What a Nephrologist Needs to Know About Acute Liver Failure

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Although relatively rare in the United States, acute liver failure (ALF) is associated with very high rates of morbidity and mortality. A leading cause of morbidity and mortality is cerebral edema and intracranial hypertension. Hypothermia, osmotic diuretics, and hyperosmolar therapy are commonly used to manage these complications; however, when these are ineffective, renal replacement therapy may be needed for volume management. Acute kidney injury is a common complication of ALF and may arise from a number of etiologies, including hepatorenal syndrome and acute tubular necrosis. Acute kidney injury is most common in patients who develop ALF because of acetaminophen toxicity or ischemia. With regard to renal replacement therapy, we will review specific considerations relevant to the management of the patient with ALF.

Key Words: Hepatic failure, Renal failure, Dialysis, N-acetylcysteine, Acetaminophen

INTRODUCTION

Acute liver failure (ALF) is characterized by the onset of hepatic encephalopathy (HE) and coagulopathy in the setting of rapidly deteriorating liver function in a person without a history of cirrhosis. Although rare, it is estimated that approximately 2000 cases of ALF occur every year in the United States.[1] Over time, there has been a shift in the major causes of ALF from viral etiologies to acetaminophen and other causes of drug-induced liver injury. In the most recent US data available, acetaminophen and drug-induced liver injury accounted for 46% and 11% of all cases of ALF, respectively, whereas hepatitis B and A accounted for 7% and 3% of all cases of ALF.[1] Other causes include autoimmune liver disease (5%) and ischemic liver injury (4%), although in many cases (14%) there is no overtly identified cause.[2] Before liver transplantation, ALF was associated with mortality rates greater than 80%.[3] With liver transplantation for ALF, the survival rates have dramatically changed—with overall survival of approximately 65%.[2] Although much of this increased survival can be attributed to disease-specific treatments (eg, *N*-acetylcysteine [NAC] for acetaminophen toxicity, routine vaccination against hepatitis B, along with antiviral therapy for infection), the availability of subspecialty care must also be considered as a reason for improvement in outcomes. Current recommendations from the American Association for the Study of Liver Diseases stress the importance of early referral of patients to liver transplantation centers.[4] These centers will not only have the requisite transplant hepatologists and surgeons but also a collection of subspecialists (including nephrologists) who are accustomed to the management of patients with ALF and the medical complications that accompany ALF. From a renal perspective, this patient population is not only at significant risk for acute kidney injury (AKI) but the clinical course is often complicated by electrolyte abnormalities, acid/base disturbances, hemodynamic instability, systemic infections, increased intracranial pressure (ICP), and complications of medication dosing.[5-7] The purpose of this article is to discuss several key issues that arise in patients with ALF that pertain primarily to the nephrologist's scope of practice. We will start with a discussion of management of intracranial hypertension (ICH) and cerebral edema (a leading cause of morbidity and mortality in these patients) with specific aspects relevant to nephrologists, followed by causes of AKI relevant to the patient with ALF and current management strategies and considerations for renal replacement therapy (RRT) in these patients.

CEREBRAL EDEMA AND ICH

In the setting of ALF, significant morbidity and mortality are attributable to ICH and cerebral edema leading to uncal herniation and brain death. In those who survive ALF, cerebral edema may lead to chronic neurologic deficits, although the incidence of chronic neurologic deficits attributed to cerebral edema is unknown.[8] Consequently, a major focus of the management of ALF is vigilance for early signs of cerebral edema, with a low threshold for treatment. It is thought that multiple factors including osmotic disturbances in the brain and increased cerebral blood flow contribute to the development of cerebral edema and ICH, although the exact pathology is not completely understood. There is evidence that serum ammonia contributes to the pathogenesis of cerebral edema/ICH—as arterial ammonia levels in humans more than 200 μg/dL are significantly associated with cerebral herniation, and ammonia infusions have led to cerebral edema in animal models.[9,10] Although there are medical options to try to prevent development of elevated ICP, it is essential for the nephrologist to be involved in patient management once ICH and cerebral edema form.

HE is common in patients with ALF and is graded from I (mild confusion, slurred speech, changes in behavior) to IV

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(coma). Cerebral edema is uncommon in patients with mild HE (stages I and II), but the incidence rises with the severity of HE and has been estimated to occur in 25% of patients with Stage III HE (stupor, incoherent speech, sleeping but wakes with stimulation) and 75% of those with Stage IV HE. Common features of elevated ICP include altered mental status (which is also a feature of HE), abnormal cranial nerve findings, and seizure. Severe elevations in ICP are associated with bradycardia, hypertension, and irregular respirations ("Cushing's triad") and large fixed pupils.

Some liver transplant centers use ICP monitors for objective evaluation of ICH; typically, an ICP less than 20 to 25 mm Hg and cerebral perfusion pressure (mean arterial pressure – ICP) greater than 50 mm Hg are targeted.[11] However, a recent retrospective study using US Acute Liver Failure Study Group (ALFSG) data demonstrated no benefit to invasive ICP monitoring in those with acetaminophen-induced ALF. Furthermore, in those with non-acetaminophen ALF, invasive ICP monitoring was actually associated with a significant increase in 21-day mortality.[12] The complication rate of ICP monitor placement was 10%, and 5% of these were felt to have directly contributed to the patient's death. Therefore, noninvasive means of ICP monitoring should be strongly considered. Newer methods such as transcranial Doppler sonography, transcranial near-infrared spectroscopy, and ultrasound evaluation of the optic nerve sheath diameter have all demonstrated promise as noninvasive measurements of ICH, but further studies are needed.[13]

CLINICAL SUMMARY

- Osmotic diuretics and hypertonic saline are the mainstay of medical therapy for those with acute liver failure (ALF) who develop cerebral edema and intracranial hypertension.
- Patients with ALF have a 45% risk of developing acute kidney injury; those with acetaminophen-induced liver injury and liver failure from ischemic shock are most likely to develop acute kidney injury.
- Continuous renal replacement therapy is considered safer in ALF than intermittent hemodialysis.
- Hypocalcemia (because of citrate in blood products) and hypophosphatemia (because of hepatic regeneration) may be more severe in patients with ALF during continuous renal replacement therapy.

If signs of ICH develop, the osmotic diuretic mannitol is recommended as the first-line therapy for ICH in those with ALF (an intravenous bolus of 0.25-1.0 g/kg) and whose serum osmolality is less than 320 mOsm/L.[4] Regardless of the source of active osmoles, mannitol is typically not used when serum osmolality exceeds 320 mOsm/L. The osmotic properties of mannitol can lead to a significant increase in intravascular volume, which in extreme cases can lead to pulmonary edema. Furthermore, it is not an adequate treatment to decrease ICP in those with severe ICH (ICP >60 mm Hg).[14] If the patient with ALF already has AKI and is oliguric or anuric, RRT may be needed for further volume management.

Another modality often used to treat ICH is hypertonic sodium chloride solutions. Hyponatremia, in and of itself, has previously been shown to be a predictor of poor outcome in ALF[15] and chronic liver disease, with different studies using cutpoints ranging from 126 to 135 meq/L in the setting of liver transplantation.[16-18] The mechanisms that result in hyponatremia in the setting of ALF are poorly described, but hyponatremia likely is at least in part mediated by decreased effective circulating volume because of decreased systemic vascular resistance resulting in increased antidiuretic hormone secretion. Factors that may exacerbate hyponatremia include AKI leading to impaired water excretion and significant free water intake, which may occur because of commonly used intravenous medications in these patients, including norepinephrine and NAC, which are frequently formulated in dextrose-containing water-based solutions. Norepinephrine can be reconstituted in isotonic saline solutions; NAC has been shown to be stable in 1/2 normal saline. Although classically used in the setting of acetaminophen toxicity, a recent study from the US ALFSG-demonstrated intravenous NAC improved the transplant-free survival in patients with early stage ALF from non-acetaminophen causes.[19] Consequently, at present, virtually all patients presenting with ALF, regardless of etiology, are empirically started on NAC until the diagnostic evaluation has been completed and have significant free water intake as a result.

Although there are several mechanisms by which hypernatremia may prevent or improve ICH, cerebral water flow is ultimately directed by changes in the active osmotic particles on either side of the blood-brain barrier.[20] In a trial targeting a serum sodium of 145 to 155 mEq/L, those randomized to receive hypertonic saline had a lower incidence of ICH compared with controls, but there was no overt survival benefit.[21] Overall, clinical trials of management of ICH in critically ill patients with and without ALF have been heterogeneous in terms of the pathology causing elevated ICP, concentration of hypertonic saline, and dosing regimen. Hypertonic saline should be used with caution in those with AKI who are not on RRT as those individuals will have limited ability to handle the sodium load. V2 receptor antagonists should be avoided in patients with ALF. Tolvaptan was associated with an increased risk of liver injury in the Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and Its Outcomes 3/4 clinical trial of CKD progression in subjects with autosomal dominant polycystic kidney disease.[22] Conivaptan is metabolized by the hepatocyte cytochrome P450 system, and levels are known to be elevated in patients with moderate hepatic impairment and have not been studied in severe liver disease.[23]

Therapeutic hypothermia has also been proposed as a mechanism for reducing ICH. It has been shown to normalize cerebral blood flow and decrease cerebral metabolic rate, with resultant decreased ICPs.[24] However, another recent study by the US ALFSG evaluated the use