Hepatorenal Syndrome

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Introduction

The risk of developing renal failure increases as the severity of liver disease worsens [1]. The etiology of kidney injury in cirrhotic patients can be classified as prerenal, intrarenal or postrenal [2]. Prerenal injury is the most common, accounting for almost 60 % of all causes of renal failure in this population. Intrarenal injury, corresponds to glomerular or tubular damage and accounts for approximately 39 % of renal failure in cirrhotic patients. In contrast, postrenal injury (obstructive reasons) is uncommon in this setting. The principle cause of prerenal injury is hypoperfusion. A failure to adequately perfuse the kidney in cirrhosis is often related to hypovolemia caused by adverse events such as gastrointestinal bleeding, severe sepsis or excessive diuretic therapy. However, renal hypoperfusion can also occur in decompensated cirrhosis in the absence of complications associated with portal hypertension.
**Hepatorenal Syndrome (HRS)** is a form of prerenal acute kidney injury that occurs in decompensated cirrhosis. The diagnosis is based on the exclusion of other causes of renal injury. Criteria for the diagnosis of HRS in cirrhosis were updated in 2007 and are displayed in Table 1 [3]. The syndrome is classified into two types: Type 1 is characterized by a doubling of the serum creatinine level to greater than 2.5 mg/dl (221 µmol/L) in less than 2 weeks while Type 2 is characterized by a stable or slower progressive course of renal failure [1]. Patients with Type 1 HRS have an extremely poor prognosis with a median survival of two to four weeks compared with Type 2 HRS, where the median survival is approximately 6 months [1].

**Table 1**: Criteria for hepatorenal syndrome from Salerno et al [3]

<table>
<thead>
<tr>
<th>Criteria 1</th>
<th>Criteria 2</th>
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<th>Criteria 4</th>
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<tbody>
<tr>
<td>Cirrhosis with ascites</td>
<td>Serum creatinine &gt;1.5 mg/dL (133 µmol/L)</td>
<td>No improvement of serum creatinine (decrease to a level of 1.5 mg/dL or less) after at least 2 days with diuretic withdrawal and volume expansion with albumin #</td>
<td>Absence of shock</td>
<td>No current or recent treatment with nephrotoxic drugs</td>
<td>Absence of parenchymal kidney disease as indicated by proteinuria &gt; 500 mg/day, microhematuria (&gt;50 red blood cells per high power field), and/or abnormal renal ultrasonography</td>
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# The recommended dose of albumin is 1 g/kg body weight per day up to a maximum of 100g per day
**Physiopathology**

Splanchnic vasodilatation due to cirrhosis is thought to be the principle cause HRS. As cirrhosis progresses, portal hypertension causes vasodilatation in the splanchnic circulation. This vasodilatation is caused by an increased production or activity of endogenous vasodilators (nitric oxide, carbon monoxide, and endogenous cannabinoids) that are synthesized in the splanchnic circulation [1, 2]. Subsequently, vasodilatation leads to relative systemic arterial underfilling. This in turn causes hyperdynamic circulatory flow and manifests as high cardiac output, low systemic resistances. The resulting fall in arterial blood pressure leads to a reduction in renal perfusion pressure.

Compensatory mechanisms are activated in response to a fall in arterial vascular filling. These include the reflex stimulation of the renin-angiotensin-aldosterone system and an increase in the sympathetic nerve activity. In addition, vasopressin secretion is increased to correct the excessive vasodilatation. Plasma levels of endogenous vasoconstrictors (norepinephrine, angiotensin-II, arginine-vasopressin) are significantly increased during HRS [2]. However, this systemic neurohormonal response predominantly affects the systemic circulation including the kidney circulation. These changes cause vasoconstriction with a decrease of the renal blood flow.

Additionally, an increase in abdominal compartment pressure due to ascites can negatively influence renal blood flow. It has been suggested that the reduction of abdominal pressure following paracentesis may improve renal function, by improving renal blood flow [4]. Finally, it has been recently suggested that the development of renal failure in patients with advanced cirrhosis and ascites could be related to a cardiac systolic dysfunction [5]. In
addition, it has been shown that a substantial proportion of patients with HRS could have underlying chronic kidney damage due to other causes [6].

**Treatment**

The definitive treatment of HRS is liver transplantation (LT). Other treatments are only used as a bridge toward LT.

**Vasoconstrictors**

Vasoconstrictors are commonly used to treat HRS. This class of drugs induces splanchnic vasoconstriction and reduces the reflex arc that drives the synthesis of vasoconstrictive neurohormones. Blood volume moves from the splanchnic venous circulation back into the systemic circulation. This in turn improves arterial underfilling, increases arterial blood pressure, decreases the renal vasoconstriction and consequently restores renal blood flow. These hypotheses are supported by clinical observations. First, administration of vasoconstrictors is consistently associated with a decrease in endogenous neurohormones such as norepinephrine, and angiotensin. Second, it has been shown that administration of the vasopressin analogue, Terlipressin in HRS patients was associated with a significant increase in both mean arterial pressure and systemic vascular resistance. As portal venous flow decreased, the hepatic arterial velocity increased. This resulted in a fall in hepatic and renal arterial resistive index. Plasma renin activity also decreased significantly. There was a notable correlation between the decline in renin activity and the decrease in renal arterial resistive index [7].

Vasopressin analogues (Terlipressin) have been extensively studied but there are some preliminary studies of adrenergic agonists (norepinephrine or Midodrine). Therapeutic
algorithms are presented in Table 2. Several randomized studies combining Terlipressin or norepinephrine with intravenous albumin have been performed in type I HRS (reviewed in [2, 8]). Terlipressin was compared to placebo or norepinephrine. Patients are usually considered to have a beneficial response if there is a reduction of serum creatinine levels below 1.5 mg/dl (133 µmol/l) [3]. Terlipressin administration was associated with an improvement in HRS in about 34 to 83 % of HRS patients. However, Terlipressin is not currently available in the USA. Norepinephrine and Midodrine are less expensive and are more widely available.

Table 2: Therapeutic algorithms for HRS adapted from Gines, Moreau and Gluud [1, 2, 8]

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Regimens</th>
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<tr>
<td>Terlipressin</td>
<td>Usual: 1-2 mg four times per day</td>
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<tr>
<td></td>
<td>Others: 0.5 to 2 mg two to six times /day</td>
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<tr>
<td>Norepinephrine</td>
<td>Titrated to increase mean arterial pressure (maximum 3mg/h or 0.7 µg/kg/min</td>
</tr>
<tr>
<td>Midodrine</td>
<td>7.5 mg orally 3 times/day, with an increase to 12.5 mg 3 times per day if needed, in association with octreotide</td>
</tr>
<tr>
<td>Albumin</td>
<td>First day: 1g/kg or 20 to 100 g</td>
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<tr>
<td></td>
<td>Following day: 20 to 80 g per day</td>
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HRS improved in 50-80% of patients who received continuous administration of norepinephrine [2]. However, to reliably determine whether norepinephrine and Terlipressin are equally efficacious in HRS will require large randomized trials [9]. It is interesting to note that most vasoconstrictors are given with albumin. The albumin itself might play an independent role in correcting hypovolemia associated with renal hypoperfusion. This has
prompted investigators to evaluate goal-directed fluid administration as a primary treatment for HRS [10].

Responders to Terlipressin exhibit an increase in mean arterial pressure and a decrease in endogenous plasma vasoactive components such as aldosterone, norepinephrine, atrial natriuretic factor and renin activity [11]. Investigators have identified factors that appear to predict a response to therapy. These include the Child-Pugh and MELD scores, serum creatinine, urine volume, and leukocyte count. A lower serum creatinine concentration at the start of treatment is a consistent predictor of a better response to vasoconstrictors. Higher creatinine values can be associated with HRS which has evolved into irreversible acute tubular necrosis. Recently, a serum baseline bilirubin of 10 mg/dL and an increase in mean arterial pressure of >5 mm Hg at day 3 of treatment were identified as independent predictors of response to treatment [11].

It is not clear if these therapeutic interventions influence mortality in HRS patients. Patients who respond to treatment appear to have a more favourable outcome than non responders [1]. A recent study showed a 57 % overall mortality in patients treated with Terlipressin plus albumin [8]. In this study, Gluud et al performed a meta-analysis that included ten randomized trials using Terlipressin alone or with albumin, octreotide plus albumin, and norepinephrine plus albumin in 376 patients. The study suggests that vasoconstrictor drugs alone or with albumin prolong short-term survival in type 1 HRS (relative risk: 0.82; 95% confidence interval: 0.70-0.96). However, the effect on mortality was only found at 15 days in subgroup analysis [8]. The authors concluded that, in agreement with previous findings, treatment was most effective in patients with the lowest baseline serum creatinine. This may
suggest that treatment should be started early, before there is a chronic deterioration in renal function that impedes recovery [8].

Treatment with vasoconstrictors has potential side effects. Major cardiovascular adverse events (myocardial infarction, intestinal ischemia, and/or circulatory overload) occurred in about 6 to 25% of the patients who received Terlipressin [2]. A meta-analysis that compared Terlipressin alone or with albumin versus no intervention or albumin revealed that the Terlipressin treatment group experienced a greater number of cardiovascular adverse events, including cardiac arrhythmia, myocardial infarction, suspected intestinal or peripheral ischemia, and arterial hypertension (14% versus 0%; Relative risk, 9.00; 95% confidence interval: 2.14-37.85) [8].

Current AASLD 2009 guidelines state that “albumin infusion plus administration of vasoactive drugs such as octreotide and Midodrine should be considered in the treatment of type I hepatorenal syndrome. Patients with cirrhosis, ascites, and type I HRS should have an expedited referral for liver transplantation [12].

Other treatments

Other therapies have been recommended in patients who do not respond to vasoconstrictive therapies (about 50% in the type I HRS). The use of molecular adsorbent recirculating system (MARS) therapy or transjugular intrahepatic portosystemic shunt have been studied. The MARS extracorporeal liver dialysis system uses two separate dialysis circuits. The first contains human albumin and is in contact with the patient’s blood through a semipermeable membrane. The second circuit is a hemodialysis machine that cleans the albumin from the
first circuit. The MARS can remove a number of toxins including ammonia, bile acids, bilirubin, copper, iron and phenols.

These treatments aim to bridge patients to liver transplantation. The first randomized trial of MARS evaluated 13 patients with type 1 HRS. Five patients treated with hemofiltration alone died within seven days whereas three of eight patients treated with MARS were alive at seven days, and two of eight were alive at 30 days [13]. In another recent randomized controlled trial, 24 patients with acute-on-chronic liver failure treated with MARS showed improvement in hyperbilirubinemia, renal function, hepatic encephalopathy and 30 day survival [14]. However in another study, MARS was found ineffective in improving systemic hemodynamics and renal function in six patients with cirrhosis, refractory ascites, and type 1 HRS who did not respond to vasoconstrictor therapy, [15]. Thus, the use of MARS remains controversial in this context and needs further study.

Transjugular intrahepatic portosystemic shunt has also been suggested as a way to reduce the intrinsic vasoconstrictive activity in type 1 HRS by increasing venous return and therefore systemic blood volume [16]. This has been evaluated in patients with moderate to severe liver failure, without a history of hepatic encephalopathy. However, since patients with type 1 HRS usually have the greatest severity of illness, they are often not candidates for TIPS and therefore it is currently not possible to determine the role of this intervention in HRS treatment [16].

Because endothelin has been implicated in the development of renal vasoconstriction, investigators have evaluated Bosentan, a nonselective endothelin-receptor antagonist They found Bosentan prevented the development of renal failure and induced a dose-related
Improvement of the glomerular filtration rate in humans [17]. However, in a recent study, the administration of Tezosentan, a nonselective endothelin-receptor antagonist, in patients with cirrhosis and type 2 HRS was associated with hypotension and impairment of renal function. This raised questions about the effectiveness of endothelin antagonists in the management of the hepatorenal syndrome [18].

Finally, renal replacement therapy can be required in HRS patients. However, there are some special considerations. First, patients with advanced HRS have a very poor prognosis. Therefore renal replacement therapy in a patient who has not responded to medical therapy should be instituted early when LT is a viable option. Whether renal replacement therapy will improve the prognosis for patients who are not candidates for LT is unanswered. Second, the optimal mode of renal replacement therapy (hemodialysis or continuous veno-venous hemofiltration) for HRS has not been determined.

Reducing the risk of Hepatorenal Syndrome

Because HRS increases mortality in cirrhotic patients, physicians should take every step to prevent the development of this syndrome. The risk of HRS in patients with spontaneous bacterial peritonitis can be effectively reduced by the addition of albumin to antibiotic therapy. Cefotaxime is added to 1.5 g/kg human albumin intravenously at the time of diagnosis of the infection and 1 g/kg is given intravenously 48 hours later [19]. Daily treatment with norfloxacin versus placebo prevented spontaneous peritonitis and hepatorenal syndrome and in patients with ascitic fluid protein <1.5 g/dL with one of the following criteria: serum creatinine >1.2 mg/dL, blood urea nitrogen >25 mg/dL, serum sodium <130 mEq/L or Child-Pugh >9 points with bilirubin >3 mg/dL.
Consequently, in 2009 the AASLD guidelines specified: “In patients with cirrhosis and ascites but no gastrointestinal bleeding, long-term use of norfloxacin (or trimethoprim/sulfamethasoxazole) is justified if the ascitic fluid protein is <1.5 g/dL and at least one of the following is present: serum creatinine >1.2 mg/dL, blood urea nitrogen >25 mg/dL, serum sodium <130 mEq/L or Child-Pugh >9 points with bilirubin >3 mg/dL”. [12].

**Liver Transplantation**

Liver transplantation is the only definitive treatment for HRS in cirrhosis. HRS often improves after LT. However, the long term post-transplant renal function of patients with HRS can be affected [20]. In a recent study of 32 patients, HRS resolved in 94 % patients in a median time of 24 days, after liver transplantation. Postoperative mortality was 34,4 % and the survival rate at one month was 72% [21]. Eight patients (25%) required postoperative renal replacement therapy. Interestingly, the survival of patients with or without postoperative renal replacement therapy was not different. High MELD score and low preoperative serum sodium were independent risk factors of patient mortality [21].

Pre-transplantation renal failure is one of the most important factors predicting post-transplant patient and graft survival [1]. The presence of HRS also carries an increased risk of postoperative morbidity, including intra-abdominal bleeding and infection, longer intensive care unit and hospital length of stay. Consequently, improving renal function in patients with HRS may be particularly relevant in patients awaiting liver transplantation since it may improve post-transplantation outcome. Patients with HRS who respond to Terlipressin and albumin may have a good post transplantation outcome, similar to that of patients without HRS with a 22 % rate of postoperative renal replacement therapy [22]. This suggests that
vasoconstrictor therapy could be an effective therapeutic option for patients with HRS awaiting liver transplantation. However, this will require further study.

Intraoperative management of LT is a crucial issue for HRS patients. Currently there are no controlled trials. Until there is further testing, intraoperative renal protection should probably be implemented for these particular patients. These strategies have been reviewed in the report of the first International Liver Transplantation Society expert panel consensus conference on renal insufficiency in liver transplantation [16]. They include strategies that avoid excessive bleeding resulting in multiple transfusions of packed red blood cell and plasma, and surgically preserving the vena cava or the use of temporary portocaval shunt. Clamping of the vena cava has been implicated as a risk factor for acute kidney injury [23]. Optimal intraoperative hemodynamic monitoring and goal-directed therapy of perioperative fluid management is associated with a positive effect on postoperative outcome in other types of surgery and should be studied during LT [24]. Similarly, maintaining an adequate arterial perfusion pressure with vasoconstrictors for example, may help additional renal insults [16].

References


15. Wing F, Raina N, Richardson R. Molecular adsorbent recirculating system is ineffective in the management of type 1 hepatorenal syndrome in cirrhotic patients with ascites who have failed vasoconstrictor therapy. Gut, 2009, Aug 25. [Epub ahead of print].


QUESTIONS

1. Physiopathology of hepatorenal syndrome is characterized by which of the following.
   a. Splanchnic production of endogenous dilatators
   b. Hypotension and high cardiac output
   c. Excessive arterial renal vasoconstriction
   d. All of the above

2. About diagnosis of hepatorenal syndrome, which of the following is true
   a. Diagnosis of hepatorenal syndrome is not possible in case of ongoing infection
   b. Diagnosis of hepatorenal syndrome is not possible in case of septic shock
   c. Diagnosis of hepatorenal syndrome is possible in non decompensated cirrhosis
   d. Diagnosis of hepatorenal syndrome is possible in case of ongoing diuretic therapy

3. Hepatorenal syndrome (one true)
   a. Is associated with a median survival of less than one month in type 1
   b. Is usually responsive to volume expansion
   c. Can not be prevented in case of spontaneous bacterial peritonitis
   d. Is a contraindication to liver transplantation

4. Vasoconstrictive therapies in hepatorenal syndrome
   a. Induce splanchnic vasoconstriction
   b. Reduce the vasoconstrictive neurohormonal response.
   c. Increase arterial blood pressure
   d. Restore renal blood flow.
5. About vasoconstrictive therapies in hepatorenal syndrome
   a. Reversal is obtained in approximately 50% of treated patients.
   b. Norepinephrine and terlipressin have similar efficacy in hepatorenal syndrome treatment.
   c. Terlipressin treatment allows a marked survival benefit.
   d. Treatment of type 1 hepatorenal syndrome with terlipressin is associated with less than 5% of major cardiovascular events.

6. Patients who did not improve their renal function under vasoconstrictive treatment
   a. Can not be referred to liver transplantation
   b. Should received MARS therapy
   c. Should be treated with transjugular intrahepatic portosystemic shunt
   d. Have worst outcome than patients who did improve their renal function under vasoconstrictive treatment

7. Patients with hepatorenal syndrome who received liver transplantation
   a. Have similar outcome than patients without hepatorenal syndrome.
   b. May have similar postoperative outcome than patients without hepatorenal syndrome if they were responsive to vasoconstrictors
   c. Do not have higher risk of postoperative renal replacement therapy
   d. Do not have increased risk of extra-renal postoperative morbidity

8. Intraoperative management of LT for hepatorenal patients
a. is based on controlled trials

b. should avoid excessive bleeding resulting in multiple transfusion of packed red blood cell and plasma

c. should not used preservation of the vena cava or temporary portocaval shunt

d. optimal intraoperative hemodynamic monitoring and goal-directed therapy of perioperative fluid management and adequate arterial perfusion pressure can not avoid additional renal insults

9. Which of the following regimen is not currently used for the hepatorenal syndrome treatment

a. Intravenous Terlipressin 1 mg every 4 to 6 hours

b. Albumin: 1g/kg the first day

c. Continuous intravenous infusion of norepinephrine titrated according to mean arterial pressure increase

d. Midodrine intravenously with octreotide

**Answers:**

1) e 2) b 3) a 4) e 5) a 6) d 7) b 8) a 9) d