

# Treatment of the hepatorenal syndrome and hyponatremia in cirrhosis - Part II

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This guideline has been approved by the Danish Society for Gastroenterology and Hepatology October 21, 2011

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Dan Med J 2012;59(1):C4372

## SUMMARY

National guidelines for treatment of ascites, spontaneous bacterial peritonitis, hepatorenal syndrome, and hyponatremia have been approved by the Danish Society of Gastroenterology and Hepatology. Ascites develops in approximately 60% of patients with cirrhosis during a 10 year period and is frequently associated with complications that determine the course of the disease and the prognosis. These evidence-based guidelines are divided in two parts and consider definitions, pathophysiology, diagnostic aspects, treatment, and prophylaxis.

## INTRODUCTION

The hepatorenal syndrome (HRS) is to be considered a diagnosis of exclusion of other causes of renal failure in patients with cirrhosis [1]. There are 2 types of HRS, type 1 HRS which is a rapidly progressive acute renal failure and type 2 HRS in which the renal function decreases over longer time [2]. The prognosis of untreated HRS has remained poor with a median survival < 1 month in HRS type 1 and < 3 months in HRS type 2, respectively [2, 3]. Hyponatremia is a common finding in patients with decompensated cirrhosis. From a pathophysiological point of view hyponatremia is related to an impairment of renal solute-free water excretion most likely due to an increased vasopressin secretion [4, 5]. Patients with cirrhosis may develop two types of hyponatremia: hypovolemic and hypervolemic hyponatremia, but only hyponatremia resulting in symptoms should be treated.

## DEFINITIONS

The hepatorenal syndrome is defined as development of renal failure in a patient with advanced cirrhosis in whom other causes for renal failure is excluded in combination with a serum creatinine

nine higher than 133  $\mu\text{mol/l}$  and lack of improvement after 48 hours discontinuation of diuretics in combination with volume expansion. The criteria are shown in Table 1.

Hyponatremia is seen as a hypervolemic as well as a hypovolemic hyponatremia with a serum sodium <130 mmol/l.

**Table 1.** Criteria for diagnosis of hepatorenal syndrome in cirrhosis

Cirrhosis with ascites  
 Serum creatinine >1.5mg/dl (133  $\mu\text{mol/l}$ ).  
 Absence of shock  
 Absence of hypovolemia as defined by no sustained improvement of renal function (creatinine decreasing to <133 $\mu\text{mol/l}$ ) following at least 2 days of diuretic withdrawal (if on diuretics), and volume expansion with albumin at 1g/kg per day up to a maximum of 100g/day.  
 No current or recent treatment with nephrotoxic drugs  
 Absence of parenchymal renal disease as defined by proteinuria < 0.5g/day, no microhaematuria (<50 red blood cells/high powered field, and normal renal ultrasonography

**Table 2.** Levels of evidence for clinical recommendations

Hepatorenal syndrome (HRS)	Level of evidence
Two types of HRS have been defined. HRS type 1: With sudden development of progressive renal failure (increasing serum creatinine > 221 $\mu\text{mol/l}$ within a two weeks period) HRS type 2: I: With less rapid renal failure (increasing serum creatinine > 133 $\mu\text{mol/l}$ ).	Evidence I A
In patients with cirrhosis, serum creatinine should be monitored often in particular during hospital stay for early identification of HRS.	Evidence I B
Monitoring should include diuresis, fluid balance and	Evidence I A

arterial blood pressure. Ideally central venous pressure should be measured to secure normovolemia.	
Terlipressin in combination with human albumin improves HRS type 1. There is insufficient evidence to recommend TIPS.	Evidence I A
Liver transplantation is the ultimate treatment.	Evidence I A

Hyponatremia	Level of evidence
Hyponatremia defined as < 130 mmol/l should in cirrhosis be considered for treatment.	Evidence III B
Hypovolemic hyponatremia is often induced by drugs and should be treated by cessation of the drug and eventually infusion of isotonic NaCl with an aimed increase in serum sodium < 0.5 mmoles/hr.	Evidence II B.
Hypervolemic hyponatremia in cirrhosis is related to reduced renal free water clearance.	Evidence I A.
If serum sodium decreases to < 120 mmol/l, diuretics should be discontinued. If cerebral symptoms develop, fluid restriction (< 1 l/day) may be tried.	Evidence III B/IV C

#### METHODS OF SEARCH

These guidelines were based on studies identified by searching electronic databases and a number of national and international reviews and guidelines, with special emphasis on conclusions from "EASL Clinical Practice Guidelines on the Management of Ascites, Spontaneous Bacterial Peritonitis and Hepatorenal Syndrome" [2]. Search in Pubmed was performed with the following MeSHs: "Hepatorenal syndrome" and "hypovolaemia". These guidelines are based on 747 references on search term "hepatorenal syndrome" and 198 references on the search term "hyponaetremia". Nine-teen of these references are cited in the present guidelines.

#### PATHOPHYSIOLOGY OF THE HEPATORENAL SYNDROME

The poor prognosis of HRS indicates that the condition is typically seen in patients with advanced disease (end-stage liver disease). The prognosis of untreated HRS has remained poor despite many attempts of treatment with a median survival < 1 month in HRS type 1 and < 3 months in HRS type 2, respectively [2, 3]. Two types of HRS have been defined. Type 1 is characterised by a rapid development of a progressive renal failure expressed as a doubling of serum creatinine to a level above 221 µmol/l over a 2 weeks period. HRS type 1 may be seen spontaneously but most often a precipitating factor is present such as sepsis, spontaneous bacterial peritonitis or severe alcoholic hepatitis. HRS type 2 is characterised by a moderate renal failure with a serum creatinine between 133 – 221 µmol/l [2]. HRS is typically seen in patients with refractory ascites and pronounced sodium retention. Pa-

tients with HRS type 2 may further progress into a HRS type 1 often in relation to a precipitating event [6].

From a pathophysiological point of view four factors are hypothesized to be involved in the pathogenesis of HRS: 1. Development of arterial vasodilatation with a decrease in mean arterial pressure; 2. Activation of various vasoactive neurohumoral systems such as the sympathetic nervous system and the renin-angiotensin-aldosterone system; 3. A cardiac systolic dysfunction due to the development of cirrhotic cardiomyopathy; and 4. Increased synthesis of several vasoactive mediators which may affect renal blood flow or glomerular microcirculatory hemodynamics (leukotrienes, F2-isoprostanes, endothelin-1 and others) [2, 6]. Owing to the poor prognosis, HRS is an indication for liver transplantation.

#### DIAGNOSTIC EXAMINATIONS IN THE HEPATORENAL SYNDROME

The diagnosis of HRS should be set as fast as possible and other causes for renal failure should be excluded such as hypovolemia, shock, parenchymal kidney disease, urinary tract obstruction, and use of nephrotoxic drugs. This is performed by analysing the urine for blood/albumin, performance of urinary microscopy and ultrasound examination of kidneys and bladder to exclude other renal and urinary diseases in particular urinary tract obstructions. Potential precipitating infections should be revealed by diagnostic paracentesis, blood culture, and pulmonary X-ray, and volume challenge (i.e. 1 l intravenously) to exclude prerenal causes. For practical purposes, the diagnosis of HRS type 2 is only made when serum creatinine exceeds 133 µmol/l and HRS type 1 when serum creatinine exceeds 221 µmol/l [2]. Spontaneous bacterial peritonitis and sepsis are important risk factors for the development of HRS and treatment of these conditions reduce the risk of development of HRS and improves survival [7-9].

#### TREATMENT

In general, treatment of HRS includes control of respiratory and circulatory function and liver function with measurement of liver enzymes, serum albumin, serum bilirubin, coagulation status, serum sodium, serum potassium, and serum creatinine. Administration of fluids should be limited to avoid over-hydration and dilutional hyponatremia. Diuretic treatment should be discontinued as soon as the diagnosis of HRS is evident. In some cases however, furosemide may be used to maintain an adequate diuresis and to avoid over-hydration. Spironolactone is contraindicated in patients with HRS because of the very high risk of hyperkalemia [2].

Specific treatment of the HRS includes administration of vasoconstrictors such as terlipressin in combination with infusion of human albumin [10, 11]. Several meta-analyses have shown that this treatment improves kidney function in patients with HRS type 1 [12, 13]. Terlipressin do not seem to have a sustained effect on patients with HRS type 2. Terlipressin should be given in a dose of 1 mg 4-6 times daily to a maximal dose of 2 mg, 6 times per day depending of the effect. Human albumin is given in a dose of 40 gram per day, equal to 200 ml 20% human albumin [2]. The treatment is sustained until normalisation of serum creatinine (below 133 µmol/l) is achieved. Repeated episodes of HRS after cessation of the treatment is seldom seen and patients may often response adequately on a repeated treatment attempt. The most frequent side effects to terlipressin are bradycardia and cardiac ischaemia or ischaemic manifestations from the gut and the peripheral circulation in the extremities and the skin. Appearance

of serious side effects, which is seen in 5-7% of the patients, should result in immediate termination of the treatment [13]. Liver transplantation is the ultimate treatment of HRS types 1 and 2 and should be considered in all patients responding to terlipressin [2]. Survival after liver transplantation in patients with HRS type 1 is, however, somewhat lower (65%) than the general survival in cirrhotic patients [14]. The presence of HRS at the time of transplantation is one of the strongest predictors for a poor prognosis after liver transplantation [11]. Patients with HRS who do not respond to terlipressin should likewise be considered for liver transplantation since the renal function usually improves after liver transplantation [14]. Selected patients with HRS and a prolonged need of dialysis (more than 12 weeks prior to liver transplantation) should be considered for a combined liver-/kidney transplantation [2].

#### PATHOPHYSIOLOGY OF HYPONATREMIA

Hyponatremia is often seen in patients with decompensated cirrhosis and is associated with the occurrence of HRS, spontaneous bacterial peritonitis and hepatic encephalopathy [15]. In patients, who are candidates for liver transplantation, hyponatremia is related to increased mortality prior to and after liver transplantation [16]. Hyponatremia that should be target for treatment is defined by a serum sodium below 130 mmol/l [17]. There are two types of hyponatremia: Hypervolemic hyponatremia or dilutional hyponatremia and hypovolemic hyponatremia.

In hypervolemic hyponatremia, the renin-angiotensin-aldosterone system is activated and the secretion of vasopressin is increased. This results in increased sodium retention and reduced renal free water clearance [4]. The total amount of sodium and water in the body are increased and the patients will often have ascites and peripheral oedema [18]. Dilutional hyponatremia can be seen spontaneously or be precipitated by infusion of fluids with low concentrations of electrolytes, such as isotonic glucose, which is associated to the development of complications of cirrhosis [4].

Patients with hypovolemic hyponatremia have a reduced extracellular volume with activation of the vasopressin system and reduced total serum sodium. The negative sodium balance is often a result of diuretic treatment or other pharmacological interventions. The patients often are without signs of ascites or peripheral oedema and they are often dehydrated. The diagnosis of hyponatremia is based on its character and ideally the extracellular volume is to be measured. However, in clinical practice this is seldom possible. If the patients do not have ascites or oedema, do present signs of dehydration, and do not receive diuretics, this support the presence of hypovolemic hyponatremia. If ascites and peripheral oedema are present and the sodium excretion is reduced, dilutional hyponatremia may be the most likely diagnosis [4, 5].

#### TREATMENT

Hypervolaemic hyponatremia should be treated in order to reduce water as well as sodium excesses. The reduced serum sodium should be adjusted because of the risk of developing cerebral oedema, other complications to cirrhosis, quality of life and because serum sodium is associated with a reduced survival after liver transplantation [5, 15, 19]. However, there are no randomized controlled trials documenting the value of adjusting serum sodium in hyponatremia. Hypovolemic hyponatremia should be treated by discontinuation of drugs such as diuretics that may cause hyponatremia. Infusion of isotonic NaCl should be consid-

ered with the aim of achieving a slowly increase in serum sodium, not more than 0.5 mmol/hr.

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