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Management of hepatorenal syndrome

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Abstract

Hepatorenal syndrome (HRS) is defined as development of renal dysfunction in patients with chronic liver diseases due to decreased effective arterial blood volume. It is the most severe complication of cirrhosis because of its very poor prognosis. In spite of several hypotheses and research, the pathogenesis of HRS is still poorly understood. The onset of HRS is a progressive process rather than a suddenly arising phenomenon. Since there are no specific tests for HRS diagnosis, it is diagnosed by the exclusion of other causes of acute kidney injury in cirrhotic patients. There are two types of HRS with different characteristics and prognostics. Type 1 HRS is characterized by a sudden onset acute renal failure and a rapid deterioration of other organ functions. It may develop spontaneously or be due to some precipitating factors. Type 2 HRS is characterized by slow and progressive worsening of renal functions due to cirrhosis and portal hypertension and it is accompanied by refractory ascites. The only definitive treatment for both Type 1 and Type 2 HRS is liver transplantation. The most suitable bridge treatment or treatment for patients who are not eligible for transplantation is a combination of terlipressin and albumin. For the same purpose, it is possible to try hemodialysis or renal replacement therapies in the form of continuous veno-venous hemofiltration. Artificial hepatic support systems are important for patients who do not respond to medical treatment. Transjugular intrahepatic portosystemic shunt may be considered as a treatment modality for unresponsive patients to medical treatment. The main goal of clinical surveillance in a cirrhotic patient is prevention of HRS before it develops. The aim of this article is to provide an updated review about the physiopathology of HRS and its treatment.

Key words: Hepatorenal syndrome; Cirrhosis; Renal failure; Vasoconstrictors; Transplantation

Core tip: Hepatorenal syndrome (HRS) is a severe complication of chronic liver diseases and is usually associated with a poor prognosis. It is not a renal disease but a renal dysfunction that develops as a result of a systemic condition associated with liver failure. To prevent HRS by taking some preventive measures is possible and although the definitive treatment is liver transplantation, a rapid diagnosis and prompt initiation of the treatment leads to an important improvement in the prognosis. In this review, we cover the physiopathology, diagnosis and treatment options of HRS.

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INTRODUCTİON

Hepatorenal syndrome (HRS) is defined as unexplainable progressively increasing serum creatinine in a patient with advanced liver disease. HRS is representative of the end stage of a process associated with progressive decrease in renal blood flow and glomerular filtration rate (GFR). Diagnosis is by exclusion of other causes of renal failure since there is no specific diagnostic test. In 1956, a special type of acute renal failure associated with low urinary output and very low urinary sodium excretion without proteinuria was defined[1]. In postmortem examination of these patients, it was observed that the kidney's histological structure was preserved. In 1969, the kidney taken from cadaveric donors with HRS functioned normally[2]. So, it is possible to conclude that HRS is not a renal disease but a renal dysfunction that occurs as a result of a systemic condition. The definitive treatment is liver transplantation (LT). HRS is an important risk factor since it increases the waiting list mortality and incidence of complications after LT[3] and renal function before LT is a predictor of survival[4]. Vasoconstrictive agents constitute the main part of pharmacological treatment, providing a bridge to LT. Hemodialysis, renal replacement therapies and artificial liver support systems may also be used as bridge treatment. The goal of treatment in HRS should be early diagnosis, effective and quick treatment and, most important of all, to take preventive measures. Despite all treatment options, likelihood of failure is still high.

DEFINITION

HRS is one of the most severe complications of cirrhosis and is defined as renal insufficiency emerging in chronic liver disease patients when all the other causes of renal failure are excluded[5]. Renal vasoconstriction, a result of progressive liver failure, is the main underlying reason for renal failure in HRS.

HRS was first classified into two groups, Type 1 and Type 2, by the International Ascites Club in 1994. According to this classification, Type 1 HRS is associated with doubling of initial serum creatinine to a level of more than 2.5 mg/dL or reduction in creatinine clearance because of a decreased glomerular filtration rate to a level less than 20 mL/min in a time period shorter than 2 wk[5-7]. Type 1 HRS usually occurs following a precipitating factor such as infectious conditions, particularly spontaneous bacterial peritonitis (SBP) which is considered the most important factor for HRS[8-11]. Type 2 HRS is a moderate and steady type of renal failure and serum creatinine level is higher than 1.5 mg/dL and often associated with sodium retention[5,7]. Type 2 HRS usually arises spontaneously as a result of refractory ascites[5].

In addition to this data, it is important to consider that the creatinine levels are not always increased in cases of renal failure in decompensated cirrhosis[12,13]. It is possible to say that even milder degrees of renal failure may be associated with a poor prognosis in cirrhotic patients[1,14]. According to the RIFLE (Risk, Injury, Failure, Loss, End stage renal disease) classification, it has been shown that even a small increase in serum creatinine level may be associated with clinically significant outcomes in patients with cirrhosis[15-17]. In accordance with this, the International Ascites Club and the Acute Dialysis Quality Initiative suggested a new definition for acute kidney injury. This new definition includes an increase in serum creatinine level to 0.3 mg/dL or more in a period less than 48 h or a 50% increase in serum creatinine level compared to the baseline levels recorded in previous 6 mo period, regardless of final serum creatinine levels[18].

PATHOPHYSIOLOGY

HRS is a sort of renal dysfunction which is generally reversible and occurs because of advanced liver disease. Although it is not completely ravelled, the most characteristic reason underlying renal dysfunction in HRS is renal vasoconstriction[19].

The four major factors considered to be responsible are: (1) decreased circulating blood volume and, as a result, decreased mean arterial blood pressure because of splanchnic vasodilatation; (2) renal vasoconstriction as a result of the activated renin-angiotensin-aldosterone system since the sympathetic nervous system has been activated; (3) cardiac dysfunction due to cirrhosis; and (4) release of several cytokines and vasoactive mediators which may affect blood flow to the kidneys and glomerular vascular bed[20,21].

The main pathophysiological mechanism in HRS is reduction of circulating blood volume due to increased resistance to blood flow in the cirrhotic liver, resulting in splanchnic blood pooling, which is in fact a multifactorial process[1]. Decreased circulating blood flow which means decreased mean arterial blood pressure causes stimulation of baroreceptors in the carotid body and consequently activation of the sympathetic nervous system. This is followed by activation of the renin-angiotensin-aldosterone system and nonosmotic release of vasopressin which causes a further decrease in systemic vascular resistance, hypotension and vasoconstriction in the renal vessels and glomerular vascular bed[22]. This vasoconstriction cannot be only explained by increased activity of endogenous vasoconstrictor systems. Because of the extreme hemodynamic changes in advanced liver diseases, renal vasodilatator systems become insufficient, creating a vicious cycle which contributes more and more to renal vasoconstriction[22-24].

Factors contributing to the persistence of renal vasoconstriction in spite of the vasodilatation of the

peripheral vasculature have been investigated in several studies. Iwao *et al*[25] investigated the contributing factors of hyperdynamic circulation in cirrhotic patients and found that mesenteric blood flow decreases as liver disease worsens. They concluded that splanchnic arterial vasodilatation plays an important role in the pathogenesis of decreased systemic vascular resistance in cirrhotic patients[25]. In accordance with this data, in some other human and animal studies, it has been shown that splanchnic circulation is the main vascular bed responsible for peripheral vasodilatation[26-29].

Advanced liver disease due to portal hypertension is characterized by a state of hyperdynamic circulation which is accompanied by increased cardiac output[30]. It is hard to understand how cardiac output is increased while myocardial function is usually impaired in cirrhotic patients. The heart in cirrhotic patients usually has several structural and functional abnormalities associated with alterations in ventricular wall size, systolic and diastolic function[31,32]. Although the reasons for these alterations are not known clearly, neurohumoral factors and continous mechanical stress may be responsible[33]. Ventricular function is inhibited due to circulating cytokines, such as tumor necrosis factor-alpha, and nitric oxide in cirrhotic patients. One of the contributing factors to the ventricular dysfunction is reduced beta adrenergic receptor signal transduction in the myocardium[34,35].

Whatever the cause, ventricular wall thickness is increased slightly and the diastolic function deteriorates, especially increasing with physical stress and with the presence of ascites and systolic dysfunction[30,34,36].

Sympathetic nervous system activity is shown to be increased in cases of portal hypertension as a result of the hepatorenal reflex[37,38]. Hepatorenal reflex activation occurs due to decreased sinusoidal blood flow or increased sinusoidal pressure in the liver, as shown in several animal models[38,39]. Increased renal sympathetic nervous system tone is held to be responsible for renal vasoconstriction together with thromboxanes, endotoxins, endothelins and neurotransmitters. Together with the activation of the sympathetic nervous system because of a low effective circulating volume stimulating baroreceptors in the carotid body and aortic arch, activation of the renin-angiotensin-aldosterone system and nonosmotic release of antidiuretic hormone occurs. Although all of these compensatory mechanisms help to provide an effective circulating volume and relatively normalize the mean arterial blood pressure, they also have important effects on renal function.

Vasoactive mediators and cytokines are the other actors in HRS, agents that affect both the systemic and renal circulation. The major ones studied include prostaglandins, endothelins, endotoxins, glucagon, nitric oxide and tumor necrosis factor-α. Among these, nitric oxide has a special role. Primary arterial vasodilatation in the splanchnic circulation, a result of portal hypertension, is the mainstay in explaining the development of renal insufficiency in cirrhotic patients[20]. The major cause of this arterial vasodilatation in the splanchnic circulation is increased synthesis and activity of nitric oxide and some other vasoactive agents[20]. The correlation between increased levels of nitric oxide and high plasma renin-angiotensin-aldosterone system activity and antidiuretic hormone levels accompanied by low urinary Na excretion in cirrhotic patients, especially with ascites, is remarkable[40,41]. It is thought that in the maintenance of hyperdynamic circulation, the hallmark of HRS, nitric oxide may be the primary factor[42]. However, increased nitric oxide levels are not able to prevent renal vasoconstriction. In the early stages of cirrhosis, renal perfusion is provided by increased synthesis and activity of renal vasodilatators, especially prostaglandins and kallikreins[43,44]. Vasodilating prostaglandins are the major actors in supplying glomerular blood flow at the beginning[45], but as the liver disease progresses, vasoconstrictor systems are further activated and synthesis and activity of renal vasodilating factors progressively decrease. The prostaglandin level in the urine of cirrhotic patients is high when compared with that of patients with HRS[46]. The reason for decreased prostaglandin production in HRS is a mystery but it is known that it is not the only factor in the development of HRS.

DIAGNOSIS

HRS is an important risk factor for renal failure in cirrhotic patients. In a prospective study, it was estimated that the 1 year probability of HRS in cirrhotic patients is 18% and the 5 year probability is 39%[47]. HRS was observed in 28% of alcoholic hepatitis cases without identifiable cirrhosis[48]. Major factors precipitating HRS are hyponatremia, high plasma renin-angiotensin-aldosterone system activity, gastrointestinal bleeding, bacterial infections, spontaneous bacterial peritonitis, large volume paracentesis without albumin infusion, some drugs, such as diuretics, aminoglycosides, non-steroid anti-inflammatory drugs, angiotensin converting enzyme inhibitors, surgical interventions and cholestasis[47,49,50]. Also, Doppler ultrasonography may be helpful to detect increased renal resistive index indicating renal vasoconstriction[19].

In chronic liver diseases, it may be difficult to diagnose renal failure since reduction in GFR is usually masked. This may be because urea and creatinine production is decreased due to chronic liver disease, the muscle mass is decreased due to chronic disease and the protein intake is decreased due to the loss of desire to eat. There are no specific diagnostic criteria for diagnosing HRS. The diagnosis is by exclusion of other causes of renal failure in cirrhotic patients. The major symptoms of HRS are decreased GFR (< 40 mL/min) and increased serum creatinine (> 1.5 mg/dL). Other symptoms defining functional characteristics

of HRS are decreased Na excretion (< 10 mmol/L), higher urine osmolality compared to plasma osmolality, hyponatremia (< 130 mmol/L) and decreased diuresis (< 500 mL).

The most widely accepted diagnostic criteria were developed in 1996 by the International Ascites Club when the major and minor criteria were defined. According to this diagnostic criteria, diagnosis of HRS requires the inclusion of all major criteria and the presence of minor criteria are thought to be suggestive for the diagnosis of HRS. Various new concepts have arisen since the first publication of the criteria for the diagnosis of HRS in 1996. These were modified in 2007 by the International Ascites Club[6]. According to current diagnostic criteria, minor criteria are omitted and concurrent bacterial infection is now not a factor that should be excluded in the diagnosis of HRS. Another important alteration is using albumin instead of 0.09% NaCl solution for plasma volume expansion.

The new diagnostic criteria defined by the International Ascites Club in 2007 are listed in Table 1.

Creatinine clearance is the most important diagnostic tool. It is important to exclude other causes of renal failure before the diagnosis of HRS. These include hypovolemia, parenchymal renal diseases, use of nephrotoxic drugs and shock. In cases of hematuria, severe proteinuria and increased renal size on USG, renal parenchymal disease should be considered in the differential diagnosis[51]. In such cases, renal biopsy is required so that the potential need for combined liver and kidney transplantation can be defined[51]. If there is an organic cause of renal insufficiency, urine analysis to see the Na concentration is clinically important. Since muscle mass and production of creatinine in the liver is decreased in chronic liver diseases, serum creatinine levels are not very reliable to evaluate renal function in liver diseases. Creatinine monitoring blood urea level is also insufficient in reflecting the GFR in cases of chronic liver disease[5,6]. So, investigations should be conducted to find more sensitive and specific markers. Some of these markers are cystatin-C, symmetric dimethylarginine, kidney injury molecule-1 and neutrophil gelatinase-associated lipocalin. Cystatin-C has been found to be more sensitive than creatinine in defining decreased GFR in cirrhotic patients[52,53]. Symmetric dimethylarginine, an endogenous inhibitor of nitric oxide synthase, has been shown to be increased in cases of HRS when compared with cirrhotic patients with normal kidney functions[54]. The investigations regarding kidney injury molecule-1 and neutrophil gelatinase-associated lipocalin which are very susceptible to ischemia and indicators of renal tubular injury are ongoing[55,56]. There are few studies about renal tubular damage markers. β2 microglobulin is one of them. It is especially increased in cases of aminoglycoside nephrotoxicity[57]. To make a differential diagnosis of HRS from acute tubular necrosis, gamma glutamyl transpeptidase, transaminase, neutrophil gelatinase-associated lipocalin, IL 8, liver type fatty acid binding protein and hepatitis virus cell receptor Type 1 are other markers which are of interest nowadays but their significance has not yet been evaluated[58].

TREATMENT

The main principle in the treatment of HRS is to bring back renal function until the patients undergo LT. So, all the therapeutic interventions for HRS are a sort of bridge therapy. During the treatment of HRS, etiology oriented treatment of liver diseases such as antiviral drug treatment should not be impeded. The choice of medical treatment depends upon several factors, including the availability of drugs, which is variable according to country and even region, whether the patient is admitted to an intensive care unit and if the patient is a candidate for LT. Cirrhotic patients with gastrointestinal system (GIS) bleeding, ascites, infections, arterial hypotension and dilutional hyponatremia should be monitored closely because of the increased risk of HRS.

Complications like GIS bleeding and spontaneous bacterial peritonitis should be prevented and urgently treated. Large volume paracentesis with plasma volume expansion decreases the incidence of HRS. Diuretic treatment may trigger HRS because of intravascular volume depletion so diuretic treatment should be stopped and electrolyte imbalances such as hyponatremia and hypocalcemia should be corrected. NSAIDs should also be stopped and appropriate infection treatment should be planned.

Effective circulating volume should be increased. Infusion of 0.9% NaCl and synthetic plasma expanders, even by monitoring central venous pressure, has not found to be helpful. It is proved that albumin is the most useful of all volume expanders. After albumin use, incidence of Type 1 HRS has been shown to be decreased. When albumin is used concomitantly with other agents, it has been observed that the effectiveness of these agents was also increased[23,51].

Prostaglandins, dopamine and endothelin receptor blockers were the first renal vasodilatators used in HRS treatment. Oral prostaglandin-E_1 analogue misoprostol or IV prostaglandin infusion did not provide a significant improvement in HRS[59,60]. Intravenous dopamine infusion has also been investigated in several studies but no improvements have been observed in renal function[61,62].

There is no specific vasoconstrictive agent used to increase systemic vascular resistance. Several vasoconstrictive agents such as norepinephrine, angiotensin 2 and vasopressin have been used for this purpose but alone they were not found to be effective. Vasoconstrictive agents, especially when used together with plasma expanders, are the most helpful pharmacological agents in the management of HRS[63,64]. Development of synthetic vasopressin analogues provides an important progression in HRS treatment. Ornipressin and terlipressin are vasoconstrictive agents that are effective on mesenteric circulation rather than renal and other vascular systems. Ornipressin is not

Table 1 Criteria for diagnosis of hepatorenal syndrome in cirrhosis

Cirrhosis with ascites
Serum creatinine > 1.5 mg/dL (133 μmol/L)
Absence of shock
Absence of hypovolemia as defined by no sustained improvement of renal function (creatinine decreasing to < 133 μmol/L) following at least 2 d of diuretic withdrawal (if on diuretics) and volume expansion with albumin at 1 g/kg per day up to a maximum of 100 g/d
No current or recent treatment with nephrotoxic drugs
Absence of parenchymal renal disease as defined by proteinuria < 0.5 g/d, no microhematuria (< 50 red cells/high powered field) and normal renal ultrasonography

being used because of its severe ischemic side effects.

Terlipressin and albumin infusion are the most important choices of treatment in Type 1 HRS[65]. It has been observed that terlipressin is effective in 40%-60% of patients with Type 1 HRS. Clinical response to terlipressin treatment is slow but the reduction in serum creatinine level is continuous[65,66]. To reverse HRS may take a long time and it has been observed that it recurred in 50% of patients. In cases of recurrence, the same treatment regimen is usually found to be successful[7]. When terlipressin and albumin treatment is successful, arterial blood pressure, urine amount and serum Na level increase. Systemic circulation improves and plasma renin and norepinephrine levels decrease significantly. Time required for recovery usually changes depending on the initial serum creatinine level but mean recovery time is 7 d. If the initial serum creatinine level is low, the recovery will be faster[23,51,67,68]. Terlipressin therapy is suggested to be used in combination with albumin. Terlipressin therapy may be given as an IV bolus (0.5-1 mg/4-6 h) or IV continuous infusion with an initial dose of 2 mg/d. During the follow-up period, if a 25% decrease is not observed in serum creatinine level, the IV bolus dose may be increased up to 2 mg/4 h or the IV continuous infusion dose may be increased up to a maximum of 12 mg/d. Monitoring CVP is essential and albumin infusion is required to retain CVP at a level of 10-15 cm H_2O. Albumin is given for 2 d in the form of IV bolus therapy with an initial dose of 1 g/kg (maximum 100 g/d) and the maintenance albumin dose should be 25-50 g/d until terlipressin therapy is ceased and serum creatinine level becomes normal[69]. There are some studies that showed nearly 75% improvement in HRS patients by using a continuous IV infusion of terlipressin. In these studies, how terlipressin is given was also found to be important[70-72]. The information about the treatment of Type 2 HRS by albumin and vasoconstrictive agents is limited. When albumin and vasoconstrictive agents are used in Type 2 HRS treatment, improvement in renal function has been observed but there is a 50% recurrence rate after the cessation of therapy[23,73,74]. The most common side effects of terlipressin treatment are cardiovascular and ischemic and are reported in nearly 12% of patients treated[20,75]. According to the 2012 Cochrane meta-analysis, GIS and infectious side effects did not increase significantly during terlipressin therapy, whereas cardiovascular side effects increased remarkably[76].

Other vasoconstrictive agents currently being used in HRS treatment are somatostatin analogues (octreotide), α-adrenergic agonists, midodrine and norepinephrine. Their effectiveness has been studied in several studies; some found that they are less effective than terlipressin[23,77,78] and some found that their effectiveness is similar to terlipressin[79,80]. Midodrine is an orally available α-adrenergic agonist. Its effect is systemic vasoconstriction. When it is used in combination with octreotide and albumin, systemic and renal hemodynamic status is improved[81]. Midodrine is given orally with an initial dose of 7.5 mg/8 h (maximum: 15 g/8 h) and octreotide may be given either as continuous infusion with a dose of 50 mcg/h or subcutaneously with a dose of 100-200 mcg/8 h. In combination with midodrine and octreotide, albumin is given as an IV bolus with an initial dose of 1 g/kg (maximum: 100 g) and a maintenance dose of 25-50 g/d. Using midodrine and octreotide in combination has been shown to decrease mortality[82]. Nevertheless, the number of patients reported using this therapy is not enough[78,83] so more trials are required for a more accurate conclusion.

Norepinephrine is a vasoconstrictive agent generally used in intensive care units since it is not convenient to use in general medical wards. It is given as an intravenous continuous infusion with a dose of 0.5-3 mg/h. The effectiveness of norepinephrine and terlipressin were shown to be similar, while norepinephrine was cheaper[80,84].

Since dopamine is known to decrease renal vascular resistance and increase renal blood flow, low doses of dopamine were tried in the past. Its clinical effectiveness could not be proved either alone or in combination with ornipressin and the results are controversial[23,78].

According to several studies, increasing mean arterial blood pressure is suggested to have favorable effects on the treatment process. The most used predictors of favorable treatment response are a serum bilirubin concentration of < 10 mg/dL and an increase in mean arterial blood pressure ⩾ 5 mmHg on the third day of treatment[68].

The principle is that the earlier the treatment has been started, the better the results are. If serum creatinine level is < 5 mg/dL when the treatment is started, the probability of a favorable response is increased.

In a study by Nazar *et al*[68] in patients with both decreased bilirubin level and increased mean arterial

blood pressure, treatment success was 100%. In patients with only a decreased bilirubin level, the success rate was found to be 53% and it was 25% in patients with only an increased mean arterial blood pressure. In the patient group, bilirubin levels did not decrease, mean arterial blood pressures did not increase and the success rate was 10%[68]. If there is treatment unresponsiveness, underlying renal disease other than HRS should be considered.

The goal of all vasopressor treatments is to achieve a 10-15 mmHg increase in the mean arterial blood pressure. Increased mean arterial blood pressure is usually associated with decreased serum creatinine levels[85].

For patients with HRS who are not admitted to an intensive care unit, combination therapy with terlipressin and albumin is suggested. If terlipressin is not available, combination therapy with midodrine, octreotide and albumin should be used in patients who are not in the intensive care unit. After two weeks of medical treatment, if there are no improvements in renal function, medical treatment is considered to be useless.

Transjugular intrahepatic portosystemic shunts (TIPS) have been reported to improve renal function in patients with Type 1 HRS[86-88] and it has also been used for the treatment of refractory ascites in patients with Type 2 HRS[89-91]. However, TIPS therapy is possible under limited circumstances because of its contraindications and complications. Major complications associated with TIPS are hepatic encephalopathy which is a common and treatable condition, worsening of hepatic function, bleeding due to the procedure and acute kidney injury because of intravenous contrast injection during the procedure[92]. The underlying mechanism explaining how renal function is improved after TIPS is not known completely. TIPS provides portal decompression in cirrhotic patients, portal pressure decreases and blood pooling in the splanchnic vascular bed returns to the systemic circulation. As a result of this, RAAS and SNS activity is suppressed and renal vasoconstriction improves. In a study investigating renal function after TIPS in seven patients with Type 1 HRS, a significant decrease in serum creatinine level and increase in urine volume was observed in six of the patients in a one month period. This was accompanied by significant improvement in renal blood flow and GFR[86]. However, amelioration of renal function may take as long as six months in some cases after TIPS[89]. Also, the effect of TIPS on survival in Type 1 HRS patients is appreciable. HRS improved in nearly 50% of patients and survival increased more than three months after TIPS[78,87]. In cases of Type 2 HRS when TIPS is applied to control ascites, it was found to be successful and 70% of patients survived the following year[87,93]. The average survival after TIPS was approximately five months which was longer than the expected survival for such patients[86]. Unfortunately, mostly it is too late for patients with HRS to undergo TIPS and so it is suggested as a choice of treatment for only a selected group of patients. Before the decision to undergo TIPS, the high incidence of complications and especially encephalopathy should be considered.

Although LT is the most effective and definitive treatment of liver failure and HRS, supportive treatment modalities are required until LT is carried out. Non biological liver support systems have been developed for this purpose. The mechanism of action is provided by detoxification through a semi-permeable membrane in these non biological support systems. During the course of liver failure, according to the dominant clinical presentation (HRS, hepatopulmonary syndrome, hyperbilirubinemia), the most appropriate type of support system, each with different prominent features, will be chosen. Whereas in HRS venovenous hemodiafiltration is the first choise of treatment in cases of treatment unresponsiveness, a molecular adsorbents recirculating system should be considered. High-flux dialysis provides effective elimination of water soluble substances such as ammonia and lactate but it is insufficient in eliminating substances binding to proteins such as bile acids. Plasma exchange is no longer being used as it is too risky since large volumes are required to be exchanged in this procedure. For that reason, nowadays continuous venovenous hemodiafiltration may be useful in patients with HRS if there is a reversible precipitating factor such as infection[71]. Hemodialysis or continuous hemofiltration is used in the treatment of acute renal failure in cirrhotic patients[94,95]. In a study by Witzke *et al*[96], thirty-day survival was reported as 50% after renal replacement therapy but it is obvious that long term survival is usually poor. According to the Acute Dialysis Quality Initiative Group, renal support therapies should be suggested for patients who are candidates for LT[71]. There are several studies reporting that albumin dialysis has been beneficial in HRS[23,97]. In a randomized controlled trial, a molecular adsorbents recirculating system was observed to be more effective and safer when compared to standard medical treatment in the management of type 3-4 hepatic encephalopathy[23,97]. However, the data about this subject in the literature is limited.

Renal transplantation is the best treatment choice for both Type 1 and Type 2 HRS patients[98]. If liver transplantation is performed after the HRS is improved, posttransplantation morbidity and mortality is decreased. Three year survival after liver transplantation in patients with HRS is 60%, while it is 70%-80% if it is performed before HRS has developed[98,99].

PREVENTION

Prevention of HRS is important since it develops with a constant frequency in cases of SBP and alcoholic hepatitis. It is possible to prevent HRS if SBP is urgently diagnosed and treated. Albumin infusion may help to prevent HRS when SBP develops. Albumin infusion is started together with antibiotherapy with an initial dose of 1.5 g/kg at the time of diagnosis of infection

and albumin infusion is repeated after 48 h with a dose of 1 g/kg[23,100]. The incidence of renal dysfunction is decreased when compared to patients who are not treated with albumin (8% *vs* 31%) and mortality is also decreased (16% *vs* 35%)[100]. Norfloxacin is recommended in selected patients with cirrhosis and ascites. Four hundred mg/day dose of oral norfloxacin in a one year time period was found to decrease SBP development (7% *vs* 61%), decrease HRS development (28% *vs* 41%) and improve survival at three months (94% *vs* 62%) and one year (60% *vs* 48%)[100,101]. In a study investigating whether pentoxifylline is beneficial or not, significant benefit with 1200 mg/d pentoxifylline was observed when compared with placebo[102] but a meta-analysis revealed that pentoxifylline has no benefit in HRS[103].

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