A step forward in the choice of fluid for early resuscitation of critically ill patients with cirrhosis

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The principles of septic shock treatment have been very similar for decades. However, the mortality from sepsis appears to have declined as suggested by several epidemiological studies [1–3]. Early recognition and timely implementation of treatment have probably contributed to improve outcomes and the management of these patients relies on the optimization of the tissue perfusion or on the hemodynamic management. The aim of the initial hemodynamic management, termed primary resuscitation, is to treat arterial hypotension. Fluid therapy is recommended in the Surviving Sepsis Guidelines as a part of the initial hemodynamic management [4]. However, fluids should be carefully prescribed to maximize their impact and limit their side effects. The amount of fluid administered has been reported at values under and over the current sepsis guidelines [5, 6]. Interestingly, limited fluid administration in sepsis patients does not seem to lead to high mortality [7] and a positive fluid balance is associated with increased mortality in septic patients [8]. More evidence is available on the type of fluids in the resuscitation of sepsis patients. Although firm evidence is lacking, balanced crystalloid solutions could have an advantage over saline. Among colloid solutions available on the market only albumin has an acceptable safety profile. In addition, albumin has a post hoc relationship with better outcomes in the SAFE trial [9] and ALBIOS trial [10]. In a predefined subgroup analysis of the Safe study, the administration of 4% albumin solution as compared to saline did not impair renal or other organ functions and may have decreased the risk of death. The findings of the Albios study showed that albumin supplementation in addition to crystalloids to correct hypoalbuminemia does not improve 90-day survival in patients with severe sepsis, as compared to the use of

crystalloids alone. However, they suggest a possible benefit in the subgroup of patients with septic shock. Albumin also has many oncotic and nononcotic properties that would logically support a beneficial effect in patients with sepsis or septic shock. Nevertheless, a definitive trial showing a solid advantage on outcomes and in particular on survival, was lacking. In the absence of such convincing data and given the high cost of albumin in some countries, its use for fluid resuscitation and/or supplementation is still based on the clinical judgment.

In this issue of *Hepatology Int.* *Philips et al.* present the results of a randomized controlled clinical trial (FRISC study) comparing the use of 5% albumin solution versus normal saline in patients with cirrhosis and sepsis-induced hypotension [11]. The paper is quite relevant for several reasons, but mainly for the two following ones. First, sepsis is more frequent in patients with cirrhosis than in the general population and represents the only major complication for which the rate of mortality did not reduce over the last decades. Second, no study was performed on hemodynamic management up to now in critically ill patients with cirrhosis and sepsis. The primary endpoint of the study was the reversal of hypotension with an absolute increase in MAP ≥ 65 mmHg at the end of the first three hours of the resuscitation period. Secondary endpoints were a mean arterial pressure ≥ 65 mmHg at the first and second hour of the study period and the effects of fluid resuscitation on heart rate, urine output, arterial lactate, and short-term mortality at the end of one week between the groups. Three hundred and eight patients with cirrhosis and sepsis-induced hypotension were enrolled and randomized into the two interventional groups. Patients received either 5% human albumin intravenous bolus, 250 ml over 15–30 min, followed by a maintenance infusion of 50 ml/h for a total of three hours, or 0.9% normal saline 30 ml/kg intravenous bolus over 15–30 min followed by a maintenance infusion of 100 ml/h for a total of three hours. In the first hour, in the whole study group, 62 patients (20.1%) responded to fluid resuscitation and this

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lasted for two hours in 42 (13.6%) patients. Improvement in $\text{MAP} \geq 65$ mmHg was seen in 25.3% ($n=39$) patients at the end of the first hour in albumin group in comparison to 14.9% ($n=23$) patients in the saline group ($p=0.03$). This sustained recovery from hypotension at end of the second hour was noted in 17.5% ($n=27$) in albumin group as compared to 9.7% ($n=15$, $p=0.06$) in the saline group. Reversal of hypotension was significantly higher in patients receiving 5% albumin than saline at the end of the three hours (11.7% and 3.2%). Sustained reduction in heart rate and hyperlactatemia was also better in the albumin group. Finally, at 1 week, the proportion of patients surviving was higher in the albumin group than those receiving saline (43.5% vs 38.3%, $p<0.05$).

The superiority shown by albumin in this specific type of patients adds to what was observed and suggested in the SAFE study and in the ALBIOS study in the general population. However, some doubt and concerns still exist according to the main limitations of this RCT that are (1) the lack of information on the management and particularly fluid management beyond the third hour; (2) the lack of a full assessment of the overall outcomes and particularly of the 28-day survival; and (3) the modest rate of responders to hemodynamic management in both groups. Anyway, while an elusive and random choice of fluid to be administered in the general population may still be justified in the course of sepsis or septic shock, after this RCT the choice of albumin solution should be strongly recommended as initial fluid management in patients with cirrhosis. In this regard, a question will remain open after the study by Philips et al.: is it preferable to use 5% or 20% albumin solution in patients with cirrhosis and sepsis? I just want to remind the readers that a multidisciplinary panel of experts had recommended in critically ill patients with cirrhosis 2016 fluid replacement with isotonic crystalloids in cases of volume loss due to diarrhea or over diuresis, blood in cases of acute gastrointestinal hemorrhage, and 20–25% albumin for infections, suspected HRS-AKI or in cases where the cause of AKI was unclear. There is no doubt that 20–25% albumin solution has potential advantages over the 4–5% albumin solution such as the lower content of sodium and, overall, of chloride. However, I think now that this answer should be addressed by another RCT.

The paper might raise also some questions concerning the mechanism of action of albumin in this clinical context. In fact, it is known that there is growing evidence that albumin appears to act through its nononcotic properties and in particular its anti-inflammatory and antioxidant activity in patients with cirrhosis [12, 13]. Thus, one would want to answer yes, considering on the one hand the population studied which is certainly characterized by a high degree of systemic inflammation and oxidative stress and on the other hand the fact that it is completely deficient in albumin and, above all, in biologically

active or native albumin. Yet, the modest dose of administered albumin and the brevity of the treatment lead us to conclude that in this case albumin seems to act mainly as a colloid and plasma expander, however, demonstrating a clear superiority over crystalloids in this specific population and clinical context.

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