De-compensated Cirrhosis and Fluid Resuscitation

Erin Maynard, MD, FACS

INTRODUCTION

Physician encounters with patients with cirrhosis have become prevalent, with 1 in 10 Americans having some form of liver disease. Despite advances in the treatment of hepatitis C, the incidence of liver disease has not decreased and according to the National Institute of Health 10% of children in the United States have non-alcoholic fatty liver disease. Cirrhosis carries a significant increase in mortality with the Centers for Disease Control and Prevention citing it as the fourth leading cause of death of Americans between the ages of 45 and 54 and the twelfth leading cause overall. In-hospital mortality is reportedly 44% to 74% in some studies with yearly costs approaching $13 billion. Given the prevalence of liver disease it is likely that all surgeons independent of specialty will encounter a patient with cirrhosis with nearly 10% of patients with cirrhosis undergoing surgery in their last 2 years of life. The understanding of resuscitation of the de-compensated patient with cirrhosis is vital to decreasing morbidity and mortality. This article enhances the understanding of the unique physiology of the patient with de-compensated cirrhosis to guide their needs in fluid resuscitation in critical illness.

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Department of Surgery, Oregon Health and Science University, 3181 SW Sam Jackson Park Road, Portland, OR 97239, USA
E-mail address: maynarde@ohsu.edu

KEY POINTS

- Understanding of the unique physiology of end-stage liver disease is imperative to resuscitation of the patient with cirrhosis.
- The effects of albumin resuscitation in the patients with cirrhosis are more than mere volume expansion.
- Decompensated cirrhotics are total body volume expanded but intravascularly volume deplete.
PHYSIOLOGY OF LIVER DISEASE

Before discussing specifics of fluid resuscitation in patients with liver disease it is imperative to understand the unique physiology of the patient with cirrhosis (Fig. 1). Portal hypertension in the setting of cirrhosis leads to splanchnic and arteriolar vasodilation. The exact mechanism of this is not exactly understood but nitric oxide is thought to play an important role. This dilation leads to a significant decrease in systemic vascular resistance, decreasing the effective arterial blood volume and blood pressure, which leads to a cascading chain of events. In response to the decrease of effective circulating blood volume the sympathetic nervous system and the renin-angiotensin system (RAAS) increase to try to compensate along with excretion of endogenous vasopressin. The activation of the RAAS leads to an increase in release of antidiuretic hormone leading to sodium and water retention with a disproportionate amount of free water retention increasing plasma volume, which can result in significant hypervolemic hyponatremia. The increase in sympathetic nervous system leads to an increase in heart rate and overall increase in cardiac output, which increases splanchnic blood flow.

DETERMINATION OF VOLUME STATUS

Determination of volume status in the patient with cirrhosis is important but often difficult to determine given that up to 50% of extracellular fluid may be in the extravascular space manifesting as ascites and edema. Patients who seem total volume expanded may often be intravascularly volume depleted putting them at risk for hepatorenal syndrome (HRS). Overresuscitation of the postoperative patient with liver disease can result in ascites and hyponatremia, which is difficult to treat. In a study aimed to evaluate the effect of plasma expansion with albumin in patients with cirrhosis with renal failure, global end-diastolic blood volume index but not central venous pressure served as an indicator of cardiac preload. When examining predictors of fluid responsiveness, central venous pressure, global end-diastolic blood volume index, stroke volume index, and cardiac index were significantly lower than in nonresponders, where a systemic vascular resistance index was significantly higher.

Fig. 1. Flowchart of physiologic events.
THE EFFECTS OF CIRRHOSIS ON ALBUMIN

Albumin is the most abundant protein in plasma and is exclusively synthesized in the liver. Besides regulating osmotic pressure, it has several other physiologic mechanisms that are altered in the setting of liver disease. Albumin serves as a carrier for water-insoluble molecules (e.g., hormones, cholesterol, drugs, free fatty acids, and bilirubin); it plays a role in maintaining the competence of capillary permeability, which can increase in inflammatory states, such as sepsis; and acts as a free radical scavenger in its reduced form decreasing oxidative stress.7 Although albumin synthesis has been demonstrated to increase during time of stress in patients without cirrhosis, synthesis can decrease 50% in the setting of cirrhosis. In addition to decreased protein synthesis patients with decompensated liver disease suffer from protein malnutrition from several sources (Box 1).8 The additive effects of decreased synthesis of albumin, impaired intake of its precursors, and increased proteolysis creates a state of global hypoalbuminemia in those with cirrhosis that decreases effective circulating volume and oncotic pressure, which leads to renal sodium and water retention with third spacing of ascites and anasarca complicating their resuscitation. The contribution of hypoalbuminemia to mortality in liver patients is recognized in the Child-Pugh score (Table 1). Besides the overall decrease of albumin the function is also altered in patients with cirrhosis and has been demonstrated in several studies. The exact cause of this dysfunction is unknown but could be caused by saturation with bilirubin or structural modifications.

THE USE OF ALBUMIN IN FLUID RESUSCITATION

The use of albumin in critically ill patients without evidence of cirrhosis has been greatly debated and the subject of several studies. The Saline versus Albumin Fluid Evaluation (SAFE) study was a large double-blind randomized trial comparing 4% human albumin solution with normal saline in nearly 7000 intensive care unit patients. The results showed no difference in intensive care unit stay, number of failing organs, or mortality rates at 28 days. In the group with severe sepsis the mortality was less in the albumin infusion group (30.7% vs 35.3%) but this did not reach statistical significance. Given these findings and the expense of albumin compared with crystalloid the use of albumin has largely been discouraged in the patient without cirrhosis.

In the patient with cirrhosis the use of albumin has been largely based on its oncotic properties to increase effective circulating volume to stop the cascade of physiologic

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**Box 1**
Sources of protein malnutrition

- Poor nutrition intake
- Anorexia from symptoms, such as early satiety from large-volume ascites and reflux
- Protein loss from large-volume paracentesis and metabolic alterations, including hormonal and nutrient utilization abnormalities, as in reduced glycogen stores creating an early fasting state that leads to concurrent breakdown of fat and amino acids
- Increased β-adrenergic activity, which leads to a hypermetabolic state creating insulin resistance, proteolysis, and amino acid use for gluconeogenesis
- Protein malabsorption secondary to increased gut permeability, reduced bile salts, and bacterial overgrowth
- Overall protein loss from reduced synthesis
events as depicted in Fig. 1 and described previously. Three specific uses of albumin in patients with cirrhosis are discussed in more detail next.

**Albumin Infusion After Large Volume Paracentesis**

Diuretic-resistant ascites happens in up to 10% of patients with end-stage liver disease. Although transjugular intrahepatic portosystemic shunt is an option for some, for many patients frequent large-volume paracentesis (LVP) is their only option. Paracentesis results in protein loss and large intracellular to extracellular volume shifts that result in vasodilatation and exacerbates the circulatory dysfunction described in Fig. 1. A randomized trial compared fluid resuscitation with albumin versus saline in the prevention of paracentesis-induced circulatory dysfunction. A total of 72 patients were randomized to receive either albumin or saline. Significant increases were found in plasma renin activity 25 hours and 6 days after paracentesis when saline was used with an increase in paracentesis-induced circulatory dysfunction in the saline group (33.3% vs 11.4%; \( P < .03 \)). No difference was found in those patients with LVP less than 6 L.9 Although most surgeons are not primarily involved in managing routine LVP in the setting of end-stage liver disease, the management of ascites plays a critical role in the acute care surgical settings in patients with ruptured umbilical hernias and ascites leak after laparotomy. Adequate resuscitation and control of excessive volume loss is critical in prevention of circulatory dysfunction to minimize mortality.

**Management of Hypervolemic Hyponatremia**

Hyponatremia (Na <130 mmol/L) is a common finding in cirrhosis and is an independent predictor of mortality, which is why it is now included in the Model of End Stage Liver Disease allocation system.7 The first step in treatment is to determine whether the patient is hypovolemic or hypervolemic. Hypovolemic hyponatremia is less typical, and presents as a patient with low serum sodium in the absence of edema and ascites. This is often secondary to overdiuresis and the first step in management is to withhold diuretics and administration of normal saline.7 There is no role or data to support the use of albumin in this setting.10 Hypervolemic hyponatremia is the production of over-secretion of antidiuretic hormone leading to an unbalanced retention of water and sodium (see Fig. 1). The primary treatment of hypervolemic hyponatremia is free water restriction (<1000 mL/d). There are no data to support saline administration in this setting. The European Association for the Study of the Liver guidelines support the use of albumin in this situation to serve as potential volume expander to decrease RAAS activity based on B2 practice guidelines.10 Hypervolemic hyponatremia can be iatrogenic after overresuscitation with crystalloid in the perioperative patient.

### Table 1

<table>
<thead>
<tr>
<th>Child-Turcotte-Pugh classification</th>
<th>1 Point</th>
<th>2 Points</th>
<th>3 Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Encephalopathy</td>
<td>0</td>
<td>1–2</td>
<td>3–4</td>
</tr>
<tr>
<td>Ascites</td>
<td>None</td>
<td>Slight</td>
<td>Moderate</td>
</tr>
<tr>
<td>Bilirubin (mg/dL)</td>
<td>&lt;2</td>
<td>2–3</td>
<td>&gt;3</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>&gt;3.5</td>
<td>2.8–3.5</td>
<td>&lt;2.8</td>
</tr>
<tr>
<td>PT prolonged (s)</td>
<td>1–4</td>
<td>5–6</td>
<td>&gt;6</td>
</tr>
<tr>
<td>INR</td>
<td>&lt;1.7</td>
<td>1.8–2.3</td>
<td>&gt;2.3</td>
</tr>
</tbody>
</table>

Child’s A = 5 to 6 points; Child’s B = 7 to 9 points; Child’s C = 10 to 15 points.

Abbreviations: INR, international normalized ratio; PT, prothrombin time.
Meticulous administration of fluids and free water restriction is paramount in avoiding this complication.

**Management of Hepatorenal Syndrome**

HRS defined by acute kidney injury in the setting of cirrhosis, no or minimal proteinuria, low sodium excretion (<10 mEq/L), and oliguria is a diagnosis of exclusion and is divided into HRS1 and HRS2. HRS2 is the less severe kind and usually found in patients with diuretic refractory ascites. HRS1 is the more severe kind and is defined by a more than two-fold increase in creatinine in less than a 2-week period and is associated with significant mortality even with treatment or transplantation. HRS is a diagnosis of exclusion and prerenal acute kidney injury and kidney injury caused by acute infection should be ruled out. Both the treatment and prevention of HRS involves the use of albumin. Albumin has been shown in randomized trial to prevent HRS and improve survival in the setting of spontaneous bacterial peritonitis. The hallmark of treatment of HRS1 is vasopressin or vasopressin analogue (eg, terlipressin) in addition to albumin administration. A randomized controlled trial in patients with HRS randomly assigned patients to either receive terlipressin (1–2 mg/4 hours) and albumin (1 g/kg followed by 20–40 g/d) or albumin alone. Primary outcomes were improvement in renal function and survival at 3 months. Results showed improvement of renal function in 43.5% of patients with combination treatment compared with 8.7% of patients treated with albumin alone ($P = .017$). Survival was not different between the two groups (27% vs 19% respectively; $P = .7$), reflecting the high mortality associated with HRS. Terlipressin therapy alone was also studied with and without albumin in a prospective nonrandomized trial. Patients either received terlipressin (0.5–2 mg/4 hours), until complete response or for 15 days, or terlipressin along with intravenous albumin. Albumin administration was the only predictive factor of complete response (77% in patients receiving combination therapy vs 25% in the terlipressin alone group; $P = .03$), demonstrating that albumin plays an important role in the treatment of HRS along with vasopressin analogues. HRS is seen in the postoperative patient given that anesthetic agents routinely increase splanchnic vasodilation and decrease hepatic blood flow. Postoperative patients with a rise in creatinine should be investigated for potential HRS and treated aggressively to minimize mortality.

**SUMMARY**

The critically ill patient with decompensated cirrhosis has a unique physiology and alterations in albumin that need to be understood to properly resuscitate them and minimize morbidity and mortality. Little data exist on specific resuscitation of the patient with cirrhosis as compared with those patients without liver disease. The effectiveness of albumin administration compared with saline administration in common settings, such as LVP, can be extrapolated to the care of the general surgical patient but further studies in this area are warranted.

**REFERENCES**


