

## Albumin administration in patients with cirrhosis: Current role and novel perspectives

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### Abstract

Mortality in cirrhosis is mostly associated with the development of clinical decompensation, characterized by ascites, hepatic encephalopathy, variceal bleeding, or jaundice. Therefore, it is important to prevent and manage such complications. Traditionally, the pathophysiology of decompensated cirrhosis was explained by the peripheral arterial vasodilation hypothesis, but it is currently understood that decompensation might also be driven by a systemic inflammatory state (the systemic inflammation hypothesis). Considering its oncotic and nononcotic properties, albumin has been thoroughly evaluated in the prevention and management of several of these decompensating events. There are formal evidence-based recommendations from international medical societies proposing that albumin be administered in individuals with cirrhosis undergoing

large-volume paracentesis, patients with spontaneous bacterial peritonitis, those with acute kidney injury (even before the etiological diagnosis), and those with hepatorenal syndrome. Moreover, there are a few randomized controlled trials and meta-analyses suggesting a possible role for albumin infusion in patients with cirrhosis and ascites (long-term albumin administration), individuals with hepatic encephalopathy, and those with acute-on-chronic liver failure undergoing modest-volume paracentesis. Further studies are necessary to elucidate whether albumin administration also benefits patients with cirrhosis and other complications, such as individuals with extraperitoneal infections, those hospitalized with decompensated cirrhosis and hypoalbuminemia, and patients with hyponatremia.

**Key Words:** Cirrhosis; Albumin; Paracentesis; Spontaneous bacterial peritonitis; Acute kidney injury; Hepatorenal syndrome

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**Core tip:** Mortality in cirrhosis is mostly associated with clinical decompensation. Albumin has oncotic and nononcotic properties, which may contribute to the prevention and management of such complications. This review discusses the current recommendations and the novel perspectives regarding the use of albumin in cirrhosis.

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## INTRODUCTION

Cirrhosis and chronic liver diseases rank as the conditions with the 10<sup>th</sup> highest mortality rate worldwide[1]. Deaths are mostly related to the development of clinical decompensation of cirrhosis, and 4%–12% of individuals with cirrhosis present with at least one episode of decompensation annually[2]. This is why preventing and treating decompensating events in cirrhosis are constant concerns of gastroenterologists and hepatologists.

Albumin administration has been studied in the prophylaxis and management of different forms of decompensation of cirrhosis for many years. Albumin is exclusively synthesized by hepatocytes, and it is characterized as a water-soluble, negatively charged, 67-kDa protein, with a half-life of approximately 20 d in normal conditions. It is the most abundant protein in serum and in extracellular fluids, and it has multiple roles, including oncotic, antioxidative, detoxifying, anti-inflammatory, endothelium stabilizing, and immunomodulatory functions[3]. Traditionally, most decompensating events of cirrhosis were explained by the peripheral arterial vasodilation hypothesis[4], and albumin was considered potentially useful mainly due to its oncotic property, as it is responsible for 75% of plasma oncotic pressure[3]. However, with the current understanding that decompensation of cirrhosis is at least partly driven by a systemic inflammatory state (the systemic inflammation hypothesis)[5-8], the nononcotic properties of albumin have gained much attention[3].

This article reviews the current role and novel perspectives for albumin administration in cirrhosis. Table 1 shows the main indications for which there are formal recommendations for the use of albumin in cirrhosis as well as other potential situations in which albumin may play a role.

## LARGE VOLUME PARACENTESIS

Large volume paracentesis (LVP) is the current standard of care for the management of refractory and tense ascites due to its efficacy and low rate of complications[9-11]. However, the drainage of large volumes of ascitic fluid increases cardiac output and reduces peripheral vascular resistance and effective circulating volume, leading to arterial hypotension, acute kidney injury (AKI), hepatic encephalopathy (HE), worsening of hyponatremia, and decreased survival rates. This severe condition is termed paracentesis-induced circulatory dysfunction (PICD) and is defined by a rise of more than 50% in the basal plasma renin activity a few days after the procedure, indicating the detrimental effect of volume depletion on effective volemia[12-15].

**Table 1** Current recommendations and potential indications for albumin administration in cirrhosis

Current recommendations <sup>1</sup>	Potential indications
Large-volume paracentesis	Modest-volume paracentesis
Acute kidney injury	Extraperitoneal infections
Hepatorenal syndrome	Long-term albumin administration in cirrhosis with ascites
Spontaneous bacterial peritonitis	Decompensated cirrhosis with hypoalbuminemia
	Hepatic encephalopathy
	Hyponatremia
	Cirrhotic cardiomyopathy
	Acute-on-chronic liver failure

<sup>1</sup>Recommendations for albumin administration according to the European Association for the Study of the Liver[9] and the American Association for the Study of Liver Diseases[11].

Several randomized controlled trials (RCTs) have shown that PICD can be prevented by intravenous human albumin administration, particularly in cases of paracentesis exceeding 5 L and that albumin is more effective than other plasma expanders[13,16-18]. In the seminal study by Ginès *et al*[13] for instance, 105 patients were randomized to be submitted to paracentesis with or without albumin infusion, and individuals receiving albumin developed less episodes of hyponatremia ( $P < 0.01$ ) and renal impairment ( $P < 0.05$ ).

In 2012, a meta-analysis of 17 RCTs, including 1225 patients with ascites undergoing LVP, showed that in comparison to alternative treatments albumin reduced the incidence of PICD [odds ratio = 0.39, 95% confidence interval (CI): 0.27-0.55], hyponatremia (odds ratio = 0.58, 95%CI: 0.39-0.87), and mortality (odds ratio = 0.64, 95%CI: 0.41-0.98), which appeared to be definitive evidence regarding the role of albumin infusion in LVP[19]. However, in 2019 another meta-analysis, including 25 RCTs, revisited this issue. According to this systematic review, there was no evidence of significant reduction in mortality or renal impairment when any volume expansion was compared to no volume expansion at all, but it should be highlighted that only one and two RCTs using albumin actually contributed to the analyses of these outcomes, respectively. When albumin was compared to other plasma expanders, there were significant benefits of using albumin regarding prevention of PICD [risk ratio (RR) = 1.98, 95%CI: 1.31-2.99] and hyponatremia (RR = 1.49, 95%CI: 1.03-2.14), but there was no evidence of significant differences between treatments regarding renal impairment (RR = 1.17, 95%CI: 0.71-1.91) and mortality (RR = 1.03, 95%CI: 0.82-1.30)[20].

The use of vasoconstrictors, such as vasopressin, midodrine, and noradrenaline, has been proposed as an alternative to albumin in order to overcome the marked arterial vasodilation and arterial hypotension associated with PICD, but evidence on the clinical utility of such drugs is limited in this context. An RCT compared the effect of midodrine and standard albumin doses in preventing PICD in 50 patients with cirrhosis and tense refractory ascites. Midodrine therapy was associated with higher incidence of AKI, worsening of hyponatremia, and higher plasma renin activity and plasma aldosterone concentration, suggesting that this drug is not as effective as intravenous albumin in preventing PICD after LVP[21].

Despite the existence of some doubts concerning the benefits of albumin on hard outcomes (renal impairment and mortality), its clear benefits on important surrogate outcomes (PICD and hyponatremia) allow albumin to be recommended in patients with cirrhosis undergoing paracentesis of more than 5 L. According to the European Association for the Study of the Liver, it should be administered at a dose of 8 g/L ascitic fluid removed[9], while the American Association for the Study of Liver Diseases recommends it is used at doses of 6-8 g/L ascites removed[11].

Modest volume paracentesis (< 5 L) seems to have less serious impacts on hemodynamic and neurohumoral systems, and therefore it might be safe to perform the paracentesis without administering albumin[22]. The exception to this seems to apply to patients with acute-on-chronic liver failure (ACLF) undergoing paracentesis < 5 L because these individuals usually have an intense hemodynamic impairment that theoretically increases the risk of PICD. A recent study randomized 80 subjects with ACLF undergoing paracentesis < 5 L to receive standard doses of albumin or no fluid expansion and demonstrated that PICD was significantly more common in the control group than in the albumin group (70.0% vs 30.0%,  $P = 0.001$ ), with significantly higher incidences of HE (50.0% vs 27.0%,  $P = 0.04$ ), hyponatremia (67.5% vs 22.5%,  $P < 0.001$ ), AKI (62.5% vs 30%,  $P = 0.001$ ), and short-term mortality (62.5% vs 27.5%,  $P = 0.003$ )[23].

## AKI AND HEPATORENAL SYNDROME

AKI is a common complication of cirrhosis, reported in up to one-third of hospitalized patients with advanced liver disease[24-27]. The diagnostic criteria of AKI in cirrhosis have evolved over the years and are currently based on an acute increase in serum creatinine by  $\geq 0.3$  mg/dL or  $\geq 50\%$  from baseline [28]. The new definition and classification proposed by the International Club of Ascites has allowed for earlier recognition of AKI and implementation of therapeutic strategies, such as intravenous albumin use.

Hypovolemia accounts for about one-half of all cases of AKI in cirrhosis, and it is often driven by excessive use of diuretics and/or fluid losses from lactulose-induced diarrhea. In addition to diuretic withdrawal, intravenous albumin at 1 g/kg/d (maximum 100 g/d) for 2 d has been recommended for volume expansion, especially in patients with AKI stage  $\geq 1b$ [9,11] since mortality appears to significantly increase from this stage on[24,29-32]. Response failure to a 2-d fluid challenge with albumin is suggestive of hepatorenal syndrome (HRS), formerly classified as type 1 and currently as HRS-AKI, once structural kidney injury has been excluded. Recent history of shock, nephrotoxic drugs, proteinuria, microhematuria, and hydronephrosis on renal ultrasound must be ruled out for the diagnosis of HRS-AKI, which is one of exclusion[9,11,28,33].

The benefits of albumin in HRS, a functional kidney injury driven by reduction in renal blood flow, extend beyond just plasma volume expansion. This has been demonstrated in a study comparing albumin with hydroxyethyl starch, a synthetic colloid, in patients with spontaneous bacterial peritonitis (SBP). Administration of albumin resulted in significant improvement on systemic hemodynamics, whereas this effect was not appreciated in the starch group[34]. Furthermore, albumin carries important anti-inflammatory and antioxidant properties, and it has been shown to bind circulating bacterial products, thus preventing their negative consequences on the systemic circulation[35,36]. This has led to the extension of albumin use past the initial fluid challenge at a recommended dose of 20-40 g/d[9,11, 28]. Although albumin alone has a limited role in HRS-AKI[37,38], the benefit of added albumin to vasoconstrictor therapy in HRS has been demonstrated in one nonrandomized study comparing terlipressin with terlipressin plus albumin. Despite being a small study, it demonstrated that the combination therapy group had a significantly higher response rate compared to terlipressin monotherapy (77% *vs* 25%,  $P = 0.03$ )[39].

It is important to note that excessive albumin use in AKI and HRS can be detrimental and contribute to development of pulmonary edema and respiratory failure. This concern has been raised in the recently published CONFIRM study, a large RCT comparing terlipressin with placebo[38]. Concomitant albumin was given in  $> 80\%$  of patients in both arms at a mean total dose of 200-240 g over 5 d (40-50 g/d). A higher incidence of respiratory failure was observed in the terlipressin group (14% *vs* 5%), presumably secondary to pulmonary edema because of the known cardiovascular effects of terlipressin in combination with excessive albumin use[40]. Thus, volume status should be closely monitored in these patients and judicious albumin use is recommended.

## SBP

Bacterial infections occur in 25%-35% of the patients hospitalized with advanced cirrhosis[41], and they are associated with increased morbidity and mortality[42,43], particularly when acquired in the hospital or in healthcare facilities, due to the presence of multidrug resistant organisms[44-48]. SBP is frequently reported as the most common infection in subjects with cirrhosis and ascites[44,45] and one of the main precipitants of ACLF[49]. It is diagnosed in the presence of a polymorphonuclear cell count  $> 250/\text{mm}^3$  in the ascitic fluid, and it is usually treated with third-generation cephalosporins in those patients with community-acquired infection[9,11].

However, since the publication of the pivotal RCT by Sort *et al*[50] in 1999, it is clear that this infection should not be treated exclusively with antibiotics. In that study, 126 hospitalized patients with SBP were randomized to receive intravenous cefotaxime *versus* intravenous cefotaxime plus albumin administered at a dose of 1.5 g/kg body weight at baseline, followed by 1 g/kg on day 3. The authors described a threefold reduction in the incidence of renal impairment favoring the albumin group (33% *vs* 10%,  $P = 0.002$ ). More importantly, 3-mo mortality was also significantly lower in the albumin group (41% *vs* 22%,  $P = 0.03$ ), which was attributed to the decrease in the incidence of AKI[50].

The benefit of using albumin in SBP was initially attributed to plasma expansion and/or prevention of circulatory dysfunction[34,50,51], but it actually seems that albumin infusion leads to a reduction of plasma levels of nitric oxide, tumor necrosis factor- $\alpha$ , endotoxin and interleukin-6[52]. These findings favor the concept that albumin is more than a colloid and that it has anti-inflammatory properties in individuals with decompensated cirrhosis[53].

In the study by Sort *et al*[50], renal impairment was negligible in both groups of patients in the presence of baseline bilirubin levels  $< 4$  mg/dL and serum creatinine level  $< 1$  mg/dL, suggesting that albumin administration might be restricted to higher-risk subjects. Nevertheless, subsequent data have disputed those findings[54,55]. In this regard, a meta-analysis including four RCTs[34,50-52] evaluated

the role of albumin in SBP and concluded that albumin was associated with a lower incidence of renal impairment and mortality, not identifying a significant difference in albumin effects according to baseline levels of bilirubin or renal function[56]. Since then, several international guidelines recommend the use of high-dose albumin in patients with SBP, even in patients at lower risk for renal impairment[9, 11,57]. However, there still is some controversy regarding albumin dosing and schedule since the use of lower doses of albumin were associated with a reduction in proinflammatory cytokines in an RCT[52], and no major differences in outcomes were observed in a subsequent Brazilian trial comparing standard *versus* lower doses of albumin in SBP[58].

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## EXTRAPERITONEAL INFECTIONS

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Infections (not only SBP) characterize state 6 (end-state) in the clinical course of cirrhosis[59], as they increase the risk for AKI, HRS, organ failure, and ACLF[60]. It has also been recently demonstrated that infections are the most important precipitating factor for acute decompensation of cirrhosis, even in patients without ACLF[61]. On the other hand, in compensated cirrhosis, the role of infections is not completely understood. A recent cohort study has demonstrated that 17% of patients with compensated cirrhosis developed infections, particularly respiratory and urinary tract infections, which led to decompensation of cirrhosis in 26% of cases and to an increased mortality rate[62].

Therefore, considering the importance of infections in the prognosis of cirrhosis, improving the efficacy of therapeutic strategies would be of the utmost importance. In SBP, as previously discussed, the addition of albumin to antibiotic treatment represented an important improvement in the therapeutic strategy[50], and it was natural to study if a similar intervention could reach the same results in extraperitoneal infections. The rationale behind this proposal is that albumin is a multifunctional protein, which also has important nononcotic properties, as previously mentioned[3]. Furthermore, individuals with cirrhosis are not only quantitatively deficient in albumin but also qualitatively, which highlights the concept of the effective albumin concentration[63,64].

Some RCTs have evaluated the subject of albumin administration in infections other than SBP. In the first of them, patients with cirrhosis and extraperitoneal infections were randomized to receive antibiotics plus albumin (same doses as for SBP) or antibiotics alone, and albumin led to improved circulatory and renal functions. In that study, there was no significant difference in 3-mo survival between groups, but albumin use was an independent predictive factor of survival after adjusting for other factors[65].

In the second RCT, despite delaying the onset of renal failure, albumin was not able to significantly reduce its incidence or improve survival. Besides, 8.3% of subjects receiving albumin developed pulmonary edema as a complication[66]. It is noteworthy, however, that the study had important methodological limitations.

In the third RCT, albumin was associated with a higher resolution of ACLF as well as with lower incidence of nosocomial infections. Nevertheless, once again, there was no significant difference between groups regarding mortality[67]. An important limitation of this study is the fact that only 23% of the estimated sample was actually enrolled in the trial[68].

In order to further examine this subject, our group has performed a meta-analysis of RCTs evaluating the role of albumin in extraperitoneal infections. In that meta-analysis, there was no evidence of significant benefit of albumin in reducing renal dysfunction (RR = 0.55, 95%CI: 0.25–1.19,  $P = 0.13$ ) or mortality in 30 d (RR = 1.62, 95%CI: 0.92–2.84,  $P = 0.09$ ) and 90 d (RR = 1.27, 95%CI: 0.89–1.83,  $P = 0.19$ ) [69]. Therefore, at this moment, a general recommendation cannot be made regarding the administration of albumin in patients with cirrhosis and extraperitoneal infections[9]. Still, there might be a role for albumin in a subgroup of extraperitoneal infections, particularly the most severe of them[70].

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## LONG-TERM ALBUMIN ADMINISTRATION

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Ascites is the most common among severe complications of cirrhosis[71], and it marks state 4 in the natural history of this disease[59]. Ascites is associated with a 5-year mortality of 50%, and persistent ascites predicts mortality independently of the Model for End-Stage Liver Disease score[59,72]. Therefore, strategies aiming at the increase in survival of patients with cirrhosis and ascites are constantly pursued.

Long-term albumin administration has been studied in the management of patients with cirrhosis and ascites for many decades. The rationale for its use relies on the hypothesis that albumin could reduce effective arterial hypovolemia through plasma expansion and that the nononcotic properties of albumin could act against the systemic inflammation that is behind decompensation of cirrhosis[3,5]. Once again, the concept of effective albumin concentration should be highlighted in this context[63]. As albumin is quantitatively and qualitatively deficient in cirrhosis, leading to alterations in the transport and metabolism of substances as well as to the impairment of systems associated with the redox balance, inflammation, and coagulation, it is hypothesized that albumin supplementation could prevent

the decompensation of cirrhosis[73-77].

Five RCTs evaluated the role of long-term albumin administration in patients with cirrhosis and ascites. The first study evaluated a small sample of subjects with persistent ascites already under treatment with diuretics. Albumin was used at doses of 25–100 g every 1–2 d according to serum colloid osmotic pressure, and 25–100 g every 1–2 wk thereafter. The osmotic pressure was improved in individuals receiving albumin, but mortality was not different between groups[78].

After that, two Italian RCTs evaluated the matter. Gentilini *et al*[79] enrolled patients with ascites unresponsive to a low-sodium diet, while Romanelli *et al*[80] studied individuals with their first episode of grade 2–3 ascites. Both studies randomized patients to receive albumin at doses of 25 g every week for 12 mo and every other week thereafter[79,80]. In the former study, albumin led to significantly lower cumulative probabilities of recurrence of ascites and hospitalization, but there was no benefit regarding mortality[79]. In the latter, though, patients receiving albumin had a significantly lower probability of recurrence of ascites and a higher cumulative survival rate[80].

Finally, in 2018, two more RCTs on long-term albumin administration were published. Solà *et al*[81] evaluated albumin at doses of 40 g twice a month in combination with midodrine for patients with cirrhosis and ascites in the waiting list for liver transplantation, but there was no significant difference in survival or in complications of cirrhosis between study groups. The high rate of transplantation in that study might have led patients to be treated with albumin for an insufficient period of time (since they were quickly transplanted). The fact that the renin-angiotensin-aldosterone system activity did not completely normalize in subjects receiving albumin also supports the hypothesis that higher doses and longer duration of albumin administration might have been necessary[81].

On the other hand, Caraceni *et al*[82] randomized patients with persistent ascites to receive albumin 40 g twice a week for 2 wk and once a week thereafter or no plasma expansion. Individuals receiving albumin had significantly better results than their counterparts regarding mortality, need for paracentesis, SBP, extraperitoneal infections, HE, renal dysfunction, HRS, hyponatremia, and hyperkalemia [82].

Considering the differences in the results of these studies, we have performed a meta-analysis on this issue. Pooling the data from all five RCTs, it was demonstrated that albumin significantly reduced recurrence of ascites/need for paracentesis (RR = 0.56, 95%CI: 0.48–0.67,  $P < 0.001$ ). There was also a trend towards a lower risk of mortality favoring albumin, but it did not reach statistical significance (RR = 0.88, 95%CI: 0.67–1.14,  $P = 0.33$ ). There was no evidence of significant differences between groups regarding refractory ascites, SBP, HE, gastrointestinal bleeding, or adverse events[83].

We understand the main reason for the study by Caraceni *et al*[82] having reached such outstanding results relates to the doses of albumin used. In a recent study, the effects of different doses of long-term albumin administration were compared. While high-dose albumin (1.5 g/kg/wk) led to normalization of serum levels of albumin, improvement of circulatory and cardiac function, and reduction in plasma levels of cytokines, low-dose albumin (1.0 g/kg every 2 wk) did not[84]. It is noteworthy that the trial by Caraceni *et al*[82] was the one using the highest dose of albumin among the five RCTs on this issue, and, even so, the dose used was only slightly higher than that considered insufficient in the abovementioned study[84]. Moreover, while changes in serum levels of albumin were not different between groups in the trial by Solà *et al*[81], the intervention group had a normalization of serum albumin in the study by Caraceni *et al*[82], which reinforces the idea of insufficient doses of albumin in the former trial.

Furthermore, in a *post hoc* analysis of the study by Caraceni *et al*[82], the authors demonstrated that a serum level of albumin of 4 g/dL at 1 mo should be the target in long-term albumin administration in order for the highest survival rates to be achieved. In that publication, the authors suggested the hypothesis of the albumin gap, associating the amount of albumin required not only to baseline albumin levels but also to the severity of liver disease and highlighting the importance of the concept of effective albumin concentration[63].

Therefore, considering the abovementioned evidence, we believe that long-term albumin administration in patients with cirrhosis and ascites will probably become a formal recommendation in the near future. It must be emphasized, though, that the most recent guidelines still did not include this indication of albumin use in cirrhosis[11,85]. Hopefully, the ongoing PRECIOSA trial (NCT03451292) will provide us with more definitive data on this issue.

## OTHER INDICATIONS

### **Decompensated cirrhosis**

A recent RCT (the ATTIRE study), including 777 patients hospitalized for decompensated cirrhosis with baseline serum albumin levels  $< 3$  g/dL, evaluated the effects of increasing these levels by daily intravenous administration of albumin. In that study, albumin administration was not superior to placebo in preventing a composite endpoint of infection, AKI and death[86].

Nevertheless, there are important points to consider. (1) No information on the distribution of patients between groups according to the Child–Pugh classification was provided. This is of great importance due to the recognized heterogeneity of such a group of patients. In fact, this could influence

the response to albumin infusion; (2) Ascites relates to the severity of circulatory dysfunction in patients with advanced cirrhosis. Although ascites was present in 62% of patients in the albumin group and in 71% in the control group, there was no information about its grade, the percentage of individuals with refractory ascites, use of diuretics, and their doses. Furthermore, there were no data on serum sodium concentration, another important marker of circulatory dysfunction; (3) There were no data on the severity or type of infections and their effects on circulatory function. Previous research suggests that giving albumin to patients with cirrhosis may be especially effective in the subset of patients with circulatory and renal dysfunction[50]; and (4) Finally, evidence shows that high doses of albumin are required for individuals with cirrhosis to benefit[84] and that the target level of serum albumin should be 4 g/dL[63]. Patients in the trial by China *et al*[86] reached levels barely over 3 g/dL. Therefore, it is likely that they did not receive enough albumin to benefit from the intervention.

The results of the ATTIRE study should be interpreted with caution, as it seems that rather than trying to make a general recommendation on albumin administration in decompensated cirrhosis, it might be more appropriate to define the best albumin administration strategy and the subgroup of patients with cirrhosis who could benefit most from its effects.

## HE

The understanding of the pathophysiology of HE has increased in recent years. Thus, besides the traditional concept that implies cerebral exposure to ammonia as the basic mechanism for HE occurrence, new proposals suggest that the activation of inflammatory mediators, cerebral blood flow alterations due to circulatory dysfunction, and oxidative stress altogether contribute to the astrocytic injury leading to HE[87]. Albumin, a multifunctional protein, as previously mentioned in this review, could therefore play an important role in the treatment of HE.

In 2004, a pilot study evaluated the effects of plasma expansion with albumin in patients with cirrhosis and diuretic-induced HE. Albumin was more effective than a gelatin-based colloid solution in improving HE grade and lowering plasma concentrations of malondialdehyde, an oxidative stress marker[88]. After that pilot study, a multicenter, double-blind RCT found no significant differences between albumin or saline solution in the resolution of HE in patients with cirrhosis hospitalized with this complication. However, the same study demonstrated a significant improvement in 90-d survival in the albumin group (69.2% *vs* 40.0%,  $P = 0.02$ )[89]. In yet another RCT that compared lactulose plus albumin (group 1) *versus* lactulose alone (group 2) for the treatment of HE, 75% of patients in group 1 and only 53% of those in group 2 had complete reversal of HE ( $P = 0.03$ ). Moreover, mortality was significantly lower in group 1 (18.3% *vs* 31.6%,  $P = 0.04$ )[90]. In this regard, a recent meta-analysis of RCTs aimed at clarifying the role of albumin in HE. In that study, albumin administration was able to significantly improve HE (RR = 0.60, 95%CI: 0.38–0.95,  $P = 0.03$ ) and mortality (RR = 0.54, 95%CI: 0.33–0.90,  $P = 0.02$ )[91].

In another clinical context, that of the prophylaxis of TIPS-induced HE, Riggio *et al*[92] compared patients receiving albumin to a historical control group and found no significant difference in the incidence of overt HE[92]. However, the important methodological limitations of that study must be kept in mind when appraising its results.

Considering what was presented, despite the absence of a formal recommendation for the administration of albumin in the treatment of HE, it seems that there is initial evidence favoring its use. Further studies should be encouraged in this regard.

## Hyponatremia

Hyponatremia is an important marker of prognosis in cirrhosis as it can induce neurological complications, and it is associated with reduced survival. Hyponatremia in cirrhosis results from a reduction in free water excretion due to nonosmotic secretion of antidiuretic hormone caused by splanchnic vasodilation. The use of albumin may decrease antidiuretic hormone secretion by improving relative hypovolemia, and therefore it might be useful in the management of hyponatremia[9].

In a small series, McCormick *et al*[93] observed complete reversal of hyponatremia after albumin infusion to three patients with decompensated cirrhosis. Moreover, an RCT evaluated the role of albumin infusion in hyponatremic subjects with cirrhosis, showing a significant improvement in serum sodium concentration, an increase in free water clearance, and a reduction in vasopressin concentration in the albumin group when compared to the placebo group[94]. Furthermore, in a large cohort of patients with cirrhosis and hyponatremia, albumin use was independently associated with the normalization of serum sodium levels[95]. More recently, in an analysis of the ATTIRE trial database, albumin infusions also led to an improvement in hyponatremia, which did not translate into benefits regarding hard outcomes[86]. Therefore, due to the scarcity of data, other studies are needed before albumin infusion can be recommended as a therapeutic option in patients with cirrhosis and hyponatremia.

## Cirrhotic cardiomyopathy

Albumin seems to prevent cardiac output reduction and plasma renin activity increase in patients with cirrhosis more effectively than other plasma expanders[3]. The increase in cardiac output induced by albumin seems to be independent of volume expansion[96], which might be explained by the reversal of

the negative effects of tumor necrosis factor-alpha and oxidative stress on cardiac contractility[97].

### **ACLF**

Considering the exacerbated systemic inflammatory state associated with the pathophysiology of ACLF and the anti-inflammatory properties of albumin, it could be hypothesized that albumin might play a role in the treatment of ACLF. There are limited data on this issue at the moment[98], but an RCT on albumin in extraperitoneal infections has demonstrated that individuals receiving this intervention had higher rates of ACLF resolution than their counterparts. Moreover, subjects receiving albumin had evidence of suppression of the systemic inflammation (decrease in white blood cells, C reactive protein, and interleukin-6), which was not specific for those with ACLF[67].

On the other hand, there remains a concern that administered albumin could be modified and added up to the pool of pathological albumin of such severely ill patients[98]. It is noteworthy that patients with cirrhosis, particularly those with advanced disease, have an impairment of albumin function in all of its domains and, therefore, a reduction in effective albumin concentration[64,76]. In this regard, research on ways of improving the quality of commercially available albumin is of the utmost importance since it could lead to an increase in albumin effectiveness as well as to a reduction in costs [3].

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## **PREDICTION OF RESPONSE TO ALBUMIN ADMINISTRATION**

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Not all patients receiving albumin will benefit from it, and biomarkers capable of identifying those most likely to benefit from it would be extremely useful[3]. Effective albumin concentration, which reflects the portion of the albumin pool with normal structure and function, is superior to total albumin in stratifying individuals with compensated cirrhosis, acute decompensation, or ACLF as well as in distinguishing patients with or without complications of cirrhosis. Therefore, effective albumin concentration seems to be promising as a predictor of prognosis and treatment response in these patients. However, further studies are required not only regarding effective albumin concentration but also for other biomarkers[64,99].

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## **ADVERSE EVENTS**

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Albumin infusion is generally safe, but careful evaluation of the patient is necessary in order to avoid complications, particularly volume overload and pulmonary edema[38,86]. Other uncommon complications of albumin might relate to contamination by blood-derived pathogens as well as to its administration to individuals allergic to albumin and to those with severe anemia, severe coagulopathy with pulmonary hemorrhage, or with subcutaneous bleeding[98,100].

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## **ECONOMIC ASPECTS**

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Albumin administration has traditionally been considered costly. However, its cost has decreased over time. More importantly, albumin administration was proven cost-effective in different settings when evaluated using a decision-tree economic model. In that study, when compared to saline, gelatin, and no fluid expansion, albumin was the dominant treatment (more effective and less costly) for patients undergoing LVP. Regarding individuals with SBP, combining albumin and antibiotics was more cost-effective than using antibiotics alone in all three evaluated countries, and it was the dominant strategy in two of them. Finally, in HRS, combining albumin and a vasoconstrictor was the dominant strategy when compared to using a vasoconstrictor alone. Therefore, the concept of albumin administration being costly should be revisited since it is not only cost-effective but also cost-saving in most settings [101].

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## **CONCLUSION**

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Due to the pathophysiological mechanisms behind decompensations of cirrhosis, albumin plays an important role in their prevention and management through its oncotic and nononcotic properties. International medical societies have made formal evidence-based recommendations for albumin administration in LVP, AKI, HRS and SBP. Promising evidence suggests that long-term albumin in patients with ascites, albumin in modest-volume paracentesis in individuals with ACLF, and albumin in HE are also probably beneficial. Further studies are needed to elucidate the role of albumin in other clinical scenarios, such as extraperitoneal infections, decompensated cirrhosis with hypoalbuminemia, and hyponatremia.



## FOOTNOTES

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