**Emerging hepatic syndromes: pathophysiology, diagnosis and treatment**

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# **Introduction**

Liver cirrhosis is a major cause of morbidity and mortality worldwide, being the 4th cause of death in Central Europe and the 12th cause of death in the US (1). Most patients with cirrhosis do not succumb from hepatocellular failure per se but from consequences of portal hypertension and pathophysiological changes induced by the progressive liver dysfunction (2). The cross talk of the cirrhotic liver with other vital organs and systems is increasingly recognized in the form of various hepatic syndromes, which deserve increased awareness from the internist so they are recognized and treated promptly (3). In the current review, we focus on the pathophysiology, diagnosis and treatment of three of these hepatic syndromes, namely the hepatorenal, hepato-adrenal and hepatopulmonary syndrome.

# **1. Hepatorenal syndrome**

The hepatorenal syndrome (HRS) is one of the most important potential causes of acute kidney injury in patients with established cirrhosis. It is a severe complication of cirrhosis and affects patients that have advanced liver disease with portal hypertension and ascites (4-6). The HRS represents the end-stage of a sequence of reductions in renal perfusion induced by increasingly severe hepatic injury.

**Definition and diagnosis**

The hepatorenal syndrome is defined as the appearance of a deterioration of renal function, and therefore kidney Injury and/or renal failure, in patients with advanced liver disease, without another clearly recognizable cause of kidney failure (4-6). HRS is a diagnosis of exclusion and other potential causes of kidney injury should be considered before a diagnosis is made. The International Ascites Club recently published revised criteria for the diagnosis of HRS that do not include threshold values for serum creatinine (5). These criteria are outlined below:

* Established diagnosis of cirrhosis/end stage liver disease and ascites;
* Diagnosis of AKI according to ICA-AKI criteria;
* No response after the diuretic withdrawal and/or a plasma volume expansion with albumin 1 g/kg of body weight for at least 2 consecutive days;
* Absence of shock and exclusion of current or previous use of nephrotoxic drugs;
* No macroscopic signs of structural kidney injury defined as absence of proteinuria, absence of microhaematuria and normal findings on renal ultrasonography

However, not all patients with HRS, particularly in the early phase of syndrome, have oliguria, thus a progressive rise in serum creatinine is more common. Urine volumes may be higher than previously appreciated. Existing data confirm that it is possible to observe a volume of urine greater than 400 ml/day with the appearance of a more marked contraction of diuresis only a few days before death (7-10). Furthermore, serum creatinine may show an increase by 0.1 mg/dL/day (9 micromol/L/day), with several periods of stabilization and/or minimal improvement.

Diagnosis of HRS is based upon clinical criteria. To this date, a specific test that can conclusively establish this diagnosis does not exist. However, there are certain blood chemistry indices, which can help, even if they have not been validated for this condition and do not appear as game-changer. Neutrophil gelatinase-associated lipocalin (NGAL) generally seems to be higher in acute tubular necrosis (ATN) if compared with HRS and pre-renal azotemia, even if a possible overlap between these mentioned diseases deserves attention.

Other apparent etiologies for AKI/ARF must be excluded, including any types of shock, cardiovascular events and active or recent treatment with nephrotoxic drugs. Also, ultra-sonographic evidence of renal disease and of high and/or low urinary tract obstruction must be searched and excluded.

Often AKI may represent a complication of spontaneous bacterial peritonitis (SBP). SBP, which may appear with or without ATN, seems to be a trigger factor of the HRS.

 In addition, HRS can also occur in patients with pre-exisitng chronic kidney disease.

**Epidemiology**

About 40% of patients with cirrhosis and ascites, develop HRS during the natural history of their disease. (4-6). Hyponatremia and a high plasma renin activity, when present, seem to identify patients at higher risk. These signs could be associated with a neuro-humoral response probably resulting from a decline in effective renal perfusion that could be explained by hemodynamic aberrations occurring in cirrhosis. [1,6].

**Classification**

Based upon the rapidity of the decline in kidney function, HRS can be divided into types I and II:

● Type I HRS is characterized by a rapid and progressive impairment of renal function with stage II or III AKI or by progression of the initial stage despite general therapeutic measures during a period of less than two weeks. The overall survival time is inferior to 2 weeks.

● Type II HRS is defined as renal impairment characterized by a subtler course that is less severe if compared with type I disease. One of the most important features in these patients is diuretic-resistant ascites. Finally subjects with type II HRS have a longer estimated survival time, with an average value of about 6 months.

***Precipitants***

The onset of HRS is commonly insidious. Nevertheless clinically important precipitating factors exist, such as bacterial infection or gastrointestinal bleeding. For example, as previously stated, SBP may appear coupled with HRS, but also pneumonia or urosepsis can trigger HRS, even if this latter most often takes place in patients who already suffer of some kind of renal failure/kidney injury or metabolic disease (8, 11). Other possible precipitant factor is the intensive use of diuretics, even if these latter do not usually have a proven direct causal role. Furthermore, diuretic-induced hyper-azotemia improves after the withdrawal of therapy and also with fluid repletion/challenge.

 ***Problems with estimating kidney function***

The serum creatinine may underestimate the kidney dysfunction in patients with liver disease and then in HRS. Urea cycle undergo to aberration in this kind of patients, the liver disease the decreased muscle mass and reduced food intake of protein contribute to a reduction in urea and creatinine production. For these reasons, a normal value of serum creatinine may mask a reduction in the glomerular filtration, which occurs in a patient with reduced basal production of nitrogen compounds. In addition, blood urea nitrogen (BUN) is not a reliable variable in these patients. If protein intake is not sufficient, low production of nitrogen compounds/urea may result in a low BUN and hence in a low BUN to creatinine ratio. Otherwise, with a normal nutrition the enhancement of tubular reabsorption typical of this population lead to higher urea absorption and then higher BUN and Bun to creatinine ratio.

**Pathophysiology**

The arterial vasodilatation theory is the most widely accepted explanation for the circulatory dysfunction in cirrhosis that could ultimately result in the hepatorenal syndrome. One of the accused mechanisms is the increased production of vasodilators and/or the enhancement of its activities, mainly in the splanchnic circulation. In this case, one of the most significant compounds seems to be nitric oxide. When liver disease becomes more severe, many hemodynamic changes occur. There is an increase of renal and femoral vascular resistance probably caused by hyperaldosteronism. Thus, there is a reduction in total systemic vascular pressure resulting in part by splanchnic dilatation that is often coupled with volume sequestration in the splanchnic circulation because of portal hypertension. In addition the bacterial translocation (BT) from the intestinal lumen initially to the mesenteric lymph nodes and subsequently to the bloodstream may play an important role in this process, participating in the systemic vasodilatation (4-6). Indeed, advanced cirrhosis is regarded as a systemic inflammatory state, even in the absence of infection, with increased levels of pro-inflammatory cytokines that aggravate the hyperdynamic circulation. The pro-inflammatory state is thought to provide the milieu for acute decompensation, acute-on-chronic liver failure, and/or HRS. Furthermore, adrenal insufficiency (discussed in detail later), could further contribute to the circulatory dysfunction of these patients.

The progressive reduction of renal perfusion in this setting is often associated with GFR decrease, electrolytes alteration and fluid dispersion (often linked to ascites and edema) resulting in arterial hypotension, despite the intense renal vasoconstriction. All these features have a net detrimental effect on renal perfusion, which feeds this vicious cycle. The importance of splanchnic vasodilatation could be indirectly demonstrated ex juvantibus by the response to terlipressin and/or other analogues of vasopressin, which is a preferential splanchnic vasoconstrictor. In patients with advanced cirrhosis, vasopressin analogues seem to be able to partially correct systemic and renal hemodynamic abnormalities that are present (12). The good response to creation of porto-systemic shunts also supports the importance of splanchnic hemodynamics in the pathogenesis of the HRS (13). The pathophysiology of HRS is summarized in Figure 1.

**Treatment**

All the current available treatments aim to correct the pathophysiological mechanisms underlying the HRS by expanding the central blood volume and simultaneously increasing the total plasma volume and reducing the intense peripheral vasodilatation.

**Albumin**

Albumin may play a role in the volume expansion caused by the relative reduction of the effective arterial blood volume. The international Ascites Club recommends to use albumin, in combination with vasoconstrictors, at an initial dose of 1 g/Kg of body weight on the first day and to continue at a dose of 20 to 40 g/day.

There is some evidence that albumin could even potentially bind vasodilators, improving the circulatory function. Nevertheless albumin alone does not seem to be as effective as in combination with vasoconstrictors to treat HRS (14).

The rationale of the use of vasoconstrictors is to reduce the extent of the systemic vasodilation. Many compounds have been studied, especially on patients with type 1 HRS, with the intent to obtain an improvement of the renal perfusion pressure and glomerular filtration through a rise in the systemic arterial blood pressure.

Vasopressin and its analogues have been widely used to improve the renal blood flow.

**Vasopressin**

Vasopressin could potentially be an alternative treatment for HRS where vasopressin analogues are not available but its use in HRS is not widespread due to concerns about ischemic side effects. However its effect was evaluated only in a retrospective study (15). Large prospective controlled studies are needed to test whether this therapeutic approach improves survival in patients with HRS.

**Terlipressin**

Terlipressin has a similar action as vasopressin but with longer activity and less ischemic side effects. Unlike vasopressin, terlipressin has been widely used in the treatment of HRS and many randomized controlled trials and meta-analyses are available.

In a pilot study of nine patients, terlipressin was used in combination with albumin to assess its efficacy and its safety profile in patients with type-1 or type-2 HRS (16). At the end of the study, 7/9 patients reverted HR with a low incidence of side effects. In a randomized controlled trial of terlipressin or placebo and albumin in 112 patients with type I HRS, terlipressin was superior to placebo for HRS reversal (34% vs. 13%) (17). A Cochrane meta-analysis including 376 patients concluded that terlipressin plus albumin might prolong short-term survival in patients with type I HRS (18).

It has been demonstrated that early treatment with terlipressin in combination with albumin is very effective in improving survival in patients with type-1 HRS associated with sepsis (19). Recently, Cavallin et al. have shown that terlipressin plus albumin is vey effective in improving renal function and survival in patients with HRS, compared with other vasoconstrictors, and this combination should be considered the first option for the management of HRS (20).

Terlipressin should be used at an initial dose of 0.5 to 2 mg every 4 to 6 hours intravenously up to 15 days with at least 40 grams of human albumin per day.

Terlipressin has also been used in the management of patients with type II HRS, significantly improving renal function (21).

**Midodrine and octreotide**

Midodrine improves systemic blood pressure acting on α-adrenergic receptors. It has been shown to be effective in non-azotemic cirrhotic patients with ascites, ameliorating systemic hemodynamics (22). The use of midodrine in combination with octreotide, a long-acting analogue of somatostatin, and albumin was associated with an improvement in renal function in patients with type-1 HRS (23, 24). The dosage of midodrine can be titrated to reach a mean arterial blood pressure of at least 90 mmHg.

Although terlipressin and albumin is better than midodrine/octreotide/albumin, the later could be a valid alternative treatment where terlipressin is not available (20).

**Norepinephrine**

Norepinephrine represents a valid alternative to terlipressin. In a randomized study it appeared to be as effective as terlipressin but at a fraction of the cost (25).

Many studies have shown that noradrenaline is effective in improving renal function and it is widely available and not expensive (26). It also appears to be effective in the management of type-2 HRS (27).

In conclusion the results of the use of noradrenaline in the management of HRS are very encouraging, considering also that it has less ischemic side effect compared with other vasoconstrictors.

**Transjugular intrahepatic porto-systemic shunt (TIPS)**

TIPS is very effective in reducing portal hypertension and it is also effective in type II HRS, but its applicability is low (as it is not suitable for all patients), and it increases the risk of encephalopathy.  Good results have been obtained in association with vasoconstrictors and albumin but its applicability remains restricted to a small number of patients (21, 24).

**Liver transplantation**

Liver transplantation is considered the definitive treatment for HRS, however not all patients are eligible and the window of opportunity might be narrow particularly in patients with type I HRS. Moreover, the return to a normal renal function post-transplant is not guaranteed for all patients, especially those with alcoholic cirrhosis (28). Even if transplantation is not available in all the patients with HRS, it has to be noted that it confers a major survival benefit compared to medical management (29). It could be very useful to identify early those patients who will not recover a normal renal function after liver transplantation and consider them for combined kidney-liver transplants (30).

**2. Hepato-Adrenal Syndrome**

The hepato-adrenal syndrome is a newly defined complication characterized by an inadequate cellular corticosteroid activity for the severity of patient’s illness. To date, adrenal dysfunction has been described in critically ill cirrhotic patients, in stable cirrhosis and in liver transplant recipients suggesting that adrenal insufficiency is a feature of liver cirrhosis per se. Cirrhosis represents a predisposing condition to adrenal insufficiency and the coexistence of the two conditions seems to be associated with a poor prognosis. Therefore, there is an urgent need to define a gold standard diagnostic method and to explore the potential benefits of corticosteroid replacement in this setting.

**Pathophysiology**

The pathogenesis of hepato-adrenal syndrome has not been clarified, but some hypotheses have been suggested (Figure 2).

*Substrates deficiency- Adrenal exhaustion syndrome*

Cholesterol is the principal precursor for steroid biosynthesis. At rest and during stress about 80% of circulating cortisol is derived from plasma cholesterol, while the remaining 20% is synthesized in situ from acetate and other precursors. The synthesis of cortisol after ACTH stimulation is therefore directly dependent on cholesterol availability (31). The vast majority of lipoprotein-derived cholesterol utilized is obtained via SR-BI mediated “selective” uptake of cholesteryl esters (32). Experimental studies suggest that HDL is the preferred cholesterol source of steroidogenic substrate in the adrenal gland (33).

Low levels of plasma cholesterol and lipoproteins are usual in cirrhosis. Cicognani et al showed that cholesterol and its fractions progressively decrease with increasing severity of the disease (34). Previous data of lipoprotein role in adrenal function are conflicting. Marik et al suggested that low levels of HDL in critically patients with liver disease may be pathogenetically linked to adrenal failure (35). A study evaluating critically ill patients with acute and acute-on chronic liver failure suggested that HDL levels are essential for on-demand cortisol secretion (36). In contrast, no significant differences in lipid profiles were observed between patients with severe liver disease with and without adrenal insufficiency (AI) (37). Recently, Acevedo et al. evaluated adrenal function in decompensated cirrhotic patients and observed no difference in lipid profile between subjects with and without AI (38).

We have recently evaluated the role of lipid profile in adrenal function of a group of stable cirrhotic patients compared to healthy subjects and we showed that basal cortisol was related to Apo-AI and triglycerides. Similarly, the dynamic adrenal response was related to triglycerides, TC, and more strictly with Apo-AI, suggesting that in cirrhosis lipoprotein levels influence adrenal response to ACTH administration (39).

*HPA axis impairment*

Patients with both acute and chronic liver disease have increased levels of circulating endotoxin and pro-inflammatory cytokines (TNF-α, IL-1 and IL-6) that are related to the severity of liver disease. It is postulated that intestinal bacterial overgrowth and bacterial translocation together with reduced Kupffer cell activity and porto-systemic shunting result in systemic endotoxaemia with increased transcription of pro-inflammatory mediators (40). The systemic inflammatory response leading to the excessive and harmful inflammatory reactions is a hallmark of acute-on-chronic liver failure. In this context the augmented levels of pro-inflammatory cytokines can induce liver and other organ failures, such as adrenocortical insufficiency (41).

TNF-α has been shown to reduce the secretion of ACTH from the pituitary gland (42). In addition, LPS as well as TNF-α may directly inhibit cortisol synthesis in a dose-dependent manner (43). Endotoxin has been shown to bind with high affinity to the HDL receptor with subsequent internalization of the receptor (44). LPS may therefore limit the delivery of HDL cholesterol to the adrenal gland (45). Furthermore, TNF-α, as well as IL-1β and IL-6 has been demonstrated to decrease hepatocyte synthesis and secretion of Apo-AI (46).

Acevedo et al. compared cytokine levels of decompensated cirrhotic patients according to adrenal function. No significant difference was observed between the two groups in terms of cytokine values (38).

*Other mechanisms*

Resistance to glucocorticoid action has been proposed as a potential mechanism of adrenal dysfunction in cirrhotic patients. The activity of glucocorticoids are mediated by the glucocorticoid receptor (GR). Two isoforms of the GR have been isolated, namely GR-α and GR-β. GR-α represents the active isoform, the GR-β is the negative isoform. Excessive inflammatory cytokines production leads to decreased numbers and binding affinity of glucocorticoid receptors (47). The role of glucocorticoid resistance has been investigated in critically patients. No data have been reported in cirrhotic patients with adrenal dysfunction.

Coagulopathy, which is common in patients with cirrhosis, may cause adrenal haemorrhage and infarction leading to structural damage of the adrenal gland, resulting in AI. In the study of Harry et al. adrenal function was evaluated in patients with acute hepatic dysfunction. The authors provided post-mortem data to identify the cause of adrenal dysfunction in this setting. The post-mortem analysis did not suggest that haemorrhage in the adrenal glands was the cause of adrenal dysfunction (48).

**Diagnostic approach**

The diagnosis of adrenal insufficiency in cirrhosis constitutes a crucial point. Published studies have used a variety of biochemical criteria to define abnormalities in adrenal function during liver cirrhosis. Common methods used in the general population to assess AI could be invalid in cirrhotic patients because there are a number of confounding factors that make interpretation difficult.

*Serum total vs. free cortisol concentrations*

Over 90% of circulating cortisol in serum is bound to proteins, namely corticosteroid-binding globulin (CBG) and albumin. Normally, 70% of circulating cortisol is bound to CBG, 20% is bound to albumin, and 10% exists as free cortisol. CBG was found to be significantly decreased in cirrhotics compared to healthy controls. In this setting, the total cortisol is reduced while free cortisol, responsible for glucocorticoid activity on peripheral organs remains unchanged. The common methods for assessing adrenal function, based on total cortisol, may lead to overestimation of AI in patients with cirrhosis. The optimal method could be the direct evaluation of free cortisol, but its measurement is difficult in daily clinical practice. Indirectly free cortisol can be calculated by the Coolens equation based on total cortisol and CBG. The free cortisol index (FCI) ratio between total cortisol and CBG concentration, was used as the surrogate marker for free cortisol and < 12 used as cut-off. Salivary cortisol has been used as a surrogate marker of free cortisol but presents limitations in cirrhosis including the high incidence of oral candidiasis, gums bleeding and parotitis especially in alcohol (49). In the study of Galbois et al. the authors assessed the prevalence of adrenal insufficiency using salivary and serum assays and investigated the correlation between salivary, serum total and free cortisol. The authors concluded that salivary cortisol correlates strictly with free cortisol and thus better reflects adrenal function in cirrhotic patients (50). Similarly Thevenot et al compared salivary cortisol concentrations with serum total cortisol in a large group of cirrhotic patients. Salivary cortisol was closely correlated with serum-free cortisol concentrations suggesting the potential use of salivary cortisol as a surrogate marker of free cortisol (51). Although these are promising results, salivary cortisol assay need to be standardized to determine the method- specific reference ranges.

*Short Synacthen Test (SST) vs. Low-dose SST*

As previously mentioned, several approaches to evaluate adrenal function in liver disease have been adopted. AI is generally diagnosed by the ACTH stimulation test, which is safe and reliable. Other tests assessing the integrity of the entire HPA axis have been used. Such tests include the insulin-induced hypoglycaemia, metyrapone testing and CRH test. All of these tests are unsafe, impractical and the data are difficult to interpret in the setting of liver disease.

The corticotropin test entails stimulation of the adrenal glands by pharmacological doses of exogenous ACTH. In the SST, plasma cortisol is measured at 0, 30 and 60 min after intravenous or intramuscular injection of 250 µg corticotrophin. Different thresholds have been used to diagnose adrenal dysfunction in liver cirrhosis, the most common cut-off used is of 550 nmol/L. SST uses a supraphysiological dose of corticotrophin and is preferentially utilized in critically ill patients. In the LDSST plasma cortisol is measured at 0, 20 and 30 min after stimulation with 1 µg intravenous corticotrophin. If peak cortisol exceeds 500 nmol/L adrenal function is normal. This test seems to be more sensitive than SST and evaluates better the stable cirrhotic patients (52).

Most of the data in the literature have used the SST and the available data on the LDSST are limited and not sufficient to make sound recommendation.

**Corticosteroid replacement: current evidences**

The published data on corticosteroid supplementation in critically cirrhotic patients are few and controversial. In a retrospective study, Harry et al. evaluated the outcome and the side-effect profile of supraphysiological doses of hydrocortisone in 20 patients with liver failure and norepinephrine dependency. Compared with a control group not treated with steroids, the authors found that supra-physiological doses of corticosteroids reduced vasopressor requirements but did not improve survival (53). Marik et al. performed a non-randomized trial including 340 patients with liver disease. The study cohort was heterogeneous including chronic liver failure, fulminant hepatic failure, immediately post-liver transplantation and remote history of liver transplantation. Between 245 patients enrolled with adrenal failure, 156 were treated with steroids. The mortality rate of treated patients was 26% compared with 46% in those who were not treated (35). Fernàndez et al. evaluated the clinical course and hospital mortality of 25 cirrhotic patients with septic shock treated with low doses of intravenous hydrocortisone compared to 50 septic and cirrhotic patients that did not receive steroids. Although the small number of patients enrolled, the authors clearly demonstrated a marked increase in shock reversal and hospital survival in patients treated with hydrocortisone (54).

Arabi et al. performed a randomized double-blind trial to examine the effect of low-dose hydrocortisone therapy in cirrhotic patients with septic shock. The trial was stopped after 75 patients were enrolled. The study confirmed the high prevalence of relative adrenal insufficiency in patients with cirrhosis presenting septic shock. Hydrocortisone therapy was associated with an early haemodynamic improvement, however at 28 days the treatment did not reduce mortality and was associated with an increase in shock relapse and gastrointestinal bleeding (55).

Etogo-Asse et al. enrolled 164 critically ill patients with acute and acute on chronic liver failure. The aim of the study was the assessment of the relationship between HDL levels and survival, predisposition to sepsis and adrenocortical function. In this setting, the authors evaluated also the potential benefit of hydrocortisone therapy on mortality. The analysis was performed in 51 patients requiring vasopressors on admission, of whom 31 received intravenous hydrocortisone at a median dose of 200 mg daily. No significant difference was observed in terms of mortality between the patients who received steroids and those who did not. Although the lack of benefit on survival, the authors highlighted that the severity of multiple organ failure was clearly greater in the former group and the predicted mortality higher. Therefore, a beneficial effect of steroid therapy cannot be excluded (36). Similarly, the use of supplemental corticosteroids in ACLF seems to play an important role in shock recovery and vasopressor requirement but no survival benefit has been shown. A large randomised clinical trial of corticosteroid supplementation in ACLF is underway (Chronic Liver Failure Consortium. <http://www.clifresearch.com/scotch/Home.aspx>).

**Conclusions**

Adrenal insufficiency is common in patients with liver disease and its prevalence is related with the severity of liver cirrhosis. Our understanding of the hepato-adrenal syndrome has been improved in recent years but different aspects need to be clarified. Further studies should be conducted to define the most accurate diagnostic method and the impact on survival of the hepato-adrenal syndrome. Similarly, the potential benefits of cortisol administration should be elucidated.

**3. Hepatopulmonary syndrome**

The hepatopulmonary syndrome (HPS) is a disorder of arterial oxygenation that occurs in patients with chronic liver disease (1, 56). Although HPS is most commonly associated with cirrhosis, it has also been diagnosed in patients with pre-sinusoidal portal hypertension (57). HPS has been attributed to alterations in pulmonary circulation that impair normal gas exchange (57). HPS should not be confused with porto-pulmonary hypertension, which is pulmonary arterial hypertension associated with portal hypertension. In recent studies, the prevalence of HPS ranges from 4 to 34% (58, 59). At present, the only definite therapy for HPS is liver transplantation (60).

**Pathophysiology**

The hallmark of HPS is abnormal pulmonary vascular dilatation, resulting in anatomical shunting and hypoxemia due to the subsequent diffusion-perfusion abnormality.

Although the pathogenesis of HPS is not fully understood, pulmonary capillary and pre-capillary dilatation, arterio-venous shunting and neo-angiogenesis are considered as the basic underlying disorders (60).

Small vessel dilatation and shunting are caused by an imbalance between vasodilating and vasoconstrictive substances (56). Although nitric monoxide (NO) overproduction in intrapulmonary circulation has traditionally been considered as the main cause of pulmonary vasodilation, studies indicate a more complex mechanism. In cirrhotic patients, increased intrapulmonary endothelin levels of hepatic origin, could contribute to NO-mediated pulmonary vasodilation (61). Similarly to NO, increased carbon monoxide level, has also been found in patients with HPS (62).

Consequently, in patients with HPS, the increase in small vessel diameter could cause poor blood oxygenation and right to left shunting. Increased vessel diameter inhibits normal blood oxygenation whereas poorly oxygenated venous blood passes through the shunts either rapidly or directly into pulmonary veins thereby causing hypoxemia and dyspnoea (60).

In addition, studies have shown an increased density of intrapulmonary capillaries in patients with HPS. Therefore, angiogenesis has been implicated in the pathogenesis of this syndrome (56). Furthermore, it has been suggested that pulmonary macrophages may become activated due to intestinal bacterial translocation. Subsequently, macrophages could adhere to the pulmonary vessels and induce the production of vasodilating and angiogenic factors such as NO and vascular endothelial growth factor (VEGF-A), respectively, and thus play a critical role in HPS **(Fig 3)** (63, 64).

**Diagnosis**

The typical although not pathognomonic symptoms of HPS are dyspnoea and platypnoea, i.e. dyspnoea that becomes paradoxically more intense in the upright position, in the setting of chronic liver disease. Platypnoea and the underlying orthodeoyxia (decrease in PaO2 in the upright compared to supine position) have been attributed to the redistribution of pulmonary blood flow that occurs in the upright position. In this context, blood is directed towards the pathologically dilated pulmonary vessels (65, 66).

HPS is defined as an arterial oxygenation defect that is associated with intrapulmonary vascular dilatations (IPVD) in patients with chronic liver disease. Therefore, the diagnosis of HPS includes i) the recognition of a defect in oxygenation and ii) evidence of intrapulmonary vascular dilatations, in such patients (56, 66).

i) *Defect in oxygenation:* Finger pulse oxymetry in the supine and recumbent position is a simple, sensitive and reproducible screening test in the diagnosis of hypoxemia in HPS. It has been suggested that a threshold value of <96% at pulse oxymetry had a sensitivity of up to 100% in the diagnosis of HPS(67). However, arterial blood gases measurement is necessary. Due to tachypnoea, arterial carbon dioxide tension (PaCO2) can be decreased even when normal arterial oxygen tension (PaO2) values are present. Hence, the alveolar–arterial oxygen tension difference, PA-a,O2 is considered as one of the most sensitive tests in HPS since it can increase prior to PaO2 drop. At sea level and while breathing room air, a resting PA–a,O2 of $\geq $15 mmHg is considered abnormal (normal range 4–8 mmHg). For patients aged over 64 years, a PA–a,O2 cutoff of ≥20 mmHg is recommended (66). PaO2 measurement is also helpful for determining the severity of HPS as shown in Table 1 (66).

ii) *Assessment of intrapulmonary vascular dilatations (IPVD):* The gold standard for the diagnosis of IPVD and intrapulmonary shunts is contrast echocardiography (CE) with saline shaken to produce microbubbles (56). In CE, normal saline is agitated and subsequently injected intravenously. The microbubbles in normal subjects are being trapped in small pulmonary capillaries and absorbed by the alveoli. In patients with HPS syndrome, however, microbubbles pass through the intrapulmonary shunts and enter the left atrium, usually after three to six cardiac circles (68). Differential diagnosis from cardiac shunting is easy as in the latter bubbles are detected in the right circulation within 1-2 cardiac circles (68). Transoesophageal echocardiogram is considered to be more sensitive than transthoracic echocardiogram (69). Echocardiographic studies are also useful for the differential diagnosis from portopulmonary hypertension (56).

In addition, scintigraphic perfusion scanning (SPS) can be used for the documentation of IPVD and intrapulmonary shunts. 99mTc albumin macro-aggregates, which are infused intravenously, are normally trapped in the pulmonary circulation. In patients with IPVD, macro-aggregates pass through the pulmonary and into the systematic circulation and are trapped in other organs such as the brain, spleen or kidneys. Most studies that compared SPS with CE in adults show that CE has greater sensitivity (68, 70). In contrast to CE, SPS permits the quantification of the degree of intrapulmonary shunting. Nevertheless, SPS cannot discriminate between intra-cardiac and intra-pulmonary shunting (71). Pulmonary angiography and high resolution CT scanning can also be useful additional diagnostic tests in selected cases (69).

Screening for HPS is necessary in patients with chronic liver disease and shortness of breath as well as in patients assessed for liver transplantation (66). Differential diagnosis of HPS includes intrinsic lung diseases such as infection and chronic obstructive pulmonary disease, pleural infusions and portopulmonary hypertension (60). Therefore, chest imaging and exclusion of other causes of hypoxemia and dyspnoea is mandatory. In patients with HPS, in the absence of other comorbid pulmonary disorders, spirometer tests are within normal limits (66).

**Treatment**

Liver transplantation (LT) is the only definite therapy for HPS (60). Administration of oxygen can partially correct hypoxaemia and should be used in symptomatic patients, however it becomes less effective in the presence of right-to-left shunting. Patients that are listed for liver transplantation and suffer from HPS have worse survival than matched controls (72). However, although HPS is associated with worse survival, in most patients the cause of death is associated with the underlying liver disease complications rather by HPS per se (56). Severe HPS is an indication rather than a contraindication for LT and indeed patients with PaO2<60 mmHg should be worked up for a LT (71). There has been an ongoing disagreement among studies as to whether the presence and/or the severity of HPS could influence the survival of patients that undergo liver transplantation. Whereas older studies as well as a recent large retrospective study suggested worse prognosis after liver transplantation in patients with HPS and additionally in patients with severe HPS, other studies showed that mortality is not affected by the presence or by the severity of the syndrome (72-75).

Despite the basic role of NO and CO in the pathogenesis of HPS, studies targeting the NO and CO pathway have shown disappointing results (56). Numerous products have been used for HPS, however available data do not support the routine use of medical therapy (56, 71). Pentoxyfilline, methylene blue and garlic have shown some promising results. However, only small, pilot studies are available with methylene blue and pentoxyfilline (76, 77) whereas two small pilot studies have shown that garlic may be of benefit (78, 79). Studies with somatostatin, indomethacin and mycophenolate mofetil have also shown contradictory results (56).

A recent review indicated that transjugular intrahepatic porto-systemic shunt (TIPS) might be helpful for patients with HPS (80). However data are conflicting and randomized trials are lacking. Therefore, TIPS placement as a sole indication for HPS is not currently recommended (71). In addition, should large arterio-venous shunts be suspected on imaging or should the oxygen deficiency be severe and poorly responsive to therapy, diagnostic and therapeutic angiography is indicated. In such rare cases, embolization of large shunts could be beneficial (60).

In conclusion, screening for HPS is necessary in patients with cirrhosis and shortness of breath as well as in all patients listed for liver transplantation. Pulse oxymetry and blood gases measurement should be used as screening tools whereas CE with micro-bubbles confirms the diagnosis. Liver transplantation remains the only successful long-term treatment.

**Conclusions**

We reviewed the current understanding of the pathophysiology, the diagnostic criteria and the available therapeutic options for patients with cirrhosis and the hepatorenal, hepato-adrenal and hepatopulmonary syndrome. The hepatorenal and hepatopulmonary syndrome usually occur in patients with advanced cirrhosis and should prompt a comprehensive evaluation for eligibility for liver transplantation. For most patients with type I HRS, the window of opportunity will be absent or very narrow, highlighting the need for earlier interventions to prevent progression. The hepato-adrenal syndrome is not fully characterized, however it offers an exciting field of research and potential therapeutic interventions.

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**Table 1.** Grading of severity of the hepatopulmonary syndrome.

|  |  |  |
| --- | --- | --- |
| Stage | PA–a,O2 (mmHg) | Pa,O2 (mmHg) |
| Mild | ≥15 | ≥80 |
| Moderate | ≥15 | ≥60-<80 |
| Severe | ≥15 | ≥50-<60 |
| Very severe | ≥15 | <50 (<300 on O2 100%) |

PA–a,O2: alveolar–arterial oxygen tension difference; Pa,O2: arterial oxygen tension. PaO2 normal range: 80-100 mmHg breathing room air at rest and at sea level. For patients aged >64 yrs, a cut-off value for PA–a,O2 of ≥20 mmHg and Pa,O2 of ≥70 mmHg is recommended.

**Figure 1.**

Pathophysiology of the hepatorenal syndrome.

**Figure 2.**

Current understanding of the pathophysiology of the hepato-adrenal syndrome.

**Figure 3.**

Pathophysiology of the hepatopulmonary syndrome.