# The Use of Albumin in Patients with Decompensated Cirrhosis: The Case in Favor

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In order to better understand the role of albumin administration in patients with decompensated cirrhosis, certain pathophysiologic considerations of ascites and renal impairment in this condition are warranted. Increased hepatic resistance to portal flow due to cirrhosis causes the gradual development of portal hypertension, collateral vein formation, and shunting of blood to the systemic circulation. As portal hypertension develops, local production of vasodilators, mainly nitric oxide, increases, leading to splanchnic arterial vasodilatation – known as the hyperdynamic circulation [1,2]. In the advanced stages of cirrhosis, splanchnic arterial vasodilatation is so pronounced that the effective arterial blood volume decreases markedly, and mean arterial pressure falls [3]. This, in turn, results in activation of both the renin-angiotensin-aldosterone system and the sympathetic nervous system. The activation of the neurohormonal system causes intrarenal changes with consequent retention of sodium and water, resulting in accumulation of ascites [3,4]. Additionally, renal perfusion pressure is reduced, leading to decreased renal blood flow [5]. Compensatory vasoconstriction occurs in some non-splanchnic vascular beds including the kidneys, thereby further reducing renal perfusion with the consequent reduction of glomerular filtration rate [6,7]. Recently, it was shown that decreased cardiac output secondary to a reduction in systemic venous return also contributes to the development of renal failure [8].

Albumin is a very attractive molecule – both biologically and therapeutically [9]. It is the most effective plasma expander currently available due to its high oncotic activity and prolonged half-life in the intravascular compartment. Therefore, albumin may be used in clinical settings of cirrhosis in which plasma expansion would reverse some of the effective arterial blood volume. Furthermore, albumin has many other biological properties, including high capacity of molecule transportation, free radical scavenging, and a modulatory effect on capillary permeability and neutrophil adhesion and activation. Albumin infusion has been widely used for many years in the management of cirrhosis and ascites. However, the use of albumin has been questioned, mainly due to the results of a recent meta-analysis showing that albumin administration may increase mortality in critically ill patients [10]. Furthermore, albumin is costly and has limited availability. Therefore, official practical guidelines on the management of patients with cirrhosis and ascites differ in their recommendations for the use of albumin in this setting [11,12].

Recently, however, evidence has accumulated supporting the use of albumin in the treatment of ascites and its complications. In particular, albumin proved useful:

- in patients with ascites treated with diuretics
- in patients with ascites treated with therapeutic paracentesis
- in the treatment of spontaneous bacterial peritonitis
- in the treatment of hepatorenal syndrome.

## Albumin in patients with ascites receiving diuretics

Diuretic-induced renal impairment occurs as a consequence of the imbalance between intravascular fluid losses caused by diuretics

and the net passage of fluid from the peritoneal cavity to the general circulation. When fluid losses are greater than the net reabsorption of ascites, a reduction in circulating blood volume will ensue, with activation of the main sodium-retaining and vasoconstricting factors and the onset of diuretic-related complications. Diuretic-induced renal impairment occurs in 20% of cirrhotic patients treated with diuretics. These complications are more frequent in patients with advanced disease, who invariably have severe alteration of systemic hemodynamics [13].

Two randomized, controlled studies were performed to establish whether intravascular volume expansion with albumin could be of value in cirrhotic patients receiving diuretics [14,15]. The first study was conducted in two phases. In the initial in-hospital period, ascitic patients were randomized to receive diuretics alone, or diuretics with albumin. Upon discharge from hospital patients on diuretics alone continued to receive the same regimen, while the other group received diuretics plus weekly intravenous albumin on an outpatient basis. The second study extended the follow-up period to 21 months (range 4–48 months) [15]. The cumulative rate of response to diuretic treatment of ascites was higher and hospital stay shorter in patients treated with diuretics plus albumin than in those given diuretics alone. After discharge patients receiving albumin on an outpatient basis had a lower cumulative probability of recurrence of ascites and a lower rate of readmission to hospital. No side effects of albumin were observed. Patients given albumin also had improved quality of life assessed by standardized tests, and a trend toward longer survival. Although no formal cost-effective analysis was performed, the study clearly showed a favorable cost/benefit ratio to albumin at least for the initial in-hospital period. These trials suggest that albumin administration in combination with diuretics is more effective than diuretics alone in determining disappearance and reducing recurrence of ascites. Furthermore, outpatient use of albumin is safe and feasible.

## Albumin in patients with ascites treated with therapeutic paracentesis

The prevention of paracentesis-induced circulatory dysfunction became a major indication for albumin administration. Currently, paracentesis is widely used in the treatment of ascites as it was found to be more effective than diuretics in mobilization of ascites [16]. Total paracentesis (complete mobilization of ascites in one tap) is preferred to repeated large-volume paracentesis in patients with massive or refractory ascites because it is associated with a lower rate of local complications. The recommended dose of albumin is 8 g/L of fluid removed [12].

When cirrhotic patients with tense ascites are submitted to therapeutic paracentesis without plasma volume expansion, the incidence of impairment in circulatory function, defined as a significant increase in plasma renin activity, may be as high as 70% [17]. The incidence of paracentesis-induced circulatory dysfunction is reduced to 35–40% when plasma volume is expanded immediately after the procedure with dextran 70, polygeline, or saline solution [18,19]. The probability of developing paracetesis-induced circulatory dysfunction in patients treated with these plasma expanders clearly depends on the volume of fluid removed, being less than 20% with <5 L of ascites fluid removed, a figure very similar to the incidence of deriorating circulatory function in cirrhotic patients with massive ascites not receiving any type of treatment. The incidence of circulatory dysfunction increases to 30% with 5–9 L of ascites fluid removed, and to 60% with >9 L removed, respectively [18]. Therefore, patients without massive ascites are at low risk for developing circulatory dysfunction following paracentesis. The incidence of paracentesis-induced circulatory dysfunction is further reduced to 15–20% if volume expansion is performed with albumin solution [18]. The incidence of circulatory dysfunction in patients treated with paracentesis and albumin is not related to the volume of ascetic fluid removed. It appears that albumin infusion totally prevents the circulatory dysfunction associated with paracentesis.

Although paracentesis-induced circulatory dysfunction is asymptomatic in most cases, it adversely affects the clinical course of patients [17–19]. Paracentesis-induced circulatory dysfunction is associated with a 20% incidence of renal impairment and/or hyponatremia immediately after the procedure, whereas this feature is observed in less than 5% of patients without circulatory dysfunction. Furthermore, paracentesis-induced circulatory dysfunction is associated with more rapid hospital readmission for ascites and shorter survival. Deteriorating circulatory function, in fact, is the most important independent predictor of survival in patients with tense ascites treated by total paracentesis and volume expansion.

Admittedly, none of these randomized controlled trials comparing albumin administration to other synthetic plasma expanders or no plasma volume expansion at all was performed with survival as an endpoint. Therefore, until further data are accumulated, it is advisable to administer albumin after total/large-volume paracentesis in cirrhotic patients with massive ascites.

## Albumin in patients with spontaneous bacterial peritonitis

SBP is a frequent precipitating factor of hepatorenal syndrome [20]. The inflammatory response in the abdominal cavity increases the local release of cytokines, which pass into the circulation, impair systemic hemodynamics and produce marked homeostatic activation of endogenous vasoconstrictors and renal failure [21]. The development of hepatorenal syndrome is the most important predictor of survival in patients with SBP, with in-hospital mortality reaching almost 100%.

A recent randomized controlled trial showed that plasma volume expansion with albumin prevents the development of circulatory dysfunction in patients with SBP, and that this effect is associated with a 60% reduction in the development of hepatorenal syndrome type 1 and hospital mortality [22]. Furthermore, the 3 month probability of survival was markedly higher in patients treated with albumin. Therefore, plasma

SBP = spontaneous bacterial peritonitis

volume expansion with albumin is an important component in the management of patients with SBP.

## Albumin in the treatment of hepatorenal syndrome

For many years hepatorenal syndrome was considered a terminal irreversible event in patients with decompensated cirrhosis. The only effective treatment was liver transplantation, but very few patients with hepatorenal syndrome type 1, associated with less than 1 month survival after the onset of renal failure, reached liver transplantation [6,7]. However, in recent years it was demonstrated that patients with hepatorenal syndrome type 1 may be effectively treated with a combination of vasoconstriction and plasma volume expansion [23]. It became apparent that this combination therapy is associated with increased survival in a significant number of patients. The rationale behind this approach is to improve circulatory function by causing vasoconstriction of the extremely dilated splanchnic arterial bed, which subsequently suppresses the activity of the endogenous vasoconstrictor system and results in an increase in renal perfusion. Vasocontrictors were given in combination with intravenous albumin plasma expansion to further improve the arterial underfilling [23]. Two types of vasoconstrictor drugs have been used so far: vasopressin analogues (ornipressin and terlipressin) and α-adrenergic agonists (norepinephrine and midodrine). The use of albumin appears to increase the efficacy of vasoconstrictor drugs [24]. Terlipressin is the vasoconstrictor that is used most frequently in hepatorenal syndrome [24–26]. Administration of this drug is associated with a complete renal response (reduction of serum creatinine below 1.5 mg/dl) in 50–75% of patients, according to various studies. Predictors of a lack of response to terlipressin include omission of concomitant albumin administration in addition to severe liver failure and old age [24,25]. Despite the improvement in glomerular filtration rate and the decrease in serum creatinine to normal or near-normal concentrations, GFR remains below normal values in most responding patients [24,26]. Recurrence of hepatorenal syndrome after treatment withdrawal in responders is uncommon (about 15% of patients) and retreatment is effective in most cases. Responders to terlipressin have better survival than non-responders, which suggests an effect of the drug on survival [24,25]. Alpha-adrenergic agonists are an attractive alternative to terlipressin because they are cheaper, widely available, and apparently as effective as terlipressin [27,28]. Octreotide, which causes splanchnic vasoconstriction probably mediated by inhibition of some vasodilator peptides of splanchnic origin, may also be effective in the management of hepatorenal syndrome [29,30]. Currently, the mainstay of treatment of hepatorenal syndrome includes vasoconstrictor drugs. Vasoconstrictor therapy is significantly more effective when combined with plasma volume expansion with albumin. This regimen not only improves renal function in the short term but also increases survival rate, which may in turn enable a large proportion of these patients to undergo liver transplantation.

GFR = glomerular filtration rate

## Cost of albumin

The opponents of the use of albumin in patients with advanced liver disease claim that the preparation is expensive. We verified the cost of albumin solution in Israel. The official price is $1 per gram of albumin. If we use albumin for paracentesis and draw 5 L of ascetic fluid and restitute 8 g/L drawn we will need 40 g (or $40). This compares well with the costs of broad-spectrum antibiotics commonly used for treatment of in-hospital infections. This calculation does not imply that administration of albumin is cost-effective, and further meticulous cost-effectiveness studies for the various indications of albumin infusion, taking many other factors into consideration such as in-hospital stay and patient survival, should be performed.

## Summary

In conclusion, in the course of patients with advanced liver disease there are several indications for institution of intravenous albumin. These include: a) enhancement of diuretic effect on mobilization of ascites fluid, b) prevention of post-paracentesis circulatory dysfunction after total/large volume paracentesis, c) prevention of hepatorenal syndrome in patients affected with SBP, and d) administration of albumin in combination with vasoconstrictor drugs as the only effective therapy for hepatorenal syndrome. Albumin is relatively inexpensive and can be given in an outpatient setting.

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