

Hepato-Renal Syndrome: A Complication of Advanced Chronic Liver Disease with Portal Hypertension

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ABSTRACT

The pathophysiology of circulatory and renal dysfunction in cirrhosis and the treatment of ascites and related conditions (hepatorenal syndrome and spontaneous bacterial peritonitis) have been research topics of major interest during the last two decades. Hepatorenal Syndrome (HRS) is a potentially reversible “functional” renal failure occurring in (a) Cirrhosis of liver with ascites (portal hypertension) and hepatic failure; (b) Acute Liver Failure and (c) Alcoholic hepatitis. However, functional renal dysfunction is present even in early stages of chronic liver diseases of any etiology, and HRS is the extreme manifestation of the same. HRS is usually seen in advanced stages presenting with azotemia and ultimately renal failure. Anatomically and histologically the kidneys are normal.

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Key words: Chronic liver diseases; Pathophysiology; Portal hypertension; Acute liver failure

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EPIDEMIOLOGY AND PATHOPHYSIOLOGY

The liver plays an important role in the regulation of renal function under normal conditions^[1]. In absence of cirrhosis, uptake of amino acids by the liver stimulates an increase in renal blood flow, glomeru-

lar filtration rate, and urine volume^[1,2].

There is gradual a deterioration in renal function as cirrhosis advances, progression of which may be influenced by several factors (Figure 1). The effect of this deterioration is basically an inability to maintain the extracellular fluid volume within normal limits. However, the exact pathophysiology of HRS is poorly understood and complex, and probably occurs in stages.

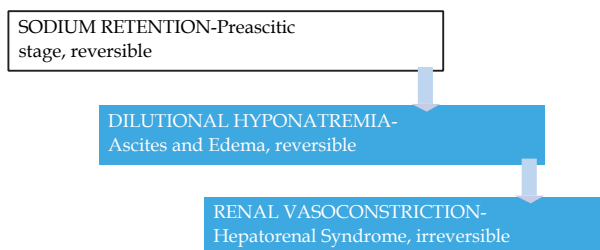


Figure 1 Chronological development of renal dysfunction in Cirrhosis.

Sodium retention by increased renal reabsorption from proximal and distal tubules, is characteristically the most common anomaly of kidney function in cirrhosis. The pathogenesis of sodium retention, the most prevalent renal function abnormality of cirrhosis, is only partially known. In approximately one third of patients with ascites, sodium retention occurs despite normal activity of the renin-aldosterone and sympathetic nervous systems and increased circulating plasma levels of natriuretic peptides and activity of the so-called natriuretic hormone. These patients present an impairment in circulatory function which, although less intense, is similar to that of patients with increased activity of the renin-aldosterone and sympathetic nervous systems, suggesting that antinatriuretic factors more sensitive to changes in circulatory function, and that these systems may be important in the pathogenesis of sodium retention in cirrhosis. It is mild in compensated cirrhosis (without ascites or edema) but increases with disease progression^[3] along with the resultant extracellular fluid retention and ascites. In preascitic stage a cirrhotic can handle this excess sodium balance as long as they keep their salt intake low. But the degree of salt and water retention varies from patient to patient and is not a fixed or unalterable disorder. Therefore, some will quickly develop edema or ascites under conditions of high sodium intake including iv salines or when taking NSAIDs or vasodilators. In cirrhosis, there is also an increased capacitance of the splanchnic vascular

bed. The sodium retention is probably a compensatory mechanism to maintain the blood volume in preascitic cirrhosis in this setting.

The renal water handling and urinary sodium excretion is also variable. Usually those patients in whom water retention is moderate, can maintain their salt and water balance by restricting water intake. However, they may not be able to prevent hyponatremia and water retention after a water load challenge. With disease progression, the severity of sodium retention increases and subsequently solute free water retention also increases leading to dilutional hyponatremia. Therefore, this is commonly seen in cirrhosis with ascites and edema. It is paradoxical in the sense that dilutional hyponatremia occurs in advanced cirrhosis in a background of an increase in total body water and sodium. Several factors can aggravate this abnormal water handling in cirrhotics e.g. iv hypotonic fluids, NSAIDs, diuretics and large volume paracentesis.

Finally there is intense renal vasoconstriction and HRS develops. Hence HRS develops essentially after undergoing the three stages mentioned above.

In portal hypertension, there is also production of several endogenous vasodilators including nitric oxide (NO), a highly diffusible gas, being the most potent vasodilator, which leads to splanchnic vasodilatation causing pooling of blood in splanchnic system^[4]. The precise factors involved in the initiation of peripheral arterial vasodilation remain obscure but possibly occurs in response to mechanical and inflammatory signals in cirrhosis.

A role for chronic increases in levels of nitric oxide has been proposed as a primary cause of both the hyperdynamic circulatory changes and the renal failure. Plasma levels of other vasodilators like glucagon, carbon monoxide (CO), prostacyclins, endogenous opiates, adrenomedullin, substance-P, and calcitonin gene-related peptide are also elevated. Calcitonin gene-related peptide is a potent vasodilator, and circulating levels are increased in patients with alcoholic cirrhosis with ascites but not in controls or cirrhotic patients without ascites^[5-10]. These vasodilators escape into the systemic circulation through the porta systemic shunts present in portal hypertension leading to systemic vasodilatation in later stages. This causes increased cardiac output and renal retention of sodium to increase total blood volume in an effort to maintain hemodynamic stability (hyperdynamic circulation)^[11]. However, there develops a “splanchnic steal” or a functional hypovolemic state whereby maldistribution of blood flow in systemic circulation including to the kidneys develop. Hence, there is actually a reduction in effective arterial blood volume (EABV). Reduced EABV then starts a cascade of compensatory events^[12]: (1) Activation of vasoconstrictor systems (SNS, Renin-angiotensin-aldosterone system and arginine vasopressin) causing sodium retention; (2) Progressive decrease in production of renal vasodilators like prostaglandins and kallikrein which favors renal vasoconstriction; (3) Reduction of renal perfusion pressure with consequent reduction of GFR and secretion of renal vasoconstrictors like endothelin which further deteriorate renal function; and (4) Altered renal autoregulation with due to increasing SNS activity leading to decreased perfusion.

In short, the renal vasoconstriction (particularly in afferent arteries and arterioles) initially starts in HRS due to a changing systemic hemodynamics which ultimately results in an imbalance in favour of vasoconstrictors over the counter-balancing effects of vasodilators in the kidneys. Recently, other factors have also being implicate apart from these e.g. hepatic Adenosine in genesis of HRS. Adenosine increases portal blood flow and stimulate renal excretion of water and sodium by a “Hepato-Renal Reflex” -- mediated principally by SNS. This reflex is hampered in cirrhosis due to increasing portal pressure leading to decreased renal blood flow and thereby may contribute to

HRS as well^[13,14].

Solute free water retention in cirrhosis results primarily from increased secretion of arginine vasopressin (AVP), reduced prostaglandin synthesis and a decrease in filtrate delivery to the ascending loop of Henle (which is the diluting segment of the nephron). Hypersecretion of AVP is a major factor in the initial stages of pathogenesis of HRS. In established renal failure, increased reabsorption of sodium and water from proximal tubules alongwith decreased filtrate delivery to distal tubules increasingly contribute as well^[15]. High AVP secretion leads to PGE2 synthesis by the kidneys to counteract the water retaining effect of AVP, but over time it gets exhausted. In addition, any factor that impairs PG synthesis (eg NSAIDs) may also facilitate dilutional hyponatremia. Dilutional hyponatremia develops over days or weeks and is associated with poor survival. It should be differentiated from true hyponatremia that occurs in some patients on high dose of diuretics. The clinical presentation here may mimick hepatic encephalopathy. If severe, it may also predispose to development of true hepatic encephalopathy^[12].

Additionally in advanced cirrhosis, the hyperdynamic circulation in decompensated cirrhosis compromises cardiac reserve and a lowering of cardiac output (systolic dysfunction), hypotension and a low mean arterial pressure (MAP). This, together with ‘cirrhotic cardiomyopathy’ are risk factors of development of HRS^[16,17,18]. HRS is likely to develop in those cirrhotics who have more severe arterial vasodilatation and lower cardiac output indicating that cardiac dysfunction is an important factor in pathogenesis of HRS. The parameters associated with a higher risk^[18,19] of HRS in cirrhosis with edema (but without azotemia) is shown in table 1. These are based on the physiological changes with their consequences as described above. The hemodynamic changes in different stages of cirrhosis are summarized in table 2.

As mentioned earlier, several clinically relevant extrarenal factors may “trigger” development of HRS in cirrhosis particularly who are hospitalized with ascites and edema by increasing sodium retention plus dilutional hyponatremia or reducing the GFR (Table 2). Infections like SBP which produce bacterial cytokines and vasoactive mediators may worsen arterial vasodilatation leading to decreased

Table 1 Predictors of HRS development.

Previous episodes of ascites
Poor nutritional status
Moderate increase in BUN and/or S. Creatinine
Serm Na<130 mEq/L
Urine Na<10 mEq/L
Plasma renin activity>4 ng/mL/hour
Mean Arterial Pressure <85 mm Hg
Low water excretion (<3 mL/min) after water load
Plasma norepine phrine>500 pg/mL
Esophageal Varices
MELD score

Table 2 Hemodynamic changes during different stages of cirrhosis.

	Compensated Cirrhosis	Diuretic responsive ascites	Diuretic resistant ascites	HRS
Splanchnic/systemic vasodilatation	Normal/ +	+	++	+++
Effective circulating volume	Normal	-	--	---
Renin, Aldosterone, Vasopressin, Norepinephrine	Normal	+	++	+++
Renal sodium retention/plasma volume	+	++	+++	++++
Renal vasoconstriction	Normal	Normal	++	++++

renal perfusion or systolic dysfunction. Volume depletion (diuresis, bleeds, GI fluid loss) is another common factor. Increased synthesis of renal and humoral vasoactive mediators is also part of HRS genesis. These mediators does not cause decreased renal blood flow, but through contraction of mesenchymal cells in the glomeruli, leads to a reduction in the capillary coefficient of glomerular ultrafiltration (Kf) and a subsequent decrease in GFR. Among these factors, endothelins, thromboxane A2, leukotrienes and isoprostanes^[20-24] can be mentioned.

Therefore, cirrhotics are often exposed to a series of clinical situations that cause predisposition towards renal insufficiency that differs from HRS and should be looked for. These include volume depletion (pre-renal azotemia), Sepsis, ATN, drug induced nephropathy NSAIDs, Antibiotics) and glomerulonephritis (in Hep B or C infection).

CLINICAL IMPLICATIONS

HRS is the third commonest complication of Cirrhosis of liver after Variceal bleed and Hepatic encephalopathy, but carries the highest mortality amongst all three. A high index of suspicion is necessary to identify these patients. Hepatorenal syndrome should be suspected in any patient with acute or chronic liver disease and portal hypertension when there is a rise in serum creatinine to above 1.5 mg/dL. The widely followed diagnostic criteria for HRS is given in table 1. Absence of intrinsic renal disease (glomerular and tubular) is mandatory as indicated by proteinuria of >500mg/d, microhematuria (>50 RBCs/hpf) or abnormal renal ultrasonogram. Many conditions may cause pre-renal volume depleted states by vomiting, diarrhea, lactulose, diuretics, ACE inhibitors that may reduce renal perfusion. A therapeutic test using rapid infusion of 1.5 L of isotonic saline solution simultaneously with withdrawal of diuretics should be performed. Improvement in renal function will be shown by a decrease in serum creatinine to less than or equal to 1.5 mg/dL or by an increase in creatinine clearance to more than or equal to 40 mL/min^[25], when HRS is not present. For HRS patients, there is no improvement in renal function following plasma expansion, and this is one of the main criterion for diagnosing HRS. Adequate volume expansion as per the IAC is done by iv albumin (1 gm/kg/d upto maximum 100 mg/d for at least 2 days) and is required before excluding pre-renal renal insufficiency. HRS patients usually have urinary sodium less than 10 mEq/L, since renal tubular function is preserved and the kidneys do not lose their capacity for sodium reabsorption.

There are several aspects that need mention in diagnosis of HRS. Early detection is crucial. It should be noted that, although serum creatinine has high specificity for detecting low GFR, its sensitivity is low, probably because of reduced endogenous production of creatinine associated with the protein undernutrition with subsequent decreased urea production that is commonly present in cirrhosis. This may delay the diagnosis as the required amount of rise in creatinine or blood urea nitrogen may be delayed. The sensitivity of 24-hour creatinine clearance for measuring GFR is greater than the sensitivity of serum creatinine, but it may give an overestimate and therefore careful 24-hour urine collection is needed. This is also frequently impaired, since such patients are mostly oliguric. Hence, Serum creatinine and creatinine clearance may be inadequate markers of renal function even in patients with well-compensated cirrhosis^[26]. In 68 nonazotemic cirrhotic patients with uncomplicated cirrhosis, evidence for renal dysfunction was detected in nearly two thirds^[27], including 21 patients with a creatinine clearance of 50 to 80 mL/min and 25 patients with a creatinine clearance of less than

50 mL/min. Detection of renal insufficiency is clinically important because there is an associated substantial increase in mortality. With a mean follow-up of 180 days, the mortality rate was 24% in patients with a creatinine clearance of 50 to 80 mL/min and 36% in those with a creatinine clearance of less than 50 mL/min, as compared with 9% in those with normal renal function^[27]. It is also important to stress that HRS patients may present with acute tubular necrosis because of intense vasoconstriction that leads to ischemia. About one third of cirrhotic patients with spontaneous bacterial peritonitis also develop renal insufficiency^[28] and one third of such cases recover after treating SBP with appropriate antibiotic therapy. Therefore, SBP needs to be excluded in HRS even if there are no symptoms of SBP.

OTHER METHODS FOR EARLY DETECTION OF HEPATORENAL SYNDROME

Ideally, the glomerular filtration rate should be measured in cirrhotic patients with the use of sensitive techniques such as iothalamate clearance, but this is not feasible in most clinical settings^[29]. Because hepatorenal syndrome is characterized by renal vasoconstriction that appears before clinically recognized disease, several studies have evaluated alternative diagnostic approaches. One of the most promising is the use of Doppler ultrasonography to assess the resistive index, a measure of renal vascular flow resistance^[30]. In 180 patients with liver disease in the absence of azotemia, renal vascular waveform analysis indicated an increase in resistive index in 42%; kidney dysfunction subsequently developed in 55%, as compared with only 6% of those with a normal resistive index. HRS occurred in 26% of those with an elevated resistive index, as compared with only 1% of those with normal values^[30]. In cirrhotic patients with renal failure, the resistive index correlates with the glomerular filtration rate, arterial pressure, plasma renin activity, and free water clearance and has a sensitivity rate and specificity rate for the detection of renal failure of 71% and 80%, respectively^[31].

The resistive index increases progressively from normal values in control patients (0.53±0.03) to higher values in non-ascitic cirrhotic patients (0.67±0.06) and those with ascites. Compared with those with class A cirrhosis values are also higher in Child-Pugh class B and C cirrhotic patients^[32]. Therefore, abnormal values may help identify high-risk patients^[30]. Operator experience is also important, and further information is required before this method can be recommended for routine use.

The cumulative likelihood of HRS occurrence in patients with cirrhosis with ascites can reach up to 18% over one year and up to 39% over five years, with a mean survival period of about two weeks after the establishment of the syndrome^[32]. Retrospective studies have identified HRS in about 17% of the patients with ascites admitted to hospital and in more than 50% of deaths occurring among cirrhotic patients with liver failure^[33,34,35]. Some clinical and laboratory findings seem to indicate a greater tendency for HRS onset, among which clear sodium retention, low water depuration, dilutional hyponatremia, and hyposmolarity. There is also an association with absence of hepatomegaly and the presence of undernutrition and esophageal varices. On the other hand, liver function laboratory tests and the Child-Pugh scale have not been associated with the likelihood of HRS appearance^[36].

HRS is classified into 2 types: type I HRS shows a rapid and progressive decline in renal function with a very poor prognosis (median survival of about 2 weeks); HRS type 2 has a more stable renal failure, with a median survival of about 6 months. Type 2 HRS consists of a moderate and steady or slowly progressive renal

failure. It represents the extreme expression of the circulatory dysfunction that spontaneously develops in patients with cirrhosis. The main clinical problem in these patients is refractory ascites. The serum creatinine levels are usually greater than 1.5 mg/dL and creatinine deuration is less than 40 mL/min. It may change to type 1, and in such cases its prognosis is also poor^[35]. Type-1 HRS is a rapidly progressive acute renal failure that frequently develops in closed temporal relationship with a precipitating event, commonly spontaneous bacterial peritonitis. It is also more frequent in cases of alcoholic hepatitis, or after acute decompensation of hepatic cirrhosis in patients who generally present significant coagulation disorders. In addition to renal failure, patients with type-1 HRS present with multi-organ dysfunction, including the heart, brain, liver, and adrenal glands. Type-1 HRS is the complication of cirrhosis associated with the worst prognosis^[37]. There is usually a doubling of the serum creatinine levels to more than 2.5 mg/dL or by 50% reduction in the initial 24-hour creatinine deuration to less than 20 mL/min within two weeks^[37]. In general, amongst hospitalized patients with decompensated cirrhosis, 39% have acute kidney injuries of various etiologies out of which HRS 1 and HRS 2 constitutes 12% and 9% respectively^[38].

A recent study^[39] has revealed that hepatorenal syndrome (HRS) was the third most common cause of admission to hospital in the intensive care unit (ICU) among 420 patients with cirrhosis, and was only surpassed by upper digestive hemorrhage and encephalopathy. Mortality occurred within one to five years in 69% to 77% of all these patients. The risk factors identified were acute physiology, age, and chronic health evaluation (APACHE) III score of >90 [hazard ratio (HR), 2.2; 95% confidence interval (CI), 1.6 to 2.8; $p < 0.0001$], the use of pressors (HR, 2.5; 95% CI, 1.9 to 3.2; $p < 0.0001$), and jaundice (HR, 1.7; 95% CI, 1.4 to 2.2; $p < 0.0001$). Mortality occurred within 30 days in 92% of the cases presenting all three of these risk factors and in 11% of the cases without any of the above risk factors.

TREATMENT OF HEPATORENAL SYNDROME

Treatment of HRS is a challenge to physicians as it is the most frequent life threatening complication in advanced liver failure with cirrhosis^[40]. It is best to try and prevent HRS rather than treat it once it has occurred. Hence a thorough search for HRS should be the order of the day in any chronic liver disease patient.

Treatment of HRS commonly starts in the setting of portal hypertension with ascites who are being treated with bed rest, sodium restriction and high dose of diuretics including spironolactone but does not respond to intensive treatment after 1 week. Therefore, 'diuretic-resistant ascites' usually is a prelude to HRS. A rise in the serum creatinine to values greater than 1.5 mg/dL in this setting represents a clinical challenge. It is also known that due to a high dose of diuretics itself, 20% of cirrhotics develop renal impairment that improves after diuretic withdrawal^[41]. Hence, deciding when and how to treat HRS involves careful assessment of many confounding factors in a given patient.

In general, there is a belief that the poor prognosis of HRS is associated with liver failure, rather than renal failure and any improvement in renal function hardly affects survival which meant that only liver transplant was the possible therapy in HRS. Inability of vasoactive drugs to be really of any value as therapeutic agents in HRS is no longer accepted. A better understanding of pathophysiology of HRS and recent observation of that reversal of renal dysfunction requires a sustained improvement of hemodynamics in cirrhotics, and finally the demonstration that renal failure per se is an important determinant of prognosis in HRS and cirrhosis of liver

has renewed interest in vasoactive drugs^[42,43].

All potential nephrotoxic agents, including NSAIDs, aminoglycosides, other antibiotics, i.v. contrasts, must be discontinued. In addition, prerenal azotemia can mimic the clinical and laboratory features of hepatorenal syndrome, including oliguria, low urine sodium concentration, and high urine osmolality. Because cirrhotic patients are at risk for prerenal azotemia caused by diuretics, bleeding, and other volume losses, an intravascular volume challenge is required in most patients and should be encouraged. This is one of the major diagnostic criteria of the International Ascites Club, which advocates diuretic withdrawal and a volume challenge of 1.5 L isotonic saline^[29]. The diagnosis of hepatorenal syndrome is one of exclusion. When in doubt, central filling pressures may be assessed by right-sided heart catheterization because, in the setting of ascites and edema, assessment of intravascular volume status may be difficult.

The emergence of diuretic resistance, related to impaired mineralocorticoid escape^[44], represents a major limitation of current treatments. Moreover, diuretic use in the setting of an elevated serum creatinine level is problematic because it increases the risk of deterioration of the GFR through effects on plasma volume. Hence, alternative therapies are often considered. Large-volume paracentesis causes a significant increase in cardiac output and a rapid fall in portal pressure, as well as a fall in plasma renin and aldosterone levels, and has been reported to improve serum creatinine and blood urea nitrogen levels^[45] but it is usually temporary even when adequate iv albumin is given. Also, it must be noted that the creatinine clearance may decrease following large-volume paracentesis, even when the blood urea nitrogen and serum creatinine remain unchanged, probably because of its effects on intravascular volume^[27]. There is also limited evidence to support extracorporeal albumin dialysis^[46], and pharmacologic treatment with low-dose dopamine, the combination of norepinephrine and dopamine^[47], terlipressin^[48], or the vasopressin analog ornipressin^[49]. Studies of these agents were not sufficiently compelling to recommend their routine application in clinical practice. However, now the focus of treatment of HRS 1 is with i.v. Albumin combined with Terlipressin^[50].

Recently 21 studies on HRS were pooled and analyzed to assess the therapeutic responses of different vasoconstrictors^[51] that included terlipressin, octreotide, midodrine and noradrenaline. The mean arterial pressure, urinary output, serum creatinine and plasma rennin activity were measured at baseline and throughout the treatment period. The conclusion was that improved mean arterial pressure and kidney function occurred irrespective of the vasoconstrictors used. However, patients on vasopressin showed a better improvement compared to those on alpha-1-adrenergic agonists.

Consequently therefore, the role of vasoconstrictors as treatment modality have been studied with renewed interest in recent times in HRS because: (1) Physiologically they decrease arterial vasodilation hence reducing the mismatch between circulatory capacitance and intravascular volume in it; (2) The resultant improved EABV decreases the various vaso-constrictor systems leading to improved renal perfusion pressure and thereby an improvement in GFR.

The 3 classes of vasoconstrictors in use are Vasopressin analogues (ornipressin, vasopressin and its analog terlipressin), alpha-adrenergic receptor agonists (norepinephrine, midodrine) and Somatostatin analogue Octreotide.

Ornipressin is not recommended because it causes severe ischemic episodes although it was the first drug to show that pharmacologically HRS can be reversed^[49] and also confirmed by others^[52]. Terlipressin is the most extensively used drug in HRS. However, in most studies

it was combined with i.v. Albumin to improve the associated circulatory dysfunction^[53]. It is a pro-drug whose metabolite—lysine-vasopressin—is gradually released over several hours which leads to minimal ischemic effects, without losing its efficacy. Surprisingly there is no standard dosing of terlipressin because of lack of dose finding studies. Generally started at 1 mg every 4-6 h, it is increased to a maximum of 2 mg every 4-6 h if there is no decrease in serum creatinine by at least 25% of the baseline value after 3 days of therapy. Treatment is continued till the serum creatinine is below 1.5 mg/dL^[54]. Response to therapy is characterized by a slow reduction of serum creatinine value, improvement in urine volume and MAP (mean arterial pressure) and serum sodium. It usually takes 2 weeks and the pre-treatment serum creatinine is obviously directly proportional to response to Terlipressin therapy. Recurrence after withdrawal is uncommon and usually responds well to re-treatment.

Terlipressin improves systemic hemodynamic circulation in cirrhosis, improves EABV, reduces SNS and RAS activity and thereby improves GFR and renal sodium excretion^[55,56].

In HRS 1 patients continuous infusion of terlipressin seems to provide more sustained portal pressure reduction compared to bolus injection with additional benefits of fewer side effects with lower daily dose^[57,58,59].

Studies of terlipressin therapy in HRS 2 is very scanty. In one study^[60] a small number of 11 HRS type 2 patients were treated for 7 days with terlipressin 1 mg 4 hourly. They showed a 73% reduction in serum creatinine value. Amongst these, 88% achieved a value below 1.5 mg/dL.

A multinational study^[61] involving 112 HRS 1 patients compared terlipressin plus albumin versus albumin alone. Compared to placebo, terlipressin group achieved significant improvement in serum creatinine ($p < 0.009$), mean day-14 model End stage liver disease score (-4.1 vs -1.7 , $p < 0.008$) and most importantly, HRS reversal (44% vs 9%, $p < 0.008$). But this study did not show any difference in terms of 6 months (longterm) overall survival or transplant-free interval. Moreover, more patients in terlipressin group (10 vs 4) had side-effects like Myocardial Infarction, or arrhythmias. Another study^[62] involving both HRS 1 and HRS 2 patients (total 46 patients), compared terlipressin 1-2 mg terlipressin plus albumin to albumin alone. Again, in the terlipressin group there was significantly higher rate of improvement kidney function (by 0.7 mg/dL vs no change in placebo), but survival at 3 months was no different and higher cardiovascular myocardial ischemic events, arrhythmia, intestinal ischemia and volume overload was noted in terlipressin group (5 vs 1 patient). Therefore, evidence suggests that short term benefits of terlipressin are not sustained in terms of long term over-all mortality in HRS.

Alpha-adrenergic receptor agonists like Midodrine and Norepinephrine (NE) have also been used in HRS. Midodrine is approved for treating postural hypotension. In a comparative study Midodrine used in cirrhosis without HRS ($n=17$) improved systemic and renal hemodynamics, increased renal sodium excretion and decreased plasma rennin activity, but in HRS 2 patients ($n=8$) these effects were found to be insignificant^[63]. Interestingly however, subsequently it was found that adding subcutaneous Octreotide to Midodrine showed these beneficial effects to be significantly more visible in HRS 1 patients. A retrospective study^[64] compared 75 patients ($n=49$ HRS 1) and ($n=26$ HRS 2) with 87 controls ($n=53$ HRS 1) and ($n=26$ HRS 2). The 75 patients received Octreotide subcutaneously, Midodrine orally and iv Albumin for a mean of 8.4+/- 9.6 days, while the control group received no therapy. In a mean follow-up of 4 months there was significant improvement of GFR

($p=0.03$), and survival ($p=0.007$ for HRS1 and $p=0.0004$ for HRS2).

Terlipressin is also used in HRS. If used alone, the one month survival is poor as compared to when combined with albumin (17% vs 87%)^[53]. Moreover, in HRS 2 terlipressin with albumin does not sustain the beneficial effects and HRS recurs after stoppage of treatment^[60].

IV albumin with dopamine does not show any benefit and the HRS 1 patients showed progressive deterioration during therapy in one study^[64]. It appears that volume expansion and vasopressors are relatively more effective in HRS 1 patients. Combination of iv albumin and vasoconstrictors shows better results especially if given intermittently rather than by continuous infusion. Short term treatment is to be avoided as improvement in circulatory status and GFR in HRS takes time and duration of therapy may need be extended than used now.

Use of NE in HRS are reported in small non-randomized studies. Reversal of HRS1 in 83% of 12 patients were reported in 12 patients in one week^[65]. Recently, NE plus albumin was compared with Terlipressin plus albumin in 9 HRS1 and 13 HRS2 patients and NE was shown to be non-inferior to terlipressin group^[66] with similar rate of side effects but lower cost in NE group. Moreover relapse was less in NE group (29% vs 60%). Similar findings are reported in another study^[67] but the cumulative survival did not differ between the two groups. In spite of cardiac side effects like ventricular hypokinesia and arrhythmias NE can be considered safe and effective as an alternative to terlipressin therapy because of its lower cost and wider availability, in HRS1 provided adequate ICU monitoring is available.

Octreide monotherapy in HRS does not seem to offer more benefit than placebo^[68] and is not recommended. It can be useful in associated variceal bleed or with midodrine as an adjunct therapy.

IV Albumin, apart from being a volume expander, also has anti-oxidant, ligand binding, anti inflammatory and other beneficial metabolic activities^[69]. A variety of albumin therapy has been carried out in HRS – with vasoconstrictors, with furosemide and only albumin. Most of them has not shown any benefit in terms of reversal or survival in HRS, particularly HRS1 and especially when infused alone^[61,62,70,71]. However, these studies included small number of patients.

To sum up the role of vasoconstrictors in HRS, we can not definitely say that they can reverse HRS due to lack of large, randomized and controlled trials. Most of the studies involve HRS1 patients. A meta-analysis^[72] assessing four randomized controlled trials concluded that terlipressin plus albumin was superior to albumin with/without placebo in cirrhotic ascites with HRS1 in improving renal function which seems to improve the likelihood of response to treatment if duration of therapy is prolonged beyond 7 days upto 20 days. Overall it was well tolerated and safe. Another meta-analysis^[73] of randomized studies using all vasoconstrictors showed that a) there was a reduction of all cause mortality favoring vasoconstrictors alone or alongwith iv albumin compared to no intervention or albumin alone in HRS, b) terlipressin with albumin was more effective in improving renal function when compared to albumin alone. In HRS2 vasoconstrictors do improve the renal function but the recurrence rate is high^[74,75]. As of now we do not know whether vasoconstrictors improves survival in HRS1 and whether they can be recommended routinely to be used in HRS2, till ongoing trials are published. A practical and basic approach to suspected cases of HRS will be: (1) Stop diuretics; (2) Volume expansion; and (3) Avoid nephrotoxic drugs.

If there is no improvement, then it is prudent to start IV Albumin, Terlipressin/Octreotide and Midodrine.

There is a subset of patients of HRS who will not respond to vasoconstrictors and will need alternative therapy. It is important to be aware of this fact, especially to identify them from amongst those who are awaiting transplant. A recent meta-analysis of clinical trials^[76] showed that the pooled rate of patients who reversed HRS after terlipressin therapy was 0.52 (95% CI, 0.42; 0.61; $P=0.0001$, $I^2=4.6\%$). The pooled Odds Ratio (OR) for mortality rate in HRS patients who were not responders to terlipressin versus responders was 5.746 (95% CI, 1.5; 21.9; $P=0.0005$).

Predictors of response was assessed in 39 cirrhotics with HRS1 treated with terlipressin plus albumin^[77]. Multivariate analysis showed that baseline serum bilirubin <10 mg/dL (indicating less severe liver disease) and an increase of MAP of >5mm on day 3 of therapy predicted HRS reversal. Another multicentre randomized, double-blind, placebo controlled study of terlipressin in HRS1^[78] found that only those with baseline serum creatinine level <5.6 mg/dL and treatment duration of >3 days of terlipressin achieved HRS reversal. Therefore, severe renal or hepatic dysfunction and lack of improved hemodynamics in first 3 days of treatment are not likely to respond to vasoconstrictors.

Reduction of portal pressure by portocaval shunt is a logical therapy in HRS. Several case reports have proposed a role for transjugular intrahepatic portosystemic shunts (TIPS) in the reversal of HRS^[79,80] in those who do not respond to vasoconstrictors. The use of TIPS alone may be appropriate for some patients with diuretic-resistant refractory ascites, but its role in hepatorenal syndrome (which commonly occurs in the setting of resistant ascites), remains to be established. Brensing *et al*^[81] analyzed the role of TIPS in four studies which included a total of 30 HRS1 patients. The procedure was successful in all patients, with one post-procedural death. GFR and serum creatinine improved significantly by 1-4 weeks and remained stable. There was a reduction in plasma rennin, aldosterone and anti-diuretic hormone levels, especially in those with refractory ascites. Post TIPS hepatic encephalopathy occurred in 9 patients and 5 of them responded to lactulose therapy. In two series transplant was not carried out, while in the other two, 3 out of 9 patients had to undergo transplant within five weeks. Post transplant survival at one, three and six months was 81%, 59% and 44% respectively. However, use of vasoconstrictors followed by TIPS has been tried. Midodrine, Octreotide and albumin therapy, when followed by TIPS in 14 HRS1 patients eventually normalized renal function over 12 months and an overall survival rate of 50%^[82]. Prior to TIPS, they had not achieved normalization of their renal function. In HRS2 terlipressin plus albumin in 11 patients followed by TIPS the serum creatinine decreased to 1.36 +/- 0.3 mg/dL in 9 patients after 1 month post-tips. Ascites disappeared in all from 2nd week onwards^[60]. Most of the cases of HRS, however, are usually not candidates for TIPS secondary to high MELD, encephalopathy or cardiac dysfunction, unless going for liver transplant.

Head-out water immersion has proved to be an interesting and valuable model for studying the pathogenesis and treatment of resistant ascites^[83,84]. In patients with ascites, head-out water immersion increases central blood volume and promotes marked natriuresis and diuresis, with two- to three-fold increases in urine volume and urine sodium excretion^[83,85]. Plasma levels and urinary excretion of norepinephrine decrease, and there generally is a prompt increase in immunoreactive atrial natriuretic factor level^[83]. Thus, if facilities are available, the hemodynamic response to immersion is favorable.

The onset of renal failure in patients with cirrhosis carries a poor prognosis. Plasma renin activity, plasma concentration of antidiuretic

hormone, and serum sodium concentration have some value as predictors of survival^[86], but in the absence of clearly reversible causes, treatment is largely supportive. The traditional view is that dialysis is futile in hepatorenal syndrome except when used as a bridge to liver transplantation^[87]. In patients with preexisting liver disease and acute renal failure (including, but not limited to, hepatorenal syndrome) that requires dialysis, the relative risk of dying is increased substantially in those with thrombocytopenia (platelet count <100000 mm³), hepatic encephalopathy, or an elevated prothrombin time. In the absence of these features, the 1-year survival is 38%^[87]. Renal failure alone in the absence of other contraindications may not exclude dialysis, but the risks are significant.

Other Treatments

The search for treatments other than vasoconstrictors and albumin are continuing without any possibility of being recommended as a treatment option in HRS in near future. Drugs like misoprostol, which is a synthetic drug similar to prostaglandin E1^[88,89], endothelin antagonists^[90], which inhibit the powerful vasoconstriction of endothelin, and n-acetylcysteine^[91], may also be useful for treating HRS^[35].

Hemodialysis, hemofiltration (arterio-venous or veno-venous) and extra-corporeal albumin dialysis are other modalities that need further assessment before their efficacy is defined in HRS. Further research is ongoing in this area. Renal replacement therapy is not justified in terminally ill patients who are not transplant candidates. Recent studies have reported MARS use for HRS treatment, showing that, in comparison with hemodialysis, MARS is better with regard to sodium, creatinine and bilirubin levels and prothrombin time, while it presents similar results for blood albumin, diuresis and mean arterial pressure. The mean survival of patients is also significantly greater with MARS than with hemodialysis or hemofiltration^[63,92].

Lumbar Sympathectomy has also been proposed as a surgical option for HRS treatment. In a small report on eight patients, Solis-Herruzo^[93] suggested that sympathetic block might improve renal function in cirrhotics with HRS, particularly among those with more impaired GFR. In this study, five patients presented basal GFR below 25 mL/min, and in these cases sympathetic block induced a significant increase in GFR, osmolal clearance, urinary sodium excretion, fractional excretion of filtered sodium and effective renal plasma flow and a decrease in plasma rennin activity.

Combined therapy of Shehuang Paste (SHP)—a traditional Chinese medicine --with colonic dialysis in treating patients with refractory cirrhotic ascites complicated with azotemia has been reported to be beneficial in reducing the long-term incidence of HRS^[94].

Liver transplantation

Liver transplantation is the definitive treatment since it eliminates the three central factors leading to pathogenesis of HRS -- liver dysfunction, portal hypertension and the hemodynamic anomalies in decompensated cirrhosis. When successful, full recovery from functional renal failure can be expected. As early as in the 1970s, Iwatsuki *et al*^[95] showed that HRS patients recovered renal function after orthotopic liver transplantation, thereby further highlighting the functional nature of the kidney dysfunction. However, HRS patients present greater morbidity and mortality, with lower survival rates. Gonwa *et al*^[96] showed that there was no difference in perioperative (90-day) mortality. One- and two-year actuarial survival rates in the non-HRS patients were 87.2% and 82.1%, respectively. The actuarial

one- and two-year survival rate for the HRS patients was 76.6% ($p > 0.005$). But the transplant recipients with hepatorenal syndrome or renal failure during transplant had a significantly decreased survival rate at 5 years compared with those without hepatorenal syndrome^[97]. In addition, longer stays in the intensive care unit, longer hospitalizations, and more dialysis sessions were required^[97]. Thus, early transplantation remains the best course whenever possible. In addition, pre-transplant treatment of HRS is logical and may improve survival^[98,99]. However, upto 40% of post transplant patients may become dialysis dependent^[100].

In those with chronic renal failure a combined liver-kidney-transplant (CLKT) may be indicated. This is a difficult issue that needs clear-cut indications e.g. irreversible renal failure or progressively worsening renal dysfunction^[101,102]. But at present, liver transplant alone is considered above CLKD even in patients requiring pre-transplant dialysis because, generally post-op outcome in CLKD is inferior to liver transplant alone^[103]. If the renal failure progresses after liver transplant, then kidney transplant may be indicated.

Prevention of HRS is possible in certain settings like SBP and severe Acute Alcoholic Hepatitis which are known to trigger HRS1. In those with Cirrhosis with SBP, iv Albumin 1.5 g/kg followed by 1g/kg 48 h later plus Cefotaxime markedly reduced HRS1 when compared with Cefotaxime alone (10% vs 33%)^[104]. In the setting of severe Alcoholic Hepatitis administration of Pentoxifyllin 400 mg tid (TNF inhibitor) have been shown to reduce occurrence of HRS1 when compared to placebo (8% vs 35%)^[105]. In addition to reducing occurrence of HRS1 both these studies showed hospital survival benefit. In low protein ascites (<1.5 gm/dL) daily prophylaxis with renally dosed norfloxacin has shown to decrease the incidence of HRS and improved 3 month survival^[106]. In future, vasoconstrictors may be included in studies to prevent HRS in cirrhotics.

CONCLUSION

The pathogenesis of circulatory dysfunction in cirrhosis and the role of local mechanisms in the development of the splanchnic arteriolar vasodilation associated with portal hypertension will continue as important topics in clinical and basic research in Hepatology.

The pathophysiology of circulatory and renal dysfunction in cirrhosis and the treatment of ascites and related conditions like hepatorenal syndrome have been research topics of major interest during the last two decades. However, many aspects of these problem remain unclear and will constitute major areas of investigation in the next millennium. The pathogenesis of sodium retention, the most prevalent renal function abnormality of cirrhosis, is only partially known.

Hepatorenal syndrome occurs in patients with advanced liver cirrhosis and is associated with functional renal impairment and poor prognosis. The main clinical problem in these patients is refractory ascites. These patients present a challenge to physicians and management strategies.

Several approaches have been used for HRS treatment including vasoconstrictor therapy. Recent evidence has shown that vasoconstrictor agents are effective and serve as a bridge to LT; the rationale for vasoconstrictors is to counteract the splanchnic arterial vasodilation and increase the effective arterial blood volume. Although various pharmacological therapies are available, large randomized controlled trials are required to determine which treatment modality is most effective to improve survival rates along with its dose and duration of treatment.

Alternative therapies such as transjugular intrahepatic portosystemic shunts (TIPS) and extracorporeal albumin dialysis (ECAD) have

given encouraging results but experience is extremely limited.

REFERENCES

- Lang F, Tschernko E, Haussinger D. Hepatic regulation of renal function. *Exp Physiol* 1992; **77**: 663-673
- Lang F, Ottl I, Häussinger D, Deetjen P, Ahloulay M, Bankir L. Renal hemodynamic response to intravenous and oral amino acids in animals. *Semin Nephrol* 1995; **15**: 415-418
- Martin PY, Gines P, Schrier RW. Nitric oxide as a mediator of hemodynamic abnormalities and sodium and water retention in cirrhosis. *N Engl J Med* 1998; **339**: 533-541
- Blendis L, Wong F. The hyperdynamic circulation in cirrhosis: an overview. *Pharmacol Ther* 2001; **89**: 221-231
- Lang F, Gerok W, Haussinger D. New clues to the pathophysiology of hepatorenal failure. *Clin Invest Med* 1993; **71**: 93-97
- Epstein M. Hepatorenal syndrome: Emerging perspectives of pathophysiology and therapy. *J Am Soc Nephrol* 1997; **4**: 1735-1753
- Castro M, Krowka MJ, Schroeder DR, Beck KC, Plevak DJ, Rettke SR, Cortese DA, Wiesner RH. Frequency and clinical implications of increased pulmonary artery pressures in liver transplant patients. *Mayo Clin Proc* 1996; **71**: 543-551
- Michielsen PP, Pelckmans PA. Haemodynamic changes in portal hypertension. *Acta Gastroenterol Belg* 1994; **57**: 194-205
- Abrams GA, Nathanson MH. Nitric oxide and liver disease. *Gastroenterologist* 1995; **3**: 220-233
- Gupta S, Morgan TR, Gordan GS. Calcitonin gene-related peptide in hepatorenal syndrome. A possible mediator of peripheral vasodilation? *J Clin Gastroenterol* 1992; **14**: 122-126
- Gines P, Schrier RW. Renal failure and cirrhosis. *N Engl J Med* 2009; **361**: 1279-1290
- Torre A, Uriz J, Guevara A et al. Severe hyponatremia as a major risk factor of hepatic encephalopathy in cirrhosis. *J Hepatol* 2005; **42**: 225-A
- Ming Z, Smyth DD, Lauth WW. Decreases in portal flow trigger a hepatorenal reflex to inhibit renal sodium and water excretion in rats: role of Adenosine. *Hepatology* 2002; **35**: 167-175
- Jalan R, Forrest EH, Redhead DN, Dillon JF, Hayes PC. Reduction in renal blood flow following acute increase in the portal pressure: evidence for the existence of a hepatorenal reflex in man? *Gut* 1997; **40**: 664-670
- Decaux G. Difference in solute excretion during correction of hyponatremic patients with cirrhosis or syndrome of inappropriate secretion of antidiuretic hormone by oral vasopressin V2 receptor antagonist VPA-985. *J Clin Med* 2001; **138**: 18-21
- Wong F. Cirrhotic cardiomyopathy. *Hepatology Int* 2009; **3**: 294-304
- Krag A, Bendtsen F, Henriksen JH, Møller S. Low cardiac output predicts development of hepatorenal syndrome and survival in patients with cirrhosis and ascites. *Gut* 2010; **59**: 105-110
- Ruiz-del-Arbol L, Monescillo A, Arocena C, Valer P, Ginès P, Moreira V, Milicua JM, Jiménez W, Arroyo V. Circulatory function and hepatorenal syndrome in cirrhosis. *Hepatology* 2005; **42**: 439-47
- Gines A, Escorsell A, Gines P, Saló J, Jiménez W, Inglada L, Navasa M, Clària J, Rimola A, Arroyo V. Incidence, predictive factors, and prognosis of hepatorenal syndrome in cirrhosis. *Gastroenterology* 1993; **105**: 229-236
- Gentilini P, Vizzuti F, Gentilini A, La Villa G. Ascites and hepatorenal syndrome. *Eur J Gastroenterol Hepatol* 2001; **13**: 313-316

- 21 Dagher L, Moore K. The hepatorenal syndrome. *Gut* 2001; **49**: 729-737
- 22 Zipser RD, Radvan GH, Kronborg IJ, Duke R, Little TE. Urinary thromboxane B2 and prostaglandin E2 in the hepatorenal syndrome: evidence for increased vasoconstrictor and decreased vasodilator factors. *Gastroenterology* 1983; **84**: 697-703
- 23 Huber M, Kastner S, Scholmerich J, Gerok W, Keppler D. Analysis of cysteinyl leukotrienes in human urine: enhanced excretion in patients with liver cirrhosis and hepatorenal syndrome. *Eur J Clin Invest* 1989; **19**: 53-60
- 24 Morrow JD, Moore KP, Awad JA, Ravenscraft MD, Marini G, Badr KF, Williams R, Roberts LJ 2nd. Marked overproduction of non-cyclooxygenase derived prostanoids (F2-isoprostanes) in the hepatorenal syndrome. *J Lipid Mediat* 1993; **6**: 417-420
- 25 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
- 26 DeSanto NG, Anastasio P, Loguercio C, Spitali L, Del Vecchio Blanco C, Corvinelli M, Girillo M. Creatinine clearance: An inadequate marker of renal filtration in patients with early posthepatic cirrhosis (Child A) without fluid retention and muscle wasting. *Nephron* 1995; **70**: 421-424
- 27 Amarapurkar DN, Dhawan P, Kalro RH. Role of routine estimation of creatinine clearance in patients with liver cirrhosis. *Indian J Gastroenterol* 1994; **13**: 79-82
- 28 Follo A, Llovet JM, Navasa M, Planas R, Fornis X, Francitorra A, Rimola A, Gassull MA, Arroyo V, Rodés J. Renal impairment after spontaneous bacterial peritonitis in cirrhosis: incidence, clinical course, predictive factors and prognosis. *Hepatology* 1994; **20**: 1495-1501
- 29 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. *Hepatology* 1996; **23**: 164-176
- 30 Platt JF, Ellis JH, Rubin JM, Merion RM, Lucey MR. Renal duplex Doppler ultrasonography: A noninvasive predictor of kidney dysfunction and hepatorenal failure in liver disease. *Hepatology* 1994; **20**: 362-369
- 31 Maroto A, Ginès A, Saló J, Clària J, Ginès P, Anibarro L, Jiménez W, Arroyo V, Rodés J. Diagnosis of functional kidney failure or cirrhosis with Doppler sonography: Prognostic value of resistive index. *Hepatology* 1994; **20**: 839-844
- 32 Sacerdoti D, Bolognesi M, Merkel C, Angeli P, Gatta A. Renal vasoconstriction in cirrhosis evaluated by duplex Doppler ultrasonography. *Hepatology* 1993; **17**: 219-224
- 33 Suzuki H, Stanley AJ. Current management and novel therapeutic strategies for refractory ascites and hepatorenal syndrome. *QJM* 2001; **94**: 293-300.
- 34 Gentilini P, Vizzuti F, Gentilini A, La Villa G. Ascites and hepatorenal syndrome. *Eur J Gastroenterol Hepatol* 2001; **13**: 313-316
- 35 Dagher L, Moore K. The hepatorenal syndrome. *Gut* 2001; **49**: 729-737
- 36 Ginès A, Escorsell A, Ginès P, Saló J, Jiménez W, Inglada L, Navasa M, Clària J, Rimola A, Arroyo V. Incidence, predictive factors, and prognosis of the hepatorenal syndrome in cirrhosis with ascites. *Gastroenterology*. 1993; **105**: 229-236
- 37 Arroyo V, Fernandez J, Ginès P. Pathogenesis and treatment of hepatorenal syndrome. *Semin Liver Dis* 2008 Feb; **28**: 81-95
- 38 Carvalho GC, Regis Cde A, Kalil JR, Cerqueira LA, Barbosa DS, Motta MP, da Silva Nery M, Pires Soares MA, Zollinger CC, Bittencourt PL. Causes of renal failure with decompensated cirrhosis and its impact in hospital mortality. *Ann Hepatol* 2012; **11**: 90-95
- 39 Gildea TR, Cook WC, Nelson DR, Aggarwal A, Carey W, Younossi ZM, Arroliga AC. Predictors of long-term mortality in patients with cirrhosis of the liver admitted to a medical ICU. *Chest* 2004; **126**: 1598-1603
- 40 Rajekar H, Chawla Y. Terlipressin in hepatorenal syndrome: Evidence for present indications. *J Gastroenterol Hepatol* 2011; **26** Suppl 1: 109-114
- 41 Rodes J, Bosch J, Arroyo V. Clinical types and drug therapy in cirrhosis. *Postgrad Med J* 1975; **51**: 492-497
- 42 Ginès P, Guevara M, Arroyo V, Rodés J. Hepatorenal syndrome. *Lancet* 2003; **362**: 1819-1827
- 43 Piekarska A, Zboinska J, Szymczak W, Kuydowicz J Independent prognostic factors in patients with liver cirrhosis. *Hepatogastroenterology* 2008; **55**: 1034-1040
- 44 Schrier RW: Peripheral arterial vasodilation in cirrhosis and impaired mineralocorticoid escape. *Gastroenterology* 1992; **102**: 2165-2168
- 45 Luca A, Feu F, García-Pagán JC, Jiménez W, Arroyo V, Bosch J, Rodés J. Favorable effects of total paracentesis on splanchnic hemodynamics in cirrhotic patients with tense ascites. *Hepatology* 1994; **20**: 30-33
- 46 Mitzner SR, Stange J, Klammt S, Risler T, Erley CM, Bader BD, Berger ED, Lauchart W, Peszynski P, Freytag J, Hickstein H, Looock J, Löhr JM, Liebe S, Emmrich J, Kortgen G, Schmidt R. Improvement of hepatorenal syndrome with extracorporeal albumin dialysis MARS: Results of a prospective, randomized, controlled clinical trial. *Liver Transpl Surg* 2000; **6**: 277-286
- 47 Durkin RJ, Winter SM. Reversal of hepatorenal syndrome with the combination of norepinephrine and dopamine. *Crit Care Med* 1995; **23**: 202-204
- 48 Hadengue A, Gadano A, Moreau R, Giostra E, Durand F, Valla D, Erlinger S, Lebrec D. Beneficial effects of the 2-day administration of terlipressin in patients with cirrhosis and hepatorenal syndrome. *J Hepatol* 1998; **29**: 565-570
- 49 Guevara M, Ginès P, Fernández-Esparrach G, Sort P, Salmieron JM, Jiménez W, Arroyo V, Rodés J. Reversibility of hepatorenal syndrome by prolonged administration of ornipressin and plasma volume expansion. *Hepatology* 1998; **27**: 35-41
- 50 Jimena Mucino-Bermejo, Carillo-Esper R, Uribe M, Mendes-Sanchez N. Acute kidney injury in critically ill cirrhotic patients: a review. *Annals of Hepatology* 2012; **3**: 301-310
- 51 Velez JC, Nietert PJ, Therapeutic responses to vasoconstrictors in hepatorenal syndrome parallels the increase in mean arterial pressure: a pooled analysis of clinical trials. *Am J Kidney Dis* 2011; **58**: 928-938
- 52 Ohnishi A, Orita Y, Takagi N, Fujita T, Toyoki T, Ihara Y, Yamamura Y, Inoue T, Tanaka T. Aquarectic effect of a potent, orally active, nonpeptide V2 antagonist in men. *J Pharmacol Exp Ther* 1995; **272**: 546-551
- 53 Ortega R, Ginès P, Uriz J, Cárdenas A, Calahorra B, De Las Heras D, Guevara M, Bataller R, Jiménez W, Arroyo V, Rodés J. Terlipressin therapy with or without albumin for patients with hepatorenal syndrome: results of a prospective, nonrandomized study. *Hepatology* 2002; **36**: 941-948
- 54 Fallon E, Ehrenwald E, Nazarian GK, Smith CI. Diagnosis, prevention and treatment of hepatorenal syndrome in cirrhosis. *Gut* 2007; **56**: 1310-1318
- 55 Krag A, Bendtsen F, Mortensen C, Henriksen JH, Møller S. Effects of a single terlipressin administration on cardiac function and perfusion in cirrhosis. *Eur J Gastroenterol Hepatol* 2010; **22**: 1085-1092
- 56 Krag A, Møller S, Henriksen JH, Holstein-Rathlou NH, Larsen FS, Bendtsen F. Terlipressin improves renal function in patients with cirrhosis and ascites without hepatorenal

- syndrome. *Hepatology* 2007; **46**: 1863-1871
- 57 Angeli P, Fasolato S, Cavallin M et al. Terlipressin given as continuous intravenous infusion is the more suitable schedule for the treatment of type 1 hepatorenal syndrome(HRS) in patients with cirrhosis: results of a controlled clinical trial(abstract). *Hepatology* 2008; **48**(suppl): 378A.
- 58 Gerbes AL, Huber E, Gulberg V. Terlipressin for hepatorenal syndrome: continuous infusion as an alternative to i.v. bolus administration. *Gastroenterology* 2009; **137**: 1179-1181
- 59 Escorsell A, Bandi JC, Moitinho E, Feu F, García-Pagan JC, Bosch J, Rodés J. Time profile of the haemodynamic effects of terlipressin in portal hypertension. *J Hepatol* 1997; **26**: 621-627
- 60 Alessandria C, Venon WD, Marzano A, Barletti C, Fadda M, Rizzetto M. Renal failure in cirrhotic patients: role of terlipressin in clinical approach to hepatorenal syndrome type 2. *Eur J Gastroenterol Hepatol* 2002; **14**: 1363-1368
- 61 Sanyal AJ, Boyer T, Garcia-Tsao G, Regenstein F, Rossaro L, Appenrodt B, Blei A, Gülberg V, Sigal S, Teuber P; Terlipressin Study Group. A randomized, prospective, double-blind, placebo controlled trial of terlipressin for type 1 hepatorenal syndrome. *Gastroenterology* 2008; **134**: 1360-1368
- 62 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; TAHRS Investigators. Terlipressin and albumin vs albumin in patients with cirrhosis and hepatorenal syndrome: a randomized study. *Gastroenterology* 2008; **134**: 1352-1359
- 63 Angeli P, Volpin R, Piovani D, Bortoluzzi A, Craighero R, Bottaro S, Finucci GF, Casiglia E, Sticca A, De Toni R, Pavan L, Gatta A. Acute effects of the oral administration of midodrine, an alpha-adrenergic agonist, on renal hemodynamics and renal function in cirrhotic patients with ascites. *Hepatology* 1998; **28**: 937-943
- 64 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
- 65 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 1 hepatorenal syndrome: a pilot study. *Hepatology* 2002; **36**: 374-380
- 66 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
- 67 Sharma P, Kumar A, Shrama BC, Sarin SK. An open label, pilot, randomized controlled trial of noradrenalin versus terlipressin in the treatment of type 1 hepatorenal syndrome and predictors of response. *Am J Gastroenterol* 2008; **103**: 1689-1697
- 68 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**: 1813-20
- 69 Wong F. Drug insight: the role of albumin in the management of chronic liver disease. *Nat Clin Pract Gastroenterol Hepatol* 2007; **4**: 43-51
- 70 Neri S, Pulvirenti D, Malaguarnera M, Cosimo BM, Bertino G, Ignaccolo L, Siringo S, Castellino P. Terlipressin and albumin in patients with cirrhosis and hepatorenal syndrome. *Dig Dis Sci* 2008; **53**: 830-835
- 71 Péron JM, Bureau C, Gonzalez L, Garcia-Ricard F, de Soyres O, Dupuis E, Alric L, Pourrat J, Vinel JP. Treatment of hepatorenal syndrome as defined by the International Ascites Club by albumin and furosemide infusion according to the central venous pressure: a prospective pilot study. *Am J Gastroenterol* 2005; **100**: 2702-2707
- 72 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
- 73 Gluud LL, Christensen K, Christensen E, Krag A. Systematic review of randomized trials on vasoconstrictor drugs for hepatorenal syndrome. *Hepatology* 2010; **51**: 576-584
- 74 Skagen C, Einstein N, Lucey MR, Said A. Combination treatment with octreotide, midodrine and albumin improves survival in patients with type 1 and type 2 hepatorenal syndrome. *J Clin Gastroenterol* 2009; **43**: 680-685
- 75 Alessandria C, Debernardi-Venon W, Carello M, Ceretto S, Rizzetto M, Marzano A. Midodrine in the prevention of hepatorenal syndrome type 2 recurrence: a case-control study. *Dig Liver Dis* 2009; **41**: 298-302
- 76 Fabrizi F, Martin P, Messa P. Recent advances in the management of hepato-renal syndrome (HRS). *Acta Clin Belg Suppl* 2007; **2**: 393-296
- 77 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
- 78 Boyer TD, Sanyal AJ, Garcia-Tsao G, Blei A, Carl D, Bexon AS, Teuber P; Terlipressin Study Group. Predictors of response to terlipressin plus albumin in hepatorenal syndrome(HRS) type 1: relationship of serum creatinine to hemodynamics. *J Hepatol* 2010 (Epub ahead of print)
- 79 Spahr L, Fenyves D, N'Guyen VV, Roy L, Legault L, Dufresne MP, Pomier-Layrargues G. Improvement of hepatorenal syndrome by transjugular intrahepatic portosystemic shunt. *Am J Gastroenterol* 1995; **90**: 1169-1171
- 80 Sturgis TM. Hepatorenal syndrome: Resolution after transjugular intrahepatic portosystemic shunt. *J Clin Gastroenterol* 1995; **20**:241-243
- 81 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 transjugular portosystemic stent-shunt in non transplant cirrhotics with hepatorenal syndrome: a phase II study. *Gut* 2000; **47**: 288-295
- 82 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
- 83 Grossman E, Goldstein DS, Hoffman A, Wacks IR, Epstein M. Effects of water immersion on sympathoadrenal and dopaminergic systems in humans. *Am J Physiol* 1992; **262**: R993-R999
- 84 Epstein M. Renal sodium retention in liver disease. *Hosp Pract* 1995; **30**: 33-37
- 85 Yersin B, Burnier M, Magnenat P. Improvement of renal failure with repeated head-out water immersions in patients with hepatorenal syndrome associated with alcoholic hepatitis. *Am J Nephrol* 1995; **15**: 260-265
- 86 Maroto A, Ginès A, Saló J, Clària J, Ginès P, Anibarro L, Jiménez W, Arroyo V, Rodés J. Diagnosis of functional kidney failure or cirrhosis with Doppler sonography: Prognostic value of resistive index. *Hepatology* 1994; **20**: 839-844
- 87 Keller F, Heinze H, Jochimsen F, Passfall J, Schuppan D, Büttner P. Risk factors and outcome of 107 patients with decompensated liver disease and acute renal failure: The role of hemodialysis. *Ren Fail* 1995; **17**: 135-146
- 88 Ginès A, Salmerón JM, Ginès P, Arroyo V, Jiménez W, Rivera F, Rodés J. Oral misoprostol or intravenous prostaglandin

- E2 do not improve renal function in patients with cirrhosis and ascites with hyponatremia or renal failure. *J Hepatol* 1993; **17**: 220-226
- 89 Fevery J, Van Cutsem E, Nevens F, Van Steenberghe W, Verberckmoes R, De Groote J. Reversal of hepatorenal syndrome in four patients by peroral misoprostol (prostaglandin E1 analogue) and albumin administration. *J Hepatol* 1990; **11**: 153-158
- 90 Soper CP, Latif AB, Bending MR. Amelioration of hepatorenal syndrome with selective endothelin-A antagonist. *Lancet* 1996; **347**: 1842-1843
- 91 Holt S, Goodier D, Marley R, Patch D, Burroughs A, Fernando B, Harry D, Moore K. Improvement of renal function in hepatorenal syndrome with N-acetylcysteine. *Lancet* 1999; **353**: 294-295
- 92 Mitzner SR, Stange J, Klammt S, Risler T, Erley CM, Bader BD, Berger ED, Lauchart W, Peszynski P, Freytag J, Hickstein H, Looock J, Löhr JM, Liebe S, Emmrich J, Kortgen G, Schmidt R. Improvement of hepatorenal syndrome with extracorporeal albumin dialysis MARS: results of a prospective, randomized, controlled clinical trial. *Liver Transpl* 2000; **6**: 277-286
- 93 Solis-Herruzo JA, Duran A, Favela V, Castellano G, Madrid JL, Muñoz-Yagüe MT, Morillas JD, Estenez J. Effects of lumbar sympathetic block on kidney function in cirrhotic patients with hepatorenal syndrome. *J Hepatol* 1987; **5**: 167-173
- 94 Tong GD, Zhou DQ, He JS. Combined therapy of shehuang paste and colonic dialysis with Chinese medicines for treatment of refractory cirrhotic ascites complicated with azotemia. *Zhongguo Zhong Xi Yi Jie He Za Zhi* 2008; **28**: 788-792
- 95 Iwatsuki S, Popovtzer MM, Corman JL, Ishikawa M, Putnam CW, Katz FH, Starzl TE. Recovery from "hepatorenal syndrome" after orthotopic liver transplantation. *N Engl J Med* 1973; **289**: 1155-1159
- 96 Gonwa TA, Morris CA, Goldstein RM, Husberg BS, Klintmalm GB. Long-term survival and renal function following liver transplantation in patients with and without hepatorenal syndrome--experience in 300 patients. *Transplantation* 1991; **51**: 428-430
- 97 Gonwa TA, Klintmalm GB, Levy M, Jennings LS, Goldstein RM, Husberg BS. Impact of pretransplant renal function on survival after liver transplantation. *Transplantation* 1995; **59**: 361-365
- 98 Nair S, Verma S, Thuluvath PJ. Pre-treatment renal function predicts survival in patients undergoing orthotopic liver transplantation. *Hepatology* 2002; **35**: 1179-1185
- 99 Gonwa TA, Klintmalm GB, Levy M, Jennings LS, Goldstein RM, Husberg BS. Impact of pre-treatment renal function on survival after liver transplantation. *Transplantation* 1995; **59**: 361-365
- 100 Marik PE, Wood K, Starzl TE. The course of type 1 hepatorenal syndrome post liver transplantation. *Nephro Dial Transplant* 2006; **21**: 478-482
- 101 Papafragkakis H, Martin P, Akalin E. Combined liver and kidney transplantation. *Curr Opin Organ Transplant* 2010; **15**: 263-268
- 102 Wong LP, Blackley MP, Andreoni KA, Chin H, Falk RJ, Klemmer PJ. Survival of liver transplant candidates with acute renal failure receiving renal replacement therapy. *Kidney Int* 2005; **68**: 362-370
- 103 Locke JE, Warren DS, Singer AL, Segev DL, Simpkins CE, Maley WR, Montgomery RA, Danovitch G, Cameron AM. Declining outcomes in simultaneous liver-kidney transplantation in the MELD era: ineffective usage of renal allografts. *Transplantation* 2008; **85**: 935-942
- 104 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. Effects of intravenous albumin on renal impairment and mortality in patients with cirrhosis and spontaneous bacterial peritonitis. *N Engl J Med* 1999; **341**: 403-409
- 105 Akriviadis E, Botla R, Briggs W, Han S, Reynolds T, Shakil O. Pentoxifylline improves short term survival in severe acute alcoholic hepatitis: a double-blind, placebo controlled trial. *Gastroenterology* 2000; **119**: 1637-1648
- 106 Munoz SJ. The hepatorenal syndrome. *Med Clin North Am* 2008; **92**: viii-ix, 813-837
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