Clinical use of albumin

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Human albumin (HA) is the most abundant circulating protein in the plasma of healthy individuals (3.5-5 g/dL) since it represents approximately 50% of the total protein content. HA is a small globular protein (molecular weight: 66.5 kDa), consisting of a single chain of 585 amino acids organised in three repeated homologue domains (sites I, II, and III), each of which comprises two separate sub-domains (A and B).

Under physiological conditions, about 10-15 grams of HA are produced in the liver by the hepatocytes every day, with none or very low intracellular storage. Its synthesis is stimulated by hormones, such as insulin, cortisol and growth hormone, while it is inhibited by pro-inflammatory substances, including interleukin-6 and tumour necrosis factor-α[1,2].

Once released in the circulation, about 30-40% is maintained in the blood stream, while the remainder is distributed in the interstitium, where its concentration is low (1.4 g/dL). The protein leaves the circulation at a rate of 5% per hour, returning to it via the lymphatic system in an amount comparable to the output. This results in a circulatory half-life of approximately 16-18 hours and in a much longer total half-life which varies from about 12 to 19 days in a healthy young adult. HA can be catabolised in many tissues, but mainly in the muscles, liver and kidneys[1-4].

HA is the main modulator of fluid distribution among the compartments of the body, providing approximately 70-80% of the total plasma oncotic pressure. Two thirds of the oncotic property derives from the direct osmotic effect related to its molecular mass and 1/3 from the Gibbs-Donnan effect, due to the negative net charge of the molecule which attracts positively charged molecules (i.e. sodium and, therefore, water) into the intravascular compartment.

However, many other non-oncotic properties which are unrelated to the regulation of fluid compartmentalisation, and are mostly the result of the peculiar structure and conformation of the molecule, have been identified in the last two decades.

HA binds and carries a great variety of hydrophobic molecules, such as endogenous (i.e., cholesterol, fatty acids, bilirubin, thyroxina) or exogenous substances (i.e., drugs and toxins), transition metal ions, and gas (nitric oxide [NO]), with consequent implications for their solubilisation, transport, metabolism, and detoxification[3,4].

HA is also the major source of extracellular reduced sulfhydryl groups, localised at the cysteine-34 (Cys-34) site, which act as potent scavengers of reactive oxygen species (ROS). The antioxidant function resides also in the capability to bind at the N-terminal portion of the molecule several metal ions, including copper, cobalt, nickel, zinc and iron. These ions are therefore inhibited to catalyse many chemical reactions generating free radicals[3,5,6]. As a result, HA represents the main circulating antioxidant system in the body.

The HA molecule also contributes to the stabilisation of the endothelial layer and to the maintenance of the normal capillary permeability probably by reducing oxidative damage and modulating inflammation[7,8].

Finally, it exerts an antithrombotic effect which appears to be related to the capacity of binding NO at the Cys-34 site with subsequent formation of the complex albumin-NO, thus preventing the rapid inactivation of NO and ultimately prolonging its anti-aggregant effect on platelets[9,10].

Evidence-based clinical indications for HA administration

As a result of its osmotic effect, most of the clinical use of HA is based on the capacity to act as a plasma-expander[1]. In recent years, several clinical and experimental studies support the assumption that part of the therapeutic activity of HA can also depend on its non-oncotic properties.

Besides some clinical indications supported by solid scientific evidence, HA administration in many other settings is still under debate or has been disproved by evidence-based medicine. Fluid resuscitation in critically ill patients, when crystalloids and non-proteic colloids are not effective or contra-indicated, and treatment or prevention of severe clinical complications in patients with advanced cirrhosis, represent the major evidence-based indications for HA administration[11-15].

HA in critically ill patients

Fluid resuscitation constitutes a mainstay in the management of patients admitted to intensive care units (ICU) for critical illnesses, such as shock, sepsis, trauma, acute respiratory distress syndrome, burns or acute clinical situations associated with hypovolaemia. The choice of fluid has been debated for decades, as either crystalloids,

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non-protein colloids and HA have been widely employed. Furthermore, it remains controversial whether the efficacy of HA is limited to specific disease conditions.

Back in the '90s, a first meta-analysis from the Cochrane group including 30 randomised clinical trials showed a higher risk of death (pooled relative risk: 1.68) in patients with hypovolaemia due to injury or surgery, burns and hypoproteinaemia receiving HA solutions[16]. Conversely, a meta-analysis published by Wilkes *et al.*, including 55 trials, did not support this detrimental effect in patients with trauma or surgery, burns, hypoalbuminaemia, ascites or high-risk neonates[17]. The finding that HA can be used safely in critically ill patients was then confirmed by the third meta-analysis published by the Cochrane group in 2004[18] and by the Saline *versus* Albumin Fluid Evaluation (SAFE study), which showed a similar 28-day mortality in 6,997 ICU patients prospectively randomised to receive saline or 4% HA solution for fluid resuscitation[19]. More recently, in 2011, another Cochrane meta-analysis comparing HA or plasma protein fraction with no HA or plasma protein fraction or with a crystalloid solution in critically ill patients with hypovolaemia, burns or hypoalbuminaemia, showed no evidence of survival benefit of HA compared to the other cheaper alternatives[20].

A clear limitation in the interpretation of the results resides in the fact that all these studies enrolled a very heterogeneous population, while the effect of HA may be quite different depending on the specific critical illness. Indeed, while HA administration should be avoided in patients with traumatic brain injury since its use has been associated to an increased risk of mortality, severe sepsis and septic shock represent specific conditions where HA may be more effective than crystalloids and other non-proteic plasma-expanders[13,21]. Indeed, in a subgroup of 1,218 patients with severe sepsis enrolled in the SAFE study, those receiving HA had, by multivariate analysis, a decreased risk of death at day 28 as compared to those receiving saline (adjusted odd ratio: 0.71)[13]. Furthermore, a recent meta-analysis by Delaney *et al.* comparing HA and crystalloids in septic patients showed a survival benefit with HA[14]. However, several methodological drawbacks apply to these latter two investigations. The SAFE study was not primarily designed to examine the benefits of HA and saline in patients with severe sepsis, which represent only a subgroup in the whole trial population. Furthermore, not even all patients with sepsis could be included in the multivariate analysis. Similarly, the weakness of the meta-analysis by Delaney resides in the fact that it included non-pre-defined subgroups of patients with sepsis enrolled in 19 trials otherwise designed to assess the mortality in a larger, much more heterogeneous population of patients with critical care illnesses[14].

Thus, in order to have a definitive answer to this controversial issue, we should await the results of prospective randomised studies comparing HA with crystalloids in patients with sepsis, severe sepsis and septic shock, including one currently ongoing in Italy (NCT 00707122, www.clinicaltrials.gov, "the ALBIOS study").

The most recent guidelines of the surviving sepsis campaign support, although with a low level of recommendation, the use of HA for fluid resuscitation in patients with severe sepsis and septic shock when substantial amount of crystalloids are required and also suggest to avoid the administration of hydroxyethyl starch[22].

Thus, if HA administration for resuscitation is now considered safe in critically patients except for those with traumatic brain injury, its benefit above cheaper alternatives (crystalloids and non-proteic colloids) has not been unequivocally demonstrated. However, recent evidence indicate that HA could be more effective at least in some specific clinical conditions, such as severe sepsis and septic shock[13,14]. Under these circumstances, besides acting as plasma-expander, the additional beneficial effect of HA may reside in its non-oncotic properties, by increasing the plasma anti-oxidant and anti-inflammatory capacity and by reducing the capillary permeability and thus the fluid loss to the interstitium[4].

HA in patients with advanced liver cirrhosis

Advanced liver cirrhosis is characterised by a typical cardiovascular scenario resulting from a marked reduction in the effective arterial volaemia (i.e. the blood volume in the heart, lungs and central arterial tree that is sensed by arterial receptors). The major pathogenetic event producing effective hypovolaemia is arteriolar vasodilation, mainly in the splanchnic circulatory area, which is caused by the increased production of vasodilators, such as NO, carbon monoxide, and endocannabinoids. A fall in cardiac output leading to an exacerbation of effective hypovolaemia is also observed in patients with very advanced disease, probably related to a clinically relevant cardiac dysfunction known as cirrhotic cardiomyopathy. The ensuing effective hypovolaemia evokes the compensatory activation of neuro-humoral systems, including the renin-angiotensin-aldosterone axis, sympathetic nervous system, and arginin-vasopressin, which can promote vasoconstriction in the kidneys and thus lead to renal retention of sodium and water[23].

These cardiovascular abnormalities are the essential background for the development of ascites and other clinical complications of cirrhosis all characterised by extreme effective hypovolaemia, such as hepatorenal syndrome (HRS), post-paracentesis circulatory

dysfunction (PPCD) and renal failure induced by spontaneous bacterial peritonitis (SBP)[24,25].

As a result, the maintenance of the central blood volume represents a major objective in the management of patients with advanced cirrhosis.

Based on its capacity to act as a plasma-expander, the use of HA is currently proposed by the international guidelines to treat HRS, in association with vasoconstrictor drugs, and to prevent PPCD and renal failure induced by SBP[11,12]. A final but very important assumption deriving from the pathophysiological scenario is that serum albumin concentration should not be a guide for HA use and the correction of hypoalbuminaemia *per se* should not be a goal to pursue.

Diagnosis and treatment of HRS

HRS is a potentially reversible renal failure characterised by severe intra-renal vasoconstriction that develops in patients with advanced cirrhosis and ascites. According to the diagnostic criteria of the International Club of Ascites, HRS is usually classified in two types: type 1 is a rapidly progressive acute renal failure, usually precipitated by a bacterial infection and characterised by a very poor prognosis; type 2 is a relatively steady but moderate degree of functional renal failure associated with refractory ascites and often hyponatraemia[24,26].

A diagnosis of HRS can be made only after the exclusion of organic and other functional forms of renal failure. In this regard, diuretic withdrawal and HA administration (1 g/kg of body weight per day up to a maximum of 100 g/day) for at least 2 days is recommended to exclude hypovolaemic renal failure. HA administration is preferred to saline because the resulting volume expansion is greater and more sustained[26].

Once diagnosis is established, the current therapeutic approach includes the administration of both vasoconstrictors and HA (20-40 g/day). Among the vasoconstrictors used in the management of type 1 HRS, terlipressin, which mainly acts on the splanchnic vascular bed where vasodilation is maximal, is the most studied[27–31]. A systematic review of randomised studies has recently shown that terlipressin and HA reverse HRS in about 40% of the cases and improve patient survival[32]. In contrast, the use of vasoconstrictors and albumin in type 2 HRS is still controversial[11,12].

Prevention of PPCD after large volume paracentesis

Paracentesis is the first-line treatment for patients with tense and refractory ascites[11,12]. PPCD is a circulatory dysfunction occurring after large-volume paracentesis which is characterised by an exacerbation of arteriolar vasodilatation, reduction of effective blood volume, rapid re-accumulation of ascites, increased risk of HRS, dilutional hyponatraemia, and increased mortality[33,34]. Several randomised clinical trials have demonstrated that administration of HA at the time of paracentesis reduces significantly the incidence of PPCD and related clinical complications[35–37]. A recent meta-analysis has confirmed the superiority of HA to lower the incidence of PPCD, hyponatraemia, and mortality when compared to either artificial plasma expanders or vasoconstrictors[38].

Based on this solid scientific evidence, the European Association for the Study of the Liver (EASL) guidelines recommend the administration of 8 g of HA per litre of ascites removed, with a greater strength of recommendation for paracentesis of at least 5 litres[11], while the American Association for the Study of Liver Disease (AASLD) guidelines state that HA infusion of 6-8 g per litre of fluid removed is indicated for large-volume paracenteses, while HA administration may not be necessary for a single paracentesis of less than 4 to 5 litres[12].

Prevention of renal failure after SBP

SBP is a frequent and severe infection in patients with advanced cirrhosis which is diagnosed when the number of neutrophils exceeds 250 per mL of ascitic fluid, in the absence of an intra-abdominal source of infection or malignancy[39]. Despite infection resolution, death still occurs in about 10-20% of cases since SBP may trigger haemodynamic decompensation and precipitate renal failure that can become progressive as type 1 HRS[40–42].

A seminal prospective randomised trial reported that administration of high-dose of HA (1.5 g/kg at diagnosis of SBP and 1 g/kg on day 3), together with antibiotic treatment, significantly decreased the incidence of type 1 HRS and improved in-hospital and 3-month survival[41]. However, whether all patients with SBP should receive HA in addition to antibiotics is still uncertain, as the most striking effects are obtained in patients with more advanced disease defined by a serum bilirubin greater than 4 mg/dL and serum creatinine greater than 1 mg/dL at the time of diagnosis, suggesting that HA administration could be restricted to these high-risk patients[41,43]. Until more information becomes available, the Clinical Practice Guidelines of the European Association for the Study of the Liver (EASL) recommend that all patients who develop SBP should be treated with broad spectrum antibiotics and HA (1.5 g/kg on day 1 and 1 g/kg on day 3)[11]. Supporting this recommendation, a very recent meta-analysis has confirmed the capacity of HA to improve outcomes in patients with SBP[44].

Besides the above universally accepted indications, the use of HA has been proposed in patients with cirrhosis for the treatment of ascites, hypervolaemic

hyponatraemia and hepatic encephalopathy, although all these indications are yet to be supported by clear scientific evidence[4,45].

When HA became available, studies performed several decades ago failed to showed a clear usefulness of this substance in relieving ascites and preventing its recurrence; however, these investigations were uncontrolled or anecdotal[46,47]. The effect of prolonged HA administration was later assessed in two relatively small controlled clinical trials conducted in Italy[48,49]. In the first study, including hospitalised patients with cirrhosis and ascites, the combination of diuretics plus HA was, overall, more effective than diuretics alone in resolving ascites and reducing the length of the hospital stay. However, these positive results were limited to the sub-set of patients receiving a low-dose of diuretics, while the advantage was lost when higher doses were needed[48]. In a subsequent cohort of 100 patients followed for a median time of 84 months, the recurrence rate of moderate-severe ascites and mortality were significantly reduced in patients supplemented with HA (25 g/week for the first year, then 25 g every 2 weeks) as compared to those receiving diuretics alone[49].

No other controlled clinical trials have been so far performed to evaluate the effectiveness of prolonged HA administration in the treatment of cirrhosis and ascites. Thus, the lack of confirmatory multicenter randomised studies, together with its high cost, explain why HA infusion is not usually included among the therapeutic options for difficult-to-treat ascites in the international guidelines.

However, a Delphi Study involving 68 centers throughout Italy, selected for their high specialization and clinical experience, showed that about 80% of the hepatologists agree that HA treatment shortens the length of hospitalization, enhances the response to diuretics, reduces the relapse rate of ascites when given at home, and improves the patient's general conditions and well-being[50].

In summary, HA administration is used in the treatment of patients with cirrhosis and ascites and physicians report its utility in the absence of strong scientific evidence supporting its clinical benefit and an adequate clinical-economic study assessing the cost/effectiveness ratio of chronic prolonged treatment.

A conclusive answer to this controversial issue will likely be provided by an open-label, multicentre, randomised clinical trial, actually ongoing in Italy, comparing the effectiveness of long-term weekly administration of HA in more than 400 patients with cirrhosis and difficult-to-treat ascites (NCT 01288794, www.clinicaltrials.gov).

At the present time, reimbursements for out-of-hospital HA prescription is allowed by the Italian National Health Service in patients with ascites not responding to the standard medical treatment with diuretics.

As indicated by preliminary clinical data, a potential beneficial role of HA administration has been proposed in other clinical situations which are quite frequent in patients with cirrhosis, i.e. bacterial infections other than SBP, hypervolaemic hyponatraemia, and hepatic encephalopathy[51,52]. However, there is no clear recommendation regarding the use of HA for these specific indications because of the lack of well-designed confirmatory clinical studies.

Finally, exogenous HA is also needed for the functioning of the extracorporeal liver support device Molecular Adsorbant Recirculating System (MARS), which is based on the binding and detoxification capacity of the molecule. Although the efficacy of the procedure is still under debate, MARS is used in a few specialised centres for the treatment of acute liver failure, acute-on-chronic liver failure, and intractable cholestatic pruritus[53-55].

Inappropriate HA prescription

As it has been consistently reported by several studies and surveys in different countries, a consistent portion of HA prescription, ranging from 40% to 90%, is not supported by clinical and scientific evidences[56-60].

Most of the inappropriate prescription derives from the use for nutritional interventions or for correcting hypoalbuminaemia *per se* (without hypovolaemia) that still occurs in many clinical areas (i.e. surgery, internal medicine, geriatrics, oncology), despite the existence of solid data confirming lack of a real benefit. Other clinical uses for HA administration not supported by solid scientific evidence are nephrotic syndrome, pancreatitis, abdominal surgery, acute distress respiratory syndrome, cerebral ischaemia, and enteric diseases[56-60].

Finally, it should be underlined that the inappropriate use of HA occurs despite the presence of clinical guidelines and recommendations, i.e. when HA is administered as first-line treatment for fluid resuscitation even if other cheaper plasma-expanders are not contraindicated or for chronic treatment of cirrhosis.

Thus, there is no doubt that the lack of definitive scientific evidence has produced some confusion and a great variability regarding which indication is perceived to be appropriate.

Can we rationalise HA prescription?

The high rate of inappropriate use, the elevated cost, the theoretical risk of disease transmission and the existence of more economical alternatives of comparable efficacy have prompted several clinical and economical evaluations that aim to rationalise and render more appropriate the use of HA[56-60].

We recently reported the impact of internal practice guidelines for the appropriate use of albumin in the S. Orsola-Malpighi Academic Hospital in Bologna, Italy, a third-level referral centre for many diseases including liver cirrhosis and transplantation, with more than 1,700 beds and 70,000 admissions per year[56]. The guidelines were elaborated in 2003 and updated with minor changes in 2007, using a systematic, literature-based consensus method. Briefly, a multidisciplinary panel of experts from various disciplines (internal medicine, anaesthesia, surgery, gastroenterology, nephrology, haematology, public health, and pharmacy) reviewed the available clinical literature and drew up draft guidelines which were submitted to a second panel of physicians from to the same scientific areas, but not involved in the writing of the first draft. A consensus was reached by the two working groups and a final version was approved and distributed among the physicians employed at the hospital. Since July 2003, the in-hospital prescription of albumin has been regulated by the recommendations reported in Table I. Schematically, they list a series of acute and chronic clinical conditions for which albumin administration is indicated as a first or second-line treatment or is not indicated at all.

While the HA consumption and costs had been relentlessly increasing in the period from 1997 to 2003, the implementation of recommendations yielded a rapid 15-20% reduction of albumin utilization, which was associated with a similar fall in the cost, expressed both in absolute terms or as a percentage of the global pharmaceutical expenditure; thereafter, albumin consumption and related costs remained substantially stable during the following six years. The trend analysis of HA consumption has clearly shown that its time-dependent increase was interrupted by the implementation of the recommendations, supporting their efficacy in regulating in-hospital albumin prescription.

Since the data were not systematically collected before 2003, we were not able to perform an accurate analysis of HA prescription comparing the years before with those after the implementation of the hospital guidelines. In an attempt to overcome this limitation, we analysed HA consumption grouping all the hospital units into three main categories: "hepatological" medical and surgical units, i.e. units representing referral centres for liver diseases, "non-hepatological" medical and surgical units, and ICUs.

Table I - Practical recommendations for the prescription of human serum albumin at the S. Orsola-Malpighi University Hospital, Bologna, Italy[56].

Acute diseases	First-line treatment	Second-line treatment
Hypovolaemic shock	Colloid/Crystalloid solutions	Human albumin if: - Sodium intake restriction - Hypersensitivity to colloids or crystalloids - Lack of response to combined use of colloids and crystalloids
Major surgery: - Cardiovascular - Other surgery	Colloid/Crystalloid solutions	Human albumin if: - Lack of response to combined use of colloid/crystalloid
Burns	Colloid/Crystalloid solutions	Human albumin plus crystalloid solutions if: - Lack of response to colloid or crystalloid solutions alone - Severe burns (>50% body surface)
Paracentesis	Human albumin 8 g/L of removed ascites if paracentesis >4 L	
Spontaneous bacterial peritonitis	Human albumin 1.5 g/kg at diagnosis of 1 g/kg on third day + antibiotic therapy	
Hepatorenal syndrome	Human albumin 1 g/kg at diagnosis followed by 20-40 g/die + vasocontrictors	
Ascites	Diuretic treatment	Human albumin if: - Ascites resistant to diuretics
Plasmapheresis	Human albumin if plasma changes >20 mL/kg per week	
Protein wasting enteropathy/malnutrition	Enteral or parenteral nutrition	Human albumin if: - Severe diarrhoea (>2 L/die) - Albuminaemia <2 g/dL - Clinical hypovolaemia

Interestingly, the decrease in HA consumption observed in the "non-hepatological" units after guideline implementation was mirrored by a parallel increase in the "hepatological" units of our hospital. Furthermore, no significant changes occurred in the prescription by physicians working in ICUs, probably because they were already accustomed to established international guidelines, despite the debate on HA administration in critically ill patients that had run for almost two decades.

In summary, the enforcement of in-hospital guidelines allowed a more liberal use of HA for indications supported by solid scientific data and avoided its futile administration in settings where there is a lack of clinical evidence of efficacy. As a result, a more appropriate HA prescription was achieved, keeping health care expenditure under control.

Conclusions

Apart from some clinical indications supported by solid scientific evidence, the efficacy of HA in many other settings is still under debate or has been disproved by evidence-based medicine.

In patients with advanced liver cirrhosis, HA is indicated to expand the central blood volume in patients with hepatorenal syndrome, post-paracentesis circulatory dysfunction, and renal failure induced by spontaneous bacterial peritonitis, conditions that are all characterised by extreme effective hypovolaemia.

HA administration for fluid resuscitation in critically ill patients is now considered safe, except in those with traumatic brain injury, and can therefore be used when crystalloids and non-proteic colloids are not effective or contra-indicated. The greater efficacy of HA in the specific setting of patients with severe sepsis and septic shock still awaits a final confirmation by the ongoing, randomised trials comparing HA and saline.

Conversely, a significant part of HA prescription is not supported by clinical and scientific evidence. The most common futile use occurs when HA is given to correct hypoalbuminaemia *per se* (i.e. not associated with hypovolaemia) or for nutritional intervention. Other clinical indications for HA administration not supported by definitive scientific evidence are long-term treatment of ascites, nephrotic syndrome, pancreatitis, abdominal surgery, acute distress respiratory syndrome, cerebral ischaemia, and enteric diseases.

The enforcement of practical clinical recommendations are needed to guarantee a more appropriate prescription of HA by allowing a more liberal use for indications supported by solid scientific data and avoiding futile administration in settings where there is a lack of clinical evidence of efficacy.

Abbreviations

HRS: hepatorenal syndrome; HA: human serum albumin; ICU: intensive care unit; NO: nitric oxide; PPCD: post-paracentesis circulatory dysfunction; SBP: spontaneous bacterial peritonitis.

Keywords: albumin, liver cirrhosis, ascites, fluid resuscitation, sepsis.

Conflicts of interest disclosure

Paolo Caraceni has served as Speakers Bureau lecturer for Grifols. The other Authors declare no conflicts of interest.

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