The clinical use of albumin: the point of view of a specialist in intensive care

Pietro Caironi, Luciano Gattinoni

Dipartimento di Anestesiologia, Terapia Intensiva e Scienze Dermatologiche, Fondazione IRCCS Ospedale Maggiore Policlinico, Mangiagalli, Regina Elena di Milano; Università degli Studi di Milano, Italy

Introduction

In the last decades, research on albumin and its administration to critically ill patients have increased considerably, both in clinical and experimental settings. The observations obtained in research ground have gradually led, on the one hand, to important results[1] with a potential clinical impact on the treatment of different pathological conditions, and, on the other hand, to discussions and controversies[2-4]. It is, therefore, mandatory to ask ourselves whether it is really so important to "care" about albumin when dealing with clinical research in intensive care and, if so, why. A rapid glance at the bulk of data available on the topic may guide the answer to these questions. In fact, it is very interesting to discover that a search for publications on "albumin" in Medline, as updated on October 2008, yields 158,083 items, which is surprisingly greater than the number of publications on "haemoglobin" (120,250), a protein that is undoubtedly quite important in human physiology and pathophysiology! Moreover, it is worth noting that almost 40% of all the publications on albumin have been concentrated in the last 10 years, once again underlying, as mentioned above, how "hot" and current this topic may be considered.

The beginning of the research on the applicability of albumin in clinical practice has generally been ascribed to World War II, with the first case series of seven very severely burned patients treated with intravenous administration of human albumin after they had been injured during the Pearl Harbour attack[5]. Actually, the first report of clinical use of human albumin in a patient with traumatic shock had been made few months before, as results from the archives of the Office of Medical History of the United States (http://history.amedd.army.mil/). The case reported concerned a 20-years old man admitted to the Walter Reed General Hospital in Washington D.C. "*after he had sustained bilateral compound fractures of tibia and fibula and fractures of five ribs; and associated pleural damage, pneumothorax, and subcutaneous emphysema*". The patient appeared confused and had severe systemic hypotension. After he had received two units of human albumin (for a total amount of about 50 g) over a short period of time (about 30 min), his systemic arterial pressure recovered progressively, and 2 hours later, once his main fractures had also been stabilised, the patient appeared to be completely normotensive. The report described successful complete fluid resuscitation during the next day with a further amount of crystalloids. Of note, at no time after intravenous administration of human albumin was there any evidence of allergic reactions and/or circulatory failure, which had been the main obstacles during a previous research project on bovine-derived albumin.

Thus, this first clinical case presented all the potentially important primary and secondary functions of albumin, such as its critical role in determining intravascular oncotic pressure and, on the other hand, its anti-inflammatory properties. From that first case on, many steps have been taken towards a precise clarification of all the characteristics of human albumin with a potential clinical impact in treating critically ill patients. In the present article, we will briefly review the clinical use of human albumin in intensive care medicine and present our point of view on this subject. To this purpose, we will first summarise the physiology and pathophysiology of

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albumin, we will then given an overview of the evidence currently available on its clinical use, and finally we will discuss the potential clinical indications for its administration, also reporting the design of a new clinical trial recently started in Italy.

Physiology and pathophysiology of albumin in humans

In humans, albumin is a protein with a molecular weight of 66,500 Daltons, and accounts for about 50% of the overall content of plasma protein. As a result of its molecular structure and its concentration, albumin is responsible for about 80% of the intravascular oncotic pressure[6].

Metabolism

The metabolism of albumin appears to reflect its importance in human physiology. In fact, under stimulation of the neuroendocrine system and the actual intravascular oncotic pressure, in adults the liver produces about 10-12 g of albumin each day, which is immediately secreted into the intravascular space by the cells without being stored[7]. The entire process of synthesis and secretion of albumin is quite rapid, taking about 30 minutes[8-10]. After entering the intravascular space, about 7 g/h of albumin passes into the interstitial space to different degrees and at different rates depending on the anatomical location, in a process called "transcapillary filtration"[11,12]. In regions characterised by endothelium with large gaps, the filtration of albumin is passive[13], while in regions with non-fenestrated endothelium, its filtration is active[14], under the particular action of a specific receptor, i.e., albondin[15]. The lack of albondin in some anatomical compartments, such as the brain, accounts for the low concentration of this protein in the cerebrospinal fluid[16]. The passage of albumin between the intravascular and the interstitial spaces is a continuous process, with a return to the blood-stream through the action of lymph drainage. At the end of the entire process, albumin is usually degraded ubiquitously, in an amount comparable to that synthesised by the liver (10-12 g/24 h)[17]. *Per se*, the rate of synthesis and degradation may be regulated at various levels. The actual intravascular oncotic pressure is considered one of the simplest mechanisms of regulation, although a clear understanding of its physiological basis has not yet been reached[18-20]. With regards to critically ill patients, it is worth noting that traumatic events, infections or any clinical conditions activating an inflammatory process may repress albumin synthesis[21-28].

Functions

The molecular structure of albumin has three main characteristics which may be considered important for critically ill patients[17]: (i) cysteine residues, (ii) domains I and II, and (iii) imidazole residues. Cysteine residues in position 34 expose a –SH radical group (thiol), which is one of the main extracellular antioxidants[29]. From this point of view, the administration of albumin to a critically ill patient during an acute pathological process usually increases the plasma concentration of thiols[30]. Moreover, –SH residues bind nitric oxide to form S-nitrous thiols, thereby neutralising one of the most important mediators of pathological conditions such as sepsis[31]. Albumin domains I and II are responsible for the transport of the numerous molecules, both endogenous and exogenous, that are extensively carried by human albumin[32]. In this regard, it is evident how albumin concentration may be important when administering drugs with a high-binding affinity, especially during acute pathological processes usually characterised by hypoalbuminaemia. In these conditions, drug toxicity or even drug inefficiency may be observed[33]. Finally, albumin has 16 histidine imidazole residues, which are responsible for the buffer function of albumin. In fact, having a pH of about 6.75, the residues may both give up or accept H^+ from the environment depending on the surrounding pH, thereby acting as a buffer molecule[34].

Pathophysiology in the critically ill

After the above overview of the physiology of albumin, we may wonder which functions are really important for the critically ill.

There is no doubt that the oncotic properties of this protein play a critical role in regulating volaemic status during clinical conditions in which volaemia is very often altered. Nonetheless, in our opinion, during critical and acute conditions, such as sepsis, infections, acute respiratory failure and others, the secondary functions of albumin, as well as the maintenance of its concentration within normal ranges, are of paramount importance.

A few examples may clarify this concept. Most of the pathological conditions in critically ill patients are

characterised by high oxidative stress. From this point of view, an essential function of albumin is to neutralise toxic compounds such as oxygen radicals and nitrite peroxides, through the action, as mentioned above, of -SH residues. Besides this action, albumin may also neutralise the vasodilating effect of nitric oxide, which may be considered the most important mediator altering vascular tone during sepsis or other pathological conditions such as hepatorenal syndrome[35]. Finally, many clinical disorders commonly encountered in intensive care units (ICU) are characterised by metabolic acidosis, in which cellular energy deficits with the production of lactic acidosis may occur. In these conditions, the presence of albumin may help to minimise wide variations of pH, especially in the extravascular space, in which albumin is the only protein with a buffer action.

The most commonly observed pathological alteration in albumin concentration in the critically ill is hypoalbuminaemia[4,33], which is usually defined as a plasma concentration of albumin below 40 g/L. Indeed, one of the main reasons for the widespread administration of albumin has been the evident strong association between hypoalbuminaemia and mortality in various clinical settings, in both acute and chronically ill patients, as well as in young and older subjects[6,36,37].

A reduction of albumin concentration is usually considered the result of decreased production, increased wasting, or an association of the two. In our opinion, however, this simplistic interpretation is incorrect, as it does not take into account the possible alteration of the "solvent", i.e., volaemia, in which the "solute", i.e., albumin, is dispersed, and does not take into account the possible distribution of albumin within the interstitial space. In fact, considering these two further abnormalities, hypoalbuminaemia may be considered the result of: (i) a decrease in its absolute content; (ii) altered water metabolism; and (iii) a redistribution from the intravascular to the interstitial space, due to increased capillary permeability. Thus, although hypoalbuminaemia is very commonly observed in critically ill patients, the dilemma is whether this alteration may really have an impact on the outcome of such patients. In other words, the real question is whether the relationship between hypoalbuminaemia and mortality is a simple association or a cause-effect relation, and, if the latter is the case, what the best cure for hypoalbuminaemia is.

Overview of the evidence available in the literature

In the attempt to determine whether hypoalbuminaemia, or, more in general, any alteration of plasma albumin concentration may affect the outcome of critically ill patients, we must consider the information available in the literature about this topic. Looking at the bulk of publications and, in particular, meta-analyses recently performed, we can conclude that we are in an era of meta-analyses. In fact, starting from the 1990s, when increased attention to cost/benefit analyses of medical treatments led to an extensive review of the indications for albumin administration, there has been a real outburst of research on this subject.

The era of meta-analyses

Everything started in 1998, when a Cochrane report based on a meta-analysis suggested the potentially harmful effect of albumin administration as compared to other fluids for volume replacement[2]. The meta-analysis, published in the British Medical Journal, included 32 clinical trials involving a total of 1,419 patients, and showed, among patients with surgery- or trauma-induced hypovolaemia, no differences in mortality between those treated with albumin and those treated with crystalloids. In contrast, patients with burns who were treated with albumin appeared to have a higher mortality rate as compared to those treated with crystalloids. When the different categories of patients were grouped together, albumin administration was observed to be associated with an increased overall mortality rate as compared to the rate in patients treated with other forms of fluid replacement. The impact of this meta-analysis on the scientific community was dramatic, and led to an extensive reduction of the use of albumin in some countries[38]. At the same time, as usually occurs with such types of analysis, many criticisms were made about the publication, especially regarding the process of study selection, the heterogeneity of the patients included and the limited number of trials considered with a sufficiently high number of subjects. Applying similar selection criteria, another meta-analysis was published in 2001, concluding that albumin administration was safe, although it had no effects on global mortality[3]. Finally, a further meta-analysis, which included nine prospective, randomised clinical

trials on critically ill patients with hypoalbuminaemia, was concluded and published in 2003[4]. This meta-analysis showed a strong, albeit not statistically significant, trend in favour of albumin administration. A statistically significant correlation was, however, observed between the rate of complications and the plasma level of albumin; similarly, the authors observed a lower rate of complications in patients treated with albumin infusion as compared to the control group in the five studies in which plasma albumin concentration was greater than 30 g/L, in contrast to what was observed in the three studies in which plasma albumin concentration was lower than 30 g/L.

In summary, the meta-analyses on the clinical use of albumin in critically ill patients produced completely opposite and controversial results. In fact, of the three largest studies concluded, the first appeared to be against[2], the second one neutral[3] and the third one in favour of the clinical use of albumin[4]. The conclusions of the three studies mentioned above once again highlight the contrasting nature of the findings obtained, and the relatively weak evidence obtained many times from such a type of analysis. While the authors of the first meta-analysis concluded that "*There is no evidence that the administration of albumin reduces mortality in critically ill patients with hypovolemia, burns, hypoalbuminemia, but rather a strong indication that it increases mortality*"[2], the authors of the second meta-analysis concluded that "*our results show that albumin is safe*"[3], and those of the third concluded: "*Currently there is no reason for not administering albumin when clinically appropriate.*"[4].

The SAFE study

To resolve the contradictory findings obtained from these meta-analyses, 16 ICU in Australia and New Zealand conducted a prospective, randomised, double-blind study, the Saline vs. Albumin Evaluation (SAFE) study, comparing the effects of the infusion of 4% albumin and saline solution (0.9% NaCl) for volume replacement in critically ill patients with hypovolemia[1]. According to the study design, the volume infused and the rate of administration were decided by the physicians taking care of the patients enrolled, in accordance with the clinical status and the response to treatment. The primary end-point was mortality rate 28 days after enrolment. Moreover, 28-day mortality rate was also analyzed in three predefined subgroups of patients with specific diseases, i.e., sepsis, trauma and acute respiratory distress syndrome. After the enrolment of about 7,000 patients, no difference in 28-day mortality, length of stay, or organ dysfunction was observed between the groups of patients receiving the two different treatment, thereby clearly demonstrating that 4% albumin infusion employed for volume replacement in a general population of critically ill patients does not offer any advantage as compared to normal saline, or, in other words, that albumin administration is "safe". Although the SAFE study had the potential to overcome several limitations of the previous meta-analyses (with the enrolment of an adequate number of patients, an accurate randomisation process, and a uniform methodology of dosages and administration), it should be acknowledged that some problems remained, particularly in the study design: the study population was heterogeneous, the degree of the severity of illness was moderate, and the amount of fluid administered for volume replacement was relatively moderate. Nonetheless, the great contribution of this study came from the subgroup analysis performed. In fact, while patients with trauma, especially after head injury, treated with albumin tended to have a higher mortality rate ($P = 0.06$), those with severe sepsis tended to show a better survival, although the difference did not reach statistical significance ($P = 0.09$). Thus, for the first time, the attention of researchers was moved towards the possible crucial role of different categories of patients, when dealing with the type of fluid to be employed for volume replacement.

The Dubois study

In 2006, another important study on the effects of albumin administration in critically ill patients was concluded and published in Critical Care Medicine[39]. This study investigated the hypothesis that correcting hypoalbuminaemia in critically ill patients in an attempt to maintain plasma albumin concentration within the normal range (greater than 30 g/L) may have beneficial effects on organ function. Patients were randomised to receive 300 mL of 20% albumin solution on the first day after randomisation and 200 mL/day if their plasma albumin concentration was lower than 31 g/L in the treated group, or to receive no albumin infusion in the control group. The primary

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end-point was organ function, as measured by the Sequential Organ Failure Assessment (SOFA)[41] score, from day 1 to day 7. After enrolment of 100 hypoalbuminaemic patients, the authors first observed a significant separation in plasma albumin concentration between the two groups of patients, with a constant increase in plasma albumin concentrations in treated patients. Moreover, patients treated with albumin infusion showed a greater improvement in organ function than that observed in the control group, mainly due to differences in the respiratory, cardiovascular and central nervous system components of the SOFA score. The authors, therefore, concluded that "*Albumin administration may improve organ function in hypoalbuminaemic critically ill patients*"[39]. Although it was not free of limitations, such as the relatively small number of patients included (and enrolled from just a single centre), and the heterogeneity of the patients randomised, this study is quite important. In fact, it provided, for the first time, some evidence about the critical role of maintaining plasma albumin concentrations within a normal range, throughout the ICU admission, with a possible impact on organ function.

Clinical indications

After this brief summary of what has been more or less clearly established regarding the possible effects of albumin administration in critically ill patients, we should consider the possible clinical indications for using this product. As clearly stated in the last recommendations on albumin administration recently published by the Italian Society of Transfusion Medicine and Immunohaematology, "*the potential limit of all these studies may reside in having grouped different and heterogeneous categories of patients…*"[40].

In our opinion, this is one of the most important and key statements regarding the possible clinical indications for albumin administration. This may be even more important when applying any possible recommendation on the use of albumin to patients admitted to an ICU, as one of the great peculiarities of this category of patients is precisely their heterogeneity. Based on these considerations, as well as on the evidence now available in critically ill patients, we think that there three important categories of critically ill patients for whom specific clinical recommendations regarding the use or not of albumin may be made: patients with traumatic brain injury, patients with peripheral oedema during their recovery phase, and patients with severe sepsis.

Patients with traumatic brain injury

As mentioned above, the SAFE study suggested that trauma patients, especially those with traumatic brain injury, treated with albumin infusion had a higher 28-day mortality rate than that of patients treated with normal saline[1]. In order to further examine this aspect, the same investigators conducted a post-hoc follow-up of the patients with traumatic brain injury previously enrolled in the SAFE study, determining their vital status and functional neurological outcome until 24 months after the randomisation[42]. In detail, 460 patients were followed-up, of whom about 70% were classified as having severe brain injury (with a Glasgow Coma Scale score between 3 and 8). At 24 months after enrolment, the mortality rate of patients treated with albumin appeared to be higher than that of patients treated with saline (33.2% vs. 20.4%, $p = 0.003$), and similar findings were observed in patients with severe traumatic brain injury, with mortality rates of 41.8% and 22.2% in patients treated with albumin or saline, respectively ($p < 0.001$). The authors, therefore, concluded that "*in this post hoc study of critically ill patients with traumatic brain injury, fluid resuscitation with albumin was associated with higher mortality rates than was resuscitation with saline*"[42]. Although these findings may appear disappointing, we should actually be rather pleased with them, as they very likely enable the first really clear recommendation regarding the use or avoidance of albumin in critically ill patients. In fact, based on the findings summarised above, we may clearly state that in this specific category of critically ill patient, i.e., patients with an active brain injury due to cerebral trauma, albumin administration should be avoided, preferring other types of fluids, such as normal saline, for acute volume resuscitation.

Patients with peripheral oedema during their recovery phase

Albumin has usually been studied in humans as a plasma substitute for volume replacement. From this point of view, the volume effect in itself, when taking into account the different characteristics of the types of fluid considered, is identical for albumin, other

forms of colloids, and crystalloids[17]. Nonetheless, at equal intravascular volumes, potential complications and advantages may depend on the different properties of the infused fluid. For example, when employing mainly crystalloids for volume replacement, the most important disadvantage is probably the greater amount of fluids to be infused in order to reach the same volume effect of albumin or other synthetic colloids, with a consequent increased risk of peripheral oedema and weight gain. On the other hand, artificial colloids may alter coagulation, essentially because of absorption of the factor VII/von Willebrand factor complex, with consequent altered platelet aggregation[43], and may lead to an increased risk of developing acute renal failure, as recently observed[43].

Along the same line of reasoning, the role of albumin, especially because of its oncotic properties, may gain even greater importance in the clinical phase that usually follows the acute phase of volume replacement and resuscitation, i.e., the recovery phase, in which, having obtained clinical stability in terms of haemodynamics and organ function, the clinical priority is normally elimination of the excessive fluid previously accumulated in the interstitial space during the resuscitation phase. The intravascular plasma concentration of albumin may be critical during the recovery phase, as it accounts for about 80% of the entire oncotic pressure of the intravascular space[6], as mentioned above. Moreover, the pathophysiological rationale for intravenous administration of albumin during this phase may be more solid than that for administration during the acute phase, as the increased permeability of the capillary barrier that usually characterises the acute florid phase during volume replacement tends to normalise. The albumin infused in this situation is, therefore, more likely to "remain" within the intravascular space than usually occurs during the acute phase. Unfortunately, no clear evidence from randomised clinical trials or other forms of large studies are currently available, probably because of the difficulty of designing studies to investigate such a heterogeneous issue. Nonetheless, in our opinion, the soundness of the biological and pathophysiological rationale may at least partially justify such an indication for albumin administration.

The following case report may help to elucidate this issue. A patient was admitted to our post-surgery ICU after he had admitted for 7 days in a neurological ICU because of traumatic spinal shock. On admission, the patient appeared to be in an oedematous state, with peripheral oedema and bilateral pleural effusion (despite a water restriction programme applied a few days previously), hypotension, oligo-anuria, and systemic arterial hypoxia. The patient's plasma albumin concentration was 13 g/L. We interpreted the patient's clinical situation as a state of anasarca in great need of elimination of the excessive accumulated fluid, probably as a consequence of the volume necessarily administered during the acute phase of the haemodynamic shock. We, therefore, continued the strategy of water restriction, but we initiated albumin administration at the maximal dose usually employed in our institution, i.e., 60 g/day, in association with a low dose of dopamine, in an attempt to obtain a higher mean arterial pressure. Within the following few days, we were able to increase the plasma albumin concentration to about 25 g/L, and we observed a parallel increase in mean arterial pressure and a marked increase of diuresis, with the possibility of obtaining a negative daily fluid balance. In association with these improvements, respiratory function ameliorated, with a significant increase of the ratio of arterial oxygen partial pressure to inspiratory oxygen fraction (PaO_2/FiO_2).

Although clear evidence derived from randomised clinical trials is still lacking with this regard, we may conclude in favour of a possible clinical benefit of albumin administration in patients with marked hypoalbuminaemia, peripheral oedema, and in serious need of water elimination, especially in their recovery phase after acute volume replacement. Although this statement may appear in open contrast with what is called "evidence-based medicine", we consider it important to highlight how lack of evidence may not necessarily exclude the possible beneficial effect of an intervention, especially when a solid pathophysiological rationale is clearly present.

Patients with severe sepsis –the ALBIOS study

Sepsis is a very dramatic syndrome commonly affecting most patients admitted to ICUs. This pathophysiological process involves many inflammatory mediators which have been considered responsible for the haemodynamic alterations and energy failure, as well the multi-organ dysfunction commonly characterising this syndrome. From this point of view, it is now well accepted that, besides its oncotic properties, albumin may play a critical role

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in aiding the normalisation of many of the inflammatory pathways potentially involved in the development of sepsis through its secondary functions, such as the modulating action on nitric oxide metabolism and free radical production[30,31], its buffer effect in the acid-base equilibrium[34], and its action as a transporter of many different substances and drugs[32]. These secondary functions may partially account for the positive trend towards a lower mortality rate observed in the subgroup of patients with severe sepsis treated with albumin, as compared to the control group, during the SAFE study[1]. Unfortunately, essentially due to a small sample size, the difference in mortality rate was not statistically significant, thereby not allowing any conclusions to be drawn on the matter. Similarly, the study by Dubois and colleagues[39], although clearly suggesting that maintaining plasma albumin concentration within the normal range could reduce organ dysfunction, also included a small number of patients and was performed in a single centre, making it impossible to extend the findings to a common general population of critically ill patients.

Based on these considerations, we have recently designed and begun a randomised, multicentre controlled study on the efficacy of albumin administration for volume replacement in patients with severe sepsis or septic shock (ALBumin Italian Outcome Sepsis –ALBIOS –study, EudraCT number 2008-003281-25, ClinicalTrials.gov number NCT00707122). This study, involving about 150 Italian ICU, aims to verify whether volume replacement with albumin and maintenance of plasma albumin concentrations within the physiological range may have beneficial effects in terms of mortality, morbidity and length of stay in patients with severe sepsis or septic shock, as compared to standard volume replacement with crystalloids. To overcome the possible bias derived from potential differences in volume effect of the two strategies, the study design includes two important features: (i) in both arms of the study population, i.e., patients treated with either albumin or crystalloids, volume replacement is performed according to the recent guidelines on the clinical treatment of septic patients[45], in other words according to the "early-goal directed therapy"[46]; (ii) during volume replacement and for the following days of treatment until the 28th day of admission in the ICU (or until the day of discharge from the ICU, whichever comes first), serum albumin level is monitored and kept to a level of 30 g/L or above only in the albumin-treated group[39]. In particular, patients in the albumin group will receive, after randomisation and simultaneously to volume replacement, 300 mL of 20% albumin solution (total amount, 60 g). From day 2 to day 28 (or until discharge from the ICU, whichever comes first), if the patients' serum albumin concentration is equal to or higher than 25 g/L and below 30 g/L, they will receive 200 mL of 20% albumin solution (total amount, 40 g); if the serum albumin concentration is below 25 g/L, they will receive 300 mL of 20% albumin solution (total amount, 60 g). Moreover, further infusions of crystalloids will be allowed, when necessary, according to clinical judgment. In contrast, patients included in the control group will receive only crystalloids both during the volume replacement phase as well as from day 2 to day 28 (or until ICU discharge, whichever comes first). No infusion of colloids, other than albumin, will be allowed in either group. The primary objective of the study is to verify the hypothesis that volume replacement with albumin and maintenance of plasma albumin levels within the predefined physiological range improves survival of patients with severe sepsis or septic shock, as compared to a volume replacement with the use of crystalloids, measured until the 28th and 90th day after randomisation. Secondary objectives are to determine whether this strategy reduces the number and severity of organ dysfunctions (as assessed by the SOFA score[41]), the time spent in the ICU, and the duration of hospital stay.

We think it is important to highlight the potential advantages of the study design. First of all, the introduction of the "early-goal directed therapy"[45] both in patients treated with albumin and in those given crystalloids, with the use of pre-defined haemodynamic targets, will standardise and optimise volume replacement for all the septic patients according to the standard of care currently suggested worldwide. Second, it will allow us to specifically observe the direct effects of albumin administration *per se* and the maintenance of its serum level within the normal range. In other words, this study design will allow us to specifically elucidate the possible role of the secondary functions of albumin on the pathophysiology of severe sepsis and, therefore, their potential impact on outcome. The study has just

started, with the randomisation of the first patient at the end of August 2008, and is planned to be completed in about 2-3 years, with an expected enrolment of about 1350 patients (for more details, see www.clinicaltrials.gov).

Conclusions

In the past decades, the research on albumin for the clinical treatment of critically ill patients has certainly yielded important information aiding more appropriate use of this product. It is now evident and quite well accepted that, apart from its oncotic properties, albumin has secondary functions that may play a critical role and have a great impact on different types of diseases. At the moment, based on the evidence currently available, we can state that albumin is not necessary for normal volume replacement in moderate critically ill patients and, furthermore, that it should be avoided in patients with traumatic brain injury[42]. In contrast, in patients with severe hypoalbuminaemia and peripheral oedema during the recovery phase after acute volume replacement, albumin administration may have a beneficial impact, especially on the elimination of the excessive accumulated volume. Finally, one of the most important categories of patients for which preliminary results suggest a potential beneficial role of albumin on outcome is that of patients with severe sepsis[1]. Whether of not this is the case should be demonstrated in the near future by a recently started, large, randomised clinical trial.

Key words: albumin, critically ill, sepsis, fluid resuscitation, traumatic brain injury

References

1) Finfer S, Bellomo R, Boyce N, et al. A comparison of albumin and saline for fluid resuscitation in the intensive care unit. N Engl J Med 2004;**350**:2247-56.
2) Human albumin administration in critically ill patients: systematic review of randomised controlled trials. Cochrane Injuries Group Albumin Reviewers. BMJ 1998;**317**:235-40.
3) Wilkes MM, Navickis RJ. Patient survival after human albumin administration. A meta-analysis of randomized, controlled trials. Ann Intern Med 2001;**135**:149-64.
4) 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**:319-34.
5) Peters T. Historical perspective. All about albumin. San Diego, California: Academic Press Limited; 1996:1-8.
6) Weil MH, Henning RJ, Puri VK. Colloid oncotic pressure: clinical significance. Crit Care Med 1979;**7**:113-6.
7) Schomerus H, Mayer G. Synthesis rates of albumin and fibrinogen in patients with protein-losing enteropathy and in a patient recovering from protein malnutrition. Digestion 1975;**13**:201-8.
8) Hafkenscheid JC, Yap SH, van Tongeren JH. Measurement of the rate of synthesis of albumin with 14C-carbonate: a simplified method. Z Klin Chem Klin Biochem 1973;**11**:147-51.
9) Gersovitz M, Munro HN, Udall J, Young VR. Albumin synthesis in young and elderly subjects using a new stable isotope methodology: response to level of protein intake. Metabolism 1980;**29**:1075-86.
10) Ballmer PE, McNurlan MA, Milne E, et al. Measurement of albumin synthesis in humans: a new approach employing stable isotopes. Am J Physiol 1990;**259**:E797-803.
11) Peters T. Metabolism: albumin in the body. All about albumin. San Diego, California: Academic Press Limited; 1996:188-250.
12) Beeken WL, Volwiler W, Goldsworthy PD, et al. Studies of I-131-albumin catabolism and distribution in normal young male adults. J Clin Invest 1962;**41**:1312-33.
13) Ganong W. Dynamics of blood and lymph flow. Review of medical physiology. Collecticut: Appleton and Lange; 1995:525-41.
14) Peters T Jr. Biosynthesis of rat serum albumin. VII. Effects observed in liver slices. Am J Physiol 1973;**224**:1363-8.
15) Schnitzer JE, Oh P. Albondin-mediated capillary permeability to albumin. Differential role of receptors in endothelial transcytosis and endocytosis of native and modified albumins. J Biol Chem 1994;**269**:6072-82.
16) Pardridge WM, Eisenberg J, Cefalu WT. Absence of albumin receptor on brain capillaries in vivo or in vitro. Am J Physiol 1985;**249**:E264-7.
17) Gattinoni L, Carlesso E, Caironi P. [Albumin administration: volume replacement or pharmacological treatment?]. Minerva Anestesiol 2005;**71**:27-40.
18) Rothschild MA, Oratz M, Mongelli J, Schreiber SS. Effect of albumin concentration on albumin synthesis in the perfused liver. Am J Physiol 1969;**216**:1127-30.
19) Dich J, Hansen SE, Thieden HI. Effect of albumin concentration and colloid osmotic pressure on albumin synthesis in the perfused rat liver. Acta Physiol Scand 1973;**89**:352-8.
20) Schmid M, Schindler R, Weigand K. Is albumin synthesis regulated by the colloid osmotic pressure? Effect of albumin and dextran on albumin and total protein synthesis in isolated rat hepatocytes. Klin Wochenschr 1986;**64**:23-8.
21) Pietrangelo A, Panduro A, Chowdhury JR, Shafritz DA. Albumin gene expression is down-regulated by albumin or macromolecule infusion in the rat. J Clin Invest 1992;**89**:1755-60.
22) Cairo G, Schiaffonati L, Aletti MG, Bernelli-Zazzera A. Effect of post-ischaemic recovery on albumin

synthesis and relative amount of translatable albumin messenger RNA in rat liver. Biochem J 1982; **204**:197-202.

23) Liao WS, Jefferson LS, Taylor JM. Changes in plasma albumin concentration, synthesis rate, and mRNA level during acute inflammation. Am J Physiol 1986;**251**:C928-34.

24) Milland J, Tsykin A, Thomas T, et al. Gene expression in regenerating and acute-phase rat liver. Am J Physiol 1990;**259**:G340-7.

25) Ozaki I, Motomura M, Setoguchi Y, et al. Albumin mRNA expression in human liver diseases and its correlation to serum albumin concentration. Gastroenterol Jpn 1991;**26**:472-6.

26) Ramadori G, Van Damme J, Rieder H, Meyer zum Buschenfelde KH. Interleukin 6, the third mediator of acute-phase reaction, modulates hepatic protein synthesis in human and mouse. Comparison with interleukin 1 beta and tumor necrosis factor-alpha. Eur J Immunol 1988;**18**:1259-64.

27) Castell JV, Gomez-Lechon MJ, David M, et al. Acute-phase response of human hepatocytes: regulation of acute-phase protein synthesis by interleukin-6. Hepatology 1990;**12**:1179-86.

28) Brenner DA, Buck M, Feitelberg SP, Chojkier M. Tumor necrosis factor-alpha inhibits albumin gene expression in a murine model of cachexia. J Clin Invest 1990;**85**:248-55.

29) King TP. On the sulfhydryl group of human plasma albumin. J Biol Chem 1961;**236**:C5.

30) Quinlan GJ, Margarson MP, Mumby S, et al. Administration of albumin to patients with sepsis syndrome: a possible beneficial role in plasma thiol repletion. Clin Sci (Lond) 1998;**95**:459-65.

31) Stamler JS, Jaraki O, Osborne J, et al. Nitric oxide circulates in mammalian plasma primarily as an S-nitroso adduct of serum albumin. Proc. Natl Acad Sci USA 1992;**89**:7674-7.

32) Sudlow G, Birkett DJ, Wade DN. The characterization of two specific drug binding sites on human serum albumin. Mol Pharmacol 1975;**11**:824-32.

33) Nicholson JP, Wolmarans MR, Park GR. The role of albumin in critical illness. Br J Anaesth 2000; **85**:599-610.

34) Reeves RB. Temperature-induced changes in blood acid-base status: Donnan rCl and red cell volume. J Appl Physiol 1976;**40**:762-7.

35) Hori N, Wiest R, Groszmann RJ. Enhanced release of nitric oxide in response to changes in flow and shear stress in the superior mesenteric arteries of portal hypertensive rats. Hepatology 1998;**28**:1467-73.

36) Powers KA, Kapus A, Khadaroo RG, et al. Twenty-five percent albumin prevents lung injury following shock/resuscitation. Crit Care Med 2003;**31**:2355-63.

37) Goldwasser P, Feldman J. Association of serum albumin and mortality risk. J Clin Epidemiol 1997;**50**:693-703.

38) Roberts I, Bunn F. Egg on their faces. The story of human albumin solution. Eval Health Prof 2002; **25**:130-8.

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

40) Liumbruno GM, Bennardello F, Lattanzio A. et al. Recommendations for the use of albumin and immunoglobulins. Blood Transfus 2009; **7**: 216-34

41) Vincent JL, de MA, Cantraine F, et al. Use of the SOFA score to assess the incidence of organ dysfunction/failure in intensive care units: results of a multicenter, prospective study. Working group on "sepsis-related problems" of the European Society of Intensive Care Medicine. Crit Care Med 1998;**26**:1793-800.

42) Myburgh J, Cooper J, Finfer S, et al. Saline or albumin for fluid resuscitation in patients with traumatic brain injury. N Engl J Med 2007;**357**:874-84.

43) de Jonge E, Levi M. Effects of different plasma substitutes on blood coagulation: a comparative review. Crit Care Med 2001;**29**:1261-7.

44) Brunkhorst FM, Engel C, Bloos F, et al. Intensive insulin therapy and pentastarch resuscitation in severe sepsis. N Engl J Med 2008;**358**:125-39.

45) Dellinger RP, Levy MM, Carlet JM, et al. Surviving Sepsis Campaign: International guidelines for management of severe sepsis and septic shock: 2008. Crit Care Med 2008;**36**:296-327.

46) Rivers E, Nguyen B, Havstad S, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med 2001;**345**:1368-77.

Correspondence: Prof. Luciano Gattinoni, MD, FRCP
Dipartimento di Anestesiologia, Terapia Intensiva e Scienze Dermatologiche,
Fondazione IRCCS - Ospedale Maggiore Policlinico, Mangiagalli, Regina Elena di Milano,
Università degli Studi di Milano,
Via F. Sforza 35,
20122, Milano, Italy
e-mail: gattinon@policlinico.mi.it