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 hepatoportal 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 10th 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].
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].

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

1Recommendations 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].
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 ≥ 0.3 mg/dL or ≥ 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 ≥ 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/mm³ 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-α, 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 these 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].

EXTRAPERITONEAL INFECTIONS

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].

LONG-TERM ALBUMIN ADMINISTRATION

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\[3\].

**PREDICTION OF RESPONSE TO ALBUMIN ADMINISTRATION**
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\[64,99\].

**ADVERSE EVENTS**
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\[98,100\].

**ECONOMIC ASPECTS**
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\[101\].

**CONCLUSION**
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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REFERENCES

1. GBOD 2019 Diseases and Injuries Collaborators. Global burden of 369 diseases and injuries in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet 2020; 396: 1204-1222 [PMID: 32069326 DOI: 10.1016/S0140-6736(20)30925-9]
2. Moon AM, Singal AG, Tapper EB. Contemporary Epidemiology of Chronic Liver Disease and Cirrhosis. Clin Gastroenterol Hepatol 2020; 18: 2650-2666 [PMID: 31401364 DOI: 10.1016/j.cgh.2019.07.060]
3. Bernardi M, Angeli P, Claria J, Moreau R, Gines P, Jalan R, Caraceni P, Fernandez J, Gerbes AL, O’Brien AJ, Trebicka J, Thevenot T, Arroyo V. Albumin in decompensated cirrhosis: new concepts and perspectives. Gut 2020; 69: 1127-1138 [PMID: 32102926 DOI: 10.1136/gutjnl-2019-318843]
4. Schrier RW, Arroyo V, Bernardi M, Epstein M, Henriksen JH, Rodés J. Peripheral arterial vasodilation hypothesis: a proposal for the initiation of renal sodium and water retention in cirrhosis. Hepatology 1988; 8: 1151-1157 [PMID: 2971015 DOI: 10.1002/hep.1840080532]
5. Bernardi M, Moreau R, Angeli P, Schnabl B, Arroyo V. Mechanisms of decompensation and organ failure in cirrhosis: From peripheral arterial vasodilation to systemic inflammation hypothesis. J Hepatol 2015; 63: 1272-1284 [PMID: 26192220 DOI: 10.1016/j.jhep.2015.07.004]
6. Moreau R, Jalan R, Gines P, Pavesi M, Angeli P, Cordoba J, Durand F, Gustot T, Saliba F, Domenicali M, Gerbes A, Wendon J, Alessandria C, Lalena W, Zeuzem S, Trebicka J, Bernardi M, Arroyo V; CANONIC Study Investigators of the EASL–CLIF Consortium. Acute-on-chronic liver failure is a distinct syndrome that develops in patients with acute decompensation of cirrhosis. Gastroenterology 2013; 144: 1426-1437, 1437.e1 [PMID: 23474284 DOI: 10.1053/j.gastro.2013.02.042]
7. Claria J, Stauber RE, Coenraad MJ, Moreau R, Jalan R, Pavesi M, Amorós À, Titos E, Alcaraz-Quiles J, Oettl K, Morales-Ruiz M, Angeli P, Domenicali M, Alessandria C, Gerbes A, Wendon J, Neves F, Trebicka J, Lalena W, Saliba F, Welzel TM, Albillos A, Gustot T, Benten D, Durand F, Ginès P, Bernardi M, Arroyo V; CANONIC Study Investigators of the EASL-CLIF Consortium and the European Foundation for the Study of Chronic Liver Failure (EF-CLIF). Systemic inflammation in decompensated cirrhosis: Characterization and role in acute-on-chronic liver failure. Hepatology 2016; 64: 1249-1264 [PMID: 27483394 DOI: 10.1002/hep.28740]
8. Trebicka J, Fernandez J, Papp M, Caraceni P, Lalena W, Gambino C, Giovo I, Uschner FE, Jimenez C, Mookerjee R, Gustot T, Albillos A, Bañares R, Janicko M, Steib C, Reiberger T, Acevedo J, Gatti P, Bernal W, Zeuzem S, Zipprich A, Piano S, Berg T, Bruns T, Bendtsen F, Coenraad M, Merli M, Stauber R, Zoller H, Ramos JP, Solé C, Soriano G, de Gottiard A, Gronbaek H, Saliba F, Trautwein C, Özdogan OC, Francque S, Ryder S, Nahon P, Romero-Gomez M, Van Vlierberghe H, Francoz C, Manns M, Garcia E, Tufoni M, Amorós A, Pavesi M, Sanchez C, Curtó A, Pitarch C, Putignano A, Moreno E, Shawcross D, Aguilar F, Claria J, Ponzo J, Jansen C, Vitalis Z, Zaccherini G, Balogh B, Vargas V, Montagnese S, Alessandria C, Bernardi M, Ginès P, Jalan R, Moreau R, Angeli P, Arroyo V; PREDICT STUDY group of the EASL-CLF Consortium. The PREDICT study uncovers three clinical courses of acutely decompensated cirrhosis that have distinct pathophysiology. J Hepatol 2020; 73: 842-854 [PMID: 32673741 DOI: 10.1016/j.jhep.2020.06.013]
9. European Association for the Study of the Liver. EASL Clinical Practice Guidelines for the management of patients with decompensated cirrhosis. J Hepatol 2018; 69: 406-460 [PMID: 29653741 DOI: 10.1016/j.jhep.2018.03.024]
10. Moore KP, Wong F, Gines P, Bernardi M, Ochs A, Salerno F, Angeli P, Porayko M, Moreau R, Garcia-Tsao G, Jimenez W, Planas R, Arroyo V. The management of ascites in cirrhosis: report on the consensus conference of the International Ascites Club. Hepatology 2003; 38: 258-266 [PMID: 12830009 DOI: 10.1053/hep.2003.50131]
11. Biggins SW, Angeli P, Garcia-Tsao G, Ginès P, Ling SC, Nadim MK, Wong F, Kim WR. Diagnosis, Evaluation, and
Management of Ascites, Spontaneous Bacterial Peritonitis and Hepatorenal Syndrome: 2021 Practice Guidance by the American Association for the Study of Liver Diseases. Hepatology 2021; 74: 1014-1048 [PMID: 33942342 DOI: 10.1002/hep.31884]

Ruiz-del-Árbol L, Monescollo A, Jiménez W, García-Plaza A, Arroyo V, Rodés J. Paracentesis-induced circulatory dysfunction: mechanism and effect on hepatic hemodynamics in cirrhosis. Gastroenterology 1997; 113: 579-586 [PMID: 9247479 DOI: 10.1053/gast.1997.v113.pm9247479]

Ginés P, Titó L, Arroyo V, Planas R, Panés J, Viver J, Torres M, Humbert P, Rimola A, Llach J. Randomized comparative study of therapeutic paracentesis with and without intravenous albumin in cirrhosis. Gastroenterology 1988; 94: 1493-1502 [PMID: 3360270 DOI: 10.1016/0016-5085(88)90699-9]

Bernardi M, Ricci CS, Zaccherini G. Role of human albumin in the management of complications of liver cirrhosis. J Clin Exp Hepatol 2014; 4: 302-307 [PMID: 25755577 DOI: 10.1016/j.jceh.2014.08.007]

Zaccherini G, Tufoni M, Iannone G, Caraceni P. Management of Ascites in Patients with Cirrhosis: An Update. J Clin Med 2021; 10 [PMID: 34830508 DOI: 10.3390/jcm10225226]

Ginés A, Fernández-Esparrach G, Monescollo A, Vila C, Domènec P, Abeceasis R, Angeli P, Ruiz-Del-Árbol L, Planas R, Solá R, Ginés P, Terg R, Ingieda L, Vaqué P, Salerno F, Vargas V, Clemente Q, Quer JC, Jiménez W, Arroyo V, Rodés J. Randomized trial comparing albumin, dextran 70, and polyethylene glycol in cirrhotic patients with ascites treated by paracentesis. Gastroenterology 1996; 111: 1002-1010 [PMID: 8831595 DOI: 10.1016/0016-5085(96)70068-9]

Sola-Vera J, Mihana J, Ricart E, Planella M, González B, Torras X, Rodríguez J, Such J, Pascual S, Soriano G, Pérez-Mateo M, Guarner C. Randomized trial comparing albumin and saline in the prevention of paracentesis-induced circulatory dysfunction in cirrhotic patients with ascites. Hepatology 2003; 37: 1147-1153 [PMID: 12717398 DOI: 10.1053/jhep.2003.50169]

Moreau R, Valla DC, Durand-Zaleski I, Bronowicki JP, Durand F, Chaput JC, Dadamessi I, Silvin C, Bonny C, Oberti F, Gournay J, Lehe M, Grouin PM, Tazir B, Tellier F. Comparison of outcome in patients with cirrhosis and ascites following treatment by 5% albumin with or without a synthetic colloid: a randomised controlled pilot trial. Liver Int 2006; 26: 46-54 [PMID: 16420599 DOI: 10.1111/j.1478-3231.2005.01188.x]

Bernardi M, Caraceni P, Navickis RJ, Wilkes MM. Albumin infusion in patients undergoing large-volume paracentesis: a meta-analysis of randomized trials. Hepatology 2012; 55: 1172-1181 [PMID: 22905893 DOI: 10.1002/hep.24786]

Simonetti RG, Perricone G, Nikolova D, Bjelakovic G, Gluud C. Plasma expanders for people with cirrhosis and large ascites treated with abdominal paracentesis. Cochrane Database Syst Rev 2019; 6: CD004039 [PMID: 31251387 DOI: 10.1002/14651858.CD004039.pub2]

Hamdy H, ElBaz AA, Hassan A, Hassanin O. Comparison of midodrine and albumin in the prevention of paracentesis-induced circulatory dysfunction in cirrhotic patients: a randomized pilot study. J Clin Gastroenterol 2014; 48: 184-188 [PMID: 23842215 DOI: 10.1097/MCG.0b013e3182ea376]

Peltekian KM, Wong F, Liu PP, Logan AG, Sherman M, Blendsis LM. Cardiovascular, renal, and neurohumoral responses to single large-volume paracentesis in patients with cirrhosis and diuretic-resistant ascites. Am J Gastroenterol 1997; 92: 394-399 [PMID: 9068457]

Arora V, Vijayaraghavan R, Maiwall R, Sahney A, Thomas SS, Ali R, Jain P, Kumar G, Sarin SK. Paracentesis-Induced Circulatory Dysfunction With Modest-Volume Paracentesis Is Partly Ameliorated by Albumin Infusion in Acute-on-Chronic Liver Failure. Hepatology 2020; 72: 1043-1055 [PMID: 31849085 DOI: 10.1002/hep.31071]

Fagundes C, Barreto R, Guevara M, García E, Solá E, Rodríguez E, Graupera I, Ariza X, Pereira G, Alfaro I, Cádiz A, Fernández J, Poch E, Ginés P. A modified acute kidney injury classification for diagnosis and risk stratification of impairment of kidney function in cirrhosis. J Hepatol 2015; 59: 477-481 [PMID: 23692284 DOI: 10.1016/j.jhep.2013.04.036]

Wu CC, Yeung HK, Tsai WS, Tseng CF, Chu P, Huang TY, Lin YF, Lu KC. Incidence and factors predictive of acute renal failure in patients with advanced liver cirrhosis. Clin Nephrol 2006; 65: 28-33 [PMID: 16429839 DOI: 10.5414/cnp65028]

Piano S, Rosi S, Maresio G, Fasolato S, Cavallini M, Romano A, Morando F, Gola E, Frigo AC, Gatta A, Angeli P. Evaluation of the Acute Kidney Injury Network criteria in hospitalized patients with cirrhosis and ascites. J Hepatol 2013; 59: 482-489 [PMID: 23665185 DOI: 10.1016/j.jhep.2013.03.039]

Sujan R, Cruz-Lemini M, Altamirano J, Simonetto DA, Maiwall R, Axley P, Richardson T, Desai V, Cabezas J, Vargas V, Kamath PS, Shah VH, Sarin SK, Bataller R, Singal AK. A Validated Score Predicts Acute Kidney Injury and Survival in Patients With Alcoholic Hepatitis. Liver Transpl 2018; 24: 1655-1664 [PMID: 30153377 DOI: 10.1002/lt.25328]

Angeli P, Ginés P, Wong F, Bernardi M, Boyer TD, Gerbes A, Moreau R, Jalan R, Sarin SK, Piano S, Moore K, Lee SS, Durand F, Salerno F, Caraceni P, Kim WR, Arroyo V, García-Tsao G. Diagnosis and management of acute kidney injury in patients with cirrhosis: revised consensus recommendations of the International Club of Ascites. J Hepatol 2015; 62: 968-974 [PMID: 25633852 DOI: 10.1016/j.jhep.2014.12.029]

Huelin P, Piano S, Solá E, Stanco M, Soló C, Moreira R, Pose E, Fasolato S, Fabregues N, de Prada G, Pilatti C, Graupera I, Ariza X, Romano A, Elia C, Cárdenas A, Fernández J, Angeli P, Ginés P. Validation of a Staging System for Acute Kidney Injury in Patients With Cirrhosis and Association With Acute-on-Chronic Liver Failure. Clin Gastroenterol Hepatol 2017; 15: 438-445.e5 [PMID: 27720915 DOI: 10.1016/j.cgh.2016.09.156]

Bansho ETO, Silva-Pires ES, Wildner LM, Mantas-Correa EB, Schiavon LL, Narciso-Schiavon JL. Prognostic Significance of The New Criteria for Acute Kidney Injury in Cirrhosis. Ann Hepatol 2018; 17: 461-469 [PMID: 29735786 DOI: 10.5064/ajh.2018.01.017.7390]

Schacher FC, Mattos AA, Mulazzani CM, Detanico RB, Favero B, Fonseca BB, Felix PH, Pase THS, Kupschi C, Machado MB, Coral GP, Wittgen D, Mattos AZ. IMPACT OF ACUTE KIDNEY INJURY STAGING ON PROGNOSIS OF PATIENTS WITH CIRRHOSIS. Arq Gastroenterol 2020; 57: 244-248 [PMID: 32935742 DOI: 10.1590/0040-0282.2020000000046]

Leo MS, de Mattos AA, Picon RV, Schacher FC, John Neto G, Zotz RF, Chiesa T, Bombassaro IZ, Possebon JPP, Coral GP, Tovo CV, de Mattos AZ. The prognostic impact of different stages of acute kidney injury in patients with
de Mattos ÂZ et al. Albumin administration in cirrhosis

decompensated cirrhosis: a prospective cohort study. Eur J Gastroenterol Hepatol 2021; 33: e407-e412 [PMID: 33731594 DOI: 10.1097/MEG.0000000000003120]

33 Angeli P, Garcia-Tsao G, Nadim MK, Parikh CR. News in pathophysiology, definition and classification of hepatorenal syndrome: A step beyond the International Club of Ascites (ICA) consensus document. J Hepatol 2019; 71: 811-822 [PMID: 3102175 DOI: 10.1016/j.jhep.2019.07.002]

34 Fernández J, Monteaudo J, Bargallo X, Jiménez W, Bosch J, Arroyo V, Navasa M. A randomized unblinded pilot study comparing albumin versus hydroxyethyl starch in spontaneous bacterial peritonitis. Hepatology 2005; 42: 627-634 [PMID: 16100826 DOI: 10.1002/hep.20829]

35 Stocker R, Glazer AN, Amnes BN. Antioxidant activity of albumin-bound bilirubin. Proc Natl Acad Sci U S A 1987; 84: 5918-5922 [PMID: 3475708 DOI: 10.1073/pnas.84.16.5918]

36 Cantin AM, Paquette B, Richter M, Larivée P. Albumin-mediated regulation of cellular glutathione and nuclear factor kappa B activation. Am J Respir Crit Care Med 2000; 162: 1539-1546 [PMID: 11029374 DOI: 10.1164/ajrccm.162.9.100106]

37 Boyer TD, Sanyal AJ, Wong F, Frederick RT, Lake JR, O'Leary JG, Ganger D, Jamil K, Pappas SC; REVERSE Study Investigators. Terlipressin Plus Albumin Is More Effective Than Albumin Alone in Improving Renal Function in Patients With Cirrhosis and Hepatorenal Syndrome Type I. Gastroenterology 2016; 150: 1579-1589.e2 [PMID: 26896734 DOI: 10.1053/j.gastro.2016.02.026]

38 Wong F, Pappas SC, Curry MP, Reddy KR, Rubin RA, Porayko MK, Gonzalez SA, Muntaz K, Lim N, Simonetto DA, Sharma P, Sanyal AJ, Mayo MJ, Frederick RT, Escalante S, Jamil K; CONFIRM Study Investigators. Terlipressin plus Albumin for the Treatment of Type 1 Hepatorenal Syndrome. N Engl J Med 2021; 384: 818-828 [PMID: 33657294 DOI: 10.1056/NEJMoa2009290]

39 Ortega R, Ginés P, Uriz J, Cárdenas A, Calahorra B, De Las Heras D, Guevara M, Bataller R, Jiménez W, Arroyo V, Rodés J. Terlipressin therapy with and without albumin for patients with hepatorenal syndrome: results of a prospective, nonrandomized study. Hepatology 2002; 36: 941-948 [PMID: 12297842 DOI: 10.1053/jhep.2002.35819]

40 Krag A, Bendsen F, Mortensen C, Henriksen JH, Møller S. Effects of a single terlipressin administration on cardiac function and perfusion in cirrhosis. Eur J Gastroenterol Hepatol 2010; 22: 1085-1092 [PMID: 20453655 DOI: 10.1097/MEG.0b013e32833a4822]

41 Mattos AA, Wilgen D, Jotz RF, Dornelles CMR, Fernandes MV, Mattos AZ. Spontaneous bacterial peritonitis and extraperitoneal infections in patients with cirrhosis. Ann Hepatol 2020; 19: 451-457 [PMID: 32533951 DOI: 10.1002/ahop.2020.04.010]

42 Gustot T, Felleiter P, Pickkers P, Sakr Y, Rello J, Velissaris D, Pierrakos C, Taconné FS, Sevcik P, Moreno C, Vincent JL; EPIC II Group of Investigators. Impact of infection on the prognosis of critically ill cirrhotic patients: results from a large worldwide study. Liver Int 2014; 34: 1496-1503 [PMID: 24606193 DOI: 10.1111/liv.12520]

43 Arvanitì V, D'Amico G, Fede G, Manousou P, Tsiochatzis E, Pleguezuelo M, Burroughs AK. Infections in patients with cirrhosis increase mortality four-fold and should be used in determining prognosis. Gastroenterology 2010; 139: 1246-1256, 1256.e1 [PMID: 20558165 DOI: 10.1053/j.gastro.2010.06.019]

44 D'Oliveira RAC, Pereira LCD, Codes L, Rocha MS, Bittencourt PL. Analysis of Healthcare Associated and Hospital Acquired Infections in Critically Ill Patients with Cirrhosis. Arq Gastroenterol 2022; 59: 102-109 [PMID: 35442319 DOI: 10.1590/S0004-2803.2020.20220001-18]

45 Fernández J, Acevedo J, Castro M, García O, de Lope CR, Roca D, Pavesi M, Sola E, Moreira L, Silva Â, Seva-Pereira T, Corradi F, Menza J, Ginés P, Arroyo V. Prevalence and risk factors of infections by multiresistant bacteria in cirrhosis: a prospective study. Hepatology 2012; 55: 1511-1561 [PMID: 22183941 DOI: 10.1002/hep.25532]

46 Piano S, Singh V, Caraceni P, Maiwall R, Alessandria C, Fernandez J, Soares EC, Kim DJ, Kim SE, Marino M, Vorobioff D, Barea CRC, Merli M, Elkrief L, Vargas V, Krag A, Singh SP, Lesmana LA, Toledo C, Marciano S, Verhelst X, Wong F, Intagliata N, Rabinowich L, Colombato L, Kim SG, Gerbas A, Durand F, Roblero JP, Bhamidimarri KR, Boyer TD, Maevskaya M, Fassio E, Kim HS, Junes CS, Ginés P, Gadano A, Sarin SK, Angeli P; International Club of Ascites Global Study Group. Epidemiology and Effects of Bacterial Infections in Patients With Cirrhosis Worldwide. Gastroenterology 2019; 156: 1368-1380.e10 [PMID: 30552895 DOI: 10.1053/j.gastro.2018.12.005]

47 Fernández J, Prado V, Trebicchia J, Amoros A, Gustot T, Wiest R, Deudefo C, García E, Acevedo J, Fuhrmann V, Durand F, Sánchez C, Papp M, Caraceni P, Vargas V, Baixas R, Piano S, Janicko M, Albillos A, Alessandria C, Soriano G, Welzel TM, Lalemam W, Gerbas A, De Gottardi A, Merli M, Coenix MD, Saliba F, Pavesi M, Jalan R, Ginés P, Angeli P, Arroyo V, European Foundation for the Study of the Chronic Liver Failure (EF-Clif). Multidrug-resistant bacterial infections in patients with decompensated cirrhosis and with acute-on-chronic liver failure in Europe. J Hepatol 2019; 70: 398-411 [PMID: 30913380 DOI: 10.1016/j.jhep.2018.10.027]

48 Costabeber AM, Mattos AA, Sakkimik T. Prevalence of bacterial resistance in hospitalized cirrhotic patients in southern brazil: a new challenge. Rev Inst Med Trop Sao Paulo 2016; 58: 36 [PMID: 27253738 DOI: 10.1590/S1678-9946201658036]

49 Fernández J, Acevedo J, Wiest R, Gustot T, Amoros A, Deudefo C, Reverter E, Martínez J, Saliba F, Jalan R, Welzel T, Pavesi M, Hernández-Tejero M, Ginés P, Arroyo V; European Foundation for the Study of Chronic Liver Failure. Bacterial and fungal infections in acute-on-chronic liver failure: prevalence, characteristics and impact on prognosis. Gut 2018; 67: 1870-1880 [PMID: 28847867 DOI: 10.1136/gutjnl-2017-314240]

50 Sort P, Navasa M, Arroyo V, Aldeguer X, Planas R, Ruiz-del-Arbel L, Castells L, Vargas V, Soriano G, Guevara M, Ginés P, Rodés J. Effect of intravenous albumin on renal impairment and mortality in patients with cirrhosis and spontaneous bacterial peritonitis. N Engl J Med 1999; 341: 403-409 [PMID: 10432325 DOI: 10.1056/NEJM199908053410603]

51 Xue H, Lin B, Mo J, Li J. Effect of albumin infusion on preventing the deterioration of renal function in patients with spontaneous bacterial peritonitis. Zhonghua Xiaohuabing Zazhi 2002; 3: 32-34 [DOI: 10.1016/j.1443-9573.2002.00602.x]

52 Chen TA, Tsao YC, Chen A, Lo GH, Lin CK, Yu HC, Cheng LC, Hsu PI, Tsai WL. Effect of intravenous albumin on endotoxin removal, cytokines, and nitric oxide production in patients with cirrhosis and spontaneous bacterial peritonitis.
Paine CH, Biggins SW, Pichler RH. Albumin in Cirrhosis: More Than a Colloid. *Curr Treat Options Gastroenterol* 2019; 17: 231-243 [PMID: 30968341 DOI: 10.1007/s11938-019-00227-4]

Terg R, Gadano A, Cartier M, Cacciato P, Lucero R, Muñoz A, Romero G, Levi D, Terg G, Miguez C, Abecasis R. Serum creatinine and bilirubin predict renal failure and mortality in patients with spontaneous bacterial peritonitis: a retrospective study. *Liver Int* 2009; 29: 415-419 [PMID: 19880387 DOI: 10.1111/j.1478-3231.2008.01877.x]

Poca M, Concepción M, Casas M, Alvarez-Urturi C, Gordillo J, Hernández-Gea V, Román E, Guarrner-Argete C, Gich I, Soriano G, Guarrner C. Role of albumin treatment in patients with spontaneous bacterial peritonitis. *Clin Gastroenterol Hepatol* 2012; 10: 309-315 [PMID: 22904025 DOI: 10.1016/j.cgh.2011.11.012]

Salerno F, Navickis RJ, Wilkes MM. Albumin infusion improves outcomes of patients with spontaneous bacterial peritonitis: a meta-analysis of randomized trials. *Clin Gastroenterol Hepatol* 2013; 11: 123-30.e1 [PMID: 23178229 DOI: 10.1016/j.cgh.2012.11.007]

Aithal GP, Palaniyappan N, China L, Hārmālâ S, Macken L, Ryan JM, Wilkes EA, Moore K, Leithhead JA, Hayes PC, O'Brien AJ, Verma S. Guidelines on the management of ascites in cirrhosis. *Gut* 2021; 70: 9-29 [PMID: 33067334 DOI: 10.1136/gutjnl-2020-321790]

de Araujo A, de Barros Lopes A, Rossi G, da Silva GV, Ananias P, Ness S, Alvaraes-da-Silva MR. Low-dose albumin in the treatment of spontaneous bacterial peritonitis: should we change the standard treatment? *Gut* 2012; 61: 1371-1372 [PMID: 22217507 DOI: 10.1136/gutjnl-2011-301739]

D’Amico G, Morabito A, D’Amico M, Pasta L, Malizia G, Rebora P, Valsecchi MG. Clinical states of cirrhosis and competing risks. *J Hepatol* 2018; 68: 563-576 [PMID: 29111320 DOI: 10.1016/j.jhep.2017.10.020]

Piano S, Angelini P. Bacterial Infections in Cirrhosis as a Cause or Consequence of Decompensation? *Clin Liver Dis* 2021; 25: 357-372 [PMID: 33838855 DOI: 10.1016/cld.2021.01.006]

Trebićka J, Fernandez J, Japp M, Caraceni P, Laleman W, Gambino C, Giovo I, Uschner FE, Jansen C, Jimenez C, Monkterje R, Gustot T, Albillos A, Bahares R, Jarcuska F, Steib C, Reiberger T, Acevedo J, Gatti P, Shawcross DI, Zouzou S, Zipprich A, Viane M, Capulti S, Berg T, Bruns T, Danielsen KV, Coenraad M, Merli M, Staubler R, Zoller H, Ramos JP, Solé C, Soriano G, de Gottardi A, Gronbaek H, Saliba F, Trautwein C, Kani HT, Francque S, Ryder S, Nahon P, Romero-Gomez M, Van Vlierberghe H, Francoz C, Manns M, Garcia-Lopez E, Tufoni M, Amoros A, Pavesi M, Sanchez C, Praktiknjo M, Curto A, Pitarch C, Putignano A, Moreno E, Bernal W, Aguilar F, Clara J, Ponzo P, Vitalis Z, Zachersini G, Balogh B, Gerbes A, Vargas V, Alessandria C, Bernardi M, Ginès P, Moreau R, Angelini P, Jalan R, Arroyo V; PREDICT STUDY group of the EASL-CLIF CONSORTIUM. PREDICT identifies precipitating events associated with the clinical course of acutely decompensated cirrhosis. *J Hepatol* 2021; 74: 1097-1108 [PMID: 33227330 DOI: 10.1016/j.jhep.2020.10.019]

Villanueva C, Albillos A, Genescà J, Garcia-Pagan JC, Brujats A, Calleja JL, Aracil C, Bahares R, Morillas RM, Poca M, Peñas B, Augustin S, Abraldes JG, Alvarado E, Torres F, Bosch J; Predesct Study Investigators. Bacterial infections adversely influence the risk of decompensation and survival in compensated cirrhosis. *J Hepatol* 2021; 75: 589-599 [PMID: 33905794 DOI: 10.1016/j.jhep.2021.04.022]

Caraceni P, Tufoni M, Zachersini G, Riggio O, Angelini P, Alessandria C, Neri S, Foschi FG, Levantesi F, Airoldi A, Simone L, Svegliati-Baroni G, Fagiuoli S, Lafridi G, Cozzolongo M, Ronchi R, Sangiovanni V, Morisco F, Toniutto F, Gasbarrini A, De Marco R, Piano S, Nardelli S, Elia C, Angeli P; ANSWER Study Investigators. On-treatment serum albumin level can guide long-term treatment in patients with cirrhosis and uncomplicated ascites. *J Hepatol* 2021; 74: 340-349 [PMID: 32853747 DOI: 10.1016/j.jhep.2020.08.021]

Baldassarre M, Naldi M, Zachersini G, Bartolletti M, Antognoli A, Laggetta M, Gigliardi M, Tufoni M, Domenciali M, Waterstradt K, Paterini P, Baldan A, Leoni S, Bartolini M, Viale P, Trevisani F, Bernardi M, Caraceni P. Determination of Effective Albumin in Patients with Cirrhosis: Clinical and Prognostic Implications. *Hepatology* 2021; 74: 2058-2073 [PMID: 33710623 DOI: 10.1002/hep.31798]

Guevara M, Terra C, Nazar A, Solá E, Fernández J, Pavesi M, Arroyo V, Ginès P. Albumin for bacterial infections other than spontaneous bacterial peritonitis in cirrhosis. A randomized, controlled study. *J Hepatol* 2012; 57: 759-765 [PMID: 22732511 DOI: 10.1016/j.jhep.2012.06.013]

Thévenot T, Bureau C, Oberti F, Anty R, Louvet A, Plessier A, Rudler M, Heurgue-Berlot A, Rosa I, Taibodec N, Tao D, Ozenne V, Carbonnel N, Cause X, Goria O, Minello A, De Ledingen VH, Amattheiu R, Barraud H, Nguyen-Khae E, Becker C, Paupard T, Botta-Fridlund D, Abdelli N, Guillemet F, Monnet E, Di Martino V. Effect of albumin in cirrhotic patients with infection other than spontaneous bacterial peritonitis. A randomized trial. *J Hepatol* 2015; 62: 822-830 [PMID: 25463345 DOI: 10.1016/j.jhep.2014.10.017]

Fernández J, Angelini P, Trebička J, Merli M, Gustot T, Alessandria C, Aagaard NK, de Gottardi A, Welzel TM, Gerbes A, Soriano G, Vargas V, Albillos A, Salerno F, Durand F, Bahares R, Stauber R, Prado V, Arteaga M, Hernández-Tejero M, Aziz F, Morando E, Jansen C, Lattanzio B, Moreno C, Campion D, Gronbaek H, Garcia R, Sánchez C, García E, Amorós A, Pavesi M, Clara J, Moreau R, Arroyo V. Efficacy of Albumin Treatment for Patients with Cirrhosis and Infections Unrelated to Spontaneous Bacterial Peritonitis. *Clin Gastroenterol Hepatol* 2020; 18: 963-973.e14 [PMID: 31394283 DOI: 10.1016/j.cgh.2019.07.055]

Mattos ÂZ, Leão GS, Mattos AA. Albumin for Infections Other Than Spontaneous Bacterial Peritonitis: Still Not an Answer. *Clin Gastroenterol Hepatol* 2020; 18: 1247-1248 [PMID: 31743756 DOI: 10.1016/j.cgh.2019.11.026]

Leão GS, John Neto G, Jotz RF, Mattos AA, Mattos ÂZ. Albumin for cirrhotic patients with extraportal infections: A meta-analysis. *J Gastroenterol Hepatol* 2019; 34: 2071-2076 [PMID: 31535630 DOI: 10.1111/jgh.14791]

Fernández J, Acevedo J, Prado V, Mercado M, Casto M, Pavesi M, Arteaga M, Sastre L, Juanaola A, Ginès P, Arroyo V. Clinical course and short-term mortality of cirrhotic patients with infections other than spontaneous bacterial peritonitis. *Liver Int* 2017; 37: 385-395 [PMID: 27558198 DOI: 10.1111/liv.13239]

John JA, de Mattos AA, da Silva Miozzo SA, Comerlato PH, Porto M, Contiero P, da Silva RR. Survival and risk factors related to death in outpatients with cirrhosis treated in a clinic in Southern Brazil. *Eur J Gastroenterol Hepatol* 2015; 27: 1372-1377 [PMID: 26426832 DOI: 10.1097/MEG.0000000000000480]
Hyponatraemia in cirrhotic patients with ascites. Hepatology 2004; 40: 802-810 [PMID: 15382176 DOI: 10.1002/hep.20405]

Bernardi M, Caraceni P. Novel perspectives in the management of decompensated cirrhosis. Nat Rev Gastroenterol Hepatology 2018; 15: 753-764 [PMID: 30026556 DOI: 10.1038/s41575-018-0045-2]

García-Martínez R, Caraceni P, Bernardi M, Gines P, Arroyo V, Jalan R. Albumin: pathophysiologic basis of its role in the treatment of cirrhosis and its complications. Hepatology 2013; 58: 1836-1846 [DOI: 10.1002/hep.26338]

Jalan R, Schnurr K, Mookejeree RP, Sen S, Cheshire L, Hodges S, Muravska V, Williams R, Matthews G, Davies NA. Alterations in the functional capacity of albumin in patients with decompensated cirrhosis is associated with increased mortality. Hepatology 2009; 50: 555-564 [PMID: 19642174 DOI: 10.1002/hep.22913]

Domenicali M, Baldassarre M, Giannone FA, Nalidi M, Mastroroberto B, Bisielli L, Lagatolla M, Patrono D, Bertucci C, Bernardi M, Caraceni P. Posttranscriptional changes of serum albumin: clinical and prognostic significance in hospitalized patients with cirrhosis. Hepatology 2014; 60: 1851-1860 [PMID: 25048618 DOI: 10.1002/hep.27322]

Bernardi M, Zacherlini G, Caraceni P. Pro: The Role of Albumin in Pre-Liver Transplant Management. Liver Transpl 2019; 25: 128-134 [PMID: 30346906 DOI: 10.1002/lt.25556]

WILKINSON P, SHERLOCK S. The effect of repeated albumin infusions in patients with cirrhosis. Lancet 1962; 2: 1125-1129 [PMID: 14000766 DOI: 10.1016/s0140-6736(62)90895-4]

Gentilini P, Casini-Raggi V, Di Fiore G, Romanelli RG, Buzzelli G, Pinzani M, La Villa G, Laffi G. Albumin improves the response to diuretics in patients with cirrhosis and ascites: a randomized, controlled trial. J Hepatol 1999; 30: 639-645 [DOI: 10.1016/S0140-6736(98)00194-9]

Romanelli RG, La Villa G, Barletta G, Vizzutti F, Lanini F, Arena U, Bodi V, Tarquini R, Pantaleo P, Gentilini P, Laffi G. Long-term albumin infusion improves survival in patients with cirrhosis and ascites: an unblinded randomized trial. World J Gastroenterol 2006; 12: 1403-1407 [PMID: 16552809 DOI: 10.3748/wjg.v12.i19.1403]

Solé E, Solé C, Simón-Talero M, Martín-Llali M, Castellote J, García-Martínez R, Moreira R, Torrens M, Mázquez F, Fábrellas N, de Prada G, Huelin P, López Benaiges E, Ventura M, Márquez M, Nazar A, Ariza V, Suhé P, Graupera I, Pose E, Colomenero I, Paisesi M, Guevara M, Navasa M, Xiol X, Córdoba J, Vargas V, Ginés P, Ginés P. MIDODRINE and albumin for prevention of complications in patients with cirrhosis awaiting liver transplantation. A randomized placebo-controlled trial. J Hepatol 2018; 69: 1250-1259 [PMID: 30138683 DOI: 10.1016/j.jhep.2018.08.006]

Caraceni P, Piggo O, Angelico M, Cacciola I, Elia G, Federico A, Massironi S, Guarisco R, Galioto A, Ballardini G, Rendina M, Nardelli S, Pasquale C, Pentassuglio I, Gioia S, Onori E, Frieri C, Salvatori FM, Merli M. No effect of albumin for prevention of early death. Metab Brain Dis 2021; 36: 609-617 [PMID: 32914468 DOI: 10.1111/j.1655-2425.2021.02014.x]

Fernández J, Claria J, Amorós A, Aguilar F, Castro M, Casulleras M, Acevedo J, Duran-Güell M, Nuñez L, Costa M, Chaves M, Álvarez-Diana C, Aagaard NK, Soriano G, Durand F, Gerbes A, Gómez S, Pereira G, Guevara M, Ginés P, Soriano G, Román E, Sánchez-Delgado J, Ferrer R, Nieto JC, Sunýé P, Fuentes I, Esteban R, Córdoba J. Effects of intravenous albumin treatment in decompensated cirrhosis (ANSWER Study Investigators). A randomized placebo-controlled trial. J Hepatol 2019; 71: 1184-1192 [PMID: 30905652 DOI: 10.1016/j.jhep.2019.03.021]

de Franchis R, Bosch J, García-Tsao G, Reiberger T, Ripoll C; Baveno VII Faculty. Baveno VII - Renewing consensus in the treatment of cirrhosis and its complications. J Hepatol 2018; 70: 2417-2429 [PMID: 29861076 DOI: 10.1016/S0168-8278(18)30840-7]

Sandi BB, Leão GS, de Mattos AA, de Mattos AZ. Long-term albumin administration in patients with cirrhosis and ascites: a meta-analysis of randomized controlled trials. J Gastroenterol Hepatol 2021; 36: 609-617 [PMID: 32914468 DOI: 10.1111/j.1655-2425.2021.02014.x]

Carravetta M, Aagaard NK, Soriano G, Durand F, Gerbes A, Gómez S, Pereira G, Guevara M, Ginés P, Soriano G, Román E, Sánchez-Delgado J, Ferrer R, Nieto JC, Sunýé P, Fuentes I, Esteban R, Córdoba J. Effects of intravenous albumin treatment in decompensated cirrhosis (ANSWER Study Investigators). A randomized placebo-controlled trial. J Hepatol 2019; 71: 1184-1192 [PMID: 30905652 DOI: 10.1016/j.jhep.2019.03.021]

China L, Freemantle N, Forrest E, Kallis Y, Ryder SD, Wright G, Portal AJ, Becares Salles N, Gilroy DW, O'Brien A; ATTIRE Trial Investigators. A Randomized Trial of Albumin Infusions in Hospitalized Patients with Cirrhosis. N Engl J Med 2021; 384: 808-817 [PMID: 33657293 DOI: 10.1056/NEJMoa221666]

Wright G, Jalan R. Ammonia and inflammation in the pathogenesis of hepatic encephalopathy: Pandora's box? Hepatology 2007; 46: 291-294 [PMID: 17616413 DOI: 10.1002/hep.21843]

Jalan R, Kapoor D. Reversal of diuretic-induced hepatic encephalopathy with infusion of albumin but not colloid. Clin Sci (Lond) 2004; 106: 467-474 [PMID: 14678008 DOI: 10.1042/CS20030357]

Simón-Talero M, García-Martínez R, Torrens M, Augustin S, Gómez S, Pereira G, Guevara M, Ginés P, Soriano G, Román E, Sánchez-Delgado J, Ferrer R, Nieto JC, Sunýé P, Fuentes I, Esteban R, Córdoba J. Effects of intravenous albumin on hepatic encephalopathy in patients with cirrhosis and episodic hepatic encephalopathy: a randomized double-blind study. J Hepatol 2013; 59: 1184-1192 [PMID: 23872605 DOI: 10.1016/j.jhep.2013.07.020]

Sharma BC, Singh J, Srivastava S, Sangam A, Mantri AK, Trehanpati N, Sarin SK. Randomized controlled trial comparing lactulose plus albumin versus lactulose alone for treatment of hepatic encephalopathy. J Gastroenterol Hepatol 2017; 32: 1234-1239 [PMID: 27885712 DOI: 10.1111/j.1650-0692.2016.13666]

Is B, Bombassarro IZ, Torov CV, de Mattos AZ, Ahlert M, Chiesa T, de Mattos AA. Albumin in the management of hepatic encephalopathy: A systematic review and meta-analysis. Ann Hepatol 2021; 26: 100541 [DOI: 34600143 DOI: 10.1016/j.annhep.2021.100541]

Riggio O, Nardelli S, Pasquale C, Pentassuglio I, Gioia S, Onori E, Frieri C, Salvatori FM, Merli M. No effect of albumin infusion on the prevention of hepatic encephalopathy after transjugular intrahepatic portosystemic shunt. Metab Brain Dis 2016; 31: 1275-1281 [PMID: 26290375 DOI: 10.1007/s11011-015-9713-x]

McCormick PA, Mistry P, Kaye G, Burroughs AK, McIntyre N. Intravenous albumin infusion is an effective therapy for hyponatraemia in cirrhotic patients with ascites. Gut 1990; 31: 204-207 [PMID: 2311979 DOI: 10.1136/gut.31.2.204]
94 Jalan R, Mookerjee R, Cheshire L, Williams R, Davies N. Albumin infusion for severe hyponatremia in patients with refractory ascites: a randomized clinical trial. J Hepatol 2007; 46 Suppl 1: S95 [DOI: 10.1016/s0168-8278(07)61830-3]

95 Bajaj JS, Tandon P, O’Leary JG, Biggins SW, Wong F, Kamath PS, Garcia-Tsao G, Malaiakkal B, Lai JC, Fallon M, Thuluvath P, Vargas HE, Subramanian RM, Thacker LR, Reddy RK. The Impact of Albumin Use on Resolution of Hyponatremia in Hospitalized Patients With Cirrhosis. Am J Gastroenterol 2018; 113: 1339 [PMID: 29880972 DOI: 10.1038/s41395-018-0119-3]

96 Shasothy SM, Kumar M, Khamuckham JS, Sarin SK. Changes in cardiac output and incidence of volume overload in cirrhotics receiving 20% albumin infusion. Liver Int 2017; 37: 1167-1176 [PMID: 28135785 DOI: 10.1111/liv.13375]

97 Bortoluzzi A, Ceolotto G, Gola E, Sticca A, Bova S, Morando F, Piano S, Fasolato S, Rosi S, Gatta A, Angeli P. Positive cardiac inotropic effect of albumin infusion in rodents with cirrhosis and ascites: molecular mechanisms. Hepatology 2013; 57: 266-276 [PMID: 22911662 DOI: 10.1002/hep.26021]

98 Jagdish RK, Maras JS, Sarin SK. Albumin in Advanced Liver Diseases: The Good and Bad of a Drug! Hepatology 2021; 74: 2848-2862 [PMID: 33772846 DOI: 10.1002/hep.31836]

99 Caraceni P, O’Brien A, Gines P. Long-term albumin treatment in patients with cirrhosis and ascites. J Hepatol 2022; 76: 1306-1317 [PMID: 35589252 DOI: 10.1016/j.jhep.2022.03.005]

100 Caraceni P, Domenicali M, Tovoli A, Napoli L, Ricci CS, Tufoni M, Bernardi M. Clinical indications for the albumin use: still a controversial issue. Eur J Intern Med 2013; 24: 721-728 [PMID: 23790570 DOI: 10.1016/j.ejim.2013.05.015]

101 Runken MC, Caraceni P, Fernandez J, Zipprich A, Carlton R, Bunke M. The cost-effectiveness of albumin in the treatment of decompensated cirrhosis in Germany, Italy, and Spain. Health Econ Rev 2019; 9: 22 [PMID: 31278624 DOI: 10.1186/s13561-019-0237-7]
