Efficacy of Albumin Treatment for Patients with Cirrhosis and Infections Unrelated to Spontaneous Bacterial Peritonitis

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BACKGROUND & AIMS: **We performed a randomized trial to determine whether albumin should be administered to patients with infections unrelated to spontaneous bacterial peritonitis (SBP).**

METHODS: **We performed a multicenter, open-label trial in which 118 patients with cirrhosis, non-SBP infections, and additional risk factors for poor outcome were randomly assigned to receive antibiotics plus albumin (study group; n = 61) or antibiotics alone (control group; n = 57). The primary outcome was in-hospital mortality; secondary outcomes were effect of albumin on disease course.**

RESULTS: **There were no significant differences at baseline between groups in results from standard laboratory tests, serum markers of inflammation, circulatory dysfunction, or liver severity scores. However, the combined prevalence of acute on chronic liver failure (ACLF) and kidney dysfunction was significantly higher in the study group (44.3% vs 24.6% in the control group; $P = .02$), indicating greater baseline overall severity. There was no significant difference in the primary outcome between groups (13.1% in the study group vs 10.5% in the control group; $P = .66$). Circulatory and renal functions improved in only the study group. A significantly higher proportion of patients in the study group had resolution of ACLF (82.3% vs 33.3% in the control group; $P = .03$). A significantly lower proportion of patients in the study group developed nosocomial infections (6.6% vs 24.6% in the control group; $P = .007$).**

Abbreviations used in this paper: ACLF, acute-on-chronic liver failure; CRP, C-reactive protein; HRS, hepatorenal syndrome; IL, interleukin; ITT, intention-to-treat; KD, kidney dysfunction; RCT, randomized controlled trial; SBP, spontaneous bacterial peritonitis; UTI, urinary tract infection; WBC, white blood cell.

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CONCLUSIONS: **In a randomized trial of patients with advanced cirrhosis and non-SBP infections, in-hospital mortality was similar between those who received albumin plus antibiotics vs those who received only antibiotics (controls). However, patients given albumin were sicker at baseline and, during the follow-up period, a higher proportion had ACLF resolution and a lower proportion had nosocomial infections. ClinicalTrials.gov no: NCT02034279.**

Keywords: Acute-on-Chronic Liver Failure; Mortality; Nosocomial Infections; Immune-Modulation.

The transition from compensated to decompensated cirrhosis occurs in the setting of an activation of the immune system, chronic systemic inflammation, and multiorgan dysfunction.[1–4] Systemic inflammation induces an immune-modulatory response that increases the risk of infection.[5] When infection develops in decompensated cirrhosis, there is a secondary burst of inflammation,[1–5] which may lead to the development of acute-on-chronic liver failure (ACLF).

The pioneer randomized controlled trial (RCT)[6] done in patients with spontaneous bacterial peritonitis (SBP) showing that intravenous albumin reduced the prevalence of type-1 hepatorenal syndrome (HRS) and hospital mortality, introduced the prophylactic use of albumin in patients with bacterial infections. However, 2 subsequent negative RCTs in patients with non-SBP infections suggested that the beneficial effects of albumin did not extend to all types of infections.[7,8] However, short-term mortality rates were very low in both studies (5%).

We performed a retrospective analysis of 3 cohorts to identify patients with cirrhosis and non-SBP infections at higher risk of hospital mortality.[9] Mortality was highly dependent of the type of infection: high in endocarditis and secondary peritonitis, intermediate in pneumonia and bacteremia, and low in urinary tract infection (UTI) and cellulitis. Hospital mortality rate of each type of infection was significantly higher in patients with poor liver/renal function.

Based on these data, we designed an RCT aimed to assess if albumin treatment impacted hospital survival among patients with cirrhosis with non-SBP infections at high risk of hospital mortality. The secondary endpoint was the effect of albumin treatment on patients' clinical course during hospitalization.

Patients and Methods

Study Oversight

The INFECIR-2 Albumin Prevention study (Albumin administration in the prevention of HRS and death in patients with cirrhosis, bacterial infections other than SBP and high risk of hospital mortality; ClinicalTrials.gov: NCT02034279) is an EASL-CLIF Consortium investigator-initiated, phase IV, randomized, open-label, parallel, multicenter European trial promoted by the Fundació Clínic (Hospital Clínic, University of Barcelona, Barcelona, Spain). Written informed consent was obtained from all patients. All authors had access to the study data, critically reviewed the manuscript, and approved the final draft. The trial was performed in 27 centers, in accordance with the Declaration of Helsinki, and was approved by the different local ethics committees and competent authorities.

Patients

Inclusion criteria. Patients with non-SBP infections were screened for eligibility. Inclusion criteria were: age $\geq$18 years; liver cirrhosis; UTI, pneumonia, spontaneous/secondary bacteremia, cellulitis, acute cholangitis, or suspected bacterial infection; and advanced liver disease (serum creatinine $\geq$1.2 mg/dL, serum sodium $\leq$130 mEq/L, and/or serum bilirubin $\geq$4 mg/dL). Patients with pneumonia or spontaneous/secondary bacteremia required the presence of at least 1 of these criteria (serum creatinine $\geq$1.2 mg/dL, serum sodium $\leq$130 mEq/L, or serum bilirubin $\geq$4 mg/dL)[9]; in the rest, at least 2 were required. Patients with UTI or suspected infections required additionally at least 1 diagnostic criterion of systemic inflammatory response syndrome (temperature $>$38°C or $<$36°C; heart rate $>$90 beats/minute; respiratory rate $>$20 breaths/minute; white blood cell (WBC) count $>$12.000 or $<$4000/mm^3); and a serum C reactive protein (CRP) level $\geq$1 mg/dL.

Exclusion criteria. The main exclusion criteria were: infections evolving for $>$72 hours, septic shock, endocarditis, severe acute respiratory distress syndrome ($Pa_{O_2}/F_{I_{O_2}}$ $\leq$100), active/recent variceal bleeding (unless controlled for $>$48 hours), type-1 HRS (International Ascites Club criteria), ACLF grade-3, malignancy (except for hepatocellular carcinoma within Milan criteria or nonmelanocytic skin cancer), chronic heart failure (New York Heart Association functional class II-IV), severe chronic pulmonary disease (Global Initiative for Chronic Obstructive Lung Disease IV), liver transplantation, human immunodeficiency virus infection, contraindications to albumin, albumin administration ($\geq$80 g) in the last 2 days, and SBP coinfection. All exclusion criteria are detailed in the Supplementary Material.

Randomization

Randomization was performed in blocks of 4 (1:1 ratio). It was centralized at the Data Management Center of the European Foundation for the Study of Chronic Liver Failure, was independent for each center, and

performed online. A computer-generated randomization list (block sizes blinded for the investigators) was used for treatment allocation. Blocks were stratified by the type (pneumonia vs other infections) and the site of acquisition of infection (nosocomial vs other).

Treatment Allocation, Study Protocol, and Follow-Up

Eligible patients were randomized to receive antibiotics alone (control group) or antibiotics plus albumin (study group). Suggestions for the choice of empirical antibiotics were given in the study protocol (Supplementary Material). The study albumin (Albutein 20%, Instituto Grifols) was administered at a dose of 1.5 g/kg body weight at Day 1 and 1 g/kg body weight at Day 3 up to a maximum of 150 g and 100 g, respectively, in patients with body weight >100 kg, and a minimum of 90 g and 60 g, respectively, in patients with body weight <60 kg. Albumin administration was started within the first 8 hours after randomization and infused in 6–12 hours with close clinical monitoring to prevent volume overload. Follow-up visits were performed on Days 3 and 7, and weekly thereafter until infection resolution. Data on liver transplantation, hospital and 90-day mortality, and causes of death were recorded within 3 months after enrollment. No other doses of albumin were allowed in both treatment arms throughout the hospitalization unless needed for the treatment of type-1 HRS, total paracentesis, or SBP.

As per protocol, routine laboratory tests, serum albumin levels, and plasma concentration of interleukin 6 (IL6) and renin (plasma renin concentration [PRC]) were measured at Days 1 and 3 (before albumin doses in the study group) and at infection resolution or Day 7. PRC and IL6 were measured by chemiluminescent immunoassay and enzyme-linked immunosorbent assay, respectively.

Assessment of Disease Severity at Enrollment and Definitions

We enrolled patients with prespecified criteria for advanced cirrhosis.[10] Disease severity at enrollment was estimated by standard tests, Child-Pugh, Model for End-Stage Liver Disease, and CLIF-Consortium organ failure scores[11] (Supplementary Table 1) and by the presence of ACLF or kidney dysfunction (KD). Reasons for considering these 2 later variables to assess disease severity are described in the Supplementary Material and in Supplementary Tables 2 and 3.

Definitions and diagnostic criteria of ACLF and bacterial infections are also detailed in the Supplementary Material.

Study Outcomes

The prespecified primary outcome was mortality in hospital. Secondary outcomes were: the grade of circulatory dysfunction (as estimated by PRC), systemic inflammation (as estimated by plasma concentration of IL6 and other biomarkers) and complications related with these abnormalities (ACLF and nosocomial bacterial infections), and 90-day mortality. We also sought to identify predictors of in-hospital and 90-day mortality, and development of ACLF, bacterial infection, and pulmonary edema during hospitalization.

Statistical Analysis

Unless specified, analyses were performed on an intention-to-treat (ITT) basis. In-hospital mortality was estimated to be about 29% in patients who did not receive albumin. Based on this assumption, a global sample size of 512 patients (256 per treatment arm) was estimated to detect an absolute reduction of 11% (18% mortality rate) in patients treated with albumin (80% statistical power).[6,9] A 2-way 5% type-I error and a 10% drop-out rate was assumed.

Statistical analysis was performed using unpaired Student *t* test for continuous variables with parametric distribution, Mann-Whitney *U* test for those with nonparametric distribution, and chi-square test for qualitative variables, applying Yate correction when required. Differences were considered significant at the level 0.05. Survival was analyzed by Kaplan-Meier method and compared between groups with log-rank test. Risk factors were assessed using univariate analysis, and variables that were significantly associated with the different outcome events were included in the multivariate analysis by fitting logistic regression models to obtain adjusted treatment estimates and independent

What You Need to Know

Background

We performed a randomized trial to determine whether albumin should be administered to patients with infections unrelated to spontaneous bacterial peritonitis (SBP).

Findings

Among patients with advanced cirrhosis and non-SBP infections, in-hospital mortality is similar between those who receive the combination of albumin and antibiotics and those who received only antibiotics. However, a higher proportion of patients given albumin have resolution of acute on chronic liver failure and a lower proportion develop nosocomial infections.

Implications for patient care

Patients with advanced cirrhosis and non-SBP infections who receive the combination of albumin and antibiotics have better outcomes than patients who receive only antibiotics.

Table 1. Characteristics of the Patients at Baseline

Characteristics	Albumin plus antibiotics (n = 61)	Antibiotics alone (n = 57)	*P* value
Demographic, clinical, and laboratory data			
Age, *y*	58.3 ± 13.7	58.5 ± 11.0	.92
Male sex, n (%)	35 (58.3)	39 (66.1)	.38
Alcoholic cirrhosis, n (%)	31 (50.8)	39 (68.4)	.05
Diabetes mellitus, n (%)	21 (35.0)	17 (28.8)	.47
Ascites, n (%)	48 (80.0)	42 (71.2)	.26
Hepatic encephalopathy, n (%)	28 (46.7)	27 (45.8)	.92
Mean arterial pressure, *mm Hg*	78.2 ± 11.7	78.4 ± 11.7	.94
Median value (interquartile range) for serum bilirubin, *mg/dL*	5.9 (6.2)	7.3 (6.8)	.25
Serum albumin, *g/L*	23.6 ± 9.1	24.0 ± 8.4	.78
Prothrombin ratio, %	49.6 ± 13.0	48.9 ± 16.5	.82
Serum creatinine, *mg/dL*	1.27 ± 0.66	1.13 ± 0.38	.16
Serum sodium, *mEq/L*	131.1 ± 6.2	132.8 ± 5.4	.12
Serum bilirubin ≥4 mg/dL, %	33 (55.9)	36 (63.2)	.43
Serum creatinine ≥1.2 mg/dL, %	32 (53.3)	28 (49.1)	.65
Serum sodium <130 mEq/L, %	35 (57.4)	26 (45.6)	.20
Serum creatinine ≥1.2 mg/dL or serum sodium <130 mEq/L, %	50 (82.0)	44 (77.2)	.52
Median values (interquartile range) for markers of systemic inflammation and circulatory dysfunction			
White blood cell count, $\times 10^9$/L	7.2 (4.8–10.5)	6.9 (4.9–10.1)	.95
Serum C-reactive protein, *mg/dL*	12.7 (4.6–46.5)	15.8 (6.4–42.1)	.63
Plasma interleukin 6, *pg/mL*	37 (21–155)	41 (24–108)	.91
Plasma renin concentration, *micro IU/mL*	242 (46–903)	125 (34–399)	.29
Presence of ACLF or kidney dysfunction, n (%)			
ACLF-1	13 (21.3)	8 (14.0)	.63
ACLF-2	4 (6.6)	1 (1.8)	
ACLF	17 (27.9)	9 (15.8)	.11
Kidney dysfunction	10 (16.4)	5 (8.8)	.21
ACLF or kidney dysfunction	27 (44.3)	14 (24.6)	.025
Liver scores			
Child-Pugh score, points	10.4 ± 9.8	10.5 ± 10.0	.77

Table 1. Continued

Characteristics	Albumin plus antibiotics (n = 61)	Antibiotics alone (n = 57)	*P* value
Model of End-stage Liver Disease score, points	19.3 ± 5.5	19.8 ± 5.1	.60
CLIF-Consortium organ failure score, points	7.4 ± 1.7	7.5 ± 1.6	.77
Site and severity of infection, n (%)			
Pneumonia	17 (27.9)	22 (38.6)	.22
Spontaneous or secondary bacteremia	15 (24.6)	11 (19.3)	.49
Urinary tract infection	12 (19.7)	8 (14.0)	.41
Cellulitis	2 (3.3)	6 (10.5)	.15
Cholangitis	3 (4.9)	0	.24
Unproven infections	10 (16.4)	9 (15.8)	.93
Other[a]	2 (3.2)	1 (1.8)	1.0
Presence of sepsis	35 (57.4)	28 (49.1)	.37
Site of acquisition of infection, n (%)			
Community-acquired	27 (45.8)	25 (42.4)	.78
Health care–associated	14 (23.3)	15 (25.0)	
Nosocomial	18 (30.0)	19 (31.7)	
Results of microbial culture, n (%)			
Culture-positive	31 (50.8)	32 (56.1)	.56
Presence of multidrug-resistant bacteria	10 (16.4)	14 (24.6)	.27

NOTE. Plus–minus values are means ± SD. Analyses were performed on an intention-to-treat basis.
ACLF, acute-on-chronic liver failure.
[a]One cholecystitis and 1 *Clostridium difficile* infection occurred in the albumin-plus-antibiotics group, and 1 spontaneous bacterial empyema in the antibiotics-alone group.

risk factors (forward stepwise selection method). Competing risk analyses were used to evaluate the impact of albumin treatment on the primary outcome, estimating the cumulative incidence of death at hospital discharge, whereas liver transplantation was treated as a competing event. Competing risk analysis was also used to estimate the cumulative incidence of new proven bacterial infection during hospitalization in both treatment arms. Liver transplantation was treated again as a competing event. The estimated cumulative incidences were compared by means of the Gray test. Analysis was done with SPSS version 18.0 (IBM, Armonk, NY) and SAS version 9.1 (SAS Institute, Cary, NC).

Results

Baseline Characteristics

Patients' enrollment. The study was started on September 1, 2014, and finished in December 31, 2016. Overall, of the 534 patients who were screened from September 2014 to April 2016, 433 were excluded (inclusion rate, 19%). Thereafter, investigators were instructed to record only those patients included. Finally, a total of 136 patients were enrolled and 18 were considered inclusion errors (Supplementary Figure 1). The final ITT population consisted of 118 patients, 61 in the study group and 57 in the control group.

Demographic characteristics and clinical data. The prevalence of alcoholic cirrhosis was higher in the control group (68.4% vs 50.8% in the study group; $P = .05$) (Table 1). There were no differences in other demographic or clinical data.

Severity of cirrhosis and systemic inflammation. There were no significant differences between groups in standard liver and renal function tests and liver scores (Table 1). However, the combined prevalence of ACLF and KD was significantly higher in the study group (44.3% vs 24.6%; $P = .025$), suggesting significantly higher disease severity.

The grade of circulatory dysfunction (PRC) was also similar between groups as well as the severity of systemic inflammation, as estimated by WBC count, plasma IL6 concentrations, and serum CRP levels.

Type, severity, and microbiology of bacterial infections. Median time from diagnosis of infection to study inclusion was 1 day in both groups. Pneumonia, bacteremia, and UTI were the most frequent infections. Sixty-three patients showed signs of sepsis. Infections

Table 2. Effects of Treatment on Standard Laboratory Tests, Biomarkers of Systemic Inflammation and Circulatory Dysfunction, and the Course of Bacterial Infection and ACLF Diagnosed at Enrollment

Variable	Albumin plus antibiotics (n = 61)	*P* value for within-group comparison[a]	Antibiotics alone (n = 57)	*P* value for within-group comparison[b]	*P* value for between-group comparison[c]
Serum albumin and liver, kidney, and circulatory function					
Serum albumin, *g/L*					
Baseline	25.9 ± 6.4		26.0 ± 5.7		
Day 3–7	31.2 ± 6.5	< .0001	25.8 ± 5.3	.5414	< .001
Median value for serum bilirubin (IQR), *mg/dL*					
Baseline	4.3 (1.7–7.8)		5.1 (2.1–11.0)		
Day 3–7	4.0 (2.3–8.7)	.8120	4.3 (1.7–9.7)	.0274	.18
Prothrombin ratio, %					
Baseline	49.6 ± 13.0		48.9 ± 16.5		
Day 3–7	48.1 ± 14.2	.3793	49.5 ± 16.1	.4155	.16
Serum creatinine, *mg/dL*					
Baseline	1.3 ± 0.7		1.1 ± 0.4		
Day 3–7	1.1 ± 0.6	.0116	1.1 ± 0.4	.1513	.18
Serum sodium, *mEq/L*					
Baseline	131.2 ± 6.2		132.7 ± 5.4		
Day 3–7	134.9 ± 5.7	< .0001	133.5 ± 5.1	.0905	.002
Mean arterial pressure, *mm Hg*					
Baseline	78.1 ± 11.7		79.1 ± 11.0		
Day 3–7	82.1 ± 11.8	.0167	80.1 ± 10.5	.4758	.18
Median value for plasma renin concentration (IQR), *μIU/m*[d]					
Baseline	242 (46–903)		125 (34–399)		
Day 3–7	161 (18–393)	.0002	91 (25–768)	.4426	.004
Median value for markers of inflammation (IQR)					
White blood cell count, $\times 10^9$/L					
Baseline	7.2 (4.8–10.5)		6.9 (4.9–10.1)		
Day 3–7	5.8 (3.9–9.0)	.0003	6.2 (4.3–10.0)	.1347	.14
Serum C-reactive protein, *mg/dL*					
Baseline	12.7 (4.6–46.5)		15.8 (6.4–42.1)		
Day 3–7	8.7 (3.0–28.0)	< .0001	11.5 (3.8–33.4)	< .0001	.81
Plasma interleukin 6, *pg/mL*[e]					
Baseline	37 (21–155)		41 (24–108)		
Day 3–7	32 (18–69)	.0322	32 (17–72)	.2900	.71
Course of infection, n (%)					
Adequate empirical antibiotics	55 (90.2)	—	51 (89.5)	—	.90
Septic shock	6 (9.8)	—	2 (3.5)	—	.17
Infection resolution	53 (89.8)	—	54 (96.4)	—	.27
Course of ACLF or kidney dysfunction, n/N (%)					
Resolution of ACLF[f]	14/17 (82.3)	—	3/9 (33.3)	—	.03
Resolution of kidney dysfunction	7/10 (70.0)	—	3/5 (60.0)	—	.28
Resolution of ACLF or kidney dysfunction	21/27 (77.8)	—	6/14 (42.9)	—	.03

NOTE. Plus–minus values are means ± SD. Analyses were performed on an intention-to-treat basis.
ACLF, acute-on-chronic liver failure; IQR, interquartile range.
[a]Comparison of baseline vs Day 3–7, in the albumin-plus-antibiotics group.
[b]Comparison of baseline vs Day 3–7, in the antibiotics-alone group.
[c]Between group comparison was performed at Day 3–7.
[d]Plasma renin concentrations were determined at Day 1, and Day 3–7 in 40 patients in the albumin-plus-antibiotics group and in 41 patients in the antibiotics-alone group.
[e]Interleukin 6 levels were determined at Day 1, and Day 3–7 in 48 patients in the albumin-plus-antibiotics group and in 47 patients in the antibiotics-alone group.
[f]The 4 patients with ACLF-2 in the albumin-plus-antibiotics group solved the syndrome; this did not occur in the single patient with ACLF-2 of the antibiotics-alone group.

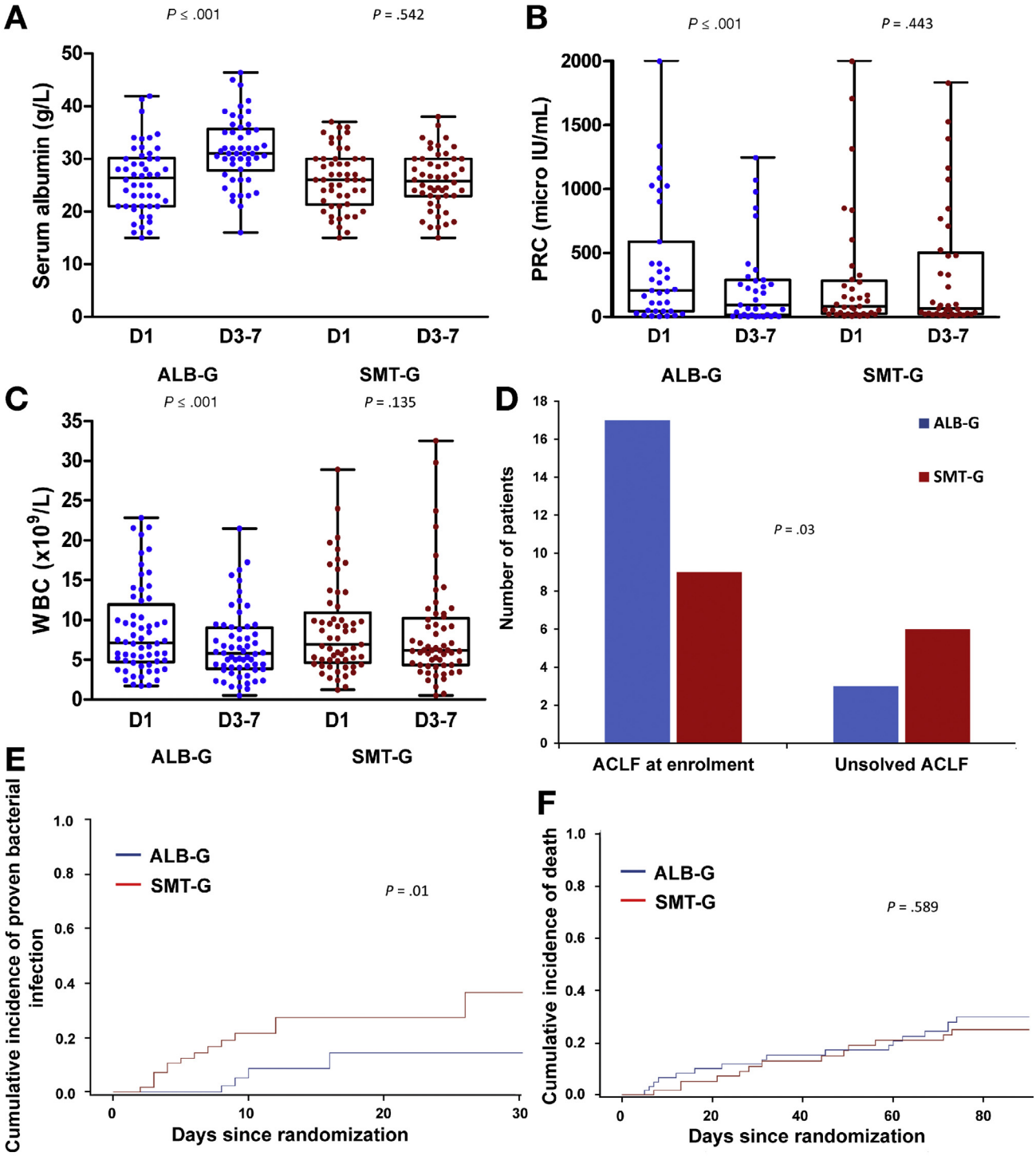

Figure 1. Albumin therapy in patients with advanced cirrhosis and non-SBP infections induces multifaceted beneficial effects but no increase in survival. (*A*) Individual changes in serum albumin concentration during treatment. Serum albumin concentration increased significantly only in patients receiving albumin; $P < .001$ for the between-group comparison. (*B*) Individual changes in PRC during treatment. Albumin treatment was associated with a marked reduction in PRC; $P = .004$ for the between-group comparison. (*C*) Individual changes in WBC during treatment. WBC decreased in both groups, but differences were statistically significant only in patients receiving albumin; *P* value not significant (0.14) for the between-group comparison. (*D*) Clinical course of ACLF diagnosed at enrollment. It resolved more frequently in patients receiving albumin. (*E*) Cumulative incidence of new proven bacterial infections was significantly higher in the control group. (*F*) Cumulative incidence of death was similar between groups. Liver transplantation was considered as a competing risk of bacterial infection development and death. In every panel, *blue color* represents patients treated with albumin and antibiotics, and *red color* those treated with antibiotics alone. ALB-G, albumin group; PRC, plasma renin concentration; SMT-G, standard medical therapy group.

Table 3. New Events During Hospitalization and Short-Term Mortality

Event	Albumin plus antibiotics (n = 61)	Antibiotics alone (n = 57)	*P* value
New bacterial infections			
Patients with infections, n (%)			
Patients with proven or unproven infections, n (%)	6 (9.8)	14 (24.6)	.03
Patients with proven infections, n (%)	4 (6.6)	14 (24.6)	.007
Type and severity of infections, n (%)			.27
Pneumonia	1 (1.6)	4 (7.0)	
Spontaneous or secondary bacteremia	1 (1.6)	4 (7.0)	
Urinary tract infection	1 (1.6)	3 (5.3)	
Spontaneous bacterial peritonitis	1 (1.6)	0	
Cellulitis	1 (1.6)	2 (3.5)	
Unproven infections	2 (3.3)	0	
Clostridium difficile infection	0	2 (3.5)	
Other	0	1 (1.8)	
Number of infectious episodes	7	16	
Presence of sepsis	4 (6.6)	6 (10.5)	.44
Microbiology and course of infection, n (% of infections)			
Culture positive[a]	1 (14.3)	10 (62.5)	.07
Multidrug-resistant bacteria	1 (14.3)	7 (43.8)	.34
Adequate empirical antibiotics	4 (57.1)	14 (87.5)	.14
Septic shock	2 (28.6)	5 (31.3)	.38
Infection resolution	4 (57.1)	12 (75.0)	.63
New episodes of ACLF, n (%)			
Patients with ACLF, n (%)			
ACLF-1	6 (9.8)	6 (10.5)	.86
ACLF-2	5 (8.2)	5 (8.8)	
ACLF-3	1 (1.6)	2 (3.5)	
Overall ACLF	12 (19.7)	13 (22.8)	.68
Potential mechanisms of the new ACLF			.17
Recurrence of a resolved ACLF	2 (3.3)	0	
Precipitated by baseline bacterial infection[b]	5 (8.2)	5 (8.8)	
Precipitated by new bacterial infection	1 (1.6)	4 (7.0)	
Unknown mechanism	4 (6.6)	4 (7.0)	
Course of ACLF			
Resolution	3 (4.9)	6 (10.5)	.39
Other clinical events, n (%)			
Variceal bleeding	4 (6.6)	2 (3.5)	.45
Nonvariceal bleeding	4 (6.3)	3 (5.3)	.77
Atrial fibrillation	2 (3.3)	0	.50
Pulmonary edema	4 (6.6)	2 (3.5)	.45
Liver transplantation and mortality, n (%)			
Liver transplantation during hospitalization	1 (1.6)	4 (7.0)	.20
Liver transplantation by 90 days	2 (3.3)	6 (10.5)	.15
Hospital mortality	8 (13.1)	6 (10.5)	.66
90-day mortality[c]	17 (27.9)	13 (22.8)	.41

NOTE. Analyses were performed on an intention-to-treat basis.
ACLF, acute-on-chronic liver failure.
[a]In the albumin-plus-antibiotics group there was 1 infection caused by extended-spectrum β-lactamase *Escherichia coli*. In the antibiotics-alone group, there were 3 infections caused by vancomycin-susceptible *Enterococcus faecium*, 3 by *E coli* (1 extended-spectrum β-lactamase), 2 *Klebsiella pneumoniae* (1 extended-spectrum β-lactamase, 1 carbapenem-resistant), and 1 by vancomycin-resistant *E faecium*.
[b]In these cases, ACLF developed during the next 7 days after inclusion with no new infections or other clinical events within this period.
[c]Seven patients were lost to follow-up at 90 days (5 in the albumin-plus-antibiotics group and 2 in the antibiotics-alone group).

were community acquired in 52 patients (Table 1). Half of the infections were associated with positive cultures (24 were caused by multiresistant bacteria). There were no significant differences between groups in the type, site of acquisition, severity, and microbiology of infections (Supplementary Material and Supplementary Table 4).

Albumin Administration

All except 5 patients in the study group received the scheduled doses of 20% albumin on Days 1 and 3. Four patients did not receive albumin on Day 3 because of pulmonary edema (n = 3) or septic shock (n = 1). Another patient received only 20 g of albumin on Days 1

and 3. Additional data on albumin treatment are shown in the Supplementary Material.

Primary Outcome

Death in hospital occurred in 8 patients (13.1%) in the study group, and 6 patients (10.5%) in the control group (hazard ratio in the study group, 1.2; 95% confidence interval, 0.5–3.4; $P = .7789$).

Secondary Outcomes

Effects of treatment on changes in baseline data. Albumin concentration increased significantly only in the study group (Table 2). However, it reached normal levels in only 12 out of the 49 patients with hypoalbuminemia at enrollment (Figure 1*A*). Patients of the study group significantly improved kidney and circulatory function within the first 7 days after enrollment (Table 2, Figure 1*B*). These patients also developed a significant suppression of systemic inflammation (decrease in WBC [Figure 1*C*], CRP, and plasma IL6 concentrations). In contrast, patients from the control group only experienced a significant decrease in CRP. Changes in these inflammatory parameters were, however, not significantly different in the between-group comparison (Table 2).

Most patients received adequate empiric antibiotic therapy (Table 2). Resolution of the baseline infection was obtained in 107 patients (90.7%), with similar rates between groups. Resolution of infection could not be determined in 3 patients (2 in the study group) who were discharged under antibiotic therapy and were lost to follow-up. The remaining 8 patients (6.8%) suffering from pneumonia (n = 4), bacteremia (n = 2), and cellulitis and UTI (n = 1, each) died before resolution of the infection. Six patients in the study group and 2 in the control group developed septic shock.

Most patients with ACLF at enrollment (17 out 26; 65.4%) resolved the syndrome. Resolution of ACLF was significantly higher in the study group (82.4% vs 33.3%; $P = .03$; Figure 1*D*). Resolution of KD at enrollment was similar in both groups (70% and 60%, respectively). Overall, the percentage of patients who resolved ACLF or KD in the 2 groups was 77.8% and 42.9%, respectively ($P = .03$).

Effects of treatment on the development of new events during hospitalization and on 90-day survival. The median (interquartile range) duration of hospitalization was 11 (6–27) and 14 (8–27) days in the study and control groups (P = NS), respectively. Twenty patients developed 23 episodes of nosocomial bacterial infections (Table 3). The most frequent infections were pneumonia and bacteremia (n = 5 each). The rate of newly developed bacterial infections (proven and unproven) was significantly lower in the study group (9.8% vs 24.6%; $P = .03$; Table 3). The rate of newly developed proven bacterial infections was also significantly lower ($P = .007$) in the study group (6.6%, vs 24.6%). After considering liver transplantation as a competing event, the cumulative incidence of new bacterial infection was significantly lower in the study group with a subdistribution hazard ratio of 0.26 (95% confidence interval, 0.09–0.77) (Figure 1*E*).

Twelve patients in the study group and 13 in the control group developed an episode of ACLF during hospitalization. ACLF grades at diagnosis were similar between groups (Table 3). The most frequent cause of ACLF during hospitalization was bacterial infections, either present at enrollment (n = 10) or developing during hospitalization (n = 5) (Table 3).

Other significant events were variceal (n = 6) and nonvariceal (n = 7) hemorrhage, atrial fibrillation (n = 2), and pulmonary edema (n = 6). There were no significant between-group differences in the overall frequency of these events (23% vs 12%; $P = .13$). Side effects potentially related with volume overload (pulmonary edema, atrial fibrillation, and variceal bleeding) were more frequent in the study group, although difference was not statistically significant (16% vs 7%; $P = .12$).

One patient in the study group and 4 in the control group were transplanted during hospitalization, and 1 and 2 additional patients, respectively, were transplanted within the first 90-day period after enrollment. Ninety-day mortality rate was 27.9% in the study and 22.8% in the control group ($P = .41$). The cumulative incidence of death at 90-days did not differ between the 2 study groups, with a subdistribution hazard ratio of 1.22 (95% confidence interval, 0.60–2.50) (Figure 1*F*).

Results of the Per-Protocol Analysis

Eleven patients, 5 in the study group and 6 in the control group, presented relevant protocol deviations and were excluded from the per-protocol analysis. Results in the per-protocol population were similar to those observed in the ITT population (Supplementary Tables 5–7, Supplementary Figure 2).

Risk Factors for Relevant Events During Hospitalization, Including Death

Factors obtained at enrollment showing significant association with relevant events occurring during hospitalization, in-hospital, and 90-day mortality are indicated in Supplementary Table 8.

Discussion

The 2 RCTs so far published assessing albumin treatment in patients with non-SBP infections[7,8] were important in the design of our trial. First, we chose hospital mortality instead of 90-day mortality rate as the main endpoint because most patients in these trials died within the first 30 days. Second, because mortality rate in

these studies was low,[7,8] we selected patients with a potential high hospital mortality rate.[9]

The current study did not show significant differences in in-hospital and 90-day mortality rates between treatment arms, confirming the results of the prior RCTs. However, our trial disclosed outstanding findings that have never been reported.

A most relevant feature, which affects the interpretation of the main clinical results of the trial, was that the combined prevalence at enrollment of 2 important predictors of mortality in patients with decompensated cirrhosis (ACLF and KD) was significantly higher in the study group. However, ACLF at enrollment was the most accurate predictor of hospital and 90-day mortality in the trial. Therefore, disease severity at enrollment was significantly greater in those patients assigned to the study group. This might explain the lack of effect of albumin treatment on mortality despite inducing significant beneficial effects on important pathophysiological mechanisms and complications.

First, we observed a potential beneficial effect of albumin on systemic inflammation within the first 7 days of treatment. Any decrease in inflammatory biomarkers in our patients could be attributed to a rapid control of the infection. However, whereas treatment with antibiotics alone was associated with a significant decrease in CRP but not in WBC or IL6, treatment with antibiotic plus albumin led to significant reduction in levels of these 3 inflammatory biomarkers. Changes were, nevertheless, not significantly different in the between-group comparison.

Second, treatment with antibiotics plus albumin but not with antibiotics alone was associated with improvement in renal and circulatory function as indicated by a significant increase in mean arterial pressure and serum sodium and decrease in PRC and creatinine in the study group but not in the control group.

Third, treatment with antibiotics plus albumin was associated with a surprisingly high-resolution rate of the ACLF present at enrollment (82.3%), significantly higher than that observed in the control group (33.3%). This resolution rate is higher than that observed in the Chronic Liver Failure Acute-on-Chronic Failure in Cirrhosis (CANONIC) study in patients not receiving albumin,[1] suggesting that albumin treatment, if administered early after diagnosis, may increase the resolution of ACLF.

Fourth and most important beneficial effect of albumin treatment was that prevalence of proven bacterial infections during hospitalization was 4-fold lower in patients receiving albumin, suggesting a preventive effect of albumin on nosocomial bacterial infections. In contrast, albumin treatment did not prevent ACLF development during hospitalization.

The beneficial effects of albumin treatment observed in the study could be related to its dampening action on excessive systemic proinflammatory signals. Excessive proinflammatory response is compensated with the activation of anti-inflammatory mediators to prevent immunopathology, favoring secondary infections.[5,12] Albumin could modulate this homeostatic compensatory reaction and therefore protect from the development of nosocomial infections.

Our trial has several limitations. The statistical power to detect a potential reduction in hospital mortality in patients treated with albumin was low because only 118 patients could be enrolled into the study. Differences in the exclusion criteria between our trial and the cohorts included in our pilot investigation[13–15] could have contributed to overestimation of the recruitment rate and hospital mortality. Finally, we did not obtain good matching between groups. Inclusion of less sick patients in the control group could explain the lower than expected hospital mortality rate in this group (10.5%). However, the strength of the study was the study design and inclusion of clinically important endpoints, including the clinical effects of albumin treatment on patients' clinical course during hospitalization.

As expected, albumin treatment significantly increased serum albumin concentration but only a minority of patients with hypoalbuminemia normalized albumin concentration. The inhibition of the hepatic synthesis of albumin by bacterial infection may account for this feature. In addition, the half-life of circulating albumin is markedly reduced when, as it occurs in cirrhosis, there is impairment in the molecular structure of the protein.[16] We have observed that the immunomodulatory effect of albumin is highly dependent on the post-treatment serum albumin concentration.[17] Therefore, current albumin dosage in patients with cirrhosis with bacterial infections may be too simplistic. A more rational approach may consist of the administration of a priming dose followed by additional periodical doses tailored by the serum albumin concentration.

Finally, the frequency of pulmonary edema was slightly higher in patients receiving albumin. When all events potentially related to volume overload were considered together, there was a trend toward a higher rate of these side effects in the albumin group.

In summary, in this trial involving patients with advanced cirrhosis and infections unrelated to SBP, in-hospital mortality was not different among patients who received albumin plus antibiotics and those who received antibiotics only. This occurred despite the beneficial effects of albumin treatment on circulatory and renal dysfunction, resolution of baseline ACLF, and prevention of nosocomial infections. Disease severity at inclusion, however, was greater in the group of patients treated with albumin. Further appropriately designed and powered RCTs are needed to ascertain if albumin treatment decreases mortality in patients with cirrhosis with non-SBP bacterial infections.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical*

Gastroenterology and Hepatology at www.cghjournal.org, and at https://doi.org/10.1016/j.cgh.2019.07.055.

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Conflicts of interest
This author discloses the following: Javier Fernandez has received research support from Grifols. The other authors disclose no conflicts. The EASL-CLIF Consortium is a network of 101 European University hospitals supported by the European Foundation for the Study of Chronic Liver Failure (EF-Clif). EF-Clif is a private nonprofit organization aimed at improving clinical and translational research in cirrhosis. The scientific agenda of the EASL-CLIF Consortium and the specific research protocols are made exclusively by the Steering Committee members without any participation of pharmaceutical companies.

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Supplementary Appendix

Patients and Methods

Exclusion Criteria. Exclusion criteria were infections evolving for >72 hours, septic shock,[1] endocarditis, fungal infection, severe acute respiratory distress syndrome (Pao_2/Fio_2 ≤100), active or recent variceal bleeding (unless controlled for >48 hours), type-1 HRS (International Ascites Club criteria),[2] ACLF grade-3 (3 or more organ failures [OFs] according to the Canonic Study criteria),[3] renal-replacement therapy, malignancy (except for hepatocellular carcinoma within Milan criteria or nonmelanocytic skin cancer), moderate or severe chronic heart failure (New York Heart Association functional class II, III, or IV), severe chronic pulmonary disease (Global Initiative for Chronic Obstructive Lung Disease IV), previous liver transplantation, severe psychiatric disorders that prevent the patient from making autonomous decisions, human immunodeficiency virus infection (except for patients under antiretroviral therapy with undetectable viral load, CD4 levels >200/mm^3, and no previous history of opportunistic infections), contraindications to albumin (allergy, signs of pulmonary edema), albumin administration (≥80 g) in the last 2 days, SBP coinfection, administration of any investigational drug within 90 days before randomization, premenopausal women not practicing an acceptable method of birth control, refusal to participate, patients who could not provide prior informed consent and when there was documented evidence that the patient had no legal surrogate decision maker and it seemed unlikely that the patient would regain consciousness or sufficient ability to provide delayed informed consent, and physician and team not committed to intensive care if needed (DNR code).

Definitions

Acute-on-chronic liver failure. The diagnosis of ACLF and its grades were performed according to the Canonic study criteria.[3] ACLF was defined as the association of acute decompensation (defined as ascites, encephalopathy, variceal hemorrhage, or any combination of these), single or multiple (≥2) OFs, and high short-term (28-day) mortality risk (>15%). OF was defined for each of the 6 major organ systems (liver, kidney, brain, coagulation, circulation, and respiration) as a CLIF-Consortium OF score of 2 or 3 (on a scale ranging from 1 to 3 for each organ system)[3] (Supplementary Table 1). In brief, for nonkidney organ systems, a score of 1 indicated normal of relatively preserved organ function; a score of 2, organ dysfunction (OD), including liver dysfunction, brain dysfunction, coagulation dysfunction, circulatory dysfunction, and respiratory dysfunction); and a score of 3, OF. For the kidney, scores of 2 and 3 indicated kidney failure. Among patients with a kidney score of 1, those who had serum creatinine levels ranging from 1.5–1.9 mg/dL were defined as having KD.

According to Canonic criteria, patients with acute decompensation are classified into 4 groups according to the number and type of OFs (Supplementary Table 2):

1. ACLF-3: 3–6 OFs (mortality risk, 75%)
2. ACLF-2: 2 OFs (mortality risk, 32%)
3. ACLF-1: Single kidney failure, or single nonkidney OF if associated with KD and/or brain dysfunction (mortality risk, 22%)
4. No ACLF: None of these characteristics (mortality risk, 4.6%). Please note that patients from this group may have single nonkidney OF (Supplementary Table 1) or single or combined OD.

Resolution of ACLF was defined as a decrease from any grade of ACLF to no ACLF.[4]

Bacterial infections. Definitions and diagnostic criteria of infections were the following. SBP: polymorphonuclear (PMN) cell count in ascitic fluid ≥250/mm^3; UTI: abnormal urinary sediment (>10 leukocytes/field) or a positive reagent strip and positive urinary culture or uncountable leukocytes per field if negative cultures; spontaneous bacteremia: positive blood cultures and no cause of bacteremia; secondary bacteremia: catheter-related infection (positive blood and catheter cultures), and bacteremia occurring within 24 hours after an invasive procedure; pneumonia: clinical signs of infection and new infiltrates on chest radiograph; bronchitis: clinical features of infection, no radiographic infiltrates, and positive sputum culture; cellulitis: clinical signs of infection associated with swelling, erythema, heat, and tenderness in the skin; cholangitis: cholestasis, right upper quadrant pain and/or jaundice, and radiologic data of biliary obstruction; spontaneous bacterial empyema: PMN count in pleural fluid ≥500/mm^3 (250/mm^3 if positive culture); secondary peritonitis: PMN count in ascitic fluid ≥250/mm^3 and evidence (abdominal computed tomography/surgery) of an intra-abdominal source of infection; *Clostridium difficile* infection: positive stool toxin in a patient with diarrhea; unproved bacterial infection: presence of fever (≥38°C) and leukocytosis (white blood cell count ≥12.000/mm^3) requiring antibiotic therapy without any identifiable source. Infections diagnosed at admission or within 2 days after admission were classified as health care–associated (HCA) in patients with a prior contact with the health care environment (hospitalization or short-term admission for at least 2 days in the previous 90 days, residence in a nursing home or a long-term care facility, or chronic hemodialysis). The remaining infections were considered community-acquired (CA) when they were present at admission or developed within the first 48 hours after hospitalization and nosocomial when the diagnosis was made thereafter.[5]

MDR was defined as acquired nonsusceptibility to at least 1 agent in 3 or more antimicrobial categories.[6] The following bacteria were considered MDR in the current study: extended-spectrum β-lactamase (mainly *Escherichia coli* and *Klebsiella pneumoniae*) or desrepressed chromosomic AmpC ß-lactamase-producing *Enterobacteriaceae* (*Enterobacter*, *Citrobacter*, and *Proteus* spp), carbapenem-resistant *K pneumoniae*, carbapenem-resistant *Pseudomonas aeruginosa*, *Stenotrophomonas maltophilia*, carbapenem-resistant *Acinetobacter baumanii*, methicillin-resistant *Staphylococcus aureus* (MRSA), and vancomycin-susceptible *Enterococcus faecium*.

Patients were considered to have systemic inflammatory response syndrome (sepsis) if they fulfilled at least 2 of the following criteria: (1) core temperature $>38^{\circ}C$ or $<36^{\circ}C$; (2) heart rate >90 beats/minute; (3) respiratory rate >20 breaths/minute in the absence of hepatic encephalopathy; and (4) white blood cell count >12.000 or <4000 /mm^3, or differential count showing $\geq 10\%$ immature PMN neutrophils. Septic shock was diagnosed by the presence of data compatible with systemic inflammatory response syndrome and need of vasopressor drugs in the setting of hypotension.[1] Recently defined sepsis criteria were not applied in the current study because they were proposed after the end of the Canonic Study.

Infections were considered cured when all clinical signs of infection disappeared and on the presence of: (1) urinary infections: normal urine sediment and negative urine culture; (2) spontaneous or secondary bacteremia: negative control cultures after antibiotic treatment; (3) pneumonia: normal chest radiograph and negative control cultures if positive at diagnosis; (4) bronchitis: negative bronchial aspirate/sputum culture; (5) cellulitis: normal physical examination of the skin and negative control cultures if positive at diagnosis; (6) cholangitis: improvement of cholestasis, resolution of clinical symptoms, and negative control cultures if positive at diagnosis; and (7) SBP and spontaneous bacterial empyema: PMN cell count in ascitic/pleural fluid <250/mm^3 and negative control cultures if positive at diagnosis. Resolution of the rest of infections was based on conventional clinical criteria.[5]

The criteria used to consider an initial antibiotic therapy appropriate were the following: culture-positive infections, if an antibiotic with an in vitro activity appropriate for the isolated pathogen or pathogens was administered at diagnosis of infection; and culture-negative infections, when the antibiotic strategies administered at the time of infection diagnosis solved the infection without need for further escalation. Otherwise, the initial therapy was considered inappropriate.[5]

Empirical Antibiotic Treatment Suggested in the Study

Empirical antibiotic treatment should be administered within the first 6 hours after infection diagnosis and will be different for infections acquired in the community (CA infections) and HCA or nosocomial infection because of the higher prevalence of multiresistant bacteria in the later infections. Treatment schedule will be adapted to the local epidemiologic pattern of multiresistance. The suggested empirical treatment in this protocol as follows.

Community-acquired infections. CA infections will be treated as follows: ceftriaxone for urinary and suspected bacterial infection; ceftriaxone plus cloxacillin or amoxicillin clavulanic-acid for cellulitis; piperacillin-tazobactam for cholangitis; and ceftriaxone and a macrolide or levofloxacin in patients with pneumonia. Ceftriaxone plus clindamycin will be administered in case of aspiration pneumonia.

Health care–associated and nosocomial infections. Empirical antibiotic regimen in HCA or nosocomial infections will be the following: carbapenem for urinary and suspected bacterial infection (plus a glycopeptide in areas with a high prevalence of *E faecium*); imipenem for cholangitis (plus a glycopeptide in areas with a high prevalence of *E faecium*); antipseudomonic carbapenem (meropenem, imipenem, or doripenem) or ceftazidime plus glycopeptide for cellulitis; and antipseudomonic carbapenem or ceftazidime plus ciprofloxacin in patients with pneumonia. Vancomycin, teicoplanin, or linezolid will be added in patients with pneumonia and risk factors for MRSA (ventilator-associated pneumonia, previous antibiotic therapy, nasal MRSA carriage).

Antibiotics will be administered intravenously at standard doses: ceftriaxone, 2 g at diagnosis followed by 1 g/12–24 hours; amoxicillin clavulanic-acid, 2–0.4 g/8 hours; cloxacillin, 2 g/6 hours; clarithromycin, 500 mg/12 hours; levofloxacin, 500 mg/12–24 hours; clindamycin, 600 mg/8 hours; piperacillin-tazobactam, 4 g/6–8 hours; meropenem, 1 g/8 hours; doripenem, 0.5 g/8 hours; imipenem, 0.5–1 g/6–8 hours; ertapenem, 1 g/12–24 hours; ceftazidime, 2 g/8 hours; ciprofloxacin, 400 mg/8–12 hours; vancomycin, 15–20 mg/kg/8–12 hours; teicoplanin, 6 mg/kg; and linezolid, 600 mg/12 hours. Doses will be adjusted to renal function (glomerular filtration rate will be estimated by the Cockcroft-Gault or the Modification of Diet in Renal Disease equations following local guidelines). De-escalation to the most appropriate antibiotic should be done early after knowing the results of the microbiologic tests.

Antibiotic treatment will be maintained until the disappearance of signs and symptoms of infection, normalization of the white blood cell count, and negative cultures. Patients with positive cultures at infection diagnosis will have to have control negative cultures before stopping antibiotics. Suggested duration of treatment in CA infections will be of 7 days except for pyelonephritis, cholangitis, and cellulitis (10 days). Suggested duration of treatment in HCA and nosocomial infections will be of 10 days, except for pneumonia and cellulitis caused by multiresistant bacteria (14 days).

Assessment of Disease Severity at Enrollment

To avoid the limitations of the previous trials regarding patients' severity, only cases with acute decompensation and significant liver and renal impairment, as prespecified by high levels of serum bilirubin and/or creatinine and/or low plasma sodium levels, were enrolled in our trial. Patient severity at enrollment was initially planned to be assessed by these measurements and by the Model for End-Stage Liver Disease and Child-Pugh scores. However, investigations published between the study design and data analysis[7-10] showed important limitations of these measurements and scores. Moreover, the diagnostic criteria of ACLF proposed by the Canonic study leave many patients with single non-kidney OF or with single or combined OD in the non-ACLF group (Supplementary Tables 1 and 2). Recent data indicate that these patients are at higher risk of developing worse clinical course or dying than those without OF or OD.[11] However, KD was found to be an accurate marker of high short-term mortality (19.2% vs 5.7% in patients with and without KD, respectively; $P = .02$) in a pilot investigation in 496 patients without ACLF from Canonic study database (Supplementary Table 3). Based on these results, we decided to add ACLF and KD at enrollment as indicators of disease severity before data analysis.

Results

Microbiology of Bacterial Infections Diagnosed at Inclusion

E coli was the most frequently isolated organism (34.8%), followed by *S aureus* (14.5%); *K pneumoniae* (10.1%); and *Streptococcus viridans*, *Enterobacter* spp, and *Enterococcus faecalis* (4.3% each). Twenty-six of the 69 organisms isolated in the study (37.7%) were multidrug-resistant organisms. They were isolated in 24 infections (20.3% of all infections, 38.1% of culture-positive infections). As a whole, extended-spectrum β-lactamase-producing *E coli* was the most frequent multidrug-resistant organism reported (n = 9), followed by MRSA (n = 4) (Supplementary Table 4).

Albumin Administration

Albumin treatment was initiated after the first 8 hours following randomization in 4 patients. Overall, the median albumin doses (interquartile range [IQR]) administered on Day 1 and Day 3 were 100 (90–110 g) and 62.5 (60–80 g), respectively. The median difference (IQR) between the scheduled dose and the administered dose of albumin on Day 1 was 0 (-2.5 to 0.5 g) and 0 (0–1 g) on Day 3. Nine patients (6 in the control group and 3 in the study group) received relevant albumin doses ($\geq$1 g/kg body weight) within the first week after randomization for the treatment of complications other than the initial infection. The median albumin doses (IQR) administered were 80 (70–100 g) in the study group and 60 (55–90 g) in the control group, respectively.

Risk Factors for Relevant Events During Hospitalization, Including Death

Factors obtained at enrollment showing significant association with relevant events occurring during hospitalization, in-hospital, and 90-day mortality are indicated in Supplementary Table 8. Albumin treatment was independently associated with lower prevalence of proven bacterial infections. Diabetes was independently related to the development of pulmonary edema. Hepatic encephalopathy and severity of systemic inflammation (as estimated by WBC) at enrollment were independently associated with a higher prevalence of ACLF. Finally, ACLF at enrollment was the only independent predictor of in-hospital mortality, the primary outcome of the trial, and was also identified as an independent predictor of 90-day mortality together with bacteremia and prothrombin index.

Baseline serum albumin levels were lower in patients included in the study group who developed ACLF or bacterial infections during hospitalization, although differences were not statistically significant (Supplementary Table 9).

Supplementary Table 10 shows details concerning the main events occurring during hospitalization in patients who died and their causes of death. Death was related with lack of resolution of bacterial infections in 11 patients (8 corresponding to infections detected at enrollment).

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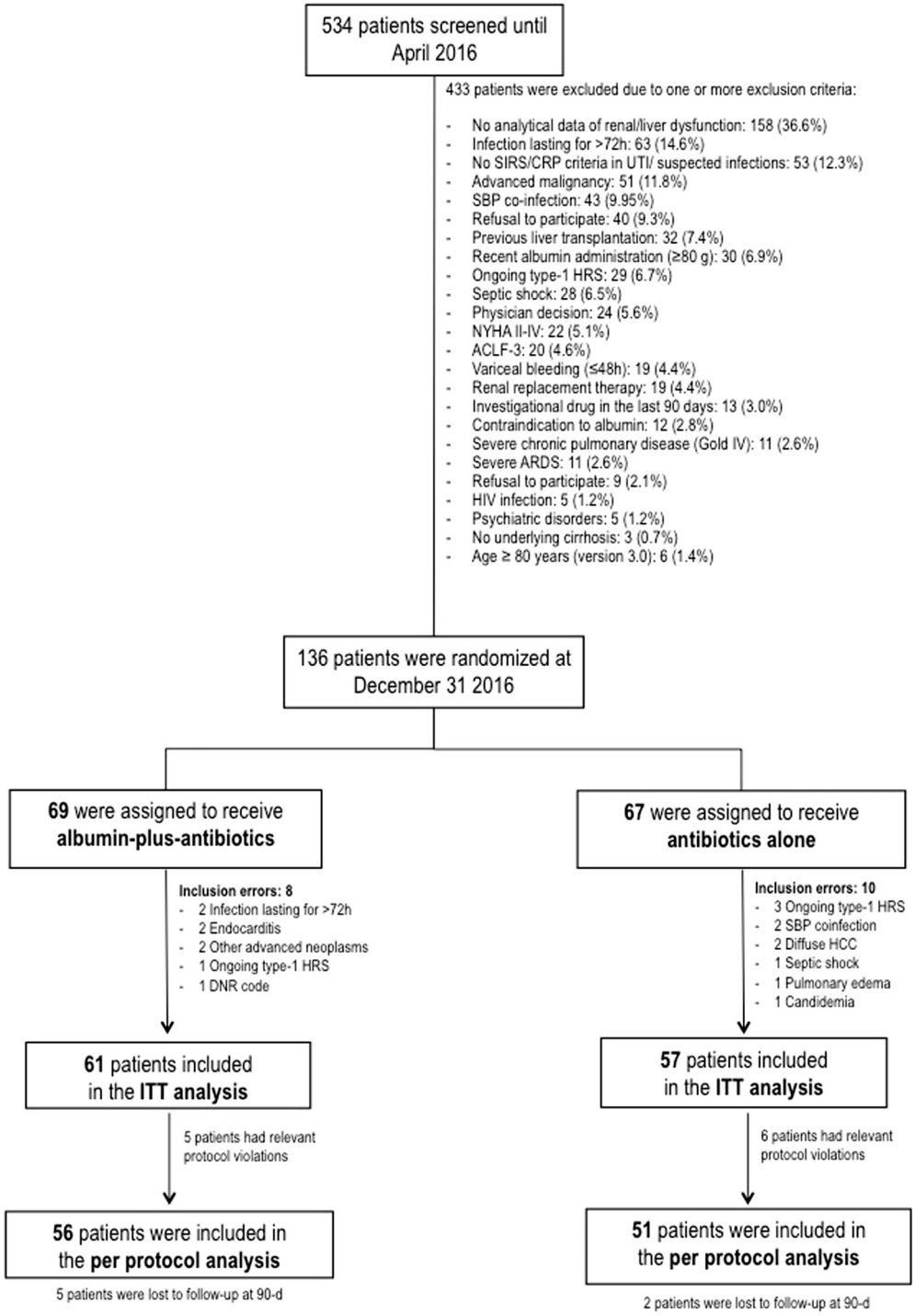

Supplementary Figure 1. Flow chart of the study. Overall, 534 patients were assessed for eligibility, and 433 subjects were excluded. A total of 136 patients were enrolled. Eighteen patients were considered inclusion errors. The final ITT population consisted of 118 patients, 61 in the study group and 57 in the control group. Eleven patients, 5 in the study group and 6 in the control group, presented relevant protocol deviations. Seven patients were lost to follow-up at 90 days. ARDS, acute respiratory distress syndrome; GOLD, Global Initiative for Chronic Obstructive Lung Disease; HCC, hepatocellular carcinoma; HIV, human immunodeficiency virus; NYHA, New York Heart Association; SIRS, systemic inflammatory response syndrome.

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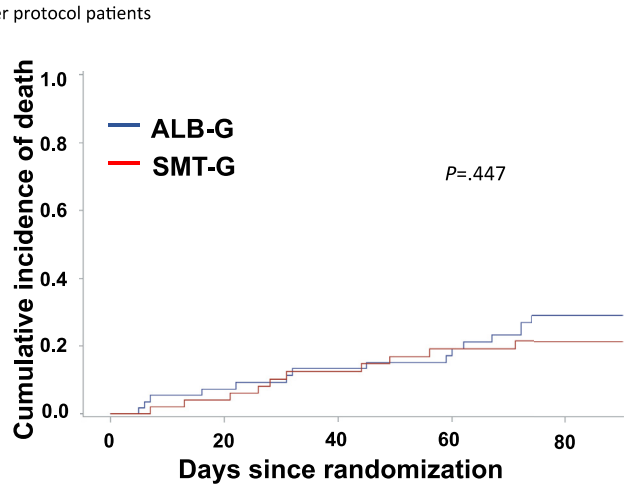

Supplementary Figure 2. Cumulative incidence of death by 90 days in the per-protocol population, when liver transplantation was taken into account as a competing risk of death. At 90 days, the estimated cumulative incidence of death was 28.9% (95% confidence interval, 17.2%–41.7%) in the albumin-plus-antibiotics group and 21.3% (95% confidence interval, 10.9%–34.1%) in the antibiotics-alone group. No significant differences were observed between groups. ALB-G, Albumin Group; SMT-G, Standard Medical Therapy Group.

Supplementary Table 1. Diagnostic Criteria of Organ Failures and Organ Dysfunctions According to the CLIF-Consortium Organ Failure Scoring System

	Scale assessing the deterioration in organ system functions		
Organ system	1 point	2 points	3 points
Liver	Bilirubin <6 mg/dL	Bilirubin ≥6 mg/dL and ≤12 mg/dL	Bilirubin >12 mg/dL
Kidney	Creatinine <2 mg/dL	Creatinine ≥2 mg/dL and <3.5 mg/dL	Creatinine ≥3.5 mg/dL or RRT
	Creatinine from 1.5 to 1.9 mg/dL		
Brain (West-Haven)	Grade 0	Grade 1–2	Grade 3–4
Coagulation	INR <2.0	2.0 ≤ INR <2.5	INR ≥2.5
Circulation	MAP ≥70 mm Hg	MAP <70	Vasopressor requirement
Respiratory[a]	>300	>200 and ≤300	≤200
Pa_{O_2}/F_{IO_2} or Sp_{O_2}/F_{IO_2}	>357	>214 and ≤357	≤214

NOTE. Adapted from Reference 3. Each organ system (liver, kidney, coagulation, brain, circulation, respiration) receives a score ranging from 1 point (normal or close to normal) to 3 points (most abnormal). Highlighted areas in blue reflect the definition of each organ failure. Highlighted areas in orange reflect the definition of each organ dysfunction. The sum of the 6 individual organ scores gives rise to an aggregated score called CLIF-Consortium organ failure score, ranging from 5 to 15, higher scores indicating more severe disease.

CLIF, chronic liver failure; F_{IO_2}, fraction of inspired oxygen; INR, international normalized ratio; MAP, mean arterial pressure; RRT, renal-replacement therapy; Sp_{O_2}, pulse oximetric saturation.

[a]Patients treated with mechanical ventilation received a respiratory organ failure score of 3 points.

Supplementary Table 2. Mortality Rates by 28 Days According to the Number and Types of In-Patients With or Without Kidney and/or Brain Dysfunction (Canonic Study)

	No kidney dysfunction and no brain dysfunction	Kidney dysfunction or brain dysfunction, or both
Number and types of OF	Mortality rate (%)	
OF absent	3.6	6.2
Single liver failure	5.9	30.3
Single cerebral failure	8.0	20.0
Single coagulation failure	5.3	22.2
Single circulation or single respiratory failure	6.7	28.6
Single kidney failure	15.8	24.1
Two OFs	28.8	38.7
Three OFs or more	86.2	61.5

NOTE. Adapted from Reference 1 (main manuscript). The highlighted colored areas show the subgroups of patients with ACLF: in blue ACLF-1, in orange ACLF-2, in yellow ACLF-3.

ACLF, acute-on-chronic liver failure; OF, organ failure.

Supplementary Table 3. Development of ACLF and Death by 28 Days Among the 496 Patients Without ACLF but With Different Types of Single Organ System Failure or Dysfunction at Enrollment (Canonic Study Patients)

Organ system	ACLF development by 28 d	*P* value	28-d mortality	*P* value
Liver, n/N (%)				
Liver dysfunction or liver failure only	12/54 (22.2)	.03	4/52 (7.7)	.76
No liver dysfunction or liver failure[a]	50/442 (11.3)		27/427 (6.3)	
Kidney, n/N (%)				
Kidney dysfunction only	12/28 (42.9)	< .0001	5/26 (19.2)	.02
No kidney dysfunction[a]	50/468 (10.7)		26/453 (5.7)	
Brain, n/N (%)				
Brain dysfunction or failure only	6/85 (7.1)	.1	3/83 (3.6)	.33
No brain dysfunction or brain failure[a]	56/411 (13.6)		28/396 (7.1)	
Coagulation, n/N (%)				
Coagulation dysfunction or failure only	1/11 (9.1)	1.0	2/11 (18.2)	.15
No coagulation dysfunction or coagulation failure[a]	61/485 (12.6)		29/468 (6.2)	

NOTE. Among the 496 patients, 62 developed ACLF and 31 died by 28 days.
ACLF, acute-on-chronic liver failure.
[a]Includes patients with or without other organ dysfunction.

Supplementary Table 4. Characteristics of Bacteria Isolated in the Different Infections Diagnosed at Enrollment in Both Treatment Arms

Characteristic	Albumin plus antibiotics (n = 61)	Antibiotics alone (n = 57)	Total
Number of isolated bacteria, n	35	34	69
Number of gram-negative bacteria	23	19	42
Number of each isolate			
Escherichia coli	13	11	24
ESBL	5	4	
Carbapenem-resistant		1	
Klebsiella pneumoniae	4	3	7
ESBL		1	
Carbapenem-resistant		1	
Klebsiella oxytoca	1		1
Enterobacter spp		3	3
Citrobacter spp	1	1	2
Proteus spp	1		1
Pseudomonas aeruginosa	1		1
Stenotrophomonas maltophilia	1		1
Acinetobacter baumanii		1	1
Bacteroides fragilis	1		1
Number of gram-positive cocci	10	13	23
Number of each isolate			
Enterococcus faecalis	2	1	3
Staphylococcus aureus	4	6	10
Methicillin-sensitive *S aureus*	2	4	
Methicillin-resistant *S aureus*	2	2	
Enterococcus faecium (VSE)	1		1
Streptococcus pneumoniae		1	1
Streptococcus viridans		3	3
Streptococcus agalactiae	2		2
Streptococcus oralis	1	1	2
Other GPC		1	1
Number of other organisms (n)	2	2	4
Haemophilus influenza	—	2	2
Clostridium difficile	2	—	2

ESBL, extended-spectrum β-lactamase; GPC, Gram positive cocci; VSE, vancomycin-susceptible *Enterococcus*.

Supplementary Table 5. Baseline Characteristics of the Per-Protocol Population

Characteristic	Albumin plus antibiotics (n = 56)	Antibiotics alone (n = 51)	*P* value
Demographic, clinical, and laboratory data			
Age, *y*	58.5 ± 13.9	57.6 ± 10.7	.71
Male sex, n (%)	34 (60.7)	33 (64.7)	.67
Alcoholic cirrhosis, n (%)	28 (50.0)	36 (70.6)	.03
Diabetes mellitus, n (%)	18 (32.1)	17 (33.3)	.90
Ascites, n (%)	44 (78.6)	38 (74.5)	.62
Mean arterial pressure, *mm Hg*	77.5 ± 11.4	79.1 ± 10.7	.46
Median value (interquartile range) for serum bilirubin, *mg/dL*	4.3 (1.8–7.0)	4.6 (2.0–11.0)	.51
Serum albumin, *g/L*	26.1 ± 6.6	26.4 ± 5.8	.85
Prothrombin ratio, n (%)	49.8 (12.7)	48.5 ± 16.3	.71
Serum creatinine, *mg/dL*	1.3 ± 0.7	1.1 (0.4)	.06
Serum sodium, *mEq/L*	131.6 (6.3)	132.4 (5.4)	.51
Serum bilirubin ≥4 mg/dL, n (%)	31 (56.4)	30 (58.8)	.80
Serum creatinine ≥1.2 mg/dL, n (%)	31 (56.4)	24 (47.1)	.34
Serum sodium <130 mEq/L, n (%)	30 (53.6)	25 (49.0)	.64
Serum creatinine ≥1.2 mg/dL or serum sodium <130 mEq/L, n (%)	45 (80.4)	39 (76.5)	.63
Median values (interquartile range) for markers of inflammation and circulatory dysfunction			
White blood cell count, $x10^9/L$	7.1 (4.8–11.5)	7.7 (4.4–11.7)	.90
Serum C-reactive protein, *mg/dL*	11.9 (4.8–48.0)	15.0 (4.1–34.2)	.91
Plasma interleukin 6, *pg/mL*	38 (22–159)	38 (18–71)	.59
Plasma renin concentration, *μIU/mL*	242 (46–903)	93 (26–327)	.18
Presence of ACLF or kidney dysfunction, n (%)			
ACLF-1	11 (19.6)	6 (11.8)	.69
ACLF-2	3 (5.4)	1 (1.9)	
ACLF	14 (25.0)	7 (13.7)	.14
Kidney dysfunction	10 (17.9)	5 (9.8)	.23
ACLF or kidney dysfunction	24 (42.8)	12 (23.5)	.03
Liver scores			
Child-Pugh score, points	10.3 ± 2.1	10.4 ± 1.9	.76
Model of End-Stage Liver Disease score, points	19.5 ± 5.6	19.4 ± 5.1	.95
CLIF-C OF score, points	7.3 ± 1.6	7.5 ± 1.7	.63
Site and severity of infection, n (%)			
Pneumonia	14 (25.0)	20 (39.2)	.11
Urinary tract infection	15 (26.8)	10 (19.6)	.38
Spontaneous or secondary bacteremia	11 (19.6)	8 (15.7)	.59
Cellulitis	2 (3.6)	5 (9.8)	.19
Cholangitis	3 (5.4)	0	.24
Unproven infections	9 (16.1)	8 (15.7)	.96
Other	2 (3.6)	0	.50
Presence of sepsis, n (%)	32 (57.1)	25 (49.0)	.40
Site of acquisition of infection, n (%)			
Community-acquired	16 (28.6)	14 (27.5)	.95
Health care–associated	36 (64.3)	34 (66.7)	
Nosocomial	4 (7.1)	3 (5.9)	
Results of microbial culture, n (%)			
Culture-positive	31 (55.4)	29 (56.9)	.88
Presence of multidrug-resistant bacteria	10 (17.9)	14 (27.5)	.24

NOTE. Plus–minus values are means ± standard deviation.
ACLF, acute-on-chronic liver failure; CLIF-C OF, CLIF-Consortium organ failure score.

Supplementary Table 6. Effects of Treatment on Standard Laboratory Tests, Biomarkers of Systemic Inflammation and Circulatory Dysfunction, and on the Course of Bacterial Infection and ACLF Diagnosed at Enrollment in the Per-Protocol Population

Variable	Albumin plus antibiotics (n = 56)	*P* value for within-group comparison[a]	Antibiotics alone (n = 51)	*P* value for within-group comparison[b]	*P* value for between-group comparison[c]
Serum albumin and liver, kidney, and circulatory function					
Serum albumin, *g/L*					
Baseline	23.6 (9.5)		24.4 (8.7)		
Day 3–7	30.6 (10.01)	< .0001	24.5 (8.3)	.1809	< .0001
Median value for serum bilirubin (IQR), *mg/dL*					
Baseline	4.3 (1.8–7.0)		4.6 (2.0–11.0)		
Day 3–7	4.0 (2.3–7.5)	.7429	4.0 (1.3–9.7)	.0174	.2033
Prothrombin ratio, %					
Baseline	49.8 (12.7)		48.5 (16.3)		
Day 3–7	48.6 (14.4)	.2785	49.1 (14.8)	.6432	.2683
Serum creatinine, *mg/dL*					
Baseline	1.3 (0.7)		1.1 (0.4)		
Day 3–7	1.1 (0.6)	.0136	1.0 (0.4)	.0821	.2788
Serum sodium, *mEq/L*					
Baseline	131.6 (6.3)		132.4 (5.4)		
Day 3–7	134.7 (5.4)	< .0001	133.3 (4.8)	.0762	.0130
Mean arterial pressure, *mm Hg*					
Baseline	77.5 (11.4)		79.1 (10.07)		
Day 3–7	82.1 (12.1)	.0050	80.9 (10.5)	.2305	.1966
Median value for plasma renin concentration, (IQR), *micro IU/mL*[d]					
Baseline	242 (46-903)		93 (26–327)		
Day 3–7	161 (18–393)	.0002	65 (24–480)	.5386	.0040
Median value for markers of inflammation (IQR)					
White blood cell count, $x10^9/L$					
Baseline	7.1 (4.8–11.5)		7.7 (4.4–11.7)		
Day 3–7	5.8 (4.0–9.0)	.0008	6.2 (4.2–9.4)	.0272	.3778
Serum C-reactive protein, *mg/dL*					
Baseline	11.9 (4.8–48.0)		15.0 (4.1–34.2)		
Day 3–7	8.7 (3.8–28.0)	< .0001	8.6 (3.8–31.0)	< .0001	.8927
Plasma interleukin 6, *pg/mL*[e]					
Baseline	38 (22–159)		38 (18–71)		
Day 3–7	32 (18–71)	.0194	28 (13–59)	.1176	.8153
Course of infection, n (%)					
Adequate empirical antibiotics	50 (89.3)		45 (88.2)		.864
Septic shock	3 (5.4)		1 (2.0)		.68
Infection resolution	50 (89.3)		49 (96.1)		.38
Course of ACLF or kidney dysfunction, n/N (%)					
Resolution of ACLF[f]	11 (78.6)		2 (28.6)		.06
Resolution of kidney dysfunction	7 (70.0)		3 (60.0)		.24
Resolution of ACLF or kidney dysfunction	18 (75.0)		5 (41.7)		.04

NOTE. Plus–minus values are means ± standard deviation.
ACLF, acute-on-chronic liver failure; IQR, interquartile range.
[a]Comparison of baseline vs Day 3–7, in the albumin-plus-antibiotics group.
[b]Comparison of baseline vs Day 3–7, in the antibiotics-alone group.
[c]Between-group comparison was performed at Day 3–7.
[d]Plasma renin concentrations were determined at Day 1, and Day 3–7 in 40 patients in the albumin-plus-antibiotics group and in 37 patients in the antibiotics-alone group.
[e]Interleukin 6 levels were determined at Day 1, and Day 3–7 in 47 patients in the albumin-plus-antibiotics group and in 43 patients in the antibiotics-alone group.
[f]The 3 patients with ACLF-2 in the albumin-plus-antibiotics group solved the syndrome; this did not occur in the single patient with ACLF-2 of the antibiotics-alone group.

Supplementary Table 7. New Events During Hospitalization and Short-Term Mortality in the Per-Protocol Population

Event	Albumin plus antibiotics (n = 56)	Antibiotics alone (n = 51)	*P* value
New bacterial infections			
Patients with infections, n (%)			
Patients with proven or unproven infections	5 (8.9)	11 (21.6)	.07
Patients with proven infections	4 (7.1)	11 (21.6)	.03
Type and severity of infections, n (%)	6	13	
Pneumonia			.30
Spontaneous or secondary bacteremia	1 (1.8)	3 (5.9)	
Urinary tract infection	1 (1.8)	4 (7.8)	
Spontaneous bacterial peritonitis	1 (1.8)	3 (5.9)	
Cellulitis	1 (1.8)	0	
Unproven infections	1 (1.8)	0	
Clostridium difficile infection	1 (1.8)	0	
Other	0	2 (3.9)	
Number of infectious episodes	4 (7.1)	3 (5.9)	.79
Presence of sepsis	0	1 (1.9)	
Microbiology and course of infection, n (% of infections)			
Culture positive[a]	1 (16.7)	9 (69.2)	.06
Multidrug-resistant bacteria	1 (14.3)	6 (46.2)	.33
Adequate empirical antibiotics	4 (66.7)	11 (84.6)	.56
Septic shock	2 (33.3)	3 (23.1)	.64
Infection resolution	4 (66.7)	10 (76.9)	.64
New episodes of ACLF, n (%)			
Patients with ACLF, n (%)			
ACLF-1	6 (10.7)	4 (7.8)	.29
ACLF-2	4 (7.1)	3 (5.9)	
ACLF-3	0	2 (3.9)	
Overall ACLF	10 (17.9)	9 (17.6)	.98
Potential mechanisms of the new ACLF, n (%)			.60
Recurrence of a resolved ACLF	1 (1.8)	0	
Precipitated by baseline bacterial infection[b]	4 (7.1)	5 (9.8)	
Precipitated by new bacterial infection	1 (1.8)	1 (1.9)	
Unknown mechanism	4 (7.1)	3 (5.8)	
Course of ACLF, n (%)			
Resolution	3 (5.4)	3 (5.9)	.49
Other clinical events, n (%)			
Variceal bleeding	4 (7.1)	2 (3.9)	.47
Nonvariceal bleeding	4 (7.1)	2 (3.9)	.47
Atrial fibrillation	2 (3.6)	0	.50
Pulmonary edema	1 (1.8)	2 (3.9)	.32
Liver transplantation and mortality, n (%)			
Liver transplantation during hospitalization	1 (1.8)	4 (7.8)	.19
Liver transplantation by 90 d	2 (3.6)	6 (11.8)	.15
Hospital mortality	6 (10.7)	5 (9.8)	.88
90-d mortality[c]	15 (26.8)	10 (19.6)	.16

NOTE. Categorical variables as number and percentage or number.

ACLF, acute-on-chronic liver failure; ESBL, extended-spectrum β-lactamase.

[a]In the albumin-plus-antibiotics group there was 1 infection caused by ESBL *Escherichia coli*. In the antibiotics-alone group there were 3 infections caused by vancomycin-susceptible *Enterococcus faecium*, 2 by *E coli* (1 ESBL), 1 by carbapenem-resistant *Klebsiella pneumoniae*, and 1 by vancomycin-resistant *E faecium*.

[b]In these cases, ACLF developed during the next 7 days after inclusion with no new infections or other clinical events within this period.

[c]Six patients were lost to follow-up at 90 days (5 in the albumin-plus-antibiotics group and 1 in the antibiotics-alone group).

Supplementary Table 8. Analysis of Risk Factors at Inclusion for the Development of New Bacterial Infections, New ACLF, Pulmonary Edema, and Short-Term Mortality

Variable	Event absent	Event present	*P* value	Odds ratio	95% confidence interval	*P* value
New proven bacterial infections						
Treatment with albumin, n/N (%)	57/100 (57.0)	4/18 (22.2)	.007	0.22	0.07–0.70	.01
New ACLF						
Hepatic encephalopathy, n/N (%)	39/93 (41.9)	16/25 (64.0)	.05	18.51	1.20–286.59	.04
Median value for white cell count, *x10-9/L* (IQR)	6.7 (4.2–11.7)	9.2 (6.5–10.0)	.02	1.22	1.01–1.47	.04
Median value for serum bilirubin, *mg/dL* (IQR)	4.3 (1.7–7.2)	6.6 (4.3–11.8)	.02			
Median value for plasma renin concentration, *μIU/mL* (IQR)	133 (28–385)	604 (149–1316)	.01			
Pulmonary edema						
Diabetes mellitus, n/N (%)	33/112 (29.5)	5/6 (83.3)	.01	12.17	1.36–108.56	.03
Serum albumin, *g/L*	24.1 (8.9)	21.2 (1.4)	.007			
Hospital mortality						
Hepatic encephalopathy, n/N (%)	45/104 (43.3)	10/14 (71.4)	.05			
ACLF at enrollment, n/N (%)	18/104 (17.3)	8/14 (57.1)	< .001	17.63	1.63–191.21	.02
ACLF or kidney dysfunction at enrollment, n/N (%)	31/104 (29.8)	10/14 (71.4)	.005			
Median value for serum bilirubin, *mg/dL* (IQR)	4.4 (1.8–7.4)	7.8 (5.5–16.7)	.004			
Prothrombin ratio, %	50.9 (14.7)	37.8 (8.7)	.005			
Median value for plasma renin concentration, *μIU/mL* (IQR)	160 (34–589)	1829 (660–4124)	.02			
90-d mortality, n/N (%)						
Hepatic encephalopathy	33/81 (40.7)	19/30 (63.3)	.03			
ACLF at study inclusion	13/81 (16.1)	11/30 (36.7)	.02	19.64	3.48–110.99	.001
ACLF or kidney dysfunction at enrollment	23/81 (28.4)	16/30 (53.3)	.02			
Spontaneous or secondary bacteremia at inclusion	13/81 (16.1)	11/30 (36.7)	.02	21.33	3.74–121.66	.001
Median value for serum bilirubin, *mg/dL* (IQR)	4.4 (1.8–7.4)	7.8 (5.5–16.7)	.004			
Prothrombin ratio, %	50.3 (14.1)	40.9 (10.5)	.007	0.94	0.89–0.996	.04

ACLF, acute-on-chronic liver failure; IQR, interquartile range.

Supplementary Table 9. Correlation Between Baseline Serum Albumin Levels and the Response to Albumin Treatment in Patients Included in the Albumin-Plus-Antibiotics Group

	Baseline serum albumin level, *g/L*	*P* value
Resolution of baseline ACLF		
No	26.9 (5.8)	
Yes	25.6 (7.5)	.6527
ACLF onset during hospitalization		
No	26.2 (5.4)	
Yes	24.9 (7.2)	.3697
Onset of new bacterial infections		
No	26.3 (6.1)	
Yes	24.1 (5.6)	.1481
Correlation with changes from baseline mean arterial pressure		
At 3 d	-0.036	.7152
At 7 d	0.160	.2992
At 3/7 d	-0.019	.8469
Correlation with changes from baseline interleukin 6		
At 3 d	0.043	.6932
At 7 d	-0.015	.9272
At 3/7 d	0.025	.8126

ACLF, acute-on-chronic liver failure.

Supplementary Table 10. Main Events Occurring During Hospitalization in Patients Who Died and Causes of Death

Patient ID	Adequate empirical antibiotics	Resolution of baseline infection	ACLF at enrollment	Resolution of ACLF at enrollment	New proven bacterial infection/day/ resolution	New ACLF/ day	Final ACLF grade	Day of death since enrollment	Cause of death
Antibiotics-alone group (n = 6)									
$1_{(02\text{-}08)}$	Yes	No	Yes	No	No/NA/NA	No/NA	ACLF-3	Day 13	Multiorgan failure; no identifiable trigger
$2_{(03\text{-}08)}$	No	Yes	No	—	Yes/Day 12/No	Yes/Day 7	ACLF-3	Day 26	Pulmonary edema
$3_{(14\text{-}01)}$	No	Yes	Yes	No	No/NA/NA	No/NA	ACLF-3	Day 28	Multiorgan failure; no identifiable trigger
$4_{(17\text{-}02)}$	Yes	Yes	Yes	Yes	Yes/Day 3/Yes Yes/Day 50/No	Yes/Day 55	ACLF-3	Day 56	Septic shock
5 $_{(21\text{-}03)}$	Yes	Yes	No	—	No/NA/NA	Yes/Day 21	ACLF-3	Day 22	Multiorgan failure; no identifiable trigger
6 $_{(24\text{-}13)}$	Yes	No	Yes	No	No/NA/NA	No/NA	ACLF-3	Day 13	Septic shock
Albumin-plus-antibiotics group (n = 8)									
$1_{(02\text{-}07)}$	Yes	Yes	Yes	Yes	Yes/Day 9/Yes Yes/Day 21/No	Yes/Day 10	ACLF-3	Day 22	Hypovolemic shock; variceal hemorrhage
$2_{(06\text{-}01)}$	No	No	Yes	No	No/NA/NA	No/NA	ACLF-3	Day 5	Septic shock
$3_{(09\text{-}08)}$	Yes	Yes	Yes	Yes	No	Yes/Day 28	ACLF-3	Day 31	Multiorgan failure without identifiable trigger
4 $_{(12\text{-}02)}$	Yes	No	No	—	No/NA/NA	Yes/Day 3	ACLF-3	Day 8	Multiorgan failure without identifiable trigger
5 $_{(14\text{-}15)}$	Yes	No	Yes	Yes	No/NA/NA	Yes/Day 12	ACLF-3	Day 12	Multiorgan failure without identifiable trigger
6 $_{(17\text{-}08)}$	No	No	No	—	No/NA/NA	Yes/Day 3	ACLF-3	Day 6	Multiorgan failure without identifiable trigger
$7_{(23\text{-}02)}$	Yes	No	No	—	No/NA/NA	Yes/Day 3	ACLF-2	Day 7	Multiorgan failure without identifiable trigger
$8_{(24\text{-}05)}$	Yes	No	No	—	No/NA/NA	Yes/Day 3	ACLF-2	Day 16	Multiorgan failure without identifiable trigger

ACLF, acute-on-chronic liver failure; NA, not available.