Effect of albumin in cirrhotic patients with infection other than spontaneous bacterial peritonitis. A randomized trial

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Abbreviations: AKI, acute kidney injury; IQR, interquartile range; LVP, large-volume paracentesis; MDRD, modification of diet in renal disease; SBP, spontaneous bacterial peritonitis; SIRS, systemic inflammatory response syndrome.

Background & Aims: Albumin infusion improves renal function and survival in cirrhotic patients with spontaneous bacterial peritonitis (SBP) but its efficacy in other types of infections remains unknown. We investigated this issue through a multicenter randomized controlled trial.

Methods: A total of 193 cirrhotic patients with a Child-Pugh score greater than 8 and sepsis unrelated to SBP were randomly assigned to receive antibiotics plus albumin (1.5 g/kg on day 1 and 1 g/kg on day 3; albumin group [ALB]: n = 96) or antibiotics alone (control group [CG]: n = 97). The primary endpoint was the 3-month renal failure rate (increase in creatinine $\geq 50\%$ to reach a final value $\geq 133 \mu$mol/L). The secondary endpoint was 3-month survival rate.

Results: Forty-seven (24.6%) patients died (ALB: n = 27 vs. CG: n = 20; 3-month survival: 70.2% vs. 78.3%; p = 0.16). Albumin infusion delayed the occurrence of renal failure (mean time to onset, ALB: 29.0 ± 21.8 days vs. 11.7 ± 9.1 days, p = 0.018) but the 3-month renal failure rate was similar (ALB: 14.3% vs. CG: 13.5%; p = 0.88). By multivariate analysis, MELD score (p < 0.0001), pneumonia (p = 0.0041), hyponatremia (p = 0.031) and occurrence of renal failure (p < 0.0001) were predictors of death. Of note, pulmonary edema developed in 8/96 (8.3%) patients in the albumin group of whom two died, one on the day and the other on day 33 following albumin infusion.

Conclusions: In cirrhotic patients with infections other than SBP, albumin infusion delayed onset of renal failure but did not improve renal function or survival at 3 months. Infusion of large amounts of albumin should be cautiously administered in the sickest cirrhotic patients.

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Introduction

Bacterial infections are common in cirrhotic patients and dramatically increase one-year mortality; with mortality reportedly up to 38% after infection [1,2]. Once infection occurs, it may lead to systemic inflammatory response syndrome (SIRS) and subsequently, renal failure, multi-organ dysfunction and death [3]. The most common infection, accounting for around one quarter of all infections in hospitalized patients, is spontaneous bacterial peritonitis (SBP), which is mainly caused by bacterial translocation [4]. About one-third of these patients go on to develop renal failure despite the resolution of infection [5,6].

Renal failure in SBP is the most powerful independent predictor of in-hospital mortality, with a median death rate of 67% in patients with renal failure, versus only 11% in patients who maintained normal renal function [7]. Renal failure has also been reported to be a strong predictor of early death in cirrhotic patients with infections other than SBP [8–10]. Deterioration of renal function during sepsis proceeds from several causes: firstly, splanchnic vasodilation, due to increased production of pro-inflammatory cytokines and vasodilatory factors, such as nitric oxide, with a subsequent reduction in effective arterial blood volume; and secondly, vasoconstriction in non-splanchnic vascular beds, including the kidney [11].

Renal hypoperfusion is further exacerbated by sepsis-related cardiomyopathy, which has been shown to be improved by albumin infusion in cirrhotic rats [12]. Intravenous albumin administration has also been shown to have beneficial effects on systemic hemodynamics and renal function in cirrhotic patients with SBP, mediated by both an improvement in cardiac function and a decrease in arterial vasodilatation [13]. More importantly, the use of albumin together with antibiotic treatment in SBP was associated with a marked decrease in 3-month mortality compared to antibiotic treatment alone [6]. The beneficial effect of albumin infusion in the context of SBP is related mostly to its oncotic effect, but may also be due to its antioxidant, immune modulatory and scavenger properties [14].

The efficacy of albumin to prevent renal impairment and reduce mortality in patients with SBP was recently confirmed in a meta-analysis [15]. Its use is endorsed by current guidelines and well-integrated in clinical practice, although the benefit of this strategy remains questionable in low-risk SBP patients [16,17]. Conversely, little is known about the effects of albumin on renal function and survival in cirrhotic patients with infections other than SBP. Only one single-center study with a relatively small sample size has addressed this issue to date [18].

Although encouraging, the overall result of this study was negative, with no significant difference in survival between groups observed at 3 months, underlining the need for a larger trial [18].

We performed a randomized, multicenter trial to determine whether albumin infusion has a beneficial effect on renal function and 3-month survival in cirrhotic patients with infections other than SBP.

Patients and methods

Study oversight

The “Albumin Administration in Cirrhotic Patients With Bacterial Infection Unrelated to Spontaneous Bacterial Peritonitis (ALB-CIRINF)” study (registered with ClinicalTrials.gov under the number NCT01359813) was a randomized, open-label, controlled, multicenter clinical trial designed by a scientific committee and supervised by an independent oversight committee (Supplementary File 1). LFB Laboratories (Courtaboeuf, France) provided the albumin vials (Vialbex®; LFB). All authors had access to the study data, critically reviewed the manuscript, and approved the final draft for submission. The trial was performed in 25 participating centers, in accordance with the Declaration of Helsinki and with the approval of our local ethics committee (CPP Est-I) on the 7th August 2008 (ref. 2008-A08478-45) (Supplementary File 2).

Patients

All consecutive cirrhotic patients with sepsis who were admitted to the participating centers were screened for eligibility. Full details of the inclusion and exclusion criteria, and the definitions of infection are given in Supplementary File 3. Briefly, inclusion criteria were: age >18 and ≤80 years, presence of sepsis or severe sepsis according to the criteria of the American College of Chest Physicians/Society of Critical Care Medicine (ACCP/SCCM) guidelines [19], and cirrhosis with a Child-Pugh score >8. Exclusion criteria were: patients with serum creatinine level >160 μmol/L, SBP, septic shock, and use of antibiotics (except antibiotic prophylaxis) during the week prior to randomization. We excluded patients with a creatinine level >160 μmol/L because the Scientific Committee considered that randomization would be unethical and not feasible in these patients.

Randomization

Randomization was performed in blocks of 4, in a 1:1 ratio, by means of an interactive voice-system response (Ascopharm, Novasco group, Paris, France) with stratification by center. The number of subjects per block was known only to the methodologist.

Treatment allocation and follow-up

Eligible patients were randomly assigned to receive either antibiotics alone (control group) or antibiotics plus albumin 20% (ALB group: 1.5 g/kg on day 1 and 1 g/kg on day 3). Albumin administration was initiated in the first 24 h after randomization, and antibiotics were to be started as soon as possible without waiting for the randomization. During the 3-month follow-up period, eight visits were planned (at days 1, 3, 6, 9, 15, 30, 60, and 90) to record clinical and biological data (Supplementary Table 1). Complications of cirrhosis were managed according to standard protocols [20]. In septic patients with ascites, diuretics had to be stopped at the time of infection and re-introduced after resolution of infection. Large-volume paracentesis (LVP >3 liters) was not authorized until after resolution of infection, but paracentesis of lesser volumes without albumin administration was authorized in cases of abdominal discomfort. Proposals for the choice of antibiotics were given in the study protocol to assist physicians (Supplementary File 3).

Endpoints and definitions

Endpoints

The primary endpoint was the rate of renal failure during the 3-month follow-up period. The secondary end-point was 3-month mortality rate.

Renal failure

Renal function was assessed by measuring serum creatinine concentration at inclusion and throughout follow-up (see Supplementary Table 1 for measurement schedule). To define renal failure, a cut-off serum creatinine level of 133 μmol/L (1.5 mg/dL) was used. For patients without pre-existing renal insufficiency, renal impairment was diagnosed whenever there was an increase in serum creatinine of >50%, reaching a final value of over 133 μmol/L. For patients with pre-existing renal insufficiency before infection, renal impairment was diagnosed by an increase in the serum creatinine level by more than 50% from baseline. Glomerular filtration rate was estimated according to the MDRD formula [21].

Statistical analysis

Quantitative variables are presented as mean ± SD or median and interquartile range (IQR), and categorical variables as number (percentage).

The sample size was estimated based on a projected 27% renal failure rate at 3 months in the control group [9] and 10% in the albumin infusion group [6]. It was calculated that 186 patients (93 per group) would yield 80% power with a two-sided alpha risk of 5%. The sample size was increased by 10% to 206 patients...
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to allow for possible drop-outs, protocol deviations and patients lost to follow-up. All analyses were performed according to the intention-to-treat principle. Continuous variables were compared using the Student t test or the Mann-Whitney test, as appropriate, and categorical variables using the $\chi^2$ test or Fisher's Exact test as appropriate. For primary and secondary end-points, the Kaplan Meier method was used to estimate cumulative rates over the 3-month follow-up. For renal failure and death, the time from date of inclusion to the date of the first increase in serum creatinine concentration defining renal failure was calculated, and occurrence of death, liver transplantation or study drop-out during follow-up were treated as censoring events. Curves for cumulative rates in both treatment arms were compared using the log-rank test. The same method was applied for the comparison of 3-month survival. Univariate analysis identified predictors of renal failure and death, which were then included in multivariate analysis using Cox's logistic regression model. All statistical analyses were performed using SAS 9.0 (SAS Institute Inc., Cary, NC, USA). A p value < 0.05 was considered statistically significant.

Results

Study population

From December 2008 through September 2013, 646 patients were screened and 193 patients were randomized (97 to the control group and 96 to the ALB group). A flow-chart of the study population is shown in Fig. 1 and the reasons for exclusion of screened patients are provided in the legend of Fig. 1. Nine patients did not meet the inclusion criteria and two other patients withdrew their consent (Fig. 1). The study oversight committee decided to prematurely interrupt the study in September 2013 due to excess mortality in patients receiving albumin infusion without significant effect on renal function. The baseline clinical and biological characteristics (Table 1), the components of SIRS and the type of infection (Table 2) were well balanced between groups, except for ascites, which was more frequently observed in the ALB group (p = 0.017). Pneumonia (33%) and urinary tract infections (31%) were the most common infections. The germ responsible for infection was identified in 55% of patients, for a total of 123 bacteria identified (Supplementary Table 2). Infections were treated empirically by antibiotics until resolution of infection (97% of cases, n = 186). In the remaining 5 patients (3%) suffering from pneumonia, infection did not resolve and all 5 subsequently died.

Albumin and antibiotics administration

Patients in the ALB group received at least one vial of albumin 20%, except for two patients on day 1, and 13 patients on day 3. The non-administration of albumin on day 1 was considered a protocol violation. Reasons for the non-administration of albumin on day 3 were early death (n = 2), discharge against medical advice (n = 3), pulmonary edema (n = 4) and unidentified reasons (n = 4). The mean albumin doses administered on day 1 and day 3 were 106 ± 22 g and 70 ± 16 g respectively. The mean difference between the scheduled dose (i.e., 1.5 g/kg on day 1 and 1 g/kg on day 3) and the administered dose of albumin on day 1 was +5 g (range: –28 to +54) and +4 g (range: –28 to +42) on day 3. Furthermore, 29 patients (17 in the control group and 12 in the ALB group) received albumin infusion (outside the protocol) after LVP during the first week after randomization. The median [IQR] albumin doses administered were 40 g [20–70] in the control group and 60 g [25–115] in the ALB group respectively. Antibiotics were consistently started before randomization and the period of time elapsed between the diagnosis of infection and the administration of the first dose of antibiotics was less than 24 h.

Effect of treatment on renal failure

Serum creatinine measures were available for 180 patients throughout the 3 months of follow-up and were missing in 11 patients for the following reasons: discharge against medical advice (n = 1), early death (n = 1) and non-compliance with the inclusion criteria (n = 9). Renal failure developed in 25 patients (14%) overall; 12/89 (13%) in the control group and 13/91 (14%) in the ALB group (Fig. 2A, log-rank test; at 3 months: p = 0.87 and at one month: p = 0.49). Such a small difference in renal failure rates between the two groups makes this trial underpowered to address our primary statistical hypothesis (i.e. a 17% difference between study arms). The mean time to onset of renal failure was 12 ± 9 days in the control group vs. 29 ± 22 days in the ALB group (p = 0.018). Renal failure was present on day 1 in one patient (not reversible) in the control group and in no patient in ALB group. The proportion of patients with renal failure at day 15 was not significantly different between groups (10 [11.2%] vs. 5 [5.6%] patients; log-rank test, p = 0.18). Serum creatinine levels were similar at baseline in both groups, but mean creatinine levels were significantly lower in the ALB group at day 9 (66 ± 24 μmol/L vs. 78 ± 48 μmol/L in the control group; p = 0.045) and on day 15 (68 ± 30 vs. 85 ± 66 μmol/L in the control group; p = 0.036, Fig. 3A). Changes in serum creatinine levels from baseline over the 3-month follow-up period were similar between groups (Fig. 3B).

Per-protocol analysis was performed, after excluding 15 patients from the ALB group who did not receive albumin infusion according to the protocol, and showed that the proportion of patients with renal failure was not significantly different between the ALB and control groups at one month (9.3% vs. 13.7%; p = 0.30, log-rank test) or at 3 months (14.7% vs. 14.6%; p = 0.77). Comparing all patients (n = 112) who actually received...
albumin infusion (regardless of the protocol recommendations) during the first week to those (n = 79) who did not receive any albumin during the same period, 3-month renal-failure-free survival was not significantly different between groups (albumin vs. control: 82.6% vs. 88.6%; log-rank test: p = 0.37). Considering our missing data on serum creatinine in 11 patients (in the
control group and 4 in the ALB group), we simulated a best-case scenario favoring albumin administration (i.e., all seven control patients and none of the four ALB group patients developed renal failure). In this analysis, 3-month renal-failure-free survival still did not differ significantly between groups (84.2% vs. 79.9%; log-rank test: \( p = 0.28 \)).

**Factors associated with renal failure**

The variables associated with renal failure are shown in Table 3. In patients with available creatinine measurements (\( n = 180 \)), death occurred in 44 patients (24.4%) overall; 29/155 (18.7%) in patients without renal failure and 15/25 (60%) in patients with renal failure (\( p < 0.001 \)). By multivariate Cox analysis, the most significant predictors of renal failure during the 3-month follow-up were older age (HR = 1.06 per additional year; 95% CI: 1.02–1.11; \( p = 0.0048 \)) and presence of bacterial culture-negative infection (HR = 4.12; 95% CI: 1.71–9.89; \( p = 0.0015 \)).

**Survival**

At the end of the 3-month follow-up period, 47/191 (25%) patients had died (27 in the ALB group and 20 in the control group) and 9 had been transplanted (5 and 4, respectively). Causes of death in the control and ALB groups were: end-stage liver failure (11 vs. 13), cardiovascular disease (3 vs. 6, endocarditis \( n = 1 \) and cardiopulmonary arrest \( n = 1 \) vs. 3 [pulmonary edema \( n = 1 \), hemorrhagic stroke \( n = 1 \) and cardiopulmonary arrest \( n = 1 \)]), gastrointestinal bleeding (3 vs. 4), pneumonia (2 vs. 5) (of which one was pulmonary nocardiosis in the control group), and hepatocellular carcinoma (1 vs. 2). Three month survival was not significantly different between the control and ALB groups (Fig. 2B, 78% vs. 70%; log-rank test: \( p = 0.16 \)). Mortality was higher in patients who developed renal failure during the study period (60% vs. 12% in patients without renal failure; \( p < 0.001 \)). Variables associated with death by univariate analysis are reported in Supplementary Table 3. By multivariate analysis (Table 4), the significant predictors of death were: high MELD score (\( p < 0.001 \)), pneumonia (\( p = 0.004 \), hyponatremia (\( p = 0.031 \)) and occurrence of renal failure (\( p < 0.001 \)). The 30-day survival was also not significantly different between the control and ALB groups (91% vs. 83%; log-rank test: \( p = 0.097 \)) but the number of deaths was low (control group, \( n = 8 \) and ALB group: \( n = 15 \)). Per-protocol analysis, excluding the 9 ineligible patients and the 15 patients who did not receive albumin infusion in the ALB group, showed that among patients with ascites who received albumin, the proportion of patients with renal failure at one month decreased (\( n = 107 \); 5.4% vs. 15.1%, log-rank test: \( p = 0.064 \)). Similarly, among patients with severe sepsis, the proportion of renal failure at one month was significantly lower among those receiving albumin (\( n = 23 \); 0% vs. 43.6%, \( p = 0.029 \)).

**Fig. 2. Survival in the albumin and control groups.** Survival free of renal failure and (B) overall survival in the albumin and control groups.

**Fig. 3. Change in serum creatinine during the study period.** (A) Serum creatinine levels (mean ± SD) and (B) changes in serum creatinine levels from baseline during the 3-month follow-up period in the albumin and control groups. *p < 0.05.
The model is adjusted for ascites (infection (Kim et al. [37]). et al. [6,13,15]) and cutaneous dysfunction related to LVP, SBP or hepatorenal syndrome [6,25,26]. However, the prophylactic use of albumin together with antibiotics in patients with bacterial infection other than SBP is less well documented. A recent study showed that albumin infusion together with antibiotics had a potential survival benefit in a per-protocol analysis compared to a control group, and this beneficial effect was attributed to an improvement in effective arterial blood volume, reflected by an improvement in renal function [18]. However, the small sample size of the study precluded any definitive conclusion on the survival endpoint, which showed an absolute difference of only 2.2% in 3-month survival between groups [18].

In our study, renal failure was chosen as the primary endpoint because it has been convincingly shown to be associated with survival. Furthermore, using mortality as an endpoint would require too high a number of patients to detect a significant difference. Despite positive scientific evidence [6,13,15] and delayed occurrence of renal failure in the ALB group, the rate of renal failure at 3 months (13.5% in the control group vs. 14.3% in the ALB group) did not decrease. Guevara et al. [18], who used the same definition of renal failure, observed similar findings, with renal failure occurring more frequently (27.4% in the control group and 23.9% in the ALB group) than in our series, probably because of differences in baseline characteristics between the two cohorts. Indeed, the Spanish study included patients with higher baseline levels of serum creatinine (control vs. ALB: 97 ± 53 vs. 114 ± 53 µmol/L; our study: 76 ± 31 vs. 74 ± 29 µmol/L respectively) and fewer alcoholic patients (44% vs. 92% in our study). Interestingly, in a per-protocol population, we observed that the proportion of patients with renal failure at one-month was lower among septic albumin infusion, decreased progressively under appropriate doses of furosemide and isosorbide dinitrate, but had probably impaired pulmonary function thereby contributing to the fatal outcome. Outcome after pulmonary edema was more favorable in the remaining six patients, in whom edema occurred within the first three days after albumin infusion. One patient in the control group died 13 days after infusion of 80 g of albumin outside the protocol. These cases of lethal pulmonary edema led the oversight committee to prematurely terminate the study in September 2013. Among variables recorded at baseline, only a high Charlson comorbidity index was associated with pulmonary edema (5.0 vs. 3.7; p = 0.014).

### Discussion

This randomized controlled trial did not show a beneficial effect of albumin infusion on the incidence of renal failure (evaluated using standard criteria) or on 3-month survival in cirrhotic patients with bacterial infection unrelated to SBP, although onset of renal failure was significantly delayed in the ALB group. More importantly, pulmonary edema occurred in 8 patients (8%) in the ALB group and was fatal in two of these patients, although the causal link between death and pulmonary edema following albumin infusion was not established. We also observed that pneumonia and urinary tract infections were the most common infections, as reported in previous studies [22–24], and pneumonia was associated with an unfavorable outcome.

Intravascular albumin administration has become the standard of care to prevent deterioration of renal function and subsequent death in cirrhotic patients with marked circulatory dysfunction. Outcome after pulmonary edema was more favorable in the remaining six patients, in whom edema occurred within the first three days after albumin infusion. One patient in the control group died 13 days after infusion of 80 g of albumin outside the protocol. These cases of lethal pulmonary edema led the oversight committee to prematurely terminate the study in September 2013. Among variables recorded at baseline, only a high Charlson comorbidity index was associated with pulmonary edema (5.0 vs. 3.7; p = 0.014).

### Table 3. Baseline characteristics according to the occurrence of renal failure during the 3-month follow-up period.

<table>
<thead>
<tr>
<th></th>
<th>No renal failure n = 155</th>
<th>Renal failure n = 25</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients treated with albumin</td>
<td>78 (50.3)</td>
<td>13 (52.0)</td>
<td>0.87</td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>54.7 ± 8.2</td>
<td>59.4 ± 10.1</td>
<td>0.011</td>
</tr>
<tr>
<td>Male gender</td>
<td>106 (68.4)</td>
<td>17 (68.0)</td>
<td>0.97</td>
</tr>
<tr>
<td>Etiology of cirrhosis: alcohol vs. other</td>
<td>142 (91.6)</td>
<td>23 (92.0)</td>
<td>1.00</td>
</tr>
<tr>
<td>Child-Pugh score</td>
<td>11.1 ± 1.4</td>
<td>11.0 ± 1.3</td>
<td>0.66</td>
</tr>
<tr>
<td>MELD score</td>
<td>20.9 ± 5.7</td>
<td>21.9 ± 5.9</td>
<td>0.42</td>
</tr>
<tr>
<td>Prothrombin time</td>
<td>43.5 ± 13.3</td>
<td>41.8 ± 12.0</td>
<td>0.53</td>
</tr>
<tr>
<td>Albumin (g/L)</td>
<td>24.5 ± 5.0</td>
<td>23.2 ± 4.6</td>
<td>0.22</td>
</tr>
<tr>
<td>Total bilirubin (µmol/L)*</td>
<td>91 (51.0-161.0)</td>
<td>110 (50.0-194.5)</td>
<td>0.41</td>
</tr>
<tr>
<td>Ascites</td>
<td>109 (70.3)</td>
<td>14 (56.0)</td>
<td>0.15</td>
</tr>
<tr>
<td>Sodium (mmol/L)</td>
<td>132.9 ± 5.1</td>
<td>133.0 ± 7.1</td>
<td>0.93</td>
</tr>
<tr>
<td>Creatinine (µmol/L)</td>
<td>74.3 ± 30.0</td>
<td>83.2 ± 29.4</td>
<td>0.17</td>
</tr>
<tr>
<td>Glomerular filtration rate (ml/min)</td>
<td>111.8 ± 50.7</td>
<td>94.7 ± 44.8</td>
<td>0.11</td>
</tr>
<tr>
<td>C-reactive protein (mg/L)*</td>
<td>34 (16.9-58.8)</td>
<td>26.6 (15.3-63)</td>
<td>0.94</td>
</tr>
<tr>
<td>Severe acute alcoholic hepatitis</td>
<td>25 (16.1)</td>
<td>3 (12.0)</td>
<td>0.77</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>52 (33.5)</td>
<td>8 (32.0)</td>
<td>0.88</td>
</tr>
<tr>
<td>Culture negative infection</td>
<td>58 (37.4)</td>
<td>18 (72.0)</td>
<td>0.0012</td>
</tr>
<tr>
<td>Severe sepsis</td>
<td>18 (11.6)</td>
<td>7 (28.0)</td>
<td>0.054</td>
</tr>
</tbody>
</table>

MELD, Model for End-stage Liver Disease.
*Median [interquartile range].

### Table 4. Factors independently related to 3-month survival by multivariate analysis (Cox model).

<table>
<thead>
<tr>
<th></th>
<th>HR (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MELD score*</td>
<td>1.10 (1.05-1.16)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>3.21 (1.86-6.89)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Natremia at risk**</td>
<td>2.02 (1.01-4.02)</td>
<td>0.044</td>
</tr>
<tr>
<td>Renal failure during the study period</td>
<td>4.11 (2.06-8.17)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age*</td>
<td>1.03 (0.99-1.07)</td>
<td>0.062</td>
</tr>
<tr>
<td>Albumin group</td>
<td>1.14 (0.59-2.20)</td>
<td>0.68</td>
</tr>
</tbody>
</table>

CI, confidence interval; HR, hazard ratio; MELD, Model for End-stage Liver Disease.
*Per unit increase in MELD score and in age. **Natremia was considered at risk of death when serum sodium level was >145 mmol/L or <135 mmol/L according to Kim et al. [37]. The model is adjusted for ascites (p = 0.63) and cutaneous infection (p = 0.58).

### Adverse effects of albumin infusion

The most noteworthy side effect of albumin administration was the development of pulmonary edema in 8/96 (8.3%) patients with alcoholic cirrhosis in the ALB group (Table 5). Two of these died: one on the day following albumin infusion but death was judged to be “unrelated” to the albumin infusion by a panel of intensive care specialists, the patient died from septic shock due to pneumonia and multiple organ failure. The other patient died on day 33 from acute respiratory distress syndrome consecutive to pneumonia; pulmonary edema had occurred on day 1 after...
patients with ascites and in patients with severe sepsis after albumin infusion. This suggests a beneficial effect of albumin in both these conditions, which are associated with critical hemodynamic impairment. Despite the difference in inclusion criteria (we excluded patients with baseline serum creatinine >160 μmol/L), whereas the corresponding exclusion threshold in the Spanish studies was 265 μmol/L, 3-month survival was similar between studies, and not significantly different in both treatment arms (control vs. ALB group; Guevara et al.: 80.4% vs. 82.6%; our study: 78.3% vs. 70.2%). These high 3-month survival rates reflect a better prognosis in cirrhotic patients with infections other than SBP, since this latter condition is associated with high in-hospital mortality [7].

Although our study failed to demonstrate a beneficial impact of albumin on survival in cirrhotic patients with infections other than SBP, the debate remains open and further trials are warranted in more selected populations with greater hemodynamic impairment. Subsequent efforts should focus on patients with severe sepsis, pneumonia or those with a “high” level of serum creatinine at the time of albumin infusion. However, the appropriate creatinine level remains to be determined.

Our study suffers from several limitations that deserve to be underlined. Firstly, we did not investigate the pathophysiological processes underlying the association between non-SBP-related infection and renal failure. In patients with SBP, the occurrence of renal failure is related to increased production of pro-inflammatory cytokines, favoring a reduction in effective blood volume together with a fall in cardiac output [11,27]. We believe that in our series, the decrease in serum creatinine levels after albumin infusion was associated with a decrease in plasma renin activity, and plasma concentrations of aldosterone and norepinephrine, as previously observed by Guevara et al. [18]. However, these parameters alone are not sufficient to recommend the use of albumin in clinical practice. Only a significant improvement in major endpoints such as renal function or survival would be of interest.

Secondly, our study did not use the new Acute Kidney Injury (AKI) criteria, which highlight the increase in morbidity and mortality observed with any abrupt decrease in renal function, even minor (defined as an increase in serum creatinine of ≥26.4 μmol/L (0.3 mg/dl) [28–31]. At the time when our study protocol was written, this new concept of AKI was not yet well recognized or widely established. However, the design of our study did allow evaluation of these criteria during the first 15 days of follow-up, by allowing a maximum time-interval between two serum creatinine dosages of 6 days (instead of 48 h). Overall, the incidence of AKI during this short period was 23% (41 patients; 22% in the control group and 24% in the albumin group; p = 0.86). All but six patients with AKI were in stage 1, thus confirming that our population did not have marked circulatory dysfunction. This finding may partially account for our negative results.

Thirdly, several protocol violations occurred in our study. Indeed, albumin was administered outside the protocol in 17 patients in the control group to compensate for LVP performed during the first week. However, our per-protocol simulation analysis, which defined new groups of patients designed to maximize the beneficial impact of albumin infusion on renal function, also failed to yield significant results.

A more troublesome observation was the 9 patients who suffered from pulmonary edema following albumin infusion, two of whom died within a short time window after albumin infusion. Although rarely reported (no case in the study by Sort et al. [6] and only three cases in the study by Guevara et al. [18]), pulmonary edema is not an unexpected adverse effect of albumin, since cardiac dysfunction is a common complication of cirrhosis [32]. Although albumin has many potential beneficial effects [14], its protective oncotic role may be diminished when capillary permeability increases, a situation that is well established in infected cirrhotic patients and worsened by deficient lymphatic function [33–35]. Increased extravasation of albumin from the capillaries would lead to accumulation of albumin in the extravascular spaces, with subsequent fluid overload [36]. From a clinical point of view, it remains difficult to determine the subgroup of infected cirrhotic patients (other than SBP) who really yield a significant benefit from albumin infusion. We suggest that this therapy should be given cautiously in patients who have previously failed to improve hypoalbuminemia or peripheral edema despite repeated use of albumin infusion. Furthermore, assessment of cardiac function should ideally be performed prior infusion of large amounts of albumin, in order to anticipate vascular overload in the sickest cirrhotic patients.

### Table 5. Characteristics of the eight patients in the albumin group who have suffered from pulmonary edema after albumin infusion.

<table>
<thead>
<tr>
<th>Pt</th>
<th>Gender/age (years)</th>
<th>Comorbidities</th>
<th>MELD score/ascites</th>
<th>BNP† (pg/ml)</th>
<th>GFR (ml/min)</th>
<th>Sepsis</th>
<th>Date/Outcome‡</th>
<th>Date/three-case scenarios</th>
<th>Date/one-case scenarios</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F/63</td>
<td>Prior history of SBP</td>
<td>8/Yes</td>
<td>&gt;1000 on day 1 after ALB</td>
<td>78</td>
<td>Urinary</td>
<td>Day 1/Alive</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>M/69</td>
<td>VB</td>
<td>32/No</td>
<td>179 one month before ALB</td>
<td>41</td>
<td>Cutaneous</td>
<td>Day 3/Alive</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>M/60</td>
<td>Arterial hypertension</td>
<td>34/Yes</td>
<td>34 one week before ALB</td>
<td>116</td>
<td>Cutaneous</td>
<td>Day 2/Alive</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>F/42</td>
<td>Atrophic gastritis</td>
<td>34/No</td>
<td>216 the day before and 704 on day 1 after ALB</td>
<td>341</td>
<td>n.d.</td>
<td>Day 1/Alive</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>F/40</td>
<td>Asthma</td>
<td>23/Yes</td>
<td>n.d.</td>
<td>191</td>
<td>Pneumonia</td>
<td>Day 1/Death at day 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>H/64</td>
<td>Dilated cardiomyopathy</td>
<td>25/Yes</td>
<td>863 the day before ALB</td>
<td>162</td>
<td>Pneumonia</td>
<td>Day 3/Alive</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>H/59</td>
<td>None</td>
<td>29/No</td>
<td>504 the day before ALB</td>
<td>122</td>
<td>Pneumonia</td>
<td>Day 3/Alive</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>H/52</td>
<td>Prior history of SBP</td>
<td>26/Yes</td>
<td>64 the day before ALB</td>
<td>203</td>
<td>Pneumonia</td>
<td>Day 1/Death at day 33</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Legend:** BNP, B-type natriuretic peptide; F, female; GFR, glomerular filtration rate; M, male; n.d., not determined; Pt, patient; SBP, spontaneous bacterial peritonitis; VB, variceal bleeding. TIPS, Transjugular Intrahepatic Portosystemic Shunt.

†The nearest value of BNP (normal value was set at 100 pg/ml) from the first albumin infusion; ‡day of pulmonary edema occurrence after the first albumin infusion; ‡outcome following pulmonary edema. This alcoholic patient was coinfected with hepatitis B and C viruses; ‡death was considered as unrelated to pulmonary edema consecutive to albumin infusion. More details are reported in Supplementary Table 4.
In summary, our findings do not show a beneficial impact of albumin infusion at standard dose on renal-failure-free or overall survival in cirrhotic patients with infection other than SBP. However, our trial is underpowered to detect a significant difference in renal failure rates between study arms. Subgroup analysis suggests that septic patients with ascites unrelated to SBP, and patients with severe sepsis may yield greater benefit from albumin infusion. Moreover, albumin may cause detrimental side effects in some patients and should be administered with caution in the sickest cirrhotic patients.

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Conflict of interest

The authors who have taken part in this study declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

LFB laboratory (France) provided partial financial support.

Authors’ contributions


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Fiona Ecarnot revised the English for payment.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jhep.2014.11.017.

References


