

Hepatology and Nephrology: Nimbus



Our two Guest Editors, Jay Koyner and Michael Heung bring forth the ever-emerging issue of concurrent liver and kidney disease and those individuals with acute or chronically impaired hepatic function who develop kidney dysfunction acutely or chronically. They note that increasingly nephrologists have specialized in areas outside their usual work, for example, the onco-nephrologist. Furthermore, they discuss the nascent subspecialist, the hepato-nephrologist.

Liver disease now hangs over kidney disease like a nimbus cloud, and it seems to be raining liver disease these days. My opinion may reflect the environment at which I work, an institution that performs liver and kidney transplants and that has a large CKD clinic situated beside a hepatology clinic. Nephrologists are needed and asked to participate in the complex care of hospitalized patients with advanced liver disease. Because of enhanced care of critically ill patients with hepatic failure, more such patients are surviving, no doubt partly because of the contribution of nephrologists who purvey various forms of kidney replacement therapy, which is frequently required in these circumstances.

Liver transplantation has grown substantially in the past 2 decades and is lifesaving for pediatric patients with congenital disorders that eventuate in cirrhosis, adolescents and young adults with acute drug toxicities, and adults with progressive liver disorders including nonalcoholic steatohepatitis. As liver transplantation has burgeoned, more patients now develop kidney disease enroute to liver transplantation or advanced medical therapy. As a case-in-point, the increasing disease frequency of hepatitis C virus stabilized by 2002 because of advances in therapy, after having been an underlying or contributory cause of mortality for nearly the previous 2 decades. The greater survivorship has translated to more CKD in hepatitis C virus (HCV)-afflicted individuals.¹ Patients with coincident liver and kidney disease frequently require liver transplantation and possibly kidney transplantation, singly or simultaneously. This latter scenario is thoroughly discussed within this journal issue. Liver patients are also referred to nephrologists as outpatients for acute or chronic kidney dysfunction, and this is our point of emphasis. For some, renal consultation of liver patients with acute kidney injury (AKI)

and/or CKD is uncommon, and for others, a nearly daily occurrence.

Confronted by liver disease, a patient with an elevated serum creatinine ushers forth several and immediate questions. Is AKI or CKD present? What diagnostic and prognostic factors are present? Which treatments will be of benefit? The classical paradigm was that of underfilling of the circulatory volume attributable to splanchnic arterial vasodilation,² an ineffective circulatory volume that provided inadequate kidney perfusion with secondary hyperaldosteronism and hypokalemia. Although excessive aldosterone-mediated potassium secretion conspires with poor intake of this mineral, the contribution of elevated plasma bile acid inactivation of 11- β -hydroxysteroid dehydrogenase type 2 must be considered as well.³ These hemodynamic alterations may conspire with an associated depression of cardiac function, a described yet poorly recognized subterfuge that persists even after normalization of afterload.² An abdominal compartment syndrome with attendant elevation of kidney venous pressure may further attenuate kidney function.

This situation represented the extreme form of type 2 hepatorenal syndrome (HRS) and was associated with a high rate of mortality. The consequences of exaggerated sympathetic nervous system activation and impaired baroreceptor stimulation and hepatic osmoreceptor activation by hypo-osmolality⁴ led to sodium retention with a low fractional sodium excretion (FENa) but disproportionate water reabsorption from elaboration of arginine vasopressin and hyponatremia. In extreme circumstances, a distal renal tubular acidosis-like picture emerged because of hyperabsorption of sodium with impaired ammoniogenesis. Volume resuscitation, often with albumin as colloid, was frequently efficacious but often only on a limited and temporal basis. The addition of terlipressin may produce a greater salutary response, but the refractoriness of type 2 HRS limits its utility.

Type 1 HRS responds more favorably to this agent and represents a form of AKI. There is often a precipitating event

in type 1 HRS, such as acute alcoholic hepatitis, bacterial infection, gastrointestinal blood loss of significant degree, or another cause for rapid reduction of effective circulatory volume. Poor survival measured in days to weeks attends type 1 HRS, and the only definitive treatment for this catastrophic disorder is orthotopic liver transplantation, often after temporizing therapies of vasoconstrictor drugs with octreotide, albumin, and even transjugular intrahepatic portosystemic shunting. Covert hepatoadrenal insufficiency may be present with diminished cortisolemia and should be considered as a cause of ongoing asthenia.⁵ Fortunately, not all forms of AKI in liver disease are as devastating, and more slowly, toxic forms of liver-kidney syndromes exist including that from androgenic, anabolic steroid use with cholestasis, and AKI. This syndrome may occur in approximately 1% of patients treated with methyltestosterone, danazol, stanozolol, or oxymetholone.^{6,7}

Molecular adsorption recirculating system (MARS) therapy is used at some centers for end-stage liver disease patients.⁸ For now, MARS remains as distant as the planet itself with small trials demonstrating no benefit of this treatment option. In the best possible situation, kidney failure is transient and rectifiable. The most common conditions for this favorable outcome are overly ambitious diuretic therapy and/or paracentesis. Routinely, 5 to 6 L volumes are removed from individuals with ascites whose vascular refill rate is impossible to ascertain by more than an educated guess. As discussed by Arroyo,⁹ therapeutic paracentesis even with prophylactic volume expansion by albumin (8 g/L ascites fluid) often results in a transient improvement in serum creatinine levels for just a day before its subsequent deterioration by 48 hours post-paracentesis.

Although FENa has differentiated oliguric states into prerenal azotemia vs non-prerenal AKI, this test is fraught with hazard when AKI occurs in the setting of end-stage liver disease. No set of commonly accepted diagnostic criteria serve the nephrologist or hepatologist well in the determination of etiology, which may have profound prognostic and management implications. In cirrhotic patients, FENa may distinguish HRS from prerenal azotemia but will not discriminate between prerenal azotemia and acute tubular necrosis. In HRS, the FENa was vanishingly small (<0.1%). However, biomarkers of tubular injury represent a viable approach to determine etiology, especially when provided as a panel of markers for individuals with worsening AKI stage. The confidence of diagnosing acute tubular necrosis increases 13-fold using a panel of 4 biomarkers vs none.¹⁰

So, at what level of serum creatinine or absolute increase of serum creatinine should one be concerned? (Box) Two recent studies shed light on this issue. In one, Fagundes and colleagues¹¹ evaluated 375 consecutive liver disease patients with acute complications. AKI Stage 1 (AKI-1) patients with serum creatinine less than 1.5 mg/dL had a 90-day probability of survival similar to that of patients without AKI. In contrast, AKI-1 patients with serum creatinine more than 1.5 mg/dL showed significantly lower 90-day probability of survival than the aforementioned 2 groups. Piano and colleagues¹² studied 233 consecutive patients with ascites. Serum creatinine was measured at admission (baseline) and daily in-hospital. In this investigation, the in-hospital mortality of patients with AKI-1 was

Box. Acute Kidney Injury Criteria in Cirrhosis

- Serum creatinine greater than 1.5 mg/dL.
- Identification of a cause of kidney disease (acute tubular necrosis, exposure to nephrotoxin, volume depletion, CKD).
- Hepatorenal syndrome, type 1 (rapid) or 2 (chronic), determined according to rate of progression of renal failure.
- Deterioration of renal function with serum creatinine increase of 50% or more from baseline to a final level of 1.5 mg/dL or more.
- Kidney failure associated with bacterial infections, in the absence of septic shock, which may follow a variable course of rapidity.

Adapted from Arroyo V. Acute kidney injury (AKI) in cirrhosis: should we change current definition and diagnostic criteria of renal failure in cirrhosis? *J Hepatol.* 2013; 59(3):415–417.

higher, although not significantly, than those without AKI. However, progression of AKI and mortality were significantly higher, whereas resolution of AKI was significantly lower in AKI-1 patients with serum creatinine more than 1.5 mg/dL compared with less than 1.5 mg/dL. Patients from both studies whose serum creatinine rose by more than 0.3 mg/dL but did not achieve a zenith of 1.5 mg/dL had a good prognosis. Additionally, kidney parenchymal disease that is slowly progressive is associated with a better prognosis than type 2 HRS (3-month survival, 73% vs 15%) and more favorable than kidney failure associated with volume depletion (46%) and infections (31%).¹³

Outpatient consultation of liver disease in the kidney clinic is represented largely by nonalcoholic fatty liver disease (NAFLD), which dominates the clinical picture along with HCV-induced disease. NAFLD is associated with obesity, insulin resistance, and diabetes. The 5'-AMP activated protein kinase energy sensor undoubtedly plays a pivotal role in both the kidney and liver disorders, with relative adiponectin deficiency playing an instrumental role. The dual dysfunction is contingent on an "interorgan communication" among adipose, liver, and kidney tissues as orchestrated by fetuin-A that inhibits insulin receptor kinase in liver and skeletal muscle and reduces adiponectin expression. Low levels of adiponectin correspond to increased hepatic fibrosis and podocytopathy through a reduction in 5'-AMP activated protein kinase stimulation.¹⁴ Kidney disease is often missed or ignored until there is an elevation of serum creatinine, edema formation, or the onset of proteinuria. Sometimes, there must be frank cirrhosis and AKI to prompt a kidney consultation, which is precisely why nephrologists must work proactively and collaboratively in an engaged fashion with liver specialists. Liver fibrosis is easier to detect with the advent of the hepatic fibroscan—hepatic ultrasonic elastography.¹⁵

This test correlates shear wave velocity with hepatic stiffness, ie, fibrosis. Combined with hepatic biomarkers, this noninvasive technique can obviate liver biopsy as it evaluates the presence of significant fibrosis fairly well and its exclusion with a sensitivity of 100% and specificity of

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