Albumin infusion in spontaneous bacterial peritonitis: another brick off the wall?

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Main text
Albumin infusion did not convey any survival benefit compared to normal saline in a randomized controlled study (RCT) which involved a very large population of ICU patients who required intravascular fluid resuscitation [1]. There was, however, a nonsignificant trend in favor of albumin in patients with severe sepsis [2]. This trend was contradicted in another RCT which did not show any difference in mortality when albumin was added to normal saline during severe sepsis or septic shock compared with saline alone [3]. Post hoc analyses, with their inherent limitation, suggested a trend for higher mortality in patients with severe sepsis without shock who received albumin and a significant reduction in mortality with albumin in patients with septic shock [3]. A conservative conclusion of all these studies is the lack of strong evidence in favor of albumin during sepsis without shock.

Spontaneous bacterial peritonitis (SBP) in cirrhotic patients is a frequent septic condition which carries an important morbidity and mortality. Patients often present all the characteristics indicating severe sepsis which would make them eligible for the above-mentioned studies [1, 3]. However, they were excluded from the ALBIOS study [3] and no detail on this specific patient population was given in the SAFE study [1, 2]. Therefore, there are no data from studies on sepsis that could suggest a potential advantage of albumin infusion over normal saline during SBP (see Table 1). Given all the above, one should not expect any major positive effect. Despite this lack of solid evidence, all guidelines on the treatment of SBP mandate the infusion of albumin in addition to antibiotics, at least for patients at risk of acute kidney injury [4–6]. In fact, this recommendation is disputable for three reasons:

1. Guidelines, even if some are posterior, do not take the above-mentioned studies into account.
2. This recommendation is based on RCTs that did not respect clinical equipoise, that is, “a genuine uncertainty within the expert clinical community, not necessarily on the part of the individual investigator regarding the comparative therapeutic merits of each arm in a trial” [7]. This is an ethical prerequisite for the scientific value of a clinical trial [7].
3. Indeed, as detailed in the princeps article by Sort et al. [8] and in a meta-analysis by Salerno et al. [9] which integrates all RCTs on albumin infusion during SBP and constitutes the cornerstone of recommendations in favor of albumin, these RCTs compared vascular filling with albumin with the absence of any intravascular fluids [8, 10, 11] or a hydroxyethyl starch infusion which was subsequently shown to be nephrotoxic [12] (Table 1). One may wonder whether such studies would get published nowadays. The only conclusion that can be drawn from these studies is the confirmation of the paramount importance of fluid resuscitation during sepsis, at least at the initial phase. In addition, most recommendations were written by experts who had financial ties with the manufacturers of albumin solutions. Many major journals now preclude that guidelines be written by authors with such ties [13]. Interestingly, the only recommendation published by authors without financial ties highlighted that the previous studies which were selected for the meta-analysis by Salerno et al. [9] could be “criticized as the control groups were not given an equivalent amount of fluid as crystallloid” and added that “further studies are required...
before making any formal recommendations about
the use of albumin in SBP” [6].

It stems from the preceding that superiority of albu-
min over normal saline has never been proved or even
tested during SBP. This is not a trivial issue when one
keeps in mind that the cost of infused albumin in pro-

tocols for SBP treatment amounts to about 300 euros
for each individual patient. Given the incidence of
SBP, million euros (or dollars) could be saved if normal
saline proved at least as effective as albumin.

Overall, there is abundant evidence that recommen-
dations for albumin during SBP have to be challenged
by trials using much cheaper alternatives such as saline
solution as comparator.

We are currently planning to undergo such a trial
for which we asked a grant from French Ministry of
Health. This study might be dedicated to Roger Waters
(with salt) and may remove another brick off the wall of
recommendations for albumin.

### Abbreviations

ICU: intensive care unit; RCT: randomized controlled study; SBP: spontaneous bacterial peritonitis.

### Authors’ contributions

All authors participated equally to the manuscript. All authors read and approved the final manuscript.

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References
1. Finfer S, Bellomo R, Boyce N, French J, Myburgh J, Norton R, et al. A comparison of albumin and saline for fluid resuscitation in the intensive care unit. N Engl J Med. 2004;350:2247–56.
2. SAFE Study Investigators, Finfer S, McEvoy S, Bellomo R, McArthur C, Myburgh J, et al. Impact of albumin compared to saline on organ function and mortality of patients with severe sepsis. Intensive Care Med. 2011;37:86–96.
3. Caironi P, Tognoni G, Masson S, Fumagalli R, Pesenti A, Romero M, et al. Albumin replacement in patients with severe sepsis or septic shock. N Engl J Med. 2014;370:1412–21.
4. Angeli P, Bernardi M, Villanueva C, Francoz C, Mookerjee RP, Trebicka J, et al. EASL Clinical Practice Guidelines for the management of patients with decompensated cirrhosis. J Hepatol. 2018;69:406–60.
5. Caraceni P, Angeli P, Prati D, Bernardi M, Alessandria C, Riggio O, et al. AISF-SIMTI position paper: the appropriate use of albumin in patients with liver cirrhosis. Dig Liver Dis. 2016;48:4–15.
6. Moore KP. Guidelines on the management of ascites in cirrhosis. Gut. 2006;55:1–12.
7. Freedman B. Equipoise and the ethics of clinical research. N Engl J Med. 1987;317:141–5.
8. Sore P, Navasa M, Arroyo V, Aldeguer X, Planas R, Ruiz-del-Arbol L, et al. Effect of intravenous albumin on renal impairment and mortality in patients with cirrhosis and spontaneous bacterial peritonitis. N Engl J Med. 1999;341:403–9.
9. Salerno F, Navickis RJ, Wilkes MM. Albumin infusion improves outcomes of patients with spontaneous bacterial peritonitis: a meta-analysis of randomized trials. Clin Gastroenterol Hepatol. 2013;11(123–130):e1.
10. Xue HP, Lin B, Mo JZ, Li XQ. Effect of albumin infusion on preventing the deterioration of renal function in patients with spontaneous bacterial peritonitis. Chin J Dig Dis. 2002;3:52–4.
11. Chen T-A, Tsao Y-C, Chen A, Lo G-H, Lin C-K, Yu H-C, et al. Effect of intravenous albumin on endotoxin removal, cytokines, and nitric oxide production in patients with cirrhosis and spontaneous bacterial peritonitis. Scand J Gastroenterol. 2009;44:619–25.
12. Mutter TC, Ruth CA, Dart AB. Hydroxyethyl starch (HES) versus other fluid therapies: effects on kidney function. Cochrane Database Syst Rev. 2013;CD007594.
13. American Society of Clinical Oncology. policy for relationships with companies. J Clin Oncol. 2017;35:796–8.
14. Fernández J, Monteagudo J, Bargallo X, Jiménez W, Bosch J, Arroyo V, et al. A randomized unblinded pilot study comparing albumin versus hydroxyethyl starch in spontaneous bacterial peritonitis. Hepatology. 2005;42:627–34.
15. Guevara M, Terra C, Nazar A, Sola E, Fernández J, Pavesi M, et al. Albumin for bacterial infections other than spontaneous bacterial peritonitis in cirrhosis: a randomized, controlled study. J Hepatol. 2012;57:759–65.
16. Thévenot T, Bureau C, Oberti F, Anty R, Louvet A, Plessier A, et al. Effect of albumin in cirrhotic patients with infection other than spontaneous bacterial peritonitis: a randomized trial. J Hepatol. 2015;62:822–30.