

# Should albumin be used in all patients with spontaneous bacterial peritonitis?

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Patients with cirrhosis who develop spontaneous bacterial peritonitis (SBP) have been reported to experience a high incidence of renal impairment and mortality. Renal dysfunction is possibly related to altered systemic hemodynamics that leads to decreased effective arterial blood volume. Albumin, a plasma volume expander, has been investigated to determine whether it plays a role in patients with SBP. The current literature suggests that albumin can reduce renal impairment and mortality in high-risk SBP patients, defined as patients with a serum bilirubin level of greater than 68.4 µmol/L, a blood urea nitrogen level of greater than 10.7 mmol/L or a serum creatinine level greater than 88.4 µmol/L. The rationale for albumin and other volume expanders in SBP is discussed, accompanied by a review of the current literature.

**Key Words:** Albumin; Ascites; Colloid; SBP; Spontaneous bacterial peritonitis; Volume expansion

Spontaneous bacterial peritonitis (SBP) is a common but treatable complication of decompensated cirrhosis. Translocation of bacteria and endotoxins from the gastrointestinal tract to peritoneal fluid is believed to be a key mechanism behind the development of SBP, and is facilitated by impaired defensive mechanisms in cirrhotic patients (1). Third-generation cephalosporins are currently the antibiotic of choice for SBP because they are active against a broad spectrum of pathogenic organisms, are relatively well tolerated and have been confirmed to afford high rates of SBP resolution (2). Despite the discovery of effective antibiotic treatments, renal failure frequently occurs and is an independent predictor of mortality in these patients (3). Renal dysfunction may be partly secondary to reduced effective circulating volume.

Albumin is the most abundant protein in the human circulatory system. Its physiological functions include maintenance of osmotic pressure, binding and transport of various ligands, and antioxidant and anti-inflammatory effects (4). Albumin has established roles as an adjunct to diuretics to improve delivery and action of diuretics in the kidneys, and in the prevention of circulatory impairment after large-volume paracentesis (5,6). Albumin is believed to be effective in these scenarios because of its ability to improve intravascular volume and bind proinflammatory molecules. The present systematic review examines whether albumin has a role as an adjunct to antibiotics in the management of patients with SBP.

## LITERATURE SEARCH

A systematic search was conducted to retrieve high-quality, peer-reviewed studies of albumin in patients with SBP. The PubMed, Medline(R), and EMBASE databases were searched with text ("albumin", "sbp", "spontaneous bacterial peritonitis", "hepatorenal", and "volume expansion") and EMTREE terms ("albumin" and "bacterial peritonitis"). An electronic search of the abstracts available online from annual congresses of the American Gastroenterological Association (2008 to 2010), United European Gastroenterology Federation (2006 to 2009), American Association for the Study of

Est-ce que tous les patients atteints d'une péritonite bactérienne spontanée devraient recevoir de l'albumine ?

Les patients cirrhotiques qui contractent une péritonite bactérienne spontanée (PBS) présentent une incidence élevée d'atteinte rénale et de mortalité. La dysfonction rénale peut être liée à une altération de l'hémodynamique systémique qui entraîne une diminution du volume sanguin artériel efficace. Les auteurs ont exploré si l'albumine, un soluté de remplissage plasmatique, joue un rôle chez les patients ayant une PBS. D'après les publications, l'albumine peut réduire l'atteinte rénale et la mortalité chez les patients atteints de PBS à haut risque, soit ceux dont le taux de bilirubine sérique est supérieur à 68,4 µmol/L, dont le taux d'azote uréique est dans le sang est de plus de 10,7 mmol/L ou dont le taux de créatinine sérique supérieur à 88,4 µmol/L. Les auteurs exposent la raison d'utiliser l'albumine et d'autres solutés de remplissage en cas de PBS et procèdent à une analyse bibliographique.

Liver Diseases (2008 to 2009) and Canadian Association of Gastroenterology (2006 to 2010) was also performed. Results were limited to English-language publications.

## PATHOPHYSIOLOGY OF RENAL FAILURE IN SBP

Despite the resolution of SBP, persistent alteration in systemic hemodynamics can lead to severe kidney failure and death. One study (7) found higher levels of inflammatory cytokines, interleukin-6 and tumour necrosis factor-alpha in the plasma and ascitic fluid of cirrhotic patients with SBP than in similar noninfected controls. Nitric oxide production is usually increased in patients with cirrhosis, and higher circulating levels have been found in patients with poorer hepatic function (8). It is believed that bacterial endotoxins and inflammatory cytokines lead to increased nitric oxide production in the systemic circulation via bacterial translocation, impaired hepatic clearance and portosystemic shunting. This worsens arterial vasodilation, causing decreased effective perfusion of the kidneys (9). Renal impairment occurs in patients with higher levels of cytokines in plasma and ascitic fluid, and is associated with marked activation of the renin-angiotensin system (7).

There are many mechanisms by which albumin may improve circulatory function and arterial perfusion. Albumin binds substances that potentially have cardiac-suppressing effects such as tumour necrosis factor-alpha and nitric oxide (10,11). Fernandez et al (12) measured different hemodynamic parameters before administration of albumin in patients with SBP and compared it with measurements after resolution of infection. They found that albumin administration improved systemic hemodynamics and prevented deterioration of renal function. Significant improvements in right atrial pressure, pulmonary artery pressure and capillary pulmonary pressure, as well as large decreases in plasma renin levels, suggest that albumin administration resulted in sustained expansion of the central blood volume. Increases in left ventricular systolic volume and ventricular stroke work index reflect improved cardiac output and increased effective arterial perfusion (12). Despite deactivation of the renin-angiotensin system, systemic

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**TABLE 1**  
**Studies evaluating standard dose albumin as an adjunctive treatment in spontaneous bacterial peritonitis (SBP)**

Author (ref), year	Subjects	Intervention/groups studied	Study type	Results
Sort et al (13), 1999	Cirrhotic patients with SBP (n=126)	Cefotaxime alone or cefotaxime plus albumin infusion (1.5 g/kg body weight within 6 h of diagnosis, 1.0 g/kg on day 3)	RCT	Patients given albumin had decreased incidence of renal failure (10% versus 33%; P=0.002), and decreased mortality rate (10% versus 29%; P=0.01)
Xue et al (14), 2002	Cirrhotic patients with SBP (n=112)	Ceftriaxone or ceftriaxone plus albumin (0.5 g/kg to 1.0 g/kg within 6 h of enrollment, same amount on day 3, every 3 days for a total of 3 weeks)	RCT	Patients given albumin had decreased incidence of renal failure (9% versus 34%; P=0.002), and decreased mortality rate (9% versus 35%; P=0.01)
Sigal et al (15), 2007	Cirrhotic patients with SBP (n=28)	Group 1 (low risk): bilirubin <68.4 µmol/L and creatinine <88.4 µmol/L received treatment in accordance with 'established guidelines'. Group 2 (high risk): bilirubin >68.4 µmol/L and/or creatinine >88.4 µmol/L – same treatment plus albumin (1.5 g/kg on day 1, 1 g/kg on day 3)	Cohort	Low-risk group: 15 patients (18 total episodes), renal impairment: 0%, mortality: 0%. High-risk group: 21 patients (26 episodes), renal impairment: 57% (66% of episodes resolved after treatment including albumin), mortality: 24%

RCT Randomized controlled trial; ref Reference

vascular resistance was increased, which also contributes to better mean arterial pressures. The mechanism behind this is not clear; however it may be related to the scavenger effect of albumin on vasodilator molecules such as nitric oxide.

#### ALBUMIN AS AN ADJUNCTIVE TREATMENT IN SBP

To date, only a few studies have assessed albumin in cirrhotic patients with SBP (Table 1). Two randomized controlled trials assessed albumin and antibiotic therapy compared with antibiotics alone in patients with SBP. Sort et al (13) randomly assigned 126 cirrhotic patients with SBP to receive either cefotaxime alone or cefotaxime plus albumin infusions. The dose of albumin was 1.5 g/kg of body weight given within 6 h of SBP being diagnosed, followed by an additional infusion of 1.0 g/kg on day 3. Patients given albumin showed no increase in plasma renin activity, a decreased incidence of renal failure (10% versus 33%; P=0.002) and a decreased mortality rate of 10% compared with 29% in patients given cefotaxime alone (P=0.01) (13). The authors concluded that the addition of albumin to antibiotics for the treatment of SBP improved survival and reduced the incidence of renal impairment. Subgroup analysis revealed that patients with a serum bilirubin level of greater than 68.4 µmol/L, a blood urea nitrogen (BUN) level of greater than 10.7 mmol/L or serum creatinine level of greater than 88.4 µmol/L appeared to benefit most. The incidence of renal impairment in patients with a serum bilirubin level of less than 68.4 µmol/L and a serum creatinine level of less than 88.4 µmol/L was very low in both treatment groups (0% and 7% in the cefotaxime plus albumin, and cefotaxime alone groups, respectively) (13). In contrast, in patients with a serum bilirubin level of greater than 68.4 µmol/L or a serum creatinine level greater than 88.4 µmol/L, the rate of renal impairment was 13% (six of 46 patients) in the cefotaxime plus albumin group and 32% (20 of 48 patients) in the cefotaxime alone group. There were no in-hospital deaths in either treatment group among patients with a BUN level of lower than 10.7 mmol/L and a serum bilirubin level of lower than 68.4 µmol/L (13). In comparison, patients with elevated BUN or bilirubin levels had mortality rates of 42% (18 of 43 patients) in the cefotaxime only group and 15% (six of 39 patients) in the cefotaxime plus albumin group.

A similar study by Xue et al (14) randomly assigned 112 patients to receive ceftriaxone or ceftriaxone plus intravenous albumin (0.5 g/kg to 1.0 g/kg within 6 h of enrollment, the same amount on the third day, and then every three days for a total of three weeks). They also found decreased rates of in-hospital mortality in the albumin group compared with the antibiotic only group (9% versus 35%, respectively; P=0.01). The incidence of renal impairment was 9% in the group treated with albumin plus ceftriaxone, compared with 34% in the ceftriaxone only group (P=0.002) (14). No subgroup analyses were reported.

The subgroup analyses reported by Sort et al (13) stimulated further study of high-risk patients. Sigal et al (15) divided 28 patients who

cumulatively experienced 38 episodes of SBP into a low-risk group with a bilirubin level of lower than 68.4 µmol/L and a creatinine level of lower than 88.4 µmol/L, and a high-risk group with elevated bilirubin and/or creatinine levels. SBP was diagnosed and treated in accordance with established guidelines; however, the high-risk group also received albumin. Among 15 patients experiencing 18 episodes, low-risk SBP resolved in all, and no patients developed renal impairment or died (15). In contrast, 57% of patients in the high-risk group sustained renal impairment, and 66% of episodes resolved after treatment including albumin. Five high-risk patients (24%) died. Although this study was limited by its small size and the absence of a control group, it supports the notion that lower-risk patients can be effectively treated without albumin. Furthermore, hemodynamic assessments in this study revealed decreases in plasma renin activity in the low-risk group of patients, suggesting improvement in effective arterial perfusion despite not receiving albumin (15).

Terg et al (3) conducted a retrospective study to analyze the utility of serum creatinine and bilirubin levels in predicting renal failure in SBP patients who did not receive plasma expansion during admission. Among 127 cirrhotic patients, 64% were classified as high risk for renal failure and mortality (bilirubin levels of greater than 68.4 µmol/L and/or creatinine levels greater than 88.4 µmol/L), and the remainder were considered to be low risk. Renal failure occurred in 23% of the high-risk patients compared with 2.6% of the lower-risk patients (P=0.006). Mortality was also significantly higher in the high-risk group (23%) compared with 6.5% among lower-risk patients (P=0.01). The authors agreed that serum bilirubin and creatinine levels could identify patients who could be managed without albumin.

In a similar retrospective study of 69 low-risk cirrhotic patients with SBP (bilirubin level lower than 68.4 µmol/L and BUN level lower than 11 mmol/L) who did not receive albumin during hospital admission (16), in-hospital mortality was 2.8% (two of 69 patients) and the incidence of renal failure was 20.2% (14 of 69 patients). However, renal impairment resolved or remained steady in all patients except one who had advanced hepatocellular carcinoma and died in hospital. These authors similarly concluded that albumin administration was not necessary in low-risk patients.

#### USE OF ALTERNATIVE VOLUME EXPANSION IN SBP (TABLE 2)

The beneficial effects reported by Sort et al (13) and Xue et al (14) may be merely due to the volume-expanding properties of albumin because neither study provided patients in the control group with any form of plasma expansion. Furthermore, albumin is a blood product that is expensive to use and carries a theoretical risk of transmitting known and unknown diseases (17). Finally, its supply is very limited because it is derived from human plasma. Concerns regarding albumin therapy have been raised in other patient populations. For instance, a Cochrane review (18) reported an increased risk of death with

**TABLE 2**  
**Studies evaluating alternatives to standard dose albumin as an adjunctive treatment in spontaneous bacterial peritonitis (SBP)**

Author (ref), year	Subjects	Intervention/groups studied	Study type	Results
Fernandez et al (19), 2005	Cirrhotic patients with SBP (n=20)	Ceftriaxone plus standard dose albumin (1.5 g/kg body weight on day 1, 1.0 g/kg on day 3) versus ceftriaxone plus HES 200/0.5 (1.5 g/kg on day 1, 1.0 g/kg on day 3)	RCT	Albumin group: significant improvements in mean arterial pressure 76 mmHg to 85 mmHg ( $P=0.01$ ), plasma renin activity 5.7 ng/mL/h to 3.1 ng/mL/h ( $P=0.04$ ), and renal function 1.6 mg/dL to 1.0 mg/dL ( $P=0.01$ ). HES group: No significant difference in mean arterial pressure or plasma renin activity. Renal function improved from 1.2 mg/dL to 1.0 mg/dL ( $P=0.02$ )
Cartier et al (22), 2010	High-risk SBP patients (bilirubin >68.4 µmol/L and/or creatinine >88.4 µmol/L) (n=29)	Each patient received ceftriaxone and polygeline (Gelafundin 4%) (1.5 g/kg at the time of diagnosis followed by 1 g/kg on day 3)	Cohort	Renal impairment in 13.8% (4 of 29 patients) and in-hospital mortality of 10.4% (3 of 29 patients)
Araujo et al (23), 2009	Cirrhotic patients with SBP (n=48)	Cefotaxime plus standard dose albumin (1.5 g/kg on day 1, 1.0 g/kg on day 3) versus cefotaxime plus dose-reduced albumin (1.0 g/kg on day 1, 0.5 g/kg on day 3)	RCT	No significant differences in renal impairment (41% versus 45%; $P=0.77$ ) or mortality (25% versus 20%; $P=0.73$ )

HES Hydroxyethyl starch; RCT Randomized controlled trial; ref Reference

albumin administration in critically ill patients. Accordingly, a subsequent unblinded trial compared the effects of albumin and hydroxyethyl starch (HES) on systemic hemodynamics and prevention of renal failure in 20 patients with SBP (19). Patients were randomly assigned to receive either albumin (n=10) or HES (n=10) at the same dose (1.5 g/kg within 12 h after diagnosis, then 1 g/kg on day 3). The study showed that only albumin administration significantly suppressed plasma renin activity and increased cardiopulmonary pressures and systolic volume. These parameters suggest that improved cardiac output and increased systemic vascular resistance both accounted for higher mean arterial pressures. In contrast, no significant changes were observed within these parameters in the HES group. No patients from the albumin group developed circulatory dysfunction or renal failure, whereas the HES group had three patients with circulatory dysfunction and one with acute renal failure (19). The authors concluded that albumin was superior to HES in preventing adverse hemodynamic changes in SBP patients. However, the HES formulation used in the study had different physical and physiological properties compared with serum albumin because it has a lower molecular weight and a half-life as short as 2 h – in contrast to albumin, which may have a half-life as long as 21 days and so, perhaps, was not a comparable agent (20).

The half-life of most artificial colloids is less than 24 h, but reaches 5 h for polygeline, and 12 h to 24 h for dextran 70 (21). Artificial colloids with longer half-lives may confer the same renal and mortality benefits as albumin (21). A recent prospective trial by Cartier et al (22) enrolled 29 patients with SBP considered to be high risk based on either a serum bilirubin level of greater than 68.4 µmol/L or a creatinine level of greater than 88.4 µmol/L. Each patient was treated with ceftriaxone and polygeline (gelafundin 4%) intravenously at 1.5 g/kg at the time of diagnosis followed by 1 g/kg on day 3. They reported renal impairment in 13.8% (four of 29 patients) and in-hospital mortality of 10.4% (three of 29 patients) – similar to rates in the high-risk

group reported by Sort et al (13) (13% and 15.3%, respectively). The cost of albumin is more than seven times that of gelafundin (22). Thus, the use of alternative volume expanders may be a viable and affordable option for high-risk SBP patients.

Although albumin is an effective volume expander for patients with SBP, the ideal dose has yet to be determined. Costs could be reduced if lower doses of albumin than that used in the study by Sort et al (13) are equally effective in patients with SBP. An ongoing double-blinded, randomized clinical trial (23) is examining a dose-reduced regimen of 1.0 g/kg at admission, followed by 0.5 g/kg on day 3, in comparison with a standard dose of 1.5 g/kg on day 1 and 1.0 g/kg on day 3. An interim analysis of 48 patients enrolled suggests no significant differences between the groups in renal impairment and in-patient mortality. Although this study (23) was underpowered to conclude equivalence, the low-dose regimen appeared to be effective.

## CONCLUSIONS

The ability of albumin to improve intravascular volume and bind inflammatory cytokines has led to the study of albumin therapy in patients with SBP. The published literature suggests that albumin in combination with antibiotics prevents renal impairment and reduces mortality in SBP. The benefit is most appreciated in higher-risk patients with elevated bilirubin levels and evidence of renal dysfunction, and negligible in SBP patients with normal bilirubin levels and renal function. Recent small studies (22,23) have also suggested that artificial colloids or lower dose albumin may be comparable with standard dose albumin for lowering renal impairment and mortality. However, large randomized controlled studies with standard dose albumin control groups are needed to confirm the efficacy of these alternatives before either can be recommended for high-risk patients with SBP.

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