Chapter 3

Acute Kidney Injury in Cirrhosis

Marco Antonio López Hernández

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.78571

Abstract

Acute kidney injury is a very relevant feature in the liver cirrhosis. Acute renal failure is due to prerenal factors, intrinsic factors of the kidney, or postrenal. Prerenal damage is the result of renal hypoperfusion without damage to the glomeruli or renal tubules. Without treatment, prerenal acute renal failure can progress to acute tubular necrosis, a type of intrinsic renal damage. Patients with cirrhosis are prone to developing acute kidney injury. The acute decrease of the kidney function contributes to the mortality of patients with cirrhosis. The potential triggers of acute kidney injury should be recognized and removed; this includes the discontinuation of diuretics and nephrotoxic drugs, the treatment of infections and gastrointestinal bleeding, and plasma expansion in case of hypovolemia. The new International Club of Ascites-Acute Kidney Injury in cirrhosis criteria provide a simple and relevant staging system for acute kidney injury in patients with liver cirrhosis based on relative increases in serum creatinine. Vasopressors such as terlipressin and norepinephrine in combination with intravenous albumin represent the first-line therapy for hepatorenal syndrome.

Keywords: acute kidney injury, hepatorenal syndrome, cirrhosis

1. Introduction

The association of acute kidney injury (AKI) in patients with liver cirrhosis has been established in the context of the hepatorenal syndrome, but there are several etiologies besides this cause.

Acute renal failure is a therapeutic challenge in patients with liver cirrhosis. This may be related to abnormal hemodynamics with systemic arterial vasodilatation and the splanchnic bed, in addition to the vasoconstriction of extrahepatic vessels, characteristic of advanced

liver cirrhosis [1]. Acute renal failure frequently occurs in the advanced stages of liver cirrhosis and entails a bad prognosis [2, 3].

Acute renal failure is due to prerenal factors, intrinsic factors of the kidney, or postrenal. Prerenal damage is the result of renal hypoperfusion without damage to the glomeruli or renal tubules. Without treatment, prerenal acute renal failure can progress to acute tubular necrosis (ATN), a type of intrinsic renal damage.

The prevalence of acute renal failure in cirrhosis has been reported from 14 to 50% in patients with cirrhosis. Its prevalence is approximately 50% in patients with cirrhosis and ascites and 20% of patients with advanced stage cirrhosis who are hospitalized [4, 5].

The definition of acute kidney injury is a reduction in the glomerular filtration rate (GFR) over a short time of period, and this is a common and severe complication in the patients with liver cirrhosis. Acute kidney failure can be triggered by a precipitating event, for example, overdose of diuretics, gastrointestinal bleeding, large-volume paracentesis without albumin replacement, bacterial infections, and so on [6]. The prevalence of acute kidney injury is approximately 20–50% among hospitalized patients with cirrhosis [6–9] and the renal failure development is more common in patients with cirrhosis compared to individuals without liver disease [10]. The presence of acute kidney failure is associated with poor prognosis in these patients and represents an important predictor for short-term mortality [11].

The criteria for acute renal failure in cirrhosis were initially proposed in 1996 [12] and redefined in subsequent years [13]. Traditionally, renal failure in cirrhosis was defined as a 50% increase in serum creatinine, with an increase greater than 1.5 mg/dL (133 μm/L) of it. The cutoff value of serum creatinine to define acute renal failure in patients with decompensated cirrhosis has changed [14, 15]. Several nephrology academic societies have proposed the use of the concept of acute renal injury to represent acute changes in kidney function. The diagnostic criteria constitute a combination of changes in the glomerular filtration rate as well as a reduction in urine output. In the past decade, the definition of acute kidney injury evolved to the classifications and diagnostic criteria known as RIFLE [16], AKIN [17], and KDIGO [18].

In 2010, the International Ascites Club (IAC) and the Acute Dialysis Quality Initiative (ADQI) decided to use the nomenclature of the Acute Kidney Injury (AKI).

In 2015, the International Ascites Club established a new definition and staging of acute renal failure for patients with liver cirrhosis [19].

2. Physiopathology of renal failure in cirrhosis

Patients with liver cirrhosis develop portal hypertension, which results in the vasodilatation of the splanchnic vascular bed, resulting in blood accumulation due to resistance in the portal venous flow. This is due to an increase in the fixed resistance of liver fibrosis, and dynamics in the splanchnic arteries is last due to

a. vasodilators such as nitric oxide, carbon monoxide, and endogenous cannabinoids [20, 21];

b. vasodilation by pro-inflammatory cytokines such as tumor necrosis factor and interleukin 6, derived from bacterial translocation of the intestine [22].

The accumulation of blood in the splanchnic bed leads to a reduction in the effective circulating volume, which leads to a compensatory increase in cardiac output through the activation of the sympathetic nervous system by the carotid baroreceptors in order to maintain adequate renal perfusion [23].

In advanced stages of cirrhosis, systemic vascular resistance is significantly reduced, and the additional increase in cardiac output cannot compensate. Thus, it is evident that cardiac output decreases as cirrhosis progresses. In advanced stages of cirrhosis, cardiac output is maintained through the activation of vasoconstrictor systems, including the sympathetic nervous system and the renin-angiotensin system, and by a non-osmotic hypersecretion of arginine-vasopressin.

These compensatory mechanisms can help to maintain effective arterial volume and of this way a relatively normal blood pressure, but this has important effects on kidney function, primarily a retention of water and sodium, which can eventually lead to the formation of ascites and edema, and renal failure conditioned by renal vasoconstriction and hypoperfusion [24, 25].

There are four factors involved in the pathogenesis of hepatorenal syndrome. These are the following:

1. Activation of the renin-angiotensin-aldosterone system and the sympathetic nervous system which causes renal vasoconstriction and a shift in the renal autoregulatory curve, which results in a renal blood flow more sensitive to changes in the arterial pressure.

2. Splanchnic vasodilatation, which causes a fall in the effective arterial blood volume and this way a decrease of the mean arterial pressure.

3. Increased synthesis of vasoactive mediators which affect renal blood flow or glomerular microcirculatory hemodynamics, such as leukotrienes, thromboxane A2, isoprostanes, and endothelin-1.

4. Impairment of cardiac function due to the development of cirrhotic cardiomyopathy, which leads to a relative impairment of the compensatory increase in cardiac output secondary to vasodilatation.

Hemodynamic disorders can have widespread impact on the body according to the severity of the cirrhosis [26]. The hemodynamic changes in cirrhosis include portal hypertension and hyperdynamic circulation which are the main cause of morbidity and mortality in patients with cirrhosis. The effective arterial blood volume and the circulating levels of RAS components and antidiuretic hormone remain normal at early stages of the disease, even with a

reduced systemic vascular resistance. The elevated cardiac output and low systemic vascular resistance are characteristics of the portal hypertension and hyperdynamic circulation in cirrhosis. Arterial vasodilation in the splanchnic circulation and the resulting decrease in systemic vascular resistance are associated with portal hypertension in cirrhosis. Compensatory mechanisms following the reduction of systemic vascular resistance lead to hyperdynamic circulation. Nevertheless, hyperdynamic circulation is insufficient to correct the effective arterial hypovolemia when the disease progresses and arterial vasodilation increases, resulting in arterial hypotension and consequent activation of the circulating renin-angiotensin-aldosterone system and the sympathetic nervous system and secretion of antidiuretic hormone [27].

In the early stages of disease, the circulating RAS is not activated at early stages of the disease. The patients at the advanced stages of cirrhosis presented an activation of peripheral and splanchnic renin-aldosterone system, and a metabolic deviation toward the RAS vasodilator axis in the splanchnic circulation (**Figure 1**).

2.1. Causes of acute kidney injury in cirrhosis

The acute kidney injury has prerenal, intrarenal, or postrenal causes (**Figure 2**). The most common causes of acute kidney injury between patients with cirrhosis are the prerenal etiologies, followed by acute tubular necrosis, and the postrenal etiology is extremely rare. The prerenal and acute tubular necrosis are the etiology of 80% of cases (49% prerenal and 35% acute tubular

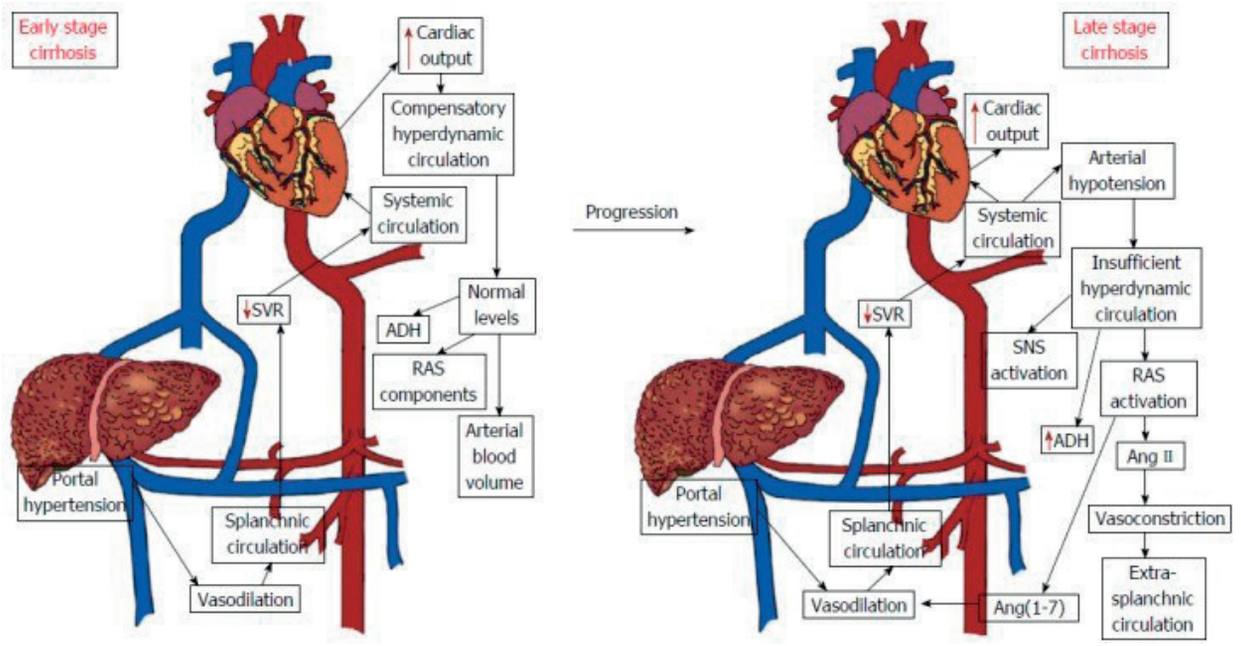

Figure 1. Hemodynamic alterations in the early and advanced stages of cirrhosis. In the early stages of cirrhosis, there is an increased cardiac output and a diminished systemic vascular resistance without changes in the circulating levels of the renin-angiotensin system components and antidiuretic hormone. In later phases of the cirrhosis, the components of the renin-angiotensin-aldosterone system are elevated, with activation of the sympathetic nervous system and secretion of the antidiuretic hormone, like a response to persistent arterial hypotension. Ang II: angiotensin II; Ang-(1–7): angiotensin (1–7); SNS: sympathetic nervous system; SVR: systemic vascular resistance.

http://dx.doi.org/10.5772/intechopen.78571

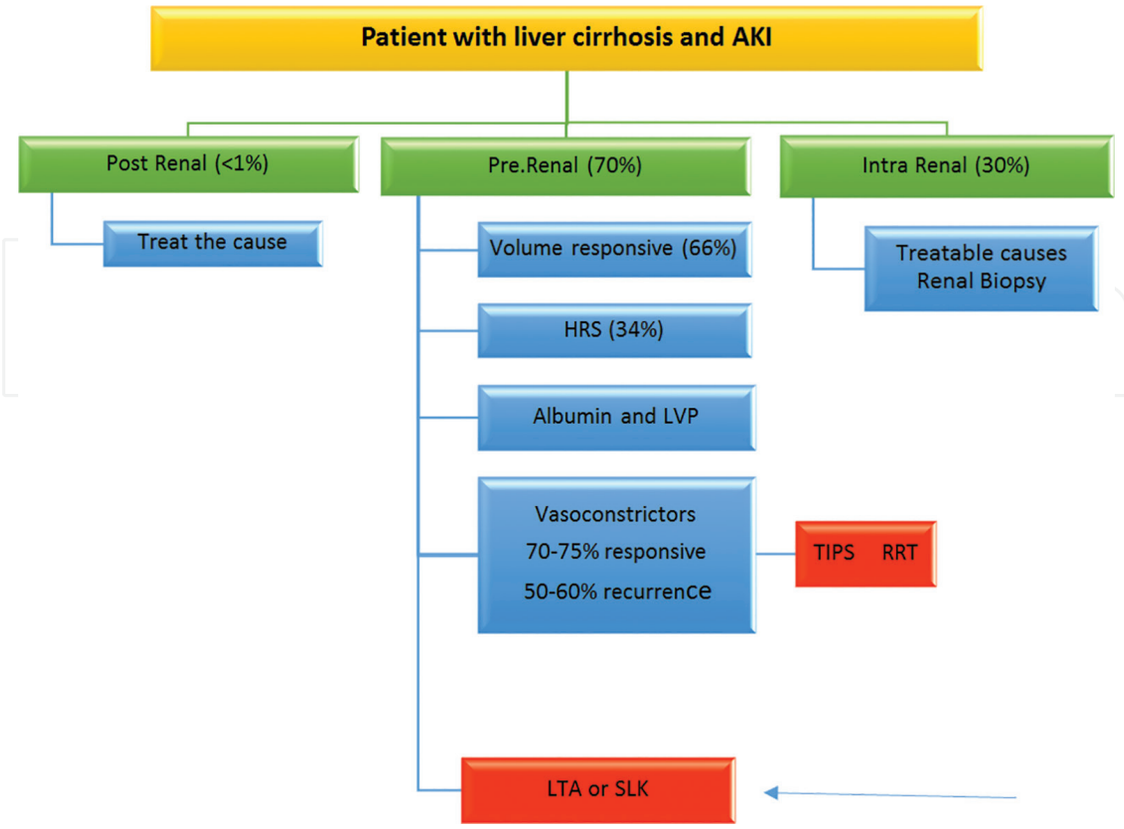

Figure 2. Management approach and algorithm for acute kidney injury in patients with cirrhosis. AKI, acute kidney injury; ESLD, end-stage liver disease; HRS, hepatorenal syndrome; LVP, large-volume paracentesis; RRT, renal replacement therapy; LTA, liver transplant alone; SLK, simultaneous liver kidney; TIPS, transjugular intrahepatic portosystemic shunt; USG, ultrasonogram.

necrosis). Postrenal injury accounted for only 0.2%. In a prospective study, among patients with cirrhosis listed for liver transplantation who had acute kidney injury, prerenal injury was the most common cause in 76% followed by intrarenal etiology in 33%, while postrenal etiology did not occur in any patient [66, 67].

3. Prerenal injury

3.1. Volume responsive prerenal AKI

The hemodynamic state in cirrhosis with vascular dilatation and reduced vascular resistance in cirrhosis is quite similar to hemodynamic state in sepsis, especially spontaneous bacterial peritonitis. Prerenal injury occurs commonly due to gastrointestinal bleeding, infections, use of diuretics, diarrhea often related to lactulose use for hepatic encephalopathy, and from large-volume paracentesis without albumin infusion. Large-volume paracentesis may be associated with intravascular volume depletion and acute kidney failure. This condition occurs in up to 70% of patients undergoing paracentesis when more

than 5 L are removed and albumin is not infused. The use of any drugs like NSAIDs can precipitate acute kidney failure by decreasing renal prostaglandins and accentuating the intrarenal vasoconstriction and further decrease renal blood flow. The advice to the patients should be provided to avoid these drugs for the management of pain. The use of intravenous contrast agents in patients with cirrhosis is another potential risk factor for acute kidney failure. The infections have common occurrence in patients with cirrhosis. Hence, superimposed infections/sepsis in cirrhosis patients worsen this physiology, causing a reduction of circulating blood volume and leading to the development of AKI. Before the widespread use of antibiotic prophylaxis for acute gastrointestinal bleeding in cirrhosis, more than 20% of patients with cirrhosis hospitalized for acute gastrointestinal bleeding had a bacterial infection present on admission, with up to 50% developing an infection while hospitalized.

3.2. Volume nonresponsive prerenal AKI: hepatorenal syndrome

The volume expansion is the first treatment after acute kidney failure is diagnosed, using crystalloids or intravenous albumin and discontinuation of precipitating medications. If renal function does not normalize or improve with this intervention, it is important to consider hepatorenal syndrome (HRS) in the differential diagnosis to consider as the cause for AKI. HRS is a functional form of renal failure without any major structural or histological changes in the kidneys that is characterized by intense renal vasoconstriction. It is important to differentiate it from another intrarenal cause, because management and prognosis differ. In the absence of renal biopsy, the diagnosis of HRS remains difficult and is essentially a diagnosis of exclusion. In patients with cirrhosis, HRS develops in about 18% at 1 year and 39% at 5 years.

Approximately, 66% of all HRS cases are type 2, or HRS-AKI which are rapidly occurring with an increase in serum creatinine to over 2.5 mg/dL over 1 or 2 weeks. Type 1 HRS has high mortality with a median survival of around 50% at 2 weeks and is usually precipitated by infections. The type 2 HRS has a better outcome with a median survival of about 6 months and a slower course in the setting of refractory ascites, with slowly increasing serum creatinine to over 1.5 mg/dL. The definition of type I HRS has been recently revised and changed the value of 2.5 mg/dL serum creatinine for diagnosis, thus avoid delaying the initiation of therapy.

3.3. Volume nonresponsive intrinsic AKI: acute tubular necrosis

The most common cause for intrarenal AKI in cirrhosis is ATN. This occurs commonly either as a complication of sepsis or due to unrecognized and untreated prerenal injury. The main cause of ATN has been attributed to sepsis, followed by hypovolemia and rarely nephrotoxic drugs.

Other less common causes of intrarenal injury include tubular damage due to bile cast nephropathy from high-conjugated bilirubin excreted through the glomeruli, membranoproliferative glomerulonephritis with or without cryoglobulinemia associated with hepatitis C, and acute interstitial nephritis due to medications, such as antibiotics, NSAIDS, and proton pump inhibitors.

4. Postrenal injury

As stated earlier, postrenal injury is a rare cause of AKI in cirrhosis [66, 68]. This etiology can easily be excluded using renal ultrasound or CT scan.

4.1. Evaluation of the renal function

The glomerular filtration rate (GFR) is the universally used index to quantify kidney function. The principle of GFR determination is to determine the body clearance of a substance with the supposed exclusive renal clearance. The substance used for determinate GFR must be freely filtered and neither reabsorbed or secreted along the renal tubule. Also, no extrarenal excretion of the substance occurs, and it cannot be stored or be bound to plasma proteins: then it can be assumed that the plasmatic clearance is only due to renal clearance. Thus, the GFR can be inferred from the plasma disappearance of the substance. It is considered that the renal clearance of a marker occurs only through glomerular filtration [28].

Calculation of the eGFR requires normalization to BSA. Studies that tested the performance of this method showed a clear trend to overestimate mGFR by 4–80%. A normalization based on the assumption that the GFR is positively correlated with the basal metabolism rate of individuals which is proportional to their stature on arbitrarily fixed body surface area (BSA) set to 1.73 m^2 is commonly done [29]. This normalization has been questioned [30] and standardization on other criteria has been proposed [31]. The formula most commonly used to determine the BSA is the Dubois formula, and the adjustment on the body surface remains widely used [32].

Historically, the Cockcroft and Gault formula was the most popular before the MDRD formula was published in the early 2000s. This formula is not adjusted to the patient BSA, and the adjustment has, theoretically, to be done afterwards (even if the relevance of this adjustment remains to be assessed in cirrhotic patients). The relationship between GFR level and overestimation could be explained by the secretion of creatinine by the tubule in patients with CKD. However, the importance of this overestimation does not seem to be related to the severity of cirrhosis.

Creatinine clearance is a simple method to estimate GFR, based on the assumption that creatinine has the characteristics of a perfect renal marker. It requests the accurate recollection of urine from a 24-h period. It has several limitations: mainly, the possible inadequate urine collection by the patients, the occurrence of tubular secretion of creatinine, which leads to overestimation of the GFR, and that is on a longer or a shorter than 24-h time period.

4.2. Definition of acute kidney injury in cirrhosis

The definition of acute kidney injury in cirrhosis consists in an acute increase in serum creatinine of >0.3 mg/dL in a time lapse of 48 h or by <50% from a stable baseline serum creatinine, in the last 3 months (presumed to have developed within the past 7 days when no prior readings are available) [19, 33]. In addition, the use of urine output as part of the diagnostic criteria was eliminated, since many patients with cirrhosis and ascites maintain a preserved renal function despite being oliguric due to sodium and water retention. The main modifications over the previous,

rather stringent, criteria that were based on absolute serum creatinine level, were abandoning the threshold of serum creatinine >1.5 mg/dL to diagnose acute kidney injury, because milder degrees of renal failure in cirrhotic patients had often remained underdiagnosed [34, 35].

Similar to the ICA-AKI criteria, most of these studies diagnosed AKI solely on serum creatinine. In 2013, a modified, AKIN-derived score for cirrhosis was developed, by division of AKI stage 1 into two groups depending on whether or not serum creatinine surpassed the threshold of 1.5 mg/dL and by merging AKI stages 2 and 3 into stage "C" [40]; this reclassification did not gain wide acceptance. Several clinical studies have evaluated the prognostic value of the AKIN/KDIGO criteria that constitute the basis for the International Club of Ascites (ICA)-AKI criteria in patients with cirrhosis [37–39]. The acute kidney injury can be classified into three stages according to severity. Stage 1 AKI is defined by rather small changes in serum creatinine, while stages 2 and 3 AKI are defined by a twofold and threefold increase in serum creatinine, respectively (**Table 1**) [36]. Since their publication in 2015, the newer and cirrhosis-specific ICA criteria have been assessed within one retrospective study in hospitalized patients with cirrhosis [41]. Within this study, approximately 40% of patients experienced AKI during their hospitalization with the majority of cases having been diagnosed at stage 1. Also, in patients with AKI stage 1 and a serum creatinine of <1.5 mg/dL, already a 3.5-fold increase in 30-day mortality as compared to patients without AKI was reported [41], again underlining the prognostic importance of even small increases in serum creatinine levels.

4.3. Hepatorenal syndrome type of acute kidney injury or type 1 hepatorenal syndrome

Hepatorenal syndrome (HRS) is defined as the occurrence of renal failure in a patient with advanced liver disease in the absence of an identifiable cause of renal failure [12].

The hepatorenal syndrome type I requires the fulfillment of several specific diagnostic criteria that are summarized in **Table 2**. This Acute Kidney Injury (HRS-AKI) is defined as >stage 2 ICA-AKI that is diagnosed after other causes of renal failure have been ruled out [35].

Acute kidney injury stages according to the International Club of Ascites criteria	
Stage 2	Increase in serum creatinine >0.3 mg/dl or Increase in serum creatinine by>50–100% from baseline
Stage 2	Increase in serum creatinine by100–200% from baseline
Stage 3	Increase in serum creatinine by 200% from baseline or Increase in serum creatinine to 4 mg/dL with an acute increase by 0.3 mg/dL or Need for renal replacement therapy

Table 1. Criteria of AKI of the International Club of Ascites [36].

Diagnostic criteria of hepatorenal syndrome
Presence of cirrhosis and ascites
No improvement in serum creatinine after 2 consecutive days of withdrawal of diuretics and plasma volume expansion with albumin (1 g per kg of body weight, maximum 100 g/day)
Absence of shock
Exclusion of recurrent or recent use of nephrotoxic agents (e.g.NSAIDs, aminoglycosides, contrast media)
Exclusion of parenchymal kidney disease: **• absence of proteinuria (>500 mg/day)** **• absence of microhematuria (>50 RBCs per high-power field)** **• normal renal ultrasonography**

Table 2. Diagnostic criteria for hepatorenal syndrome [12].

The Guidelines of the European Association for the Study of Liver Diseases (EASL) and the American Association for the Study of the Liver (AASLD) Clinical Practice Guidelines for ascites and hepatorenal syndrome still proclaim the threshold of 2.5 mg/dL for diagnosing HRS-AKI [42, 43]. The use of this threshold in clinical practice would mean that proper diagnosis and treatment of HRS would be withheld as long as serum creatinine does not reach this threshold. In order to prevent misclassification or even treatment delay, the newer International Club of Ascites criteria focus on the relative increase in creatinine rather than absolute values, since also smaller rises in serum creatinine have been shown to have a negative prognostic impact in patients with cirrhosis [44].

The hepatorenal syndrome is classified in two types. HRS type 1 is a quickly progressive acute renal failure. It commonly occurs in patients with end-stage cirrhosis following a septic insult such as spontaneous bacterial peritonitis or severe alcoholic hepatitis; this kind of hepatorenal syndrome frequently is developed in temporal relationship with a precipitating factor for a deterioration of liver function together with a deterioration of other organ function, although it may occur in the absence of any identifiable triggering event. Type 1 HRS is only diagnosed when the serum creatinine increases more than 100% from baseline to a final level of greater than 2.5 mg/dL.

Patients with type 2 HRS may eventually develop type 1 HRS; this can be spontaneously or following a precipitating event such as an infection [12].

HRS should be diagnosed and excludes other known causes of renal failure and by demonstrating a significant increase in serum creatinine. For practical purposes, HRS is usually diagnosed only when serum creatinine increases to >133 mol/L (1.5 mg/dL). Repeated measurement of serum creatinine over time, particularly in hospitalized patients, is helpful in the early identification of HRS.

The diverse etiologies of renal failure in cirrhosis should be excluded before to conclude the diagnosis of HRS. Parenchymal renal diseases should be suspected if there is significant

proteinuria or micro-hematuria, or if renal ultrasonography demonstrates abnormalities in kidney size. The hypovolemia, shock, parenchymal renal diseases, and concomitant use of nephrotoxic drugs are common causes of acute kidney injury and must be excluded before to diagnose HRS. Renal biopsy is important in these patients to help plan the further management, including the potential need for combined liver and kidney transplantation [42].

4.3.1. Treatment

The initial management of acute kidney injury should focus on the early recognition and correction of potential trigger events and on preventing further hemodynamic deterioration [25, 33, 45]. In volume-depleted patients, diuretic therapy and/or lactulose should be withdrawn and plasma volume should be expanded with albumin, or blood transfusions in anemic patients due to gastrointestinal blood loss, is important the careful review of all medications, and consider the withdrawn of nephrotoxic agents. The use of medications that may induce or aggravate arterial should be carefully evaluated [46, 47].

Bacterial infections are a common precipitant of acute kidney injury, including the hepatorenal syndrome; in cirrhosis, these patients should be thoroughly screened for. The early initiation of empiric antibiotic treatment based on clinical suspicion and the local epidemiology and resistance patterns must be considered [48, 49].

The therapeutic response is defined as a decrease of creatinine in serum to a value within 0.3 mg/dL of baseline; in this case, the patients should be followed up closely for the early detection of recurrent episodes kidney failure. It is necessary to consider the possibility of hepatorenal syndrome In case of stage 2 or 3 or progression to a higher acute kidney injury stage, diuretics should be withdrawn immediately. The patients should receive plasma volume expansion with albumin for 2 consecutive days (1 g per kg of body weight, maximum 100 g/day). Albumin is particularly beneficial in patients with sepsis because in addition to its volume-expanding effect, it has antioxidant, scavenging, and endothelial-stabilizing functions [50]. A follow-up assessment of creatinine every 2–4 days during hospitalization and every 2–4 weeks during the first 6 months after discharge is advised [35].

In stages 2 and 3, the patients who meet diagnostic criteria of HRS-AKI should be treated with vasoconstrictors in combination with albumin [35]. The albumin initial dose is 1 g/kg body weight up to 100 g on the first day, then ongoing with 20–40 g/day, as it has been shown that the effects of intravenous albumin in the prevention and treatment of HRS are dose-dependent, with better results when higher cumulative doses were administered [51, 52]. In all large-volume paracentesis (>5 L, with 8 g/L of ascites removed), albumin should be administered since it prevents post-paracentesis circulatory dysfunction, which reduces the risk of renal dysfunction and improve survival [53, 54].

The first-line drug therapy of type 1 hepatorenal syndrome is the use of terlipressin (1 mg/4–6 h intravenous bolus) in combination with albumin. The therapeutic target improves renal function enough to decrease serum creatinine to less than 133 mol/L (1.5 mg/dL); this is considered a complete response. If serum creatinine does not decrease at least 25% after 3 days, the dose of terlipressin should be increased in a stepwise manner up to a maximum of 2 mg/4 h. For patients with partial response (serum creatinine does not decrease <133 mol/L) or in those patients without reduction of serum creatinine, treatment should be discontinued within 14 days.

The terlipressin is the most intensively studied vasoconstrictor for the treatment of HRS-AKI. A bolus of terlipressin induces a significant reduction in the portal pressure for over a 3- to 4-h period and also increases the mean arterial pressure [55]. Hyponatremia must be considered, and this commonly occurs in less advanced liver disease and normal baseline serum sodium levels [56, 57]. Considering the pharmacodynamic profile and the costs of terlipressin, continuous infusion might be preferred over bolus administration. Although terlipressin has been consistently shown to improve renal function, its impact on survival is less clear [58]. Terlipressin is particularly beneficial in patients with sepsis and might also prevent variceal bleeding during the period of discontinuation of nonselective beta blockers [59].

Norepinephrine is an alternative to the use of terlipressin with an initial dose: 0.5 mg/h, and a max. Dose studied in randomized controlled trials of 3 mg/h, norepinephrine is equally effective and inexpensive. A meta-analysis of four randomized-controlled trials demonstrated similar efficacy for HRS, when compared to terlipressin [60]. The therapy recommended for type 2 hepatorenal syndrome is similar [61, 62]; however, HRS type 2 commonly recurs after termination of treatment with vasoconstrictors [63].

Complete response is defined by a decrease in serum creatinine to a value within 0.3 mg/dL of baseline, while a regression of at least one AKI stage is considered as partial response [35]. If there is no response after 3 days of treatment, the vasoconstrictor dose should be increased. In nonresponders, treatment should be discontinued after 14 days. In responders, longer treatment durations can be used as a bridging therapy to liver transplantation.

Potential alternative therapies to terlipressin include norepinephrine or midodrine plus octreotide, both in association with albumin, but there is very limited information with respect to the use of these drugs in patients with type 1 HRS. Treatment with terlipressin should be repeated and is frequently successful. The recurrence of type 1 HRS after discontinuation of terlipressin therapy is relatively uncommon.

Cardiovascular ischemic disease is a contraindication to terlipressin therapy. Patients on terlipressin should be carefully monitored for signs of splanchnic or digital ischemia, the development of cardiac arrhythmias and fluid overload, and treatment modified or stopped accordingly.

The use of TIPS may improve renal function in some patients; there are insufficient data in patients with type 1 HRS to support the use of TIPS as a treatment. The renal replacement therapy may be useful when the patients do not respond to vasoconstrictor therapy. There are limited data on the use of artificial liver support systems, and further studies are required for its use [43].

4.4. Hepatitis C and acute kidney injury

Hepatitis C (HCV) infection can induce kidney injury, mainly due to the formation of immune complexes and cryoglobulins, and possibly to a direct cytopathic effect. HCV is responsible for membranous glomerulonephritis or mesangiocapillary and accelerates the progression of chronic kidney disease due to other causes. It may cause acute kidney injury as a part of systemic vasculitis and augments the risk of AKI due to other etiologies. HCV-infected patients are at an

increased risk of acute posttransplant complications. HCV infection increases cardiovascular and liver-related mortality in patients on regular dialysis. Long-term graft survival is compromised by chronic transplant glomerulopathy or recurrent or de novo glomerulonephritis. The increased incidence of diabetes, sepsis, posttransplant lymphoproliferative disease, and liver failure compromises the patient survival. Directly acting antiviral agents (DAAs) are currently available for treatment at different stages of kidney disease. It is concluded that the thoughtful use of DAAs will result in a significant change in the epidemiology and clinical profiles of kidney disease, as well as improvement of dialysis and transplant outcomes, in endemic areas [64].

The acute kidney failure induced by HCV is a systemic disease reported in <5% of HCV-infected (HCV+ve) patients. It is characterized by multiorgan involvement, mainly affecting the lungs and kidneys, skin, musculoskeletal system, and peripheral nerves. The fundamental lesion is endothelial injury, perivascular inflammation with lymphocytic and neutrophilic infiltration, small vessel necrosis, and luminal occlusion by cryoglobulins and fibrin thrombi.

4.5. Cryoglobulinemic vasculitis

In the kidneys, this leads to focal fibrinoid necrosis of the glomerular tufts, often with crescent formation (**Figure 3**). The renal tubules are affected by ischemic and inflammatory lesions and contain hyaline and blood casts. The ureteric and bladder mucosa may display vasculitic purpuric lesions. The interstitium is infiltrated with inflammatory cells and found edematous.

The mechanism of vascular injury is typically attributed to component C1q of the complement, complement activation generates chemotactic factors, C3a and C5a, which recruit and activate pro-inflammatory leucocytes. It also leads to the formation of C5–9, the membrane attack complex that may have an important role in endothelial damage, the active complement component incorporated within the cryoglobulin complex. This leads to endothelial injury by dual effects, namely the activation of the complement cascade via the classical pathway and binding to endothelial complement receptors, thereby localizing the injury in target capillary beds.

The clinical presentation has a wide range from isolated hematuria to acute kidney injury, sometimes associated with thrombotic microangiopathy (**Figure 4**). If left untreated, the

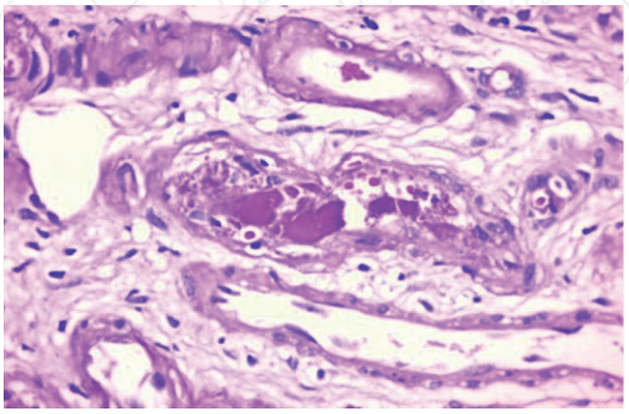

Figure 3. Cryoglobulinemic renal vasculitis. Renal arteriole showing endothelialitis and cryoglobulin deposits in a patient with AKI due to HCV-associated cryoglobulinemia. Hematoxylin and eosin stain. Reproduced with permission from Ref. [64].

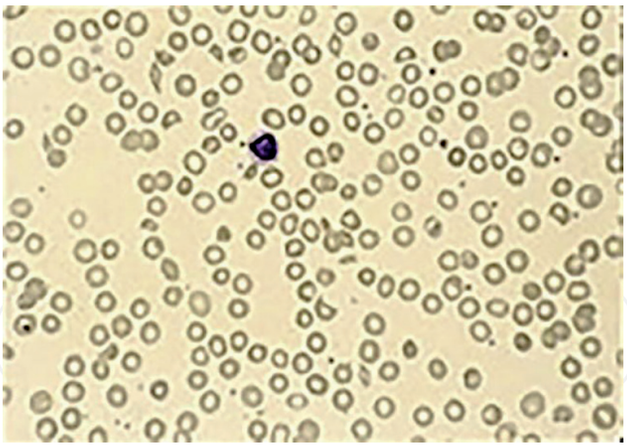

Figure 4. Blood smear in a patient with cryoglobulinemic vasculitis and thrombotic microangiopathy. Note the red cell fragmentation with microcytes and schistocytes.

prognosis becomes bad for the renal function, as well as patient survival. The successful treatment may lead to complete or partial recovery, unless the damage has already been extensive, leading to healing with focal or global sclerosis.

4.6. Non-cryoglobulinemic AKI

HCV-infected patient, compared to the general population are at many-fold risk of developing acute kidney injury of diverse etiology. The most frequent cause of kidney injury is hypovolemia associated with excessive vomiting or diarrhea. The second common cause was bacterial infection in the lungs, urinary, or gastrointestinal tract; 7.3% of patients had advanced cirrhosis and developed AKI following an episode of hematemesis, presumably due to ischemic acute tubular necrosis, and 6.5% were associated with hepatic encephalopathy including the hepatorenal syndrome. Decompensated liver disease, diabetes mellitus, history of intravenous drug abuse, and high baseline serum creatinine were independent predictors of developing AKI. End-stage kidney disease eventually developed in 17.5% of patients who developed AKI, compared to 1% of those who did not. Risk factors for end-stage renal kidney disease were preexisting hypertension, diabetes, or chronic kidney disease [65].

5. Summary

Patients with cirrhosis are prone to developing acute kidney failure. The acute decrease of the kidney function contributes to the mortality of patients with cirrhosis. The criteria of the International Club of Ascites for acute kidney injury provide a simple and relevant staging system for acute kidney injury in patients with liver cirrhosis based on relative increases in serum creatinine. It is very important to consider the potential triggers of renal failure, and this should be recognized early and removed; this includes discontinuation of nephrotoxic drugs and diuretics, treatment of infections and gastrointestinal bleeding, and plasma expansion in case of hypovolemia.

Cardiovascular ischemic disease is a contraindication to terlipressin therapy. Patients on terlipressin should be carefully monitored for signs of splanchnic or digital ischemia, the development of cardiac arrhythmias and fluid overload, and treatment modified or stopped accordingly.

Author details

Marco Antonio López Hernández

Address all correspondence to: niklaus2003@yahoo.com.mx

Internal Medicine Department, Tacuba General Hospital, Mexico City, Mexico

References

[1] Wong F. Recent advances in our understanding of hepatorenal syndrome. Nature Reviews. Gastroenterology & Hepatology. 2012;**9**:382-391

[2] D'Amico G, Garcia-Tsao G, Pagliaro L. Natural history and prognostic indicators of survival in cirrhosis: A systematic review of 118 studies. Journal of Hepatology. 2006; **44**:217-231

[3] du Cheyron D, Bouchet B, Parienti JJ, Ramakers M, Charbonneau P. The attributable mortality of acute renal failure in critically ill patients with liver cirrhosis. Intensive Care Medicine. 2005;**31**:1693-1699

[4] Montoliu S, Ballesté B, Planas R, Alvarez MA, Rivera M, Miquel M, et al. Incidence and prognosis of different types of functional renal failure in cirrhotic patients with ascites. Clinical Gastroenterology and Hepatology. 2010;**8**:616-622

[5] Wu CC, Yeung LK, Tsai WS, Tseng CF, Chu P, Huang TY, et al. Incidence and factors predictive of acute renal failure in patients with advanced liver cirrhosis. Clinical Nephrology. 2006;**65**:28-33

[6] Gerbes AL. Liver cirrhosis and kidney. Digestive Diseases. 2016;**34**:387-390

[7] Piano S, Rosi S, Maresio G, et al. Evaluation of the Acute Kidney Injury Network criteria in hospitalized patients with cirrhosis and ascites. Journal of Hepatology. 2013;**59**:482-489

[8] Follo A, Llovet J, Navasa M, et al. Renal impairment after spontaneous bacterial peritonitis in cirrhosis: Incidence, clinical course, predictive factors and prognosis. Hepatology. 1994;**20**:1495-1501

[9] Hampel H, Bynum GD, Zamora E, El-Serag HB. Risk factors for the development of renal dysfunction in hospitalized patients with cirrhosis. The American Journal of Gastroenterology. 2001;**96**:2206-2210

[10] Garcia-Tsao G, Parikh CR, Viola A. Acute kidney injury in cirrhosis. Hepatology. 2008; **48**:2064-2077

[11] Cardenas A, Gines P, Uriz J, et al. Renal failure after upper gastrointestinal bleeding in cirrhosis: Incidence, clinical course, predictive factors, and short-term prognosis. Hepatology. 2001;**34**:671-676

[12] Arroyo V, Gines P, Gerbes AL, et al. Definition and diagnostic criteria of refractory ascites and hepatorenal syndrome in cirrhosis. Hepatology. 1996;**23**:164-176

[13] Salerno F, Gerbes A, Gines P, et al. Diagnosis, prevention and treatment of the hepatorenal syndrome in cirrhosis a consensus workshop of the International Ascites Club. Gut. 2007;**56**:1310-1318

[14] Wong F, Nadim MK, Kellum JA, et al. Working Party proposal for a revised classification system of renal dysfunction in patients with cirrhosis. Gut. 2011;**60**:702-709

[15] Angeli P, Sanyal A, Moller S, et al. Current limits and future challenges in the management of renal dysfunction in patients with cirrhosis: Report from the International Club of Ascites. Liver International. 2013;**33**:16-23

[16] Bellomo R, Ronco C, Kellum JA, Mehta RL, Palevsky P; Acute Dialysis Quality Initiative workgroup. Acute renal failure–Definition, outcome measures, animal models, fluid therapy and information technology needs: The Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. Critical Care 2004;**8**:R204-R212

[17] Mehta RL, Kellum JA, Shah SV, Molitoris BA, Ronco C, Warnock DG, et al. Acute Kidney Injury Network: Report of an initiative to improve outcomes in acute kidney injury. Critical Care. 2007;**11**:R31

[18] Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO clinical practice guideline for acute kidney injury. Kidney International. 2012;**2**(Suppl 1):1-138

[19] 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. Gut. 2015;**64**:531-537

[20] Martin PY, Ginès P, Schrier RW. Nitric oxide as a mediator of hemodynamic abnormalities and sodium and water retention in cirrhosis. The New England Journal of Medicine. 1998;**339**:533-541

[21] Ros J, Clària J, To-Figueras J, Planagumà A, Cejudo-Martín P, Fernández-Varo G, et al. Endogenous cannabinoids: A new system involved in the homeostasis of arterial pressure in experimental cirrhosis in the rat. Gastroenterology. 2002;**122**:85-93

[22] Navasa M, Follo A, Filella X, Jiménez 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**:1227-1232

[23] Ginès P, Schrier RW. Renal failure in cirrhosis. The New England Journal of Medicine. 2009;**361**:1279-1290

[24] Schrier RW, Arroyo V, Bernardi M, Epstein M, Henriksen JH, Rodés J. Peripheral arterial vasodilatation hypothesis: A proposal for the initiation of renal sodium and water retention in cirrhosis. Hepatology. 1988;**8**:1151-1157

[25] Arroyo V, Ginès P, Gerbes AL, et al. Definition and diagnostic criteria of refractory ascites and hepatorenal syndrome in cirrhosis. Hepatology. 1996;**23**:164-176

[26] Kim MY, Baik SK, Lee SS. Hemodynamic alterations in cirrhosis and portal hypertension. The Korean Journal of Hepatology. 2010;**16**:347-352

[27] Vilas-Boas WW, Ribeiro-Oliveira A, Pereira RM, Ribeiro Rda C, Almeida J, Nadu AP, Simões e Silva AC, dos Santos RA. Relationship between angiotensin-(1-7) and angiotensin II correlates with hemodynamic changes in human liver cirrhosis. World Journal of Gastroenterology. 2009;**15**:2512-2519

[28] Israni AK, Kasiske BL. Laboratory assessment of kidney disease: Clearance, urinalysis and kidney biopsy. In: Brenner and Rector's The Kidney. 8th ed. Philadelphia: Saunders Elsevier; 2008. pp. 724-750

[29] Mccance RA, Widdowson EM. The correct physiological basis on which to compare infant and adult renal function. Lancet. 1952;**2**:860-862

[30] Delanaye P, Krzesinski JM. Indexing of renal function parameters by body surface area: Intelligence or folly? Nephron. Clinical Practice. 2011;**119**:c289-c292

[31] Eriksen BO, Melsom T, Mathisen UD, Jenssen TG, Solbu MD, Toft I. GFR normalized to total body water allows comparisons across genders and body sizes. Journal of the American Society of Nephrology. 2011;**22**:1517-1525

[32] Du Bois D, Du Bois EF. A formula to estimate the approximate surface area if height and weight be known. Nutrition. 1989;**5**:303-311

[33] Garcia-Tsao G, Parikh CR, Viola A. Acute kidney injury in cirrhosis. Hepatology. 2008; **48**:2064-2077

[34] Wong F, O'Leary JG, Reddy KR, et al. New consensus definition of acute kidney injury accurately predicts 30-day mortality in patients with cirrhosis with infection. Gastroenterology. 2013;**145**:1280-1288

[35] Angeli P, Wong P. Hepatology snapshot: New diagnostic criteria and management of Acute Kidney Injury Hepatology Snapshot. Journal of Hepatology. 2016;**xx**:1-2

[36] Angeli P, Gine's P, Wong F, et al. Diagnosis and management of acute kidney injury in patients with cirrhosis: Revised consensus recommendations of the International Club of Ascites. Journal of Hepatology. 2015;**62**:986-974

[37] Angeli P, Rodrıguez E, Piano S, et al. Acute kidney injury and acute-on-chronic liver failure classifications in prognosis assessment of patients with acute decompensation of cirrhosis. Gut. 2015;**64**:1616-1622

[38] Bucsics T, Mandorfer M, Schwabl P, et al. Impact of acute kidney injury on prognosis of patients with liver cirrhosis and ascites: A retrospective cohort study. Journal of Gastroenterology and Hepatology. 2015;**30**:1567-1565

[39] Elia C, Graupera I, Barreto R, et al. Severe acute kidney injury associated with non-steroidal antiinflammatory drugs in cirrhosis: A case-control study. Journal of Hepatology. 2015;**63**:593-600

[40] Fagundes C, Barreto R, Guevara M, et al. A modified acute kidney injury classification for diagnosis and risk stratification of impairment of kidney function in cirrhosis. Journal of Hepatology. 2013;**59**:474-481

[41] Tandon P, James MT, Abraldes JG, Karvellas CJ. Relevance of new definitions to incidence and prognosis of acute kidney injury in hospitalized patients with cirrhosis: A retrospective population-based cohort study. PLoS. 2016;**11**:1-15

[42] Runyon BA. AASLD practice guideline: Management of adult patients with ascites due to cirrhosis: Update 2012. AASLD Practice Guidelines. 2012. pp. 1-96

[43] European Association for the Study of the Liver. EASL clinical practice guidelines on the management of ascites, spontaneous bacterial peritonitis, and hepatorenal syndrome in cirrhosis. European Journal of Hepatology. 2010;**53**:397-417

[44] Wong F, O'Leary JG, Reddy KR, et al. New consensus definition of acute kidney injury accurately predicts 30-day mortality in patients with cirrhosis with infection. Gastroenterology. 2013;**145**:1280-1288

[45] Wong F. Diagnosing and treating renal disease in cirrhotic patients. Minerva Gastroenterologica e Dietologica. 2016;**62**:253-266

[46] Mandorfer M, Bota S, Schwabl P, et al. Nonselective b blockers increase risk for hepatorenal syndrome and death in patients with cirrhosis and spontaneous bacterial peritonitis. Gastroenterology. 2014;**146**:1680-1690

[47] Mandorfer M, Reiberger T. Beta blockers and cirrhosis, 2016. Digestive and Liver Disease. 2017;**49**:3-10

[48] Arabi YM, Dara SI, Memish Z, et al. Antimicrobial therapeutic determinants of outcomes from septic shock among patients with cirrhosis. Hepatology. 2012;**56**:2305-2315

[49] Jalan R, Fernandez J, Wiest R, et al. Bacterial infections in cirrhosis: A position statement based on the EASL Special Conference 2013. Journal of Hepatology. 2014;**60**: 1310-1324

[50] Bernardi M, Ricci CS, Zaccherini G. Role of human albumin in the management of complications of liver cirrhosis. Journal of Clinical and Experimental Hepatology. 2014; **4**:302-311

[51] Afinogenova Y, Tapper EB. The efficacy and safety profile of albumin administration for patients with cirrhosis at high risk of hepatorenal syndrome is dose dependent. Gastroenterology Report (Oxf). 2015;**3**:216-221

[52] Salerno F. Albumin treatment regimen for type 1 hepatorenal syndrome: A dose–response meta-analysis. BMC Gastroenterology. 2015;**15**:1-11

[53] Bernardi M, Caraceni P, Navickis RJ, Wilkes MM. Albumin infusion in patients undergoing large-volume paracentesis: A meta-analysis of randomized trials. Hepatology. 2012;**55**:1172-1181

[54] Gine's P, Tilo L, Arroyo V, et al. Randomized comparative study of therapeutic paracentesis with and without intravenous albumin in cirrhosis. Gastroenterology. 1988; **94**:1493-1502

[55] Escorsell A, Bandi JC, Moitinho E, et al. Time profile of the haemodynamic effects of terlipressin in portal hypertension. Journal of Hepatology. 1997;**26**:621-627

[56] Sola E, Lens S, Guevara M, et al. Hyponatremia in patients treated with terlipressin for severe gastrointestinal bleeding due to portal hypertension. Hepatology. 2010;**52**: 1783-1790

[57] Cavallin M, Piano S, Romano A, et al. Terlipressin given by continuous intravenous infusion versus intravenous boluses in the treatment of hepatorenal syndrome: A randomized controlled study. Hepatology. 2016;**63**:983-992

[58] Boyer TD, Sanyal AJ, Wong F, et al. Terlipressin plus albumin is more effective than albumin alone in improving renal function in patients with cirrhosis and hepatorenal syndrome type 1. Gastroenterology. 2016;**150**:1579-1589

[59] Choudhury A, Kedarisetty CK, Vashishtha C, et al. A randomized trial comparing terlipressin and noradrenaline in patients with cirrhosis and septic shock. Liver Int. 2017 Apr;**37**(4):552-561

[60] De Mattos ÂZ, De Mattos AA, Ribeiro RA. Terlipressin versus noradrenaline in the treatment of hepatorenal syndrome: Systematic review with meta-analysis and full economic evaluation. European Journal of Gastroenterology & Hepatology. 2016;**28**:345-351

[61] Alessandria C, Venon WD, Marzano A, Barletti C, Fadda M, Rizzetto M. Renal failure in cirrhotic patients: Role of terlipressin in clinical approach to hepatorenal syndrome type 2. European Journal of Gastroenterology & Hepatology. 2002;**14**:1363-1368

[62] Piano S, Tonon M, Cavallin M, et al. Reply to: 'A cut-off serum creatinine value of 1.5 mg/dl for AKI—to be or not to be'. Journal of Hepatology. 2015;**62**:744-746

[63] Rodriguez E, Pereira GH, Solá E, et al. Treatment of type 2 hepatorenal syndrome in patients awaiting transplantation: Effects on kidney function and transplantation outcomes. Liver Transplantation. 2015;**21**:1347-1354

[64] Rashad S, Emad AW, Soha SK. Hepatitis C and kidney disease: A narrative review. Journal of Advanced Research. 2017 Mar;**8**(2):113-130

[65] Satapathy SK, Lingisetty CS, Williams SE. Acute kidney dysfunction in patients with chronic hepatitis C virus infection: Analysis of viral and non-viral factors. Journal of Clinical and Experimental Hepatology. 2014;**4**(1):8-13

[66] Moreau R, Durand F, Poynard T, Duhamel C, Cervoni JP, Ichaï P, et al. Terlipressin in patients with cirrhosis and type 1 hepatorenal syndrome: A retrospective multicenter study. Gastroenterology. 2002;**122**:923-930

[67] Russ KB, Kuo YF, Singal AK. Renal function and acute kidney injury among cirhosis patients listed for liver transplantation: A prospective study. The American Journal of Gastroenterology. 2014;**109**:S173

[68] Kirk BR, Todd MS, Singhal AK. Acute kidney injury in patients with cirrhosis. Journal of Clinical and Translational Hepatology. 2015;**3**:195-204

IntechOpen