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CLINICAL COMMENTARY

Albumin in Patients with Cirrhosis, When Does it Help?

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Albumin as a colloid replacement is a logical fluid replacement in cirrhotic patients who are hypoalbuminemic due to liver disease. The high cost and the transient nature of albumin repletion, returning to the abdomen 6 hours after infusion, have created a controversy about widespread use. Cirrhosis classically involves hepatocyte damage, obstruction of hepatic or biliary ducts that can result in an increase in proto-hepatic pressure, a decrease in hepatic synthetic function, and spleno-megaly.[1-4] Acute liver injury and oncologic infiltration while involving some aspects of cirrhosis may behave differently than patients with classic cirrhosis. Vascular compromise like in Budd-Chiari syndrome has a more acute onset and may not respond to the usual therapies that would be indicated in cirrhosis.

Renal dysfunction occurs in about 33% of cirrhotic inpatients, and it is the number one indicator of mortality.[1-4] There are several causes of potential renal dysfunction in cirrhosis, pre renal states, acute tubular necrosis (usually temporarily), and hepatorenal syndrome which is generally progressive. It is important to distinguish pre renal physiology, acute tubular necrosis, and hepatorenal syndrome. Typically this is accomplished by 48 hours of hydration of albumin (1g/Kg/day), with confirmation of a urine sodium <10meq/L at initial time and at 48 hours post hydration. There are many triggers of hepatorenal syndrome (HRS) and the particular trigger does not distinguish one disorder from the other. Rather it is the renal perfusion as gauged by urinary sodium measurements.[4-6] Please see Figure 1 for algorithm to distinguish pre renal acute kidney injury (AKI) in cirrhosis, from acute tubular necrosis (ATN), and from HRS.

Hepatorenal syndrome occurs because there is baseline pathological splanchnic vasodilation due to impaired hepatic regulation of circulating vasodilators. This results in impaired renal perfusion at baseline and renin angiotensin aldosterone system (RAAS) upregulation. In situations like spontaneous bacterial peritonitis and dehydration the ongoing hypotension worsens the baseline renal hypoperfusion. Due to the liver dysfunction that often accompanies triggers of hepatorenal syndrome, pre-renal physiology persists after appropriate volume resuscitation.[2]

The worsening renal afferent arteriolar vasoconstriction continues with increased RAAS stimulation which in turn results in worsening renal function due to ongoing ischemia from renal hypoperfusion. The most metabolically active part of the kidneys (the proximal convoluted tubules) are fed by the vasa recta. These “watershed” circulation vessels are prone to hypo-perfusion and, as such, the metabolically active part of the kidney is prone to ischemia. Figure 2 illustrates pathophysi-ology of hepatorenal syndrome.[2]

The literature has not shown a definitive role for albumin alone in preventing morbidity and mortality in cirrhotic patients in all cases.[3] Physiologically this makes sense since the main issue is due to prostaglandin dysregulation and possible dysregulation of other chemical and hormonal factors due to liver dysfunction resulting in the pathophysiological splanchnic vasodilation. That is why once the diagnosis of hepatorenal syndrome has been made, the standard therapy is to provide blood volume repletion and if pre renal state persists to increase blood pressure with midodrine and octreotide to induce splanchnic vasoconstriction to increase renal perfusion and prevent on-going ischemia.[3,4,6,7]

Once hepatorenal syndrome is diagnosed, albumin and terlipressin alone have not been proven effective in reversing established hepatorenal syndrome beyond standard therapy of octreotide and midodrine. Some small and preliminary studies suggest combination therapy of intravenous albumin with oral octreotide and subcutaneous midodrine may improve survival to liver transplantation, which is the definitive management of HRS.[8] More recent, studies have shown a synergistic effect of albumin and terlipressin in combination that is greater than either drug alone. While available in Europe, terlipressin is not yet available in the United States outside of the US FDA conducting phase III clinical trials.[9]

Other studies support selective use of albumin. One is treatment of spontaneous bacterial peritonitis, particularly in the presence of renal injury, not necessarily HRS.[10] There are also proven benefits of albumin use to ameliorate cardiovascular shifts that occur after large volume paracentesis (>3.5 L) that could lead to a pre renal state and could trigger the hypotensive cascade and increased RAAS activation leading to hepatorenal syndrome.[11] Similarly for reason albumin is used in severely

hypoalbuminemic patients (<2 grams/L) with nephrotic syndrome in need of extensive diuresis.[12] Finally albumin maybe advantageous if used with octreotide and midodrine or terlipressin in clinical attempts to reverse HRS type 1 (rapid onset) or type 2 (subacute to chronic onset).[6]

Table 1 presents recognized evidence based indications for albumin use in cirrhotics and examples of studies that support their use. In short, albumin is best used in combination with more standard medical therapy or new vasopressors to reverse active hepatorenal syndrome. It is also useful in select populations of cirrhotic patients for specific indications.[8-11]

Figure 1: Acute kidney injury in cirrhosis- pre renal versus acute tubular necrosis versus hepatorenal syndrome

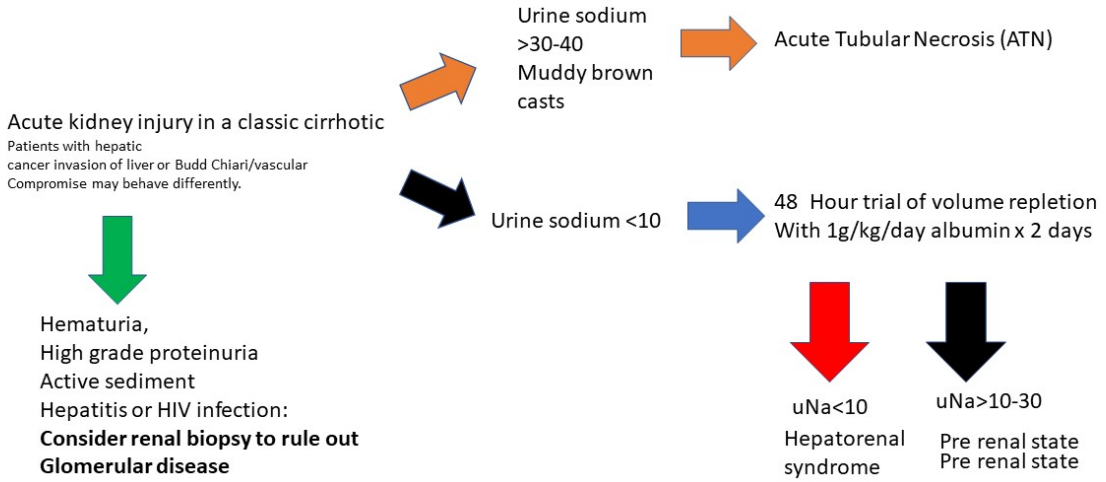

Figure 1: differential diagnosis of acute kidney injury in cirrhotic patient

Figure 2: Pathophysiology of hepatorenal syndrome with simplified anatomy

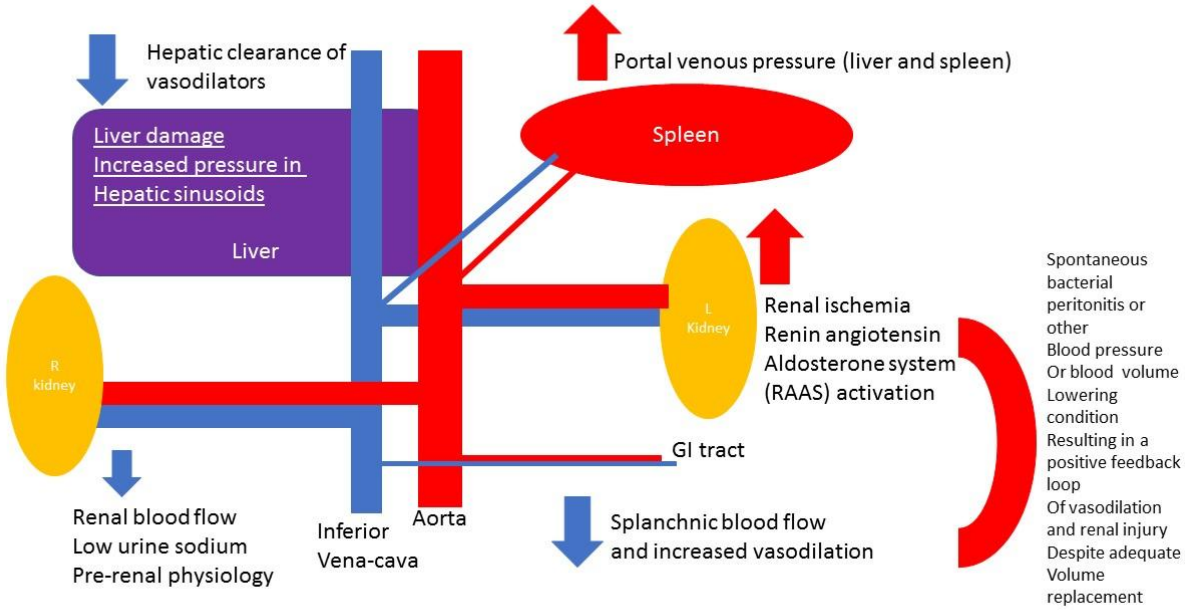

Figure 2: pathophysiology of hepatorenal syndrome in cirrhotic patients

Table 1: indications for albumin use in cirrhotics with example supporting studies

Trial of rehydration in suspected pre renal state versus HRS (1-3).

Use in combination with octreotide and midodrine (8).

Use in established hepatorenal syndrome in combination with terlipressin (9).

Use in cirrhotics with spontaneous bacteria peritonitis and renal injury (10).

Use in cirrhotics getting large volume (>3.5 Liters) paracentesis (11).

Table 1: current indications for albumin use in cirrhotic patients

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