CHAPTER

53

Liver Disease and Chronic Kidney Disease

Joel Neugarten, Ladan Golestaneh

Albert Einstein College of Medicine, Renal Division, Montefiore Medical Center, Bronx, NY, United States

Abstract

Recent investigations have established the existence of robust cross talk between the liver and kidney. These bidirectional interactions mediate deleterious effects of liver disease on the development and progression of kidney disease as well as effects of kidney disease on liver injury and hepatic drug metabolism. Although the full spectrum and consequences of liver/kidney cross talk remains to be elucidated, the clinical relevance of these interactions is clear.

INTRODUCTION

The association of liver disease with immunologically mediated glomerular disease and tubulointerstitial renal injury has long been recognized (Table 53.1). However, more recently, attention has focused on the existence of bidirectional cross talk between the liver and the kidneys. It has been suggested that chronic liver disease may accelerate the progression of CKD and that CKD may accelerate the progression of chronic liver disease, as well as alter hepatic drug metabolism. The existence of cross talk between the liver and the kidney may affect therapeutic interventions directed toward slowing the progression of both liver and kidney disease and may significantly influence drug dosing in patients with combined liver and renal disease.

HEPATORENAL SYNDROME

The most dramatic manifestation of liver/kidney cross talk is the development of hepatorenal syndrome (HRS).[1–5] Our understanding of the pathogenesis of the HRS has undergone a dramatic evolution in the past decade. From its initial conception as a functional disorder mediated by systemic circulatory dysfunction accompanying decompensated liver failure, HRS has been transformed into a more complex systemic disorder characterized by systemic inflammation and multiorgan dysfunction.[1–5] In 2015, the International Club of Ascites redefined HRS to incorporate a modified version of the Kidney Disease: Improving Global Outcomes criteria for the diagnosis of acute kidney injury (AKI).[6,7] HRS-AKI was defined as AKI that developed in a patient with cirrhosis and ascites that did not respond to diuretic withdrawal and plasma expansion in the absence of shock, nephrotoxic drugs, or evidence of structural renal injury.

The classification of HRS into types 1 and 2 was not incorporated into the new definition. In earlier nomenclature, type 1 HRS was characterized by rapidly progressive renal failure, whereas type 2 HRS referred to a more indolent decline in renal function that was more moderate in severity. Type 2 HRS was characterized by refractory ascites and diuretic resistance, with an average survival of 6 months.[1,3] Type 2 HRS is now referred to as HRS-CKD.

Role of Systemic Circulatory Dysfunction in HRS

HRS-AKI has primarily been defined as a renal event; however, new insights into the pathophysiology of decompensated liver disease suggest that HRS is also an indicator of severe systemic inflammation, indolent multiorgan dysfunction, and failure of hemodynamic compensatory mechanisms. Cirrhosis is characterized by deranged liver architecture, leading to increased intrahepatic vascular resistance that in turn leads to increased portal vein pressure.[1–5] Release of systemic vasodilators, classically thought to arise as a response to portal hypertension, leads to peripheral vasodilation and decreased vascular resistance. Numerous vasodilatory agents have been proposed as pathogenetic mediators.[1–5] Decompensated cirrhosis is associated with increased endothelial cell production of nitric

Chronic Renal Disease, Second Edition
https://doi.org/10.1016/B978-0-12-815876-0.00053-X

TABLE 53.1 Kidney Lesions Associated with Liver Disease*

Hepatitis C	Membranoproliferative glomerulonephritis with or without cryoglobulinemia
	Membranous nephropathy
	Focal and segmental glomerulosclerosis
	Immunoglobulin A nephropathy
	Fibrillary glomerulopathy
	Immunotactoid glomerulopathy
	Thrombotic microangiopathy
	Amyloidosis
	Interstitial nephritis
	Diabetic nephropathy
Hepatitis B	Membranous nephropathy
	Immunoglobulin A nephropathy
	Membranoproliferative glomerulonephritis
	Minimal change disease
	Focal and segmental glomerulosclerosis
	Crescentic glomerulonephritis
	Polyarteritis nodosa
	Cryoglobulinemia
	Amyloidosis
Alcoholic cirrhosis	Immunoglobulin A nephropathy
	Membranoproliferative glomerulonephritis with immunoglobulin A deposition
Primary sclerosing cholangitis	Membranous nephropathy
	Membranoproliferative glomerulonephritis
	Tubulointerstitial nephritis
	Antineutrophil cytoplasmic antibody-associated vasculitis/glomerulonephritis
Primary biliary cirrhosis	Interstitial nephritis
	Membranous nephropathy
	Antineutrophil cytoplasmic antibody-associated vasculitis/glomerulonephritis
	Antiglomerular basement membrane disease
Alpha-1 antitrypsin deficiency	Membranous nephropathy
	Antiglomerular basement membrane disease

* *Cause and effect relationships have not been established in all cases.*

oxide, carbon monoxide, prostacyclin, calcitonin gene-related peptide, adrenomedullin, endocannabinoids, and plasma substance P which may contribute to arterial vasodilatation.[1–5] An increase in regional blood flow in response to portal hypertension, splanchnic vasodilation, and portosystemic shunting leads to pooling of blood in the splanchnic circulation.[1–5] The recruitment of compensatory mechanisms to maintain renal perfusion in the face of reduced effective arterial volume constitute the hallmark of HRS. These compensatory mechanisms include release of systemic vasoconstrictors, upregulation of the renin–angiotensin system, and activation of the sympathetic nervous system.

Animal models of portal vein hypertension support a direct neural connection between hepatic osmo- and baroreceptors and the kidney.[8,9] Acute induction of experimental portal hypertension activates hepatic baroreceptors, which in turn increase renal sympathetic efferent nerve activity. Activation of the renal sympathetic nervous system is associated with renal vasoconstriction and reduced renal blood flow, increased renin release, and enhanced renal tubular salt and water reabsorption.[1–5] Reduced effective circulating volume also leads to increased nonosmotic release of vasopressin and increased generation of potent vasoconstrictors, including leukotrienes and endothelin-1.[1–5] In contrast, local compensatory renal vasodilators, such as prostaglandins, are reduced.[1–5] Consistent with this scenario, an increased renal resistive index on renal Doppler ultrasonography, an index of reduced diastolic renal blood flow, predicts the subsequent development of HRS.[10–12]

Lack of cardiac compensation in response to severe systemic vasodilation worsens this cycle. In early stages of cirrhosis, increased cardiac output maintains renal perfusion.[1–5] However, in advanced cirrhosis, the ability of the heart to compensate is limited by cirrhotic cardiomyopathy and cardiac output declines. In this setting, beta blockers are deleterious to cardiac function and worsen hemodynamic dysfunction by sensitizing the sympathetic nervous system. In addition, renin–angiotensin blockade may increase renal vasoconstriction and promote AKI. Because cardiac preload may play a crucial role in cardiac function in this setting, nitrates are also contraindicated.

Hepatorenal Syndrome as a Systemic Inflammatory State

It has recently been suggested that the primary factor responsible for the release of vasodilatory mediators in HRS is increased circulating levels of cytokines and chemokines resulting from chronic inflammation associated with decompensated liver disease.[2,13] Cirrhosis is associated with increased gastrointestinal permeability, altered gastrointestinal microbiome, and translocation

of bacteria and bacterial products (pathogen-associated molecular patterns) from the gastrointestinal tract into the circulation.[2] These bacterial products, along with danger-associated molecular patterns released by apoptotic and necrotic hepatocytes, stimulate the production of proinflammatory cytokines and chemokines, reactive oxygen and nitrogen species, and activate immune cells, which in turn magnifies the proinflammatory response.[2]

Decompensated cirrhosis is associated with increased circulating levels of proinflammatory cytokines and chemokines including interleukin-6 (IL-6), IL-8, and tumor necrosis factor-alpha (TNF-α), which may contribute to renal injury.[2,5,13,14] Circulating levels of IL-6, TNF-α, and vascular cell adhesion molecules are higher in patients with cirrhosis and HRS-AKI compared with those without HRS-AKI.[5] Patients with spontaneous bacterial peritonitis and renal dysfunction have higher IL-6 and TNF-α levels than patients with spontaneous bacterial peritonitis without renal dysfunction.[14] Similarly, other investigators have correlated renal dysfunction associated with decompensated liver failure with circulating levels of IL-6, IL-8, and irreversibly oxidized nonmercaptalbumin 2.[13]

The functional nature of HRS has recently been challenged. Renal histologic injury has never been systematically excluded because careful renal biopsy studies in patients who satisfy the clinical criteria used to diagnose HRS have not been performed. Urinary biomarkers suggest tubular injury in HRS-AKI diagnosed by traditional criteria.[5,15] Pathogen-associated molecular patterns and danger-associated molecular patterns may be injurious to proximal tubule epithelial cells and downregulate mitochondrial metabolism. Lastly, it has been suggested that cholestasis, with resultant hyperbilirubinemia, may promote deposition of bilirubin in the renal tubular lumen to induce tubular obstruction and direct toxic tubular injury.[16,17] This disorder has been referred to as bile cast nephropathy.[16,17] Bile acid casts were demonstrated in 11 of 13 renal specimens obtained from patients meeting the clinical criteria for HRS.[17]

HRS-CKD

HRS-CKD is uncommon, accounting for only 5−11% of patients with cirrhosis and renal dysfunction. Treatment with intravenous albumin and terlipressin or noradrenaline can reverse HRS-CKD in more than half the cases.[18,19] However, responders experience a high relapse rate early after withdrawal of therapy. Relapse occurs in two-thirds of initial responders.[18,19] Multiple relapses in the same patient are also frequent.[18,19] It has been postulated that a persistent proinflammatory state or rebound activation of vasoconstrictor pathways are responsible for this high relapse rate.[18]

Treatment of HRS-CKD with albumin volume expansion and vasoconstrictors is controversial and is not recommended by international practice guidelines due to inconsistent outcomes data.[2,18] In a retrospective study of 56 patients with "type 2" HRS awaiting liver transplant and treated with terlipressin and albumin, no difference in pretransplantation or posttransplantation outcomes was observed between responders and nonresponders.[19] There was no difference in the mortality of wait-listed responders and nonresponders. After liver transplantation, there was no difference in estimated glomerular filtration rate (eGFR) or in the development of CKD on follow-up, ranging up to 1 year, based on response to therapy. Length of hospitalization, development of AKI, need for renal replacement therapy (RRT), and survival did not differ between responders and nonresponders. The authors suggest that the failure of therapy to improve outcomes in these patients may reflect unrecognized underlying renal parenchymal injury.

Transjugular intrahepatic portosystemic shunting as a bridge to orthotopic liver transplantation has been associated with improved renal function in patients classified as type 2 HRS.[20] European Association for the Study of the Liver Clinical Practice Guidelines state that transjugular intrahepatic portosystemic shunting "could be suggested in selected patients with HRS-NAKI."[2]

Intra-abdominal hypertension may also contribute to hemodynamic-mediated renal dysfunction in patients with decompensated cirrhosis with ascites. Clinical studies of decompensated liver disease have demonstrated correlations between intra-abdominal pressure and sodium avidity and azotemia. A reduction of intra-abdominal pressure by paracentesis is associated with an improvement in renal blood flow and urine output in patients with decompensated cirrhosis and intra-abdominal hypertension.[4,21] In a murine model of cirrhosis, increased intra-abdominal pressure was associated with renal dysfunction.[22] It is postulated that nephro-congestion leads to an increase in intratubular pressure, a reduced pressure gradient for filtration, and reduced glomerular filtration rate.

Serum creatinine concentration (S[Cr]) is a poor marker of renal disease in liver failure, frequently overestimating renal function and underestimating renal injury. Because the Model for End-Stage Liver Disease score uses S[Cr] as a marker of renal disease, the lack of sensitivity of S[Cr] for the diagnosis of CKD or AKI is highly problematic vis-a-vis allocation of donor liver organs. In patients with cirrhosis, where significant muscle atrophy, reduced hepatic conversion of creatine

into creatinine, and reduced tubular secretion of creatinine are commonplace, significant renal dysfunction may be masked by an ostensibly normal S[Cr] value.

HEPATITIS C VIRUS INFECTION

Hepatitis C virus (HCV) infection affects approximately 3.5 million Americans and over 71 million individuals worldwide.[23] The annual incidence rate in the US is estimated to be 13.9 cases per 100,000 population.[24] HCV infection is among the most common causes of liver transplantation in the US and Europe. HCV infection disproportionately affects patients with CKD and end-stage renal disease (ESRD). Among CKD patients who have never been transfused, the prevalence of HCV antibody is approximately 10-fold higher than in the blood donor population.[25] HCV infection not only represents a major cause of morbidity and mortality in the CKD population but may also independently influence the natural history of the underlying kidney disease.

Numerous investigators have suggested that HCV infection is associated with the development and accelerated progression of CKD leading to an increased risk for ESRD. Although many epidemiologic studies show an association between HCV infection and CKD, as do several meta-analyses, the results have not been entirely consistent. In fact, some studies have found a protective effect of HCV infection on CKD.

Fabrizi et al.[26] performed a meta-analysis of 40 studies, containing over 4 million patients, that used multivariate analysis to examine the association of HCV infection with CKD. An association between HCV infection and an increased incidence of CKD was demonstrated in 15 longitudinal studies containing 2,299,134 patients (295,773 of whom were HCV-infected) (HR 1.54). The diagnosis of HCV infection was based on anti-HCV seropositivity, detection of HCV RNA, or an administrative code indicating a diagnosis of HCV infection. The risk of CKD increased with aging and duration of follow-up. HCV infection was also associated with the prevalence of proteinuria in 10 cross-sectional studies containing 378,769 patients (63,365 of whom were HCV-infected) (HR 1.63). Overall, no association between HCV and an increased prevalence of CKD was observed. However, an association between HCV and an increased prevalence of CKD was demonstrable in Asian populations (HR 1.2).

A recent report by Tartof et al.[27] found that the risk of a 25% reduction in eGFR or progression to ESRD was greater in a cohort of 1603 subjects with CKD and HCV infection compared with 151,974 subjects with CKD alone.

Another meta-analysis examined the association of HCV with CKD in human immunodeficiency virus (HIV)/HCV coinfected patients.[28] An association between HCV infection and increased risk of incident CKD was demonstrated in eight longitudinal studies of 105,462 coinfected patients (HR 1.64). HCV infection was also an independent risk factor for proteinuria in six studies that included 26,835 coinfected patients (HR 1.23). In contrast, in five cross-sectional studies of 13,853 patients, the prevalence of CKD was not increased in HIV/HCV coinfected patients.

Representative of studies that reported no effect or a protective effect of HCV infection on CKD is a cohort of over 13,000 anti-HCV seropositive subjects from an urban area with a high prevalence of HIV studied by Moe at al.[29] In a cross-sectional analysis of these subjects, HCV infection was associated with a reduced prevalence of CKD compared with anti-HCV seronegative subjects. In a longitudinal analysis of a subset of over 7000 subjects without CKD followed for a median of 3.5 years, there was no difference in the incidence of CKD in adjusted analysis. In another adjusted analysis of a demographically diverse cohort of insured individuals followed for a mean of over 2 years, Asrani et al.[30] found no difference in the prevalence, incidence, or rate of progression of CKD among 13,384 HCV-infected subjects compared with 154,185 subjects without HCV infection.

HCV infection was associated with proteinuria and an increased mean eGFR, but not with CKD, among participants in the 1988–1994 and 1999–2012 National Health and Nutritional Examination Survey ($n = 33,729$ and 15,029, respectively).[31,32] Rogal et al.[33] followed 71,528 US veterans for a mean of 6 years. Recent HCV seroconversion was documented in 2599 of the cohort. They found that HCV-infected individuals were less likely to develop CKD, but showed no difference in the rate of progression of CKD. However, in a much larger cohort of 920,531 uninfected and 100,518 HCV-infected US Veterans, Molnar et al.[34] found an association between HCV infection and increased incidence of CKD, progressive loss of renal function, and the development of ESRD.

In adjusted analysis of HCV/HIV coinfected women, Tsui et al.[35] reported no association between HCV infection and the prevalence of CKD, but found that in those with established CKD, HCV infection was associated with accelerated progression. In a large cohort of 474,369 US Veterans (52,874 of whom were anti-HCV seropositive), Tsui et al.[36] found that although the prevalence of CKD was lower in infected patients and there was no significant difference in the rate of progression of CKD, HCV-infected patients who did progress did so at a more rapid rate, leading to a higher incidence of ESRD.

Interpretation of available clinical studies is complicated by heterogeneity in subject demographics, including differences in age, sex, ethnicity, socioeconomic status, alcohol use, angiotensin-converting enzyme inhibitor therapy, and coinfection with HIV or hepatitis B virus (HBV), and by differences in the number of treatment-naïve vs. experienced patients. Methods to identify HCV infection differ among the studies, and include detection of anti-HCV antibody, detection of HCV RNA, and use of administrative codes to diagnose HCV infection. Because only 60–70% of HCV-infected patients demonstrate chronic viremia, diagnosis of HCV infection solely by the detection of HCV RNA may miss mild cases, leading to severity bias. Errors in administrative coding may also lead to misclassification. In addition, multiple confounding factors must be considered. Patients infected with HCV are more likely to suffer from diabetes, hypertension, obesity, HIV, cirrhosis, coronary artery disease, and hyperlipidemia and to have a history of intravenous drug use. Unmeasured confounding variables represent a significant issue in analyses of these data. A longer duration of HCV infection has been associated with an increased risk of CKD.[37] In this regard, many of the cohorts that failed to demonstrate an association between HCV infection and incident CKD were followed for only 2–3 years. Patients with HCV may also receive a higher intensity of medical care with more frequent follow-up visits, leading to detection bias due to earlier detection of CKD.

The REVEAL-HCV Study Group[38] found an increased CKD prevalence in those infected with genotype 2. This observation might help explain inconsistent data regarding the association of HCV infection and CKD. Meta-analysis has shown that the pooled risk for CKD among HCV-infected cohorts is higher in Asian populations than in the US or Europe.[26] These geographic variations in CKD risk parallel the relative prevalence of the HCV genotype 2. However, another publication from the REVEAL-HCV Study Group reported that genotype 1, not genotype 2, was a strong predictor of ESRD in their cohort.[39] Numerous other investigators found no association between HCV genotype and the incidence or prevalence of CKD.[37,40] Studies seeking to establish an association between CKD and viremia in HCV-infected patients have also yielded inconsistent results.[37–43] Peters et al.[40] reported an association between HCV viremia and the incidence rate of CKD among over 8000 HIV/HCV coinfected patients. Those who cleared their viremia showed an incidence rate similar to anti-HCV seronegative patients. Similarly, a high plasma HCV RNA level was associated with the prevalence of CKD in separate cohorts of 434 and 552 anti-HCV seropositive patients, as well as with the risk of progressive CKD in a third cohort of 34,441 HIV/HCV coinfected patients.[37,38,42] However, other investigators found no relationship between viremia and the incidence, prevalence, or rate of progression of CKD.[41,44]

Numerous mechanisms have been suggested to explain the purported association of HCV with CKD. Glomerular disease is a well-described, albeit uncommon, extrahepatic manifestation of HCV infection.[45–47] A systemic immune response to HCV infection is thought to contribute to glomerular injury. Glomerular disease may be mediated by HCV-antibody immune complex deposition with or without cryoglobulin formation. Deposition of immune complexes containing viral antigens has been demonstrated in mesangial and subendothelial locations. The most common histologic pattern of glomerular injury is membranoproliferative glomerulonephritis; however, membranous glomerulopathy, focal and segmental glomerulosclerosis, IgA nephropathy, immunotactoid and fibrillary glomerulopathies, amyloidosis and thrombotic microangiopathy have been described in HCV-infected patients (Table 53.1).[45–49] The prevalence of membranoproliferative glomerulonephritis and of cryoglobulinemia in patients chronically infected with HCV, identified by administrative codes reported to the National Inpatient Sample of the Healthcare Cost and Utilization project, has been reported to be 0.38% and 0.33%, respectively.[50] Similarly, the prevalence of membranoproliferative glomerulonephritis and of cryoglobulinemia, identified by administrative codes, among 34,204 HCV-infected hospitalized US veterans was 0.36% and 0.57%, respectively.[51] Postmortem series have identified a higher prevalence of nondiabetic glomerular disease in HCV-infected subjects, ranging from 8.8 to over 50% of cases.[47,52] A series of kidney biopsies obtained from liver transplant recipients showed glomerulonephritis in over 83% of cases.[49] Perhaps the inconsistencies in these data can be reconciled by the observation that many patients with membranoproliferative glomerulonephritis documented by kidney biopsy have clinically silent renal involvement.[49]

HCV may also exert direct cytopathic effects in renal tissue.[45,46,53] HCV viral particles or antigen has been identified in glomeruli, endothelial cells, and tubules in renal biopsy specimens from HCV-infected patients.[45,46] HCV exposure has also been associated with increased expression of toll-like receptors in renal glomeruli.[54] HCV core protein also directly inhibits insulin signaling, leading to a state of insulin resistance associated with compensatory hyperinsulinemia.[45,46,55] HCV activates the mammalian target of

rapamycin/ribosomal S6 kinase signal transduction pathway, which in turn alters the function of glucose transporters, insulin receptors, and the gluconeogenesis enzyme phosphoenolpyruvate carboxykinase 2, leading to insulin resistance.[45,46,55] HCV core protein induces increased oxidative stress and induces endothelial dysfunction by decreasing endothelial nitric oxide synthase activity and nitric oxide synthesis. HCV also exerts immunomodulatory effects.[45,46,55] HCV infects peripheral dendritic cells, monocytes, and macrophages and stimulates B cells, which in turn modulates B- and T-cell function. HCV core protein increases the synthesis of proinflammatory cytokines including IL-6, C-reactive protein, and nuclear factor kappa-light-chain enhancer of activated B cells (NF-κB).[55] Other downstream effects of HCV include increased levels of insulin-like growth factor-1, transforming growth factor-beta (TGF-β), and endothelin-1, and increased angiotensin II type 1 receptor density.

Use of DAA Medications to Eradicate HCV in Patients with CKD

Newer and highly effective therapeutic strategies for treatment of HCV have had a significant impact in the CKD and ESRD populations and may play a role in the prevention of HCV-related kidney injury. In the past, interferon and ribavirin constituted the only treatment option for HCV, and outcomes were suboptimal because of adherence issues related to toxicity.[56] By far, the most serious complication was hemolytic anemia associated with ribavirin, which precluded its use in most CKD patients. Research into the HCV life cycle identified the opportunity to arrest viral replication and infectivity within hepatocytes.[57] The four types of direct acting antivirals (DAAs) that were developed include (1) NS3/4A protease inhibitors, (2) NS5A inhibitors, (3) NS5B nonnucleoside polymerase inhibitors, and (4) NS5B nucleoside polymerase inhibitors.[57] They are given for a finite duration, usually in combination, avoid the difficult adverse effects of interferon-based therapies, and are curative. HCV type 1 is most successfully treated with combination DAA therapy, with cure rates exceeding 90%.[57] Initial DAA regimens used these agents in conjunction with pegylated interferon and ribavirin. Sofosbuvir-containing regimens later supplanted these strategies, and though effective, were contraindicated in patients with a GFR less than 30 mL/min.[58] Sofosbuvir is a nucleotide prodrug inhibitor of NS5B polymerase whose active metabolite is eliminated predominantly through the kidney.[58,59] Phase 3 clinical studies examining sofosbuvir and ledpasvir combinations did not include patients with CKD.[59–61] However, sofosbuvir was subsequently found to be well tolerated and effective in patients with stages 3–5 CKD, including dialysis-dependent CKD.[58,62–66] Notwithstanding these data, FDA approval of sofosbuvir is limited to individuals with an eGFR >30 mL/min/1.73 m^2. Other regimens are now available for advanced CKD[58,62]

The C-SURFER trial was the first to examine an all oral, ribavirin-free treatment for HCV in patients with stages 4 and 5 CKD.[67] The regimen used was grazoprevir (NS 3/4A protease inhibitor) in combination with elbasvir (NS5A inhibitor). The recruited patients were infected with HCV genotype 1; 76% were dialysis-dependent. Less than 1% of the grazoprevir and elbasvir combination is excreted by the kidney and less than 5% of grazoprevir is removed by hemodialysis.[67,68] The regimen was generally well tolerated and after 12 weeks of therapy, 99% achieved a sustained virologic response (SVR).[67] In the RUBY-1 trial of 20 patients with hepatitis C infection and stage 4 CKD (14 of whom required dialysis), the combination of ombitasvir/partparevir/ritonavir and dasabuvir with or without ribavirin was examined.[69] After 12 weeks of therapy, all 20 patients had completed the trial and 18 achieved SVR. A phase 3 multicenter, open-label trial (EXPEDITION 4) evaluated a 12 week course of therapy with combination of glecaprevir (NS3/4A protease inhibitor) and pibrentasvir (NS5A inhibitor) in 104 patients infected with HCV genotypes 1, 2, 3, 4, 5, or 6 and a baseline eGFR <30 mL/min/1.73 m^2.[70] SVR was achieved in 98% of patients. The current DAA regimens approved for use in patients with advanced CKD (stages 4 and 5) include Zepatier (combination of grazoprevir and elbasvir), Viekira (combination of ombitasvir, paritaprevir, dasabuvir, and ritonavir), and Mavyret (combination of glecaprevir and pibrentasvir).

The European Association for the Study of the Liver Recommendations on Treatment of Hepatitis C, 2018 state that "All patients with HCV infection must be considered for therapy, including treatment-naïve and individuals who failed to achieve SVR after prior treatment."[71] Many commentators have suggested that patients with mild to moderate CKD are especially attractive candidates for therapy and strongly recommended universal therapy of such patients. They emphasize the potential benefits of SVR on prevention of diabetes mellitus, improvement in glycemic control and cardiovascular outcomes and amelioration of CKD progression. The purported benefits of SVR on CKD are based on an emerging body of evidence suggesting that SVR is associated with a reduced incidence and prevalence of CKD, an improvement in eGFR, a slower rate of progression of CKD, and a reduced incidence of ESRD. Although the benefit of HCV therapy and SVR on renal outcomes in HCV-associated

glomerulonephritis is well established, the effects of therapy designed to achieve SVR on renal outcomes in the broader CKD population have not been entirely consistent. Moreover, studies are often compromised by small numbers of subjects, the frequent lack of an untreated control group, and heterogeneity in treatment regimens. These studies must also be interpreted in light of the bias inherent in the selection of patients for treatment.

Feng et al.[72] performed a meta-analysis of 11 clinical trials involving 225 patients with HCV-associated glomerulonephritis treated with interferon-based antiviral therapy. They reported a 2.71 g/24 h decrease in urinary protein excretion associated with SVR. Mean S[Cr] fell by 0.23 mg/dL. Others have found that DAA therapy is associated with a full or partial remission of cryoglobulinemic glomerulonephritis in nearly two-thirds of cases.[73]

Among 12,384 Taiwanese HCV-infected patients who were treated with pegylated interferon plus ribavirin and followed for over 8 years, the multivariate-adjusted risk of ESRD, identified by administrative codes, was reduced by 85% compared with propensity score-matched untreated HCV controls.[74] Among 919 HCV-infected patients treated with an interferon-based regimen in the same Taiwanese cohort, the 7-year cumulative incidence of CKD was lower by 58% in adjusted analysis compared with propensity score-matched untreated HCV controls.[75] Similar results have been reported by other investigators using interferon-based regimens to treat HCV.[37,74,76,77] In a cross-sectional study of 552 HCV-infected patients, there was a fivefold decrease in CKD in those who were treated with an interferon-based regimen during a 7-year follow-up.[37] Among 650 HCV-infected patients treated with interferon with or without ribavirin, the failure to achieve a SVR was associated with a 2.67-fold greater risk of developing CKD.[76] Among 12,534 HCV-infected patients treated with pegylated interferon and ribavirin and followed for a mean of 3.3 years, antiviral therapy was associated with a lower risk of ESRD in adjusted analysis (HR 0.15).[74] Consistent with these observations, Park et al.[77] observed a 30% reduction in the risk of developing CKD among 55,000 newly diagnosed HCV-infected individuals treated with interferon with or without ribavirin or boceprevir, telaprevir, sofosbuvir, or simeprevir plus pegylated interferon and ribavirin or all oral therapy.

Similar benefits have been described among patients treated exclusively with DAA therapies.[58,78,79] Sise et al.[58] treated 98 HCV-infected patients with stages 1–3 CKD with a sofosbuvir-based regimen. In those with an eGFR less than 60 mL/min/1.73 m^2 at baseline, a multivariate linear regression model indicated that SVR was associated with a 9.3 mL/min/1.73 m^2 improvement in GFR over a 6-month posttreatment follow-up period. In contrast, no change in eGFR was observed in those with stage 1 or stage 2 CKD at baseline. However, this study did not include an untreated control group. Medeiros et al.[79] also observed an increase in eGFR in HCV-infected patients 1 year after treatment with a sofosbuvir-based regimen.

In contrast, other studies show no improvement in renal outcome after DAA therapy and SVR.[43,80,81] A pooled analysis of phase 3 clinical trials of therapy with ombitasvir/paritaprevir/ritonavir or dasbuvir with or without ribavirin involving 5539 genotype 1 HCV-infected patients with stages 2–5 CKD and 464 placebo-treated controls followed for 52 weeks post treatment showed no significant change in eGFR from baseline, assessed 52 weeks after therapy.[81] However, those patients with stage 1 CKD at baseline experienced a significant decline in eGFR. One year after treatment of 523 HCV-infected patients with mostly sofosbuvir-containing DAA regimens, the rate of decline in eGFR in those who achieved SVR was not different from untreated HCV-infected patients but was less than in treated patients who failed to achieve SVR.[80] Rossi et al.[43] also failed to find an association between SVR and the rate of eGFR decline in HCV/HIV coinfected patients.

First-generation DAAs have been associated with transient AKI during therapy, and in the case of telaprevir, with long-term reductions in eGFR.[82,83] Several trials of second-generation DAAs report an increased, albeit low, incidence of AKI during therapy, which may occur more frequently with sofosbuvir-containing regimens and in those with more advanced CKD at baseline.[43,84–88] However, this signal has not been observed in other trials.[58,89] The use of different criteria among various trials to define adverse renal events confounds interpretation of data. A persistent reduction in eGFR measured 12 weeks after the end of therapy with second-generation DAAs as compared with baseline values has also been reported in many studies.[85,86,90,91] Saxena et al.[84] reported AKI, identified by administrative codes, in 2% of all patients treated with a sofosbuvir-containing regimen. However, the rate of AKI rose to 15% in those with an eGFR less than 45 mL/min/1.73 m^2 at baseline. Among 43 HCV-infected patients treated with sofosbuvir-containing regimens, eGFR fell more than 6 mL/min/1.73 m^2 at the end of therapy and, in those with cirrhosis, failed to recover 24 weeks after therapy. A meta-analysis of 13 trials which included 6884 HCV-infected subjects

found that DAA therapy was associated with renal functional deterioration in those with advanced CKD at baseline.[92] In contrast, the incidence of sosofovir-induced AKI was not increased among 98 HCV-infected patients with stages 1–3 CKD at baseline who were treated with a sosofovir-based regimen.[58] Although nearly 7% of patients experienced a transient episode of AKI with full recovery of renal function, in all but one case, the investigators deemed all these episodes to be unrelated to sofosbuvir therapy.

Several studies suggest that therapy of HCV-infected liver transplant recipients with antiviral therapy has a beneficial effect on renal outcomes.[93–95] Satapathy et al.[94] treated 204 liver transplant recipients with interferon and/or DAA and followed them for a median of 5.5 years. They found an 88% lower risk of CKD, a less steep rate of decline of eGFR over time and an 85% lower risk of ESRD in treated patients. Similarly, in a study of 99 HCV-infected liver transplant recipients with stage 2 CKD at baseline who were treated with pegylated interferon and ribavirin and followed for up to 5 years, SVR was associated with a 16 mL/min/1.73 m^2 improvement in eGFR compared with nonresponders.[93] However, among 31 treated patients with stage 3 CKD at baseline, there was no difference in eGFR between responders and nonresponders.

The decision whether or not to treat an HCV-infected individual suffering from late-stage CKD with a second-generation DAA entails consideration of the individual's kidney transplantation status. Immediate therapy may be warranted in living donor kidney transplant candidates, CKD due to HCV-related glomerulonephritis or in those suffering from advanced liver disease at high risk for decompensated liver failure. However, successful treatment of an HCV-positive candidate for a deceased donor kidney may result in a substantial delay or a lost opportunity for transplantation. The wait list for a kidney harvested from a deceased HCV-positive donor is on average one year shorter, and up to several years shorter, than for a HCV-negative deceased donor, giving HCV-positive recipients a substantial advantage in securing a kidney transplant.[96] Thus, deferring DAA therapy until after kidney transplantation may result in a substantial reduction in wait time. This advantage is greater in geographic regions with a high prevalence of anti-HCV seropositive deceased kidney donors and in those regions with a long wait list. Of course, patient preference and whether or not the local kidney transplant center accepts anti-HCV seropositive deceased donor kidneys are of paramount importance. Other considerations include HIV coinfection, which may increase the risk of decompensated liver failure, dialysis vintage which determines accumulated wait time credit, the average wait time for a deceased donor kidney in the local geographic area, and the HCV genotype which determines the complexity of treatment.

HEPATITIS B VIRUS INFECTION

Controversy also surrounds the relationship between CKD and HBV infection. A meta-analysis of four longitudinal studies which included 184,937 subjects, 36,192 of whom were infected with HBV, found that HBV infection was associated with incident ESRD (HR 3.78 [1.48,6.25]) as well as incident CKD, however, the latter association did not achieve statistical significance.[97] In contrast, the meta-analysis found no relationship between HBV infection and the prevalence of CKD in seven cross-sectional or case-control studies which included 109,889 subjects, 8023 of whom were infected with HBV. The meta-analysis also found no relationship between HBV infection and the prevalence of proteinuria. More recently, several large studies have confirmed the association of HBV with CKD. Si et al.[98] found an association between HBV infection and incident CKD, identified by administrative codes, among 469,459 subjects followed for 9.1 years, of which 14,871 were seropositive for HB surface antigen. Similarly, Hong et al.[99] found an association between HBV infection and incident proteinuria, but not incident eGFR <60 mL/min/1.73 m^2, among 299,913 subjects followed for 5.6 years, of which 11,209 were seropositive for HB surface antigen. Unlike the aforementioned meta-analysis, Kim et al.[100] found an association between HBV infection and prevalent eGFR <60 mL/min/1.73 m^2 and proteinuria among 265,086 subjects, of which 10,048 were seropositive for HB surface antigen.

Many of the same limitations identified in studies of HCV infection and CKD also apply to studies that address the relationship between HBV infection and CKD. Similarly, the mechanisms invoked to explain the effects of HBV infection on the development and progression of CKD are analogous to those postulated to mediate the effects of HCV infection on CKD. Proposed mediators include enhanced oxidative stress, upregulation of inflammatory cytokines, insulin resistance, modulation of immune responses, and cytopathic effects of HBV on renal tissue.

Therapy of HBV-associated glomerulonephritis with an interferon-based regimen or with lamivudine leads to remission of proteinuria in nearly two-thirds of cases and reduces the risk of progression to ESRD.[52,101–103] Eradication of HBV infection reduced the risk of incident ESRD in a propensity-matched cohort of HBV-infected subjects with CKD.[103] On the other hand, most of the nucleos(t)ide analogs used to treat HBV infection have

been associated with deterioration of renal function, likely related to the nephrotoxicity of these agents.[104] The sole exception is tebivudine which was associated with an increase in eGFR in treated patients which persisted after 4–6 years of follow-up. The mechanisms responsible for this effect are unclear insofar as no relationship was observed between sustained viral response and the improvement in eGFR.[104]

NONALCOHOLIC FATTY LIVER DISEASE

Nonalcoholic fatty liver disease (NAFLD) represents a burgeoning public health concern of enormous importance. NAFLD is defined by the accumulation of liver fat exceeding 5% of liver weight in the absence of significant alcohol intake or other secondary causes of chronic liver disease.[105–111] NAFLD encompasses a spectrum of liver injury ranging from simple steatosis to the more severe inflammatory form, nonalcoholic steatohepatitis (NASH), and ultimately advanced fibrosis and cirrhosis.[105–111] 20–30% of the adult population of western countries are estimated to suffer from NAFLD.[105–111] The prevalence of NALFD is even greater among the obese and among diabetics. NAFLD is generally regarded as the hepatic manifestation of the metabolic syndrome.

Complex interrelationships have been proposed to explain cross talk between the liver and kidney in NAFLD. Cross talk may be mediated by the synthesis and systemic release of proinflammatory and procoagulant factors released by steatotic, necrotic, and apoptotic hepatocytes, nonparenchymal Kupffer cells and hepatic stellate cells. Cross talk may also be mediated by insulin resistance or dyslipidemia associated with NAFLD. Specifically, NAFLD has been associated with increased circulating levels of inflammatory cytokines and other inflammatory mediators (TNF-α, TGF-β, IL-6, and C-reactive protein), a procoagulant profile (increased plasminogen activator inhibitor-1, decreased tissue plasminogen activator, and decreased fibrinolytic factors), and evidence of increased oxidative stress.[105–111] Increased production of fetuin A by the liver in NAFLD promotes insulin resistance by inhibiting insulin signal transduction and by reducing adiponectin levels in adipose tissue and in plasma.[105–111] A fall in adiponectin levels reduces activation of the energy sensor, 5′ adenosine monophosphate activation protein kinase, which in turn acts to decrease insulin sensitivity and induce insulin resistance and dyslipidemia. These effects are mediated by the influx of free fatty acids into the liver to increase liver gluconeogenesis, lipogenesis, and fatty acid oxidation.[105–111] These actions promote hepatic inflammation, cell proliferation, and fibrosis. An increase in proinflammatory cytokines and a decrease in protective adipokines released from inflamed visceral adipose tissue may also contribute to both liver and kidney injury.[105–111] These metabolic alterations make the liver both a target and a contributor to a systemic inflammatory response in which the kidney is also a target. In addition, endothelial dysfunction and activation of the renin–angiotensin system have been postulated to play a role in liver-kidney cross talk in NAFLD.

Despite the elucidation of intricate pathways that might mediate liver-kidney cross talk in this disorder, the clinical data supporting the role of NAFLD in promoting CKD remains controversial. Recent studies have demonstrated an association between NAFLD and CKD which survives multivariate analysis, leading to the suggestion that NAFLD may be an independent risk factor for the development and progression of CKD.[105–111] However, NAFLD and CKD share multiple common risk factors, and both have been associated with abdominal obesity, hypertension, diabetes mellitus, dyslipidemia, and insulin resistance.[105–111] The paramount issue revolves around the role that common pathogenic mechanisms and shared risk factors play, and whether or not the purported effects of NAFLD on the progression of CKD are truly independent of these shared risk factors.

Most studies demonstrate an association between the presence and the severity of NAFLD and the risk and severity of CKD after adjusting for traditional risk factors. In these cohorts, the prevalence of CKD in patients with NAFLD ranges from 10% to 20%.[112] In addition, most liver biopsy cohorts have shown a correlation between the histologic severity of NASH and renal dysfunction.[112]

Musso et al.[112] performed a meta-analysis of 20 cross-sectional and 13 longitudinal studies that included nearly 64,000 screened individuals. Patient-level data were available in nearly half of the subjects. Prevalent CKD was over twice as common in NAFLD compared with controls, and incident CKD was 1.8 times more common in NAFLD compared with controls. The severity of NAFLD was associated with the severity of CKD. In adjusted analyses of liver biopsy studies, the presence of NASH increased the prevalence of CKD by 2.5-fold, and increased the incidence of CKD by over 2-fold compared with simple steatosis. The presence of advanced fibrosis increased the prevalence of CKD by 5.2-fold and increased the incidence of CKD by 3.3-fold compared with nonadvanced fibrosis.

Mantovani et al.[113] performed a meta-analysis of nine prospective or retrospective observational cohorts consisting of nearly 100,000 subjects followed for a mean of 5.2 years. They found that NAFLD was associated with a 40% increase in the incidence of CKD. Furthermore, increased severity of NAFLD was associated with an increased risk of developing CKD.

Newer noninvasive techniques to detect NAFLD have recently been employed to study the relationship between CKD and NAFLD. The use of transient elastography to generate a controlled attenuation parameter score to quantitate steatosis and a liver stiffness score to quantitate fibrosis led to the observation that over 85% of patients with CKD had NAFLD, and that the severity of CKD correlated with the severity of hepatic steatosis.[114] Similar findings have been reported by other investigators.[115,116]

The limitations of the studies that report an association between NAFLD and CKD are significant and arguably compromise the validity of conclusions drawn from the accumulated data. The observational nature of these studies does not allow for a conclusion of causality. Despite utilization of multivariate analysis, residual unmeasured confounding factors cannot be excluded. Studied cohorts have been heterogeneous and vary by age, ethnicity, duration of follow-up, and prevalence of diabetes and hypertension. In addition, there is heterogeneity of kidney disease outcome parameters. Most population-based cohort studies rely on liver enzyme abnormalities or ultrasound examination to diagnose NAFLD without liver biopsy confirmation. Even liver biopsy diagnosis is subject to sampling error, because NAFLD may be patchy in distribution. Moreover, cohorts that underwent liver biopsies have been small in size, generally lack a control group, and suffer from selection bias. Misclassification of NAFLD cases due to the low sensitivity of liver enzyme abnormalities and ultrasound examination may obscure relationships between NAFLD and CKD. Ultrasound-based diagnosis is subjective and qualitative in nature and in cases where less than 30% of hepatocytes are steatotic, the sensitivity is limited to 60–90%.[105–111] However, in more severe NAFLD, the sensitivity rises to 85–94% with a specificity in the mid-90s range. Use of abnormal liver enzymes as a surrogate marker for NAFLD lacks both sensitivity and specificity. In fact, liver enzyme tests may be normal in up to 50% of patients with NAFLD.[105–111]

Misclassification of CKD cases due to overestimation of kidney function in liver disease may also obscure relationships between NAFLD and CKD. The equations used to estimate GFR overestimate renal function in severe liver disease and underestimate the incidence and prevalence of CKD in this population, which may mask relationships between NAFLD and CKD. Although patients with cirrhosis were excluded from most studies, S[Cr] tends to be lower in patients with severe liver disease due to muscle wasting, reduced hepatic generation of creatinine from creatine, and increased tubular secretion of creatinine.

MECHANISMS OF KIDNEY-LIVER CROSS TALK

The existence of renal-hepatic cross talk has been clearly established in animal models of CKD. However, to what extent these experimental observations in animal models of CKD can be extrapolated to CKD in humans is not clear. Unilateral nephrectomy promotes liver injury and the development of steatohepatitis. Unilateral nephrectomy is associated with dysregulation of lipid metabolism, insulin resistance, hyperglycemia, and a redistribution of fat from adipose to nonadipose tissue.[117] There is evidence of ectopic fat deposition in the liver and kidney and increased oxidative stress and upregulation of TGF-β in both organs. These metabolic alterations are mediated by the renin–angiotensin system insofar as angiotensin-converting enzyme inhibitors reverse these effects.

Studies performed by Park et al.[118] have implicated inflammatory cytokines as the primary mediators of remote hepatic injury associated with renal disease. Bilateral nephrectomy in the rat was associated with elevated transaminase levels and hepatocellular injury characterized by apoptosis and inflammation. These distant effects on the liver were attributed to increased synthesis and release of IL-17A by intestinal Paneth cells. Increased systemic delivery of IL-17A to the liver by circulating macrophages induced hepatic neutrophil infiltration, hepatic cellular necrosis and apoptosis, transaminitis, and increased hepatic expression and release of IL-6 and TNF-α. The latter cytokines magnified tissue injury. Administration of neutralizing antibodies to IL-17A, genetic deficiency of IL-17A, or genetic or pharmacologic depletion of Paneth cells reduced hepatic injury after bilateral nephrectomy, supporting the putative role of IL-17A in mediating the remote effects of renal injury on the liver. Also of interest is the observation that bilateral nephrectomy exacerbated hepatic injury after hepatic ischemia reperfusion.

Studies by other investigators have focused on the role of oxidative stress in mediating remote hepatic injury associated with renal disease.[119–121] Following bilateral nephrectomy in rats, hepatic lipid peroxidation products increased, whereas levels of the antioxidant molecule glutathione decreased.[121] Enzyme markers of liver injury were transiently increased in association with histologic evidence of hepatic cellular injury including apoptosis, leukocyte infiltration, and vascular congestion. Levels of TNF-α and the antiinflammatory cytokine IL-10 were elevated. An important role for increased oxidant stress in mediating these remote effects on the liver was suggested by the ability of infused reduced glutathione to partially prevent hepatic injury

and blunt hepatic lipid peroxidation. An important role for increased oxidative stress in mediating kidney/liver cross talk was also demonstrated in a protein overload nephropathy model.[119,120]

HEPATIC DRUG METABOLISM

CKD alters the pharmacokinetics of over 75 drugs whose elimination depends on nonrenal, predominantly hepatic, clearance. In general, CKD is associated with reduced hepatic drug clearance, although in some cases hepatic clearance is enhanced. The magnitude of the change in hepatic drug clearance generally correlates with the degree of renal functional impairment.

Cytochrome P450 (CYP) enzymes are a superfamily of hemoproteins that play a key role in the metabolism of endogenous substrates, therapeutic agents, and environmental chemicals.[116,122–128] The CYP3 family is responsible for most CYP-mediated drug metabolism. These enzymes are present in a variety of organs but are most abundant in the liver.[116,122–128] Experimental evidence suggests CKD influences CYP-mediated hepatic drug metabolism by multiple different mechanisms: by directly inhibiting CYP enzyme activity, by influencing CYP gene transcription, and by acting at posttranslational and epigenetic levels.[116,122–128] The remote effects of CKD on CYP enzymes are likely mediated by both the accumulation of uremic toxins and by the generation of cytokine mediators.[116,122–128] Although CKD generally inhibits CYP enzyme activity and suppresses CYP protein expression, CYP inducibility is retained, with important clinical implications.[129,130]

The effect of subtotal nephrectomy on hepatic drug clearance pathways has been studied by several investigators. Leblond et al.[129,130] found a reduction in total hepatic microsomal CYP activity associated with a reduction in the protein expression of several hepatic CYP proteins. These changes paralleled a reduction in the clearance of drugs that are known substrates for these hepatic CYP enzymes. The reduction in CYP activity correlated with the severity of renal functional impairment in this as well as in other studies.[129–133] Although total hepatic microsomal CYP activity was reduced, inducibility by dexamethasone and phenobarbital was retained.[129,130] The reduction in CYP protein expression was transcriptionally mediated, as evidenced by a parallel reduction in mRNA levels. The relationship between subtotal nephrectomy and CYP activity and protein expression has been replicated by other investigators, although the pattern of CYP alterations has not been entirely consistent.[131–135]

The metabolic activity of hepatic CYP2D was assessed in an isolated rat liver preparation using a specific CYP substrate as a probe. Hepatic drug clearance declined when normal rat livers or livers from rats made uremic with uranyl nitrate were perfused with uremic blood.[136] Hepatic drug clearance was restored when livers from uremic rats were perfused with normal blood. The rapidity of onset of the effects of uremic serum suggests a direct and reversible inhibitory effect of a circulating uremic toxin on CYP enzyme activity.

Michaud et al.[137] showed that incubation of normal rat hepatocytes with serum from patients with CKD had a widespread suppressive effect on CYP enzyme activity and protein expression, and that these effects were mediated at a transcriptional level. Several small molecular weight uremic toxins have been identified that inhibit CYP activity *in vitro* at concentrations achieved in humans with CKD.[131,138] Yoshitani et al.[138] found that incubation of hepatic microsomal preparations from normal livers with uremic serum obtained from rats with bilateral ureteral ligation reduced the metabolism of a specific CYP substrate probe, and that this effect was reproduced by exposure of the microsomal preparations to the putative uremic toxin indoxyl sulfate. Barnes et al.[131] found a potent suppressive effect of several known uremic toxins on CYP activity in human liver microsomes. These data support the hypothesis that circulating uremic toxins mediate the inhibitory effects of CKD on CYP activity, protein expression, and mRNA levels. It would follow that removal of these toxins by RRT or kidney transplantation would restore hepatic drug metabolism. Several studies have demonstrated that both RRT and kidney transplantation reverse the inhibitory effects of uremic serum on the hepatic clearance of drugs that are specific substrates for hepatic CYP enzymes, as well as on hepatic CYP protein expression and mRNA levels in hepatocyte microsomal preparations and in isolated hepatocytes.[139,140]

The inhibitory factor in CKD serum has been isolated to a serum fraction that contained parathyroid hormone and proinflammatory cytokines.[137] Several investigators have suggested that proinflammatory cytokines such as IL-6, TNF-α, and NF-κB mediate the effects of CKD on CYP activity and protein expression. The NF-κB signaling pathway may be the final common pathway transducing the suppressive effects of other proinflammatory cytokines. Michaud et al.[139] proposed that the inhibitory effects of uremic human serum on CYP expression in normal rat hepatocytes were mediated by NF-κB, because inhibition of NF-κB reversed these effects. Michaud et al.[141] also suggested a prominent role for elevated parathyroid hormone levels in mediating the suppressive effects of uremic sera on CYP activity and protein synthesis and went on to hypothesize that this effect is mediated through NF-κB. The suppressive effects of serum from rats made uremic with subtotal nephrectomy on CYP protein expression, mRNA levels,

and enzyme activity in preparations of normal rat hepatocytes correlated with parathyroid levels. These effects were reversed by parathyroidectomy or depletion of parathyroid hormone by immunoadsorption and were restored by administration of exogenous parathyroid hormone. Inhibition of NF-κB prevented the effects of exogenous parathyroid hormone on CYP activity. However, other investigators failed to find a correlation between CYP activity and parathyroid hormone levels.[140]

In a subtotal nephrectomy model, Velenosi et al.[142] proposed that the effects of CKD on hepatic CYP activity, protein expression, and mRNA levels occur both at transcriptional and epigenetic levels. Several CYP isoforms are transcriptionally regulated by the nuclear receptors pregnane X receptor and hepatic nuclear factor 4α. These investigators demonstrated reduced nuclear receptor binding and decreased histone acetylation of CYP promoter regions in CKD animals. Interestingly, Gu et al.[143] have shown that the ability of TNF-α to suppress CYP3A4 is mediated by NF-κB. NF-κB prevents the association of the pregnane X receptor with the retinoid X receptor, which in turn prevents the heterodimer from binding to the promoter region of CYP3A4. Watanabe et al.[144] reported that CYP3A was downregulated in rat primary hepatoctyes by parathyroid hormone through multiple signal transduction pathways. Increased intracellular cyclic adenosine monophosphate levels led to activation of phosphatidylinositol 3-kinase-protein kinase B/protein kinase C/protein kinase A/NF-κB pathways which ultimately suppressed pregnane X receptor activity. They further demonstrated that administration of a calcimimetic partially reversed CYP inhibition in a subtotal nephrectomy model. Thus, the NF-κB pathway may be crucial to interactions between CKD and hepatic CYP activity and may represent a final common pathway for the effects of proinflammatory cytokines and PTH on CYP activity.

Using specific hepatic CYP substrates as probes to assess hepatic CYP activity in humans, investigators have confirmed that experimental observations on interactions between CKD and CYP activity translate to clinical practice.[116,122–128] Reductions in CYP activity observed in experimental models parallel increased bioavailability of numerous drugs known to be specific CYP substrates in humans with both dialysis-dependent and nondialysis-dependent CKD.[116,122–128] The magnitude of the effects of CKD on hepatic drug metabolism correlates with renal function, and the effects are reversed by RRT or kidney transplantation.

Active transport of drugs across the sinosoidal membrane of hepatocytes to access hepatic metabolic enzymes is mediated by transporters such as the organic anion transporting polypeptide family of transporters, expressed on the sinosoidal surface of hepatocytes.[116,122–128] P-glycoprotein and multidrug resistance-associated protein-2 are energy-dependent efflux transporters on the canalicular membrane of hepatocytes, responsible for extrusion of drug metabolites into bile canaliculi.[116,122–128] Drug uptake and efflux transporters regulate intracellular exposure of substrates to hepatic CYP and may be rate-limiting for hepatic drug metabolism. These transporters are also expressed on renal proximal tubules and enterocytes.[116,122–128]

Hepatic organic anion transporting polypeptide protein-mediated uptake of specific drug probes is reduced in humans with ESRD.[126] In addition, organic anion transporting polypeptide activity is inhibited *in vitro* by uremic toxins.[145] In a subtotal nephrectomy model and in *in vitro* studies of normal rat hepatocytes incubated with uremic rat serum, Naud et al.[146] showed reduced organic anion transporting polypeptide protein expression in the absence of changes in mRNA levels. However, data on the effects of CKD on P-glycoprotein and multidrug resistance-associated protein expression and mRNA levels in the subtotal nephrectomy model have been inconsistent.[146,147]

Although the majority of drug metabolized by the liver undergoes oxidation, the hepatic elimination of other drugs is mediated by conjugation reactions, including glucuronidation and acetylation, mediated by the enzyme uridine diphosphate-glucuronosyl transferase, and N-acetyl-transferase, respectively.[122,123,126,148] Using drug probes, investigators have demonstrated reduced hepatic acetylation in humans with ESRD.[122,123] Reversal of the uremic milieu by renal transplantation restores hepatic clearance of drugs whose elimination is dependent on acetylation.[122,123] Similarly, normal rat hepatocytes incubated with uremic serum from rats which had undergone subtotal nephrectomy show reduced N-acetyl-transferase activity and protein expression mediated at a transcriptional level.[148] These effects were reversed by parathyroidectomy and reproduced by incubation of rat hepatocytes with exogenous parathyroid hormone. Using drug probes, investigators have also demonstrated reduced hepatic drug glycuronidation in humans with CKD, the magnitude of which correlated with the level of renal function.[126] P-cresol, a putative uremic toxin, inhibited uridine diphosphate-glucuronosyl transferase activity in human liver microsomes.[131] However, other experimental data have yielded inconsistent results. No changes in uridine diphosphate-glucuronosyl

transferase activity or in protein expression were observed in a subtotal nephrectomy model of CKD in the rat.[149]

Adding further complexity to the situation is the fact that effects of CKD on hepatic CYP and drug transporter protein function may not necessarily translate into the change in serum drug concentration that might be expected from the observed changes in hepatic metabolism. CKD may have effects on CYP and drug transporter protein activity in the intestine or kidney than are opposite to those seen in the liver. Furthermore, CKD may have additional effects on organ perfusion, drug plasma protein binding and volume of distribution, renal clearance, and extrahepatic metabolism that offset or magnify the effects of CKD on the hepatic metabolism of a given drug. Thus, the net effect on drug pharmacokinetics is a complex interplay between all these competing or complementary actions, and further translational research will be critical.

CONCLUSIONS

Accumulating evidence derived from basic science and clinical studies supports the existence of bidirectional cross talk between the kidney and the liver. These studies suggest that chronic liver disease promotes the development and accelerates the progression of CKD, and that CKD accelerates the progression of chronic liver disease. The data are most robust for interactions between the kidney and decompensated liver disease in the context of HRS-CKD, in HCV-related liver disease and in NAFLD. Upregulation of proinflammatory cytokines plays a paramount role in mediating these interactions. CKD also alters hepatic drug metabolism *via* effects on hepatic CYPs and hepatic drug transporter proteins, mediated by the accumulation of uremic toxins and release of proinflammatory cytokines. These interactions significantly influence drug dosing in patients with combined liver and renal disease. Opportunities for future research may be directed toward enhancing our understanding of the molecular pathways that mediate liver-kidney cross talk. Elucidation of the complex interactions between the liver and kidney may lead to therapeutic interventions directed toward slowing the progression of both liver and kidney disease and may provide novel therapeutic strategies, directed primarily toward the liver, to retard the progression of CKD in patients with combined liver and kidney disease. The emergence of newer DAAs warrant a reappraisal of the effects of sustained viral remission on the progression of CKD, to better inform our therapeutic decisions in HCV-infected patients with CKD.

References

1. Davenport A, Sheikh MF, Lamb E, Agarwal B, Jalan R. Acute kidney injury in acute-on-chronic liver failure: where does hepatorenal syndrome fit? *Kidney Int* 2017;**92**(5):1058–70.
2. European Association for the Study of the Liver. EASL Clinical Practice Guidelines for the management of patients with decompensated cirrhosis. *J Hepatol* 2018;**69**(2):406–60.
3. Gines P, Sola E, Angeli P, Wong F, Nadim MK, Kamath P. Hepatorenal syndrome. *Nat Rev Dis Primers* 2018;**4**(1):23.
4. Golestaneh L, Neugarten J. Dual organ duel: the hepatorenal axis. *Adv Chron Kidney Dis* 2017;**24**(4):253–60.
5. Sole C, Pose E, Sola E, Gines P. Hepatorenal syndrome in the era of acute kidney injury. *Liver Int* 2018;**38**(11):1891–901.
6. Angeli P, Gines P, Wong F, Bernardi M, Boyer TD, Gerbes A, et al. Diagnosis and management of acute kidney injury in patients with cirrhosis: revised consensus recommendations of the International Club of Ascites. *J Hepatol* 2015;**62**(4):968–74.
7. Wong F, Nadim MK, Kellum JA, Salerno F, Bellomo R, Gerbes A, et al. Working Party proposal for a revised classification system of renal dysfunction in patients with cirrhosis. *Gut* 2011;**60**(5):702–9.
8. Kostreva DR, Castaner A, Kampine JP. Reflex effects of hepatic baroreceptors on renal and cardiac sympathetic nerve activity. *Am J Physiol* 1980;**238**(5):R390–4.
9. Koyama S, Nishida K, Terada N, Shiojima Y, Takeuchi T. Reflex renal vasoconstriction on portal vein distension. *Jpn J Physiol* 1986;**36**(3):441–50.
10. Platt JF, Ellis JH, Rubin JM, Merion RM, Lucey MR. Renal duplex Doppler ultrasonography: a noninvasive predictor of kidney dysfunction and hepatorenal failure in liver disease. *Hepatology* 1994;**20**(2):362–9.
11. Maroto A, Gines A, Salo J, Claria J, Gines P, Anibarro L, et al. Diagnosis of functional kidney failure of cirrhosis with Doppler sonography: prognostic value of resistive index. *Hepatology* 1994;**20**(4 Pt 1):839–44.
12. Mindikoglu AL, Dowling TC, Wong-You-Cheong JJ, Christenson RH, Magder LS, Hutson WR, et al. A pilot study to evaluate renal hemodynamics in cirrhosis by simultaneous glomerular filtration rate, renal plasma flow, renal resistive indices and biomarkers measurements. *Am J Nephrol* 2014;**39**(6):543–52.
13. Claria J, Stauber RE, Coenraad MJ, Moreau R, Jalan R, Pavesi M, et al. Systemic inflammation in decompensated cirrhosis: characterization and role in acute-on-chronic liver failure. *Hepatology* 2016;**64**(4):1249–64.
14. Navasa M, Follo A, Filella X, Jimenez W, Francitorra A, Planas R, et al. Tumor necrosis factor and interleukin-6 in spontaneous bacterial peritonitis in cirrhosis: relationship with the development of renal impairment and mortality. *Hepatology* 1998;**27**(5):1227–32.
15. Fagundes C, Pepin MN, Guevara M, Barreto R, Casals G, Sola E, et al. Urinary neutrophil gelatinase-associated lipocalin as biomarker in the differential diagnosis of impairment of kidney function in cirrhosis. *J Hepatol* 2012;**57**(2):267–73.
16. Bairaktari E, Liamis G, Tsolas O, Elisaf M. Partially reversible renal tubular damage in patients with obstructive jaundice. *Hepatology* 2001;**33**(6):1365–9.
17. van Slambrouck CM, Salem F, Meehan SM, Chang A. Bile cast nephropathy is a common pathologic finding for kidney injury associated with severe liver dysfunction. *Kidney Int* 2013;**84**(1):192–7.
18. Angeli P, Piano S. Is type 2 hepatorenal syndrome still a potential indication for treatment with terlipressin and albumin? *Liver Transplant* 2015;**21**(11):1335–7.
19. Rodriguez E, Henrique Pereira G, Sola E, Elia C, Barreto R, Pose E, et al. Treatment of type 2 hepatorenal syndrome in patients awaiting transplantation: effects on kidney function and transplantation outcomes. *Liver Transplant* 2015;**21**(11):1347–54.

20. Testino G, Ferro C, Sumberaz A, Messa P, Morelli N, Guadagni B, et al. Type-2 hepatorenal syndrome and refractory ascites: role of transjugular intrahepatic portosystemic stent-shunt in eighteen patients with advanced cirrhosis awaiting orthotopic liver transplantation. *Hepatogastroenterology* 2003;**50**(54):1753–5.
21. Desai N, Neugarten J, Dominguez M, Golestaneh L. Hepatic vein pressure predicts GFR in cirrhotic patients with hemodynamic kidney dysfunction. *Phys Rep* 2017;**5**(11).
22. Chang Y, Qi X, Li Z, Wang F, Wang S, Zhang Z, et al. Hepatorenal syndrome: insights into the mechanisms of intra-abdominal hypertension. *Int J Clin Exp Pathol* 2013;**6**(11):2523–8.
23. http://www.who.int/news-room/fact-sheets/detail/hepatitis-c.
24. www.cdc.gov/hepatitis/hcv/hcvfaq.htm#section1.
25. Fabrizi F, Marcelli D, Bacchini G, Guarnori I, Erba G, Locatelli F. Antibodies to hepatitis C virus (HCV) in chronic renal failure (CRF) patients on conservative therapy: prevalence, risk factors and relationship to liver disease. *Nephrol Dial Transplant* 1994; **9**(7):780–4.
26. Fabrizi F, Donato FM, Messa P. Association between hepatitis C virus and chronic kidney disease: a systematic review and meta-analysis. *Ann Hepatol* 2018;**17**(3):364–91.
27. Tartof SY, Hsu JW, Wei R, Rubenstein KB, Hu H, Arduino JM, et al. Kidney function decline in patients with CKD and untreated hepatitis C infection. *Clin J Am Soc Nephrol* 2018; **13**(10):1471–8.
28. Fabrizi F, Dixit V, Martin P, Messa P. Hepatitis C virus increases the risk of kidney disease among HIV-positive patients: systematic review and meta-analysis. *J Med Virol* 2016;**88**(3): 487–97.
29. Moe SM, Pampalone AJ, Ofner S, Rosenman M, Teal E, Hui SL. Association of hepatitis C virus infection with prevalence and development of kidney disease. *Am J Kidney Dis* 2008;**51**(6): 885–92.
30. Asrani SK, Buchanan P, Pinsky B, Rey LR, Schnitzler M, Kanwal F. Lack of association between hepatitis C infection and chronic kidney disease. *Clin Gastroenterol Hepatol* 2010;**8**(1):79–84.
31. Kurbanova N, Qayyum R. Association of hepatitis C virus infection with proteinuria and glomerular filtration rate. *Clin Transl Sci* 2015;**8**(5):421–4.
32. Tsui JI, Vittinghoff E, Shlipak MG, O'Hare AM. Relationship between hepatitis C and chronic kidney disease: results from the third national health and nutrition examination survey. *J Am Soc Nephrol* 2006;**17**(4):1168–74.
33. Rogal SS, Yan P, Rimland D, Lo Re 3rd V, Al-Rowais H, Fried L, et al. Incidence and progression of chronic kidney disease after hepatitis C seroconversion: results from ERCHIVES. *Dig Dis Sci* 2016;**61**(3):930–6.
34. Molnar MZ, Alhourani HM, Wall BM, Lu JL, Streja E, Kalantar-Zadeh K, et al. Association of hepatitis C viral infection with incidence and progression of chronic kidney disease in a large cohort of US veterans. *Hepatology* 2015;**61**(5):1495–502.
35. Tsui J, Vittinghoff E, Anastos K, Augenbraun M, Young M, Nowicki M, et al. Hepatitis C seropositivity and kidney function decline among women with HIV: data from the Women's Interagency HIV Study. *Am J Kidney Dis* 2009;**54**(1):43–50.
36. Tsui JI, Vittinghoff E, Shlipak MG, Bertenthal D, Inadomi J, Rodriguez RA, et al. Association of hepatitis C seropositivity with increased risk for developing end-stage renal disease. *Arch Intern Med* 2007;**167**(12):1271–6.
37. Satapathy SK, Lingisetty CS, Williams S. Higher prevalence of chronic kidney disease and shorter renal survival in patients with chronic hepatitis C virus infection. *Hepatol Int* 2012;**6**(1): 369–78.
38. Lai TS, Lee MH, Yang HI, You SL, Lu SN, Wang LY, et al. High hepatitis C viral load and genotype 2 are strong predictors of chronic kidney disease. *Kidney Int* 2017;**92**(3):703–9.
39. Lai TS, Lee MH, Yang HI, You SL, Lu SN, Wang LY, et al. Hepatitis C viral load, genotype, and increased risk of developing end-stage renal disease: REVEAL-HCV study. *Hepatology* 2017;**66**(3): 784–93.
40. Peters L, Grint D, Lundgren JD, Rockstroh JK, Soriano V, Reiss P, et al. Hepatitis C virus viremia increases the incidence of chronic kidney disease in HIV-infected patients. *AIDS* 2012;**26**(15): 1917–26.
41. Butt AA, Wang X, Fried LF. HCV infection and the incidence of CKD. *Am J Kidney Dis* 2011;**57**(3):396–402.
42. Mocroft A, Neuhaus J, Peters L, Ryom L, Bickel M, Grint D, et al. Hepatitis B and C co-infection are independent predictors of progressive kidney disease in HIV-positive, antiretroviral-treated adults. *PLoS One* 2012;**7**(7):e40245.
43. Rossi C, Saeed S, Cox J, Vachon ML, Martel-Laferriere V, Walmsley SL, et al. Hepatitis C virus cure does not impact kidney function decline in HIV co-infected patients. *AIDS* 2018;**32**(6): 751–9.
44. Lucas GM, Jing Y, Sulkowski M, Abraham AG, Estrella MM, Atta MG, et al. Hepatitis C viremia and the risk of chronic kidney disease in HIV-infected individuals. *J Infect Dis* 2013;**208**(8): 1240–9.
45. Barsoum RS. Hepatitis C virus: from entry to renal injury–facts and potentials. *Nephrol Dial Transplant* 2007;**22**(7):1840–8.
46. Barsoum RS, William EA, Khalil SS. Hepatitis C and kidney disease: a narrative review. *J Adv Res* 2017;**8**(2):113–30.
47. Gopalani A, Ahuja TS. Prevalence of glomerulopathies in autopsies of patients infected with the hepatitis C virus. *Am J Med Sci* 2001;**322**(2):57–60.
48. Arase Y, Ikeda K, Murashima N, Chayama K, Tsubota A, Koida I, et al. Glomerulonephritis in autopsy cases with hepatitis C virus infection. *Intern Med* 1998;**37**(10):836–40.
49. McGuire BM, Julian BA, Bynon Jr JS, Cook WJ, King SJ, Curtis JJ, et al. Brief communication: glomerulonephritis in patients with hepatitis C cirrhosis undergoing liver transplantation. *Ann Intern Med* 2006;**144**(10):735–41.
50. Tong X, Spradling PR. Increase in nonhepatic diagnoses among persons with hepatitis C hospitalized for any cause, United States, 2004-2011. *J Viral Hepat* 2015;**22**(11):906–13.
51. El-Serag HB, Hampel H, Yeh C, Rabeneck L. Extrahepatic manifestations of hepatitis C among United States male veterans. *Hepatology* 2002;**36**(6):1439–45.
52. Available from: www.cdc.gov/diabetes/statistics/esrd.
53. Kasuno K, Ono T, Matsumori A, Nogaki F, Kusano H, Watanabe H, et al. Hepatitis C virus-associated tubulointerstitial injury. *Am J Kidney Dis* 2003;**41**(4):767–75.
54. Wornle M, Schmid H, Banas B, Merkle M, Henger A, Roeder M, et al. Novel role of toll-like receptor 3 in hepatitis C-associated glomerulonephritis. *Am J Pathol* 2006;**168**(2):370–85.
55. Chen YC, Chiou WY, Hung SK, Su YC, Hwang SJ. Hepatitis C virus itself is a causal risk factor for chronic kidney disease beyond traditional risk factors: a 6-year nationwide cohort study across Taiwan. *BMC Nephrol* 2013;**14**:187.
56. Perico N, Cattaneo D, Bikbov B, Remuzzi G. Hepatitis C infection and chronic renal diseases. *Clin J Am Soc Nephrol* 2009; **4**(1):207–20.
57. Carvalho-Filho RJ, Feldner AC, Silva AE, Ferraz ML. Management of hepatitis C in patients with chronic kidney disease. *World J Gastroenterol* 2015;**21**(2):408–22.
58. Sise ME, Backman E, Ortiz GA, Hundemer GL, Ufere NN, Chute DF, et al. Effect of sofosbuvir-based hepatitis C virus therapy on kidney function in patients with CKD. *Clin J Am Soc Nephrol* 2017;**12**(10):1615–23.
59. Foster GR, Afdhal N, Roberts SK, Brau N, Gane EJ, Pianko S, et al. Sofosbuvir and velpatasvir for HCV genotype 2 and 3 infection. *N Engl J Med* 2015;**373**(27):2608–17.

60. Foster GR, Mangia A, Sulkowski M. Sofosbuvir and velpatasvir for patients with HCV infection. *N Engl J Med* 2016;**374**(17):1687–8.
61. Struble K, Chan-Tack K, Qi K, Naeger LK, Birnkrant D. Benefit-risk assessment for sofosbuvir/velpatasvir/voxilaprevir based on patient population and hepatitis C virus genotype: U. S. Food and Drug Administration's evaluation. *Hepatology* 2018; **67**(2):482–91.
62. Desnoyer A, Pospai D, Le MP, Gervais A, Heurgue-Berlot A, Laradi A, et al. Pharmacokinetics, safety and efficacy of a full dose sofosbuvir-based regimen given daily in hemodialysis patients with chronic hepatitis C. *J Hepatol* 2016;**65**(1):40–7.
63. Goel A, Bhadauria DS, Kaul A, Verma P, Mehrotra M, Gupta A, et al. Daclatasvir and reduced-dose sofosbuvir: an effective and pangenotypic treatment for hepatitis C in patients with eGFR <30 mL/min. *Nephrology (Carlton)* 2019;**24**(3):316–21.
64. Taneja S, Duseja A, De A, Mehta M, Ramachandran R, Kumar V, et al. Low-dose sofosbuvir is safe and effective in treating chronic hepatitis C in patients with severe renal impairment or end-stage renal disease. *Dig Dis Sci* 2018;**63**(5):1334–40.
65. Choudhary NS, Kumar A, Bodh V, Bansal SB, Sharma R, Jain M, et al. Efficacy and safety of sofosbuvir-based regimens in chronic hepatitis C patients on dialysis. *Indian J Gastroenterol* 2017;**36**(2): 113–6.
66. Kumar MNS, Gupta E, Kataria A, Sarin SK. Generic sofosbuvir-based direct-acting antivirals in heptitis C virus-infected patients with chronic kidney disease. *Liver Int* 2018;**38**:2137–48.
67. Roth D, Nelson DR, Bruchfeld A, Liapakis A, Silva M, Monsour Jr H, et al. Grazoprevir plus elbasvir in treatment-naive and treatment-experienced patients with hepatitis C virus genotype 1 infection and stage 4-5 chronic kidney disease (the C-SURFER study): a combination phase 3 study. *Lancet* 2015; **386**(10003):1537–45.
68. Papudesu C, Kottilil S, Bagchi S. Elbasvir/grazoprevir for treatment of chronic hepatitis C virus infection. *Hepatol Int* 2017; **11**(2):152–60.
69. Pockros PJ, Reddy KR, Mantry PS, Cohen E, Bennett M, Sulkowski MS, et al. Efficacy of direct-acting antiviral combination for patients with hepatitis C virus genotype 1 infection and severe renal impairment or end-stage renal disease. *Gastroenterology* 2016;**150**(7):1590–8.
70. Gane E, Lawitz E, Pugatch D, Papatheodoridis G, Brau N, Brown A, et al. Glecaprevir and pibrentasvir in patients with HCV and severe renal impairment. *N Engl J Med* 2017;**377**(15):1448–55.
71. Liver EAftSot. EASL recommendations on treatment of hepatitis C 2018. *J Hepatol* 2018;**69**(2):461–511.
72. Feng B, Eknoyan G, Guo ZS, Jadoul M, Rao HY, Zhang W, et al. Effect of interferon-alpha-based antiviral therapy on hepatitis C virus-associated glomerulonephritis: a meta-analysis. *Nephrol Dial Transplant* 2012;**27**(2):640–6.
73. Rutledge SM, Chung RT, Sise ME. Treatment of hepatitis C virus infection in patients with mixed cryoglobulinemic syndrome and cryoglobulinemic glomerulonephritis. *Hemodial Int* 2018; **22**(Suppl. 1):S81–96.
74. Hsu YC, Ho HJ, Huang YT, Wang HH, Wu MS, Lin JT, et al. Association between antiviral treatment and extrahepatic outcomes in patients with hepatitis C virus infection. *Gut* 2015; **64**(3):495–503.
75. Chen YC, Hwang SJ, Li CY, Wu CP, Lin LC. A Taiwanese nationwide cohort study shows interferon-based therapy for chronic hepatitis C reduces the risk of chronic kidney disease. *Medicine (Baltim)* 2015;**94**(32):e1334.
76. Arase Y, Suzuki F, Kawamura Y, Suzuki Y, Kobayashi M, Matsumoto N, et al. Development rate of chronic kidney disease in hepatitis C virus patients with advanced fibrosis after interferon therapy. *Hepatol Res* 2011;**41**(10):946–54.
77. Park H, Chen C, Wang W, Henry L, Cook RL, Nelson DR. Chronic hepatitis C virus (HCV) increases the risk of chronic kidney disease (CKD) while effective HCV treatment decreases the incidence of CKD. *Hepatology* 2018;**67**(2):492–504.
78. Anty RFG, Coilly A, Rossignol E, Houssel-Debry P, Duvoux C, De Ledinghen V, Di Martino V, Leroy V, Radenne S, Kamar N, Canva V, D'Aleroche L, Durand F. Safety of sofosbuvir-based regimens after liver transplantation: longitudinal assessment of renal function in the prospective ANRS CO23 CUPILT study. *Aliment Pharmacol Ther* 2017;**47**:1682–9.
79. Medeiros T, Rosario NF, Saraiva GN, Andrade TG, Silva AA, Almeida JR. Renal safety after one year of sofosbuvir-based therapy for chronic hepatitis C: a Brazilian "real-life" study. *J Clin Pharm Ther* 2018;**43**(5):707–13.
80. Aby ES, Dong TS, Kawamoto J, Pisegna JR, Benhammou JN. Impact of sustained virologic response on chronic kidney disease progression in hepatitis C. *World J Hepatol* 2017;**9**(36): 1352–60.
81. Mehta DA, Cohen E, Charafeddine M, Cohen DE, Bao Y, Sanchez Gonzalez Y, et al. Effect of hepatitis C treatment with ombitasvir/paritaprevir/R + dasabuvir on renal, cardiovascular and metabolic extrahepatic manifestations: a post-hoc analysis of phase 3 clinical trials. *Infect Dis Ther* 2017;**6**(4):515–29.
82. Sise ME, Backman ES, Wenger JB, Wood BR, Sax PE, Chung RT, et al. Short and long-term effects of telaprevir on kidney function in patients with hepatitis C virus infection: a retrospective cohort study. *PLoS One* 2015;**10**(4):e0124139.
83. Mauss S, Hueppe D, Alshuth U. Renal impairment is frequent in chronic hepatitis C patients under triple therapy with telaprevir or boceprevir. *Hepatology* 2014;**59**(1):46–8.
84. Saxena V, Koraishy FM, Sise ME, Lim JK, Schmidt M, Chung RT, et al. Safety and efficacy of sofosbuvir-containing regimens in hepatitis C-infected patients with impaired renal function. *Liver Int* 2016;**36**(6):807–16.
85. Chen J, Zhang X, Luo H, Wu C, Yu M, Liu D, et al. Changes in renal function indices in cirrhotic chronic hepatitis C patients treated with sofosbuvir-containing regimens. *Oncotarget* 2017; **8**(53):90916–24.
86. Taramasso L, Di Biagio A, Bovis F, Nicolini LA, Antinori A, Milazzo L, et al. Trend of estimated glomerular filtration rate during ombistasvir/paritaprevir/ritonavir plus dasabuvir +/- ribavirin in HIV/HCV co-infected patients. *PLoS One* 2018; **13**(2):e0192627.
87. Dashti-Khavidaki S, Khalili H, Nasiri-Toosi M. Potential nephrotoxicity of sofosbuvir-based treatment in patients infected with hepatitis C virus: a review on incidence, type and risk factors. *Expert Rev Clin Pharmacol* 2018;**11**(5):525–9.
88. Butt AA, Ren Y, Puenpatom A, Arduino JM, Kumar R, Abou-Samra AB. Effectiveness, treatment completion and safety of sofosbuvir/ledipasvir and paritaprevir/ritonavir/ombitasvir + dasabuvir in patients with chronic kidney disease: an ERCHIVES study. *Aliment Pharmacol Ther* 2018;**48**(1):35–43.
89. Dumortier J, Bailly F, Pageaux GP, Vallet-Pichard A, Radenne S, Habersetzer F, et al. Sofosbuvir-based antiviral therapy in hepatitis C virus patients with severe renal failure. *Nephrol Dial Transplant* 2017;**32**(12):2065–71.
90. Alvarez-Ossorio MJ, Sarmento ECR, Granados R, Macias J, Morano-Amado LE, Rios MJ, et al. Impact of interferon-free regimens on the glomerular filtration rate during treatment of chronic hepatitis C in a real-life cohort. *J Viral Hepat* 2018;**25**(6): 699–706.
91. Butt AA, Ren Y, Marks K, Shaikh OS, Sherman KE, study E. Do directly acting antiviral agents for HCV increase the risk of hepatic decompensation and decline in renal function? Results from ERCHIVES. *Aliment Pharmacol Ther* 2017;**45**(1):150–9.

92. Kao CC, Lin YS, Chu HC, Fang TC, Wu MS, Kang YN. Association of renal function and direct-acting antiviral agents for HCV: a network meta-analysis. *J Clin Med* 2018;**7**(10).
93. Ble M, Aguilera V, Rubin A, Garcia-Eliz M, Vinaixa C, Prieto M, et al. Improved renal function in liver transplant recipients treated for hepatitis C virus with a sustained virological response and mild chronic kidney disease. *Liver Transplant* 2014;**20**(1): 25–34.
94. Satapathy SK, Joglekar K, Molnar MZ, Ali B, Gonzalez HC, Vanatta JM, et al. Achieving sustained virological response in liver transplant recipients with hepatitis C decreases risk of decline in renal function. *Liver Transplant* 2018;**24**(8):1040–9.
95. Beig J, Orr D, Harrison B, Gane E. Hepatitis C virus eradication with new interferon-free treatment improves metabolic profile in hepatitis C virus-related liver transplant recipients. *Liver Transplant* 2018;**24**(8):1031–9.
96. Kucirka LM, Singer AL, Ros RL, Montgomery RA, Dagher NN, Segev DL. Underutilization of hepatitis C-positive kidneys for hepatitis C-positive recipients. *Am J Transplant* 2010;**10**(5): 1238–46.
97. Fabrizi F, Donato FM, Messa P. Association between hepatitis B virus and chronic kidney disease: a systematic review and meta-analysis. *Ann Hepatol* 2017;**16**(1):21–47.
98. Si J, Yu C, Guo Y, Bian Z, Qin C, Yang L, et al. Chronic hepatitis B virus infection and risk of chronic kidney disease: a population-based prospective cohort study of 0.5 million Chinese adults. *BMC Med* 2018;**16**(1):93.
99. Hong YS, Ryu S, Chang Y, Cainzos-Achirica M, Kwon MJ, Zhao D, et al. Hepatitis B virus infection and development of chronic kidney disease: a cohort study. *BMC Nephrol* 2018;**19**(1):353.
100. Kim SE, Jang ES, Ki M, Gwak GY, Kim KA, Kim GA, et al. Chronic hepatitis B infection is significantly associated with chronic kidney disease: a population-based, matched case-control study. *J Korean Med Sci* 2018;**33**(42):e264.
101. Fabrizi F, Dixit V, Martin P. Meta-analysis: anti-viral therapy of hepatitis B virus-associated glomerulonephritis. *Aliment Pharmacol Ther* 2006;**24**(5):781–8.
102. Tang S, Lai FM, Lui YH, Tang CS, Kung NN, Ho YW, et al. Lamivudine in hepatitis B-associated membranous nephropathy. *Kidney Int* 2005;**68**(4):1750–8.
103. Chen YC, Li CY, Tsai SJ, Chen YC. Nationwide cohort study suggests that nucleos(t)ide analogue therapy decreases dialysis risk in Taiwanese chronic kidney disease patients acquiring hepatitis B virus infection. *World J Gastroenterol* 2018; **24**(8):917–28.
104. Gane EJ, Deray G, Liaw YF, Lim SG, Lai CL, Rasenack J, et al. Telbivudine improves renal function in patients with chronic hepatitis B. *Gastroenterology* 2014;**146**(1):138–146 e5.
105. 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):406–12.
106. Marcuccilli M, Chonchol M. NAFLD and chronic kidney disease. *Int J Mol Sci* 2016;**17**(4):562.
107. Musso G, Cassader M, Cohney S, De Michieli F, Pinach S, Saba F, et al. Fatty liver and chronic kidney disease: novel mechanistic insights and therapeutic opportunities. *Diabetes Care* 2016;**39**(10): 1830–45.
108. Musso G, Cassader M, Cohney S, Pinach S, Saba F, Gambino R. Emerging liver-kidney interactions in nonalcoholic fatty liver disease. *Trends Mol Med* 2015;**21**(10):645–62.
109. Orlic L, Mikolasevic I, Bagic Z, Racki S, Stimac D, Milic S. Chronic kidney disease and nonalcoholic fatty liver disease-is there a link? *Gastroenterol Res Pract* 2014;**2014**:847539.
110. Targher G, Chonchol M, Zoppini G, Abaterusso C, Bonora E. Risk of chronic kidney disease in patients with non-alcoholic fatty liver disease: is there a link? *J Hepatol* 2011;**54**(5):1020–9.
111. Targher G, Chonchol MB, Byrne CD. CKD and nonalcoholic fatty liver disease. *Am J Kidney Dis* 2014;**64**(4):638–52.
112. Musso G, Gambino R, Tabibian JH, Ekstedt M, Kechagias S, Hamaguchi M, et al. Association of non-alcoholic fatty liver disease with chronic kidney disease: a systematic review and meta-analysis. *PLoS Med* 2014;**11**(7):e1001680.
113. Mantovani A, Zaza G, Byrne CD, Lonardo A, Zoppini G, Bonora E, et al. Nonalcoholic fatty liver disease increases risk of incident chronic kidney disease: a systematic review and meta-analysis. *Metabolism* 2018;**79**:64–76.
114. Mikolasevic I, Racki S, Bubic I, Jelic I, Stimac D, Orlic L. Chronic kidney disease and nonalcoholic fatty liver disease proven by transient elastography. *Kidney Blood Press Res* 2013;**37**(4–5): 305–10.
115. Yeung MW, Wong GL, Choi KC, Luk AO, Kwok R, Shu SS, et al. Advanced liver fibrosis but not steatosis is independently associated with albuminuria in Chinese patients with type 2 diabetes. *J Hepatol* 2018;**68**(1):147–56.
116. Zeng J, Sun C, Sun WL, Chen GY, Pan Q, Yan SY, et al. Association between non-invasively diagnosed hepatic steatosis and chronic kidney disease in Chinese adults on their health check-up. *J Dig Dis* 2017;**18**(4):229–36.
117. Zhao HL, Sui Y, Guan J, He L, Zhu X, Fan RR, et al. Fat redistribution and adipocyte transformation in uninephrectomized rats. *Kidney Int* 2008;**74**(4):467–77.
118. Park SW, Chen SW, Kim M, Brown KM, Kolls JK, D'Agati VD, et al. Cytokines induce small intestine and liver injury after renal ischemia or nephrectomy. *Lab Invest* 2011;**91**(1):63–84.
119. Sheng X, Nakajima T, Wang L, Zhang X, Kamijo Y, Takahashi K, et al. Attenuation of kidney injuries maintains serum sulfatide levels dependent on hepatic synthetic ability: a possible involvement of oxidative stress. *Tohoku J Exp Med* 2012;**227**(1): 1–12.
120. Zhang X, Nakajima T, Kamijo Y, Li G, Hu R, Kannagi R, et al. Acute kidney injury induced by protein-overload nephropathy down-regulates gene expression of hepatic cerebroside sulfotransferase in mice, resulting in reduction of liver and serum sulfatides. *Biochem Biophys Res Commun* 2009;**390**(4): 1382–8.
121. Golab F, Kadkhodaee M, Zahmatkesh M, Hedayati M, Arab H, Schuster R, et al. Ischemic and non-ischemic acute kidney injury cause hepatic damage. *Kidney Int* 2009;**75**(8):783–92.
122. Dreisbach AW. The influence of chronic renal failure on drug metabolism and transport. *Clin Pharmacol Ther* 2009;**86**(5): 553–6.
123. Dreisbach AW, Lertora JJ. The effect of chronic renal failure on drug metabolism and transport. *Expert Opin Drug Metabol Toxicol* 2008;**4**(8):1065–74.
124. Ladda MA, Goralski KB. The effects of CKD on cytochrome P450-mediated drug metabolism. *Adv Chron Kidney Dis* 2016;**23**(2): 67–75.
125. Lane K, Dixon JJ, MacPhee IA, Philips BJ. Renohepatic crosstalk: does acute kidney injury cause liver dysfunction? *Nephrol Dial Transplant* 2013;**28**(7):1634–47.
126. Momper JD, Venkataramanan R, Nolin TD. Nonrenal drug clearance in CKD: searching for the path less traveled. *Adv Chron Kidney Dis* 2010;**17**(5):384–91.
127. Nolin TD, Frye RF, Matzke GR. Hepatic drug metabolism and transport in patients with kidney disease. *Am J Kidney Dis* 2003; **42**(5):906–25.
128. Nolin TD, Naud J, Leblond FA, Pichette V. Emerging evidence of the impact of kidney disease on drug metabolism and transport. *Clin Pharmacol Ther* 2008;**83**(6):898–903.
129. Leblond F, Guevin C, Demers C, Pellerin I, Gascon-Barre M, Pichette V. Downregulation of hepatic cytochrome P450 in chronic renal failure. *J Am Soc Nephrol* 2001;**12**(2):326–32.

130. Leblond FA, Giroux L, Villeneuve JP, Pichette V. Decreased in vivo metabolism of drugs in chronic renal failure. *Drug Metab Dispos* 2000;**28**(11):1317–20.
131. Barnes KJ, Rowland A, Polasek TM, Miners JO. Inhibition of human drug-metabolising cytochrome P450 and UDP-glucuronosyltransferase enzyme activities in vitro by uremic toxins. *Eur J Clin Pharmacol* 2014;**70**(9):1097–106.
132. Uchida N, Kurata N, Shimada K, Nishimura Y, Yasuda K, Hashimoto M, et al. Changes of hepatic microsomal oxidative drug metabolizing enzymes in chronic renal failure (CRF) rats by partial nephrectomy. *Jpn J Pharmacol* 1995;**68**(4): 431–9.
133. Velenosi TJ, Fu AY, Luo S, Wang H, Urquhart BL. Down-regulation of hepatic CYP3A and CYP2C mediated metabolism in rats with moderate chronic kidney disease. *Drug Metab Dispos* 2012;**40**(8):1508–14.
134. Leber HW, Schutterle G. Oxidative drug metabolism in liver microsomes from uremic rats. *Kidney Int* 1972;**2**(3):152–8.
135. Okabe H, Hasunuma M, Hashimoto Y. The hepatic and intestinal metabolic activities of P450 in rats with surgery- and drug-induced renal dysfunction. *Pharm Res* 2003;**20**(10): 1591–4.
136. Terao N, Shen DD. Reduced extraction of I-propranolol by perfused rat liver in the presence of uremic blood. *J Pharmacol Exp Ther* 1985;**233**(2):277–84.
137. Michaud J, Dube P, Naud J, Leblond FA, Desbiens K, Bonnardeaux A, et al. Effects of serum from patients with chronic renal failure on rat hepatic cytochrome P450. *Br J Pharmacol* 2005; **144**(8):1067–77.
138. Yoshitani T, Yagi H, Inotsume N, Yasuhara M. Effect of experimental renal failure on the pharmacokinetics of losartan in rats. *Biol Pharm Bull* 2002;**25**(8):1077–83.
139. Michaud J, Nolin TD, Naud J, Dani M, Lafrance JP, Leblond FA, et al. Effect of hemodialysis on hepatic cytochrome P450 functional expression. *J Pharmacol Sci* 2008;**108**(2):157–63.
140. Nolin TD, Appiah K, Kendrick SA, Le P, McMonagle E, Himmelfarb J. Hemodialysis acutely improves hepatic CYP3A4 metabolic activity. *J Am Soc Nephrol* 2006;**17**(9):2363–7.
141. Michaud J, Naud J, Chouinard J, Desy F, Leblond FA, Desbiens K, et al. Role of parathyroid hormone in the downregulation of liver cytochrome P450 in chronic renal failure. *J Am Soc Nephrol* 2006; **17**(11):3041–8.
142. Velenosi TJ, Feere DA, Sohi G, Hardy DB, Urquhart BL. Decreased nuclear receptor activity and epigenetic modulation associates with down-regulation of hepatic drug-metabolizing enzymes in chronic kidney disease. *FASEB J* 2014;**28**(12): 5388–97.
143. Gu X, Ke S, Liu D, Sheng T, Thomas PE, Rabson AB, et al. Role of NF-kappaB in regulation of PXR-mediated gene expression: a mechanism for the suppression of cytochrome P-450 3A4 by proinflammatory agents. *J Biol Chem* 2006;**281**(26): 17882–9.
144. Watanabe H, Sugimoto R, Ikegami K, Enoki Y, Imafuku T, Fujimura R, et al. Parathyroid hormone contributes to the down-regulation of cytochrome P450 3A through the cAMP/PI3K/PKC/PKA/NF-kappaB signaling pathway in secondary hyperparathyroidism. *Biochem Pharmacol* 2017;**145**: 192–201.
145. Sun H, Huang Y, Frassetto L, Benet LZ. Effects of uremic toxins on hepatic uptake and metabolism of erythromycin. *Drug Metab Dispos* 2004;**32**(11):1239–46.
146. Naud J, Michaud J, Leblond FA, Lefrancois S, Bonnardeaux A, Pichette V. Effects of chronic renal failure on liver drug transporters. *Drug Metab Dispos* 2008;**36**(1):124–8.
147. Laouari D, Yang R, Veau C, Blanke I, Friedlander G. Two apical multidrug transporters, P-gp and MRP2, are differently altered in chronic renal failure. *Am J Physiol Renal Physiol* 2001;**280**(4): F636–45.
148. Simard E, Naud J, Michaud J, Leblond FA, Bonnardeaux A, Guillemette C, et al. Downregulation of hepatic acetylation of drugs in chronic renal failure. *J Am Soc Nephrol* 2008;**19**(7): 1352–9.
149. Yu C, Ritter JK, Krieg RJ, Rege B, Karnes TH, Sarkar MA. Effect of chronic renal insufficiency on hepatic and renal udp-glucuronyltransferases in rats. *Drug Metab Dispos* 2006;**34**(4): 621–7.

QUESTIONS AND ANSWERS

Question 1

A 54-year-old man infected with HCV develops the acute onset of oliguric AKI in the setting of decompensated cirrhosis which fails to respond to diuretic withdrawal or intravenous albumin infusion. Which of the following statements about the patient is most likely to be correct?

A. The renin–angiotensin system is suppressed
B. Arginine vasopressin levels are reduced
C. Nitric oxide levels are low
D. Cardiac output is reduced
E. A beneficial effect of blockade of the renin–angiotensin system is anticipated

Answer: D

Cirrhosis is characterized by deranged liver architecture leading to increased intrahepatic vascular resistance which in turn leads to increased portal vein pressure.[1–5] Release of systemic vasodilators, classically thought to arise as a response to portal hypertension, leads to peripheral vasodilation and decreased vascular resistance. The recruitment of compensatory mechanisms to maintain renal perfusion in the face of reduced effective arterial volume constitutes the hallmark of the HRS. These compensatory mechanisms include release of systemic vasoconstrictors, upregulation of the renin–angiotensin system, and activation of the sympathetic nervous system, increased nonosmotic release of vasopressin, and increased generation of potent vasoconstrictors. In early stages of cirrhosis, increased cardiac output maintains renal perfusion. However, in advanced cirrhosis, the ability of the heart to compensate is limited by cirrhotic cardiomyopathy and cardiac output declines.

Question 2

A 35-year-old woman with alcoholic cirrhosis develops the acute onset of oliguric AKI in the setting of decompensated cirrhosis which fails to respond to diuretic withdrawal or intravenous albumin infusion. Which of the following statements about the patient is most likely to be correct?

A. TNF-α levels are suppressed
B. Interleukin-6 levels are reduced
C. Urinary biomarkers of renal injury are absent
D. Circulating pathogen-associated molecular patterns are absent
E. An inflammatory state exists

Answer: E

It has recently been suggested that the primary factor responsible for the release of vasodilatory mediators in the HRS is increased circulating levels of cytokines and chemokines resulting from chronic inflammation associated with decompensated liver disease.[2,13] Cirrhosis is associated with increased gastrointestinal permeability, altered gastrointestinal microbiome, and translocation from the gastrointestinal tract of bacteria and bacterial products into the circulation. These bacterial products along with mediators released by apoptotic and necrotic hepatocytes stimulate the production of proinflammatory cytokines and chemokines, reactive oxygen species, and nitrogen species and activate immune cells. Decompensated cirrhosis is associated with increased levels of interleukin-6, interleukin-8, and TNF-α. Renal dysfunction in patients with decompensated liver failure has been correlated with circulating levels of proinflammatory cytokines.

Question 3

A 24-year-old woman with alcoholic cirrhosis develops a slowly progressive rise in the level of S[Cr] from 0.4 to 1.6 mg/dL over 3 weeks, which fails to respond to diuretic withdrawal or intravenous albumin infusion. Which of the following statements about the patient is most likely to be correct?

A. This is the most common clinical presentation of the HRS
B. This disorder is likely to show a sustained response to intravenous albumin and terlipressin
C. Post liver transplant renal outcomes are favorably influenced by therapy with intravenous albumin and terlipressin
D. This disorder is not associated with an inflammatory state
E. Even if intravenous albumin and terlipressin improve renal function in the short term, relapse is frequent

Answer: E

HRS-CKD is uncommon, accounting for only 5–11% of patients with cirrhosis and renal dysfunction. Treatment with intravenous albumin and terlipressin or noradrenaline can reverse HRS-CKD in more than half the cases.[18,19] However, responders experience a high relapse rate early after withdrawal of therapy. Relapse may occur in two-thirds of initial responders. Treatment of HRS-CKD with albumin volume expansion and vasoconstrictors is controversial and is not recommended by international practice guidelines due to inconsistent outcomes data.[2] After liver transplantation, there was no

difference in eGFR or in the development of CKD on follow-up, ranging up to 1 year, based on response to therapy.[19]

Question 4

A 69-year-old man with stage 5 chronic kidney disease is begun on therapy with warfarin, a drug that is subject to cytochrome P450 metabolism. Which of the following statements about the patient is most likely to be correct?

A. His chronic kidney disease status will have no effect on hepatic drug metabolism
B. The patient may require a lower dose of warfarin as a result of chronic kidney disease
C. Chronic kidney disease is associated with upregulation of most cytochrome P450 enzymes
D. Parathyroid hormone is not involved in cross talk between the kidney and hepatic drug metabolism
E. Chronic kidney disease does not influence gastrointestinal absorption of some drugs

Answer: B

CKD alters the pharmacokinetics of over 75 drugs whose elimination depends on nonrenal, predominantly hepatic clearance. In general, CKD is associated with reduced hepatic drug clearance, although in some cases hepatic clearance is enhanced. The magnitude of the change in hepatic drug clearance generally correlates with the degree of renal functional impairment. The remote effects of CKD on cytochrome P450 enzymes and drug transport proteins in the liver, kidney, and gastrointestinal tract are likely mediated by both the accumulation of uremic toxins including parathyroid hormone and by the generation of cytokine mediators.

Question 5

A 24-year-old HCV-infected man presents with microscopic hematuria and nephrotic syndrome. Which of the following statements about the patient is most likely to be correct?

A. Focal and segmental glomerulosclerosis is the most likely cause of nephrotic syndrome in this patient
B. Deposition of immune complexes containing viral antigens will not be demonstrated on kidney biopsy
C. HCV infection probably did not play a role in the development of glomerulonephritis in this patient
D. Interleukin-6 levels are reduced in this patient
E. Membranoproliferative glomerulonephritis is the most likely cause of nephrotic syndrome in this patient

Answer: E

Glomerular disease is a well-described extrahepatic manifestation of HCV infection.[45–47] A systemic immune response to HCV infection is thought to contribute to glomerular injury. Glomerular disease may be mediated by HCV-antibody immune complex deposition with or without cryoglobulin formation. Deposition of immune complexes containing viral antigens has been demonstrated in mesangial and subendothelial locations. The most common histologic pattern of glomerular injury is membranoproliferative glomerulonephritis; however, membranous glomerulopathy, focal and segmental glomerulosclerosis, IgA nephropathy, immunotactoid and fibrillary glomerulopathies, amyloidosis, and thrombotic microangiopathy have been described in HCV-infected patients.

Question 6

A 35-year-old HCV-infected man with stage 5 chronic kidney disease presents for antiviral therapy. Which of the following statements about the patient is most likely to be correct?

A. Sofosbuvir is approved by the Food and Drug Administration to treat this patient
B. Newer DAA agents may be expected to achieve a SVR in 25% of such cases
C. Transplantation status is not relevant to the decision whether or not to delay antiviral therapy in this patient
D. An interferon-based regimen is preferred due to the patient's age
E. A regimen containing grazoprevir and elbasvir is approved by the Food and Drug Administration to treat this patient

Answer: E

In the past, interferon and ribavirin constituted the only treatment option for HCV, and outcomes were suboptimal because of adherence issues related to toxicity.[56] Research into the HCV life cycle identified new opportunities to arrest viral replication and infectivity within hepatocytes. The four types of DAAs that were developed include (1) NS3/4A protease inhibitors, (2) NS5A inhibitors, (3) NS5B nonnucleoside polymerase inhibitors, and (4) NS5B nucleoside polymerase inhibitors.[57] They are given for a finite duration, usually in combination, avoid the difficult adverse effects of interferon-based therapies, and are curative. The current DAA regimens approved for use in patients with advanced CKD (stages 4 and 5) include Zepatier (combination of grazoprevir and elbasvir), Viekira (combination of ombitasvir, paritaprevir, dasabuvir, and ritonavir), and Mavyret

(combination of glecaprevir and pibrentasvir). FDA approval of sofosbuvir is limited to individuals with a GFR>30 mL/min/m^2. The decision whether or not to treat an HCV-infected individuals suffering from late-stage CKD with a second-generation DAA entails consideration of the individual's kidney transplantation status. Successful treatment of an HCV-positive candidate for a deceased donor kidney may result in a substantial delay or a lost opportunity for transplantation.[96]