

## REVIEW ARTICLE



# Use of albumin: an update

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Human albumin (HA) is widely used for volume replacement or correction of hypoalbuminaemia. The value of HA in the clinical setting continues to be controversial, and it is unclear whether in today's climate of cost consciousness, there is still a place for such a highly priced substance. It is therefore appropriate to update our knowledge of the value of HA. With the exception of women in early pregnancy, there appears to be few indications for the use of HA to correct hypovolaemia. Some studies of traumatic brain injury and intensive care patients suggest negative effects on outcome and organ function of (hyperoncotic) HA. Modern synthetic colloids appear to be a cheaper alternative for maintaining colloid oncotic pressure. The value of using HA to correct hypoalbuminaemia has not been clearly justified. Theoretical and pharmacological benefits of HA, such as oxygen radical scavenging or binding of toxic substances, have not as yet been shown to have beneficial clinical consequences. Experimental data from cell lines or animals do not appear to mimic the clinical setting. Convincing data justifying the use of HA either for treating hypovolaemia or for correcting hypoalbuminaemia are still lacking. A restricted use of HA is recommended.

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Human albumin (HA) is the most expensive non-blood plasma substitute used to treat hypovolaemia. HA is also used in many centres to correct hypoalbuminaemia. The role of HA is, however, still controversial and its use may be based more on custom than on a scientific basis. Because of its limited availability and high cost, it is imperative that the use of HA is restricted to indications for which it is efficacious. The arguments over its pros and cons are long-standing. Some meta-analyses which have tried to clarify the place of HA have resulted in widely divergent conclusions. There are a number of problems with these meta-analyses, including: comparing the use of HA with other plasma substitutes without clearly specifying the type of the non-protein plasma substitute used, different kind of patients (general surgery, cardiac, trauma, septic patients, burns, adults, the elderly), patients with different co-morbidities, studies that did not use goal-directed volume replacement therapy but fixed doses, studies with different endpoints using different definitions for identifying beneficial effects of HA, for example, outcome measures from studies more than 20 yr old although patients' management has markedly changed over that time.

Despite these meta-analyses, it still remains unclear when to use HA. An evaluation in 53 hospitals in the USA showed that based on guidelines developed by the

University HealthSystem Consortium (UHC),<sup>67</sup> HA was inappropriately used for 57.8% of adult patients and 52.2% of paediatric patients.<sup>66</sup> Thus, the aim of this review was to define the role of HA in the clinical setting.

### Albumin solution

HA is prepared from pooled human plasma by alcoholic precipitation. For pathogen inactivation, albumin is pasteurized for at least 10 h at +60°C. On the basis of manufacturing process and the pathogen inactivation involved, albumin preparations are considered to carry no risk of transmitting infections. Up to 3.2 g litre<sup>-1</sup> sodium octanoate and 4.29 g litre<sup>-1</sup> acetyltryptophan are added as stabilizers. Albumin preparations contain <200 µg litre<sup>-1</sup> of aluminium. Albumin solutions do not contain isoagglutinins or blood group substances and can thus be administered independent of the recipient's blood group. HA solutions are either slightly hypo-oncotic (4% HA solutions), iso-oncotic (5% HA solutions), or hyperoncotic (20–25% HA solutions). The effective component is HA with a molecular weight (Mw) of around 66 kDa consisting of 584 amino acids of known sequence. Albumin solutions are dissolved in saline solution containing 154 mmol litre<sup>-1</sup> of sodium and 154 mmol litre<sup>-1</sup> of chloride.

## Physiological properties and function of albumin

The albumin concentration in plasma in healthy humans ranges between 33 and 52 g litre<sup>-1</sup>. Albumin is synthesized exclusively in the liver. The normal rate of albumin synthesis is ~0.2 g kg<sup>-1</sup> body weight per day. Extravascular colloid oncotic 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, that is, natural or synthetic colloids.<sup>45</sup> A lasting increase in albumin concentration can only be achieved by adequate 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, that is, a fixed percentage of ~10% of plasma albumin content is metabolized per day.<sup>35</sup> Its half-life is inversely proportional to the plasma albumin concentration, that is, a decreased albumin content results in increased half-life, whereas increasing albumin concentrations cause the metabolic rate to increase by up to 50%.

The distribution of albumin is adequately described by a two-compartment model where about 40% is taken up by the intravascular and 60% by the extravascular space.<sup>35 54</sup> The balance between plasma and interstitial space is established at varying rates with respect to the two subcompartments of the extravascular albumin pool.<sup>35 37</sup> The total exchange rate between intra- and extravascular volume (transcapillary escape rate) amounts to ~5% of the intravascular albumin content per hour. The transcapillary escape rate of albumin is increased in a variety of diseases (Fig. 1).<sup>44 47</sup>

## Volume replacing effects of albumin

Albumin has a high capacity for binding water (~18 ml g<sup>-1</sup>), an intravascular residence time of ~4 h, presupposing physiological capillary permeability,<sup>44</sup> and an *in vivo* half-life of ~18–21 days.<sup>35 37</sup> Although albumin comprises only about 50–60% of the total protein content of plasma, it is responsible for about 80% of intravascular COP.

- |                                |                                 |
|--------------------------------|---------------------------------|
| • Hypertension                 | • Major surgery and trauma      |
| • Congestive heart failure     | • Fluid loading                 |
| • Exercise                     | • Chemotherapy                  |
| • Catecholamines               | • Vasculitis/glomerulonephritis |
| • Diabetes mellitus            | • Cardiopulmonary bypass        |
| • Infection, sepsis, and shock | • Ischaemia/reperfusion         |
| • Hypothyroidism               | • Burns                         |

**Fig 1** Clinical conditions associated with increased albumin transvascular escape rate.

## 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 (Fig. 2). Although these transport qualities are of physiological and pharmacological importance, at present no relevant therapeutic has been shown for using HA to improve transport function.

## Albumin solutions for correcting hypovolaemia

### Volume replacement in the perioperative period

Neither benefit nor harm was shown when using HA to maintain haemodynamic stability in the perioperative period when compared with crystalloids or any other colloidal volume substitute.<sup>7 44 74</sup>

HA has been considered to be indicated for volume replacement in cardiac surgery.<sup>29</sup> The risk of excessive bleeding associated with older synthetic colloids [dextrans, first-generation hydroxyethyl starch (HES)] is seen as a rationale for the use of HA in this setting,<sup>4 9 14 34</sup> since no relevant substance-specific alterations of coagulation have been reported for HA. The majority of the studies reporting benefits with HA in cardiac surgery originate from the USA where modern synthetic colloids with few adverse effects on coagulation have not been available for long. A retrospective analysis that reported a lower mortality in cardiac surgery patients when using HA<sup>58</sup> must be interpreted with caution, as the alternatives to HA used were substances with known negative effects on coagulation. A meta-analysis from 2001<sup>75</sup> compared the risk of postoperative bleeding after administration of HA or the older HES preparations showing a high or medium Mw and a high

- |                  |   |
|------------------|---|
| <b>Vascular</b>  | <ul style="list-style-type: none"> <li>• Maintenance of oncotic pressure</li> <li>• Microvascular integrity</li> </ul>  |
| <b>Transport</b> | <ul style="list-style-type: none"> <li>• Hormones (steroids, thyroxine)</li> <li>• Fatty acids</li> <li>• Bile salts</li> <li>• Bilirubin</li> <li>• Ca<sup>2+</sup>, Mg<sup>2+</sup>, and other metals (copper, zinc)</li> <li>• Drugs: - warfarin<br/>- diazepam</li> </ul> |
| <b>Metabolic</b> | <ul style="list-style-type: none"> <li>• Acid–base balance</li> <li>• Antioxidant</li> <li>• Anticoagulant</li> </ul>   |

**Fig 2** Physiological functions of albumin in the plasma.

degree of substitution (MS) in cardiac surgery patients. HA and HES, respectively, were administered as volume replacement before and after cardiopulmonary bypass and also as constituents of the priming fluid of the extracorporeal circuit. In nine trials involving 354 patients, the effects of a first-generation HES (Mw 450 kDa, MS 0.7) and HA were compared. Postoperative blood loss was significantly lower in patients given to HA than in those receiving HES. If, in contrast, a newer synthetic colloid solution was used (Mw 200 kDa, MS 0.5; eight trials involving 299 patients),<sup>75</sup> there was no longer any statistically significant difference in comparison with HA. In a recent study,<sup>5</sup> hypoalbuminaemic elderly cardiac surgery patients were given either 5% HA or modern (third generation) 6% HES 130/0.4 to maintain normovolaemia perioperatively. No differences in haemodynamics, inflammatory response, endothelial integrity, and kidney function between HA- and HES-treated patients were noted more than ~60 days after surgery.

#### *Volume replacement in intensive care unit patients*

The largest trial currently available included ~7000 patients and used a prospective, randomized, double-blind design to compare volume substitution in intensive care patients with either crystalloid substitutes (saline solution) or HA 4% [Saline vs Albumin Fluid Evaluation (SAFE) study].<sup>22</sup> No significant beneficial effect of HA was found with respect to either morbidity and mortality or days spent in the intensive care unit (ICU) or in hospital. In a smaller randomized, controlled study in adult patients with sepsis and suspected hypovolaemia, HES 200/0.5 (second-generation HES) was shown to be as effective as HA for volume resuscitation.<sup>24</sup> In a recent study, the effects of crystalloids and colloids, including HA, on pulmonary oedema in hypovolaemic septic and non-septic patients with, or at risk of, acute lung injury/acute respiratory distress syndrome were assessed.<sup>68</sup> Pulmonary oedema and lung injury score were not affected by the type of fluid indicating that HA was not superior to cheaper alternatives.

In a cohort, multicentre, observational study of 3147 ICU patients, the use of HA in European ICUs and its relationship to outcome were assessed.<sup>71</sup> The indication for giving albumin was not specified (hypovolaemia or hypoalbuminaemia). Three hundred and fifty-four patients (11.2%) received albumin and 2793 patients (88.8%) did not. Albumin administration was associated with decreased survival in this population of acutely ill patients. An international prospective cohort study including 1013 ICU patients needing fluid resuscitation for shock documented that the use of hyperoncotic albumin (20% HA) was significantly associated with occurrence of negative renal events (two-fold increase in creatinine or need for dialysis) and an increased risk of death in ICU.<sup>57</sup>

International guidelines for the management of severe sepsis and septic shock<sup>15</sup> do not specifically recommend

the use of HA for volume replacement for haemodynamic stabilization in this setting.

#### *Volume replacement in burn patients*

Burns are seen as a potential indication for administration of HA, but not in the first 24 h after burn trauma.<sup>6</sup> Crystalloid solutions are preferred as volume replacement.<sup>6</sup> The lack of effect of 5% HA for burn shock resuscitation on the incidence of multiple organ dysfunction was recently described in burn adults.<sup>13</sup> In paediatric burn patients, HA was not associated with improved outcome measures.<sup>30</sup>

#### *Volume replacement in trauma patients*

In trauma patients with severe hypovolaemia, rapid correction using HA is not possible as it is supplied in glass bottles and high-volume pressure infusion is not possible. The use of HA to correct hypovolaemia in trauma patients has not been shown to have a significant benefit in survival when compared with other plasma substitutes.<sup>67 74</sup> In contrast, in patients with traumatic brain injury, a *post hoc* follow-up analysis of the data from the SAFE study showed a significantly increased mortality for the group treated with HA as opposed to the non-albumin-treated group.<sup>55</sup>

#### *Volume replacement in pregnant women*

There are no controlled studies on volume substitution to correct hypovolaemia in early pregnancy. The use of HA for this purpose has also not been established in controlled clinical trials. Animal reproduction studies have not been conducted with HA [e.g. product information Plasbumin® ([www.talecris-pi.info/inserts/plasbumin20la.pdf](http://www.talecris-pi.info/inserts/plasbumin20la.pdf))]. It is not known whether albumin solutions can cause fetal harm when given to a pregnant woman or can affect reproductive capacity. However, severe hypovolaemia during the first months of pregnancy (e.g. in the context of surgical intervention) may be a possible indication for HA administration as the manufacturers of most synthetic colloids recommended not to use them due to lack of data. The guideline on the Core Summary of Product Characteristics (SPC) for Human Albumin Solution states that 'clinical experience with albumin suggests that no harmful effects on the course of pregnancy, or on the foetus and the neonate are to be *expected*'. Nevertheless, HA should be given to a pregnant woman only if really needed.

#### *Volume replacement in hepatic surgery (including liver transplantation)*

Correction of hypovolaemia in patients undergoing major liver surgery or liver transplantation has long been considered an indication for using HA. However, such patients have also successfully been treated with synthetic colloids.

There are no large-scale prospective trials.<sup>8</sup> In a prospective study of 40 patients after living related liver transplantation, patients were randomized to an HA group ( $n=20$ ), where 20% HA was given to maintain serum albumin level  $\geq 3$  g dl<sup>-1</sup>, and a control group ( $n=20$ ), where there was no correction for serum albumin.<sup>42</sup> Postoperative HA administration did not produce significant clinical benefits in these patients.

### *Volume replacement in children*

The use of HA has long been regarded as the treatment of choice for volume substitution in young children. There are only a few reports of effects on haemodynamics, organ function or outcome of the use of HA in neonates, premature infants, and children under the age of 12 months. Even in high-risk neonates, overall survival was not increased after HA administration.<sup>74</sup> Safe and effective volume replacement in children is also possible using colloid solutions.<sup>12 59 63–65</sup>

### *Volume replacement using hyperoncotic albumin solutions*

A systematic review of randomized clinical trials on small-volume resuscitation with hyperoncotic albumin (20% HA) included 25 randomized clinical trials with a total of 1485 patients.<sup>32</sup> Considerable benefits were documented when using hyperoncotic HA, but survival was unaffected. Shorter hospital stay and lower costs were shown when using hyperoncotic HA for correction of hypovolaemia patients with liver disease. Two studies, which were more than 15 yr old, reported reduced disability after using hyperoncotic albumin in brain injury. This review conflicts with negative results from large studies showing increased mortality after the use of HA in brain injury patients<sup>55</sup> and increased incidence of renal failure in ICU patients after 20% HA.<sup>57</sup>

## **Albumin for correcting hypoalbuminaemia**

Hypoalbuminaemia has been shown to be associated with poor clinical outcome.<sup>69 70</sup> Thus, correction of hypoalbuminaemia may be an indication for giving HA. In human plasma, albumin concentration ranges around 3.5–4.5 g dl<sup>-1</sup> and amounts to ~60% of the total plasma proteins (6–8 g dl<sup>-1</sup>). Around 30–40% of the replaceable albumin pool is located in the plasma compartment (~120 g in a 3 litre plasma volume).<sup>31</sup> Concentration in the tissue spaces is considerably lower (1.4 g dl<sup>-1</sup>; ~160 g in 10–12 litre of interstitial volume). Under normal conditions, the liver produces around 200 mg kg<sup>-1</sup> per day of albumin, corresponding to around 15 g per day of a 70 kg person. The main factor governing production of albumin is COP in the extravascular space of the liver. In sepsis, infection, trauma, or major surgery, albumin level decreases by ~1–1.5 g dl<sup>-1</sup>

over 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 decrease in serum albumin concentration in critical illness. The most significant cause of the reduced albumin level is apparent redistribution (e.g. shift into the interstitial space), catabolism, or both. In patients with sepsis, an increased vascular permeability (capillary leak) plays an important role in developing hypoalbuminaemia by the shift of albumin from the intravascular to the interstitial compartment.<sup>23</sup>

After infusion of HA, its distribution within the extravascular compartment is complete after 7–10 days. Approximately 10% of the infused HA migrates from the intravascular space within 2 h,<sup>48</sup> 75% of transfused albumin is distributed into the extravascular space after 2 days.<sup>31</sup> Under certain conditions (e.g. in sepsis), this distribution process happens more rapidly. In this setting, capillary leak of albumin can increase to 13 times its normal level.<sup>11</sup> Thus, the more the endothelial integrity is disrupted the greater the leakage and the lower the albumin plasma levels appear to be.

### *Correction of hypoalbuminaemia in surgical or ICU patients*

Hypoalbuminaemia is a predictor of increased mortality and morbidity in surgical or ICU patients.<sup>35 37 69 70</sup> It is not yet established what plasma albumin concentration can be considered to be tolerable and whether there is a 'critical' threshold value below which giving HA is beneficial or even essential. A meta-analysis of cohort studies and controlled trials in acutely ill patients showed that each decrease of 10 g litre<sup>-1</sup> in plasma albumin concentration significantly raised the odds of mortality by 137%, morbidity by 89%, prolonged ICU and hospital stay, respectively, by 28% and 71%, and increased resource utilization by 66%.<sup>69</sup> The benefit of correcting hypoalbuminaemia by HA in this situation has not been clearly established. Two prospective randomized studies showed that with albumin levels <31 g litre<sup>-1</sup> (total protein concentrations <60 g), HA administration significantly improved respiratory, cardiovascular, and central nervous system function. Enteral feeding was also better tolerated, oxygenation improved in acute pulmonary failure and a less positive fluid balance was achieved.<sup>16 36</sup> Both studies were with a small number of patients and did not have a another substance for HA which also increased COP.

There is evidence that correction of hypoalbuminaemia does not beneficially influence outcome. In a prospective, randomized study of 127 patients with hypoalbuminaemia after gastrointestinal surgery, no benefits of HA were shown.<sup>76</sup> Although 3- and 5-day recovery ratios were similar between HA- and saline-treated patients, 7-day recovery ratios were significantly lower in the HA group. The authors concluded that HA administration in the early stage of postoperative hypoalbuminaemia did not benefit



clinical outcomes. A cohort, multicentre, observational study of 3147 ICU patients showed that HA administration was associated with decreased survival in these patients.<sup>22</sup> In two meta-analyses of adults and children, correction of hypoalbuminaemia showed no benefit with regard to morbidity and mortality over an untreated control.<sup>33 74</sup>

In summary, more reports confirmed that although hypoalbuminaemia is associated with increased mortality, the use of albumin in critically ill patients with a serum albumin concentration  $\leq 25$  g litre<sup>-1</sup> is not associated with reductions in mortality, duration of ICU stay or mechanical ventilation, or in the use of renal replacement therapy.<sup>43</sup> Thus, there is limited evidence to justify the use of (hyperoncotic) HA for resuscitation or supplementation in these patients.<sup>43</sup>

#### *Use of HA in undernutrition, malnutrition, and enteropathies/malabsorption syndrome*

No benefit for the administration of HA in undernutrition, malnutrition, and enteropathies/malabsorption syndrome has been shown. Its composition of amino acids which has a low ratio of some essential amino acids (tryptophan, methionine, and isoleucine) and its long biological half-life of around 19–21 days makes HA unsuitable for use in parenteral nutrition.

#### *Correction of hypoalbuminaemia in patients with liver cirrhosis*

In cirrhotic patients with ascites, there is some evidence that HA leads to a reduction in morbidity and mortality.<sup>26 62</sup> However, hypoalbuminaemia *per se* is not a confirmed indication in patients with established liver cirrhosis and ascites. The decision on need for volume replacement or use of HA depends on the degree of severity of liver cirrhosis and the extent of the haemodynamic, hormonal, and immunological deficits.

Three clinical situations have been described where the use of HA may be indicated: spontaneous bacterial peritonitis (SBP), hepatorenal syndrome (HRS), and post-paracentesis syndrome (PPS).

The guidelines of the American Association for the Study of Liver Diseases (AASLD) define SBP by the detection of neutrophil granulocytes ( $>250$  mm<sup>-3</sup> of ascites) in the absence of an intra-abdominal source of infection.<sup>52</sup> A single randomized controlled trial involving patients with ascites and SBP investigated the administration of cefotaxime plus albumin [ $1.5$  g kg<sup>-1</sup> body weight at the time of SBP diagnosis (day 1) and  $1$  g kg<sup>-1</sup> body weight on day 3] and compared this with treatment with cefotaxime alone without plasma volume expansion.<sup>62</sup> Renal impairment was prevented by the additional use of HA, and the mortality rate at 3 months was significantly improved. However, the control group in this study did not receive adequately controlled fluid replacement

and thus remained hypovolaemic. A subgroup analysis of this study showed that the incidence of renal impairment after SBP was almost exclusive in patients with elevated creatinine levels at the time of SBP diagnosis and serum bilirubin levels of at least  $4$  mg dl<sup>-1</sup>. A randomized unblinded pilot study of 20 patients compared the administration of 20% HA ( $n=10$ ) for 6 h and the administration of a second-generation HES preparation (6% HES 200/0.5) ( $n=10$ ) for 18 h on haemodynamic and renal complications in patients with SBP.<sup>21</sup> There were fewer renal complications in the HA group in comparison with the HES group (three *vs* five patients).

In the majority of the trials on the treatment of HRS, vasoconstrictors were used in combination with HA.<sup>3 17 40 60</sup> In a prospective, non-randomized study, patients receiving terlipressin combined with HA ( $1$  g kg<sup>-1</sup> body weight on day 1 and 20–40 g albumin per day on consecutive days if central venous pressure  $\leq 18$  mm Hg) were compared with patients receiving terlipressin alone.<sup>46</sup> A greater rate of complete response was with HA therapy. However, this trial has a methodological flaw in that after the enrolment of 13 patients the protocol (terlipressin plus albumin) was modified.

Paracentesis for drainage of ascites without volume compensation is associated with the risk of developing PPS. The incidence of PPS is associated with a considerably higher risk of developing renal failure and an overall increased mortality.<sup>28 39</sup> To prevent PPS, volume substitution should be given after each paracentesis.<sup>38 39</sup> Randomized clinical trials of the choice of the plasma substitute used to prevent PPS have compared HA (6–8 g litre<sup>-1</sup> of ascitic fluid) with dextran 70,<sup>20 27 50</sup> polygeline,<sup>27 41 56</sup> dextran 40,<sup>25</sup> and HES.<sup>2</sup> These trials had considerable differences regarding volume and number of paracenteses, the degree of severity of liver disease, the length of follow-up, and the definition of clinical complications. There were no significant differences between the individual groups regarding mortality and incidence of clinical complications.

The use of HA over a long time-period in this setting may be of advantage. A randomized, unblinded, non-placebo controlled clinical trial of patients with liver cirrhosis and first onset ascites compared a standard therapy (without other colloid volume replacement) with and without administration of HA (25 g per week in the first year and 25 g every 2 weeks thereafter).<sup>53</sup> It was found that the HA-treated group had a significantly greater cumulative survival rate.

There is only one case-control trial of the effect of the volume of ascitic fluid evacuated and the type of plasma expander therapy, which found no PPS if the volume of ascitic fluid evacuated was  $<5$  litre and without plasma expander.<sup>49</sup> There is one randomized controlled trial comparing HA and 3.5% saline after paracentesis.<sup>61</sup> There was a higher incidence of PPS when 3.5% saline was used, but not in a subpopulation for whom  $<6$  litre of ascitic fluid was evacuated. A consensus guideline proposes that this

evidence is not strong enough to deny plasma expander therapy to those patients in whom <6 litre of ascitic fluid is to be evacuated, and recommended the use of synthetic plasma substitutes.<sup>38</sup>

### *Correction of hypoalbuminaemia in nephrotic syndrome*

In nephrotic syndrome, albumin is lost via the kidneys. Compensation of the resulting hypoalbuminaemia is not useful as most of it is quickly eliminated again.

### **Albumin improving transport capacity for drugs**

Albumin serves as a transport protein for many substances (e.g. bilirubin and drugs).<sup>18</sup> It is doubtful whether in the case of hypoalbuminaemia, there may also be an increase in the 'free' unbound (biologically active) fraction of drugs. 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 hypoalbuminaemia 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.

### **Albumin as free radical scavenger and for binding toxic substances**

Albumin acts as a free radical scavenger and is able to bind toxic substances (e.g. free fatty acids). Therefore, there could be an indication for HA in patients with sepsis because toxic oxygen radicals play a role in pathogenesis and maintenance of sepsis,<sup>51</sup> and have a beneficial effect in these patients. However, to date, there are no confirmed data on the benefit of HA therapy regarding morbidity or mortality in humans. In addition, it is uncertain whether HA preparations currently commercially available have the same (radical scavenger) properties as natural albumin or whether they are altered by the manufacturing process.

### **Negative effects of HA**

No substance-specific clinically relevant alterations in the coagulation capacity nor alterations in organ function due to iso-oncotic HA therapy have been reported.<sup>72</sup> Although albumin is prepared from pooled plasma, HA preparations currently available are considered to be non-allergenic due to the manufacturing process.

An investigation of the safety of HA<sup>72</sup> showed that between 1990 and 2000, ~112 million units of HA were

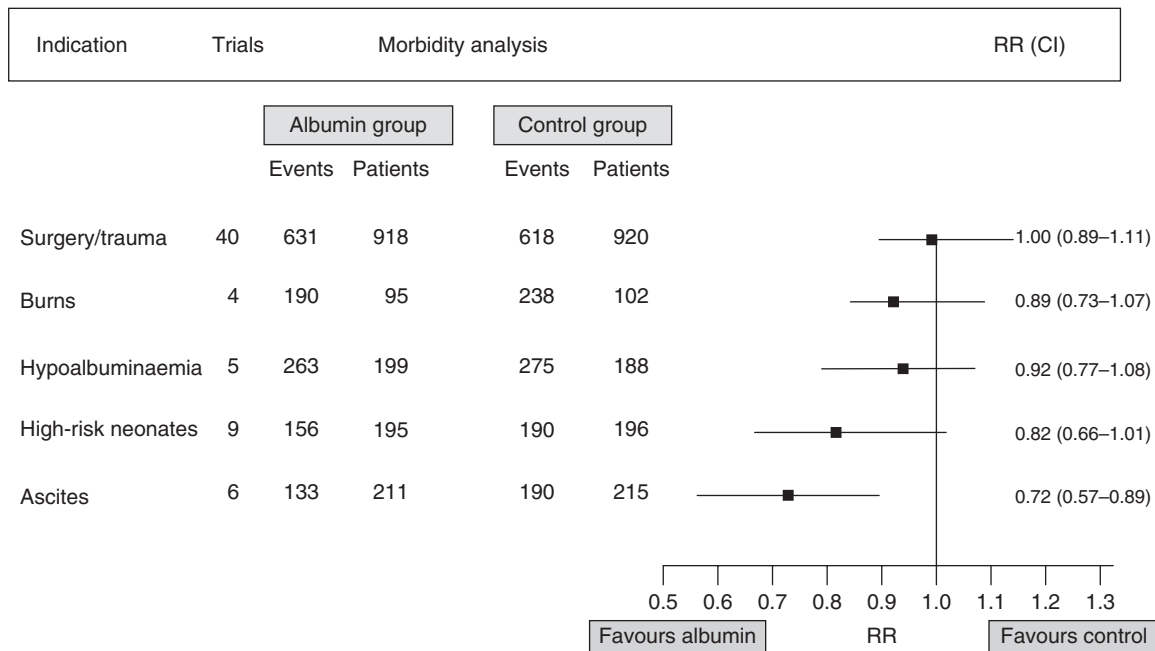
administered worldwide, whereas from 1998 to 2000, ~10<sup>7</sup> units of 40 g each were administered. Adverse effects that were directly associated with albumin were an extremely rare event during this observation period. There are, however, more recent reports that the use of (hyperoncotic) HA is associated with significant damage for some patients. A *post hoc* follow-up analysis of data from the SAFE study showed a significantly increased mortality for patients with traumatic brain injury treated with HA as opposed to the non-albumin group.<sup>55</sup> An international prospective cohort study of 1013 ICU patients needing fluid resuscitation for shock showed that the use of hyperoncotic 20% HA was significantly associated with adverse renal effects.<sup>57</sup>

### **Absolute and relative contraindications**

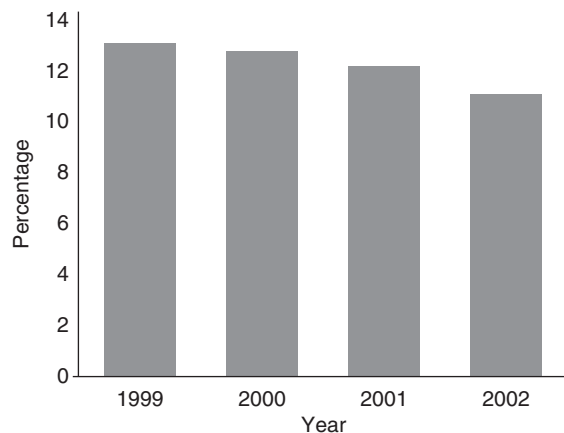
The only substance-specific contraindication for albumin is an established allergy against HA, or rather against the solubilizing agent. As any HA infusion (e.g. to compensate hypovolaemia) simultaneously causes increased intravascular volume, any hypervolaemic state is to be considered a contraindication. Particular caution is required in patients with severely restricted cardiac function. As is true for all volume substitutes, congestive heart failure with pulmonary oedema and hypocoagulopathy due to dilution are contraindications for using HA.

In conclusion, the widespread use of HA worldwide appears to be based on strong views rather than controlled study results. The wider use of HA should not be based on presumed potential benefits in selected patient groups. It has been shown that the most common indications for using HA were hypotension in haemodialysis (18.9%), volume replacement (15%), and correction of hypoalbuminaemia (14.8%).<sup>19</sup> In 9.4%, no indication for HA was identified.<sup>19</sup> These indications are questioned by the *Cochrane Review* on albumin which found that for patients with hypovolaemia, there is no evidence that albumin reduces mortality when compared with cheaper alternatives.<sup>1</sup> This *Cochrane Review* also showed that there is no evidence that albumin reduces mortality in critically ill patients with burns and hypoalbuminaemia. As mortality may not be the ideal endpoint for assessing the value of HA, morbidity appears to be of increasing interest. A meta-analysis of randomized, controlled trials showed that except in patients with ascites, the use of HA was not associated with significantly improved morbidity (Fig. 3).<sup>70</sup>

In times of increasing cost consciousness and cost containment, costs of HA are notable and ranging from two- to 20-fold of that of synthetic colloids.<sup>10</sup> Costs for albumin have a significant impact on all ICU drug costs<sup>73</sup> (Fig. 4). In a prospective cohort study of 1361 ICU patients, the influence of more restrictive use of HA on mortality and cost savings was assessed.<sup>1</sup> Implementing restrictive albumin use guidelines resulted in a 54%



**Fig 3** Effects of use of HA on risk ratio (RR) and confidence interval (CI) for morbidity in different clinical settings (data taken from Vincent and colleagues).<sup>69</sup>



**Fig 4** Per cent of ICU costs by fiscal year by albumin use (data taken from Weber and colleagues).<sup>73</sup>

reduction in HA use. This restrictive use of HA had no negative impact on ICU mortality but a substantial cost saving was realized (56% reduction in cost). It is apparent that we need more strict recommendations and guidelines to limit non-justified use of HA. These savings can be better used for other cost-intensive strategies in the management of the critically ill.

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