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Hepatorenal Syndrome: Clinical Considerations

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BACKGROUND

The hepatorenal syndrome (HRS) is a life-threatening form of functional renal failure associated with advanced liver disease. Its management poses one of the most challenging problems in clinical medicine. There are more reviews than original articles on HRS, reflecting the difficulty in investigating this syndrome. Clinical studies likely to generate data for an evidence based approach to the management of HRS are difficult, considering the gravity of the condition and multiple problems of advanced liver failure that usually coexist in the patient afflicted with HRS. Furthermore, no experimental model has been developed for HRS. Many aspects of HRS are therefore still poorly understood. The aim of this article is to review the definition, diagnosis, pathogenesis and rational basis of current therapy in HRS.

EPIDEMIOLOGY

HRS occurs in about 4% of patients admitted with decompensated cirrhosis. The cumulative probability of developing HRS in decompensated cirrhosis is 18% at one year, increasing to 39% at five years[5]. Retrospective studies indicate that HRS is present in ~17% of patients admitted to hospital with ascites and in >50% of cirrhotics dying from liver failure.

DEFINITION

The term 'hepatorenal syndrome' was first coined by surgeons in the 1930s to describe renal failure occurring after biliary surgery or hepatic trauma in patients with previously normal renal function[1]. Interest in this condition was revived after the pioneering study of Hecker and Sherlock in 1956 which showed that renal failure in cirrhosis follows a progressive course may appear in close temporal relationship with complications such as gastrointestinal hemorrhage or bacterial infections and has a poor prognosis[2]. During the 1960s American nephrologists popularized this term for describing an unusual form of renal failure seen in liver cirrhosis. In Europe, however, the terms 'functional renal failure' or 'renal failure of cirrhosis' were preferred by most hepatologists. In 1978, the first consensus conference to define HRS and propose diagnostic criteria, was organized in Sassari, Italy[3]. The International Ascites Club (IAC), founded in Florence, Italy, in 1990, has taken sustained interest in evolving definitions and consensus in this difficult and contentious area. In the light of new developments in the field of HRS research, it proposed a revised definition and diagnostic criteria for HRS, after a consensus conference in Chicago in 1994 that were published in 1996[4] and are currently followed.

To quote the IAC verbatim:

"Hepatorenal syndrome is a syndrome that occurs in patients with chronic liver disease, portal hypertension and advanced hepatic failure. It is characterized by impaired renal function, marked abnormalities in arterial circulation and activity of endogenous vasoactive systems. In the kidney, there is marked renal vasoconstriction that results in low GFR. In the extrarenal circulation there is predominance of arteriolar vasodilation, that results in reduction of total systemic vascular resistance and arterial hypotension. A similar syndrome may also occur in the setting of acute liver failure."

Put more simply, HRS is a complication seen in the setting of portal hypertension and advanced liver failure that is characterized by functional renal failure due to

renal vasoconstriciton in the absence of underlying renal pathology.

DIAGNOSIS

HRS is diagnosed when renal failure develops in the presence of liver disease in an appropriate setting and after exclusion of pre-renal factors, intrinsic renal diseases and complications that could result in an intrinsic renal disease viz. acute renal failure due to acute tubular necrosis (ATN). HRS is a diagnosis of exclusion since no specific diagnostic tests are available to distinguish between HRS and other causes of renal failure occurring in cirrhosis and is based on certain major and minor criteria described in Table 1. There has been some confusion in literature regarding the role of sepsis, SBP, gastrointestinal hemorrhage and other complications in the causation of HRS. Earlier definitions emphasized the exclusion of these factors before diagnosing HRS on the basis that these factors commonly cause intrinsic renal failure due to ATN. However, lately, it has been recognized that these very same factors have a critical role in precipitating HRS type 1 or contributing to the progression of HRS type 2 to type 1. Thus, one of the most common causes of acute renal failure in cirrhotics is the development of spontaneous bacterial peritonitis (SBP), with up to 30% of patients with SBP developing renal failure, which is often HRS type 1. This change is due to the realization that, while these factors of themselves, if severe enough, can precipitate intrinsic renal failure due to ATN, in cirrhotics with liver failure, where HRS physiology is already operating, lesser degrees of severity of these complications can trigger intense renal vasoconstriction and precipitate HRS type 1.

Table 1: Diagnostic criteria for HRS (IAC, 1996)[4]

Major criteria
• Chronic or acute liver disease with advanced hepatic failure and portal hypertension
• Low glomerular filtration rate (serum creatinine > 1.5 mg/dL or 24-h creatinine clearance < 40 mL/min)
• No sustained improvement in renal function following diuretic withdrawal and plasma volume expansion with 1.5 L isotonic saline
• Proteinuria < 500 mg/dL and no ultrasonographic evidence of obstructive uropathy or parenchymal disease
• Absence of shock, ongoing bacterial infection, current or recent treatment with nephrotoxic drugs, excessive gastrointestinal or renal fluid losses
Minor criteria
• Urine volume < 500 mL/day
• Urine sodium < 10 mmol/day
• Urine osmolality greater than plasma osmolality
• Urine red blood cells < 50 per high power field
• Serum sodium concentration < 130 mmol/L
• Only major criteria are required for diagnosis

Renal Failure

The diagnosis of HRS is only made when serum creatinine rises above 1.5 mg/dl. Low GFR is defined by serum creatinine >1.5 mg/dl without diuretic therapy for at least 5 days, though it is realized that serum creatinine levels do not provide a precise estimation of GFR in cirrhosis. Serum creatinine levels are lower than expected due to low endogenous production of creatinine, related to the reduced muscle mass that frequently occurs in advanced cirrhosis and the presence of liver disease. However, other measures of GFR also have limitations and are more cumbersome. Thus, endogenous creatinine clearance, though slightly better, may overestimate GFR by up to 50% and is difficult to perform since it depends on accurate, timed 24-hour urine collection, which is often unsatisfactory in oliguric patients. Inulin clearance for estimation of GFR is expensive and cumbersome, and is not used clinically. Thus, despite limitations, serum creatinine concentration is currently used to estimate GFR in cirrhosis.

Urinary Electrolytes

Most patients with HRS have urine sodium below 10 mEq/L and urine osmolality higher than plasma osmolality because of avid sodium retention with preserved tubular function. Nevertheless, a minority of patients may have higher urine sodium and low urine osmolality similar to values found in acute tubular necrosis, often due to the use of diuretics for oliguria. Conversely, some cirrhotic patients with acute tubular necrosis may have low urine sodium and high urine osmolality. For these reasons, urinary indices are not considered major criteria for the diagnosis of HRS.

Volume Depletion

Factors that may predispose to pre-renal failure such as gastrointestinal fluid losses due to vomiting or diarrhea, or renal fluid losses due to excessive diuretic therapy are common in cirrhotic patients and should be sought meticulously. When azotemia is pre-renal, renal function improves after the intravenous administration of fluids (i.e. 1,500 ml of isotonic saline), whereas no improvement occurs in patients with HRS. Though

resistance to volume expansion is a key factor in diagnosing HRS, caution must be exercised while mounting a 1.5 L fluid challenge in an oliguric patient which might push the patient into pulmonary edema if there is existing or impending fluid overload. Though monitoring the central venous pressure (CVP) is helpful, its limitations must be recognized as CVP may be factitiously low due to peripheral vasodilatation. A careful clinical evaluation of the state of hydration is required, including assessment for fluid balances in the preceding 3-5 day period or since the development of oliguria. In the non-oliguric patient who has been on diuretic therapy and develops renal failure, lack of improvement in renal function following diuretic withdrawal and plasma expansion is highly suggestive of HRS.

Intrinsic Renal Disease

Other causes of renal failure in cirrhosis such as acute tubular necrosis, drug-induced nephrotoxicity, renal failure due to radio-contrast agents, and glomerulonephritis in patients with hepatitis B or C should be excluded before the diagnosis of HRS is made. Insignificant proteinuria, normal urine sediment and a normal renal ultrasound are required to rule out intrinsic renal disease before diagnosing HRS. Proteinuria (>500 mg/day) and/or ultrasonographic abnormalities in the kidneys indicate organic renal disease or obstructive uropathy.

Other criteria include absence of clinical conditions that predispose to the development of acute renal failure (i.e. volume depletion, shock, bacterial infections, or nephrotoxic drugs). Shock, before the development of renal failure in a cirrhotic patient, precludes the diagnosis of HRS, and usually indicates that renal failure is due to ATN. In the presence of significant bacterial infections, the diagnosis of HRS should only be made if renal failure persists after complete resolution of the infection.

TYPES OF HRS

Two patterns of HRS are observed in clinical practice and have been defined by the International Ascites Club.[4]

Type 1 hepatorenal syndrome is an acute form of HRS in which renal failure occurs spontaneously in patients with severe liver disease and is rapidly progressive. It is characterized by rapid reduction, within two weeks, and marked reduction of renal function, as defined by doubling of the initial serum creatinine to a level greater than 2.5 mg/dl or a 50% reduction in initial 24 hour creatinine clearance to <20 ml/min. The development of type 1 HRS signifies very poor prognosis with 80% mortality within two weeks. Rarely, renal function may recover spontaneously following dramatic improvement in liver function. HRS type 1 may occur in the setting of acute liver failure, alcoholic hepatitis, or following acute decompensation on a background of cirrhosis, so-called acute-on-chronic liver failure (ACLF). These patients are usually deeply jaundiced and have significant coagulopathy. Death often results from a combination of hepatic and renal failure or variceal bleeding.

Type 2 hepatorenal syndrome usually occurs in patients with diuretic resistant ascites and is often considered synonymous with refractory ascites (RA). Renal failure has a slow course and may deteriorate over months. It is associated with a poor prognosis, although survival is longer than in patients with type 1 HRS. A variable proportion evolves to HRS type 1, usually in the setting of acute complications.

PATHOPHYSIOLOGY

The pathophysiologic hallmark of HRS is severe vasoconstriction of the renal circulation. Pathogenesis of this vasoconstriction involves a complex interaction between increased portal pressure, changes in the systemic arterial circulation, activation of vasoconstrictor factors and suppression of vasodilator factors acting on the renal circulation. The theory that best explains the relationship among changes in the renal circulation, activation of vasoconstrictor mechanisms, and presence of marked disturbances in systemic hemodynamics is the *arterial vasodilatation theory*. This theory proposes that renal hypoperfusion and vasoconstriction represent an extreme expression of arterial underfilling secondary to a marked vasodilatation of the splanchnic vascular bed.

The first step in the development of HRS is the development of intense splanchnic arterial vasodilatation, mediated by increased production of local vasodilator substances, mainly nitric oxide. This is due to advanced liver failure, which may be of rapid onset, as in alcoholic hepatitis superimposed on alcoholic cirrhosis or in other forms of ACLF and in ALF, and may be exacerbated by complications such as infections (SBP) and gastrointestinal hemorrhage. This intense splanchnic vasodilatation results in systemic arterial underfilling, that may clinically manifest as arterial hypotension, and leads to a baroreceptor-mediated activation of powerful endogenous vasoconstrictor and antinatriuretic systems, notably the renin-angiotensin-aldosterone system (RAAS), the sympathetic nervous system (SNS), and arginine vasopressin (AVP). This

compensation results in sodium and water retention as well as vasoconstriction not only in the renal circulation but also in other vascular beds.

In the early stages of cirrhosis, renal blood flow may be kept within normal limits due to the effect of local vasodilators such as prostaglandins, nitric oxide, and natriuretic peptides that antagonize the renal vascular effect of systemic vasoconstrictors and maintain renal perfusion and glomerular filtration rate (GFR). The renal production of prostaglandins and circulating levels of natriuretic peptides are increased from the early stages of the disease, even in patients with cirrhosis and ascites without HRS. However, with disease progression intense splanchnic vasodilatation results in extreme arterial underfilling causing maximal activation of vasoconstrictor systems and decreased activity of renal vasodilators, leading to severe renal vasoconstriction and reduction in GFR. At this critical point HRS 1 ensues. In some cases a precipitating cause of circulatory dysfunction such as spontaneous bacterial peritonitis (SBP) leads to worsening of renal vasoconstriction. Once vasoconstriction develops, intrarenal mechanisms perpetuate HRS due to the development of intrarenal vicious cycles in which hypoperfusion leads to an imbalance in intrarenal vasoactive systems that in turn causes more vasoconstriction.

DIFFERENTIAL DIAGNOSIS

This includes all the various causes of acute renal failure in patients with cirrhosis or advanced liver failure.

Prerenal

- Gastrointestinal, renal fluid losses
- Hemorrhage
- Shock
- Sepsis
- Congestive heart failure
- Medications: NSAIDs, radiocontrast agents

Intrinsic Renal

- Tubular necrosis
- Ischemia: all causes of prerenal azotemia
- Toxins: aminoglycosides, radiocontrast agents
- Interstitial nephritis
- Immuno-allergic (drugs)
- Infection
- Glomerulonephritis
- Infection

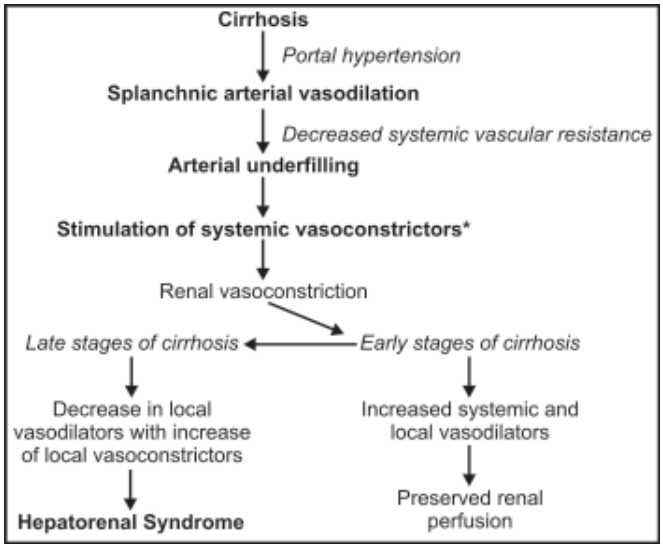

Fig. 1: Pathophysiology of hepatorenal syndrome

Postrenal

- Obstruction of urinary outflow tract.

Prerenal failure must be differentiated from intrinsic renal failure. HRS, by definition a form of functional renal failure, is an extreme example of prerenal failure, where the renal failure is not corrected by volume restitution. It shows all the lab characteristics of prerenal failure and is diagnosed by excluding other causes of prerenal failure in cirrhosis such as overzealous use of diuretics, other drugs (ACD inhibitors, NSAIDs), diarrhea, vomiting and other forms of GI fluid losses. Often, this is best done by fluid challenge.

Table 2: Difference between prerenal vs. intrinsic renal failure

Index	*Prerenal causes*	*Renal causes*
Urinary sodium concentration (mmol/L)	< 20	> 40
Fractional excretion of sodium (%)	< 1	> 1
Ratio of urinary to plasma creatinine	> 40	< 20
Ratio of urinary to plasma osmolality	> 1.5	< 1.1

PROGNOSIS

HRS carries the worst prognosis of all the complications of cirrhosis. Without treatment, the median survival time of patients with type 1 HRS is <2 wk and practically all patients die within 8–10 wk after the onset of renal failure[6]. On the other hand, patients with type 2 HRS have a longer median survival time of approximately 6 months.

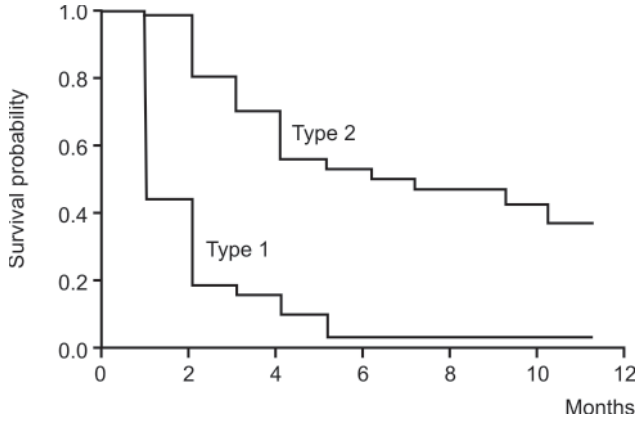

Fig. 2: Survival of the patients with cirrhosis with type 1 and type 2 HRS[6]

MANAGEMENT

Type 1 HRS develops in the setting of advanced liver disease in most cases but in some others it occurs in the setting of acute liver failure. In both situations, patients are very sick and unstable and require hospitalization, preferably in an intensive care unit. A crucial aspect of further management is a quick assessment of the patient's candidacy for liver transplantation. If the patient is a candidate for liver transplantation, the focus of further management is to optimize his condition for the surgery, in as short a time as possible, in order to obtain the best possible outcome after transplantation. To improve renal function the aggressive use of splanchnic vasoconstrictor therapy and other supportive measures such as TIPS, MARS and Prometheus is best justified in this setting.

General Measures

Continuous monitoring of vital signs, fluid intake, daily weights, blood chemistries, and urinary output should be performed. Central venous access with CVP measurement is helpful in assessing volume status, particularly when intravenous fluid challenge is administered to rule out prerenal failure. Although useful, this measure may not be necessary in all cases. In patients with dilutional hyponatremia, fluid restriction to 1 L/day is recommended. Diuretics must be stopped as they can cause worsening renal failure and, in the case of spironolactone, severe hyperkalemia. In patients with tense ascites, large volume paracentesis with albumin infusion (6-8 g/L tapped) may aid in providing symptomatic relief. However, it is not known whether large amounts of ascites can be safely tapped in type 1 HRS without causing further deterioration of renal function. Since most patients have ascites, diagnostic paracentesis must be performed to rule out SBP.

Specific Interventions

Available therapies for type 1 HRS include the use of splanchnic vasoconstrictors and transjugular intrahepatic portosystemic shunts (TIPS). Patients with type 2 HRS are less sick and for the most part have refractory ascites that can be managed with large volume paracentesis and albumin infusion. Suitable candidates need to be evaluated for liver transplantation. Limited data suggest that these patients also respond well to vasoconstrictors and TIPS.

Vasoconstrictor Therapy

The realization that the basic problem in HRS was intense renal vasoconstriction resulted in initial efforts towards achieving renal vasodilatation by various pharmacologic interventions. However, the use of renal vasodilators such as dopamine and prostaglandin and analogues was abandoned due to lack of adequate data confirming benefit and side effects. Other drugs such as endothelin blockers (BQ 123) and N-acetylacysteine are promising, but larger pilot studies followed by controlled studies are needed to establish their role in the therapy of HRS[7].

Systemic vasoconstriction with plasma volume expansion is currently the best medical therapy for HRS type 1, as borne out by several uncontrolled studies confirming benefit. The rationale for the apparently paradoxical use of vasoconstrictors to reverse intense renal vasoconstriction is that systemic infusion of vasodilatation that is at the root of development of HRS, removing the stimulus that reduces effective arterial blood volume and perpetuates HRS. At the same time, albumin infusions expand the effective arterial blood volume and correct the severe apparent 'underfilling'. This approach effectively suppresses the powerful compensatory response mediated by the RAAS, SNS, AVP, etc. and reverses renal vasoconstriction, thus improving renal function.

Vasoconstrictors used in HRS include vasopressin analogues (ornipressin and terlipressin), somatostatin analogues (octreotide), and alpha-adrenergic agonists (midodrine and noradrenaline). Vasopressin analogues have a marked vasoconstrictor effect on the splanchnic circulation and have been used for several years in the management of acute variceal bleeding in cirrhotic patients. Ornipressin, although effective in HRS, caused significant ischemic side effects and was abandoned. The most studied vasopressin analogue in HRS is

terlipressin. The administration of terlipressin and albumin is associated with a significant improvement of GFR and reduction of serum creatinine to below 1.5 mg/dl in approximately 60-75% of patients with type 1 HRS[8]. There is a low incidence of ischemic side effects (<5%) as demonstrated by several studies that pool over 150 patients.

In most studies vasoconstrictors were given in combination with albumin, which improved the efficacy of treatment. Patients with Child-Pugh scores >13 and those who do not receive albumin expansion did not respond well to this treatment. Reversal of HRS occurred over several days but despite improvement in GFR and serum creatinine to normal or near-normal levels, GFR remained below normal values in most patients who responded. Recurrence after stopping treatment in responders was uncommon (≤15% of patients); for recurrent HRS, a repeat course of terlipressin with albumin was usually effective[9]. Administration of midodrine, an oral α1 agonist, in association with octreotide, which inhibits release of glucagon and other vasodilator peptides, and albumin also improved renal function in cirrhotic patients with HRS, although data about this therapeutic approach are limited. A recent study revealed that patients with HRS 1 treated successfully with vasopressin analogues and albumin before liver transplantation had post-transplantation outcome and survival similar to that in patients transplanted witout HRS[16]. This study supports the concept that HRS should be treated aggressively before liver transplantation because improvement in renal function is associated with better outcome. Non-transplant candidates also benefit from this therapy and have reduced morbidity and mortality.

Transjugular Intrahepatic Portosystemic Shunt (TIPS)

TIPS, the non-selective, non-surgical shunt, is a method of portal decompression that reduces portal pressure and returns some of the volume of blood pooled in the splanchnic circulation to the systemic circulation, thus expanding effective circulating arterial blood volume. This suppresses RAAS and SNS activity and ameliorates their vasoconstrictor effect on the renal circulation. Small uncontrolled studies indicated that TIPS may improve renal function and GFR as well as reduce the activity of RAAS and SNS in cirrhotics with type 1 HRS[10]. Improvement in renal function after TIPS placement alone is generally slow with success in approximately 60% of patients[11]. However, the effects on renal function and the clinical course of patients after TIPS insertion are variable: some have a delayed response while others actually worsen. As with surgical nonselective shunts, TIPS carries the risk of worsening of hepatic encephalopathy (HE) and worsening of liver failure. A problem with studies assessing TIPS for type 1 HRS has been the exclusion of those with Child-Pugh score >12 due to the risk of worsening liver failure and/or hepatic encephalopathy. Unfortunately, it is this group that commonly develops type 1 HRS and needs TIPS.

In patients with type 2 HRS, TIPS improves renal function and reduces ascites. However, experience from a large series of cirrhotic patients undergoing TIPS for refractory ascites indicates that those with hepatic encephalopathy, liver failure, and severe coagulopathy are prone to develop further complications. Although uncontrolled studies suggest that TIPS improves prognosis in patients with type 1 and 2 HRS, the impact of this therapy on patient survival remains to be assessed.

Dialysis

Small uncontrolled studies using hemodialysis and peritoneal dialysis suggest that both are ineffective mainly due to a high incidence of severe side effects, including arterial hypotension, coagulopathy, gastro-intestinal bleeding and increased mortality. In some

Table 3: Pharmacological management of hepatorenal syndrome

Drug and references	*Dose range*	*Maximum duration of therapy (days)*	*Potential side-effects*
Terlipressin	0.5-2.0 mg every 4 hour as intravenous bolus	15	Peripheral, splanchnic, or cardiac ischemia
Norepinephrine	0.5-3.0 mg/hour intravenous infusion	15	Peripheral, splanchnic, or cardiac ischemia
Midodrine	7.5-12.5 mg every 8 hour by mouth	Indefinite?	Not reported

centers, hemodialysis is routinely used to treat patients with HRS waiting for liver transplantation. However the effectiveness of dialysis in this setting has not been adequately studied. Continuous arterio-venous or veno-venous hemofiltration have also been used but their efficacy remians to be determined. Although hemodialysis is not routinely recommended in HRS, it may be a reasonable option in suitable liver transplant candidates as a bridge to transplantation when there is no response to vasoconstrictors or TIPS or in patients who develop severe volume overload, metabolic acidosis, or refractory hyperkalemia.

ALBUMIN DIALYSIS

Currently, three systems are available for albumin dialysis.

1. **MARS** (**M**olecular **A**dsorbent **R**ecirculating **S**ystem). MARS was designed by Stange and Mitzner from Germany in 1993 by converting the albumin circuit into a closed circuit and recirculating a fixed volume of dialysate[12]. The system consists of three compartments: a blood circuit, an albumin circuit, and a renal circuit (hemofiltration/hemodialysis). Blood flows through a hollow fiber dialysis module, where it is dialyzed across an albumin-impregnated high-flux polysulfone dialysis membrane; 600 ml of 20% human albumin in the albumin circuit acts as the dialysate, and is passed through the dialysate compartment of the blood dialyzer. Albumin-bound toxins in the plasma pass on to the mebrane-impregnated albumin. These toxins are subsequently picked up by the albumin dialysate, which, in turn, is regenerated by hemofiltration/hemodialysis. Substances with a molecular weight of more than 50 kDa such as essential hormones bound to carrier proteins, growth factors, and albumin are not removed from the perfused plasma because of the pore size of the MARS membrane. A recent randomized-controlled trial evaluated 13 patients with acute-on-chronic renal failure (ACLF) and type 1 HRS who were treated with either MARS (n=8) or standard medical therapy including hemodiafiltration (n=5)[18]. The mortality rate was 100% in the group receiving hemodiafiltration at day 7 compared with 62.5% in the MARS group at day 7 and 75% at day 30, respectively ($p< 0.01$). Mean survival was longer in the MARS group and was accompanied by significant decrease in serum bilirubin and creatinine and rise in serum sodium and prothrombin activity. At the end of treatment, mean arterial pressure (MAP) was significantly higher in the MARS group. Although increase in urine output was not significant in the MARS group, 4 of the 8 patients showed an increase compared with none in the control group.
2. **Prometheus**. First described in 1999, Prometheus acts on the principle of fractioned plasma separation and adsorption, i.e. fractionation of the plasma with the subsequent detoxification of the native albumin by adsorption. It uses an albumin-permeable membrane with a pore size cut-off of 250 kDa. Albumin crosses the membrane and passes through special adsorbers that remove toxins. The cleansed albumin is returned to the plasma. Recently, the results of Prometheus treatment in 11 patients with ACLF and accompanying renal failure have been published[19]. Improvement was noted in serum levels of conjugated bilirubin, bile acids, ammonia, cholinesterase, creatinine, urea, and blood pH. Another study compared alternating treatments with MARS and Prometheus in five patients with ACLF. Reduction ratios of both bilirubin and urea were more with Prometheus. Their safety profiles were found to be comparable. More data from prospective controlled trials are needed to confirm these results and assess the place of the Prometheus system in HRS.
3. **Single pass albumin dialysis (SPAD)**. The newly developed SPAD system dialyzes blood/plasma against a 4.4% solution of albumin, which is disposed of after a single pass. A standard renal replacement therapy machine is used without any additional perfusion pump system, making the equipment required simpler. *In vitro* studies suggest that its detoxifying capacity is similar to, or even greater than that of MARS, especially with regard to bilirubin and ammonia clearance. *In vivo,* however, the only clinical use reported has been in a case of fluminant Wilson's disease, where it was found to efficiently clear bilirubin and copper, both protein-bound, from the plasma. Further experience is required before considering it for routine clinical use[20].

LIVER TRANSPLANTATION

The functional nature of HRS was first proposed by Koppel, et al, in 1969 who noted reversal of renal dysfunction following transplantation of cadaveric kidneys from patients with HRS into patients with a normal liver[13]. This reversal was later confirmed by Iwatsuki, et al in 1973 who demonstrated recovery from HRS after OLT[14]. There is now ample literature documenting recovery of HRS following OLT[15]. Liver only transplantation rather than CKLT should, therefore,

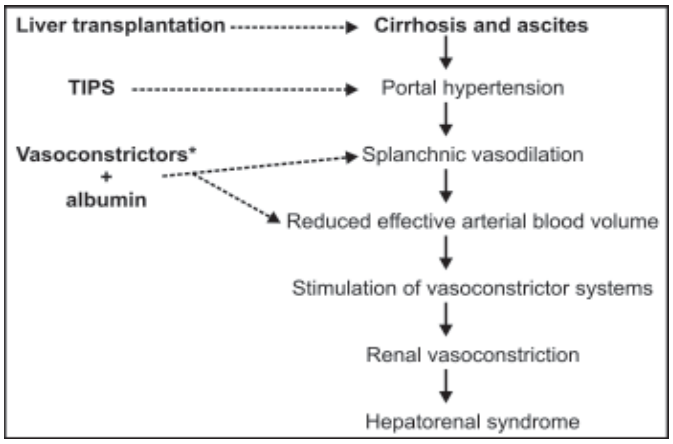

Fig. 3: Rationale of modern therapy in HRS

be the initial option considered in patients with ESLD and associated HRS. Liver transplantation is the best treatment for suitable candidates with HRS, as it offers a cure to both the diseased liver and the circulatory and renal dysfunction. Unfortunately, transplantation for type 1 HRS is limited by the fact that the window available for LT, when the patient is in good condition for the surgery, is very narrow due to short survival for untreated HRS and long waiting times for a suitable donor organ in most centers, so that there is significant waiting list mortality or worsening necessitating removal from the transplant list. The key to successful LT for HRS type 1 is prolonging survival while improving renal function, thus improving the outcome of LT. Patients with HRS 1 treated with vasopressin analogues and albumin before transplantation have a good outcome similar to that of non-HRS patients. The 3-year probability for survival after LT for patients with HRS treated with terlipressin and albumin was excellent (100%) and slightly better than that of cirrhotic patients without HRS (83%) in this study[16].

Prevention

HRS can be prevented in two clinical settings. First, in patients with SBP the administration of albumin (1.5 g/kg at diagnosis of infection and 1 g/kg 48 hours later) prevents the circulatory dysfunction and subsequent development of HRS[17]. The rationale for albumin administration is to prevent arterial underfilling and subsequent activation of vasoconstrictor systems during the infection. The dose of albumin was arbitrarily chosen and it is not known whether smaller doses or other plasma expanders will confer similar benefit in preventing renal failure in the setting of SBP. The incidence of HRS in patients with SBP receiving albumin together with antibiotic therapy is 10%, compared with an incidence of 33% in patients not receiving albumin[17]. Second, in patients with acute alcoholic hepatitis the administration of pentoxifylline, an inhibitor of tumor necrosis factor, (400 mg tid orally for 28 days) reduces the incidence of HRS and mortality (8% and 24%, respectively) with respect to a control group (35% and 46%, respectively)[17]. Further studies confirming these results are lacking. However, the use of albumin infusions in patients with SBP has many benefits and is supported by other studies confirming better control of infection and ascites apart from prevention of HRS. Though popular, the use of pentoxifylline does not enjoy similar support from published studies and its use should be evaluated further before its general use can be recommended.

In conclusion, HRS type 1 remains one of the most serious complications of advanced liver failure and carries a high mortality. It is often the knockout blow for a patient with very poor liver function, reeling from other complications of ESLD such as variceal bleeding and severe infections. It is common in patients with acute-on-chronic liver failure (ACLF) that develops when a severe hepatitic insult, commony due to severe acute viral or alcoholic hepatitis, is superimposed on a cirrhotic liver. Recent advances in the medical management of this condition, particularly the use of vasoconstrictors with plasma volume expansion, have improved the gloomy outlook associated with this complication. In selected patients with HRS 1, where the prospects for liver transplantation are bright, careful management of HRS with optimization of the patient's condition followed by successful liver transplantation can cure this dreaded complication. Judicious use of therapies such as TIPS or some form of albumin dialysis allows the clinician to buy time while optimizing the patient and bridging him to successful liver transplantation. Even in patients who are not transplant candidates, aggressive management of HRS may reverse the acute destabilization that has triggered HRS 1, allowing for recovery from HRS, particularly when there are reversible precipitating events such as bleeding, SBP, other serious infections and potentially reversible illnesses such as ALF and ACLF. Current reports suggest that recurrence of HRS after successful therapy is rare. More work and further studies are required to adequately explore the best ways of applying currently available therapeutic modalities and to develop better ways to deal with this dreaded complication.

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