In this multicentre study, 193 cirrhotic patients with infections other than SBP, were randomly assigned to receive albumin infusion or no treatment in addition to antibiotics. The primary outcomes were renal failure and mortality rates. The study failed to show any beneficial effect on these outcomes, although albumin infusion delayed the onset of renal failure. However, in our opinion, some bias could have influenced the results. First, the prevalence of ascites was significantly higher in the patients randomized to albumin and antibiotics than in the patients assuming antibiotics alone (75.8 *vs.* 59.6%; $p = 0.017$). The development of infection and the consequent increase in vasodilatation may have influenced the rate of renal failure and prognosis of the former group differently from the control group in which the number of patients with ascites was lower. Second, the success or failure of antibiotic therapies were not analyzed and, as we know, the course of infections is a further important parameter for the prognosis of cirrhotic patients [5,6]. Third, as also discussed by the authors, many violations occurred in the protocol and 17 patients in the control group also received albumin for large volume paracentesis during the first week.

Thus, in our opinion, the results of the present study should not discourage further investigations in cirrhotic patients with infections also considering the wide range of potential benefits of albumin administration in this setting (antioxidant function, immunomodulation, anti-inflammatory activity and transport of many endogenous and exogenous substances), in addition to its well-known effect as plasma expander [7]. Among these additional properties, in particular, the effect of the albumin infusion during the therapy with moderately/highly protein-bound antibiotics should also be evaluated, considering the relevant role of hypoalbuminemia on the pharmacokinetics of these antibiotics [8].

Conflict of interest

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

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Reply to "Albumin infusion in cirrhotic patients with non-SBP infections: End of the story?"

To the Editor:

We greatly appreciate the comments by Lucidi *et al.* [1]. Firstly, we acknowledge that, despite well-conducted randomization to reduce the risk of selection bias at trial entry [2], the presence of ascites was more frequently reported in the albumin (ALB) group as compared with the control group (75.8 *vs.* 59.6; $p = 0.017$). We have to remember that using an alpha risk of 5%, the probability of there being no imbalance between groups for any one baseline characteristic is 0.95. Assuming the characteristics are independent, there is a non-negligible $1 - (0.95)^n$ probability of observing a significant imbalance between groups when comparing n baseline characteristics. For instance, in Table 1 showing the baseline characteristics of patients [2], there were at least 10 independent variables meaning that the chance of at least one statistically significant imbalance was 0.40. In order to improve the precision of the treatment effect estimate, and to avoid any confounding, the two Cox multivariate analyses performed to determine predictive variables associated with renal failure and death at 3 months were adjusted for ascites, which was no longer significant.

Secondly, Lucidi *et al.* are right in stressing that we omitted to accurately classify infections into healthcare-associated, nosocomial or community-acquired, to analyze the pathogenic organisms identified and the antibiotic resistance pattern, and to prospectively record the occurrence of a second infection [3]. All of these data are of considerable importance for outcome in cirrhotic patients. Our multicenter trial mainly aimed to evaluate the effectiveness of albumin in real-life practice, without any restriction on antibiotic prescriptions. In our study, nosocomial infections were not significantly associated with renal failure ($p = 0.53$ by univariate Cox model) or death at 3 months ($p = 0.13$).

Finally, Lucidi *et al.* also underline the protocol violations which may have diluted the treatment effect. These violations are common in interventional research [4,5] and to counteract such limitations, we performed sensitivity analyses to assess the robustness of our results regarding our primary endpoint, namely 3 month renal-failure-free survival. We performed; (1) a per-protocol analysis, in which the 15 patients who did not receive albumin infusion in the ALB group were excluded from the analysis; (2) an as-treated analysis, in which patients were analyzed according to the treatment they actually received; and (3) a best-case scenario favouring albumin administration by considering that all seven control patients and none of the four ALB group patients with missing data on serum creatinine developed renal failure [2]. All these sensitivity analyses showed that the 3 month renal-failure-free survival was not significantly different between the ALB and control groups.

Despite these overall negative results, we observed that the proportion of patients with renal failure at one-month was lower among septic patients with ascites and in patients with severe sepsis after albumin infusion, suggesting a beneficial effect of albumin in both these dramatic conditions. Clearly, our message was not to scare practitioners prescribing albumin in the setting of liver cirrhosis, since this drug is largely used all over the world in a wide variety of clinical settings [6], and recent advances in this field have proved that albumin exerts a protective effect by modulating inflammation, oxidative and cellular stress [7]. However, it is our duty to recommend caution regarding high volumes of albumin administered and rapid infusion rates, which may lead to fluid overload in some patients with unrecognized heart disease.

Conflict of interest

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

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Randomized study of danoprevir/ritonavir-based therapy for HCV genotype 1 patients with prior partial or null responses to peginterferon/ribavirin

To the Editors:

With great interest I read the article by Prof. Feld *et al.* [1], which concluded that danoprevir/r, mericitabine plus PegIFNα-2a/ribavirin produced high rates of sustained virological response 24 weeks after the end of treatment in prior partial and null responders.

It is well know that the body mass index is associated with the rates of sustained virological response (a body mass index greater