Acute Kidney Injury in Liver Disease: Role of Biomarkers

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Acute kidney injury (AKI) is a common complication in patients with advanced cirrhosis and is associated with significant mortality. The most common etiologies of AKI in this setting are prerenal azotemia, acute tubular necrosis, and hepatorenal syndrome. Despite the overall poor outcomes of patients with cirrhosis and AKI, potentially efficacious therapies exist but must be tailored to the specific AKI etiology. Unfortunately, determining the etiology of AKI in the setting of cirrhosis is notoriously difficult. Many of the standard diagnostic tools, such as urine microscopy and the fractional excretion of sodium, have traditionally been ineffective. Novel biomarkers of kidney tubular injury may be able to assist with differential diagnosis and the appropriate targeting of treatments by distinguishing structural from functional causes of AKI. In recent studies, both urinary neutrophil gelatinase-associated lipocalin and interleukin-18 have shown the ability to distinguish hepatorenal syndrome from prerenal azotemia and acute tubular necrosis. In addition, multiple biomarkers, including neutrophil gelatinase-associated lipocalin and interleukin-18, have demonstrated the ability to independently predict both progression of AKI and mortality. Critically, recent research also indicated that commonly available tests, fractional excretion of sodium and proteinuria, may also be able to distinguish etiologies of AKI in cirrhosis, but diagnostic cutoffs must be re-conceptualized specifically to this unique AKI setting.

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BACKGROUND

Acute kidney injury (AKI) is a common and devastating complication in patients with cirrhosis, occurring in an estimated 19% of hospitalizations,[1] and is associated with significant mortality, 55% to 91%.[2–4] The clinical impact of this grave confluence of illnesses will continue to worsen as the incidence of both AKI and cirrhosis are increasing.[5] The impact of AKI on mortality is not homogeneous but instead contingent on the etiology of AKI.[6] The primary causes of AKI in patients with cirrhosis are prerenal azotemia (PRA), acute tubular necrosis (ATN), and hepatorenal syndrome (HRS). The prevalence of these diagnoses among patients with cirrhosis and AKI is shown in Figure 1.[3,7–12] Of these, HRS portends the worst prognosis, with type 1 associated with a median untreated survival of 2 weeks. HRS develops in patients with cirrhosis when portal hypertension stimulates an abundance of vasodilatory factors, leading to increased splanchnic vasodilatation. As systemic vascular resistance begins to markedly decline, various pathways are activated including the renin-angiotensin system, sympathetic nervous system, and arginine vasopressin, resulting in profound kidney vasoconstriction and hypoperfusion. When vasoconstriction is sufficiently advanced, kidney hypoperfusion is no longer reversible with volume resuscitation and patients experience the progressive and unrelenting decline in kidney function characteristic of HRS. AKI in such patients is, therefore, primarily functional in nature.

Despite this grim outlook, the potential exists in for the treatment of AKI in cirrhosis if efficacious interventions are applied to correctly phenotyped patients. Arriving at an accurate diagnosis is imperative because these treatments vary greatly, entail significant expense, use scarce resources, and have potentially significant toxicity. Patients with cirrhosis and PRA require fluids, but the deleterious consequences of overzealous fluid administration, as occurs when ATN is misdiagnosed, are increasingly recognized.[13] In spite of the severity of kidney dysfunction, kidneys in patients with HRS are primarily structurally intact. Kidney function in this setting, therefore, can be markedly improved if kidney blood flow is restored. Terlipressin, a V_1-vasoconstrictor that acts to augment systemic circulating volume and, thereby, improve kidney perfusion has shown great promise for the treatment of HRS.[14] In addition, in patients with advanced cirrhosis, liver transplantation can restore systemic vascular resistance, mitigate systemic and kidney vasoconstriction, and restore normal kidney hemodynamics. Patients with HRS at the time of liver transplantation can, thus, experience rapid improvement in kidney function post-transplant.[15] Patients with ATN should be dialyzed if clinically indicated, but in such patients with frank structural injury, interventions to restore kidney perfusion do not result in resolution of AKI and application of vasoconstrictors or liver transplantation is, therefore, inappropriate. Finally, patients with ATN must be differentiated from patients with HRS when considering a combined liver/kidney transplant.

Current Diagnostic Strategies for AKI in Cirrhosis Are Inadequate

Unfortunately, current diagnostic strategies are often unable to distinguish between functional and structural injury. As a result, the potential exists for misallocation

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of scarce resources and potentially harmful unnecessary treatments. Presently, attempts to distinguish PRA, HRS, and ATN begin (outside assessing the clinical context) with withholding diuretics and volume resuscitating the patient with albumin at 1 g/kg/d for 2 days. If the AKI resolves, they are considered to have had PRA. The chief difficulty is in distinguishing HRS from ATN. The primary indicator of AKI, creatinine, is a marker of filtration and, therefore, detects declines in kidney function but cannot determine whether such a decline is because of hypoperfusion or to structural injury. Many tests typically used to identify ATN in the general population are ineffective in the setting of cirrhosis. The fractional excretion of sodium (FENa), although ubiquitously applied by nephrologists evaluating AKI, has historically been difficult to interpret in patients with cirrhosis. Cirrhotic patients frequently present with low urine sodium irrespective of AKI[16] because of extreme renal sodium avidity and even ATN can present with an FENa less than 1%.[17] The traditional dichotomy where an FENa less than 1% indicates hypoperfusion and more than 1% to 2% signifies tubular dysfunction, and ATN is, therefore, inapplicable, and the test is historically not typically used in cirrhotic patients. Similarly, urine microscopy is potentially helpful in the differential diagnosis of AKI but can be complicated in cirrhosis by biliary staining of sediment and has not been rigorously evaluated in this setting. The gold standard for diagnosing AKI, kidney biopsy, is rarely performed in patients with advanced cirrhosis for fear of bleeding complications.

CLINICAL SUMMARY

- Differential diagnosis and prognosis are extremely challenging in patients with cirrhosis and acute kidney injury (AKI).
- Biomarkers reflecting structural kidney injury have shown the ability to differentiate acute tubular necrosis and hepatorenal syndrome.
- Fractional excretion of sodium may also be able to distinguish acute tubular necrosis and hepatorenal syndrome but requires a re-conceptualizing of diagnostic cutoffs.
- Kidney biomarkers may be able to predict progression and death in patients with AKI and may be able to diagnose AKI earlier than change in creatinine or estimated glomerular filtration rate.

In lieu of these traditional tests, the international ascites club (IAC) attempted to standardize the diagnosis of HRS by establishing 6 clinical criteria.[18] Once PRA has been ruled out by failure to improve withholding of diuretics and albumin resuscitation, those patients meeting 6/6 IAC criteria have been considered to have HRS, whereas those who do not are assumed to have ATN (barring signs consistent with a glomerulonephritis). Unfortunately, these criteria lack specificity as patients with ATN often (1) present with ascites, (2) have creatinine more than 1.5 mg/dL, (3) do not respond to volume resuscitation, (4) lack significant proteinuria or hematuria, and (5) have no gross structural changes to the kidney. Although ATN can certainly be associated with shock, (6) ischemic ATN can develop in the absence of shock and, indeed, frequently occurs in the setting of ostensibly normal blood pressure.[19] In addition, the degree of creatinine elevation does not distinguish ATN from HRS.[20] Very recently, the IAC have proposed a new definition of AKI in cirrhosis based on the adaptation of a modification of the Kidney Disease Improving Global Outcome criteria.[21] As long as they meet these criteria (an increase in creatinine of ≥0.3 mg/dL within 48 hours or an increase of ≥50% from baseline within 7 days) for having AKI and fulfill the other 5 traditional IAC criteria for HRS, there is no longer a fixed creatinine threshold that patients much cross before being diagnosed with HRS.[22] In addition, as long as patients present with Stage 2 or 3 AKI or progress from one stage to a higher stage, the creatinine no longer must be more than 2.5 mg/dL before treatment with vasoconstrictive agents is indicated. These extremely welcome changes will enhance sensitivity and facilitate timely treatment of HRS. However, the lack of specificity inherent to a diagnosis centered on creatinine will remain problematic.

Novel Biomarkers Can Improve Diagnostic Accuracy and Treatment Allocation

The critical diagnostic shortcoming is that serum creatinine is a marker of kidney filtration, not injury, and, thus, cannot distinguish functional from structural etiologies of AKI. More discriminating tests are urgently needed to make this distinction to guide the allocation of potent and scarce treatments and to help predict progression of AKI and mortality. Nearly 30 biomarkers of kidney tubular injury have recently been investigated for early detection, differential diagnosis, and prognosis of AKI.[23] Such biomarkers reflect frank structural injury and, thus, should appear in consort with an acute drop in glomerular filtration rate (GFR) attributable to structural damage. Among the most promising are interleukin-18 (IL-18), kidney injury molecule-1 (KIM-1), liver-type fatty acid-binding protein (L-FABP), and neutrophil gelatinase-associated lipocalin (NGAL). These biomarkers appear and peak in the urine at different times after injury ranging from NGAL at 2 hours to KIM-1 at 12 hours.[24] Such differences in expression patterns not only suggest the potential utility in a biomarker panel but also must be kept in mind as a possible limitation when interpreting experimental results. Injury biomarkers have recently been successfully investigated in multiple clinical settings including cardiac surgery,[25] intensive care units,[26] contrast administration,[27] kidney transplant,[28] and general hospital wards.[29]

Given the tremendous physiological difference between functional and structural AKI in cirrhosis and the impact this distinction has on the potential for successful treatment, injury biomarkers would seem particularly well suited for use in this setting. The critical need for research in this area was recognized by the study group on HRS at the Eighth International Consensus Conference of the