Editorial Commentary

Albumin use in cirrhosis: a nephrology viewpoint on key considerations and cautionary notes

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The constant need to reduce the variability of clinical practice and to improve the quality of care of the patients and their outcomes have led to the increasing emphasis on evidence-based medicine. When there is a paucity of robust data on a specific topic or there are conflicting conclusions from available studies, clinical practice recommendations may prove helpful to fill the gap and assist with clinical decision-making. There are a variety of such recommendations, such as consensus statements, practice guidelines, and position statements, each with a specific set of methodology and objectives. Position statements are comprehensive documents meant to elucidate, justify, and recommend a particular approach to a clinical problem. These papers often present a detailed understanding of the issues in question, discuss the pros and cons of the available options, and provide the rationale for the position that is set forth. Like other forms of clinical practice consensus, position statements innately provide information on the level of evidence and the strength of what the panel of experts agrees on. There are several consensus group methods by which these statements can be developed. Delphi is a systematic process to create and measure consensus, which is particularly well suited where input is required from a large number of geographically dispersed experts.

The use of albumin in patients with cirrhosis reflects a common clinical scenario in which some of the findings of the available studies have been conflicting and there is substantial variability in practice worldwide. As such, it is a perfect example where clinical practice recommendations are needed to fill the current knowledge gap until the data generated by future studies can answer key questions surrounding the use of albumin in this setting. It is within this context that Bai *et al*. recently published a position statement by an international panel of experts on the use of albumin infusion for cirrhosis-related complications (1). The panel was comprised of 33 investigators from 19 countries in five continents. A three-round Delphi consensus process was performed to condense the input of the group and develop the position statement. They provided 12 position statements for several cirrhosis-related complications such as hepatorenal syndrome, hepatic encephalopathy, and hyponatremia. The median rating of the evidence on these specific topics was 5 out of 5 (agreement between 88 and 100 percent), and there was an excellent degree of consensus among the participants (reported "very high" for four statements, and "high" for the rest).

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The main advantage of this position statement is that it encompasses input from a large group of experts who are representatives of several countries and regions in the world. Moreover, the methodology that has been used to develop these statements (i.e., Delphi) is well established and widely used due to its reliability and the potential to prevent undue dominance by specific individuals and group conformity. Finally, the high level of agreement among these experts on what they set forth as recommendations for clinicians increases their reliability and is likely to lead to their wider acceptance.

What could be considered a shortcoming of this work is that it provides yet another set of recommendations that is added to all previous guidelines, consensus statements from academic societies, and associations from a variety of countries. However, due to its recent publication, it is obviously more up-to-date and takes into consideration the findings from more recent studies (e.g., ATTIRE) compared with previously published statements (2). The panelists have taken a conventional retrospective approach. As such, the paper lacks info on emerging concepts and questions and does not provide what may be considered a more futuristic view.

One of the strongest indications of albumin infusion in the setting of cirrhosis is the management of hepatorenal syndrome. There is growing evidence on the contribution of the heart to this clinical scenario, albeit to a variable extent (3-5). It is postulated that a subset of patients diagnosed with hepatorenal syndrome may indeed have concomitant cardiorenal syndrome as an adjunct or predominant underlying mechanism linking the liver to the kidney beyond splanchnic arterial pooling and maladaptive neurohormonal activation (hence the term hepatocardiorenal syndrome). In this integrated model, the involvement of the heart in cirrhosis (cirrhotic cardiomyopathy) contributes to clinical or subclinical cardiocirculatory dysfunction that can initiate the pathophysiologic pathways leading to impairment in renal function and urinary sodium excretion (cardiorenal syndrome). With regard to albumin infusion, there are two implications for this new model. First, albumin's properties beyond volume expansion (e.g., anti-oxidative and anti-inflammatory) may be responsible for reversing the mechanisms involved in cirrhotic cardiomyopathy hence improving renal function through the effect on cardiac function. This would explain why similar salutary cardiac effects are not observed with other solutions that expand intravascular volume (e.g., starch and normal saline) (6). Second, if cardiorenal syndrome is the predominant underlying pathway in a subset of these patients, not only should all such patients undergo cardiac evaluation to explore subclinical cardiac dysfunction, but consideration should also be given to the unnecessary use of albumin for them, which can have detrimental effects. This subject has attracted increased scrutiny, particularly following results from the CONFIRM trial, which suggested an increased incidence of respiratory complications among patients administered both terlipressin and albumin for the treatment of hepatorenal syndrome (7). The increased afterload associated with terlipressin, coupled with its potential direct impact on pulmonary vasculature, is believed to be a contributing factor, while the augmentation of preload by albumin is deemed to play a significant role in this phenomenon. Interestingly, in a recent study, the majority of patients diagnosed with hepatorenal syndrome by conventional clinical criteria were found to have elevated cardiac filling pressures (8). Notably, intravenous diuretics, instead of albumin infusion, was associated with improvement of renal function in these patients.

Therefore, to ensure the prudent utilization of this double-edged sword, an objective assessment of fluid status at the bedside is imperative. Point-of-care ultrasound (POCUS) is increasingly recognized as a valuable resource for fulfilling this need. It constitutes a clinician-performed focused ultrasound examination aimed at addressing clinical questions at the bedside and guiding immediate management. While it's important to recognize that POCUS isn't a panacea, its strategic deployment within the appropriate clinical framework significantly aids in narrowing down the differential diagnosis and carefully selecting patients who would benefit from albumin and those at risk of complications. In brief, a quick POCUS of the kidneys aids in excluding obstructive nephropathy, a rare but potentially reversible condition when promptly treated. Additionally, scenarios such as an obstructed Foley catheter or mistaking pelvic ascites for a full bladder by automated bladder scanners are not uncommon, and POCUS facilitates the diagnosis of such cases (9). Simultaneously, ascites and signs of increased abdominal pressure can be assessed, prompting therapeutic paracentesis to improve renal perfusion. Subsequently, we can evaluate a patient's fluid tolerance. Put simply, if there is increased extravascular lung water or sonographic indication of elevated right atrial pressure, the potential risks associated with albumin administration may outweigh the benefits. Lung ultrasound surpasses auscultation in detecting extravascular lung water and exhibits higher sensitivity than chest radiography for detecting cardiogenic pulmonary edema (10). Additionally, anteroposterior chest radiographs in cirrhotic patients

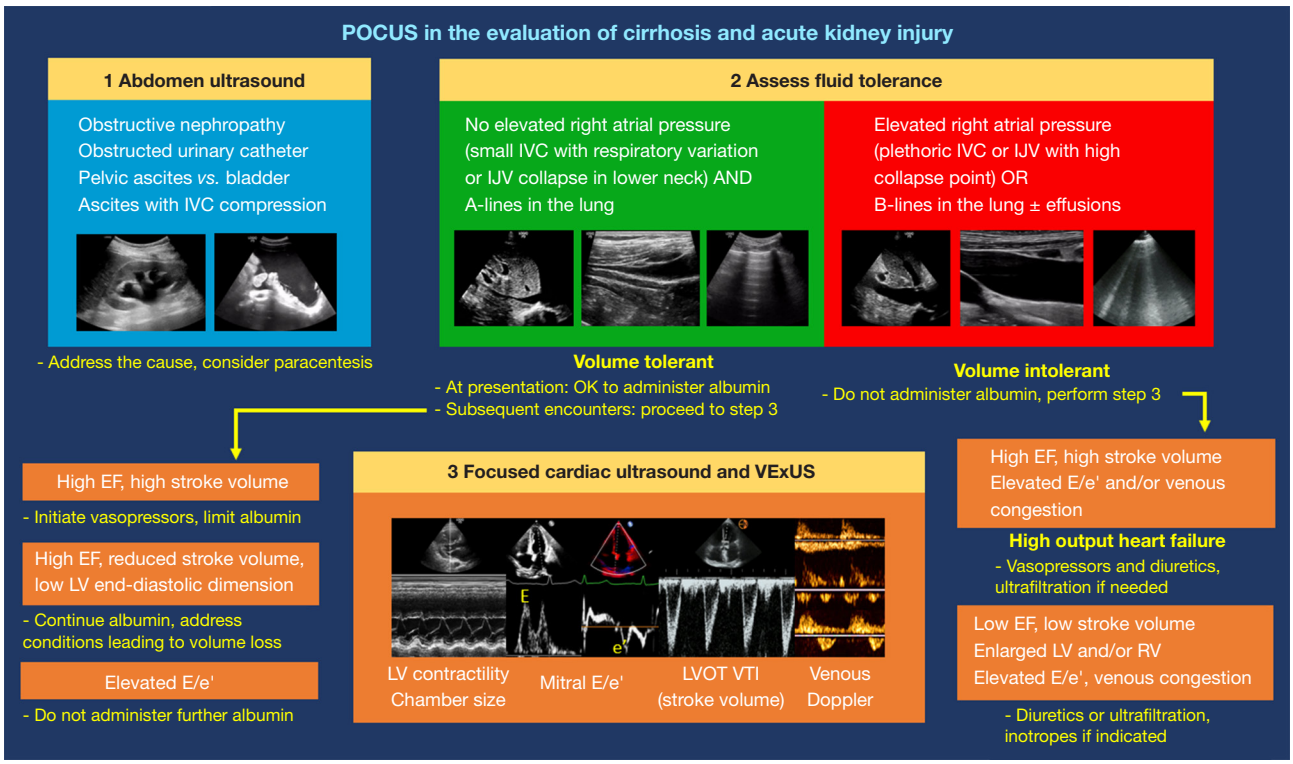

Figure 1 A conceptual framework for using POCUS in the evaluation of cirrhosis and acute kidney injury. A-lines, horizontal artifacts signifying normal lung ultrasound; B-lines, vertical artifacts suggestive of interstitial edema. IJV collapse point denotes narrowing/collapse of the venous column demonstrated by ultrasound, analogous to the highest point of venous pulsations on the inspection method. POCUS, point-of-care ultrasound; IVC, inferior vena cava; IJV, internal jugular vein; EF, ejection fraction; LV, left ventricle; E/e', ratio of the early transmitral diastolic wave velocity and the mitral annular tissue velocity in early diastole; VExUS, venous excess ultrasound (Doppler-assisted venous congestion assessment); LVOT VTI, left ventricular outflow tract velocity time integral; RV, right ventricle.

failed to identify approximately 40% of effusions visible on ultrasound in one study (11). The inferior vena cava (IVC) serves as a standard parameter for estimating right atrial pressure on echocardiography and can be readily performed at the bedside. IVC POCUS has revealed the misclassification of acute kidney injury in a cohort of patients diagnosed with hepatorenal syndrome based on clinical criteria (12). However, IVC may not always be reliable in cirrhosis due to local structural alterations and intraabdominal hypertension compressing the vessel. In such cases, internal jugular vein ultrasound serves as a reasonable alternative, which has shown to outperform IVC in estimating right atrial pressure in cirrhotic patients (13). Even in patients with normal lung and IVC POCUS, if focused cardiac ultrasound demonstrates elevated cardiac output typically assessed using left ventricular outflow tract Doppler, the utility of albumin as a volume expander becomes questionable. Furthermore, evidence of elevated left ventricular filling pressures, assessed using transmitral Doppler and mitral annular tissue Doppler (E/e'), places the patient at high risk of developing pulmonary edema. High-output cardiac failure is relatively common in cirrhotic patients and is often underrecognized (14), as most physicians limit their thought process to 'preserved or low left ventricular ejection fraction' when considering cardiac function. POCUS also enables the assessment of gross valvular abnormalities (e.g., mitral regurgitation leading to pulmonary edema) and Doppler assessment of venous congestion, further guiding the management (15). *Figure 1* depicts our proposed conceptual framework for utilizing POCUS in evaluating a patient with cirrhosis and acute kidney injury. In conclusion, albumin can play a dual role as an ally and an adversary if not carefully employed in cirrhosis. Future research endeavors should leverage tools like POCUS to investigate the most effective utilization of albumin in these medically complex patients.

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