JIM Letter to the Editor

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Authors' reply: Hypoalbuminemia in COVID-19

Dear Editor,

We thank Dr. Domenico Lapenna for his interesting comment [1], which gives us the opportunity to further underline the complexity of the topic of hypoalbuminemia in COVID-19, both from the pathophysiologic point of view and from the treatment perspective.

As we tried to highlight in the introduction of our manuscript [2], nowadays it is known that albumin has a wide range of non-oncotic or pleiotropic properties. It affects innate and adaptive immune responses, maintains vascular endothelial integrity and acid–base balance, acts as a carrier molecule, interacts with bioactive lipid mediators, protects against oxidative damage, contributes to endothelial stabilization, and possibly exerts antithrombotic functions.

Apart from liver failure, in which the hepatic albumin fractional synthesis rate is mainly decreased, in many inflammatory conditions and in critically ill patients, the physiological response to increased albumin loss (due to augmented breakdown, capillary escape, and external losses) may involve an increased synthesis rate [3], which in chronic processes such as "inflammaging" can partially act as a compensatory mechanism, but becomes highly insufficient in such overwhelming states as the systemic cytokine storm of severe COVID-19.

The therapeutic use of human albumin solution (HAS) is still an open matter of debate, with changing fortunes over time. Nowadays, there is no proven efficacy of HAS use for fluid resuscitation in critically ill patients [4]. Moreover, there is a dearth of evidence regarding the role of HAS in COVID-19, which is characterized by the so-called "endothelialitis", significantly contributing to the pathogenesis of immunothrombosis. Therefore, the results from previous studies on HAS should not be applied *tout court* to COVID-19. Moreover, the surviving sepsis campaign guidelines recommend against the routine use of albumin for the initial resuscitation of adults with COVID-19 and shock [5]. According to these premises, COVID-19 patients have been excluded from an ongoing large prospective randomized controlled trial on HAS in critically ill patients in Italy (ALBIOSS-BALANCED, NCT03654001).

We believe that, given the complexity of the processes activated by SARS-CoV-2 and the dynamic change of underlying mechanisms, several issues which are inherent both to the subjects to be treated and to the treatment itself should be considered.

The severity of the clinical picture at the time of albumin administration is among the main points to be evaluated. Inputs from postmortem studies suggest that even from the histopathological point of view, lung damage usually goes through several stages, which may overlap, but usually are characterized by predominantly exudative features early in the clinical course, while proliferative patterns predominate in the subsequent phases. Especially in the early stages, when the endothelial-alveolar barrier is most damaged, HAS administration might further worsen exudation with impact on gas exchange and lung mechanics. Therefore, in COVID-19-related acute respiratory distress syndrome (ARDS), careful evaluation of the potential pros and cons of HAS administration is warranted, since it is known that HAS may be even detrimental in conditions which are characterized by impairment of highly specialized endothelial beds, as may occur in traumatic brain injury [6].

Crucial aspects to be addressed when planning to administer HAS may include the most appropriate serum albumin cut-off to rule in patients for such a treatment, the best dose, rate and type (bolus vs. continuous) of infusion, albumin concentration (iso-oncotic vs. hyperoncotic albumin), duration of fluid exposure, types of targets (hemodynamic vs. serum concentration), and parameters to monitor the response.

Regarding the pleiotropic properties of albumin, remarkable concerns have been raised about commercial albumin solutions, which significantly differ from native albumin. There is wide variability between manufacturers in extraction processes,

which may affect protein content, charge, buffers, and stabilizers use, and electrolyte composition, with subsequent significant impact on albumin properties. The oxidative status may be impaired [7], and the supposed beneficial immunomodulatory properties may also be affected, even with harmful effects [8].

Our study highlighted that in severe COVID-19 patients, the alteration of the endothelial-alveolar barrier with the opening of the junctional complexes is much more pronounced than in other conditions known to impair endothelial function, such as H1N1- and bacterial-ARDS cases, Legionella, and other bacterial pneumonia without ARDS. In the context of a multifactorial dynamic condition, the contribution of trans-capillary albumin leak to the significant hypoalbuminemia detected in most of these patients is probably far from negligible. The awareness of these pivotal underlying mechanisms should lead to judicious use of HAS in severe COVID-19. Further evidence from large studies with well-defined inclusion criteria and endpoints is needed to assess the effects of HAS administration in severe COVID-19 patients.

Conflict of interest

The authors declare no conflict of interest.

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