Care Med 2011;39:386–391.

20 Dellinger RP, Levy MM, Rhodes A, et al: Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. Crit Care Med 2013;41:580–637.

21 Dykes PW: A study of the effects of albumin infusions in patients with cirrhosis of the liver. Q J Med 1961;30:297–327.

22 Dzik WH, Arkin CF, Jenkins RL, Stump DC: Fibrinolysis during liver transplantation in humans: role of tissue-type plasminogen activator. Blood 1988;71:1090–1095.

23 European Association for the Study of the Liver: EASL clinical practice guidelines on the management of ascites, spontaneous bacterial peritonitis, and hepatorenal syndrome in cirrhosis. J Hepatol 2010;53:397–417.

24 Fan E, Stewart TE: Albumin in critical care: SAFE, but worth its salt? Crit Care 2004;8:297–299.

25 Ferguson ND, Stewart TE, Etchells EE: Human albumin administration in critically ill patients. Intensive Care Med 1999;25:323–325.

26 Fernandez J, Monteagudo J, Bargallo X, et al: A randomized unblinded pilot study comparing albumin versus hydroxyethyl starch in spontaneous bacterial peritonitis. Hepatology 2005;42:627–634.

27 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;350:2247–2256.

28 Finfer S, Bellomo R, McEvoy S, et al: Effect of baseline serum albumin concentration on outcome of resuscitation with albumin or saline in patients in intensive care units: analysis of data from the saline versus albumin fluid evaluation (SAFE) study. BMJ 2006;333:1044.

29 Fleck A, Raines G, Hawker F, et al: Increased vascular permeability. Major cause of hypoalbuminaemia in disease and injury. Lancet 1985;i:781–784.

30 Gentilini P, Casini-Raggi V, diFiori G, et al: Albumin improves the response to diuretics in patients with cirrhosis and ascites: results of a randomized, controlled trial. J Hepatol 1999;30:639–645.

31 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;111:1002–1010.

32 Ginès P, Tito L, Arroyo V, et al: Randomized comparative study of therapeutic paracentesis with and without intravenous albumin in cirrhosis. Gastroenterology 1988;94:1493–1502.

33 Gluud LL, Christensen K, Christensen E, Krag A: Systematic review of randomized trials on vasoconstrictor drugs for hepatorenal syndrome. Hepatology 2010;51:576–584.

34 Goodwin CW, Dorethy J, Lam V, Pruitt BA Jr. Randomized trial of efficacy of crystalloid and colloid resuscitation on hemodynamic response and lung water following thermal injury. Ann Surg 1983;197:520–531.

35 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.

36 Groeneveld AB, Navickis RJ, Wilkes MM: Update on the comparative safety of colloids: a systematic review of clinical studies. Ann Surg 2011;253:470–483.

37 Groenland HN, Porte RJ, Metselaar HJ: Liver transplantation and risk of bleeding. Curr Opin Organ Transplant 2007;12:287–293.

38 Gupta D, Lis CG: Pretreatment serum albumin as a predictor of cancer survival: a systematic review of the epidemiological literature. Nutr J 2010;9:69.

39 Guthrie RD Jr, Hines C Jr: Use of intravenous albumin in the critically ill patient. Am Coll Gastroenterology 1991;86:255–263.

40 Han JJ, Yim HE, Lee JH, et al: Albumin versus normal saline for dehydrated term infants with metabolic acidosis due to acute diarrhea. J Perinatol 2009;29:444–447.

41 Hanart C, Khalife M, De Villé A, et al: Perioperative volume replacement in children undergoing cardiac surgery: albumin versus hydroxyethyl starch 130/0.4. Crit Care Med 2009;37:696–701.

42 Haynes GR, Navickis RJ, Wilkes MM: Albumin administration – what is the evidence of clinical benefit? A systematic review of randomized controlled trials. Eur J Anaesthesiol 2003;20:771–793.

43 Heier HE, Bugge W, Hjelmeland K, Søreide E, Sørlie D, Håheim LL: Transfusion vs. alternative treatment modalities in acute bleeding: a systematic review. Acta Anaesthesiol Scand 2006;50:920–931.

44 Himpe D: Colloids versus crystalloids as priming solutions for cardiopulmonary bypass: a meta-analysis of prospective, randomized clinical trials. Acta Anaesthesiol Belg 2003;54:207–215.

45 Hosono S, Ohno T, Kimono H, et al: Effects of albumin infusion therapy on total and unbound bilirubin values in term infants with intensive phototherapy. Pediatr Int 2001;43:8–11.

46 Jacob M, Chappell D, Conzen P, Wilkes MM, Becker BF, Rehm M: Small-volume resuscitation with hyperoncotic albumin: a systematic review of randomized clinical trials. Crit Care 2008;12:R34.

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

48 Jee BC, Suh CS, Kim YB, et al. Administration of intravenous albumin around the time of oocyte retrieval reduces pregnancy rate without preventing ovarian hyperstimulation syndrome: a systematic review and meta-analysis. Gynecol Obstet Invest 2010;70:47–54.

49 Jelenko C III, Williams JB, Wheeler ML, et al: Studies in shock and resuscitation, I: use of a hypertonic, albumin-containing, fluid demand regimen (HALFD) in resuscitation. Crit Care Med 1979;7:157–167.

50 Kang YG, Martin DJ, Marquez J, et al: Intraoperative changes in blood coagulation and thrombelastographic monitoring in liver transplantation. Anesth Analg 1985;61:888–896.

51 Kim J, Hayton WL, Robinson JM, Anderson CL: Kinetics of FcRn-mediated recycling of IgG and albumin in human: pathophysiology and therapeutic implications using a simplified mechanism-based model. Clin Immunol 2007;122:146–155.

52 Kuo TT, Aveson VG: Neonatal Fc receptor and IgG-based therapeutics. MAbs 2011;3:422–430.

53 Ladegaard-Pedersen HJ: Plasma volume and plasma colloid osmotic pressure. Scand J Clin Lab Invest 1969;23:153–158.

54 Lasky LC, Finnerty EP, Genis L, Polesky HF: Protein and colloid osmotic pressure changes with albumin and/or saline replacement during plasma exchange. Transfusion 1984;24:256–259.

55 Li L, Zhang Y, Tan Y, Xu S: Colloid or crystalloid solution on maternal and neonatal hemodynamics for cesarean section: a meta-analysis of randomized controlled trials. J Obstet Gynaecol Res 2013;39:932–941.

56 Liberati A, Moja L, Moschetti I, Gensini GF, Gusinu R: Human albumin solution for resuscitation and volume expansion in critically ill patients. Intern Emerg Med 2006;1:243–245.

57 Liet JM, Kuster A, Denizot S, et al: Effects of hydroxyethyl starch on cardiac output in hypotensive neonates: a comparison with isotonic saline and 5% albumin. Acta Paediatr 2006;95:555–560.

58 Liumbruno GM, Bennardello F, Lattanzio A, Piccoli P, Rossettias G; Italian Society of Transfusion Medicine and Immunohaematology (SIMTI): Recommendations for the use of albumin and immunoglobulins. Blood Transfus 2009;7:216–234.
59 Lynch SK, Mullett MD, Graeber JE, et al: A comparison of albumin-bolus therapy versus normal saline-bolus therapy for hypotension in neonates. J Perinatol 2008;28:29–33.
60 Maitland K, Kiguli S, Opoka RO, et al: Mortality after fluid bolus in African children with severe infection. N Engl J Med 2011;364:2483–2495.
61 Margarson MP, Soni N: Serum albumin: touchstone or totem? Anaesthesia 1998;53:789–803.
62 Martin-Llahi M, Pepin MN, Guevara M, et al: Terlipressin and albumin vs albumin in patients with cirrhosis and hepatorenal syndrome: a randomized study. Gastroenterology 2008;134:1352–1359.
63 Mathru M, Rao TL, Kartha RK, Shanmugham M, Jacobs HK: Intravenous albumin administration for prevention of spinal hypotension during cesarean section. Anesth Analg 1980;9:655–658.
64 McLeod BC: Plasma and plasma derivatives in therapeutic plasmapheresis. Transfusion 2012;52(suppl 1):38–44.
65 Mendez CM, McClain CJ, Marsano LS: Albumin therapy in clinical practice. Nutr Clin Pract 2005;20:314–320.
66 Mitra S, Samanta M, Sarkar M, et al: Pre-exchange 5% albumin infusion in low birth weight neonates with intensive phototherapy failure – a randomized controlled trial. J Trop Pediatr 2011;57:217–221.
67 Mobarhan S: The role of albumin in nutritional support. J Am Coll Nutr 1988;7;445–452.
68 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.
69 Navickis RJ, Haynes GR, Wilkes MM: Effect of hydroxyethyl starch on bleeding after cardiopulmonary bypass: a meta-analysis of randomized trials. J Thorac Cardiovasc Surg 2012;144:223–230.
70 Neri S, Pulvirenti D, Malaguarnera M, et al: Terlipressin and albumin in patients with cirrhosis and type I hepatorenal syndrome. Dig Dis Sci 2008;53:830–835.
71 Oca MJ, Nelson M, Donn SM: Randomized trial of normal saline versus 5% albumin for the treatment of neonatal hypotension. J Perinatol 2003;23:473–476.
72 Oganesyan V, Damschroder MM, Cook KE, et al: Structural insights into neonatal Fc receptor-based recycling mechanisms. J Biol Chem 2014;289:7812–7824.
73 Oratz M, Rothschild MA, Schreiber SS: Effect of dextran infusions on protein synthesis by hepatic microsomes. Am J Physiol 1970;218:1108–1112.
74 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;37:643–648.
75 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;32:239–244.
76 Perel P, Roberts I: Colloids versus crystalloids for fluid resuscitation in critically ill patients. Cochrane Database Syst Rev 2011;3:CD000567.
77 Porte RJ, Bontempo FA, Knot EAR, Lewis JH, Kang YG, Starzl TE: Systemic effects of tissue plasminogen activator-associated fibrinolysis and its relation to thrombin generation in orthotopic liver transplantation. Transplantation 1989;47:978–984.
78 Pulimood TB, Park GR: Debate: albumin administration should be avoided in the critically ill. Crit Care 2000;4:151–155.
79 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;32:755–759.
80 Quintero E, Ginès P, Arroyo V, et al: Paracentesis versus diuretics in the treatment of cirrhotics with tense ascites. Lancet 1985;16:611–612.
81 Reinhart K, Perner A, Sprung CL, et al: Consensus statement of the ESICM task force on colloid volume therapy in critically ill patients. Intensive Care Med 2012;38:368–383.
82 Roberts I, Blackhall K, Alderson P, Bunn F, Schierhout G: Human albumin solution for resuscitation and volume expansion in critically ill patients. Cochrane Database Syst Rev 2011;11:CD001208.
83 Rossign N: Intra- and extravascular distribution of albumin and immunoglobulin in man. Lymphology 1978;11:138–142.
84 Ruiz del Arbol L, Monescillo A, Jiménez W, Garcia-Plaza A, Arroyo V, Rodes J: Paracentesis-induced circulatory dysfunction: mechanism and effect on hepatic hemodynamics in cirrhosis. Gastroenterology 1997; 113:579–586.
85 Russell JA, Navickis RJ, Wilkes MM: Albumin versus crystalloid for pump priming in cardiac surgery: meta-analysis of controlled trials. J Cardiothorac Vasc Anesth 2004;18:429–437.
86 S2k-Leitlinie Prävention, Diagnose, Therapie und Nachsorge der Sepsis. AWMF Register No. 079/001 *www.awmf.org/uploads/tx_szleitlinien/079–001l_S2k_Sepsis_2010-abgelaufen.pdf* (under revision, last retrieved July 27, 2015)
87 German S3-Guideline Ascites, Spontaneous Bacterial peritonitis, Hepatorenal Syndrome (in German). AWMF Register No. 021/017 *www.awmf.org/uploads/tx_szleitlinien/021–017l_S3_Aszites_2011.pdf* (last retrieved July 27, 2015).
88 German S3-Guideline on Treatment of Patients with Severe and Multiple Injuries. AWMF Register No. 012/019e. *.www.awmf.org/fileadmin/user_upload/Leitlinien/012_D_Ges_fuer_Unfallchirurgie/012–019e_S3_Severe_and_Multiple_Injuries_2015–01.pdf* (last retrieved July 27, 2015)
89 S3-Leitlinie zur intensivmedizinischen Versorgung herzchirurgischer Patienten, Hämodynamisches Monitoring und Herz-Kreislauf-Therapie. AWMF Register No. 001/016 *www.awmf.org/uploads/tx_szleitlinien/001–016l_S3_Intensivmedizinische_Versorgung_herzchirurgischer_Patienten_2010-gelabelt.pdf* (under revision, last retrieved July 27, 2015)
90 Sagi SV, Mittal S, Kasturi KS, Sood GK: Terlipressin therapy for reversal of type 1 hepatorenal syndrome: A meta-analysis of randomized controlled trials. J Gastroenterol Hepatol 2010;25:880–885.
91 Salerno F, Navickis RJ, Wilkes MM: Albumin infusion improves outcomes of patients with spontaneous bacterial peritonitis: a meta-analysis of randomized trials. Clin Gastroenterol Hepatol 2013;11:123–130.e1.
92 Sanyal AJ, Boyer T, Garcia-Tsao G, et al: A randomized, prospective, double-blind, placebo-controlled trial of terlipressin for type 1 hepatorenal syndrome. Gastroenterology 2008;134:1360–1368.
93 Saw MM, Chandler B, Ho KM: Benefits and risks of using gelatin solution as a plasma expander for perioperative and critically ill patients: a meta-analysis. Anaesth Intensive Care 2012;40:17–32.
94 Schortgen F, Girou E, Deye N, Brochard L; CRYCO Study Group: The risk associated with hyperoncotic colloids in patients with shock. Intensive Care Med 2008;34:2157–2168.
95 Schrier RW: Fluid administration in critically ill patients with acute kidney injury. Clin J Am Soc Nephrol 2010;5:733–739.
96 Shahian M, Moslehi MA: Effect of albumin administration prior exchange transfusion in term neonates with hyperbilirubinemia – a randomized controlled trial. Indian Pediatr 2010;47:241–244.
97 Sharma P, Kumar A, Sharma BC, Sarin SK: An open label, pilot, randomized controlled trial of noradrenaline versus terlipressin in the treatment of type 1 hepatorenal syndrome and predictors of response. Am J Gastroenterol 2008;103:1689–1697.
98 Solà R, Vila MC, Andreu M, et al: Total paracentesis with dextran 40 vs. diuretics in the treatment of ascites in cirrhosis: a randomized controlled study. J Hepatol 1994;20:282–288.
99 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;18:152–156.
100 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;37:1147–1153.
101 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;342:403–409.
102 Standl T, Lochbuehler H, Galli C, et al: HES 130/0.4 (Voluven®) or human albumin in children younger than 2 yr undergoing non-cardiac surgery. A prospective, randomized, open label, multicenter trial. Eur J Anaesthesiol 2008;25:437–445.
103 Standl T: Albumin; in Boldt J (ed): Volumenersatztherapie. Stuttgart, Thieme, 2001, pp 39–61.
104 Subcommittee of the Victorian Drug Usage: Human albumin solutions: consensus statements for use in selected clinical situations. Advisory Committee. Med J Aust 1992;157:340–343.
105 Thomas-Rueddel DO, Vlasakov V, Reinhart K, et al: Safety of gelatin for volume resuscitation – a systematic review and meta-analysis. Intensive Care Med 2012;38:1134–1142.
106 Tito L, Ginès P, Arroyo V, et al: Total paracentesis associated with intravenous albumin management of patients with cirrhosis and ascites. Gastroenterology 1990;98:146–151.
107 Trotter J, Pieramici E, Everson GT: Chronic albumin infusions to achieve diuresis in patients with ascites who are not candidates for transjugular intrahepatic portosystemic shunt (TIPS). Dig Dis Sci 2005;50:1356–1360.
108 Venetis CA, Kolibianakis EM, Toulis KA, Goulis DG, Papadimas I, Tarlatzis BC: Intravenous albumin administration for the prevention of severe ovarian hyperstimulation syndrome: a systematic review and metaanalysis. Fertil Steril 2011;95:188–196.
109 Vincent JL, Dubois MJ, Navickis RJ, Wilkes MM: Hypoalbuminemia in acute illness: is there a rationale for intervention? A meta-analysis of cohort studies and controlled trials. Ann Surg 2003;237:319–334.
110 Vincent JL, Navickis RJ, Wilkes MM: Morbidity in hospitalized patients receiving human albumin: a meta-analysis of randomized, controlled trials. Crit Care Med 2004;32:2029–2038.
111 Vincent JL, Wilkes MM, Navickis RJ: Safety of human albumin – serious adverse events reported worldwide in 1998–2000. Br J Anaesth 2003;91:625–630.
112 Webb AR: The appropriate role of colloids in managing fluid imbalance: a critical review of recent meta-analytic findings. Crit Care 2000;4(suppl 2):26–32.
113 Whatling PJ: Intravenous fluids for abdominal aortic surgery. Cochrane Database Syst Rev 2000;3:CD000991.

114 Wilkes MM, Navickis RJ, Sibbald WJ: Albumin versus hydroxyethyl starch in cardiopulmonary bypass surgery: a meta-analysis of postoperative bleeding. Ann Thorac Surg 2001;72:527–533.

115 Wilkes MM, Navickis RJ: Patient survival after human albumin administration – a meta-analysis of randomized controlled trials. Ann Intern Med 2001;135: 149–164.

116 Winstedt D, Hanna J, Schött U: Albumin-induced coagulopathy is less severe and more effectively reversed with fibrinogen concentrate than is synthetic colloid-induced coagulopathy. Scand J Clin Lab Invest 2013; 73:161–169.

117 Youssef MA, Al-Inany HG, Evers JL, Aboulghar M: Intra-venous fluids for the prevention of severe ovarian hyperstimulation syndrome. Cochrane Database Syst Rev 2011;2:CD001302.

118 Yuan XY, Zhang CH, He YL, et al: Is albumin administration beneficial in early stage of postoperative hypoalbuminemia following gastrointestinal surgery? A prospective randomized controlled trial. Am J Surg 2008;196:751–755.