Clinical use of albumin in hepatology

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Introduction

Albumin has been the subject of much discussion and research for a long time. Hippocrates first mentioned some of its physiological properties, but albumin was not named or studied until the early 1800s. The modern use of human albumin was established during World War II due to the demand for plasma substitutes, while the first documented clinical use of human albumin occurred in 1941 in seven sailors severely burned during the attack at Pearl Harbour. The first report of administration of albumin to patients with cirrhosis was published by Janeway et al., who treated six patients with cirrhosis with 25 g albumin per day.

This protein was introduced as a treatment in the 1950s and was incorporated for many years in the management of patients with decompensated cirrhosis. There were, however, always varied opinions among hepatologists in relation to the use of albumin in liver cirrhosis. This review aims to highlight current thinking regarding albumin therapy in the setting of hepatology and also discusses its potential therapeutic applications based on the complex biochemistry of this multifunctional plasma protein.

Properties and physiological functions of albumin

Human serum albumin is an abundant multifunctional non-glycosylated, negatively charged plasma protein, which is synthesised primarily in the liver and is thought to be a negative acute-phase protein. In healthy adults, albumin synthesis occurs predominantly in polysomes of hepatocytes (10-15 g/day) and accounts for 10% of total liver protein synthesis. Relatively small amounts of albumin are hepatologically stored (<2 g), the majority being released into the vascular space. Approximately 30%-40% of the albumin synthesised is retained within the plasma compartment. The remaining pool is located in tissues such as muscle and skin. Albumin is not stored hepatically and there is, therefore, no reserve for release on demand. However, under physiological circumstances only 20-30% of hepatocytes produce albumin and synthesis can, therefore, be increased on demand by 200-300%. Synthesis is a constant process, regulated at both transcriptional and post-transcriptional levels by specific stimuli, but a change in interstitial colloid oncotic pressure is thought to be the predominant regulatory influence. Albumin homeostasis is maintained by balanced catabolism occurring in all tissues, with most albumin (40%-60%) being degraded in muscles, the liver, and the kidneys. Studies of radiolabelled albumin catabolism in normal healthy young adult males indicate that the protein has a mean half-life of 14.8 days.

Colloid oncotic pressure

Human serum albumin accounts for some 60% of the intravascular protein pool in healthy individuals, thereby being responsible for approximately 60% of plasma colloid oncotic pressure. Albumin is also responsible for water retention as the negative charges surrounding the protein molecules attract sodium ions. Its remaining contribution to colloid oncotic pressure is due to the Gibbs-Donnan effect of attracting other active positive ions, further enhancing its water-retaining effect. In patients with hypoalbuminaemia (especially when it is associated with inflammation or sepsis) whose capillaries are known to be...
hyperpermeable, the leakage of albumin into the interstitial space draws water with it, producing oedema. Moreover, albumin may influence vascular integrity both directly, by binding in the interstitial matrix and subendothelium and reducing the permeability of these layers to large molecules, and indirectly, through its scavenging properties.

**Antioxidant functions**

While oxygen-containing end products of aerobic metabolism are relatively innocuous, many intermediates thereby formed are potentially, or directly, capable of reacting with other molecules, which leads to the accumulation of toxic end products, the reactive oxygen species and nitrogen species. Normally, the body uses protective (i.e., antioxidant) and reparative systems that limit the effects of oxidative stress. Albumin is the major extracellular source of thiols, which are present on the molecule's only free cysteine residue and act as scavengers of reactive oxygen and nitrogen species. *In vitro* studies have shown that albumin can bind and, therefore, remove neutrophil-derived reactive oxygen species, thereby regulating cell-signalling moieties that are active in mediating the inflammatory reaction. Albumin has also been shown to offer antioxidant protection against the oxidative effects of carbon tetrachloride and uraemic toxins, findings with implications for both hepatic and renal failure. In human studies, albumin has a favourable influence on plasma thiol-dependent antioxidant status, thereby reducing the extent of protein oxidative damage in patients with acute lung injury. Persistent hypoalbuminaemia is also associated with peroxidation of erythrocyte membranes in patients undergoing chronic haemodialysis, indicating that albumin protects against lipid oxidation. Human serum albumin may play a supportive antioxidant role in vivo, through its ability to bind and transport substances with known antioxidant function, and in particular, bilirubin and nitric oxide, which are effective lipid phase antioxidants. Bilirubin may also protect albumin from oxidant-mediated damage.

**Ligand-binding**

Albumin binds many endogenous and exogenous compounds, including fatty acids, metal ions, pharmaceuticals, and metabolites, with implications for drug delivery and efficacy, detoxification, and antioxidant protection.

**Metal-binding**

Haem is thought to have pro-oxidant properties the result of the redox properties of iron. Human serum albumin is an effective haem-binding protein. Once bound to albumin, such pro-oxidant properties are decreased, indicating an antioxidant function, although under physiological circumstances the haem-binding plasma protein haemopexin provides most of this form of antioxidant protection.

**Pro-oxidant implications**

Paradoxically, and in common with other redox active antioxidant substances, albumin can display pro-oxidant properties, through its ability to redox cycle/recycle transition metal ions such as iron and copper from the less reactive (ferric/cupric) to more pro-oxidant (ferrous/cuprous) states. Indeed, albumin administration was reported recently to be adversely associated with a decline in iron-binding antioxidant protection in patients with acute lung injury, an effect thought to be related to the redox cycling of iron. Intravenous albumin may, therefore, be inadvisable in circumstances in which pronounced extracellular iron mobilisation or overload are complicating factors.

**Clinical use of albumin in hepatology**

The natural history of cirrhosis depends on the aetiology and treatment of the underlying cause, and on the development of decompensation; once this has occurred the mortality rate in all types of liver disease is, without transplantation, as high as 85% over 5 years. Albumin, with its multiple physiological effects of volume expansion, antioxidant and endothelial protection, would seem an ideal treatment solution for patients with cirrhosis and its complications. The current evidence-based indications for plasma expansion with human albumin in patients with cirrhosis are the treatment of hepatorenal syndrome, the prevention of circulatory dysfunction which
follows therapeutic paracentesis, and the prevention of circulatory dysfunction and hepatorenal syndrome in patients with spontaneous bacterial peritonitis. In the following paragraphs these indications for the use of albumin will be discussed along with their pathological context. Moreover the role of albumin in acute/acute-on-chronic liver failure and in other less established situations will be discussed.

Complications of cirrhosis and their pathogenesis

In the course of time there have been several hypotheses about how ascites and other complications develop in patients with liver cirrhosis. The various theories developed in the last decades agree that patients with advanced cirrhosis characteristically suffer from circulatory disturbance. In the classic experiments carried out by Starling in animals with hepatic vein ligation, portal hypertension and hypoalbuminaemia were considered as the main factors in the pathogenesis of renal dysfunction and ascites formation in cirrhosis. Since there was no medical treatment of portal hypertension, the only way to improve the haemodynamic imbalance in the hepatic and splanchnic microcirculation was to increase the serum albumin concentration and, consequently, the oncotic pressure. This is why intravenous administration of albumin was widely used for the management of cirrhotic patients with hypoalbuminaemia and ascites during the 1950s and 1960s. In the following years the so-called “overflow theory” proposed by Lieberman et al. suggested the key role of a sodium-retaining signal triggering in renal tubules of patients with portal hypertension. A subsequent renal retention of sodium and water would result in an expansion of plasma volume and adaptive circulatory changes (high cardiac output and low systemic vascular resistance) to challenge the excess intravascular volume. The overflow theory of ascites led to a decline in the use of albumin in the management of patients with cirrhosis and ascites. The overflow theory did not satisfy many investigators in the field of ascites because it did not offer a rational explanation of the main clinical features of cirrhotic patients with ascites, namely, that these patients have a low arterial pressure despite an increased plasma volume and cardiac index and marked activation of the sympathetic nervous system and renin-angiotensin system.

In 1988 a new theory to explain the pathogenesis of ascites and renal dysfunction was proposed by Schrier et al. This theory, integrating several of the earlier hypotheses, reconsiders that sodium and water retention and ascites formation are secondary to the circulatory abnormalities and that the circulatory abnormality causing renal dysfunction is in the arterial vascular compartment. According to this theory, portal hypertension is the initial event, which results in splanchnic arterial vasodilatation, also thanks to the markedly increased production of local splanchnic vasodilators, especially nitric oxide (peripheral arterial vasodilatation hypothesis). This leads to high cardiac output and heart rate and reduced peripheral vascular resistance and arterial pressure, the features of the so-called hyperdynamic circulation. However, although the circulation of these patients is expanded and hyperdynamic, from a functional point of view they are hypovolaemic. The splanchnic arterial vasodilatation is thus responsible for both an increase in splanchnic capillary pressure and permeability and a decrease in effective arterial blood volume. The increased production of lymph fluid and the compensatory activation of the renin-angiotensin-aldosterone system and sympathetic nervous system and hypersecretion of antidiuretic hormone eventually lead to the formation of ascites. In addition to that the splanchnic arterial vasodilatation leads to a compensatory vasoconstriction in the remaining major vascular organs such as the kidneys, brain, muscle and skin. Hepatorenal syndrome in this theory is considered to be the extreme expression of this impairment in circulatory function, secondary to the splanchnic arterial vasodilatation. Renal dysfunction and the formation of ascites in cirrhosis are, therefore, mainly related to events occurring in the arterial vascular compartment.

Paracentesis-induced circulatory dysfunction and albumin

When patients do not respond to diuretic treatment and sodium restriction or develop side effects of diuretic treatment, they are considered to have refractory ascites. The severe prognosis associated with refractory ascites should always lead to the consideration of liver transplantation. Waiting for liver transplantation or as regular treatment, the management options are therapeutic paracentesis or transjugular intrahepatic portosystemic shunts (TIPS).
Paracentesis has been widely used in the treatment of ascites for more than 20 years, when the first randomised controlled trial was published showing that it is more effective than diuretic therapy in mobilising the ascitic fluid, associated with a considerably reduced hospital stay and, therefore, with lower treatment costs. However, this therapeutic option is not free of complications, the most common one being paracentesis-induced circulatory dysfunction (PICD).

This is a pathophysiological state characterised by exaggerated systemic arterial vasodilatation, effective intravascular volume depletion and an intense stimulation of the endogenous vasoactive systems (elevated renin and aldosterone levels). Circulatory dysfunction can develop especially after large-volume paracentesis and is clinically recognised as renal impairment, with a decrease in both renal blood flow and glomerular filtration rate, and electrolyte imbalance, particularly hyponatraemia. The development of complications such as hepatorenal syndrome and spontaneous bacterial peritonitis are thus facilitated. By a still not completely understood mechanism, this PICD is not spontaneously reversible and significantly reduces the probability of survival.

For the clinician the most interesting feature is that this complication of paracentesis can be almost totally prevented if the procedure is performed in association with an expansion of plasma volume. But which plasma expanders can be used? Albumin has been compared with an isotonic saline solution for substitution during paracentesis; among patients who underwent large-volume paracentesis of more than 6 L, the incidence of PICD was significantly higher in those receiving saline (33% versus 14%). Similar studies have been conducted with other plasma expanders, such as dextran-70 and polygelien; the results obtained in those studies were better than those reported for saline, but albumin remained the best substitution. As a current gold standard the International Ascites Club recommends that, until further results are available, 6-8 g of intravenous albumin be infused per litre of ascitic fluid removed for paracentesis volumes greater than 5-6 L, while up to 5 L ascitic fluid can be tapped without the need for albumin as a substitute for the reduced plasma volume.

The lowest incidence of PICD is seen when this advice regarding substitution is followed.

Spontaneous bacterial peritonitis and albumin

Spontaneous bacterial peritonitis (SBP) is a common and often fatal complication of cirrhosis; it is an infection of ascitic fluid in patients with cirrhosis and is defined by an ascitic polymorphonuclear leucocyte count of higher than 0.25 x 10⁹/L. This clinical syndrome, in which ascites becomes infected in the absence of a recognisable cause of peritonitis, is thought to develop as a result of delayed intestinal transit and increased permeability of the intestinal wall. In this setting bacteria migrate from the intestinal lumen to the mesenteric lymph nodes, a process known as bacterial translocation. The defective immune system in cirrhotic patients facilitates colonisation of bacteria in the mesenteric lymph nodes. Via the circulation bacteria can travel to other locations, including the ascitic fluid. The inflammatory response in the abdominal cavity increases the local release of cytokines which pass into the circulation, impairs systemic haemodynamics and produces marked homeostatic activation of the endogenous vasoconstrictor systems and renal failure. These patients are, therefore, at high risk of developing renal insufficiency. The development of renal failure is the most important indicator of reduced survival in patients with SBP compared with patients without SBP.

Two trials have shown that the administration of albumin during SBP markedly reduces the incidence of hepatorenal syndrome. In the first one 126 patients were randomly allocated to receive either cefotaxime alone (third-generation cephalosporins and amoxicillin-clavulanic acid are the recommended and most commonly used antibiotics for SBP) or cefotaxime plus albumin infusion. Patients who were given cefotaxime plus albumin infusion showed no increase in plasma renin activity, a decreased incidence of renal failure and a decreased hospital mortality rate (29% versus 10% and p<0.01 for mortality rate). In the second trial the same authors compared infusion of hydroxyethyl starch for the prevention of renal failure in patients with SBP, in order to address a criticism that questioned the validity of their prior study. The findings of this study also supported the superiority of albumin in preventing the development of renal failure in patients with SBP. These data show that plasma volume expansion with albumin prevents the development of circulatory dysfunction in patients with SBP, who have a high
risk of morbidity and mortality. In fact the most recent International Ascites Club clinical recommendations indicate that the incidence of hepatorenal syndrome in patients with SBP may be reduced by the administration of albumin. The suggested dose of albumin is 1.5 g/kg body weight on the first day and 1 g/kg body weight on the third day, up to a maximum of 150 and 100 g, respectively. In addition to that albumin administration is clearly indicated for patients with SBP and serum bilirubin levels >4 mg/dL or serum creatinine levels >1 mg/dL.

**Hepatorenal syndrome and albumin**

As already explained in the previous sections, portal hypertension leads to mesenteric vasodilatation, while peripheral vascular resistance is decreased thus triggering a hyperdynamic circulation. Due to the pooling of blood in the splanchnic vessels, central blood volume is diminished and endogenous vasoconstricter systems are activated in compensation. The patients are vulnerable to further haemodynamic insults and, if renal auto-regulation is overwhelmed, acute renal failure is a common complication. This dreaded complication of advanced cirrhosis is called hepatorenal syndrome (HRS) and is defined as the development of renal failure in patients with advanced liver failure in the absence of any identifiable causes of renal pathology. The hallmark is renal hypoperfusion, which is caused by both active renal vasoconstriction and a reduction in the renal perfusion pressure. Various pharmacotherapies for HRS have been designed to reduce systemic vasodilatation and activation of vasoconstrictor systems. In fact systemic vasoconstrictors such as vasopressin analogues and α-adrenergic agonists have been used to treat HRS, with some success. In most studies, vasoconstrictor therapy has been given in combination with albumin infusions to further improve arterial underfilling. Albumin is traditionally considered to improve circulatory function in cirrhosis by expanding central blood volume and increasing cardiac output. It is, therefore, conceivable that an improvement of renal function in patients with HRS treated with vasoconstrictors and albumin is due to the additive effects that the two compounds have on plasma expansion and peripheral arterial circulation.

Two early studies demonstrated that a long-term infusion of ornipressin, combined with albumin or dopamine, normalised serum creatinine concentrations in many patients with type-1 HRS. However, the drawback with ornipressin was the frequent occurrence of ischaemic complications. The widespread use of vasoconstrictors in patients with HRS only became clinically feasible with the advent of safer compounds such as terlipressin, a vasopressin analogue with longer activity, and the α2-agonist midodrine combined with octreotide. All these drugs have been shown to be more effective when given in combination with albumin. Moreover, when patients with HRS are treated with both albumin and terlipressin before liver transplantation the chance of recovery after the transplant is comparable to that of patients without HRS prior to transplantation.

According to the recent guidelines from the International Ascites Club, vasoconstrictors and albumin are recommended as first-line treatment for type-1 HRS, terlipressin being the most widely used vasoconstrictor with midodrine+octreotide and noradrenaline as possible alternatives. The daily dose of albumin is generally 20 - 40 g, preceded in some studies by a load of 1 g/kg body weight. With the use of terlipressin (2 - 12 mg/day) and albumin about 60% of cases of renal failure recover. Therefore, according to currently available data, plasma volume expansion with albumin is an essential part of the pharmacological treatment of type-1 HRS.

**Ascites and chronic use of albumin**

The use of intravenous albumin as a chronic treatment for ascites in patients with end-stage liver disease dates back 60 years. As theories regarding the nature of vascular control and ascites formation developed, and with a better understanding of the use of diuretics and other management strategies, the use of albumin for the treatment of this condition declined. However, nowadays, many hepatologists are treating a growing number of patients in whom diuretics are ineffective or associated with serious side effects and TIPS may be contraindicated with chronic administration of albumin, thus moving back to therapies that were used by their predecessors over half a century ago. Although there is no evidence from randomised studies supporting the long-term administration of albumin in patients with cirrhosis and ascites, this practice is nevertheless widely used, at least in Italy, as shown by a study aimed at reaching a consensus that involved 68 hepatology centres. In the opinion of most experts, long-term albumin
infusion usually produces a subjective feeling of “well-being”, improving the patient’s general conditions. Seventy-seven percent of the experts involved in this survey agreed that albumin administration can shorten a hospital stay or reduce the number of hospital admissions.

In an era of evidence-based medicine only a few studies have investigated the role of albumin in the treatment of ascites and prevention of its recurrence, and these have been uncontrolled investigations involving small numbers of patients. For example, Schindler and Ramadori treated 12 patients with refractory ascites with a mean of 22.1 g/day of intravenous albumin for up to 31 days. These investigators demonstrated a mean loss of body weight of 10.1 kg and a significant improvement in urinary sodium excretion, urine output and serum albumin levels. In addition to that, the mean daily dose of aldactone necessary decreased from 222 to 133 mg and the mean dose of furosemide from 32 to 5 mg.

Another study showed that chronic intravenous infusion of 50 g albumin per week was an effective therapy for many patients with refractory ascites who were unable to undergo TIPS. More consistent results were obtained by Gentilini et al., who randomised 81 patients who failed to respond to bed-rest and sodium restriction to diuretic therapy or diuretic therapy with albumin infusions (25 g/week for 1 year, followed by 25 g every 2 weeks for up to an additional 2 years). In the end there was evidence of benefit for the albumin-treated patients regarding recurrence of ascites, cumulative probability of readmission to hospital and number of days spent in hospital (90.5% versus 74.7%, p<0.05), but not regarding either improvement in survival or a lower incidence of complications. The same investigators subsequently extended the follow-up period up to 62.7 ± 4.2 (mean ± SD) months. The main result of this extended study was that administration of human albumin to patients affected by liver cirrhosis (25 g/week in the first year and 25 g every two weeks thereafter) resulted in a significantly higher cumulative survival rate. In addition, as in the previous investigation, albumin administration markedly reduced the recurrence of ascites. In a pilot study the use of albumin combined with these drugs produced a significant reduction in plasma renin and aldosterone concentrations and a trend towards a reduction in the volume of ascites removed by paracentesis without an effect on renal function.

In conclusion, long-term albumin administration to patients with cirrhosis after the first ascitic episode may improve survival and decreases the risk of ascites recurrence, but well-designed, randomised, controlled trials are certainly needed in order to establish the benefits of albumin in the clinical setting of cirrhotic ascites.

**Molecular adsorbent recirculating system**

Liver failure can occur in different ways: acute liver failure (ALF) is the development of severe acute liver injury with impaired hepatic synthetic function and encephalopathy in a patient without previous liver disease; acute-on-chronic liver failure (AoCLF) is defined as acute deterioration in liver function over a 2- to 4-week period in a patient with pre-existing chronic liver disease, while chronic decompensation results in end-stage liver disease. The loss of the metabolic and regulatory functions of the liver in these situations results in life-threatening complications that may include bleeding, renal failure, hepatic encephalopathy, cardiovascular failure, and susceptibility to infections culminating in multi-organ failure. The liver often maintains some regenerative potential, so the rationale for supportive therapy and extracorporeal systems is to provide an environment facilitating recovery to create or prolong a window of opportunity for liver transplantation or until the native liver recovers in ALF or a period of stability for those with AoCLF.

In the last years albumin has been used not as a drug to be administrated, but as a part of a haemodialysis regimen in patients with hepatic failure, in the so-called molecular adsorbent recirculating system (MARS). This artificial liver support was originally developed in 1993 by Stange and colleagues, who designed a device in which the albumin dialysate, after removal of toxins from the blood, was cleaned in a three-step process and reutilised. The system consists, therefore, of a blood circuit, an albumin circuit, and a classic ‘renal’ circuit. Blood is dialysed across an albumin-impregnated, high-flux dialysis membrane; albumin-bound toxins
in blood are released to the membrane. Albumin avidly binds toxins, including bilirubin, copper ions, and protein breakdown products, substances that accumulate in primary liver diseases including cirrhosis, hepatitis C infection, and Wilson’s disease. The toxins are picked up by albumin in the dialysate, which then undergoes haemodialysis/haemofiltration if required. The albumin dialysate is subsequently cleaned by passage across two sequential adsorbent columns containing activated charcoal and anion exchange resin. These columns remove most of the water-soluble and albumin-bound toxins.

Because of the pore size of the membrane, substances with a molecular weight of more than 50 kDa, such as essential hormones and growth factors bound to albumin, are not removed.

In liver failure, a variety of ‘toxins’ accumulate as a result of impaired hepatic function and clearance. Ammonia, inflammatory cytokines, aromatic amino acids, and endogenous benzodiazepines have been implicated in the development of hepatic encephalopathy and cerebral oedema. Other systemic factors such as nitric oxide and cytokines have been linked with circulatory and renal dysfunction in liver failure. The ability of MARS to remove toxins and pro-inflammatory stimuli, such as lipopolysaccharides, chemokines, lipid peroxidation end-products, xenobiotics and free haem/haemoglobin, may have implications for limiting the inflammatory response. This is why MARS has been used to treat liver dysfunction and failure: it has been shown to improve renal function and haemodynamics, and to decrease brain oedema and hepatic encephalopathy.

Although studies in both ALF and AoCLF have shown reductions in biochemical markers and hepatic encephalopathy in patients on MARS, to date no conclusive benefit with regards to mortality has been demonstrated. Studies are currently in progress to address this issue, as all the studies existing in the literature are pilot studies involving small numbers of patients and without a control arm, with a paucity of robust randomised studies. Nevertheless these new techniques using albumin dialysis represent potentially exciting advances in desperately ill patients with ALF and AoCLF. The challenge is to learn how to best exploit these therapies to the patients’ advantage. It is important to determine which biochemical and clinical parameters correlate best with patients’ outcomes such as overall survival, bridging to liver transplantation, and prevention of multi-organ failure.

Conclusions
It has been known since the 1950s that advanced stages of cirrhosis are characterised by protein wasting and hence albumin depletion. Albumin infusion has, therefore, been used for many years as a way to improve plasma oncotic pressure in cirrhotic patients with ascites and hypoalbuminaemia. As a result of better understanding of both the pathophysiology of end-stage liver disease and the physiological properties of albumin, the role of this serum protein in the management of complication of cirrhosis has rapidly evolved in the last decades. To date, with several randomised trials and pilot studies having indicated that albumin is extremely effective in the prevention and treatment of circulatory dysfunction and hepatorenal syndrome in patients with cirrhosis, this molecule has become an essential treatment in clinical hepatology. The role of albumin is being redefined given its properties beyond being simply a plasma expander and the increasing knowledge of the mechanisms of action of albumin will probably widen the therapeutic indications for this molecule. One example of this new role of albumin is the MARS, which has opened the haemodialysis world to patients with acute and chronic liver failure.

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