Pathogenesis, Diagnosis and Treatment of Renal Dysfunction in Cirrhosis

Rolando José Ortega Quiroz, MD,[1] Luis Gonzalo Guevara Casallas, MD,[2] Jaime Holguín Rojas, MD,[3] Adalgiza Reyes Romero, MD, MSc,[4] Jhon Edinson Prieto Ortiz, MD.[5]

1 Internal Medicine, Gastroenterology and Clinical Hepatology. Research Fellow at the August Pi i Sunier Institute of Biomedical Research at the University of Barcelona. Director of the Division of Hepatology at the Clínica General del Norte in Barranquilla, Colombia. Institute for Biomedical Research in the Faculty of Health Sciences at the University of San Buenaventura in Cartagena de Indias, Colombia. rolandoortegaquiroz@gmail.com
2 Internal Medicine, Gastroenterology and Clinical Hepatology. Director of Clinical Gastroenterology and Hepatology at the Hospital Universitario San Vicente de Paul in Medellín, Colombia
3 Internal Medicine and Clinical Hepatology. Director of the Division of Hepatology at Clínica Imbanaco in Cali, Colombia
4 Fellow in Liver Surgery and Transplantation at the Hospital Cliníc of the Universidad de Barcelona in Barcelona, Spain
5 Internal Medicine, Gastroenterology, and Clinical Hepatology. Hepatologist for Organization Sanitas, Professor at Fundación Universitaria Sanitas in Bogota, Colombia

Received: 17-07-14
Accepted: 06-04-15

Abstract

Patients with cirrhosis of the liver are susceptible to deterioration of renal function which may be functional or structural. Prerenal acute renal failure which occurs in 68% of these cases is the most common form. It includes a special type of functional renal failure known as hepatorenal syndrome (HRS). Serum creatinine remains the best biomarker for acute renal failure in cirrhosis despite its recognized limitations. Acute tubular necrosis and HRS can be differentiated by using urinary biomarkers such as urinary neutrophil gelatinase-associated lipocalin (uNGAL). Risk factors for acute renal failure in cirrhosis include bacterial infections, gastrointestinal bleeding, loss of gastrointestinal and renal fluids, paracentesis without albumin, and nephrotoxic agents. The new criteria for staging acute kidney injury (AKI) in cirrhosis have improved patient outcomes by enabling earlier interventions by starting when serum creatinine increases above 0.3 mg/dl in less than 48 hours. The diagnosis of HRS is established by excluding causes of pre-renal azotemia, acute tubular necrosis and volume expansion with albumin. The use of splanchnic vasoconstrictors such as terlipressin together with albumin can reverse up to 40% of cases of SHR. Liver transplantation is the definitive treatment for patients with hepatorenal syndrome.

Keywords

Acute renal failure, infection, hepatorenal syndrome, splanchnic vasoconstrictors, albumin.

INTRODUCTION AND OVERVIEW

Cirrhosis is the most advanced stage of chronic liver disease. It is characterized by a diffuse fibrotic process, formation of nodules and microthrombosis which together cause changes in liver architecture. It is the 5th leading cause of death in the UK, the 12th leading cause of death in the US and the sixth leading cause of mortality worldwide. Up to 40% of cases can be diagnosed in early stages when the disease is compensated and pharmacological interventions can improve life expectancy (1, 2).

Patients with cirrhosis may develop significant complications such as bleeding varices, ascites, infections, hepatic encephalopathy and hepatocellular carcinoma (3, 4). The appearance of cirrhosis affects survival and is used to define five stages of forecasts. In Stage 1 varices are absent while in Stage 2 varices have developed but the diseases is compensated. The one year mortality rate for patients with Stage 1 cirrhosis is 1% while the one year mortality rate for patients with Stage 2 cirrhosis is 3.4%. Stage 3 is characterized by the appearance of ascites and bleeding varices. Stage 4 is decompensated cirrhosis. The one year mortality rate for

patients with Stage 3 cirrhosis is 20% while the one year mortality rate for patients with Stage 4 cirrhosis is 57% (5). Stage 5 is related to bacterial infections. The one year mortality rate for this stage is 63% (6).

Renal failure, the most serious common complication of decompensated liver cirrhosis, has important implications for morbidity and mortality. During hospitalization patients with acute renal failure frequently suffer respiratory failure, cardiovascular deterioration and long stays in the ICU (7). A recent study of 5,969 patients, 1,827 of whom were suffering from renal failure and 4,142 who were not, confirms that cirrhotic patients suffering from renal failure have an overall mortality rate of 67%. Fifty-eight percent die within one month, and 63% die within 12 months (Figure 1) (8). Renal failure prior to liver transplantation is a strong independent predictor of mortality within 12 months of transplantation (9). The etiology of renal failure associated with cirrhosis may be functional and/or structural. The spectrum of structural kidney damage has been studied by histopathology using transjugular biopsies, observing glomerular abnormalities (mesangial glomerulonephritis, IgA nephropathy), non-glomerular abnormalities (acute and chronic tubulointerstitial nephritis and fibrous endarteritis) and changes related to diabetic nephropathy (10, 11). It is possible to identify a number of renal conditions associated with liver diseases that have implications for patients' clinical presentations and evolution (12, 13). The most important are mentioned in Table 1.

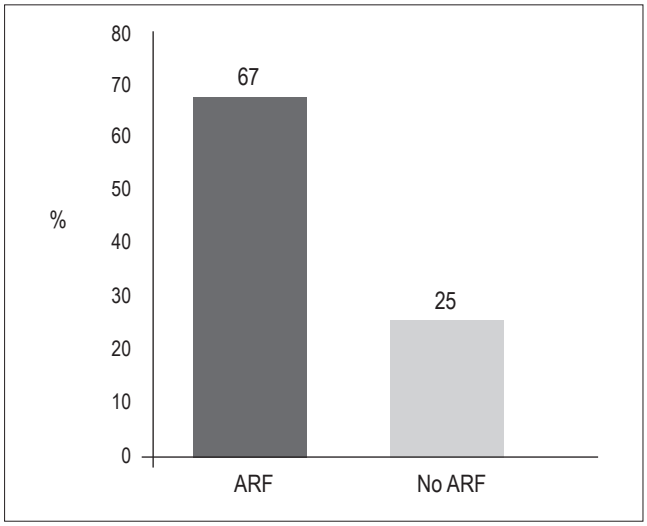

Figure 1. One-year mortality from acute renal failure (ARF) in patients with cirrhosis.

Acute renal failure may occur in up to 20% of hospitalized cirrhotic patients. The most common cause is pre-renal hypoperfusion (68% of cases). Forty-five percent of these have pre-renal azotemia and improve with volume expansion, but 23% have hepatorenal syndrome (HRS) and do not improve. Intrinsic renal failure (acute tubular necrosis and glomerulonephritis) accounts for 32% of cases and post-renal failure accounts for less than 1% (14-16).

Table 1. Renal conditions associated with liver diseases (12)

Liver Disease	Renal Condition (82% Glomerular)
Hepatitis C Hepatitis B	Membranous and Membranous Proliferative Glomerulonephritis
Alcoholic Cirrhosis	IgA nephropathy
Primary biliary cirrhosis	Tubule interstitial nephritis, chronic tubulointerstitial damage
Primary biliary cirrhosis and Wilson's disease	Renal tubular acidosis
NASH	Diabetic Glomeruloeslerosis, atherosclerosis
Hepatitis and cholestatic hepatitis	ACE ATG angiotensin

Hepatorenal syndrome (HRS) is a type of severe functional pre-renal failure which is potentially fatal. It occurs in patients with advanced cirrhosis and accounts for 23% of cases of pre-renal failure. It is characterized by rapid deterioration of renal function in the context of changes in systemic hemodynamics, vasodilation in the splanchnic vascular bed, reduced blood pressure, insufficient cardiac output, release of vasoconstrictors and renal ischemia (17, 18).

The main causes of acute renal failure in patients with cirrhosis can be seen in Table 2.

Table 2. Etiology of acute renal failure in patients with cirrhosis

Hepatorenal syndrome (splanchnic vasodilatation-cirrhotic cardiomyopathy)
Bacterial infections (SBP, urinary tract infections, pneumonia, bacteremia)
Lactulose diarrhea, vomiting
GI bleeding,
Excessive diuresis
Medications: NSAIDs, aminoglycosides, ACE inhibitors, angiotensin receptor antagonists, clonidine, Beta blockers

A recent study of 463 patients has demonstrated that the etiology of renal failure has prognostic implications in patients with cirrhosis: 46% were related to infections, 32% were related to hypovolemia, 13% were related to hepatorenal syndrome, and 9 % and were related to parenchymal nephropathy. The probability of survival at three months was 73% for patients with parenchymal renal disease, 46% for those with acute renal failure due to hypovolemia, 31% for those with acute renal failure due to infections and 15% for those patients with hepatorenal syndrome (19).

DIAGNOSIS OF ACUTE RENAL FAILURE CIRRHOSIS

Serum creatinine (SCr) is the simplest and most widely used kidney function biomarker for use in the general population. Its inclusion in the MELD score with bilirubin and INR, make creatinine an important marker for cirrhosis because it highlights the prognostic significance of interactions between liver function and kidney function. However, creatinine should be interpreted with caution because it tends to overestimate renal function in cirrhotic patients. This is related to the fact that patients with cirrhosis may have falsely decreased creatinine due to a combination of factors such as low protein intake, loss of muscle mass resulting in decreased synthesis of creatinine, a higher volume of ascites and interference with creatinine tests by high levels of bilirubin.

Equations based on creatinine for estimating the glomerular filtration rate, including the Cockcroft- Gault, MDRD and CKD-EPI equations, are unsafe measurements of cirrhosis and tend to overestimate the actual value. This could also be related to variations related to age, weight and race included in these formulas. Measuring the clearance of exogenous markers such as inulin (gold standard because inulin is filtered by the glomeruli and is not secreted, reabsorbed, metabolized or synthesized by the kidneys) requires continuous infusion and collection of urine for several hours which make this method impractical. Radio-labile substances such as Cr-EDTA, Tc-DTPA, I-iothalamate and nonradioactive substances such as iohexol and iothalamate are administered as a single dose and require no urine collection, but have not been extensively tested for measuring cirrhosis. Cystatin C is a low molecular weight protein produced at a constant rate in all nucleated cells which is eliminated entirely by glomerular filtration whereupon it is reabsorbed and catabolized by renal tubular cells. Unlike creatinine, it is not influenced by age, sex, muscle mass and bilirubin. A cut-off of 1.25 mg/dl is similar for diagnosis of AKI in cirrhotic and non-cirrhotic patients. However, the cost is higher compared to creatinine, it requires greater standardization and is influenced by infections and medications such as corticosteroids, ACE inhibitors and inhibitors of calcineurin (20, 21).

It is difficult to differentiate between acute tubular necrosis and hepatorenal syndrome (HRS) because of the lack of specificity of the classic markers of tubular damage such as urinary sodium, fractional excretion of sodium, and the presence of cylindrical and/or tubular epithelial cells. For this reason various urinary biomarkers such as kidney damage molecule (KIM-1), heart-type fatty acid binding protein (hFABP), interleukin 18 (IL-18) and neutrophil gelatinase-associated lipocalin (NGAL). The latter is a 25 kDa protein which may be expressed in various tissues whose levels increase rapidly in the urine of patients with acute renal failure. Because it is easier to preserve and store than are other biomarkers, it could be reliably incorporated into clinical practice. Please note that urinary tract infections can give false high values (22, 23).

NGAL has been assessed in studies of patients with cirrhosis for whom it has allowed differentiation between acute tubular necrosis (values greater than 400 ug/g creatinine) and hepatorenal syndrome type 1 (70-100 ug/g creatinine). Patients with type 1 Hepatorenal Syndrome and bacterial infections have higher NGAL values than do patients without infections. Patients with Hepatorenal Syndrome Type 2 (stable) and patients with pre-renal azotemia have similar values (20 ug/g creatinine) of NGAL which are well below those of the previous two groups (24). NGAL levels in the range of HRS are independent predictors of mortality (25). The incorporation of biomarkers for acute tubular necrosis into clinical practice has the potential to allow diagnosis in patients with underlying structural lesion and to provide a guide to treatment of these patients. More studies are needed in patients with hepatorenal syndrome (26).

FUNCTIONAL PATHOPHYSIOLOGY OF RENAL FAILURE IN PATIENTS WITH CIRRHOSIS

The functional nature of hepatorenal syndrome has been established by the absence of significant histological changes in renal structure, normalization or improvement of renal function after transplantation and reversibility with drug treatment. Hepatorenal syndrome in patients with cirrhosis produces a hyper-dynamic circulatory state with increased cardiac output, increased heart rate and decreased systemic vascular resistance. The main cause of the decrease in renal function leading to hepatorenal syndrome is impaired circulatory function caused by vasodilation in the splanchnic bed secondary to portal hypertension. This is related to mass production of nitric oxide (shear stress), endocannabinoids, and carbon monoxide. As cirrhosis progresses, bacterial translocation to the mesenteric lymph nodes causes an inflammatory response with release of cytokines favoring splanchnic and systemic vasodilation (27-29).

In early stages of cirrhosis, when portal hypertension is moderate, an increase in cardiac output compensates for the decrease in systemic vascular resistance. This allows blood pressure and the effective circulating volume to remain within normal limits. As cirrhosis progresses, splanchnic vasodilatation notably increases in response to increased bacterial translocation with massive release of vasodilator substances, neoangiogenesis in the mesenteric arteries, and decreased response to vasoconstrictors (30, 31). This causes a severe decrease in effective circulating volume that cannot be compensated by an increase in cardiac output.

This may be further diminished by reduced contractile response to stress, a phenomenon known as cirrhotic cardiomyopathy (32). At this stage, blood pressure stimulates baroreceptors which activate neurohormonal vasoconstriction systems. The renin angiotensin aldosterone system, the sympathetic nervous system and non-osmotic hypersecretion of ADH maintain blood pressure but have deleterious effects on renal function. These include sodium retention which results in ascites and edema, retention of free water which causes hypervolemic hyponatremia, and vasoconstriction of the renal circulation which reduces blood flow and glomerular filtration rate and leads to kidney failure. In response to renal vasoconstriction, intra-renal vasodilators such as adenosine, kallikreins and prostaglandins are initially released. They make these patients highly sensitive to NSAIDs. Subsequently, sustained renal hypoperfusion leads to intrarenal release of vasoconstrictors such as thromboxane A2, leukotrienes, F2-isoprostanes and endothelin-1 which perpetuate kidney damage. Other extrarenal tissues including the liver, the brain and the adrenal system remain vasoconstricted which leads to increased portal pressure, encephalopathy and adrenal insufficiency (33, 34).

Cirrhotic patients with first hit spontaneous circulatory dysfunction manifested by effective hypovolemia, increased vasoconstrictor system activity and systemic inflammatory response are more susceptible to acute tubular necrosis and hepatorenal syndrome associated with triggers (second shots) such as bacterial infections, gastrointestinal bleeding, hypovolemia (gastrointestinal losses from diarrhea or kidney losses due to excessive diuresis), paracentesis greater than five liters without albumin replacement, alcoholic hepatitis and nephrotoxic agents (Figure 2) (35-37).

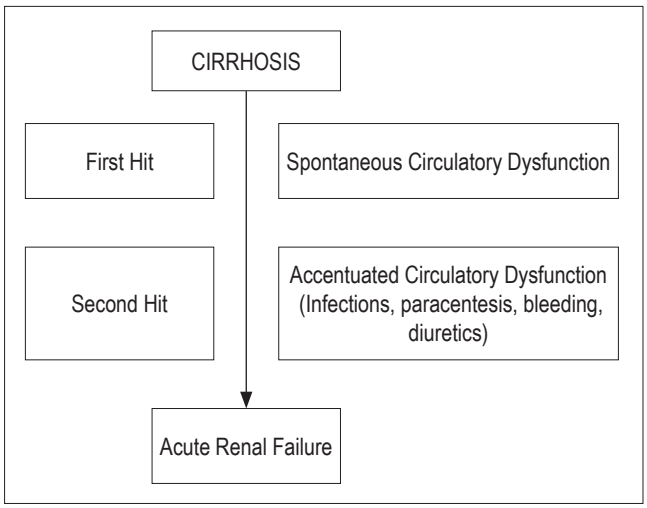

Figure 2. Two hit mechanism in acute renal failure in patients with cirrhosis

Studies have shown that infections in cirrhotic patients may cause a high incidence of acute renal failure (up to 30%) with a mortality rate between 23% and 67% (38-41). Alcoholic hepatitis can cause kidney failure in 28% of cases with a mortality rate of 56% (Table 3) (42).

NEW DEFINITIONS OF ACUTE RENAL FAILURE IN PATIENTS WITH CIRRHOSIS

The definition of acute renal failure in patients with cirrhosis by a static cut-off point of 1.5 mg/dl is probably not the most appropriate because it is related to a severe deterioration of glomerular filtration rate (<30 mL/min). Also, it does not take into account dynamic changes in creatinine that occur in the previous days and weeks that might be necessary to differentiate between acute renal failure and chronic renal failure which is necessary for effective therapy (43-45).

Recently a group of experts has proposed that acute renal failure in patients with cirrhosis should be defined by a combination of the criteria of the Acute Kidney Injury Network (AKIN) criteria and the Risk, Injury, Failure, Loss, End-stage kidney disease (RIFLE) criteria and the Acute Dialysis Quality Initiative (ADQI) working group criteria (ADQI) (46-48). This has resulted in the AKI-IAC (Acute Kidney Injury AKI and IAC International Ascites Club) criteria which has recently been published (49, 50). It uses parts of the AKIN criteria including serum creatinine over 0.3 mg/dl within 48 hours or over 50% of baseline, and then adds parts of the ADQI criteria including serum creatinine over 50% within a week. The main difference with the other criteria is abandonment of creatinine levels over 1.5 mg/dl for the diagnosis of acute renal failure (33). In addition, it has been proposed that a system of staging (stages 1, 2 and 3) be implemented on the basis of changes of creatinine levels over time. One week is arbitrarily set as the assessment time for progression or regression of the stages. It was decided to eliminate the definition based on decreased urine output because cirrhotic patients with ascites often have oliguria and high levels of sodium retention but with normal GFR. Their urinary volume may actually increase as the result of the use of diuretics (Table 4) (49, 50).

A slight increase in creatinine to over 0.3 mg/dl within 48 hours can cause a significant increase in mortality. Various recent studies have shown that the AKI-IAC criteria for patients with cirrhosis is a good predictor of hospital mortality. Patients with acute renal failure (AKI) within these criteria have a mortality rate of 52.7% vs. 29.9% in those without acute renal failure (51). The mortality rate increases as the AKI-IAC stage increases from Stage 1 to Stage 3.

Table 3. Incidence of acute renal failure associated with infections and mortality rates

Author	Cause	n.º	Incidence %	Mortality %	Controls %	P value
Tandon (38)	PBE	2381	30	67	11	0,001
Hung (39)	PBE	2592	12	44	18	0,001
Pereira (40)	Skin	92	22	23	4	0,001
Guevara (41)	No PBE	223	27	65	19	0,001
Altamirano (42)	Hepatitis alcoholic	103	28	56	7	0,001

Table 4. New definitions for the diagnosis and management of AKI in patients with cirrhosis (AKI-IAC) (49, 50)

Terminology	Definition		
Baseline Serum Creatinine (BSC)	BSC value obtained in the previous 3 months, when available, can be used as the baseline BSC. In patients with more than one value in the previous 3 months, the measurement closest to hospital admission should be used. In patients without BSC, the admission result can be used as basal BSC.		
Acute Kidney Injury AKI	BSC> 0.3 mg/dl within 48 hours or an increase of 50% of known or presumed BSCl within the previous 7 days.		
Stages of AKI	*Stage 1:* BSC> 0.3 mg/dl or an increase of 1.5 to 2 times baseline. *Stage 2:* BSC> 2 to 3 times baseline. *Stage 3:* BSC> 3 times baseline or BSC> 4 mg/dl with an increase> 0.3 mg/dl, or start of renal replacement therapy (RRT)		
Progression of AKI	**Progression** Progression to a higher stage or start of RRT		**Regression** Regression to a lower stage
Response to Treatment	**No response** No Progression of AKI	**Partial Response** Regression to Previous Stage and reduction of SCr ≥0.3 mg/dl above baseline	**Complete Response** Return of SCr to a value within 0.3 mg/dl of baseline

Stage 1 patients who do not have renal failure have mortality rates between 3.8% and 13.5%. The mortality rate of Stage 2 patients is 37.8%, and the mortality rate of Stage 3 patients 43.2% (52). Patients with cirrhosis and acute irreversible renal failure have 30 day mortality rates that are 10 times higher than those of cirrhotic patients without renal failure. These patients also have greater higher requirements for ICUs and mechanical ventilation and longer hospital stays (53). Patients who develop acute renal failure during hospitalization have a higher mortality than those admitted with renal failure, and mortality rates are higher for those whose AKI-IAC stage increases during hospitalization (54). Even small increases in creatinine levels that are below 1.5 mg could have potentially deleterious effects on patients with decompensated cirrhosis (55).

Even though small increases in the SCr level can be sued to make an early diagnosis of acute renal failure (AKI) in patients with cirrhosis, it has not been clearly shown to improve predictions of mortality in these patients relative to the current cut-off point of 1.5 mg/dl nor to be a good indicator for early pharmacological interventions. At least two studies of patients with cirrhosis and serum creatinine levels below 1.5 mg/dl have published lower mortality rates for these patients than for those whose SCr levels are higher (56, 57). Based on this, patients with AKI Stage 1 can be divided into two groups. Stage 1-A consists of those patients who reach a peak creatinine of less than 1.5 mg/dl, who have a short-term mortality rate similar to patients without AKI, and who frequently regress to a lower stage. Stage 1-B consists of those patients whose peak SCr is over 1.5 mg/dl and whose short-term mortality is higher than that of patients without AKI (49, 50). Because small increases in creatinine can be potentially deleterious for the prognosis of patients with decompensated cirrhosis, it is possible that in the near future further studies should be done to decide whether or not the current definition of Type 1 hepatorenal syndrome should be modified to reducing the indication for starting treatment with vasoconstrictors and albumin below the currently recommended 2.5 mg/dl (58-60).

NEW DEFINITION OF HEPATORENAL SYNDROME (HRS)

A study from the 1990s showed that the incidence of hepatorenal syndrome in patients with advanced cirrhosis varied from 18% at one year to 39% at 5 years (17). A more recent study of 263 patients in Spain has shown a proba-

bility of developing functional renal failure of 23.6% at 12 months with a 50% mortality rate (61). Another series that included 253 patients in Italy showed a prevalence of hepatorenal syndrome of 45.8% (30% type 1 and 15.8% type 2) with a three month mortality rate of 80% (62).

The definition of hepatorenal syndrome and diagnostic criteria were established in 1996 based on three concepts (63):

1. Functional renal failure caused by marked intrarenal arteriolar vasoconstriction.
2. Systemic circulatory dysfunction caused by an extrarenal vasodilation.
3. Plasma volume expansion does not improve renal failure.

In 2007, four new concepts were added (64):

1. Extra-renal vasodilation occurs primarily in the splanchnic circulation while other tissues remain vasoconstricted.
2. Cardiac output may be low, normal or high but is insufficient for the needs of the patient in relation to decreased peripheral vascular resistance.
3. Bacterial infections, primarily spontaneous bacterial peritonitis, are the principal triggers.
4. Medical treatment restores renal functioning and is associated with improved survival.

The diagnostic criteria for HRS have been redefined on the basis of the new definitions of acute renal failure (AKI) presented by the AKI-IAC. HRS type 1, previously defined by a creatinine increase of 100% in two weeks with a final value over 2.5 mg/dl is now defined as AKI Stage 2 or 3. HRS type 2, defined previously by stable creatinine over 1.5 mg/dl over the course of months is now defined as a form of chronic renal impairment in cirrhotic patients characterized by a glomerular filtration rate of less than 60 ml/min for more than 3 months (46). These new definitions affect the type of therapeutic intervention indicated for patients. Baseline creatinine stands out as a very important issue. We recommend using the nearest measurement within 7 days prior to admission. If this is not available, we recommend using the most recent last measurement within the 3 months prior to admission. A community-acquired AKI can be diagnosed if creatinine has increased 50% over the last value available. In patients with creatinine levels over 1.5 mg/dl at admission, the presence of an identifiable risk factor such as bacterial infection must be assumed, and it must be assumed that it is case of AKI (49, 50). The revised criteria for HRS can be seen in Table 5.

Table 5. New Hepatorenal syndrome diagnostic criteria (49, 50)

1. Diagnosis of cirrhosis and ascites
2. Diagnosis of acute renal failure (AKI) according to the AKI-IAC criteria
3. No response after 2 days. Suspend diuretics, plasma expansion with 1g/k/day Albumin
4. No shock
5. No current or recent treatment with nephrotoxic agents. (NSAIDs, aminoglycosides, iodinated contrast)
6. Absence of parenchymal renal disease (proteinuria> 500 mg/24 hours, microhematuria> 50 GR per field, abnormal renal ultrasound)

GENERAL ASSESSMENT AND ACTION

Once the Stage 1 AKI-IAC diagnosis of acute renal failure (AKI) is made on the basis of creatinine over 0.3 mg in less than 48 hours, treatment depends on identification of possible causes. A detailed medical history is needed to assess precipitating factors such as infections, gastrointestinal bleeding, hypovolemia due to volume loss, and exposure to nephrotoxic agents. Here are some important recommendations to follow:

Stage 1 AKI-IAC: (SCr> 0.3 mg/dl or an increase of more than 1.5 to 2 times the baseline)

1. Stop all medications that:
   - Cause loss of volume (lactulose, diuretics)
   - Cause vasodilation (ACE inhibitors, angiotensin receptor antagonist, clonidine)
   - Relate to renal vasoconstriction (NSAIDs)
   - Relate to nephrotoxicity (aminoglycosides, iodinated contrast)
2. Establish whether there are any infections through blood and urine cultures, chest x-ray, paracentesis with neutrophil count and cultivation of ascites in blood culture.
3. When hypovolemia is suspected, volume expansion with crystalloids or colloids should be initiated. Packed red blood cells should be used if there is gastrointestinal bleeding.

Stage 2 and 3 of AKI-IAC: (SCr> 2-3 times the baseline)

1. Plasma volume expansion with albumin 1g/k day to a maximum of 100 g for two days should be initiated in patients who do not respond to previous measures. Diuretics should be discontinued if they have not already been discontinued. Patients who do not respond require differential diagnosis between intrinsic acute renal failure post renal AKI.
2. When acute tubular necrosis due to septic or hypovolemic shock is suspected, or when there is evidence of exposure to nephrotoxins, early initiation of renal replacement therapy should be evaluated.
3. When patients without evidence of shock do not respond to general measures and volume expansion with albumin, urinary biomarkers of tubular damage such as NGAL should be evaluated to differentiate among

acute tubular necrosis (high values), pre-renal azotemia (low values) and hepatorenal syndrome (intermediate values) (35, 37, 49, 50, 65).

PREVENTION OF HEPATORENAL SYNDROME

Because of the severity of hepatorenal syndrome it high rate of mortality, preventing its occurrence is a priority in patients with cirrhosis. At least six scenarios favor the following interventions (33-36, 63):

1. The risk of hepatorenal syndrome reaches 30% in patients with spontaneous bacterial peritonitis. Administration of 1.5 g/kg on the first day and 1 g/kg on the third day decreases mortality from this complication by 10% to 30%. It is mainly recommended for patients with creatinine> 1.0 mg/dl, BUN> 30 mg/dl and bilirubin> 4 mg/dl.
2. For patients with cirrhosis and ascites whose protein concentration is less than 1.5 g, who have advanced cirrhosis with a Child score of over ten, bilirubin> 3 mg/dl, renal dysfunction with creatinine> 1.2 mg/dl and sodium <130 mEe/l, the use of 400 mg oral norfloxacin daily until transplantation, decreases hepatorenal syndrome from 41% to 28%.
3. For patients with alcoholic hepatitis, 400 mg/8 hours of pentoxifylline for 28 days decreases hepatorenal syndrome from 35% to 8%.
4. Total paracentesis over 5 liters with 8 g/liter albumin expansion reduces the risk of circulatory dysfunction from 72% to 17% and also reduces the risk of acute renal failure.
5. The use of antibiotics for 7 days in patients with bleeding gastrointestinal varices reduces the risk of mortality from 24% to 15% and reduces the risk of rebleeding and acute renal failure.
6. It has recently been shown that the use of beta blockers in patients with cirrhosis and spontaneous bacterial peritonitis increases the risk of hepatorenal syndrome from 11% to 24% and decreases survival without transplantation. For this reason it is recommended that these drugs be discontinued in these patients and in patients with refractory ascites (66).

TREATMENT OF HEPATORENAL SYNDROME

Large-Volume Paracentesis

Total paracentesis (full mobilization of ascites) is a fast, safe and effective treatment for refractory ascites which is a common manifestation of hepatorenal syndrome treatment. Up to 70% of patients may have a circulatory dysfunction that results in exacerbation of splanchnic vasodilation. When more than 5 liters of ascitic fluid is removed, hypotension can be easily prevented by simultaneous administration of intravenous albumin (67).

The use of TIPS (Transjugular intrahepatic portosystemic shunts) has been evaluated in six randomized controlled trials that compared TIPS with paracentesis. The trials concluded that TIPS facilitates control of ascites, reduces the risk of hepatorenal syndrome and improves survival without transplantation. However, there is a risk of severe encephalopathy so further studies are required to assess the real benefit of TIPS in daily practice (68, 69).

Recently, an automated low-flow pump system has been added to the therapeutic armory for fighting refractory ascites. It consists of an intra-peritoneal catheter connected to a subcutaneous power source connected to a second catheter which drains into the bladder. Literally, patients urinate the ascites out of their bodies. The system uses a set of sensors that prevents abdominal pressure drops and/or increases in intravesical pressure. A significant proportion of patients need repeated interventions for complications including bacterial colonization, bacteremia, plastic peritonitis and death. The prosthesis must be removed prior to transplantation because it may cause complications (70).

Vasoconstrictors and albumin

The use of vasoconstrictors represents a paradox in the treatment of patients with severe renal vasoconstriction. The reason is its effect on the state of splanchnic circulation. It effectively reverses hypovolemia associated with decreased effective circulating volume secondary to marked vasodilation. By doing so, vasoconstrictors inactivate neurohormonal systems and cause renal vasoconstriction with improved plasma flow and glomerular filtration (71).

Terlipressin is a vasopressin agonist (triglycyl-lysine vasopressin) with vasoconstrictor activity on V1 receptors in the splanchnic bed (72, 73). Use in patients with hepatorenal syndrome has proven effective in 40% to 60% of uncontrolled studies using different criteria including the criterion of SCr increases of over 100% in 2 weeks and the criterion of a larger final value of 2.5 mg/dl (74). The benefits have been confirmed in two randomized, controlled trials which managed to reverse HRS in 40% of the patients. They achieved a complete response with creatinine decreased to less than 1.5 mg/dl in an average of 7 days. Improved survival was observed by respondents with no serious adverse effects (75, 76). The predictors of response were creatinine levels before treatment lower than 5 mg/dl, baseline bilirubin less than 10 mg/dl, and mean arterial blood pressure increased by 5 mmHg in the first 72 hours (77-80).

Recurrence occurs in up to 15% of patients but can be treated with a new course of terlipressin. Three meta-analyses of controlled studies have shown that the combination of terlipressin and albumin is able to reverse hepatorenal syndrome with improved short-term survival (81-83). The European guidelines recommend the use of terlipressin associated with albumin as first-line treatment in patients with hepatorenal syndrome (84). With the addition of albumin to terlipressin, response increases threefold compared over the response to terlipressin alone (85). This can be explained by the effects of volume expansion (oncotic pressure increases), the antioxidant's action and anti-inflammatory albumin that can help improve endothelial dysfunction (86). In patients with hepatorenal syndrome associated with infections, antibiotic treatment does not reverse 67% of cases and is associated with high mortality (87). Early use of the combination of terlipressin and albumin is associated with marked improvement in blood pressure and suppression of vasoconstrictor systems in 67% of patients and has a good safety profile (88).

Terlipressin has not been approved by the FDA in the United States, so the therapy of choice there is the combination of dose 7.5 to 12.5 mg every 8 hours of midodrine (an alpha adrenergic agonist) with 100-200 ug subcutaneous octreotide (a somatostatin agonist) every 8 hours plus albumin (31). A recent multicenter study comparing the terlipressin and albumin combination with the midodrine, octreotide and albumin combination has demonstrated greater efficacy of the terlipressin based combination for recovery of renal function (70.4% vs. 28.6%) with improvement in survival related to the reversal of renal failure and low baseline MELD (89).

Norepinephrine is an adrenergic agonist that has proven useful for treatment in type 1 hepatorenal syndrome. After an initial pilot study in which 83% of patients responded, three studies with small numbers of patients compared norepinephrine with terlipressin and found responses ranging from 40% to 50% (90-93). Table 6 shows recommendations on the use of vasoconstrictors and albumin in patients with hepatorenal syndrome. Considering that the higher the SCr level, the poorer is the response, the possibility of initiation of treatment with vasoconstrictors and albumin at SCr levels lower than 2.5 mg/dl still needs to be evaluated in further studies. According to the new criteria proposed by the AKI-IAC, when a patient is diagnosed as AKI Stage 2 or Stage 3, or when a patient progresses to one of these stages, and if HRS continues despite initial therapeutic measures, a combination of vasoconstrictor and albumin should be started independent of the final level of SCr (49, 50).

Table 6. Use of vasoconstrictors in HRS

Vasoconstrictors
1. Terlipressin: 1 mg/4-6 h IV. After 3 days, the dose is increased up to 2 mg every 4-6 hours if there is a decrease in creatinine> 25% of pretreatment values. Complete response is indicated by a return of creatinine to within 0.3 mg/dl of baseline and to below 1.5 mg/dl. The treatment is maintained for five to fifteen days. Baseline creatinine <5 mg/dl, bilirubin <10 mg/dl and increased mean arterial pressure (MAP)> 5 mm Hg on the third day are predictors of response. Terlipressin is suspended if creatinine does not decrease more than 50% by the seventh day after start.
2. Norepinephrine: 0.5-3 mg/h continuous infusion, MAP> 10 mmHg.
Albúmina
Administration concomitant with vasoconstrictor (1g/k/day, followed by 20-40 g/k/day according to blood volume).

Non-pharmacological treatment

The use of TIPS has been evaluated by at least six studies with a small number of patients. Reversal of HRS reached 50% with short-term improvement in survival. The combination of TIPS with a vasoconstrictor improves kidney function and eventually normalizes creatinine after several months. However, advanced disease prevents the use of TIPS in a large percentage of patients (94). The use of albumin dialysis (MARS and Prometheus) has been tested in a small number of patients with hepatorenal syndrome without results in terms of patient survival that would allow widespread use in clinical practice except for in patients with MELD scores over thirty (95). Renal replacement therapy is indicated only if no response is achieved with a vasoconstrictor combined with albumin for patients on the transplant list and for cases in which there is volume overload, metabolic acidosis and hyperkalemia. Renal replacement therapy for more than 8 weeks is an indication for combined liver-kidney transplant (31, 33, 34, 69).

Transplantation

Liver transplantation is the definitive choice for the treatment of patients with hepatorenal syndrome since it resolves liver disease and reverses functional renal failure (17, 33, 44). Pretransplant renal dysfunction may be associated with decreased survival after transplantation (96). Transplant patients with hepatorenal syndrome have a marked survival benefit. It is unclear whether the combination of vasoconstrictors with albumin affects post-transplantation survival, but terlipressin administered to improve kidney function delays the need for renal replacement therapy, improves survival in transplant candidates, and helps these patients

achieve a transplant (97-99). Reversing hepatorenal may have the paradoxical effect that patients' lower MELD scores delay transplantation. The recommendation should be to maintain the MELD score from prior to drug treatment and prioritize transplantation considering the specific impact of HRS on three-month mortality rates (100).

CONCLUSIONS AND RECOMMENDATIONS

Acute renal failure (AKI) in cirrhotic patients has serious implications for clinical outcomes and mortality. The new AKI-IAC criteria for acute renal failure in patients with cirrhosis who have creatinine> 0.3 mg/dl within 48 hours should be followed. If they are, it will result in early initiation of interventions to rule out infections, evaluate loss of blood volume, change doses of diuretics and nephrotoxic drugs and begin removing volume expansion. If no response is obtained, the criteria should be applied to assess the presence of hepatorenal syndrome, including expansion with albumin for two days, ruling out organic pathologies, and depending on the patient's development, diagnosis and treatment of Stage 2 or Stage 3 of the AKI-IAC stages which involves initiation of a combination of vasoconstrictors and albumin independent of the final value of the SCr. It is possible that the level of 2.5 mg/dl required for confirmation of a diagnosis of more severe stages of hepatorenal syndrome should be modified since this would allow starting treatment earlier and provide greater chances for reversal of renal failure. Throughout the evaluation, whether there is a structural component such as acute tubular necrosis should be investigated using biomarkers such as NGAL. Finally, acute renal failure in cirrhotic patients often represent a catastrophic event, so it is important to manage it in coordination with transplant centers.

REFERENCES

1. Tsochatzis E, Bosch J, Burroughs A. Liver cirrhosis. Lancet. 2014;383:1749-61.
2. Tsochatzis E, Bosch J, Burroughs A. Prolonging survival in patients with cirrhosis: Old drugs with new indications. Gastroenterology. 2010;139:1813-15.
3. Liou I. Management of end-stage liver disease. Med Clin N Am. 2014;98:119-52.
4. Bruix J, Gores G, Mazzaferro V. Hepatocellular carcinoma: clinical frontiers and perspectives. Gut. 2014;63:844-55.
5. Garcia-Tsao G, Friedman S, Iredale J, Pinzani M. Now there are many (stages) where before was one: In search of a pathophysiological classification of cirrhosis. Hepatology. 2010;51:1445-9.
6. Arvaniti V, D´Amico G, Fede G, Monousou P, Tsochatzis E, Pleguezuelo M, et al. Infections in patients with cirrhosis increase mortality four-fold and should be used in determining prognosis. Gastroenterology. 2010;139:1246-56.
7. Du Cheyron D, Bouchet B, Patienti J, Ramakers M, Charbonneau P. The attributable mortality of acute renal failure in critically ill patients with liver cirrhosis. Intensive Care Med. 2005;31:1693-9.
8. Fede G, D´Amico G, Arvaniti V, Tsochatzis E, Germani G, Georgiadi D, et al. Renal failure and cirrhosis: A systematic review of mortality and prognosis. J Hepatol. 2012;56:810-8.
9. Weismuller T, Prokein J, Becker T, Barg-Hock H, Klempnauer J, Manns M, et al. Prediction of survival after liver transplantation by pre-transplant parameters. Scand J Gastroenterol. 2008;43:736-46.
10. Galmus Y, Conti F, Cluzel P, Hill G, Antoine C, Scatton O, et al. Prospective assessment of renal histopathological lesions in patients with end-stage liver disease: Effects on long term renal function after liver transplant. J Hepatol. 2012;57:572-6.
11. Trawale JM, Paradis V, Rautou JM, Francoz C, Escolano S, Sallee M, et al. The spectrum of renal lesions in patients with cirrhosis: a clinicopathological study. Liver Internat. 2009;30:725-32.
12. Wong F. Renal diseases and the liver. Clin Liver Dis. 2011;15:39-53.
13. Hartleb M, Gutkowski K. Kidney in chronic liver disease. World J Gastroenterol. 2012;18:3035-49.
14. Garcia-Tsao G, Parikh Ch, Viola A. Acute kidney injury in cirrhosis. Hepatology. 2008;48:1-14.
15. Angeli P, Merkel C. Pathogenesis and management of hepatorenal syndrome in patients with cirrhosis. J Hepatol. 2008;48:S93-S103.
16. Cárdenas A, Ginés P. A patient with cirrhosis and increasing creatinine level: what is it and what to do? Clin Gastroenterol Hepatol. 2009;7:1287-91.
17. Guevara M, Arroyo V. Hepatorenal syndrome. Expert Opin Pharmacother. 2011;12:1405-17.
18. Kopacova M. Hepatorenal syndrome. World J Gastroenterol. 2012;18:4978-84.
19. Martin-Llahi M, Guevara M, Torre A, Fagundes C, Restuccia T, Gilabert R, et al. Prognostic importance of the cause of renal failure in patients with cirrhosis. Gastroenterology. 2011;140:488-96.
20. Francoz C, Glotz D, Moreau R, Durand F. The evaluation of renal function and disease in patients with cirrhosis. J Hepatol. 2010;52:605-13.
21. Cholongitas E, Shusang V, Marelli L, Nair D, Thomas M, Patch D, et al. Review article. Renal function assessment in cirrhosis difficulties and alternative measurements. Aliment Pharmacol Ther. 2007;26:969-78.
22. Carter J, Lamb E. Evaluating new biomarkers for acute kidney injury: putting the horse before the cart. Am J Kidney Dis. 2014;63:543-6.
23. Qasem A, Farag S, Hamed E, Emara M, Bihery A, Pasha H. Urinary biomarkers of acute kidney injury in patients with liver cirrhosis. Nephrology. 2014;11:1-7.
24. 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;57:267-73.

25. Verna E, Brown R, Farrand E, Pichardo E, Forster C, Sola-del valle D, et al. Urinary neutrophil gelatinase-associated lipocalin predicts mortality and identifies acute kidney injury in cirrhosis. Dig Dis Sci. 2012;57:2362-70.
26. Belcher J, Sanyal A, Peixoto A, Parazella M, Lim J, Thiessen-Philbrook H, et al. Kidney biomarkers and differential diagnosis of patients with cirrhosis and acute kidney injury. Hepatology. 2014;60:622-32.
27. Guevara M, Ortega R, Ginés P, Rodes J. Pathogenesis of renal vasoconstriction in cirrhosis. En: Ginés P, Arroyo V, Rodes J, Schrier R. Ascites and renal dysfunction in liver disease. 2nd edition. Massachussets: Blackwell Publishing; 2005. p. 329-40.
28. Cárdenas A, Ortega R, Ginés P. The hepatocirculatory syndrome in cirrhosis. En: Arroyo V, Bosch J, Bruix J. Therapy in hepatology. Barcelona: Ars Medica; 2001. p. 33-42.
29. Bolognesi M, Di Pascoli M, Verardo A, Gatta A. Splanchnic vasodilation and hyperdynamic circulatory syndrome in cirrhosis. World J Gastroenterol. 2014;20:2555-63.
30. Wadei H. Hepatorenal syndrome: A critical update. Semin Resp Crit Care Med. 2012;33:55-69.
31. Wong F. Recent advances in our understanding of hepatorenal syndrome. Nat Rev Gastroenterol Hepatol. 2012;9:382-91.
32. Wiese S, Hove J, Brendtsen F, Moller S. Cirrhotic cardiomiopathy: pathogenesis and clinical relevance. Nat Rev Gastroenterol Hepatol. 2014;11:177-86.
33. Ginés P, Schrier R. Renal failure in cirrhosis. N Eng J Med. 2009;361:1279-90.
34. Fagundes C, Ginés P. Hepatorenal syndrome: A severe, but tratable, cause of kidney failure in cirrhosis. Am J kidney Dis. 2012;59:874-85.
35. Laithead J, Hayes P, Ferguson J. Review article: Advances in the management of patients with cirrhosis and portal hypertension-related renal dysfunction. Aliment Pharmacol Ther. 2014;39:699-711.
36. Arroyo V, Fernández J. Management of hepatorenal syndrome in patients with cirrhosis. Nat Rev Nephrol. 2011;7:517-26.
37. Moller S, Krag A, Bendtsen F. Kidney injury in cirrhosis: pathophysiological and therapeutic aspects of hepatorenal syndrome. Liver Internat. 2014;34:1153-63.
38. Tandon P, Garcia-Tsao G. Renal dysfunction is the most important independent predictor of mortality in cirrhotic patients with spontaneous bacterial peritonitis. Clin Gastroenterol Hepatol. 2011;9:260-5.
39. Hung TS, Tsai Ah, Hsieh Y, Tsai Ch, Tseng Ch, Tsai J. Effect of renal impairment on mortality of patients with cirrhosis and spontaneous bacterial peritonitis. Clin Gastroenterol Hepatol. 2012;10:677-81.
40. Pereira G, Guevara M, Fagundes C, Sola E, Rodríguez E, Fernández J, et al. Renal failure and hiponatremia in patients with cirrhosis and skin and soft tissue infections. A retrospective study. J Hepatol. 2012;56:1040-6.
41. Guevara M, Terra C, Nazar A, Sola E, Fernández J, Pavesi M, et al. Albumin for bacterial infections other tan spontaneous bacterial peritonitis. A randomized controlled study. J Hepatol. 2012;57:759-65.
42. Altamirano J, Fagundes C, Dominguez M, Garcia E, Michelena J, Cárdenas A, et al. Acute kidney injury is an early predictor of mortality for patients with alcoholic hepatitis. Clin Gastroenterol Hepatol. 2012;10:65-71.
43. Bellomo R, Kellum J, Ronco C. Acute kidney injury. Lancet. 2012;380:756-66.
44. Lomeire N, Bagga A, Cruz D, Maeseneer J, Endre Z, Kellum J, et al. Acute kidney injury: An increasing global concern. Lancet. 2013;382:170-9.
45. Belcher J, Parikh C, Garcia-Tsao G. Acute kidney injury in patients with cirrhosis: perils and promise. Clin Gastroenterol Hepatol. 2011;11:1550-8.
46. Wong F, Nadim M, Kellum J, Salerno F, Bellomo R, Gerbes A, et al. Working party proposal for revised classification system of renal dysfunction in patients with cirrhosis. Gut. 2011;60:702-9.
47. Mucino-Bermejo J, Carrillo-Esper R, Uribe M, Mendez-Sanchez N. Acute kidney injury in critically ill cirrhotic patients: a review. Ann Hepatol. 2012;11:301-10.
48. Mindiklogu A, Weir M. Current concepts in the diagnosis and classifications of renal dysfunction in cirrhosis. Am J Neprhol. 2013;38:345-54.
49. Angeli P, Gines P, Wong F, Bernardi M, Boyer T, Gerbes A, et al. Diagnosis and management of acute kidney injury in cirrhosis: revised recommendations of the international ascites club. Gut. 2015;64:531-7.
50. Angeli P, Gines P, Wong F, Bernardi M, Boyer T, Gerbes A, et al. Diagnosis and management of acute kidney injury in cirrhosis: revised recommendations of the international ascites club. J Hepatol. 2015;62:968-74.
51. Ribeiro de Carvalho J, Villela-Nogueira C, Luiz R, Guzzo P, Silva Rosa J, Rocha E, et al. Acute kidney injury network criteria as a predictor of hospital mortality in cirrhotic patients with ascites. J Clin Gastroenterol. 2012;46:21-6.
52. Scott R, Austin A, Kolhe N, McIntyre C, Selby N. Acute kidney injury is independently associated with death in patients with cirrhosis. Frontine Gastroenterol. 2013;4:191-7.
53. Wong F, O´Leary J, Reddy K, Patton H, Kamath P, Fallon M, et al. New consensus definition of acute kidney injury accurately predicts 30-day mortality in patients with cirrhosis and infection. Gastroenterology. 2013;145:1280-8.
54. Belcher J, Garcia-Tsao G, Sanyal A, Bhogal H, Lim J, Ansari N, et al. Association of AKI with mortality and complications in hospitalized patients with cirrhosis. Hepatology. 2013;57:753-62.
55. Tsien C, Rabie R, Wong F. Acute kidney injury in decompensated cirrhosis. Gut. 2013;62:131-7.
56. Fagundes C, Barreto R, Guevara M, Garcia E, Sola E, Rodriguez E, et al. A modified acute kidney injury classification for diagnosis and risk stratification of impairment of kidney function in cirrhosis. J Hepatol. 2013;59:474-81.
57. Piano S, Rosi S, Maresio G, Fasolato S, Cavalin M, Romano A, et al. Evaluation of the acute kidney injury network criteria in hospitalized patients with cirrhosis and ascites. J Hepatol. 2013;59:482-9.
58. Arroyo V. Acute kidney injury in cirrhosis: should we change current definitions and diagnostic criteria of renal failure in cirrhosis? J Hepatol. 2013;59:415-7.

59. Schrier R, Shchekochikhin D, Gines P. Renal failure in cirrhosis: Prerenal azotemia, hepatorenal syndrome and acute tubular necrosis. Nephrol Dial Transplant. 2012;27:2625-8.
60. Moore K. Acute injury in cirrhosis: a changing spectrum. Hepatology. 2013;57:435-7.
61. Montoliu S, Balleste B, Planas R, Álvarez M, Rivera M, Miquel M, et al. Incidence and prognosis of different types of functional renal failure in cirrhotic patients with ascites. Clin Gastroenterol Hepatol. 2010;8:616-22.
62. Salerno F, Cazzaniga M, Merli M, Spinzi G, Saibeni S, Salmi A, et al. Diagnosis, treatment and survival of patients with hepatorenal syndrome: A survey on daily medical practice. J Hepatol. 2011;55:1241-8.
63. Ginés P, Guevara M, Arroyo V, Rodes J. Hepatorenal syndrome. Lancet. 2003;362:1819-27.
64. Salerno F, Gerbes A, Ginés P, Wong F, Arroyo V. Diagnosis, prevention and treatment of hepatorenal syndrome in cirrhosis. Gut. 2007;56:1310-8.
65. Ming Ming Loo N, Fernandez Souza F, Garcia-Tsao G. Non-hemorrhagic acute complications associated with cirrhosis and portal hypertension. Best Pract Res Clin Gastroenterol. 2013;27:665-78.
66. Mandorfer M, Bota S, Schwabl P, Bucsics T, Pfiester N, Kuzik M, et al. Non selective B blockers increase risk for hepatorenal syndrome and death in patients with cirrhosis and spontaneous bacterial peritonitis. Gastroenterology. 2014;146:1680-90.
67. Bernardi M, Caraceni P, Navickis R, Wilkes M. Albumin infusion in patients undergoing large volume paracentesis: A meta-analysis of randomized trials. Hepatology. 2012;55:1172-81.
68. Bai M, Qi X, Yang Z, Yang M, Fan D, Han G. TIPS improves liver transplantation-free survival in cirrhotic patients with refractory ascites: An updated meta-analyses. World J Gastroenterol. 2014;20:2704-14.
69. Bhogal H, Sanyal A. Using transyugular intrahepatic portosystemic shunts for complications of cirrhosis. Clin Gastroenterol Hepatol. 2011;9:936-46.
70. Bellot P, Welker M-W, Soriano G, et al. Automated low flow pump system for the treatment of refractory ascites: A multicenter safety and efficacy study. J Hepatol. 2013;58:922-7.
71. Leung W, Wong F. Hepatorenal syndrome: Do the vasoconstrictors work. Gastroenterol Clin NA. 2011;581-98.
72. Sarin SK, Sharma P. Terlipressin: An asset for hepatologist. Hepatology. 2011;54:724-8.
73. Rajekar H, Chawla Y. Terlipressin in hepatorenal syndrome: Evidence for present indications. J Gastronterol Hepatol. 2011;26:109-14.
74. Davenport A, Ahmad J, Al-Khafaji A, Kellum J, Genyk Y, Nadim M. Medical management of hepatorenal syndrome. Nephrol Dial Transplant. 2012;27:34-41.
75. Sanyal A, Boyer T, Garcia-Tsao G, Regenstein F, Rossaro L, Appenrodt B, et al. A randomized, prospective, double blind, placebo-controlled trial of terlipressin for type 1 hepatorenal syndrome. Gastroenterology. 2008;134:1360-8.
76. Martin-LLahi M, Pepin MN, Guevara M, Díaz F, Torre A, Monescillo A, et al. Terlipressin and albumin vs albumin in patients with cirrhosis and hepatorenal syndrome: a randomized study. Gastroenterology. 2008;134:1352-9.
77. Nazar A, Pereira G, Guevara M, Matin-Llahi M, Pepin MN, Marineli M, et al. Predictors of response to therapy with terlipressin and albumin in patients with cirrhosis and type 1 hepatorenal syndrome. Hepatology. 2010;51:219-26.
78. Boyer T, Sanyal A, Garcia-Tsao G, Blei A, Carl D, Bexon A, et al. Predictors of response to terlipressin plus albumin in hepatorenal syndrome type 1: Relationship of serum creatinine to hemodynamics. J Hepatol. 2011;55:315-21.
79. Velez J, Nietert P. Therapeutic response to vasoconstrictors in hepatorenal syndrome parallels increase in mean arterial pressure: A pooled analysis of clinical trials. Am J Kidney Dis. 2011;58:928-38.
80. Ginés P. Pharmacological management of hepatorenal syndrome: Lessons from non-responders. J Hepatol. 2011;55:268-9.
81. Fabrizi F, Dixit V, Messa P, Martin P. Terlipressin for hepatorenal syndrome: A meta-analisys of randomized trials. Int J Artif Org. 2009;32:133-40.
82. Gluud L, Christensen K, Christensen E, Krag A. systematic review of randomized trials on vasoconstrictors drug for hepatorenal syndrome. Hepatology. 2010;51:576-84.
83. Gluud L, Christensen K, Christensen E, Krag A. Terlipressin for hepatorenal syndrome. Cochcrane Database Library. 2012;9:CD005162.
84. EASL clinical practice guidelines on the management of ascites, spontaneous bacterial peritonitis, and hepatorenal syndrome. J Hepatol. 2010;53:397-417.
85. Ortega R, Ginés P, Uriz J, Cárdenas A, Calahorra B, De las Heras D, et al. Terlipressin therapy with and without albumin for patients with hepatorenal syndrome: Results of a prospective, non-randomized trial. Hepatology. 2002;36:941-8.
86. Garcia-Martinez R, Caraceni P, Bernardi M, Ginés P, Arroyo V, Jalan R. Albumin: Pathophysiologic basis of its role in the treatment of cirrhosis and its complications. Hepatology. 2013;58:1836-46.
87. Barreto R, Fagundes C, Guevara M, Sola E, Pereira G, Rodríguez E, et al. Type 1 hepatorenal syndrome associated with infections in cirrhosis: Natural history, outcome of kidney function, and survival. Hepatology. 2014;59:1505-13.
88. Rodriguez E, Elia Ch, Sola E, Barreto R, Graupera I, Andrealli A, et al. Terlipressin and albumin for type 1 hepatorenal syndrome associated with sepsis. J Hepatol. 2014;60:955-61.
89. Cavallin M, Kamath P, Merli M, Fasolato S, Toniutto P, Salerno F, et al. Terlipressin plus albumin versus midrodine and octreotide plus albumin in the treatment of hepatorenal syndrome. Hepatology. 2015; doi:101002/hep.27709.
90. Duvoux Ch, Zanditenas D, Hezode Ch, Chauvat A, Monin J, Roudout F, et al. Effects of noradrenalin and albumin in patients with type 1 hepatorenal syndrome: A pilot study. Hepatology. 2002;36:374-80.
91. Alessandria C, Ottobrelli A, Venon W, Todros L, Cerenzia T, Martini S, et al. Noradrenalin vs terlipressin in patients with hepatorenal syndrome: a prospective, randomized, unblinded, pilot study. J Hepatol. 2007;47:499-505.

92. Sharma P, Kumar A, Sharma B, Sarin S. An open label, pilot, randomized controlled trial of noradrenaline vs terlipressin in the treatment of type 1 hepatorenal syndrome and predictors response. Am J Gastroenterol. 2008;103:1689-97.
93. Singh V, Ghosh S, Singh B, Kumar P, Sharma P, Bhalla A, et al. Noradrenaline vs terlipressin in the treatment of hepatorenal syndrome: A randomized study. J Hepatol. 2012;56:1293-8.
94. Rossle M, Gerbes A. TIPS for the treatment of refractory ascites, hepatorenal syndrome and hepatic hydrothorax: A critical update. Gut. 2010;59:988-1000.
95. Kribben A, Gerken G, Haag S, Herget-Rosenthal S, Treichel U, Betz Ch, et al. Effects of fractionated plasma separation and absorption on survival in patients with acute on chronic liver failure. Gastroenterology. 2012;142:782-9.
96. Bahirwani R, Campbell M, Siropaides T, Markmann J, Olthoff K, Shaked A, et al. Transplantation: Impact of pretransplant renal insufficiency. Liver Transplant. 2008;14:665-71.
97. Restuccia T, Ortega R, Guevara M, Ginés P, Alessandria C, Ozdogan O, et al. Effects of treatment of hepatorenal syndrome before transplantation on post-transpantation outcome. A case control study. J Hepatol 2004;40:140-6.
98. Boyer T, Sanyal A, Garcia-Tsao G, Regenstein F, Rossaro L, Appendort B, et al. Impact of liver transplantation on the survival of patients treated for hepatorenal syndrome type 1. Liver Transplant. 2011;17:1328-32.
99. Ginés P. Hepatorenal syndrome, pharmacological therapy and liver transplant. Liver Transplant. 2011;17:1244-6.
100. Angeli P, Ginés P. Hepatorenal syndrome, MELD score, and liver transplantation: An evolving issue with relevant implications for clinical practice. J Hepatol. 2012;57:1135-40.