World Journal of Gastrointestinal Pharmacology and Therapeutics

Online Submissions: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.4292/wjgpt.v5.i3.156

World J Gastrointest Pharmacol Ther 2014 August 6; 5(3): 156-168
ISSN 2150-5349 (online)

REVIEW

Renal dysfunction in patients with cirrhosis: Where do we stand?

Chrysoula Pipili, Evangelos Cholongitas

Chrysoula Pipili, Department of Nephrology, Laiki Merimna, 17343 Athens, Greece
Evangelos Cholongitas, 4th Department of Internal Medicine, Medical School of Aristotle University, Hippokration General Hospital of Thessaloniki, 54642 Thessaloniki, Greece
Author contributions: Pipili C and Cholongitas E contributed equally to this paper.
Correspondence to: Evangelos Cholongitas, Senior Lecturer of Internal Medicine, 4th Department of Internal Medicine, Medical School of Aristotle University, Hippokration General Hospital of Thessaloniki, 49, Konstantinopoleos Street, 54642 Thessaloniki, Greece. cholongitas@yahoo.gr
Telephone: +30-23-10892110 Fax: +30-23-10992940
Received: December 10, 2013 Revised: February 8, 2014
Accepted: May 8, 2014
Published online: August 6, 2014

Abstract

Patients with cirrhosis and renal failure are high-risk patients who can hardly be grouped to form precise instructions for diagnosis and treatment. When it comes to evaluate renal function in patients with cirrhosis, determination of acute kidney injury (AKI), chronic kidney disease (CKD) or AKI on CKD should be made. First it should be excluded the prerenal causes of AKI. All cirrhotic patients should undergo renal ultrasound for measurement of renal resistive index in every stage of liver dysfunction and urine microscopy for differentiation of all causes of AKI. If there is history of dehydration on the ground of normal renal ultrasound and urine microscopy the diuretics should be withdrawn and plasma volume expansion should be tried with albumin. If the patient does not respond, the correct diagnosis is HRS. In case there is recent use of nephrotoxic agents or contrast media and examination shows shock, granular cast in urinary sediment and proteinuria above 0.5 g daily, acute tubular necrosis is the prominent diagnosis. Renal biopsy should be performed when glomerular filtration rate is between 30-60 mL/min and there are signs of parenchymal renal disease. The acute renal function is preferable to be assessed with modified AKIN. Patients with AKIN stage 1 and serum creatinine $\geqslant$ 1.5 mg/dL should be at close surveillance. Management options include hemodynamic monitoring and management of fluid balance and infections, potentially driving to HRS. Terlipressin is the treatment of choice in case of established HRS, administered until there are signs of improvement, but not more than two weeks. Midodrine is the alternative for therapy continuation or when terlipressin is unavailable. Norepinephrine has shown similar effect with terlipressin in patients being in Intensive Care Unit, but with much lower cost than that of terlipressin. If the patient meets the requirements for transplantation, dialysis and transjugular intrahepatic portosystemic shunt are the bridging therapies to keep the transplant candidate in the best clinical status. The present review clarifies the latest therapeutic modalities and the proposed recommendations and algorithms in order to be applied in clinical practice.

Key words: Renal dysfunction; Cirrhosis; Assessment; Management; Hepatorenal syndrome

Core tip: Close surveillance, well -classified definitions and scoring systems will be helpful in recognizing the renal dysfunction. Noninvasive biomarkers (NGAL, sCysC) reflect the prospective method in identifying kidney damage and kidney function. The acute renal function is proposed to be assessed with modified acute kidney injury network (AKIN) and the baseline renal function in stable patients with MDRD-6 formula or chronic kidney disease epidemiology collaboration Cys C-Cr equation. MBRS score or RIFLE criteria for AKI evaluation should be tried in critically ill cirrhotic patients, while in candidates for transplantation, glomerular filtration rate should be preferably measured with exogenous markers for accurate assessment of renal function. Amelioration of the underlined liver disease is very impressive in patients with alcoholic liver disease after recovery from

alcoholic hepatitis, and in patients with decompensated cirrhosis due to hepatitis B virus infection after receiving antiviral therapy.

Pipili C, Cholongitas E. Renal dysfunction in patients with cirrhosis: Where do we stand? *World J Gastrointest Pharmacol Ther* 2014; 5(3): 156-168 Available from: URL: http://www.wjgnet.com/2150-5349/full/v5/i3.156.htm DOI: http://dx.doi.org/10.4292/wjgpt.v5.i3.156

INTRODUCTION

Physicians involved in the care of patients with cirrhosis recognize that the development of renal dysfunction is associated with significant morbidity and mortality[1-3]. Methods for early and accurate diagnosis of acute renal failure may assist initiate specific treatment at earlier stage and improve the outcome. Patients with cirrhosis can develop three main forms of acute renal failure and may suffer also from underline chronic kidney disease. Prerenal azotemia is the basis of acute renal injury, which can trigger hepatorenal syndrome type 1 (HRS-type 1) and evolve to acute tubular necrosis - according to the degree of splanchnic vasodilation/renal hypoperfusion and the reduced cardiac output[4]. HRS type-1 is a prevalently functional disease observed in patients with decompensated cirrhosis, which might remain in a chronic form with less severe renal impairment (HRS-type 2), or progress to acute tubular necrosis[5-7] and exaggerate systemic inflammatory response resulting in multiorgan failure[8]. Recently, patients with cirrhosis who have decreased renal plasma flow with normal or low/normal glomerular filtration rate (GFR) before to develop HRS were defined to be in "Pre-HRS" renal disease[6]. Moreover, the term 'Hepatorenal Disorders' has been proposed to group all forms of kidney disease in patients with cirrhosis so as to describe their prognosis and to assist treatment decisions[9]. However, in the majority of patients, HRS type-1 still remains a terminal condition of advanced liver disease requiring coordinated affords in the field of diagnosis, pathophysiology and treatment. In this paper, we are going to address the current knowledge on the evaluation and management of acute and chronic kidney failure presented on patients with cirrhosis. All the suggested directions highlight, to the best extent possible, the bibliographic studies, the expert opinions and recommendations.

BASELINE DIRECTIONS FOR ASSESSMENT OF KIDNEY INJURY IN PATIENTS WITH CIRRHOSIS

The appropriate clinical, biochemical and radiological markers with proven sensitivity for the diagnosis of renal disease in patients with cirrhosis have not been established yet. There are only recommendations for the unique form of kidney injury in patients with cirrhosis, the HRS (Table 1). Renal pathology in patients with cirrhosis includes not only functional abnormalities (developed as a result of changes in hemodynamics, in renal auto-regulation and cardiac dysfunction) but structural abnormalities as well[5].

Physicians caring for patients with cirrhosis should recognize the acute or chronic character of renal disease; the causes of renal injury; the clinical conditions leading concomitantly to acute kidney injury (AKI) and liver dysfunction, and the prognostic factors associated with the progression of AKI. Hypovolemia (due to diuretics, hemorrhage, diarrhoea), acute tubular necrosis, sepsis, nephrotoxic agents (such as nonsteroidal antiinflammatory drugs, aminoglycosides radiological contrasts) and hepatorenal syndrome-type 1 are the most common causes of AKI in cirrhotic patients[4]. It is underlined that type-1 HRS is considered a specific form of AKI[9]. The chronic causes include hepatorenal syndrome-type 2, glomerulonephritis due to hepatitis C virus and hepatitis B virus infection, IgA nephropathy mainly presenting in patients with alcoholic cirrhosis and diabetic nephropathy mainly combined with non alcoholic steatohepatitis[4]. The situations which may worsen the renal and liver function at the same time might be autoimmune diseases, granulomatous diseases, autosomal dominant polycystic kidney disease, shock, pregnancy induced liver disease and drugs (aspirin, NSAIDs and angiotensin converting enzyme inhibitors[4,10,11]. Ultimately, factors associated with the progression of AKI were the hepatic encephalopathy, severe liver and circulatory failure, chronic kidney disease (CKD), low serum sodium concentration and high leukocyte count[12]. This knowledge should be in hand when time for assessment of patients with cirrhosis comes.

In general, differentiation of the main causes of AKI, prerenal "Pre-HRS", HRS and acute tubular necrosis presents great influence on therapeutic decisions and patients' prognosis. An easily applicable algorithm proposed by Angeli *et al*[5], offer great assistance in clarification of the cause of the AKI in patients with cirrhosis. When there is history of dehydration, excessive use of diuretics and bacterial infection on the ground of normal urinary sediment, proteinuria below 0.5 g daily and normal renal ultrasound, the diuretics should be withdrawn and plasma volume expansion should be tried with albumin. If the patient responds to treatment the diagnosis is prerenal. If the patient does not respond, the correct diagnosis is HRS. In case there is recent use of nephrotoxic agents or contrast media and examination shows shock, granular cast in urinary sediment and proteinuria above 0.5 g daily, acute tubular necrosis is the prominent diagnosis. Furthermore, physicians should take into account that one form may convert into another thus HRS may develop on patient with chronic renal disease or evolve in time[4,5].

Moreover, the stage of liver disease will provide considerable hints for the evaluation of kidney injury. At the beginning of cirrhosis splanchnic vasodilatation is masked by increased cardiac output thus glomerulal filtration rate (GFR) is increased[13]. Patients with ascites present severe impairment of renal blood flow[14] and considerable

Table 1 International Ascites Club definition and diagnostic criteria for hepatorenal syndrome[7,116]

1996 criteria
Major criteria
Chronic or acute liver disease with advanced hepatic failure and portal hypertension
Serum creatinine > 1.5 mg/dL or 24-h creatinine clearance of < 40 mL/min
Absence of shock, ongoing bacterial infection, and current or recent treatment with nephrotoxic drugs. Absence of gastrointestinal fluid losses (repeated vomiting or intense diarrhea) or renal fluid losses
No sustained improvement in renal function defined as a decrease in serum creatinine to < 1.5 mg/dL or increase in creatinine clearance to 40 mL/min or more following diuretic withdrawal and expansion of plasma volume with 1.5 L of isotonic saline
Proteinuria < 500 mg/dL and no ultrasonographic evidence of obstructive uropathy or parenchymal renal disease
Minor criteria
Urine volume < 500 mL/d Urine osmolality > plasma osmolality
Urine sodium < 10 mEq/L Urine red blood cells < 50 per high power field

fluctuation of serum creatinine (sCr)[15]. Wide variations may be observed, in regards to volume paracentesis and volume expansion[15]. Patients with advanced liver disease and high bilirubin show overestimation of GFR if evaluation of renal function is based on sCr, since significant interaction may be observed between serum bilirubin and sCr[16,17]. Cirrhotic patients admitted to intensive care unit (ICU) have high mortality rates and may present separate predictors and scoring systems for hospital mortality[18-20]. Emphasis should be given to accurate assessment of renal function in candidates for liver transplantation[21].

The best method for renal function assessment in patients with cirrhosis is the clearance of exogenous markers such as iothalamate, 51Cr-EDTA and inulin[15]. However, its application is limited by the cost and complexity while other equivalent methods for estimating the GFR in patients with cirrhosis have not been established[15]. sCr still remains the key biomarker for the diagnosis of AKI in patients with cirrhosis. Despite all sCr limitations, there have not been detected other widely available and superior serum markers for assessing renal function and predicting outcome in patients with cirrhosis[15]. sCr is still the most practical serum marker for estimation of renal function in cirrhotic patients, it consists the basis of existing definitions of AKI and it is included in the Model for End -Stage Liver Disease (MELD) score {MELD = 3.8 [Ln serum bilirubin (mg/dL)] + 11.2 (Ln INR) + 9.6 [Ln serum creatinine (mg/dL)] + 6.4}, which is used to allocate patients for liver transplantation[22]. Nevertheless, sCr should be interpreted with caution, since there is no universal standardized creatinine assay; there are interlaboratory variations, interactions with bilirubin and great influence by numerous non-renal factors such as body weight, race, age, gender[23-25]. Moreover, sCr within the normal ranges does not exclude significant renal impairment in patients with cirrhosis[26] as it overestimates renal function due to decreased creatine production by liver malnutrition and muscle wasting[27].

RECENT KNOWLEDGE ON EVALUATION OF RENAL DYSFUNCTION IN PATIENTS WITH CIRRHOSIS

So far, the most widely used criterion for the diagnosis of acute renal failure in patients with cirrhosis is the sCr level ⩾ 1.5 mg/dL (133 μmol/L) (conventional criteria). A propose for the improvement on the current classification of acute renal dysfunction in cirrhosis is the diagnostic criteria developed by the Acute Kidney Injury Network (AKIN)[28] (Table 2). This is a consensus definition for acute kidney injury (AKI), a new term for acute renal failure, in order to be identified earlier patients with worse prognosis. According to AKIN criteria, AKI is defined as an increase in sCr level ⩾ 0.3 mg/dL (⩾ 26.4 μmol/L) or ⩾ 150% (1.5 fold from baseline) within 48 h from the first measurement or a urine output of less than 0.5 mL/kg per hour for more than 6 h[28-30] and is divided in three stages. AKIN criteria in cirrhotic patients have been validated with six prospective clinical trials[8,12,20,31-33]. The patient population in the five studies included hospitalized cirrhotic patients with or without ascites[8,12,31-33], while in one study patients with cirrhosis were admitted in ICU[20]. All studies concluded that AKIN criteria accurately predicted in- hospital mortality, length of hospital stay and organ failure. However, when AKIN criteria compared to conventional criteria, they were not found to be superior[33]. The authors of this study noted that the addition of either the progression of AKIN stage or the cut off sCr ⩾ 1.5 mg/dL to the AKIN improved their prognostic accuracy[33]. A step forward in this evaluation was made by Fagundes *et al*[12] who proposed modified cirrhosis-AKI classification and validated it in 375 consecutive patients hospitalized for complications of cirrhosis. Patients with cirrhosis were categorized into three groups: (1) patients with AKI stage 1 and peak of sCr ⩽ 1.5 mg/dL; (2) Patients with AKI stage 1 and peak of sCr > 1.5 mg/dL; and (3) patients with AKI stage 2 or 3. By applying this modified classification a better risk stratification for patients with cirrhosis was achieved considering also the cause of AKI.

Serum Cystatin C (CysC) is another marker for evaluation of acute renal dysfunction preferably in female patients with progressive cirrhosis[34]. It has been shown that in this cirrhotic population (women with cirrhosis Child - Pugh score C)[34]. CysC presented high diagnostic sensitivity, greater than sCr in detection of acute renal impairment[34,35]. Indeed it was proved that CysC correlated with the severity of liver fibrosis and with the GFR better than sCr[35-37], but this has not been confirmed in other studies[38].

Table 2 Acute kidney injury network and risk, injury, failure, loss, and end stage criteria for the diagnosis of acute kidney injury[117]

AKIN criteria	Urine output	RIFLE criteria	
Serum creatinine	(common to both AKIN and RIFLE)	Class	Serum creatinine or GFR
Stage 1 Increase of more than or equal to 0.3 mg/dL (≥ 26.5 μmol/L) or increase to more than or equal to 150% to 199% (1.5- to 1.9-fold) from baseline	Less than 0.5 mL/kg per hour for more than 6 h	Risk	Increase in serum creatinine × 1.5 or GFR decrease > 25%
Stage 2 Increased to more than 200% to 300% (≥ 2- to 2.9-fold) from baseline	Less than 0.5 mL/kg per hour for more than 12 h	Injury	Serum creatinine × 2 or GFR decreased > 50%
Stage 3 Increased to more than 300% (≥ 3-fold) from baseline, or more than or equal to 4.0 mg/dL (≥ 354 μmol/L) with an acute increase of at least 0.5 mg/dL (44 μmol/L) or on RRT	Less than 0.3 mL/kg per hour for 24 h or anuria for 12 h	Failure	Serum creatinine × 3, or serum creatinine > 4 mg/dL (> 354 μmol/L) with an acute rise > 0.5 mg/dL (> 44 μmol/L) or GFR decreased > 75%
		Loss	Persistent acute renal failure = complete loss of kidney function > 4 wk
		End-stage kidney disease	ESRD > 3 mo

For conversion of creatinine expressed in SI units to mg/dl, divide by 88.4. For both AKIN stage and RIFLE criteria, only one criterion (creatinine rise or urine output decline) needs to be fulfilled. Class is based on the worst of either GFR or urine output criteria. GFR decrease is calculated from the increase in serum creatinine above baseline. For AKIN, the increase in creatinine must occur in < 48 h. For RIFLE, AKI should be both abrupt (within 1–7 d) and sustained (more than 24 h). AKI: Acute kidney injury; AKIN: Acute Kidney Injury Network; ESRD: End-stage renal disease; GFR: Glomerular filtration rate; RIFLE: Risk, injury, failure, loss, and end stage; RRT: Renal replacement therapy.

Promising information for acute kidney dysfunction in cirrhotic could be also derived from urine. A novel kidney biomarker associated with early detection of acute tubular injury is neutrophil gelatinase -associated lipocalin (NGAL) measured in blood and in urine. Many studies in several clinical situations[39-41] have underlined that the NGAL increased two hours after the induction of AKI, before of the sCr elevation. In cirrhotic patients, preliminary studies have reported that NGAL levels were higher in those with HRS[42] compared to those without renal disease; NGAL was associated with the prediction of short-term mortality[43,44] and it could be used for differentiation of prerenal azotemia, acute tubular necrosis and HRS[45]. Urinary NGAL has been found to be 20 ng/mL in healthy population and in prerenal azotemia, 105 ng/mL in HRS, 325 ng/mL in AKI and 50 ng/mL in CKD[44]. Furthermore, another powerful tool in renal disease detection could be the ratio of urinary sodium to potassium. If that ratio in a random urine sample of patients with decompensated cirrhosis and ascites is less than 1 the diagnosis of renal dysfunction (GFR < 60 mL/min) is possible[46]. Nevertheless all these findings require confirmation in additional studies.

Ultimately, encouraging method for early acute detection of renal hemodynamic disturbances of patients with cirrhosis showed the measurement of renal resistive index (RI) by renal duplex doppler ultrasound. In general, a RI more the 0.7 is indicative of renal failure, confirming high blood velocity waveform of renal artery and high peripheral arterial resistance[47]. In patients with cirrhosis RI over 0.7 has been predictor of renal dysfunction and HRS[48,49] and it has correlated significantly with MELD score, MELD-Na score, sCr and hyponatriemia as well[50]. In addition, it might demonstrate the progress of renal disease since it reached its highest levels in patients with refractory ascites compared with patients with compensated cirrhosis and those with diuretic responsive ascites[48]. Future research is needed to elucidate RI role in this patient population.

In regards to the evaluation of CKD, the Kidney Disease Outcomes Quality Initiative (KDOQI) Clinical Practice Guidelines have been suggested[9]. According to KDOQI[51], CKD is defined as a GFR of less than 60 mL/min for more than three months, calculated using the modified diet in renal disease (MDRD)-6 formula (Appendix 4) supporting its potential usefulness in the decision making for simultaneous liver and kidney transplantation. This hypothesis has been tested in patients with stable cirrhosis in the study of Francoz *et al*[52]. They showed that MDRD-6 formula was superior to MDRD-4 and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formulas identifying stable cirrhotic patients with markedly impaired renal function, including those with ascites (Table 3). However, MDRD-6 formula underestimated renal function in patients with GFR more than 30 mL/min subjecting them to possible unnecessary combined kidney and liver transplantation. Recently, CKD-EPI Cys C-Cr equation was shown to be the most accurate GFR-estimating formula compared to sCr or CysC-based formulas in cirrhosis. This formula was proposed to evaluate non AKI in cirrhosis until a brand, radical and specific for this population equation is discovered[53].

Accurate evaluation of renal function in cirrhotic patients, who are candidates for liver transplantation (LT) is crucial. Kidney disease is the key factor for determination of transplant status and highly affects the choice

Table 3 Formulas for estimating the glomerular filtration rate: modified diet in renal disease-4, modified diet in renal disease-6, chronic kidney disease epidemiology collaboration (mL/min per 1.73 m^2)[118-120]

MDRD-4 formula (1)	186 × [creatinine (mg/dL)] -1.154 × [age (yr)] 0.203 × (0.742 if patient is female) × (1.21 if patient is black)
MDRD-6 formula (2)	170 × sCr (mg/dL)-0.999 × age-0.176 × 1.180 (if black) × 0.762 (if female) × serum urea nitrogen-0.170 × albumin 0.138
CKD-EPI equation (3)	141 × min (sCr/κ, 1)α × max (sCr/κ, 1)-1.209 × 0.993 Age × 1.018 (if female) × 1.159 (if black)

MDRD: Modified diet in renal disease; CKD-EPI: Chronic kidney disease epidemiology collaboration.

of simultaneous kidney and renal transplantation, the initial immunosuppression and the survival of these patients[54-56]. GFR, sCr and serum sodium have been recognized as independent predictors of mortality in patients with decompensated cirrhosis[57,58]. In this case estimation of GFR should be made accurately by exogenous filtration markers. Particularly for patients with established HRS, a modification of MELD calculation has been proposed, to obtain patients with HRS the right priority in the waiting list, concerning that therapy can reduce their baseline MELD score[59]. According to this modification, the baseline MELD score before starting therapy should be used in patients with HRS who have been stabilized with therapy; the MELD score considering the pharmacological treatment as dialysis should be applied in patients with continuous recurrence of HRS and the highest MELD-Na over time should be received in patients with repeated recurrence of HRS type-2. Renal biopsy is advisable if GFR is between 30-60 mL/min and there are signs of parenchymal renal disease -hematuria (more the 50 red cells per high power field), proteinuria > 0.5 g/daily-and chronic renal abnormalities on the ground of comorbidities such as diabetes mellitus, hypertension and viral infection[15]. The detection of potential reversible renal disease and vascular lesions- hazardous for calcineurin-inhibitors nephrotoxicity- may be of value for the management before and after transplantation.

Kidney failure at admission or during ICU stay is a crude predictor of mortality in critically ill patients with cirrhosis. Despite supportive treatment measures, mortality was high and the risk for death was multiplied with the increasing severity of the kidney disease[1,60]. In this patient population, RIFLE classification presents the best predictive ability for ICU and hospital mortality[18,19]. The RIFLE denomination is an acronym which refers to risk (risk of renal dysfunction); injury (injury or damage to the kidney); failure (renal failure); loss (loss of kidney function); end (end stage renal disease) (Table 2). It was entered by Acute Dialysis Quality Initiative (ADQI) as an attempt to standardize the definition of acute renal failure and to describe the severity of AKI[61]. It allows the evaluation of the progression of renal injury as AKI is a dynamic process[62]. However, RIFLE score lack of a uniform approach in a patient population presenting with multiorgan failure, since it is focused only on kidney pathology. In keeping with this, a new score (MBRS) has been introduced combining four parameters: mean arterial pressure, bilirubin, respiratory failure and sepsis displayed an excellent area under the receiver operating characteristic curve (0.898 ± 0.031) for prognosis of mortality. This tool has been applied in a total of 301 critically ill cirrhotic patients[63,64] and proved that is an accurate, handy, user-friendly and low -cost scoring system. If it is above 2, cirrhotic patients should be prioritized for LT[64].

Overall, when it comes to evaluate renal function in patients with cirrhosis determination of AKI, CKD or AKI on CKD should be made. HRS diagnosis is the first which should be excluded by the algorithm of Angeli *et al*[5]. The acute renal function is proposed to be assessed with modified AKIN and the baseline renal function in stable patients with MDRD-6 formula or CKD-EPI Cys C-Cr equation. MBRS score or RIFLE criteria for AKI evaluation should be tried in critically ill cirrhotic patients, while in candidates for transplantation, GFR should be preferably measured with exogenous markers for accurate assessment of renal function. Serial plasma measurements with delayed sampling to allow equilibrium between plasma and intracellular space, especially ascitic fluid would give a more precise GFR[65]. All cirrhotic patients should undergo renal ultrasound for measurement of RI, in every stage of liver dysfunction and urine microscopy for differentiation of all causes of AKI. Renal biopsy should be performed when GFR is between 30-60 mL/min and there are signs of parenchymal renal disease (Table 4).

INACCURACIES OF RENAL ASSESSMENT STRATEGIES IN PATIENTS WITH CIRRHOSIS

Regarding the AKIN criteria, the urine volume cannot be applied in patients with cirrhosis since it may be markedly biased. Errors in the timing and the complete of urine collection are very common. Moreover, AKIN overestimate mortality, because they detect earlier patients with worse prognosis[32]. Since sCr cannot be removed from clinical practice, physicians should use it with caution in patients with advanced cirrhosis. The inadequacies of sCr are more pronounced in this patient group, due to high bilirubin and refractory ascites. The establishment of creatinine levels with enzymatic assays partially overcame this problem, but there are more expensive[66]. Similarly, none of the creatinine -based mathematical equations are precise acute markers for renal function evaluation in cirrhosis[67]. The body weight cannot be accurately estimated on the ground of ascites and edema, and there is disproportional high creatinine secretion from the tubules in regards to the level of creatinine filtered by the glomerulus[23]. Similarly, evidence has not clarified whether sCysC offers clear advantage comparing to sCr in all cirrhotic patients,

Table 4 Recomendations for renal function evaluation in subgroups of patients with cirrhosis

Differentiate prerenal kidney disease, hepatorenal syndrome and acute tubular necrosis	Angeli *et al*[5] algorithm
Acute kidney injury	Modified cirrhosis–acute kidney injury classification sCr increase ⩾ 0.3 mg/dL (⩾ 26.4 μmol/L) or more than 150% (1.5 fold from baseline) within 48 h from the first measurement[12]
Chronic kidney disease	KDOQI[49] guidelines Glomerular filtration rate below 60 mL/min for more than three months, calculated using the modified diet in renal disease-6 formula chronic kidney disease epidemiology collaboration Cys C-Cr equation[51]
Critically ill cirrhotic patients	RIFLE score[18,19] MBRS score[61,62] combining mean arterial pressure, bilirubin, respiratory failure and sepsis
Candidates for liver transplantation	Exogenous filtration markers If there is suspicion for parenchymal disease and Glomerular filtration rate is between 30-60 mL/min consider renal biopsy
Advanced cirrhosis	Cystatin C
Difficulties in differentiation of acute tubular necrosis	NGAL
All patients with cirrhosis in every stage of liver disease	Renal resistive index estimation by renal duplex doppler ultrasound

KDOQI: Kidney disease outcomes quality initiative.

neither improve the predictive power of MELD score[68]. sCysC may also be influenced by body composition, abnormal thyroid function, systemic inflammation and corticosteroid use, while its assay although easy applicable is of high cost[41]. In parallel substitution of sCr by sCysC did not improve the prognositic ability of MELD-score and creatinine -based equations[38,68]. Estimating GFR with the gold standard measures is the method of choice, but in every day routine is expensive, time-consuming, radioactivity transmitter and fatiguing[21]. Ultimately, renal biopsy is not easily applicable to patients with cirrhosis. Coagulation disorders are common in cirrhotic and the prolonged INR predispose to high risk of hemorrhages. In this situation, transjugular route is preferable than the percutaneous route, since it has been proved equivalent efficient[69]. Contraindications for biopsy are small size kidneys, large volume ascites and poor cortical differentiation[15].

MANAGEMENT OF RENAL FUNCTION IN PATIENTS WITH CIRRHOSIS

Research has made an enormous progress by finding treatment directions for HRS, which was previously fatal within a few days or weeks. However, no guidelines have been established for the treatment of patients with cirrhosis and kidney disease. Management options should be based on expert recommendations[9], proposed algorithms[33] and knowledge of the nature of renal disease[6,8]. It is essential to recognize early AKI - mainly diagnosis of HRS, which should be detected within 48 h, following the currently accepted guidelines[10,59] (Table 1) - to determine the chronic damage of the kidneys and to take the best measures for improving hepatic function. Patients with renal disease due to HRS, have much worse prognosis compared to patients with parenchymal renal disease[59]. Amelioration of the underlined liver disease is very impressive in patients with alcoholic liver disease after recovery from alcoholic hepatitis, therapy with baclofen[70] and in patients with decompensated cirrhosis due to hepatitis B virus infection after receiving antiviral therapy[71-73]. The choice of therapy depend upon the experience of the medical centre, the availability of certain drugs, the unit in which patient is admitted (ICU or not ICU) and whether the patient is a candidate for LV.

First line treatment

First line treatment should aim at the elimination of the potential pathophysiological factors resulting on HRS. Hemodynamic monitoring and management of fluid balance is essential for preventing the relative renal hypoperfusion, maintaining effective circulatory volume and renal perfusion pressure. Traditional measures of intravascular volume evaluation such as right atrial and pulmonary artery pressures are not considered inadequate for this patient group, so continuous central venous pressures and serial indirect or/and direct measurements of cardiac indices are preferable[9]. The current classification systems are helpful in early recognition of AKI indices and therefore withdrawing the potential causes of renal injury. Patients with AKIN stage 1 and sCr ⩾ 1.5 or initial AKIN stage > 1 should be at close monitoring and receive therapeutic measures for maximum two days[33]. These involve nephrotoxic medications-antibiotics and analgetics-, gastrointestinal bleeding and diuretics, which exacerbate hypovolemia and trigger sympathetic and renin-angiotensin-aldosterone system (RAAS). High level of suspicion is needed regarding the spontaneous bacterial peritonitis since infections very common trigger HRS. Moreover, albumin infusions will correct hypoalbuminemia and partial ascites evacuation will alleviate circulation[33,74]. In the setting of alcohol-related cirrhosis and ascites, the intestinal decontamination with rifaximin may also improve systemic hemodynamics and renal function[75]. If the clinical condition of congested patients (the groups previously mentioned) does not improve within two days, differential diagnosis with HRS should be done

Table 5 Recomendations for management of patients with cirrhosis

First line therapy	
Recognize and withdraw all causes of acute kidney disease	
Resolve primary liver disease	
Encounter hypoalbuminemia with albumin infusion and tension ascites with repeated paracentesis plus albumin	
Have a high level of suspicion and treat spontaneous bacterial peritonitis	
Be vigilant and have into close monitoring patients win acute kidney injury network stage 1 and sCr > 1.5 mg/dL (133 μmol/L) or initial acute kidney injury network stage > 1	
If there is no improvement within 2 d, proceed to specific treatment measures	
Second line therapy	
Patients hospitalized at the ward	If the diagnosis of hepatorenal syndrome has been placed: Give albumin and terlipressin in continuous infusion If there is improvement within 4 d continue with oral midrodrine When terlipressin is unavailable: Give midrodrine plus octreotide plus albumin
Patients admitted to intensive care unit	Norepinephrine plus albumin
Third line therapy	
Patients who qualify for transplant	Consider liver or simultaneous liver kidney transplantation Give therapeutic bridges – Dialysis, transjugular intrahepatic portosystemic shunt
Patients who do not qualify for transplant	Continue the combination of terlipressin plus albumin Dialysis, TIPS

and other specific regimens are required[5] (Table 5).

Second line treatment

Second line therapy encompasses measures undertaken after posing the diagnosis of HRS. The supportive measures are directed mainly into portal hypertension and arterial vasodilatation reversal. Albumin effusion combined with vasoconstrictors is the basic therapy for effective management of hypovolemia[5,9]. The main effect of albumin is the oncotic pressure increase resulting in volume expansion. However, albumin shows additional effects which make it extremely beneficial for patients with HRS. It shows metabolic, immune and vasoconstrictor effects, through binding of endotoxin, nitric oxide, bilirubin, bile acid and fatty acids[76,77] and improves cardiac output, through improvement of cardiac contractility, cardiac preload and volume expansion[78,79]. On the other side, terlipressin is an agonist of renal vasopressin V2 receptors, which reduce splachnic vasodilatation, increase the MAP and reduce the nitric oxide synthesis during sepsis[80]. The combination of them leads to renal function normalization in 34%-65% of cases[81,82], expends the number of patients undergoing LT[83], additionally improving their outcome[84] and it increases short -term survival by 34%-43%[82,85,86]; while it is hypothesized that ameliorates also tubular damage[5]. They have been applied in a special protocol which has shown efficacy in 59% of cases[87] and its discontinuation has been followed by HRS recurrence in 15%-22%[82,85,86,88-91]. The protocol has been proposed to be administered until there are signs of improvement, but not more than two weeks. The decrease of sCr <1.5 mg/dL (133 μmol/L) or the decrease of sCr > 50% but ⩾ 1.5 mg/dL (133 μmol/L), the decrease of bilirubin < 10mg/dL and the elevation of MAP ⩾ 5 mmHg at day 3 of treatment are the predictors of response[87,92,93]. If patient respond, some centers continue therapy with midodrine (an oral α1-adrenergic agonist with vasoconstrictive properties) indefinitely to keep higher MAP and to compensate refractory ascites[94]. If there is no improvement in renal function after two weeks, the protocol maybe repeated -there have been reports for protocol administration up to eight months[9,74,95,96] - or other interventional options are applied regarding the patient status and the available treatment options of the centre. Moreover, changes on terlipressin administration modality (given as continuous infusion instead of *iv* pulses) accounted for enhancement of its efficacy[5,97] (Table 6).

In some cases terlipressin is not applicable. These are when there are contraindications of its use, when there is not available and when the patient is admitted on ICU. In general, the contraindications of terlipressin use are ischemic cardiovascular disease, heart failure, arrhythmias, asthma, respiratory failure and heavy hyponatriemia[4]. Terlipressin use is limited in some countries because of its high cost and the lack of randomized trials proving superiority of terlipressin in comparison to other vasoconstrictors. When patients are admitted to ICU they usually treated with terlipressin[76,98-100] in patients being in ICU and because the cost of norepinephrine therapy is three times less than the cost of terlipressin[100]. Norepinephrine is difficult to be administered in the ward since it requires continuous intravenous infusion and hemodynamic monitoring, so instead of terlipressin, other vasoconstrictors maybe used in combination with albumin. These are octreotide, a synthetic analog of somatostatin and midodrine. However, the effect of octreotide, either used alone or with albumin, does not appear to be beneficial for renal function improvement[99,101] and midodrine alone or in combination with albumin has not been evaluated in patients with HRS type -1. Only when octreotide was used in conjunction with midodrine and albumin has normalized renal function in 49%[77,102,103], has increased MAP[77] and survival[102].

Table 6 Scheme for terlipressin and albumin administration[5,97]

Terlipressin is given as an intravenous bolus 1 to 2 mg every four to six hours	Albumin is given for two days as an intravenous bolus 1 g/kg per day (100 g maximum) followed by 25 to 50 g /d until terlipressin therapy is discontinued

Table 7 Published guidelines on selection criteria for simultaneous liver-kidney transplantation

Davis *et al*[121], 2007
Patients with CKD with CrCl (preferentially iothalamate) of ≤ 30 mL/min for > 3 mo
Patients with AKI and/or HRS on dialysis for ≥ 6 wk
Patients with prolonged AKI with kidney biopsy showing fixed renal damage
SLK was not recommended in patients with AKI not requiring dialysis
Eason *et al*[122], 2008
Patients with CKD with GFR ≤ 30 mL/min > 3 mo
Patients with AKI/HRS with sCr ≥ 2 mg/dL and on dialysis ≥ 8 wk
Patients with evidence of CKD and kidney biopsy with > 30% GS or 30% fibrosis
Other criteria that was recommended to be considered: Presence of co-morbidities: Diabetes, Hypertension, age > 65 yr, renal size and duration of sCr > 2 mg/dL
Nadim *et al*[123], 2012
Persistent AKI ≥ 4 wk with one of the following:
Increase Scr ≥ 3-fold from baseline or on dialysis
GFR ≤ 35 mL/min (MDRD-6) or ≤ 25 mL/min (iothalamate)
CKD ≥ 3 mo with one of the following:
eGFR ≤ 40 mL/min (MDRD-6) or ≤ 30 mL/min (iothalamate)
Proteinuria ≥ 2 g/d
Kidney biopsy showing > 30% GS or > 30% interstitial fibrosis
Note: Higher GFR threshold with MDRD-6 was to account for the approximate 30%- 40% overestimation that has been described when compared to iothalamate.

CKD: Chronic kidney disease; CrCl: Creatinine clearance; HRS: Hepatorenal syndrome; AKI: Acute kidney injury; SLK: Simultaneous Liver-Kidney; sCr: Serum creatinine; GFR: Glomerular filtration rate; GS: Glomerulosclerosis; MDRD-6: Modification of diet in renal disease formula calculated using six variables of serum creatinine, serum urea, serum albumin, age, gender.

Third line treatment

When pharmacological measures are insufficient, transplantation is the treatment of choice[8]. MELD score permits selection of patients needing liver transplant, while patients who are risk for not -recovery of renal function simultaneous kidney and liver transplant is required[9]. In the direction of combined liver and kidney transplantation leads the duration of HRS (more than four weeks), AKI on CKD, and baseline diseases (such as hypertension, diabetes and obesity) which predispose to kidney disease progression (Table 7). If the patient meets the requirements to be listed for transplant, dialysis and transjugular intrahepatic portosystemic shunt (TIPS) are the bridging therapies to keep the transplant candidate in the best clinical status. It is essential to resolve HRS since is associated with many perioperative complications and decreases patient survival.

In general, dialysis procedures have not improved the long -term survival in patients with HRS and they have been associated with high risk of blood pressure decline, hypothermia, bradycardia, tissue hypoxia and clotting[4]. That is why they are applied under special situations, when there are indications for reversibility of AKI, hyperkalemia, hypervolemia not responding to diuretics, severe metabolic acidosis, acute on chronic liver failure and fulminant liver failure[9,104,105]. The choice of modality [continuous renal replacement therapy, intermittent hemodialysis, Molecular Adsorbent Recirculating System (MARS)] depends on the abilities and the experience of the centre, while non standard anticoagulation measures are indicated. Schemes with saline flushing, minimal dose of heparin or minimal dose of citrates are preferable. Peritoneal dialysis may be another option to remove ascites and resolve cirrhosis complications, such as encephalopathy, without exposing patient to anticoagulation and to other dialysis complications[106,107].

TIPS is an intervention that enhances the return of blood in the right heart and resolve the reduced sympathetic and RAAS activity in HRS type Ⅱ, suggesting an improvement in systematic hemodynamics[108-110]. It is indicated in cirrhotic patients with refractory ascites requiring repeated paracentesis[109-112] because it has conferred positive impact on ascites and renal function amelioration. Nevertheless, it has not improved significantly mortality[113]. Furthermore, renal function improvement does not come fast, it comes after weeks or months[114], so very ill patients, without significant liver function reserve (INR > 2, bilirubin> 5 mg/dL or Child Plugh > 11), hepatic encephalopathy and cardiopulmonary disease[9] should not undergo it. Complications of TIPS procedure are high rates of encephalopathy, liver insufficiency, cardiac failure, infection of the stent and hemolysis[111,115]. In patients with HRS 1, preliminary studies[108,111] about TIPS showed improvement of renal function in parallel with survival, but it cannot be applied in clinical practice yet as a main treatment. At present, TIPS can be used in selected patients without severe liver dysfunction as a bridge for LT or in patients with stabilized liver function not enlisted, as a long term -therapy[74] (Table 5).

CONCLUSION

Patients with cirrhosis and renal failure are high-risk patients who can hardly be grouped to form precise instructions for diagnosis and treatment. AKI is a portentous manifestation of circulatory dysfunction on patients with cirrhosis, which has a detrimental impact on their recovery and survival. Close surveillance, well -classified definitions and scoring systems (AKIN, RIFLE) aim in early recognition of renal disease. Attempts are made to correlate non invasive biomarkers of kidney damage and kidney function (NGAL, sCysC) to pathological findings. Studies on better using pharmacological and interventional measures are underway promising better and quick recovery. Physicians should be updated on new therapeutic modalities, proposed recommendations and algorithms in order to translate them into clinical practice.

REFERENCES

1 **Cholongitas E**, Senzolo M, Patch D, Shaw S, O'Beirne J, Burroughs AK. Cirrhotics admitted to intensive care unit: the impact of acute renal failure on mortality. *Eur J Gastroenterol Hepatol* 2009; **21**: 744-750 [PMID: 20160527 DOI: 10.1097/MEG.0b013e328308bb9c]

2 **Garcia-Tsao G**, Parikh CR, Viola A. Acute kidney injury in cirrhosis. *Hepatology* 2008; **48**: 2064-2077 [PMID: 19003880 DOI: 10.1002/hep.22605]

3 **Ginès P**, Schrier RW. Renal failure in cirrhosis. *N Engl J Med* 2009; **361**: 1279-1290 [PMID: 19776409 DOI: 10.1056/NEJMra0809139]

4 **Hartleb M**, Gutkowski K. Kidneys in chronic liver diseases. *World J Gastroenterol* 2012; **18**: 3035-3049 [PMID: 22791939 DOI: 10.3748/wjg.v18.i24.3035]

5 **Angeli P**, Sanyal A, Moller S, Alessandria C, Gadano A, Kim R, Sarin SK, Bernardi M. Current limits and future challenges in the management of renal dysfunction in patients with cirrhosis: report from the International Club of Ascites. *Liver Int* 2013; **33**: 16-23 [PMID: 22507181 DOI: 10.1111/j.1478-3231.2012.02807]

6 **Mindikoglu AL**, Weir MR. Current concepts in the diagnosis and classification of renal dysfunction in cirrhosis. *Am J Nephrol* 2013; **38**: 345-354 [PMID: 24107793 DOI: 10.1159/000355540]

7 **Salerno F**, Gerbes A, Ginès P, Wong F, Arroyo V. Diagnosis, prevention and treatment of hepatorenal syndrome in cirrhosis. *Gut* 2007; **56**: 1310-1318 [PMID: 17389705]

8 **Wong F**, O'Leary JG, Reddy KR, Patton H, Kamath PS, Fallon MB, Garcia-Tsao G, Subramanian RM, Malik R, Maliakkal B, Thacker LR, Bajaj JS. New consensus definition of acute kidney injury accurately predicts 30-day mortality in patients with cirrhosis and infection. *Gastroenterology* 2013; **145**: 1280-1288.e1 [PMID: 23999172 DOI: 10.1053/j.gastro.2013.08.051]

9 **Nadim MK**, Kellum JA, Davenport A, Wong F, Davis C, Pannu N, Tolwani A, Bellomo R, Genyk YS. Hepatorenal syndrome: the 8th International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. *Crit Care* 2012; **16**: R23 [PMID: 22322077 DOI: 10.1186/cc11188]

10 **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. *J Hepatol* 2010; **53**: 397-417 [PMID: 20633946 DOI: 10.1016/j.jhep.2010.05.004]

11 **Sersté T**, Francoz C, Durand F, Rautou PE, Melot C, Valla D, Moreau R, Lebrec D. Beta-blockers cause paracentesis-induced circulatory dysfunction in patients with cirrhosis and refractory ascites: a cross-over study. *J Hepatol* 2011; **55**: 794-799 [PMID: 21354230 DOI: 10.1016/j.jhep.2011.01.034]

12 **Fagundes C**, Barreto R, Guevara M, Garcia E, Solà E, Rodríguez E, Graupera I, Ariza X, Pereira G, Alfaro I, Cárdenas A, Fernández J, Poch E, Ginès P. A modified acute kidney injury classification for diagnosis and risk stratification of impairment of kidney function in cirrhosis. *J Hepatol* 2013; **59**: 474-481 [PMID: 23669284 DOI: 10.1016/j.jhep.2013.04.036]

13 **Wong F**, Massie D, Colman J, Dudley F. Glomerular hyperfiltration in patients with well-compensated alcoholic cirrhosis. *Gastroenterology* 1993; **104**: 884-889 [PMID: 8440439]

14 **De Waele JJ**, De Laet I, Kirkpatrick AW, Hoste E. Intra-abdominal Hypertension and Abdominal Compartment Syndrome. *Am J Kidney Dis* 2011; **57**: 159-169 [PMID: 21184922 DOI: 10.1053/j.ajkd.2010.08.034]

15 **Francoz C**, Glotz D, Moreau R, Durand F. The evaluation of renal function and disease in patients with cirrhosis. *J Hepatol* 2010; **52**: 605-613 [PMID: 20185192 DOI: 10.1016/j.jhep.2009.11.025]

16 **Badiou S**, Dupuy AM, Descomps B, Cristolead JP. Comparison between the enzymatic vitros assay for creatinine determination and three other methods adapted on the Olympus analyzer. *J Clin Lab Anal* 2003; **17**: 235-240 [PMID: 14614747 DOI: 10.1002/jcla.10103]

17 **Durand F**, Valla D. Assessment of prognosis of cirrhosis. *Semin Liver Dis* 2008; **28**: 110-122 [PMID: 18293281 DOI: 10.1055/s-2008-1040325]

18 **Cholongitas E**, Calvaruso V, Senzolo M, Patch D, Shaw S, O'Beirne J, Burroughs AK. RIFLE classification as predictive factor of mortality in patients with cirrhosis admitted to intensive care unit. *J Gastroenterol Hepatol* 2009; **24**: 1639-1647 [PMID: 19788604 DOI: 10.1111/j.1440-1746.2009.05908.x]

19 **Jenq CC**, Tsai MH, Tian YC, Lin CY, Yang C, Liu NJ, Lien JM, Chen YC, Fang JT, Chen PC, Yang CW. RIFLE classification can predict short-term prognosis in critically ill cirrhotic patients. *Intensive Care Med* 2007; **33**: 1921-1930 [PMID: 17605129 DOI: 10.1007/s00134-007-0760-6]

20 **Tu KH**, Jenq CC, Tsai MH, Hsu HH, Chang MY, Tian YC, Hung CC, Fang JT, Yang CW, Chen YC. Outcome scoring systems for short-term prognosis in critically ill cirrhotic patients. *Shock* 2011; **36**: 445-450 [PMID: 21841535 DOI: 10.1097/SHK.0b013e31822fb7e2]

21 **Cholongitas E**, Shusang V, Marelli L, Nair D, Thomas M, Patch D, Burns A, Sweny P, Burroughs AK. Review article: renal function assessment in cirrhosis - difficulties and alternative measurements. *Aliment Pharmacol Ther* 2007; **26**: 969-978 [PMID: 17877504 DOI: 10.1111/j.1365-2036.2007.03443.x]

22 **Wiesner R**, Edwards E, Freeman R, Harper A, Kim R, Kamath P, Kremers W, Lake J, Howard T, Merion RM, Wolfe RA, Krom R. Model for end-stage liver disease (MELD) and allocation of donor livers. *Gastroenterology* 2003; **124**: 91-96 [PMID: 12512033 DOI: 10.1053/gast.2003.50016]

23 **Cholongitas E**, Xirouchakis E, Garcovich M, Burroughs AK. Evaluation of renal function in patients with cirrhosis. *J Hepatol* 2010; **53**: 589 [PMID: 20452084 DOI: 10.1016/j.jhep.2010.02.018]

24 **Cholongitas E**, Marelli L, Kerry A, Goodier DW, Nair D, Thomas M, Patch D, Burroughs AK. Female liver transplant recipients with the same GFR as male recipients have lower MELD scores--a systematic bias. *Am J Transplant* 2007; **7**: 685-692 [PMID: 17217437 DOI: 10.1111/j.1600-6143.2007.01666.x]

25 **Cholongitas E**, Marelli L, Kerry A, Senzolo M, Goodier DW, Nair D, Thomas M, Patch D, Burroughs AK. Different methods of creatinine measurement significantly affect MELD scores. *Liver Transpl* 2007; **13**: 523-529 [PMID: 17323365 DOI: 10.1002/lt.20994]

26 **Sherman DS**, Fish DN, Teitelbaum I. Assessing renal function in cirrhotic patients: problems and pitfalls. *Am J*

Kidney Dis 2003; **41**: 269-278 [PMID: 12552488 DOI: 10.1053/ajkd.2003.50035]
27 **Cholongitas E**, Germani G, Burroughs AK. Prioritization for liver transplantation. *Nat Rev Gastroenterol Hepatol* 2010; **7**: 659-668 [PMID: 21045793 DOI: 10.1038/nrgastro.2010.169]
28 **Mehta RL**, Kellum JA, Shah SV, Molitoris BA, Ronco C, Warnock DG, Levin A. Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. *Crit Care* 2007; **11**: R31 [PMID: 17331245 DOI: 10.1186/cc5713]
29 **Cruz DN**, Bagshaw SM, Ronco C, Ricci Z. Acute kidney injury: classification and staging. *Contrib Nephrol* 2010; **164**: 24-32 [PMID: 20427990 DOI: 10.1159/000313717]
30 **Ricci Z**, Cruz D, Ronco C. The RIFLE criteria and mortality in acute kidney injury: A systematic review. *Kidney Int* 2008; **73**: 538-546 [PMID: 18160961]
31 **Belcher JM**, Garcia-Tsao G, Sanyal AJ, Bhogal H, Lim JK, Ansari N, Coca SG, Parikh CR. Association of AKI with mortality and complications in hospitalized patients with cirrhosis. *Hepatology* 2013; **57**: 753-762 [PMID: 22454364 DOI: 10.1002/hep.25735]
32 **de Carvalho JR**, Villela-Nogueira CA, Luiz RR, Guzzo PL, da Silva Rosa JM, Rocha E, Moraes Coelho HS, de Mello Perez R. Acute kidney injury network criteria as a predictor of hospital mortality in cirrhotic patients with ascites. *J Clin Gastroenterol* 2012; **46**: e21-e26 [PMID: 21934526 DOI: 10.1097/MCG.0b013e31822e8e12]
33 **Piano S**, Rosi S, Maresio G, Fasolato S, Cavallin M, Romano A, Morando F, Gola E, Frigo AC, Gatta A, Angeli P. Evaluation of the Acute Kidney Injury Network criteria in hospitalized patients with cirrhosis and ascites. *J Hepatol* 2013; **59**: 482-489 [PMID: 23665185 DOI: 10.1016/j.jhep.2013.03.039]
34 **Gerbes AL**, Gülberg V, Bilzer M, Vogeser M. Evaluation of serum cystatin C concentration as a marker of renal function in patients with cirrhosis of the liver. *Gut* 2002; **50**: 106-110 [PMID: 11772976]
35 **Seo YS**, Jung ES, An H, Kim JH, Jung YK, Kim JH, Yim HJ, Yeon JE, Byun KS, Kim CD, Ryu HS, Um SH. Serum cystatin C level is a good prognostic marker in patients with cirrhotic ascites and normal serum creatinine levels. *Liver Int* 2009; **29**: 1521-1527 [PMID: 19725889 DOI: 10.1111/j.1478-3231.2009.02105.x]
36 **Takeuchi M**, Fukuda Y, Nakano I, Katano Y, Hayakawa T. Elevation of serum cystatin C concentrations in patients with chronic liver disease. *Eur J Gastroenterol Hepatol* 2001; **13**: 951-955 [PMID: 11507361]
37 **Ustundag Y**, Samsar U, Acikgoz S, Cabuk M, Kiran S, Kulah E, Aydemir S. Analysis of glomerular filtration rate, serum cystatin C levels, and renal resistive index values in cirrhosis patients. *Clin Chem Lab Med* 2007; **45**: 890-894 [PMID: 17617033]
38 **Xirouchakis E**, Marelli L, Cholongitas E, Manousou P, Calvaruso V, Pleguezuelo M, Guerrini GP, Maimone S, Kerry A, Hajjawi M, Nair D, Thomas M, Patch D, Burroughs AK. Comparison of cystatin C and creatinine-based glomerular filtration rate formulas with 51Cr-EDTA clearance in patients with cirrhosis. *Clin J Am Soc Nephrol* 2011; **6**: 84-92 [PMID: 20829419 DOI: 10.2215/CJN.03400410]
39 **Haase M**, Bellomo R, Devarajan P, Schlattmann P, Haase-Fielitz A. Accuracy of neutrophil gelatinase-associated lipocalin (NGAL) in diagnosis and prognosis in acute kidney injury: a systematic review and meta-analysis. *Am J Kidney Dis* 2009; **54**: 1012-1024 [PMID: 19850388 DOI: 10.1053/j.ajkd.2009.07.020]
40 **Singer E**, Elger A, Elitok S, Kettritz R, Nickolas TL, Barasch J, Luft FC, Schmidt-Ott KM. Urinary neutrophil gelatinase-associated lipocalin distinguishes pre-renal from intrinsic renal failure and predicts outcomes. *Kidney Int* 2011; **80**: 405-414 [PMID: 21412214 DOI: 10.1038/ki.2011.41]
41 **Kokkoris S**, Pipili C, Grapsa E, Kyprianou T, Nanas S. Novel biomarkers of acute kidney injury in the general adult ICU: a review. *Ren Fail* 2013; **35**: 579-591 [PMID: 23472851 DOI: 10.3109/0886022X.2013.773835]
42 **Cavallin M,** Fasolato S, Sticca A, Gola E, Bortoluzzi A, Gatta A, Angeli P. Increased urinary level of neutrophil gelatinase-associated lipocalin (NGAL) in patients with cirrhosis and type 1 HRS. *Hepatology* 2011; **54**: 1254A-1255A [DOI: 10.1002/hep.24666]
43 **Gungor G**, Ataseven H, Demir A, Solak Y, Gaipov A, Biyik M, Ozturk B, Polat I, Kiyici A, Cakir OO, Polat H. Neutrophil gelatinase-associated lipocalin in prediction of mortality in patients with hepatorenal syndrome: a prospective observational study. *Liver Int* 2014; **34**: 49-57 [PMID: 23799980 DOI: 10.1111/liv.12232]
44 **Verna EC**, Brown RS, Farrand E, Pichardo EM, Forster CS, Sola-Del Valle DA, Adkins SH, Sise ME, Oliver JA, Radhakrishnan J, Barasch JM, Nickolas TL. Urinary neutrophil gelatinase-associated lipocalin predicts mortality and identifies acute kidney injury in cirrhosis. *Dig Dis Sci* 2012; **57**: 2362-2370 [PMID: 22562534 DOI: 10.1007/s10620-012-2180-x]
45 **Fagundes C**, Pépin MN, Guevara M, Barreto R, Casals G, Solà E, Pereira G, Rodríguez E, Garcia E, Prado V, Poch E, Jiménez W, Fernández J, Arroyo V, Ginès P. Urinary neutrophil gelatinase-associated lipocalin as biomarker in the differential diagnosis of impairment of kidney function in cirrhosis. *J Hepatol* 2012; **57**: 267-273 [PMID: 22521351 DOI: 10.1016/j.jhep.2012.03.015]
46 **Cholongitas E**, Goulis J, Arsos G, Birtsou C, Nakouti T, Papadopoulou S, Chalevas P, Karakatsanis K, Akriviadis E. Association between ratio of sodium to potassium in random urine samples and renal dysfunction and mortality in patients with decompensated cirrhosis. *Clin Gastroenterol Hepatol* 2013; **11**: 862-867 [PMID: 23403009 DOI: 10.1016/j.cgh.2013.02.005]
47 **Platt JF**, Rubin JM, Ellis JH. Acute renal failure: possible role of duplex Doppler US in distinction between acute prerenal failure and acute tubular necrosis. *Radiology* 1991; **179**: 419-423 [PMID: 2014284]
48 **Fouad YM**, Mokarrab H, Elgebaly AF, El-Amin H, Abdel-Raheem EM, Sharawy MA, Shatat ME. Renal duplex Doppler ultrasound in patients with HCV related liver cirrhosis. *Trop Gastroenterol* 2009; **30**: 213-218 [PMID: 20426281]
49 **Kastelan S**, Ljubicic N, Kastelan Z, Ostojic R, Uravic M. The role of duplex-doppler ultrasonography in the diagnosis of renal dysfunction and hepatorenal syndrome in patients with liver cirrhosis. *Hepatogastroenterology* 2004; **51**: 1408-1412 [PMID: 15362765]
50 **Umbro I**, Tinti F, Fiacco F, Zavatto A, Piselli P, Di Natale V, Lai S, Vitarelli A, Corradini SG, Rossi M, Poli L, Berloco PB, Mitterhofer AP. Resistive index and MELD-Na: nephrologic monitoring in cirrhotic patients awaiting liver transplantation. *Transplant Proc* 2013; **45**: 2676-2679 [PMID: 24034022 DOI: 10.1016/j.transproceed.2013.07.040]
51 **National Kidney Foundation.** K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kidney Dis* 2002; **39**: S1-266 [PMID: 11904577]
52 **Francoz C**, Nadim MK, Baron A, Prié D, Antoine C, Belghiti J, Valla D, Moreau R, Durand F. Glomerular filtration rate equations for liver-kidney transplantation in patients with cirrhosis: validation of current recommendations. *Hepatology* 2014; **59**: 1514-1521 [PMID: 24037821 DOI: 10.1002/hep.26704]
53 **Mindikoglu AL**, Dowling TC, Weir MR, Seliger SL, Christenson RH, Magder LS. Performance of chronic kidney disease epidemiology collaboration creatinine-cystatin C equation for estimating kidney function in cirrhosis. *Hepatology* 2014; **59**: 1532-1542 [PMID: 23744636 DOI: 10.1002/hep.26556]

54 **Davis CL**, Gonwa TA, Wilkinson AH. Identification of patients best suited for combined liver-kidney transplantation: part II. *Liver Transpl* 2002; **8**: 193-211 [PMID: 11910564]

55 **Emre S**, Gondolesi G, Polat K, Ben-Haim M, Artis T, Fishbein TM, Sheiner PA, Kim-Schluger L, Schwartz ME, Miller CM. Use of daclizumab as initial immunosuppression in liver transplant recipients with impaired renal function. *Liver Transpl* 2001; **7**: 220-225 [PMID: 11244163 DOI: 10.1053/jlts.2001.22455]

56 **Nair S**, Verma S, Thuluvath PJ. Pretransplant renal function predicts survival in patients undergoing orthotopic liver transplantation. *Hepatology* 2002; **35**: 1179-1185 [PMID: 11981768 DOI: 10.1053/jhep.2002.33160]

57 **Cholongitas E,** Arsos G, Goulis J, Birtsou C, Haidich AB, Nakouti T, Chalevas P, Ioannidou M, Karakatsanis K, Akriviadis E. Glomerular filtration rate is an independent factor of mortality in patients with decompensated cirrhosis. *Hepatol Res* 2013 Oct 11; Epub ahead of print [PMID: 24119148 DOI: 10.1111/hepr.12259]

58 **Lim YS**, Larson TS, Benson JT, Kamath PS, Kremers WK, Therneau TM, Kim WR. Serum sodium, renal function, and survival of patients with end-stage liver disease. *J Hepatol* 2010; **52**: 523-528 [PMID: 20185195 DOI: 10.1016/j.jhep.2010.01.009]

59 **Angeli P**, Gines P. Hepatorenal syndrome, MELD score and liver transplantation: an evolving issue with relevant implications for clinical practice. *J Hepatol* 2012; **57**: 1135-1140 [PMID: 22749942 DOI: 10.1016/j.jhep.2012.06.024]

60 **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 Med* 2005; **31**: 1693-1699 [PMID: 16244877 DOI: 10.1007/s00134-005-2842-7]

61 **Bellomo R**, Ronco C, Kellum JA, Mehta RL, Palevsky P. 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. *Crit Care* 2004; **8**: R204-R212 [PMID: 15312219 DOI: 10.1186/cc2872]

62 **Bagshaw SM**, George C, Dinu I, Bellomo R. A multi-centre evaluation of the RIFLE criteria for early acute kidney injury in critically ill patients. *Nephrol Dial Transplant* 2008; **23**: 1203-1210 [PMID: 17962378 DOI: 10.1093/ndt/gfm744]

63 **Fang JT**, Tsai MH, Tian YC, Jenq CC, Lin CY, Chen YC, Lien JM, Chen PC, Yang CW. Outcome predictors and new score of critically ill cirrhotic patients with acute renal failure. *Nephrol Dial Transplant* 2008; **23**: 1961-1969 [PMID: 18187499 DOI: 10.1093/ndt/gfm914]

64 **Pan HC**, Jenq CC, Tsai MH, Fan PC, Chang CH, Chang MY, Tian YC, Hung CC, Fang JT, Yang CW, Chen YC. Risk models and scoring systems for predicting the prognosis in critically ill cirrhotic patients with acute kidney injury: a prospective validation study. *PLoS One* 2012; **7**: e51094 [PMID: 23236437 DOI: 10.1371/journal.pone.0051094]

65 **Davenport A**, Cholongitas E, Xirouchakis E, Burroughs AK. Pitfalls in assessing renal function in patients with cirrhosis--potential inequity for access to treatment of hepatorenal failure and liver transplantation. *Nephrol Dial Transplant* 2011; **26**: 2735-2742 [PMID: 21690201 DOI: 10.1093/ndt/gfr354]

66 **Delanghe JR**, Cobbaert C, Harmoinen A, Jansen R, Laitinen P, Panteghini M. Focusing on the clinical impact of standardization of creatinine measurements: a report by the EFCC Working Group on Creatinine Standardization. *Clin Chem Lab Med* 2011; **49**: 977-982 [PMID: 21428858 DOI: 10.1515/CCLM.2011.167]

67 **Francoz C**, Prié D, Abdelrazek W, Moreau R, Mandot A, Belghiti J, Valla D, Durand F. Inaccuracies of creatinine and creatinine-based equations in candidates for liver transplantation with low creatinine: impact on the model for end-stage liver disease score. *Liver Transpl* 2010; **16**: 1169-1177 [PMID: 20879015 DOI: 10.1002/lt.22128]

68 **Finkenstedt A**, Dorn L, Edlinger M, Prokop W, Risch L, Griesmacher A, Graziadei I, Vogel W, Zoller H. Cystatin C is a strong predictor of survival in patients with cirrhosis: is a cystatin C-based MELD better? *Liver Int* 2012; **32**: 1211-1216 [PMID: 22380485 DOI: 10.1111/j.1478-3231.2012.02766.x]

69 **Cluzel P**, Martinez F, Bellin MF, Michalik Y, Beaufils H, Jouanneau C, Lucidarme O, Deray G, Grenier PA. Transjugular versus percutaneous renal biopsy for the diagnosis of parenchymal disease: comparison of sampling effectiveness and complications. *Radiology* 2000; **215**: 689-693 [PMID: 10831685 DOI: 10.1148/radiology.215.3.r00ma07689]

70 **Runyon BA**. Introduction to the revised American Association for the Study of Liver Diseases Practice Guideline management of adult patients with ascites due to cirrhosis 2012. *Hepatology* 2013; **57**: 1651-1653 [PMID: 23463403 DOI: 10.1002/hep.26359]

71 **Veldt BJ**, Lainé F, Guillygomarc'h A, Lauvin L, Boudjema K, Messner M, Brissot P, Deugnier Y, Moirand R. Indication of liver transplantation in severe alcoholic liver cirrhosis: quantitative evaluation and optimal timing. *J Hepatol* 2002; **36**: 93-98 [PMID: 11804670 DOI: 10.1016/S0168-8278(01)00228-8]

72 **Villeneuve JP**, Condreay LD, Willems B, Pomier-Layrargues G, Fenyves D, Bilodeau M, Leduc R, Peltekian K, Wong F, Margulies M, Heathcote EJ. Lamivudine treatment for decompensated cirrhosis resulting from chronic hepatitis B. *Hepatology* 2000; **31**: 207-210 [PMID: 10613747 DOI: 10.1002/hep.510310130]

73 **Papatheodoridis GV**, Cholongitas E, Archimandritis AJ, Burroughs AK. Current management of hepatitis B virus infection before and after liver transplantation. *Liver Int* 2009; **29**: 1294-1305 [PMID: 19619264 DOI: 10.1111/j.1478-3231.2009.02085.x]

74 **Lata J**. Hepatorenal syndrome. *World J Gastroenterol* 2012; **18**: 4978-4984 [PMID: 23049205 DOI: 10.3748/wjg.v18.i36.4978]

75 **Kalambokis GN**, Mouzaki A, Rodi M, Pappas K, Fotopoulos A, Xourgia X, Tsianos EV. Rifaximin improves systemic hemodynamics and renal function in patients with alcohol-related cirrhosis and ascites. *Clin Gastroenterol Hepatol* 2012; **10**: 815-818 [PMID: 22391344 DOI: 10.1016/j.cgh.2012.02.025]

76 **Alessandria C**, Ottobrelli A, Debernardi-Venon W, Todros L, Cerenzia MT, Martini S, Balzola F, Morgando A, Rizzetto M, Marzano A. Noradrenalin vs terlipressin in patients with hepatorenal syndrome: a prospective, randomized, unblinded, pilot study. *J Hepatol* 2007; **47**: 499-505 [PMID: 17560680 DOI: 10.1016/j.jhep.2007.04.010]

77 **Angeli P**, Volpin R, Gerunda G, Craighero R, Roner P, Merenda R, Amodio P, Sticca A, Caregaro L, Maffei-Faccioli A, Gatta A. Reversal of type 1 hepatorenal syndrome with the administration of midodrine and octreotide. *Hepatology* 1999; **29**: 1690-1697 [PMID: 10347109 DOI: 10.1002/hep.510290629]

78 **Sort P**, Navasa M, Arroyo V, Aldeguer X, Planas R, Ruizdel-Arbol L, Castells L, Vargas V, Soriano G, Guevara M, Ginès P, Rodés J. Effect of intravenous albumin on renal impairment and mortality in patients with cirrhosis and spontaneous bacterial peritonitis. *N Engl J Med* 1999; **341**: 403-409 [PMID: 10432325 DOI: 10.1056/NEJM199908053410603]

79 **Papparella I,** I Cavalli M, Sticca A, Franco L, Bova S, Semplicini A, Gatta A, Angeli P. First evidence that albumin can directly improve cardiac contractility in cirrhotic rats. *Hepatology* 2007; **46** (Suppl 1): 865A-866a [DOI: 10.1002/hep.22022]

80 **Fernández J**, Navasa M, Garcia-Pagan JC, G-Abraldes J, Jiménez W, Bosch J, Arroyo V. Effect of intravenous albumin on systemic and hepatic hemodynamics and vasoactive neurohormonal systems in patients with cirrhosis and spontaneous bacterial peritonitis. *J Hepatol* 2004; **41**: 384-390 [PMID: 15336440 DOI: 10.1016/j.jhep.2004.05.009]

81 **Martín-Llahí M**, Pépin MN, Guevara M, Díaz F, Torre A, Monescillo A, Soriano G, Terra C, Fábrega E, Arroyo V, Rodés J, Ginès P. Terlipressin and albumin vs albumin in patients with cirrhosis and hepatorenal syndrome: a randomized study. *Gastroenterology* 2008; **134**: 1352-1359 [PMID: 18471512 DOI: 10.1053/j.gastro.2008.02.024]

82 **Sanyal AJ**, Boyer T, Garcia-Tsao G, Regenstein F, Rossaro L, Appenrodt B, Blei A, Gülberg V, Sigal S, Teuber P. A randomized, prospective, double-blind, placebo-controlled trial of terlipressin for type 1 hepatorenal syndrome. *Gastroenterology* 2008; **134**: 1360-1368 [PMID: 18471513 DOI: 10.1053/j.gastro.2008.02.014]

83 **Angeli P**. Review article: prognosis of hepatorenal syndrome--has it changed with current practice? *Aliment Pharmacol Ther* 2004; **20** Suppl 3: 44-46; discussion 47-48 [PMID: 15335400 DOI: 10.1111/j.1365-2036.2004.02113.x]

84 **Restuccia T**, Gomez-Anson B, Guevara M, Alessandria C, Torre A, Alayrach ME, Terra C, Martin M, Castellvi M, Rami L et al: Effects of dilutional hyponatremia on brain organic osmolytes and water content in patients with cirrhosis. *Hepatology* 2004; **39**: 1613-1622 [DOI: 10.1002/hep.20237]

85 **Fabrizi F**, Dixit V, Messa P, Martin P. Terlipressin for hepatorenal syndrome: A meta-analysis of randomized trials. *Int J Artif Organs* 2009; **32**: 133-140 [PMID: 19440988]

86 **Triantos CK**, Samonakis D, Thalheimer U, Cholongitas E, Senzolo M, Marelli L, Leandro G, Patch D, Burroughs AK. Terlipressin therapy for renal failure in cirrhosis. *Eur J Gastroenterol Hepatol* 2010; **22**: 481-486 [PMID: 19952764 DOI: 10.1097/MEG.0b013e3283345524]

87 **Rajekar H**, Chawla Y. Terlipressin in hepatorenal syndrome: Evidence for present indications. *J Gastroenterol Hepatol* 2011; **26** Suppl 1: 109-114 [PMID: 21199521 DOI: 10.1111/j.1440-1746.2010.06583.x]

88 **Dobre M**, Demirjian S, Sehgal AR, Navaneethan SD. Terlipressin in hepatorenal syndrome: a systematic review and meta-analysis. *Int Urol Nephrol* 2011; **43**: 175-184 [PMID: 20306131 DOI: 10.1007/s11255-010-9725-8]

89 **Gluud LL**, Christensen K, Christensen E, Krag A. Systematic review of randomized trials on vasoconstrictor drugs for hepatorenal syndrome. *Hepatology* 2010; **51**: 576-584 [PMID: 19885875 DOI: 10.1002/hep.23286]

90 **Sagi SV**, Mittal S, Kasturi KS, Sood GK. Terlipressin therapy for reversal of type 1 hepatorenal syndrome: a meta-analysis of randomized controlled trials. *J Gastroenterol Hepatol* 2010; **25**: 880-885 [PMID: 20074149 DOI: 10.1111/j.1440-1746.2009.06132.x]

91 **Solà E**, Lens S, Guevara M, Martín-Llahí M, Fagundes C, Pereira G, Pavesi M, Fernández J, González-Abraldes J, Escorsell A, Mas A, Bosch J, Arroyo V, Ginès P. Hyponatremia in patients treated with terlipressin for severe gastrointestinal bleeding due to portal hypertension. *Hepatology* 2010; **52**: 1783-1790 [PMID: 20931555 DOI: 10.1002/hep.23893]

92 **Boyer TD**, Sanyal AJ, Garcia-Tsao G, Blei A, Carl D, Bexon AS, Teuber P. Predictors of response to terlipressin plus albumin in hepatorenal syndrome (HRS) type 1: relationship of serum creatinine to hemodynamics. *J Hepatol* 2011; **55**: 315-321 [PMID: 21167235 DOI: 10.1016/j.jhep.2010.11.020]

93 **Nazar A**, Pereira GH, Guevara M, Martín-Llahi M, Pepin MN, Marinelli M, Solá E, Baccaro ME, Terra C, Arroyo V, Ginès P. Predictors of response to therapy with terlipressin and albumin in patients with cirrhosis and type 1 hepatorenal syndrome. *Hepatology* 2010; **51**: 219-226 [PMID: 19877168 DOI: 10.1002/hep.23283]

94 **Singh V**, Dhungana SP, Singh B, Vijayverghia R, Nain CK, Sharma N, Bhalla A, Gupta PK. Midodrine in patients with cirrhosis and refractory or recurrent ascites: a randomized pilot study. *J Hepatol* 2012; **56**: 348-354 [PMID: 21749847 DOI: 10.1016/j.jhep.2011.04.027]

95 **Caraceni P**, Santi L, Mirici F, Montanari G, Bevilacqua V, Pinna AD, Bernardi M. Long-term treatment of hepatorenal syndrome as a bridge to liver transplantation. *Dig Liver Dis* 2011; **43**: 242-245 [PMID: 20833118 DOI: 10.1016/j.dld.2010.08.001]

96 **Piano S**, Morando F, Fasolato S, Cavallin M, Boscato N, Boccagni P, Zanus G, Cillo U, Gatta A, Angeli P. Continuous recurrence of type 1 hepatorenal syndrome and long-term treatment with terlipressin and albumin: a new exception to MELD score in the allocation system to liver transplantation? *J Hepatol* 2011; **55**: 491-496 [PMID: 21334405 DOI: 10.1016/j.jhep.2011.02.002]

97 **Morelli A**, Ertmer C, Lange M, Westphal M. Continuous terlipressin infusion in patients with septic shock: less may be best, and the earlier the better? *Intensive Care Med* 2007; **33**: 1669-1670 [PMID: 17530219 DOI: 10.1007/s00134-007-0676-1]

98 **Duvoux C**, Zanditenas D, Hézode C, Chauvat A, Monin JL, Roudot-Thoraval F, Mallat A, Dhumeaux D. Effects of noradrenalin and albumin in patients with type I hepatorenal syndrome: a pilot study. *Hepatology* 2002; **36**: 374-380 [PMID: 12143045 DOI: 10.1053/jhep.2002.34343]

99 **Kiser TH**, Fish DN, Obritsch MD, Jung R, MacLaren R, Parikh CR. Vasopressin, not octreotide, may be beneficial in the treatment of hepatorenal syndrome: a retrospective study. *Nephrol Dial Transplant* 2005; **20**: 1813-1820 [PMID: 15956066 DOI: 10.1093/ndt/gfh930]

100 **Singh V**, Ghosh S, Singh B, Kumar P, Sharma N, Bhalla A, Sharma AK, Choudhary NS, Chawla Y, Nain CK. Noradrenaline vs. terlipressin in the treatment of hepatorenal syndrome: a randomized study. *J Hepatol* 2012; **56**: 1293-1298 [PMID: 22322237 DOI: 10.1016/j.jhep.2012.01.012]

101 **Pomier-Layrargues G**, Paquin SC, Hassoun Z, Lafortune M, Tran A. Octreotide in hepatorenal syndrome: a randomized, double-blind, placebo-controlled, crossover study. *Hepatology* 2003; **38**: 238-243 [PMID: 12830007 DOI: 10.1053/jhep.2003.50276]

102 **Esrailian E**, Pantangco ER, Kyulo NL, Hu KQ, Runyon BA. Octreotide/Midodrine therapy significantly improves renal function and 30-day survival in patients with type 1 hepatorenal syndrome. *Dig Dis Sci* 2007; **52**: 742-748 [PMID: 17235705 DOI: 10.1007/s10620-006-9312-0]

103 **Wong F**, Pantea L, Sniderman K. Midodrine, octreotide, albumin, and TIPS in selected patients with cirrhosis and type 1 hepatorenal syndrome. *Hepatology* 2004; **40**: 55-64 [PMID: 15239086 DOI: 10.1002/hep.20262]

104 **Davenport A**. Management of acute kidney injury in liver disease. *Contrib Nephrol* 2010; **165**: 197-205 [PMID: 20427970 DOI: 10.1159/000313759]

105 **Wong F**, Nadim MK, Kellum JA, Salerno F, Bellomo R, Gerbes A, Angeli P, Moreau R, Davenport A, Jalan R, Ronco C, Genyk Y, Arroyo V. Working Party proposal for a revised classification system of renal dysfunction in patients with cirrhosis. *Gut* 2011; **60**: 702-709 [PMID: 21325171 DOI: 10.1136/gut.2010.236133]

106 **Mackelaite L**, Alsauskas ZC, Ranganna K. Renal failure in patients with cirrhosis. *Med Clin North Am* 2009; **93**: 855-869, viii [PMID: 19577118 DOI: 10.1016/j.mcna.2009.03.003]

107 **Pipili C**, Polydorou A, Pantelias K, Korfiatis P, Nikolakopoulos F, Grapsa E. Improvement of hepatic encephalopathy by application of peritoneal dialysis in a patient with non-end-stage renal disease. *Perit Dial Int* 2013; **33**: 213-216 [PMID: 23478376 DOI: 10.3747/pdi.2011.00271]

108 **Guevara M**, Ginès P, Bandi JC, Gilabert R, Sort P, Jiménez W, Garcia-Pagan JC, Bosch J, Arroyo V, Rodés J. Transjugular intrahepatic portosystemic shunt in hepatorenal syndrome: effects on renal function and vasoactive systems. *Hepatology* 1998; **28**: 416-422 [PMID: 9696006 DOI: 10.1002/hep.510280219]

109 **Quiroga J**, Sangro B, Núñez M, Bilbao I, Longo J, García-Villarreal L, Zozaya JM, Betés M, Herrero JI, Prieto J. Transjugular intrahepatic portal-systemic shunt in the treatment

of refractory ascites: effect on clinical, renal, humoral, and hemodynamic parameters. *Hepatology* 1995; **21**: 986-994 [PMID: 7705810 DOI: 10.1016/0270-9139(95)90245-7]

110 **Wong F**, Sniderman K, Liu P, Allidina Y, Sherman M, Blendis L. Transjugular intrahepatic portosystemic stent shunt: effects on hemodynamics and sodium homeostasis in cirrhosis and refractory ascites. *Ann Intern Med* 1995; **122**: 816-822 [PMID: 7741365 DOI: 10.7326/0003-4819-122-11-199506010-00002]

111 **Brensing KA**, Textor J, Perz J, Schiedermaier P, Raab P, Strunk H, Klehr HU, Kramer HJ, Spengler U, Schild H, Sauerbruch T. Long term outcome after transjugular intrahepatic portosystemic stent-shunt in non-transplant cirrhotics with hepatorenal syndrome: a phase II study. *Gut* 2000; **47**: 288-295 [PMID: 10896924 DOI: 10.1136/gut.47.2.288]

112 **Somberg KA**, Lake JR, Tomlanovich SJ, LaBerge JM, Feldstein V, Bass NM. Transjugular intrahepatic portosystemic shunts for refractory ascites: assessment of clinical and hormonal response and renal function. *Hepatology* 1995; **21**: 709-716 [PMID: 7875668 DOI: 10.1016/0270-9139(95)90522-7]

113 **Testino G**, Ferro C, Sumberaz A, Messa P, Morelli N, Guadagni B, Ardizzone G, Valente U. Type-2 hepatorenal syndrome and refractory ascites: role of transjugular intrahepatic portosystemic stent-shunt in eighteen patients with advanced cirrhosis awaiting orthotopic liver transplantation. *Hepatogastroenterology* 2003; **50**: 1753-1755 [PMID: 14696397]

114 **Wong F**, Sniderman K, Liu P, Blendis L. The mechanism of the initial natriuresis after transjugular intrahepatic portosystemic shunt. *Gastroenterology* 1997; **112**: 899-907 [PMID: 9041252 DOI: 10.1053/gast.1997.v112.pm9041252]

115 **Martinet JP**, Fenyves D, Legault L, Roy L, Dufresne MP, Spahr L, Lafortune M, Pomier-Layrargues G. Treatment of refractory ascites using transjugular intrahepatic portosystemic shunt (TIPS): a caution. *Dig Dis Sci* 1997; **42**: 161-166 [PMID: 9009133]

116 **Arroyo V**, Ginès P, Gerbes AL, Dudley FJ, Gentilini P, Laffi G, Reynolds TB, Ring-Larsen H, Schölmerich J. Definition and diagnostic criteria of refractory ascites and hepatorenal syndrome in cirrhosis. International Ascites Club. *Hepatology* 1996; **23**: 164-176 [PMID: 8550036]

117 **KDIGO.** Clinical Practice Guideline for Acute Kidney Injury. *Kidney Inter Suppl* 2012; **2**: 19-36 [DOI: 10.1038/kisup.2011.32]

118 **Levey AS**, Coresh J, Greene T, Stevens LA, Zhang YL, Hendriksen S, Kusek JW, Van Lente F. Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. *Ann Intern Med* 2006; **145**: 247-254 [PMID: 16908915 DOI: 10.7326/0003-4819-145-4-200608150-00004]

119 **Lewis EJ**, Hunsicker LG, Bain RP, Rohde RD. The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. The Collaborative Study Group. *N Engl J Med* 1993; **329**: 1456-1462 [PMID: 8413456]

120 **Levey AS**, Stevens LA, Schmid CH, Zhang YL, Castro AF, Feldman HI, Kusek JW, Eggers P, Van Lente F, Greene T, Coresh J. A new equation to estimate glomerular filtration rate. *Ann Intern Med* 2009; **150**: 604-612 [PMID: 19414839]

121 **Davis CL**, Feng S, Sung R, Wong F, Goodrich NP, Melton LB, Reddy KR, Guidinger MK, Wilkinson A, Lake J. Simultaneous liver-kidney transplantation: evaluation to decision making. *Am J Transplant* 2007; **7**: 1702-1709 [PMID: 17532752]

122 **Eason JD**, Gonwa TA, Davis CL, Sung RS, Gerber D, Bloom RD. Proceedings of Consensus Conference on Simultaneous Liver Kidney Transplantation (SLK). *Am J Transplant* 2008; **8**: 2243-2251 [PMID: 18808402 DOI: 10.1111/j.1600-6143.2008.02416.x]

123 **Nadim MK**, Sung RS, Davis CL, Andreoni KA, Biggins SW, Danovitch GM, Feng S, Friedewald JJ, Hong JC, Kellum JA, Kim WR, Lake JR, Melton LB, Pomfret EA, Saab S, Genyk YS. Simultaneous liver-kidney transplantation summit: current state and future directions. *Am J Transplant* 2012; **12**: 2901-2908 [PMID: 22822723 DOI: 10.1111/j.1600-6143.2012.04190.x]

P- Reviewer: Pan Q **S- Editor:** Ma YJ **L- Editor**: A
E- Editor: Lu YJ

Published by **Baishideng Publishing Group Inc**
8226 Regency Drive, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
http://www.wjgnet.com