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EDITORIAL

Moving albumin into the small volume resuscitation era

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Physicians have an intense 70-year history of enthusiasm, skepticism, fear, and reconciliation with albumin products since their market introduction in the late 1940s [1]. Despite its cumbersome production method and costs, albumin became popular soon after its debut. Advances in its production technique, producing purer formulations with less prekallikrein activators, turned it into a compound with few immediate adverse reactions that appeared to be safe [1]. However, the most recent turbulent episodes of albumin use (still known by most critical care physicians) start with the notorious meta-analysis suggesting harm [2], passes through a redemption clinical trial [3], and lands on more recent studies that may point to a specific direction, but yet provide no conclusive data [4]. There are still several gaps in our knowledge about albumin resuscitation. One of the most pressing questions is whether, given that higher positive fluid balance is associated with worse clinical outcome [5] and that albumin is safe [3], a resuscitation strategy based on hyperoncotic (20%) albumin resuscitation would be useful? If so, which would be the ideal comparator: isoncotic albumin or crystalloids? While comparing 20% albumin to crystalloids would make sense considering the cost of high albumin, one would be left unsure if differences would be due to the presence of albumin by itself or, maybe, due to the side effects of some crystalloids solutions (especially saline), so isoncotic albumin seemed like a rational comparator for a first peek. The first step to answer this question is now discussed in the paper by Mårtensson and coworkers (the SWIPE trial) in a recent article in *Intensive Care Medicine* [6]. In this well-conducted pilot study, 330 patients (out of an expected 400 patients) from Australia and UK were randomized to receive 20% or 4–5% albumin preparations in the first 48 h after ICU admission. As a result of the study's pilot nature, the authors were interested in physiological effects and (appropriately) chose cumulative volume of resuscitation fluid as their primary outcome. Rich data on physiological and hemodynamic variables also allow us to obtain a good picture of how the interventions differed.

Close inspection of the randomized population shows that most (close to 70%) patients were admitted after surgery (mostly elective procedures). The baseline values of arterial pressure and the relatively low number of patients receiving norepinephrine corroborate the idea that patients were not severely hypotensive at randomization. Finally, volume of resuscitation fluid was low in both arms (even lower in 20% albumin groups, as we will discuss later). All these findings suggest that the trial included a low-risk population. Consequently, rates of acute kidney injury and hospital mortality were low.

However, important information can be obtained from the trial. Patients in the 20% group indeed received less fluid (450 mL less), had their albumin levels increased by 3 g/L more while having similar urinary output. This is an important finding, since increase in plasma oncotic pressure could theoretically decrease glomerular filtration rate and reduce diuresis [7], which could minimize the impact of a lower fluid infusion volume on total fluid balance as a result of a reduction in urinary output. The net effect seen in SWIPE was a lower fluid balance in the 20% group (difference of approximately 570 mL). Hemodynamic trends were mostly similar. Changes in

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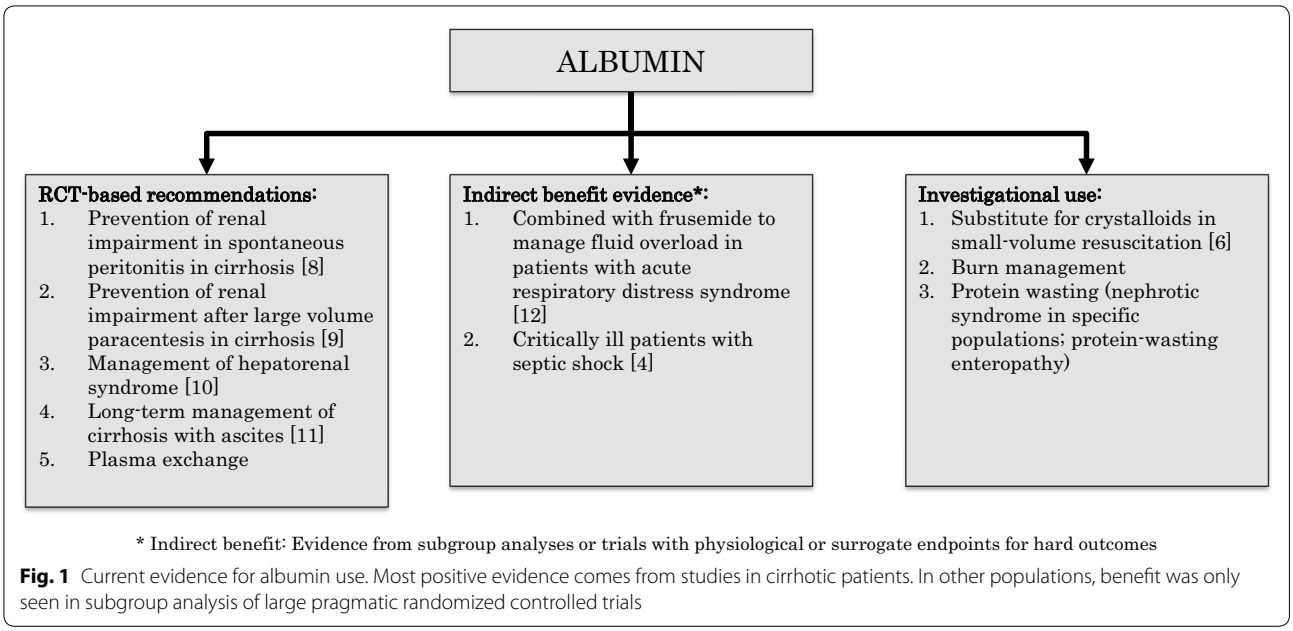

Fig. 1 Current evidence for albumin use. Most positive evidence comes from studies in cirrhotic patients. In other populations, benefit was only seen in subgroup analysis of large pragmatic randomized controlled trials

electrolyte levels were small, albeit statistically significant, with unclear clinical significance. Lack of blinding could, as always, have played a role in many of the outcomes assessed by the authors, especially total infused volume. Physicians could, for example, consider that true fluid expansion with 20% albumin would be twice the one expected with 4–5% albumin and therefore interrupt earlier fluid resuscitation. From the SAFE trial, however, we know that in practice, when blinding is applied, albumin 4% use results in a more modest fluid-sparing effect when compared to crystalloids (1:1.3). Would the same happen if blinding was applied when comparing 20% to 4–5% albumin?

Secondary results of SWIPE show no clear signal of harm associated with 20% albumin (similar occurrence of acute kidney injury, mortality, and survival). These findings should be interpreted with caution, since the low number of patients and the low illness severity constrain both the power to detect difference and generalization of the results. Although the authors report that no heterogeneity in treatment effect was seen between important subgroups (including septic patients), all subgroups were small, which hampers any reliable conclusion about this finding.

The SWIPE trial was a necessary step prior to a large randomized controlled trial (RCT) comparing different albumin concentrations in critically ill patients. We are left wondering whether future large-scale RCTs will show an overall benefit of 20% albumin vs. 4/5% albumin (or crystalloids). If so, would it be related to lower cumulative fluid balance? Would it be mediated by the higher serum albumin levels, which could have anti-inflammatory and adsorptive properties? Maybe lower chloride levels could also play a role? All of the above? These questions highlight how hard and complex any discussion is involving benefits and harms of fluids: there is never one unique mechanism involved. Albumin has a long history of clinical trials, but robust evidence sustaining its use is still scant (Fig. 1). Most high-quality evidence is limited to management of cirrhosis and its complications. We hope that future trials provide more definitive answers in albumin's troubled history.

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Compliance with ethical standards

Conflicts of interest
Both authors declare they have no conflicts of interest.

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