9-1-2015

Hepatology and Nephrology: Nimbus

Jerry Yee
Henry Ford Health, JYEE1@hfhs.org

Recommended Citation
Yee J. Hepatology and nephrology: Nimbus. Adv Chronic Kidney Dis 2015; 22(5):331-334.

ACKD
Advances in Chronic Kidney Disease
A Journal of the National Kidney Foundation®

Vol 22, No 5, September 2015

EDITORIAL

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-osmolality[4] 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 ammoniagenesis. 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

1548-5595/$36.00
http://dx.doi.org/10.1053/j.ackd.2015.07.001

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 methyltesterone, 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 colleagues[11] 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 colleagues[12] studied 233 consecutive patients with ascites. Serum creatinine was measured at admission (baseline) and daily inhospital. In this investigation, the inhospital mortality of patients with AKI-1 was 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]

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.

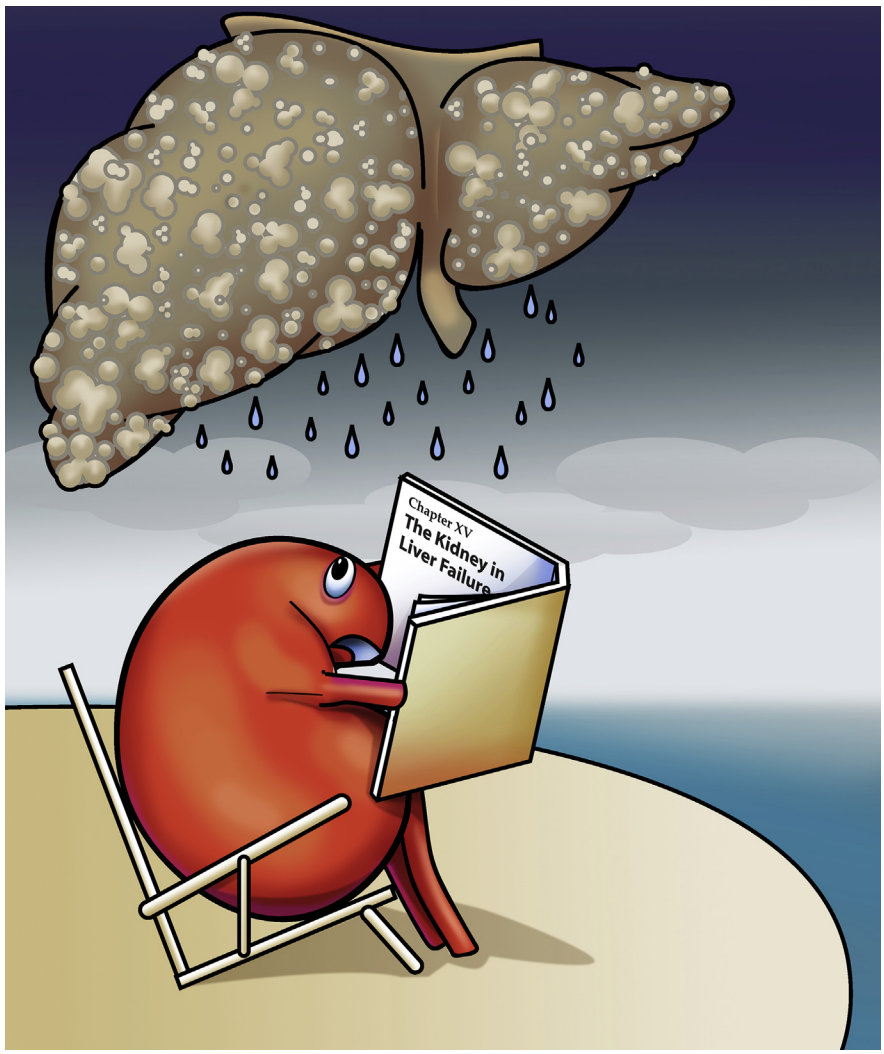
Outpatient consultation of liver disease in the kidney clinic is represented largely by nonalcoholic fatty liver disease (NAFLD), which dominates the clinical picture along with HCV-induced disease. NAFLD is associated with obesity, insulin resistance, and diabetes. The 5′-AMP activated protein kinase 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

91%. However, it performs less well for intermediate stages of fibrosis and cannot be adequately performed in obese patients or those with ascites. In these cases, magnetic resonance imaging elastography that has a technical success rate of 96% (vs 92% for shear wave elastography) may be performed, but this cross-validated technique is technically more demanding.[16]

In patients with advanced liver disease, the serum creatinine is subject to multiple influences and may not reflect the true glomerular filtration rate (GFR). Among these influences are an impairment of protein intake and sarcopenia from chronic illness. Although a 24-hour urine creatinine collection may mirror the true GFR better than any serum creatinine-estimating equation, proximal tubular secretion of creatinine still muddies the plasma water, which may be further obfuscated by elevated bilirubin levels (depending on the creatinine measurement technique). Cystatin C-based equations are rarely used to interpret the GFR in liver patients despite their superiority in this particular context.[17] Others advocate for the use of the Modification of Diet in Renal Disease (MDRD) Equation 6 in liver disease.[18] Recall that in Equation 6, GFR is a function of age, creatinine, race, and sex as with the MDRD Equation 4 plus albumin and blood urea nitrogen. Hypoalbuminemia and elevated blood urea nitrogen serve to lower GFR. Although a Danish group strongly advised against using MDRD equations for GFR estimation in solid organ transplant recipients, Shaffi and colleagues[19] concluded that the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) and MDRD equations were the most suitable for GFR estimation in these patients. More recently, another group demonstrated that the most accurate equation by Bland-Altman analysis was a creatinine and ^{51}Cr-EDTA-based equation that proved superior to 2 creatinine-based and three cystatin C-based formulas.[20]

HCV-associated kidney disease is most frequently associated with histologically evident membranoproliferative glomerulonephritis but may manifest much less commonly as a membranous nephropathy. Mixed, essential cryoglobulinemic vasculitis that involves humoral immunity with participant B and T cells but not the virus itself[21] may generate a kidney failure-hypertension syndrome without glomerulitis.[22] Now, HCV is more curable than previously and to a far greater extent. The nucleoside analogue, ribavirin, added to alpha-interferon (IFN) therapy substantially improved virologic remission rates



Hepato-nephrologist busily at work. Original artwork by Thomas Mattix, Mattix Illustrations, Columbus, Ohio.

compared with interferon alone. Yet anti-HCV treatment with these agents was shunned by the liver- and kidney-treating communities at relatively well-preserved levels of GFR, attributable to fears of inducing hemolytic anemia from ribavirin. This denial of treatment occurred despite successful pegylated interferon plus ribavirin therapy with plasma trough level monitoring in patients with GFRs in the range of 10 to 65 mL/min and in dialysis patients who required high dosages of erythropoietin.[23,24]

Treatment of HCV today is at a tipping point and the therapeutic lever that balances costs of treatment against newer NS5B RNA polymerase inhibitors pivots on a fulcrum of dollars.[25] In 2013, sofosbuvir was Food and Drug Administration approved. It can be combined with ribavirin for treatment of HCV genotypes 2 and 3. For the more vexing genotypes 1 and 4, pegylated IFN is added. In 2014, non-IFN-based therapy of genotype 1 HCV was approved as the combination of sofosbuvir and ledipasvir, an NS5A inhibitor. Although the efficacy of these newer agents is not in dispute, their associated costs have provided a reverberating debate. The volume of this fierce dialog may soon subside with the introduction of several competitor agents in the near term.[26] Overall, the scourge of HCV could be substantially contained pending worldwide availability and distribution of these agents. Let's hope so, as this will help the rates of hepatocellular carcinoma and cirrhosis from HCV to fall along with the accompanying burden of CKD. The implications for improvement in worldwide health would be incredible, particularly in countries where HCV is highly endemic such as Egypt, multiple other African countries, and Pakistan.

ACKNOWLEDGMENTS

The author expresses his gratitude to Stephanie Stebens and Sarah Whitehouse for their expert contributions to this article.

Jerry Yee, MD
Editor-in-Chief
Detroit, MI

Financial Disclosure: The author reports holding stock in Gilead, the manufacturer of sofosbuvir (Sovaldi®) and ledipasvir/sofosbuvir (Harvoni®).

REFERENCES

1. Everhart JE. Viral hepatitis. In: Everhart JE, ed. *Burden of Digestive Diseases in the United States Report. US Department of Health and Human Services, Public Health Service, National InstituteS of Health, National Institute of Diabetes and Digestive and Kidney Diseases.* Washington, DC: US Government Printing Office; 2008:13-23 (Chapter 3). Viral hepatitis. http://www.niddk.nih.gov/about–niddk/strategic–plans–reports/Pages/burden–digestive–diseases–in–united–states–report.aspx. Accessed June 15, 2015
2. Moller S, Henriksen JH. Cirrhotic cardiomyopathy: a pathophysiological review of circulatory dysfunction in liver disease. *Heart.* 2002;87(1):9-15.
3. Quattropani C, Vogt B, Odermatt A, Dick B, Frey BM. Reduced activity of 11b–hydroxysteroid dehydrogenase in patients with cholestasis. *J Clin Invest.* 2001;108(9):1299-1305.
4. Lechner SG, Markworth S, Poole K, et al. The molecular and cellular identity of peripheral osmoreceptors. *Neuron.* 2011;69(2):332-344.
5. Arroyo V, Fernandez J. Management of hepatorenal syndrome in patients with cirrhosis. *Nat Rev Nephrol.* 2011;7(9):517-526.
6. Singh C, Bishop P, Willson R. Extreme hyperbilirubinemia associated with use of anabolic steroids, health/nutritional supplements, and ethanol: response to ursodeoxycholic acid treatment. *Am J Gastroenterol.* 1996;91(4):783-785.
7. Luciano RL, Castano E, Moeckel G, Perazella MA. Bile acid nephropathy in a bodybuilder abusing an anabolic androgenic steroid. *Am J Kidney Dis.* 2014;64(3):473-476.
8. Wong R, Raina N, Richardson R. Molecular adsorbent recirculating system is ineffective in the management of type 1 hepatorenal syndrome in patients with cirrhosis with ascites who have failed vasoconstrictor treatment. *Gut.* 2010;59(3):381-386.
9. 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.
10. Belcher JM, Sanyal AJ, Peixoto AJ, et al. Kidney biomarkers and differential diagnosis of patients with cirrhosis and acute kidney injury. *Hepatology.* 2014;60(2):622-632.
11. Fagundes C, Barreto R, Guevara M, et al. A modified acute kidney injury classification for diagnosis and risk stratification of impairment of kidney function in cirrhosis. *J Hepatol.* 2013;59(3):474-481.
12. Piano S, Rosi S, Maresio G, et al. Evaluation of the Acute Kidney Injury Network criteria in hospitalized patients with cirrhosis and ascites. *J Hepatol.* 2013;59(3):482-489.
13. Martin–Llahi M, Guevara M, Torre A, et al. Prognostic importance of the cause of renal failure in patients with cirrhosis. *Gastroenterology.* 2011;140(2):488-496. e484.
14. Ix JH, Sharma K. Mechanisms linking obesity, chronic kidney disease, and fatty liver disease: the roles of fetuin–A, adiponectin, and AMPK. *J Am Soc Nephrol.* 2010;21(3):406-412.
15. Yoon JH, Lee JM, Woo HS, et al. Staging of hepatic fibrosis: comparison of magnetic resonance elastography and shear wave elastography in the same individuals. *Korean J Radiol.* 2013;14(2):202-212.
16. Venkatesh SK, Yin M, Ehman R. Magnetic resonance elastography of liver: technique, analysis and clinical applications. *J Magn Reson Imaging.* 2013;37(3):544-555.
17. Hoek FJ, Kemperman FA, Krediet RT. A comparison between cystatin C, plasma creatinine and the Cockcroft and Gault formula for the estimation of glomerular filtration rate. *Nephrol Dial Transplant.* 2003;18(6):2024-2031.
18. Weber ML, Ibrahim HN, Lake JR. Renal dysfunction in liver transplant recipients: evaluation of the critical issues. *Liver Transpl.* 2012;18(11):1290-1301.
19. Shaffi K, Uhlig K, Perrone RD, et al. Performance of creatinine–based GFR estimating equations in solid–organ transplant recipients. *Am J Kidney Dis.* 2014;63(6):1007-1018.
20. Xirouchakis E, Marelli L, Cholongitas E, et al. Comparison of cystatin C and creatinine-based glomerular filtration rate formulas with 51Cr-EDTA clearance in patients with cirrhosis. *Clin J Am Soc Nephrol.* 2011;6(1):84-92.
21. Cacoub P, Saadoun D. Hepatitis C virus infection induced vasculitis. *Clin Rev Allergy Immunol.* 2008;35(1–2):30-39.
22. D'Amico G. Renal involvement in hepatitis C infection: cryoglobulinemic glomerulonephritis. *Kidney Int.* 1998;54(2):650-671.
23. Bruchfeld A, Lindahl K, Stahle L, Soderberg M, Schvarcz R. Interferon and ribavirin treatment in patients with hepatitis C–associated renal disease and renal insufficiency. *Nephrol Dial Transplant.* 2003;18(8):1573-1580.
24. Bruchfeld A, Stahle L, Andersson J, Schvarcz R. Ribavirin treatment in dialysis patients with chronic hepatitis C virus infection—a pilot study. *J Viral Hepat.* 2001;8(4):287-292.
25. Steinbrook R, Redberg RF. The high price of the new hepatitis C virus drugs. *JAMA Intern Med.* 2014;174(7):1172.
26. Hoofnagle JH, Sherker AH. Therapy for hepatitis C—the costs of success. *N Engl J Med.* 2014;370(16):1552-1553.