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Albumin in Cirrhosis: More Than a Colloid

Cary H. Paine, MD[1,*]
Scott W. Biggins, MD[2,3]
Raimund H. Pichler, MD[1]

Address
[*,1]Division of Nephrology (Kidney-Liver Program), Department of Medicine, University of Washington, 356521, 1959 NE Pacific Street, Seattle, WA, 98195-6521, USA
Email: chpaine@uw.edu
[2]Division of Gastroenterology, Department of Medicine, University of Washington, Seattle, WA, USA
[3]Center for Liver Investigation Fostering discovEry (C-LIFE), University of Washington, Seattle, WA, USA

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Abstract

Purpose of review Albumin has repeatedly been shown to be beneficial in treating patients with decompensated cirrhosis. We reviewed the medical literature regarding indications for the use of intravenous albumin in cirrhosis, with particular focus on the ways in which albumin can help mitigate hepatorenal physiology.
Recent findings Albumin has long been used as the preferred agent for volume expansion in patients with decompensated cirrhosis. It is used in conjunction with vasoconstrictors for the treatment of type 1 hepatorenal syndrome, and in combination with antibiotics for the treatment of spontaneous bacterial peritonitis. When given at the time of large volume paracentesis, albumin is known to help reduce the incidence of post-paracentesis circulatory dysfunction. Recently, albumin has been shown to improve outcomes in hospitalized patients with cirrhosis and hyponatremia, and has also shown promise in reducing mortality and hospitalizations in outpatients with both diuretic resistant and uncomplicated ascites. It is increasingly clear that these benefits derive from a combination of the oncotic and non-oncotic properties of albumin, and from the effects of albumin administration on effective arterial blood volume.
Summary Albumin is an effective treatment for multiple complications encountered in patients with decompensated cirrhosis.

Introduction

In this review, we will outline the physiologic basis for the beneficial effects of albumin in patients with cirrhosis, examine the many, exciting applications for albumin that have emerged in recent years, and share observations from our clinical practice where relevant. Over the last several decades, administration of intravenous human albumin has become an invaluable tool in the treatment of patients with decompensated cirrhosis; however, the medical use of albumin long predates its application in liver disease.

Therapeutic infusion of human albumin was initially pioneered by the United States Military Human Albumin Program [1]. Albumin was first used in 1940 at Walter Reed Hospital in the treatment of a young man with hypovolemic shock, then subsequently administered to a cohort of seven soldiers who had sustained severe burn injuries at Pearl Harbor. The following decades brought growing interest in the use of albumin as an intravenous resuscitation fluid. In 1975, Dr. John Skillman and his colleagues at Beth Israel Deaconess Hospital in Boston, MA, published the first randomized controlled trial using human albumin, in which they demonstrated a positive correlation between circulating albumin mass and colloid oncotic pressure, as well as an increase in colloid oncotic pressure following infusion of albumin as compared with isotonic crystalloid solutions [2]. A link between serum albumin level and mortality was established in the 1990s, and thereafter, many studies proposed using intravenous albumin administration as a way to help mitigate this mortality risk in various patient populations [3].

Enthusiasm for the therapeutic use of albumin was tempered considerably in 1998, when the Cochran Injuries Group released their report of a systematic review of 30 randomized controlled trials examining the use of human albumin in critically ill patients [4]. They observed that albumin use was associated with an increased risk of mortality of approximately 6%; increased risk was observed in all subgroups analyzed, including patients with burn injuries and hypoproteinemia. Notably absent from the review were any studies focusing specifically on patients with decompensated cirrhosis; thus, when the FDA issued a "Dear Doctor" letter in August of 1998 urging "treating physicians to exercise discretion in use of albumin," there was no mention of cirrhotic patients as a distinct population with potentially different risks and benefits as it pertains to albumin administration [5].

In the ensuing 20 years, there have been several additional studies looking at the benefits of albumin in diverse populations of critically ill patients, and results have been mixed. The SAFE trial, published in 2004, demonstrated no difference in mortality between those given crystalloid and those given albumin for volume resuscitation in the intensive care unit [11]. In response, the FDA issued a follow-up to its earlier letter, noting that the trial "resolved the prior safety concerns raised by the Cochrane Injuries Group in 1998" [12]. In 2014, results of the ALBIOS trial were reported, examining albumin versus crystalloid in patients with severe sepsis [13]. No difference in mortality was observed; however, post hoc subgroup analyses did appear to hint at a mortality benefit for albumin-treated patients with septic shock. Thus, the most recent iteration of the international Surviving Sepsis Guidelines offers the "weak recommendation" that albumin be used in addition to crystalloids "when patients require substantial amounts of crystalloids"; however, overall enthusiasm for the use of albumin in broadly defined cohorts has waned [14].

This stands in stark contrast to the rapidly expanding body of literature on the benefits of albumin in patients with cirrhosis (Table 1). The physiology of decompensated cirrhosis is unique, such that cirrhotic patients represent a distinct phenotypic subgroup with specific challenges requiring targeted interventions that may not be generalizable to non-cirrhotic patients. Administration of intravenous albumin appears to be one of the most effective means for manipulating cirrhotic physiology, and has repeatedly been shown to improve outcomes in cirrhotic patients, so much so that in recent years, albumin has been embraced as a potential "disease modifying treatment in patients with decompensated cirrhosis" [10••]. Herein, we outline how intravenous albumin, in cirrhosis, is more than a mere colloid.

Table 1. Benefits of albumin administration for complications of decompensated cirrhosis

Indication	Benefit of albumin	Dosing regimen
Type 1 hepatorenal syndrome	1. Preferred agent for volume expansion in the diagnostic phase 2. Improves renal function and decreases mortality when given in conjunction with vasoconstrictors	1. Diagnosis: 1 g/kg per day (up to 100 g per day) for 48 h 2. Treatment: 20–40 g per day in conjunction with vasoconstrictor therapy [6, 7]
Diuretic-resistant ascites and type 2 hepatorenal syndrome	Recently shown to decrease mortality and hospitalizations	20 g twice weekly, given in the outpatient setting [8••]
Prevention of post-paracentesis circulatory dysfunction	Reduces the incidence of procedure-associated acute kidney injury and electrolyte abnormalities when given at the time at large volume paracentesis	6–8 g per liter of ascitic fluid removed when removing more than 5 L. (Use of albumin controversial when less than 5 L) [6, 7]
Hyponatremia in cirrhosis	Recently associated with resolution of hyponatremia and decreased mortality in a retrospective analysis	Optimal dosing not known [9••]
Spontaneous bacterial peritonitis	Decreases incidence of acute kidney injury and mortality when given in conjunction with antibiotics	1.5 g/kg on day 1 followed by 1 g/kg on day 3 [53]
Cirrhosis with uncomplicated ascites	Decreases mortality, hospitalizations, and incidence of cirrhosis-associated complications	40 g twice weekly for 2 weeks, then 40 g weekly, given in the outpatient setting. [10••]

Properties of albumin: oncotic and non-oncotic effects

Albumin is a 66.5-kDa protein produced exclusively in the liver and degraded in a variety of tissues at a rate of roughly 9–14 g per day [15]. Human serum albumin is the most abundant protein in plasma, and hypoalbuminemia has long been associated with edematous states such as cirrhosis and the nephrotic syndrome. With respect to intravascular fluid balance, albumin is most well-known for its contribution to the capillary oncotic pressure, first described by Starling in 1896 [16]. In recent years, understanding of these classical opposing forces has evolved considerably. Albumin does indeed account for approximately 75–80% of colloid oncotic pressure; however, the maintenance of intravascular fluid balance is far more complicated than initially thought, related as much to the health of the vascular endothelium as to the inwardly directed oncotic force exerted by albumin [17]. A functional vascular barrier relies on the interaction between plasma proteins like albumin and the endothelial glycocalyx layer; when the plasma albumin concentration drops to a critically low level, as in inflammatory conditions like cirrhosis and sepsis, the vascular barrier ceases to function properly and fluid extravasation can occur [18].

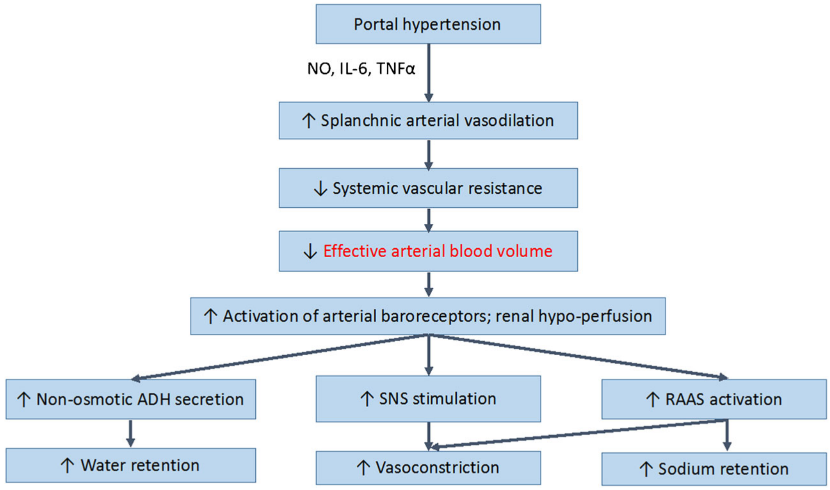

Fig. 1. The physiology of decompensated cirrhosis. NO, nitric oxide; IL-6, interleukin 6; TNFα, tumor necrosis factor alpha; ADH, antidiuretic hormone; SNS, sympathetic nervous system; RAAS, renin-angiotensin-aldosterone system.

Albumin has many notable effects that extend beyond its role in maintaining fluid balance. Albumin binds to a number of small solutes including, but not limited to, bilirubin, glucose, calcium, and magnesium [15]. Variation in the serum albumin concentration can therefore have significant implications for maintenance of stable serum electrolyte concentrations and for clearance of albumin bound toxins via either the kidney or renal replacement therapy. (Note that this is the principle behind the use of albumin in extracorporeal liver support devices such as the Molecular Adsorbent Recirculating System, a very promising use of albumin in liver disease that is beyond the scope of this review.) Additionally, albumin binds many exogenous substances, including loop diuretics and multiple antibiotics, which can significantly impact the bioavailability of these medications in patients with cirrhosis [19–21].

Perhaps most relevant with respect to cirrhotic physiology, albumin has several potent anti-inflammatory effects [22]. Albumin is a well-established antioxidant, deriving from its ability to bind iron and copper [23–25]. It also acts as a scavenger of reactive oxygen and nitrogen species, including nitric oxide (NO), which has repeatedly been shown to play a critical role in the causal pathway of decreased systemic vascular resistance (SVR) in advanced cirrhosis, as discussed below [23, 25]. All told, the combined effect of these non-oncotic properties of albumin is arguably just as important as its oncotic properties in the treatment of patients with cirrhosis.

The physiology of decompensated cirrhosis

Nowhere are the benefits of albumin as clearly demonstrated as in the treatment of disorders of hepatorenal physiology, by which we intend to refer to the constellation of clinical complications resulting from abnormal kidney function in the setting of cirrhosis. This includes type 1 hepatorenal syndrome (HRS), the most well-defined clinical entity on the spectrum of hepatorenal physiology, but is not limited to this severe and relatively rare complication. Diuretic-resistant ascites and the less well-defined type 2 HRS, post-paracentesis circulatory dysfunction (PCD), and even hypervolemic hyponatremia can all be viewed as different clinical phenotypes on the hepatorenal spectrum, and any discussion about the therapeutic role of albumin administration in cirrhosis must be predicated on a thorough understanding of this complex underlying physiology.

The development of portal hypertension is the sentinel event from which most downstream cirrhotic complications follow (Fig. 1). Portal hypertension leads to splanchnic arterial vasodilation and the local release of endogenous vasodilators such as NO, inflammatory cytokines like interleukin-6 (IL-6) and tumor necrosis factor alpha (TNFα), and endogenous cannabinoids [26–29]. The systemic activity of these various substances, combined with increased translocation of enteric bacteria across a weakened intestinal epithelium, leads to a decrease in systemic vascular resistance resulting in a lack of effective arterial blood volume (EABV), the hallmark of circulatory dysfunction in decompensated cirrhosis [30, 31].

Lack of EABV leads to renal hypo-perfusion and the stimulation of carotid baroreceptors, which, in turn, trigger the upregulation of various compensatory mechanisms including the sympathetic nervous system, the renin-angiotensin-aldosterone system (RAAS), and the non-osmotic release of antidiuretic hormone (ADH). The aggregate effect of these physiologic responses is arteriolar vasoconstriction, including in the kidney microvasculature, and decreased renal sodium and water excretion, which can help to maintain circulatory integrity by increasing EABV up to a point. When the ability of these compensatory mechanisms to increase EABV is overwhelmed, either due to progression of the underlying liver disease or to a superimposed complication such as infection, intravascular volume depletion, bleeding, or cirrhotic cardiomyopathy, the result is a cascade of events characterized by worsening hypotension, electrolyte abnormalities, fluid overload, kidney failure, shock, and ultimately death [32, 33]. As such, any intervention that can help to preserve EABV may be beneficial in preventing or delaying the downstream consequences of worsening hepatorenal physiology, and it is precisely via this mechanism that albumin has proven uniquely beneficial in the treatment of each of these individual hepatorenal complications [34].

Albumin for the diagnosis and treatment of type 1 hepatorenal syndrome

Albumin serves as a critical tool in both the diagnosis and treatment of type 1 HRS. As outlined above, type 1 HRS is caused by lack of EABV leading to a functional prerenal state [31]. Therefore, the first step in differentiating HRS from cases of potentially reversible prerenal azotemia—as occurs in instances of volume depletion from over-diuresis, for example—is a trial of volume expansion. International guidelines recommend against the routine use of crystalloid in suspected cases of HRS, and instead advocate a trial of volume expansion with intravenous albumin, administered at a dose of 1 g per kg of body weight per day for two consecutive days [6, 7]. Only those cases that fail to reverse with volume administration remain potentially consistent with HRS.

Following volume expansion, the mainstay of treatment for type 1 HRS is vasoconstrictor therapy, the particulars of which are beyond the scope of this review; however, all available evidence suggests that any vasoconstrictor regimen should be given in conjunction with daily infusions of intravenous albumin. A recent meta-analysis identified 13 randomized controlled trials comparing various vasoconstrictor regimens for the treatment of type 1 HRS, comprised primarily of terlipressin, norepinephrine, or the combination of midodrine and octreotide, against either an alternate vasoconstrictor regimen or placebo [35]. Every treatment arm studied also included the administration of intravenous albumin, typically at a dose of 20–40 g per day. At our institution, our practice is to administer 25% albumin 25 g daily in conjunction with either continuous infusion of norepinephrine or the combination of oral midodrine and subcutaneous octreotide, as terlipressin remains unavailable in the USA.

Only rarely has the inclusion of albumin in therapeutic regimens for the treatment of type 1 HRS been tested. In 2003, Ortega et al. published results of a non-randomized study in which patients were treated either with terlipressin alone or terlipressin plus albumin [36]. Patients in the terlipressin plus albumin group demonstrated a remarkable improvement in serum creatinine, such that 77% had a complete response to therapy, compared with only 25% in the terlipressin alone group. Moreover, at the end of treatment, patients in the albumin group were noted to have significantly lower serum aldosterone levels and a marked decrease in plasma renin activity when compared to pretreatment serum levels. A similar effect was not demonstrated in the terlipressin alone group, suggesting that the inclusion of albumin was responsible for decreased RAAS activation, likely via improvement in EABV and enhanced renal perfusion.

Interestingly, it appears that the effects of albumin on EABV in HRS stem as much from albumin's non-oncotic properties as from its contribution to colloid oncotic pressure. Perhaps most compelling is the work of Brinch and colleagues, in which it was recapitulated that administration of intravenous albumin increases total plasma volume and decreases plasma renin activity and plasma aldosterone concentrations, suggesting an improvement in EABV [37]. The increase in total plasma volume was noted to be proportional to the oncotic load delivered. Interestingly, albumin administration was associated with more profound decreases in plasma renin activity and aldosterone concentrations in patients with more severe cirrhosis, despite having less of an impact on plasma volume expansion in this patient group. This would suggest that the increase in EABV appears to be independent of plasma volume expansion and at least in part secondary to albumin's non-oncotic properties.

Albumin for type 2 hepatorenal syndrome and diuretic-resistant ascites

Type 2 HRS is a less well-defined clinical syndrome than its type 1 counterpart; however, it is generally agreed upon that patients with type 2 HRS have similar underlying physiology but less severe renal dysfunction and slower progression. Type 2 HRS is frequently associated with diuretic-resistant ascites, which results from increased renal salt and water retention as discussed above [38]. There are few effective treatment strategies for patients with type 2 HRS, owing in part to its more nebulous phenotype. One study of patients with type 2 HRS, all of whom were awaiting liver transplant, compared treatment with terlipressin plus albumin against standard medical therapy. Sixty-one percent of patients in the treatment arm responded to therapy, but more than half relapsed after treatment withdrawal, and there was no difference in mortality or renal outcomes post-liver transplant when compared with those who did not receive terlipressin and albumin [39]. This data is consistent with prior trials showing some limited success in reversing renal dysfunction with vasoconstrictors and albumin, but a high rate of relapse after treatment withdrawal [40]. Accordingly, use of vasoconstrictors for the treatment of type 2 HRS has not been widely adopted, and there is interest in exploring more sustainable, long-term treatments for this challenging subset of patients.

To this end, Di Pascoli and colleagues recently published some very compelling data demonstrating improved outcomes in patients with diuretic-resistant ascites who were administered twice weekly infusions of human albumin, 20 g per dose, in the outpatient setting [8••]. When compared against standard medical care, the patients who received albumin had significantly lower 2-year mortality and fewer hospitalizations. Incidence of encephalopathy, ascites, spontaneous bacterial peritonitis (SBP), and non-SBP infections was all lower in the albumin group, and there was a non-statistically significant trend towards better renal function in the treatment group. It remains to be seen whether this benefit will extend to patients with abnormal renal function; however, these results are particularly alluring given the relatively low burden of twice weekly outpatient infusions when viewed in the context of the prolonged clinical course, and frequent hospital readmission rates, that is typical of patients with diuretic-resistant ascites and type 2 HRS.

It is worth noting briefly that data showing a benefit of albumin in the management of diuretic-resistant ascites with hepatorenal physiology is consistent with our experience using intravenous albumin to help augment diuresis in patients that have proven refractory to conventional doses of loop diuretics, as well as in those who have demonstrated worsening kidney function in the face of active diuresis. The strategy of co-administration of loop diuretics and albumin has been shown to improve urinary sodium excretion and diuresis in patients with cirrhosis and other hypoalbuminemic states, most notably nephrotic syndrome [41–43]. At our institution, we frequently administer 12.5 g of 25% albumin in conjunction with each dose of intravenous diuretics in patients that have cirrhosis, volume overload, and acute kidney injury.

Albumin for prevention of post-paracentesis circulatory dysfunction

Post-paracentesis circulatory dysfunction (PCD), characterized by worsening hypotension and renal dysfunction following large volume paracentesis (LVP), is, at its essence, an accelerated hepatorenal phenotype. This well-defined clinical entity is relatively common, with some degree of hemodynamic worsening occurring in approximately 75% of patients after LVP, and renal dysfunction occurring in up to 20% of patients [44]. Ruiz del Arbol and colleagues demonstrated clearly that patients with PCD have a decrease in systemic vascular resistance and a marked increase in plasma renin activity and plasma norepinephrine concentrations, suggesting that paracentesis induces abrupt fluid shifts leading to a precipitous decline in EABV followed by stimulation of the same compensatory response mechanisms seen in HRS [45]. The administration of colloid volume expanders has long been known to decrease the incidence of PCD, and albumin has consistently been shown to be superior to synthetic colloids in preventing this complication [46, 47]. Indeed, international guidelines explicitly advocate the use of intravenous albumin for volume expansion post-paracentesis, at a dose of 6–8 g of albumin for every liter of ascitic fluid removed [6, 7].

The seminal study demonstrating a benefit from intravenous albumin in preventing PCD was published in 1988, and hints at the mechanism by which albumin exerts its beneficial effect [44]. Gines et al. observed 105 patients undergoing LVP who were randomly allocated to receive either 40 g of intravenous albumin after paracentesis or standard medical care without colloid infusion. In the non-albumin group, paracentesis was not surprisingly associated with worsening renal function, a decrease in serum sodium level suggesting increased stimulation of ADH, and an increase in plasma renin and aldosterone concentrations suggesting RAAS activation. In contrast, those patients who received albumin did not demonstrate any change in renal function, serum sodium level, plasma renin activity, or aldosterone concentration suggesting that albumin is capable of preserving EABV even in instances of rapid fluid shifting as occurs after LVP. No difference in mortality was noted in this study; however, a subsequent meta-analysis did conclude that albumin administration after LVP was associated both with decreased morbidity and mortality [48].

Albumin for treatment of hyponatremia in cirrhosis

Some of the most exciting recent data with the broadest potential for clinical benefit in cirrhotic patients relates to the use of intravenous albumin for the treatment of hyponatremia. Hyponatremia is a common and very serious complication of decompensated cirrhosis. Given that the development of hyponatremia in cirrhotic patients extends from the same hepatorenal physiology as the development of HRS, it makes logical sense to employ similar therapeutic interventions for its treatment. In recent years, data has emerged that vasoconstrictors like midodrine and octreotide may have a role in treating hyponatremia in cirrhosis [49]. Similarly, administration of intravenous albumin has been suggested as a potentially beneficial intervention, a benefit that extends "predominantly from the restoration of intravascular volume" [50].

In a recent retrospective analysis of a cohort of hospitalized patients with cirrhosis, Bajaj and colleagues demonstrated that albumin administration was associated with better clinical outcomes, including higher rates of hyponatremia resolution and improved 30-day survival [9••]. This observation held true despite the fact that patients who received intravenous albumin appear to have had more severe disease, with higher average Model for End

Stage Liver Disease scores, lower serum sodium levels, and higher serum creatinine concentrations. The authors clearly note that albumin is likely to improve hyponatremia via both oncotic and non-oncotic mechanisms, and we believe that this is true; the sum total of albumin's unique properties leads to improved EABV and decreased secretion of ADH. As we have written elsewhere, this study is entirely consistent with our clinical experience in caring for cirrhotic patients with hyponatremia, and we now routinely use intravenous albumin in the treatment of this challenging complication [51].

Albumin use in the treatment of cirrhosis-associated infections

The use of albumin in the setting of cirrhosis-associated infections warrants special mention. Indeed, intravenous administration of large doses of human albumin for patients with SBP is one of the most well studied and widely adapted uses for albumin, and is strongly supported by international guidelines [52]. This treatment approach was elegantly studied in the work of Sort et al., a randomized controlled trial published in 1999, in which patients with documented SBP were given either antibiotics alone or antibiotics plus albumin on days 1 and 3 after diagnosis [53]. Patients in the albumin group were noted to have a decrease in plasma renin activity, as well as a marked reduction in both renal impairment and death. The authors went on to show that the development of renal dysfunction correlated strongly with an increase in plasma renin activity, confirming that RAAS activation parallels the development of acute kidney injury (AKI) in the setting of SBP, and that this can be mitigated by the administration of intravenous albumin. Elsewhere, a similar benefit has also been demonstrated in cirrhotic patients with non-SBP infections [54, 55].

The use of albumin for treatment of cirrhosis-associated infections effectively highlights the uniquely beneficial non-oncotic properties of albumin. SBP is associated with increased concentrations of several endogenous vasodilators known to exacerbate hemodynamic compromise in decompensated cirrhosis [56, 57]. To observe the effects of albumin administration on concentrations of these inflammatory mediators, Chen and colleagues randomized patients with SBP to receive either antibiotics or antibiotics plus albumin, then measured levels of NO, IL-6, and TNFα on days 1 and 6 after treatment. Albumin administration was associated with significantly lower levels of all inflammatory mediators in both the serum and ascitic fluid. Elsewhere, it has been demonstrated that improvement in NO and inflammatory cytokine concentrations in the setting of SBP is associated with improvement in circulatory function, as determined by an increase in mean arterial pressure and SVR, as well as an improvement in renal function [57].

The future: albumin as a disease-modifying agent in cirrhosis

With so many clinical indications for the use of albumin in specific subpopulations of cirrhotic patients, it is worth asking whether albumin might prove beneficial in more broadly defined cohorts. With this in mind, Caraceni et al. recently published the results of an 18-month randomized controlled trial in which they enrolled 440 patients with cirrhosis and uncomplicated ascites to receive either standard medical treatment or standard medical treatment plus weekly outpatient infusions of albumin, 40 g per dose [10••]. The authors demonstrated that albumin administration improves overall survival, reduces the incidence of cirrhosis-related complications, and significantly reduces hospitalizations. Furthermore, they recommend consideration of albumin as a potential "disease modifying treatment in patients with cirrhosis." It should be noted that the participants enrolled in this trial had considerably less severe disease than cohorts from prior studies of albumin use in cirrhosis. As such, the generalizability of these findings is broad, and the number of patients that seek to benefit is large. We find this data compelling and very exciting—rarely has such a low-risk intervention shown as much promise in the treatment of this complex patient population.

Conclusion

Liver transplantation remains the only long-term treatment for patients with decompensated cirrhosis. Pretransplant care should therefore be focused on enhancing quality of life and improving overall clinical stability. The complex nature of cirrhotic physiology makes this a challenging task, particularly as the underlying liver disease progresses and the downstream effects of advanced organ dysfunction mount, and clinicians are equipped with a woefully limited set of tools with which to work. Fortunately, intravenous albumin has emerged over the last few decades as a potential treatment for a long and growing list of complications frequently encountered in decompensated cirrhosis. In recent years, albumin has been shown not only to improve symptom management but also to reduce hospitalizations, limit end organ damage, and even improve mortality. The benefits of albumin stem from its unique ability to alter the complex circulatory dysfunction seen in hepatorenal physiology, which helps to explain why albumin appears beneficial in cirrhotic patients while simultaneously having a rather limited application elsewhere in medicine. We look forward to future studies in which we eagerly anticipate that the benefits of albumin will be extended to even more patients with cirrhosis.

Compliance with Ethical Standards

Conflict of Interest

Cary H. Paine declares that he has no conflict of interest. Scott W. Biggins declares that he has no conflict of interest. Raimund H. Pichler declares that he has no conflict of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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