Brain: Looking beyond
Minimal hepatic encephalopathy: how to diagnose, which impact, how to manage

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Hepatic encephalopathy can be defined as a complex neuropsychiatric syndrome that occurs in patients with liver dysfunction, ranging from minimal behavioral abnormalities to deep coma. The clinical prognosis is poor after HE has developed, with 1-year survival estimated at 42% and 3-year survival at 23%[1]. HE is classified in three types: type A, associated with acute liver failure; type B, related to portal-systemic shunting without intrinsic liver disease; and type C, linked to cirrhosis[2]. West Haven Criteria are routinely used to grade the severity of manifestations. Between 30%-50% of cirrhotic patients, who do not have HE symptoms, show minimal hepatic encephalopathy (MHE)[3]. This entity represents the first stage in HE spectrum. MHE is defined as the presence of cognitive abnormalities in patients with liver disease, which are not detected with common examinations; it is diagnosed using sensitive neuropsychological and neurophysiological tests[4]. Hepatic encephalopathy has relevant socio-economic impact since HE reduces quality-of-life and is associated with higher mortality rate[5]. As a consequence, the appropriate scientific bodies (American Association for the Study of Liver Diseases and the European Association for the Study of the Liver) had, for the first time in 2014, released practice guidelines for the management of HE[6]. Further, 30% to 50% of cirrhotic patients showed minimal hepatic encephalopathy (MHE)[7] when tested by neuropsychological tests such as Psychometric Hepatic Encephalopathy Score (PHES) or neurophysiological methods such as critical flicker frequency (CFF), representing the first stage in the HE spectrum.[8] MHE is defined as the presence of cognitive abnormalities in patients with liver disease, which are not detected with the standard examinations, but rather is only diagnosed using sensitive neuropsychological and neurophysiological tests.[9] MHE predicts the appearance of overt HE in cirrhotic patients[10], impairs motor vehicle driving abilities[11,12], and increases the risk of falling-over.[13]

The human glutaminase gene (OMIM: 138280) is located on chromosome 2 (2q32-q34). The full-length gene includes 84,675 basepairs and the glutaminase mRNA has 4784 basepairs (GenBank NM_014905)[14]. In a prospective study (109 patients with cirrhosis in the estimation cohort, 177 patients in the validation cohort, and 107 healthy controls), Romero-Gomez et al. identified a microsatellite in the promoter region of the glutaminase gene (kidney type) to be between 8 to 29 fold repeat of GCA. The longest microsatellite correlated with higher glutaminase activity in vivo. It increased the risk for overt HE in cirrhotic patients from 20% to 40% (Hazard Ratio 3.12 [CI: 1.39-7.02]; P=0.006) (Figure 5) [15]. Furthermore, they carried out a functional analyses that showed how longer forms of the microsatellite promoted higher activity in vitro, which implied that it also promoted higher activity of the glutaminase gene, increasing number of glutaminase molecules and thus may enhance glutamine degradation and ammonia production[16]. Therefore, authors concluded that this factor was a genetically determined difference in the conversion rate of glutamine to ammonia, explaining at least in part the variability in clinical presentation of HE. Mayer et al, confirmed these results in a cohort of 158 patients with liver cirrhosis most of them in Child B/C. The long-long homozygous form (also called major homozygous) was independently associated with hepatic encephalopathy irrespective of age or transhepatic porto-systemic shunts (TIPS) [17].

CFF, as a measure of MHE, had an impact on long-term overall survival[18]. The debate continues regarding the most appropriate method(s) to detect MHE, especially between psychometric (ranging from PHES to computerized tests) and neurophysiological tests (e.g. CFF). Conversely, West Haven criteria and Glasgow coma scale have been used widely in determining overt HE staging. The concerns exist because patients with low-grade HE may be missed if not systematically assessed. It is thought that psychometric and neurophysiological methods are complementary since they explore different pathways and mechanisms of the disease. However, the spectrum of HE is a continuum and, sometimes, it is difficult to establish cut-offs between stages. For example, modified PHES [19] and different cut-offs for CFF [20] have been proposed. Specifically, PHES has been shown to be influenced by age, education level and cultural issues. Detection of MHE is essential because of its relationship with falls,[21] impairment of motor vehicle driving abilities,[22] overt HE[23] and, now, survival. A few studies evaluating the impact of MHE on survival have been reported. Amodio et al reported the first study on this topic. They enrolled 94 consecutive cirrhotic patients and 80 control individuals. Cognitive alterations were assessed using NCT and a set of computerized psychometric tests. Of the tests employed, Scan and Choice2 tests had prognostic value with respect to survival in the first year of follow-up (median follow-up 14.2 months)[24]. Hartmann et al included 116 consecutive cirrhotic...
patients for a median follow-up of 29 months (range 1–49 months), and assessed MHE using NCT-A, DST and electroencephalogram. Their results showed that patients with MHE had more frequent HE events during follow-up, albeit overall survival was similar (p=0.26). [25] In 2004, we evaluated 126 consecutive cirrhotic patients (median follow-up: 25 months) and assessed MHE using NCTs, DST and block design test (BDT). Our results indicated that presence of MHE was not related to survival (p=0.23). However, in multivariate analyses, patients with MHE and abnormal oral glutamine challenge (OGC) had elevated mortality risk (HR 5.5; 95%CI: 1.81-16.6; p=0.0039). [26] Dhiman et al studied 104 consecutive cirrhotic patients (median follow-up: 22 months) and 83 healthy control subjects. MHE was diagnosed when PHES ≤ -5. Additionally, an age-adjusted Z score ≤ -2 on the CFF was considered abnormal. MHE was associated with poor prognosis in univariate analysis (39.1% vs. 22.9%). However, MHE diagnosed using PHES needed to be modified (using ROC curves for best discrimination) to become an independent predictor of mortality in multivariate analysis (PHES ≤ -6; HR: 2.42; 95%CI: 1.01-5.77; p=0.046). [27] Patidar et al assessed the impact of covert HE on overt HE, hospitalization and death/liver transplant over a follow-up period of 13.0±14.6 months. A standard paper-pencil cognitive battery was administered to evaluate covert HE. The group of patients with covert HE had more deaths than the group without (17.9% vs. 5.3%, respectively). This variable was related to death/transplant occurrence (HR: 3.4; 95%CI: 1.2-9.7; p<0.05). [28] Interestingly, patients having MELD <10 showed an excellent survival rate (>90% remained alive at conclusion of follow-up) regardless of the presence of MHE. Jacob et al studied survival rates in 3838 patients following first elective liver transplant. The patients were segregated according to their MELD scores (<10, 11-18, 19-24, 25-35, or >36). The 90-day survival was 92.6% in those patients with MELD score <10 [29]. CFF has been found critical in the prognosis of patients with MELD ≥10. In patients with MELD 10-15 and MELD ≥15, the presence of MHE (CFF<39Hz) showed a poorer prognosis. Specifically, only 16% of patients with MHE and MELD ≥15 remained alive in the five years of follow-up. Of note is that patients having MELD 10-15 and MHE showed a poorer survival than those with MELD ≥15 without MHE (45% vs. 69%). The addition of MHE to the MELD score could enable the identification and selection of subgroups of patients who ought to be prioritized in the liver transplantation option, or referred to appropriate prophylactic therapy. [30]

Several ammonia-lowering drugs are also able to avoid glutamine accumulation (that could serve as substrate for glutaminase transforming it into glutamate and ammonia –Trojan Horse hypothesis-) excreting by urine it in form of phenylacetyl-glutamine. Ornithine-phenylacetate and glycerol or sodium phenylacetate belonged to this type of drugs. CB-839 a glutaminase inhibitor demonstrated in portacaval shunted rats its ability as ammonia lowering drug. Lastly, metformin has been found able to reduce ammonia and improves systemic inflammation [31]. The role of these drugs in management of MHE requires future studies.

References


Overt hepatic encephalopathy: most common causes, current and future treatment strategies
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Introduction:
Hepatic encephalopathy (HE) represents a diverse spectrum of complex neuropsychiatric disturbance resulting from liver disease and its concomitant metabolic and immunological derangements. It is characterised by deficits in cognitive, psychiatric and motor function and can range in severity from minimal (or covert) hepatic encephalopathy (MHE) to overt hepatic encephalopathy (OHE), coma and death. In cirrhotics, overt HE occurs in 30-50%, [1] while MHE can affect 30-84% of cirrhotic patients. [2] HE is a frequent and debilitating manifestation of decompensated liver disease affecting carers and families alike. Patients with MHE demonstrate neuropsychological alterations including disrupted sleep-wake cycle, personality changes, impairment of attention, cognitive dysfunction and memory, changes in motor function and incoordination. These can progress through to higher grades of OHE, including lethargy, stupor, coma and death. In cirrhosis, the presence of at least one acute episode of HE is associated with mortality of 58% at one year. MHE, detectable using psychometric testing, was associated with a one-year mortality rate of 39.1% [3] and was predictive of future episodes of OHE. [4]

Pathogenesis of Overt HE:
(i) Ammonia
Ammonia has long been regarded as the key metabolic factor underpinning the development of HE since the original description of the ‘meat intoxication syndrome’ in portocaval shunted dogs at the end of the 19th century. In the presence of liver failure, decreased utilisation of ammonia as a substrate in the hepatic urea cycle (the major mammalian ammonia detoxification pathway) and portosystemic shunting leads to accumulation of ammonia in the systemic circulation which readily crosses the blood brain barrier. The majority of ammonia is generated from the gut. The main energy source for enterocytes in the small bowel is the amino acid glutamine. With the enzyme k-phosphate activated glutaminase (k-PAG), enterocytes convert glutamine to glutamate. This produces energy, as well
as nucleotides and ammonia. Although the colon does also produce ammonia from the breakdown of amino acids, the majority of the colon’s ammonia production results from the breakdown of urea by intestinal flora-derived urease. The formation of a portocaval shunt reduces ammonia detoxification capacity by 50%, and following a transjugular intrahepatic portosystemic shunt (TIPSS) this can be as high as 93%. The kidneys play an important role in regulating ammonia. Under normal physiological conditions they are a net producer of ammonia. In hyperammonemia the kidney becomes a net excretor of ammonia.

Cerebral ammonia detoxification occurs via glutamine synthetase, exclusively expressed in cerebral astrocytes in the formation of glutamine, an important precursor of the main excitatory and inhibitory neurotransmitters, glutamate and gamma-hydroxybutyric acid (GABA), respectively. Astrocytic glutamine accumulation exerts an osmotic effect resulting in swelling which causes low grade brain oedema in patients with cirrhosis; the extent of this oedema does not correlate with the level of HE, and it is reversed following liver transplantation.

In the brains of cirrhotic patients who died of HE, an Alzheimer's type II astrocytosis is seen: astrocytes have a large swollen nucleus, expansion of cytoplasm and proliferation of organelles.

(ii) Inflammation

Circulating hyperammonemia does not however explain all of the pathophysiological processes underpinning the development of HE in cirrhosis. Arterial ammonia concentrations correlate poorly with clinical presentations of HE in cirrhosis and increasingly recognised is the importance of the synergistic role between hyperammonemia and inflammation/infection in the development of HE. Infection was shown to exacerbate neurocognitive dysfunction following an ammonia load in patients with cirrhosis which resolved following antibiotic therapy. Bile-duct ligated cirrhotic rats progressed to pre-coma stages of encephalopathy following intraperitoneal administration of lipopolysaccharide (LPS), a gram negative cell wall peptidoglycan. A proinflammatory cytokine plasma milieu and not arterial ammonia or the severity of liver disease, has been shown to independently correlate with the presence and severity of HE. Potential pathophysiological mechanisms explaining the susceptibility to developing HE during episodes of infection include cerebral hyperemia with increased brain ammonia delivery, astroglial oxidative stress with microglial activation and neuronal dysfunction, and innate immune dysfunction arising from systemic inflammation and circulating endotoxemia. The maintenance of a high index of suspicion of infection underlying clinical presentations of HE and expedient treatment remains pivotal in its management.

(iii) The Intestinal Microbiome

Changes in the gut microbiota of patients with cirrhosis are considered central in the development of bacterial translocation, endotoxemia and systemic inflammation that can result in the development of HE. More recently, the advent of culture-independent techniques in quantitating and speciating bacterial colonic flora has sparked a burgeoning interest in the role of the intestinal microbiota in HE. Overgrowth of pathogenic bacteria in the gut microbiome relative to autochthonous (commensal) bacteria correlates with worsening liver disease severity with studies demonstrating that the change in composition of the microbiota is associated with higher MELD scores. Furthermore significant changes in enteric microbiota have been described between patients with MHE and OHE, with the latter group demonstrating a higher ‘dysbiosis ratio’.

Current treatment strategies:

A low threshold of suspicion and early specialist review, complex neuropsychological evaluation, and identification and treatment of precipitants is required in the approach to the patient with cirrhosis and altered mentation. Initial management of an acute episode of OHE in a cirrhotic patient, is to treat the precipitant cause, followed by supportive treatment and ammonia/inflammation reduction therapies. A summary of therapeutic strategies for HE are shown in Figure 2. An increasing number of treatments are aimed at reducing inflammation, and this will likely continue as new therapeutic targets are identified in the inflammatory response in OHE.

Figure 1: Proposed strategy for the recognition and management of hepatic encephalopathy in patients with decompensated liver disease. Please refer to the recently published Joint American Association for the Study of Liver Disease and the European Association for the Study of the Liver Guidelines.
EXTRA-HEPATIC INVOLVEMENT IN CHRONIC LIVER DISEASES

(i) Lactulose
Lactulose is a non-absorbable disaccharide which has a pleiotropic role in the treatment of HE and has long formed the cornerstone of empirical HE treatment. It has been shown to change the colonic pH favouring retention of ammonium salts in the bowel lumen, and exerts a prebiotic effect favouring the colonisation of *Lactobacillus* and *Bifidobacterium*; it also reduces intestinal transit time and may therein reduce ammonia absorption.

(ii) Non-absorbable antibiotics
Antibiotics such as neomycin, vancomycin, and metronidazole have previously been used to reduce ammonia-producing bacteria in the gut, and therefore reduce the occurrence of HE. Furthermore, non-absorbable antibiotics have been shown to be superior to non-absorbable disaccharides in the treatment of acute HE. [18] The long-term use of these non-absorbable antibiotics however has largely been discontinued due to their toxicities. [19] Rifaximin-α is a non-absorbable antibiotic that maintains remission from OHE with a reduction in hospitalisations due to HE over a six month period. [20] Interestingly, it was not shown to alter the relative abundance of pathogenic bacteria and instead it may be exerting its therapeutic effect by reducing circulating endotoxemia and manipulating bacterial function and virulence. [21]

Future Treatment Strategies:
L-ornithine phenylacetate is a novel treatment for HE that aims to combine the effects of L-ornithine observed from treatment with LOLA, and the benefits of sodium phenylacetate without sodium loading. It aims to have a synergistic effect by both providing more glutamate, and encouraging increased glutamine excretion in the urine, thus reducing the ammonia load. [22] It has been shown to reduce cerebral oedema and ammonia concentrations in ALF in pigs, [23] and one study in humans has shown it is well tolerated in decompensated cirrhotics with a reduction in plasma ammonia and glutamine. [24] Phenylacetyl-glutamine is renally excreted. A functional glomerular filtration rate is therefore required for these nitrogen excretion pathways to be efficacious.

Novel Therapies on the horizon:
In the next five years we are likely to benefit from optimisation and further trialling of some novel treatments, as well as the advent of specific targeted therapies. Further studies of the effect of treatments that have the dual effect of lowering both ammonia level and inflammation, such as rifaximin and plasmapheresis, may well reveal that this combined effect provides better responses. Brand new treatments that look to reduce systemic inflammation, such as Toll-like receptor antagonists, have the potential to be future therapeutic targets, and their introduction to animal models of HE will play an important part in assessing this.

Summary:
HE remains one of the major challenges and morbidities facing patients with decompensated liver cirrhosis. It exerts a profound influence on patient quality of life and functional capability and confers a damning prognosis. Recurrent encephalopathy is in itself an extended criterion for consideration of liver transplantation. Increasing understanding of the interplay between the liver, the intestinal microbiome and the innate immune system is allowing for the development of exciting new technologies and treatments to include in the clinician’s armoury in tackling this neurophysiological manifestation of decompensated liver disease.
References


Other neurologic complications beyond hepatic encephalopathy: hepatocerebral degeneration, Wernicke encephalopathy and others – the role of the neuroradiologist

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Introduction:
Hepatic encephalopathy (HE) reflects a spectrum of neuropsychiatric abnormalities occurring in patients with liver dysfunction. Most cases are associated with cirrhosis and portal hypertension or portal-systemic shunts, but the condition can also be seen in patients with acute liver failure and, rarely, with portal-systemic bypass and no associated intrinsic hepatocellular disease [1-2].

Imaging features of hepatic encephalopathy:
Pathogenic mechanisms that may be responsible for HE include accumulation in blood of several compounds that are efficiently metabolized by the liver under normal circumstances, such as manganese and ammonia, which when accumulated within the brain they induce disturbances in astrocyte and neuron function [3-4].

The best diagnostic clue of chronic HE is bilateral T1WI hyperintensity in basal ganglia, particularly globus pallidus. The most plausible explanation for this is a rise in manganese concentration (a paramagnetic substance) in the CNS. Other features include hyperintensity in T1WI of the pituitary gland, hypothalamus and mesencephalon surrounding red nuclei. Atrophy, especially affecting cerebellum can also be shown in later phases. Nevertheless bilateral T1 bright signal intensity within the globi pallidi can be observed in a number of disorders that are not related to elevated manganese levels [5]. In acute HE MRI can show high signal in T2WI in most of the cerebral cortex, sparing periorbital and occipital regions and DWI and FLAIR sequences can show lesions in periventricular white matter, thalami and posterior limb of internal capsule [6]. There are other clinical entities that can happen along HE and have characteristic imaging features that should be included in differential diagnosis like Wernicke encephalopathy that result in glutamate accumulation / cell damage due to thiamine deficiency that can be diagnosed by mammillary body, medial thalamus, hypothalamus, periaqueductal gray abnormal signal / enhancement.

Conclusions:
Different MR imaging data obtained in patients with different types of liver failure have improved the understanding of the pathogenesis of HE, such as the involvement of manganese deposition in parkinsonism and the development of mild grade cerebral edema and osmotic abnormalities secondary to the increase in brain ammonia. Moreover studies show that in acute hepatic encephalopathy, there can be characteristic regions of involvement visualized on MR imaging and that both the clinical and MR imaging findings can be reversible. All these data support the use of MR imaging as a useful tool to study the pathogenesis of HE in humans.

References
Pulmonary manifestations: From pathophysiology to supportive treatment and liver transplantation
Hepatopulmonary Syndrome
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Abstract
Hepatopulmonary syndrome (HPS) is the consequence of intrapulmonary vascular dilatations, mainly located in the basal parts of the lung, resulting in disturbed gas exchange. The pathogenic basis of HPS consists of a combination of excessive endothelin-1 release and bacterial translocation, resulting from liver injury and/or portal hypertension, that leads to nitric and carbon monoxide mediated and angiogenesis mediated intrapulmonary vasodilation. Mortality is around 30% after liver transplantation for severe HPS, especially if PaO2 is below 50 mmHg. The diagnosis of HPS is made by calculating the alveolar-arterial oxygen (A-a) O2 gradient and by performing contrast echocardiography or macroaggregated albumin lung scan. Medical therapy fails and the only long-term treatment available is liver transplantation. More than 85% of the patients experience significant improvement or complete resolution of hypoxemia, which however may take more than 1 year.

Hepatopulmonary syndrome
• Definition
Hepatopulmonary syndrome (HPS) is the consequence of intrapulmonary vascular dilatations (IPVD) occurring in a subgroup of patients with cirrhosis and/or portal hypertension [1].

HPS is characterised by the following clinical triad:
- presence of liver disease and/or portal hypertension
- widened alveolar-arterial oxygen (A-a) O2 gradient while breathing room air P(A-a) > 15 mmHg or > 20 mmHg if ≥ 65 year
- intrapulmonary vascular dilatations (capillary, precapillary, arterio-venous malformations)

• Prevalence and natural history
The prevalence of HPS in patients with chronic liver disease ranges from 4% to 47% depending on methods and diagnostic criteria used [2,3]. HPS is a progressive disease, however, there is no clear relationship between severity of hepatic dysfunction and severity of hypoxemia and shunting. Over time, HPS alters quality of life and survival in these patients [2].

• Pathogenesis of HPS
An imbalance between vasodilators and vasoconstrictors in favour of vasodilation plays an important role in the development of HPS. The central pathological processes are nitric (NO) and carbon (CO) monoxide mediated vasodilation and angiogenesis.

- Nitric monoxide (NO) and carbon monoxide (CO) mediated IPVD
Liver injury triggers the release of endothelin (ET)-1 from activated hepatic stellate cells and biliary epithelium [4-8]. ET-1 reaches the pulmonary circulation, where it preferentially interacts with endothelial ETB-receptors. In this setting, it acts as an endocrine vasodilator by stimulating endothelial NO production (through endothelial nitric monoxide synthase, eNOS), resulting in intrapulmonary vasodilation [9-14]. A specific upregulation of the ‘B-type’ of ET-receptors (which, in contrast to the ‘A-type’, results in vasodilation after stimulation) has been described in animals with cirrhosis and portal hypertension [3,10]. On the other hand, liver injury and/or portal hypertension lead to bacterial translocation, which triggers recruitment and accumulation of macrophages in the pulmonary vascular lumen. These macrophages stimulate the production of NO, by upregulation of inducible nitric monoxide synthase (iNOS), and CO, by haeme-oxygenase-1, which finally contributes to intrapulmonary vasodilatation [8,11-14]. Administration of pentoxifylline (non-specific TNFα, iNOS, angiogenesis inhibitor) and specific monoclonal anti-TNFα antibodies have shown to improve HPS in a rat model of cirrhosis [15,16]. Besides, norfloxacin has been demonstrated to reduce the severity of experimental HPS by its intestinal decontaminating properties [17].

Increased concentrations of exhaled NO and plasma carboxyhemoglobin levels have been found in patients with HPS compared with patients without HPS [18-20]. In these patients there was a significant correlation between carboxyhemoglobin, exhaled NO and (A-a) O2 gradient.

Taken together, these studies suggest that local production of NO and CO in the lung plays an important role in HPS.
Pathophysiology of hypoxemia in HPS [23]

Hypoxemia in patients with HPS is caused by 3 mechanisms [1]:

a. Ventilation-perfusion mismatch
b. Diffusion restriction
c. Intrapulmonary shunting

a. Ventilation-perfusion mismatch means an overperfusion of the alveolar capillary bed with normal to low ventilated alveoli especially in the basal parts of the lung, leading to hypoxemia.

b. Diffusion restriction
Because the enlarged diameter of the intrapulmonary capillaries, oxygen molecules of the adjacent alveoli cannot reach the centre of the dilated vessel, which leads to non-oxygenated haemoglobin despite a normal oxygen pressure in the alveolus, resulting in hypoxemia. When alveolar oxygen pressure is increased, it provides enough driving pressure for the oxygen molecules to diffuse into the centre of the dilated blood vessel, improving oxygenation.

Increased cardiac output associated with liver cirrhosis further limits the oxygenation, as it reduces the erythrocyte transit time through the lung vasculature and the amount of time available for the oxygenation of haemoglobin.

c. Intrapulmonary shunting
Besides intrapulmonary vasodilation, also direct arteriovenous malformations can develop in HPS. These shunts bypass the site of physiological gas exchange, pulmonary capillaries and alveoli. This is a third mechanism by which mixed venous blood passes into the central circulation.

Clinical manifestations
Clinical manifestations are dyspnoea and platypnea (shortness of breath that exacerbates in upright and improves in supine position) [24]. Because the vascular abnormalities predominate in the middle lobe to lower lobes, where gravitational effects result in an increase in blood flow, worsening of hypoxemia can occur in upright position and is called orthodeoxia due to increased shunting and ventilation/perfusion mismatching [24]. Spider angiomata are markers of IPVD and are associated with an enlarged alveolar-arterial oxygen gradient. Clubbing and distal cyanosis can also occur. Lung function examination reveals normal lung volumes and expiratory flow rates but the diffusion capacity for CO (DLCO) is impaired [24].
Pulmonary angiography can distinguish 2 different radiological patterns of HPS: type 1 is characterised by diffuse, spider like vascular abnormalities; type 2 is characterised by localised arteriovenous communications and is associated with a poor response to extra oxygen supply [24]. Recently, it has been shown that high resolution computed tomography of the lungs can also contribute to the diagnosis of arteriovenous communications [32]. Other studies explored left atrial and ventricular enlargement or serum concentration of biomarkers (vascular cell adhesion molecule 1, intercellular cell adhesion molecule 3 and von Willebrand Factor) as feasible parameters to detect HPS, but the use of these techniques has to be validated in larger groups of patients [33-36].

• Treatment of HPS

Cirrhotic patients with HPS have a higher mortality (RR >2) than patients without HPS, regardless of the Child-Pugh score, age and kidney function [2]. Medical therapy fails and the only long-term treatment available is liver transplantation [24,37].

Medical therapy (methylene blue, garlic, nitric oxide synthase inhibitors, octreotide, propranolol, almitrine bismesylate) is disappointing and none can be recommended at this time.

Angiography can be used to treat large type 2 lesions with occlusion of the arteriovenous communications by using coils [24,37].

Liver transplantation is nowadays indicated for patients with HPS. Severe HPS increases post-transplant mortality (30%) especially if PaO2 is below 50 mmHg. More than 85% experience significant improvement or complete resolution in hypoxemia, which however may take more than 1 year (2-14 months) [24,37,38].

References

Pulmonary hypertension (PH) is a haemodynamic state defined by a resting mean pulmonary artery pressure (PAP) ≥ 25 mmHg as assessed by right heart catheterization (RHC) [1-3]. Since this is a haemodynamic definition (Table 1), PH can be found in a variety of clinical conditions, which have been grouped in 6 different clinical categories each of them with specific characteristics (Table 2) [2,4]. PH encompasses both pulmonary arterial hypertension (PAH) as well as pulmonary venous hypertension due to left heart disease, pulmonary hypertension due to lung disease and/or hypoxia, chronic thromboembolic PH and PH due to miscellaneous conditions [2,5,6].

PAH is a progressive condition characterised by elevated PAP, high pulmonary vascular resistance (PVR) leading to right heart failure, exercise limitation and premature death. PAH is a form of pre-capillary PH (i.e., with normal left ventricular filling pressures), and its diagnosis requires the exclusion of other forms of pre-capillary PH such as PH due to lung disease and/or hypoxia, chronic thromboembolic PH, and PH with unclear and/or multifactorial mechanisms [3,7]. The definition of PAH also requires the demonstration of a normal pulmonary artery occlusion pressure (PAOP) in order to exclude that the elevation in PAP is not simply due to elevated left ventricular filling pressures [5]. Although most commonly idiopathic, PAH may also be associated with other conditions such as connective tissue diseases (as systemic sclerosis), congenital heart disease, HIV infection, and portal hypertension, the latter association termed portal-pulmonary hypertension (PoPH) [2,7-10].

A mild increase in PAP is commonly seen in patients with cirrhosis and/or portal hypertension, although this is generally due to the usual hyperdynamic state characteristic of liver disease and driven by splanchnic bed vasodilation [11] or due to elevated left ventricular filling pressures [5]. Although most commonly idiopathic, PoPH may also be associated with other conditions such as connective tissue diseases (as systemic sclerosis), congenital heart disease, HIV infection, and portal hypertension, the latter association termed portal-pulmonary hypertension (PoPH) [2, 7-10].

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A mild increase in PAP is commonly seen in patients with cirrhosis and/or portal hypertension, although this is generally due to the usual hyperdynamic state characteristic of liver disease and driven by splanchnic bed vasodilation [11] or due to elevated left ventricular filling pressures in the context of a volume overload state. In contrast, PoPH is a severe pulmonary vasculopathy, defined by the presence of PAH in the setting of portal hypertension with or without underlying advanced liver disease and in the absence of other causes of PAH [8]. It is now a well-recognised cause of PAH in the 2013 Updated classification of PH (Table 2) [12]. Accordingly, it is defined by resting mean PAP ≥ 25 mmHg, raised PVR (≥ 3 Wood units, WU) and a PAOP ≤ 15 mmHg, in a patient with a clinical diagnosis of portal hypertension [8, 13].
PoPH is a relatively rare condition. Although most commonly observed in patients with end-stage liver disease, PoPH has also been identified in the context of non-cirrhotic portal hypertension, including nodular regenerative hyperplasia, portal vein thrombosis, Budd Chiari syndrome, and schistosomiasis (itself a cause of PAH) [14-17]. This observation supports the notion that portal hypertension, rather than cirrhosis, is the key factor for the development of PoPH. The actual incidence and prevalence of PoPH are unknown. Very few descriptive epidemiological studies are available and the majority of estimates are in patients with end-stage liver disease undergoing evaluation for LT. Moreover, since there are no standard criteria for its screening, published reports on the epidemiology of PoPH vary greatly according to the criteria used to define this condition as well as to the population studied.

PoPH is most commonly diagnosed in the fourth and fifth decades of life, and generally several years after the diagnosis of portal hypertension is made [18-20]. Nevertheless, symptoms of PH may, albeit rarely, precede those of portal hypertension [19].

Few studies have attempted to determine which factors may be associated with the emergence of PoPH in patients with advanced liver disease. A multicentre case-control study conducted by Kawut et al found that female sex and underlying autoimmune hepatitis were independently associated with an increased risk of PoPH [21]. On the other hand, hepatitis C infection appeared to be protective compared to other aetiologies of liver disease [21]. The female predominance mirrors that also observed for idiopathic PAH [22] and women have nearly 3 times the risk of men, even there are more men affected with cirrhosis. The same study while reporting that age was not a risk factor for the development of PoPH, showed an average age at presentation of 53 years old which is 17 years older than that observed in patients with idiopathic PAH [21, 23]. A recent retrospective case-control study showed that the presence of large spontaneous portosystemic shunts, and in particular splenorenal shunts, was significantly associated with moderate and severe PoPH compared with mild or absent PoPH, and with a lack of response to treatment [24].

Although one early study found a higher frequency of PoPH in cirrhotic patients complicated by refractory ascites [25], it does not seem that either the prevalence or the severity of PoPH is correlated with the severity of liver dysfunction, as measured by the Child-Turcotte-Pugh or the Model of End-stage Liver Disease (MELD) scores, or the degree of portal hypertension [21, 26, 27].

PoPH may be asymptomatic at presentation or only accompanied by non-specific symptoms, patients with portal hypertension undergoing pre-LT evaluation as well as those who develop dyspnoea require a thorough cardio-pulmonary evaluation. In patients who are not awaiting LT, PoPH should be screened if in the presence of suggestive symptoms and signs and after other cardio-pulmonary disorders have been excluded [7]. On the other hand, screening for PoPH should be performed in all patients being evaluated for LT regardless of their signs or symptoms, since the presence and the severity of PoPH may affect their transplant candidacy [28]. The screening test of choice is the transthoracic echocardiography (TTE) [2, 7, 29, 30]. In one study, 165 patients being evaluated for LT underwent both TTE and RHC as part of their evaluation [31]. Using a cut-off value of 30 mmHg, 17 patients met the criteria for PoPH on TTE, and in 10 of them RHC confirmed the presence of PoPH. Positive and negative predictive values in this study were 59% and 100% respectively [31]. Using a cut-off value of 50 mmHg in order to identify patients with moderate-to-severe PoPH, Kim et al reported a sensitivity and specificity of 97% and 77% respectively [32]. Later, a prospective study from the same centre, in which 101 cirrhotic patients with a RVSP > 50 mmHg were submitted to RHC, showed that 65% of those met the haemodynamic criteria for PoPH [27]. Taken together, these studies show that a RVSP < 30 mmHg can be used to exclude PoPH, while a RVSP > 50 mmHg is predictive of PoPH, and therefore the latter group of patients should undergo RHC [29, 33]. Although useful as a screening strategy, TTE estimates have a relatively low positive predictive value and display poor correlation with RHC measurements [27]. Thus, all patients with TTE findings suggestive of PH (even with normal or borderline elevations in RVSP) must undergo a haemodynamic assessment by RHC, which is required for the definitive diagnosis of PoPH [3]. It should be stressed that PoPH diagnosis requires a RHC with a mean PAP ≥ 25 mmHg and a PAOP ≤ 15 mmHg and a PVR > 3 WU coupled with clinical evidence and/or haemodynamic confirmation (by measuring portal pressure during hepatic vein catheterisation) of portal hypertension [13].

In the setting of chronic liver disease, the calculation of the trans-pulmonary gradient (TPG) – i.e., mean PAP minus the PAOP – is of particular significance, in view of common circulatory changes seen in this group of patients [11]. A TPG > 12 mmHg can be used to exclude those patients with portal hypertension with an elevated mean PAP due to the hyperdynamic state who would otherwise be wrongly classified as having PoPH [34, 35]. Thus, a TPG > 12 mmHg is highly indicative of PoPH and should be included in its diagnostic criteria [13, 29]. This differentiation is very
important in terms of prognosis, since cirrhotic patients with an increased mean PAP due to the hyperdynamic circulation do not have the same dismal prognosis as those with true PoPH [36]. PVR, adjusting TPG to CO, is also a valid measure for the discrimination of PoPH from hyperdynamic states (Table 3).

The natural history of PoPH has been difficult to assess, although it is well established that it is associated with right ventricle dysfunction, exercise limitation and reduced survival. One study performed before the era of PAH-specific therapies reported a mean survival of just 15 months [20]. Almost 15 years later, Kawut et al published a retrospective study including patients with PoPH and with other causes of PAH; patients with PoPH had a higher cardiac index and a lower PVR compared to patients with idiopathic PAH, although PAP did not differ between the two groups [37]. Despite this more favourable haemodynamic profile, patients with PoPH had an almost three times higher risk of death [37].

Since PoPH belongs to the wider PAH spectrum of disease, the principles guiding PAH therapy have been applied to these patients. However, the presence of liver disease must be taken into consideration, which results in some differences in the management of the two groups of patients. First of all, while current guidelines recommend the initiation of calcium channel blockers in those PAH patients who demonstrate a favourable response to acute vasoreactive testing during RHC [2], they are not indicated in the setting of PoPH in view of its mesenteric dilation properties which may result in worsening of portal hypertension [38, 39]. On the other hand, despite the widespread use of B-blockers for primary and secondary prophylaxis of gastrointestinal bleeding in the setting of portal hypertension, these agents must be used with caution, and if possible avoided, in PoPH patients as their use was shown to be associated with a significant worsening of exercise capacity and pulmonary haemodynamics, due to right ventricular function impairment. [40]. The use of oxygen supplementation and diuretics follow the same rules as for PAH, and are thus indicated if hypoxemia or fluid overload respectively are present [2].

In the past few decades several advances have been made in the treatment of PAH. The approval of new therapies has resulted in improvements in morbidity and survival of patients with diverse forms of PAH [41]. Current available therapies span three drug classes which target three different PH disease pathways: prostanoids, ET receptor antagonists and phosphodiesterase type 5 inhibitors [2]. However, until recently, patients with PoPH have historically been excluded from all PAH randomised clinical trials (RCT), and therefore information regarding the overall efficacy of the new therapies in PoPH was lacking. Recently, PATENT-1 trial with riociguat, a soluble guanylate-cyclase stimulator, included 13 patients with PoPH, 11 in the active treatment group. The study showed that riociguat significantly improved functional capacity of PAH patients. However, no subgroup analysis was made with regard to the group of PoPH patients [42]. Nevertheless, the data obtained from those RCTs have been translated to the PoPH setting and their clinical efficacy has meanwhile been documented in some case reports and series.

Without LT, PoPH prognosis is dismal with 5-years survival of less than 30%. However, PoPH is not an indication for LT, and when severe, it contraindicates the procedure due to an increased intra and postoperative mortality. Nevertheless, various studies have recently shown that it is possible to improve pulmonary haemodynamic measurements by means of vasodilation therapy, thus allowing LT to be performed with significantly lower perioperative risk. In addition, there are reports suggesting that LT may resolve PoPH [43, 44]. A study by Sussman et al aimed to analyse feasibility and the effects of LT following vasodilation therapy; treatment with epoprostenol resulted in haemodynamic profile improvement in 7 of 8 severe PoPH cirrhotic patients. LT was performed in 4 of those 7 patients, and patients remained well after 9 to 19 months post-LT [45]. In another study, 16 of the 20 patients with moderate-to-severe PoPH, and who were otherwise suitable for LT, were treated with epoprostenol either alone or in combination with bosentan. In 12 of those patients mean PAP decreased to a level < 35 mmHg, which allowed LT to be performed in 11 cases; 1- and 5-years survival in this population was 91% and 67% respectively [46]. Based on these studies, it is now accepted that some selected patients with moderate-to-severe PoPH, who would otherwise not be candidates for LT, can receive medical therapy in order to decrease their mean PAP and PVR so that they can then eventually undergo LT [30]. A small subset of these patients have been able to successfully discontinue vasodilation therapy following LT [47].

### Table 1 - Haemodynamic definitions of pulmonary hypertension

<table>
<thead>
<tr>
<th>Condition</th>
<th>Definition</th>
<th>Example</th>
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<tr>
<td>Pre-capillary PH</td>
<td>Mean PAP ≥ 25 mmHg</td>
<td>PHT (excluding PPH)</td>
</tr>
<tr>
<td></td>
<td>PVR ≤ 5 mmHg</td>
<td>Chronic thromboembolic PH</td>
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<td></td>
<td>TPG &gt; 15 mmHg</td>
<td>PH with unclear mechanisms</td>
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<tr>
<td>Post-capillary PH</td>
<td>Mean PAP ≥ 25 mmHg</td>
<td>PHT due to left heart disease</td>
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<td></td>
<td>PVR &gt; 15 mmHg</td>
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PPH, Pulmonary Hypertension; PAP, Pulmonary Arterial Pressure; PAOP, Pulmonary Arterial Occlusive Pressure; PHT, Pulmonary Hypertension; PPH, Pulmonary Hypertension
EXTRA-HEPATIC INVOLVEMENT IN CHRONIC LIVER DISEASES

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Hepatic Hydrothorax

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Hepatic hydrothorax (HH) is a rare complication of cirrhosis and portal hypertension. It is defined as a transudative pleural effusion in the absence of underlying cardiac, pulmonary or malignant disease. It occurs in 4 – 16 % of patients with cirrhosis, but only a few of them require repeated thoracocentesis. [1,2]

Pathophysiology
The pathophysiology of HH is only partially known. It may involve diaphragmatic defects, leading to a passage of ascites from the abdominal cavity to the pleural space, facilitated by negative intrathoracic pressure during inspiration. This concept is supported by the result of peritoneal scintigraphy with 99Tc Albumin, or 99Tc colloids [3-5]. However, the cause of the diaphragmatic defects is unclear. It may be favored by poor nutritional status and muscle waste.

Diagnosis
Hepatic hydrothorax is the most frequent cause of pleural effusion in patients with cirrhosis and ascites. However, in a retrospective study another cause than cirrhosis was found in 30% of the patients [6]. HH is usually right sided (73%), less frequently left sided (17%) or bilateral (10%) [7]. HH is usually associated with severe cirrhosis (MELD score > 16). The majority of patients (90%) with HH have ascites, but its absence does not rule out the diagnosis. Because of the constraints of the thoracic cavity, HH becomes symptomatic with a lower volume than ascites. It is responsible for cough, shortening of breath, hypoxemia and may cause respiratory failure [7].

Thoracocentesis should be performed to assess the diagnosis and to identify potential other causes of pleural effusion, and to diagnose a complication such as infection. Therapeutic thoracocentesis, by removing a large amount of fluid, usually improves respiratory status.

Outcome
As refractory ascites, HH seems to be associated with an increased risk of mortality independent of the MELD score, even if data from large series of patients are missing. Mortality is related to HH or to the liver. Complications of HH are respiratory failure, spontaneous bacterial pleuritis, and complication of thoracocentesis.

Spontaneous bacterial pleuritis (SBPL) is defined as an infection of the pleural effusion without underlying pneumonia. It should be suspected in patients with fever, encephalopathy, chest pain, jaundice or acute kidney injury. The diagnosis is based on a pleural fluid analysis. The diagnosis criteria proposed are: positive pleural fluid culture with a neutrophil count above 250/ mm3, or a negative culture but a compatible clinical course and a pleural fluid neutrophil count greater than 500/mm3. Almost half of the patient presenting with SBPL had non concomitant SBP, justifying concomitant ascites and pleural analysis if an infection in suspected [9]. SBPL treatment is based on antibiotics. Albumin infusion has not been evaluated in this indication. Chest tube insertion should be avoided, because of a high prevalence of complications including pneumothorax, secondary infection, prolonged drainage length [10,11].

Treatment
As refractory ascites, HH is associated with a poor prognosis, and in absence of comorbidities patients should be evaluated for liver transplantation. The medical treatment of HH is similar to the one of ascites and includes the etiologic treatment of underlying liver disease, moderate sodium restriction and diuretics [12].

- Thoracocentesis
If tense ascites is present, abdominal paracentesis may improve the HH and dyspnea. If dyspnea persists despite paracentesis, thoracocentesis should be performed. It is effective to remove pleural fluid. The volume of fluid removed is often mild (rarely up to 2 – 2.5L) and compensation with colloids or albumin...
has not been tested. However it seems reasonable to recommend compensation if ascites is removed at the same time, according to practice guidelines.

Thoracocentesis is a relatively safe procedure in a general population [13], however a higher rate of complications has been described in cirrhotic patients (6). Moreover, even if the risk of complications such as pneumothorax, bleeding or reexpansion pulmonary edema is low (<5 %), the need of repeated thoracocentesis increases this risk. Thus thoracocentesis should only be used as a palliative treatment.

In the other side, chest tube placement is at high risk of complication: hemorrhage, pneumothorax, infection, acute kidney injury, protein loss, and long length of drainage; and should be used only in case of empyema, or pleuropneumothorax [11].

- Transjugular intrahepatic portosystemic shunt (TIPS)

TIPS is effective for the treatment of refractory ascites [14], however the improvement of survival is still a matter of debate. It has contra-indication (encephalopathy, liver insufficiency) and the procedure has a certain level of morbidity. As in refractory ascites, TIPS seemed to be an effective treatment of refractory HH, with an improvement in 58-82 % of the patients [15-17]. Risk factors for mortality are the same as refractory ascites and has been suggested in this special population [18, 19]. Risk factors are: Child-Pugh C, MELD score > 15, mild elevation of creatinine.

As in refractory ascites, TIPS may improve symptoms, but can only be proposed to highly selected patient. It can be used as bridge therapy for liver transplant.

- Thoracic surgery

Pleurodesis has been tested for refractory HH. It can be associated with video-assisted thoracoscopic surgery (VATS). The rapid accumulation of pleural fluid and limited inflammatory response lead to poor efficacy (40 to 70%) and high morbidity and mortality rate [20, 21].

A recent series reported a high rate of improvement following thoracoscopic mesh repair of diaphragmatic defects [22]. These results need to be confirmed.

- Pleural catheter

Indwelling pleural catheter and pleural implantable access system have been validated in the management of malignant pleural effusion [23]. Because hepatic hydrothorax is often recurrent, the use of indwelling pleural catheter has been proposed. A recent pilot study reported promising results but a higher proportion of infection than in patient with malignant pleural effusion (24). Pleural implantable catheter has the advantage of being a close system requiring a simple puncture into the chamber. Its use has been reported in a small series and seems safe. It avoids thoracocentesis and may be a bridge therapy to liver transplant, or a palliative treatment for patient with TIPS contraindication.

- Liver transplantation

Liver transplantation is the best treatment option for patient with decompensated cirrhosis and therefore for patient with refractory HH. The presence of hydrothorax prior to transplantation does not imply a worse outcome, mortality and post operative morbidity are the same as patient transplanted for end stage liver disease [25, 26].

Conclusion

Hepatic hydrothorax is a rare condition in patients with end stage liver disease. It should be suspected in any patient with cirrhosis and pleural effusion. The best treatment option is liver transplantation if HH becomes refractory. TIPS or implantable pleural catheter are effective as bridge therapy to liver transplantation or palliative treatment if transplantation in contraindicated.

References


Miscellanea
Beta-blockers for portal hypertension: where do we stand?
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The rational
Portal hypertension is defined as a pressure gradient between the portal vein and systemic circulation of more than 5 mmHg [1]. Portal hypertension especially in the beginning of liver disease is induced by the increased hepatic resistance. Hepatic resistance increases due to the morphological changes (fibrosis) and the dynamic changes (vasoconstriction) in the liver [1]. With the progression of portal hypertension extrahepatic changes take place, especially in the splanchnic vessels. The splanchnic and systemic vessels are dilated and show hypocontractility, which require a higher cardiac output in order to maintain the mean arterial pressure [2]. This situation also known as the hyperdynamic circulation is a hallmark maintaining and promoting portal hypertension [2]. Non-selective beta-blockers (NSBB) have been introduced 35 years ago by Lebrec et al to treat portal hypertension [3]. NSBB lower cardiac output and increase splanchnic vascular tone curtailing the portal venous inflow [4]. Especially in the last years besides the classical NSBB such as propranolol, also carvedilol has been investigated with significantly better efficacy profile than propranolol, probably due to the additional partial alpha-1-adrenoceptor blocking properties decreasing hepatic resistance [5,6].

Variceal bleeding
NSBB decrease portal pressure sufficiently to prevent variceal bleeding and in combination with endoscopic therapy also reduces rebleeding and improves survival in patients with cirrhosis and varices [7]. NSBB failed to prevent the development of varices (pre-primary prophylaxis), probably because they are only effective in patients with clinical significant portal hypertension defined as hepatic-venous pressure gradient of 10mmHg or more [8,9]. However, patients under primary or secondary prophylaxis with NSBB still experience bleeding and progression of liver disease.

Ascites and renal dysfunction
The development of ascites is a clinical milestone in the natural history of liver cirrhosis [10]. The last years an on-going debate has taken place regarding use of NSBB in refractory ascites. The same group introducing NSBB for the therapy of portal hypertension showed that NSBB might have deleterious effects in patients with refractory ascites [11]. Since then many groups have shown different experiences in favour or against the use of NSBB in patients with refractory ascites, which might be dependent on the dose used in the different cohorts [12]. Retrospective analyses suggest that NSBB might induce acute kidney injury and hepatorenal syndrome in patients in case of infections or other insults, probably due to the restriction in cardiac output [13].

Infections and Acute on Chronic liver failure
Infections, especially spontaneous bacterial peritonitis (SBP), are frequent in cirrhotic patients and might lead to extrahepatic organ failure defining acute-on-chronic-liver failure (ACLF) [14]. One of the major mechanisms leading to SBP and infections is bacterial translocation, which might predispose also to variceal bleeding [15]. Interestingly, bacterial translocation is decreased under NSBB, offering another mechanism of action of NSBB apart from hemodynamic response [15]. In the CANONIC cohort of patients admitted for decompensation of cirrhosis, patients under NSBB showed less severe systemic inflammation and improved survival in patients developing ACLF [16]. One possible explanation might be that upon stimulation PBMC produce less proinflammatory cytokines after preincubation with NSBB (own data). Therefore, one might think that NSBB might prevent the development of a severe systemic inflammatory response when the patients experience SBP or other infections.

Conclusions
NSBB decrease portal pressure, reduce bacterial translocation and prevent severe inflammatory response in patients with cirrhosis. These effects are beneficial and warrant a further use of NSBB in cirrhotic patients. Care is required in dosing and managing the patients prone to decompensation. Further investigation of NSBB in specific patients cohorts is required.
References


Iron, chronic liver disease and inflammation: looking beyond the liver

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As the main iron storage site in the body and the main source of the iron-regulatory hormone, hepcidin, the liver plays a central role in iron homeostasis [1]. Iron is among the most abundant elements on Earth, it is an essential component of human body, and an important micronutrient in human diet. However, it is a double-edged element in humans. On one hand it is essential for life, due to its crucial role in many cellular functions and metabolic processes, such as hemoglobin, myoglobin and DNA synthesis, mitochondrial respiration, oxidative phosphorylation, and other enzymatic functions. On the other hand, because of its ability to participate in the Fenton and Haber-Weiss chemistry, when not bound by appropriate ligands or proteins excess redox-active iron may lead to reactive oxygen species production with consequent damage of DNA, membranes and proteins, and potential for tissue damage and organ disease, including liver, heart, pancreas, endocrine glands, CNS or joints. Thus both iron deficiency and iron excess represent pathologic conditions with high health and socio-economical burden worldwide. In fact disorders of iron homeostasis are among the most common diseases of humans, and encompass a broad spectrum of pathologic conditions ranging from iron deficiency, to iron misdistribution, and iron overload, with diverse clinical manifestations and etiology (either hereditary or acquired or mixed origin).

Given the essential need for iron and the fact that in mammals there is no active mechanism for iron excretion, a tight regulation of iron absorption and recycling is required. The key regulator of iron homeostasis is hepcidin, a small hormone synthesized mainly by the liver and secreted in the bloodstream [2]. It is a defensine-like antimicrobial peptide, firstly isolated from human blood ultrafiltrate and identified in human urine, that likely evolved in humans as part of the innate immune defense, further strengthening the pivotal role of the liver in the immune response. In fact hepatocytes, constitutively and/or in response to pathogenic and inflammatory signals, produce and secrete to the bloodstream several proteins that play important roles in innate immunity, including bactericidal proteins, opsonins, different soluble factors that regulate LPS (lipopolysaccharide) signaling, liver enriched transcription factors regulating the expression of innate immunity proteins, fibrinogen, and iron-sequestering proteins such as hepcidin [3].

This peptide diffuses through the body interacting with the transmembrane protein ferroportin, the sole iron exporter present at the surface of duodenal enterocytes, macrophages, placental cells, and hepatocytes. As a result of this interaction, ferroportin is internalized and degraded, and the unneeded iron remains in the cell, where it is saved for future use in the form of ferritin. In this manner, circulating iron remains at levels capable of meeting the bone marrow needs without posing an oxidative threat to the cells.

Since the discovery of hepcidin in 2000, several signals from the body have been demonstrated to regulate liver hepcidin levels and consequently systemic iron levels and distribution.

Both circulatory and tissue iron upregulate hepcidin transcription, via the Bone Morphogenetic Protein-Small Mothers Against Decapentaplegic (BMP-SMAD) signaling cascade, as a negative feedback mechanism that protects the body from excessive iron accumulation. Inflammation also stimulates hepcidin transcription, mainly via the Signal Transducer and Activator of Transcription 3 (STAT3) signaling pathway likely in cooperation with the BMP-SMAD pathway. Hepcidin is also produced in small amount by monocytes/macrophages during infections in response to the inflammatory mediators acting through Toll-like receptors (TLRs) dependent pathway. The increased production of hepcidin under infectious/inflammatory status may be considered as a protective innate immune defense to limit iron availability for invading pathogens or tumoral cells. However, if upregulation of hepcidin persists, iron-restricted erythropoiesis and anemia of chronic disease will follow [5]. Endoplasmic reticulum (ER) stress due to a variety of pathological signals has been shown to trigger hepcidin expression, indicating that not only extracellular but also intracellular signals might influence hepcidin levels and systemic iron homeostasis. Recently, using starvation as a model of activated gluconeogenesis and insulin resistance, it has been demonstrated in mice that gluconeogenic signals are able to modulate iron homeostasis through hepcidin, indicating a possible mechanism for iron misdistribution or excess in insulin-resistance related human diseases. Inhibitory stimuli for hepcidin also exist, such as bone marrow signals/erythropoietic needs, iron depletion, hypoxia, and oxidative stress. For example, alcohol and hepatitis C virus (HCV) have been demonstrated to down-regulate hepcidin expression through hepatic oxidative stress signaling.
More recently, also epidermal and hepatocyte growth factors and testosterone have been reported to down-regulate hepcidin transcription.

Overall these recent acquisitions highlight the role of hepcidin, and therefore also of the liver, as body sensor involved in the response of the human organism to stressors, pathogens, injuries, and metabolic challenges, eventually leading to body iron modulations. Thus hepcidin may be considered as a hepatic hormone peptide linking different physiologic and pathophysiologic signals (ranging from inflammation/infections, nutrient/hormone/metallic changes including iron levels changes, hypoxia or erythropoiesis) to body and cell iron homeostasis. However the variations in iron levels and/or tissue distribution, that evolved as defensive/conservative mechanisms, may become deleterious when perpetuated or in excess [6].

Better understanding of these regulatory and molecular mechanisms will help to dissect the pathophysiology of iron-related human diseases, eventually contributing to their prevention and cure. For example, all forms of hereditary hemochromatosis are characterized by inadequate hepcidin synthesis or activity that leads to progressive plasma and tissue iron overload and, eventually, hepatic and extra-hepatic organ damage and disease. Untreated hereditary hemochromatosis can lead to liver cirrhosis, diabetes mellitus, cardiomyopathy, hypogonadism, arthopathy, and skin pigmentation. Also other very rare hereditary iron overload diseases show a systemic involvement, including extra-hepatic targets of iron toxicity. Moreover hepatocellular and/or mesenchymal iron deposition, usually slight or mild, might be found in chronic non-cirrhotic liver diseases, regardless of its cause. Various non-specific factors (mainly inflammation and cell necrosis), together with polymorphisms in iron-related genes or pathogenic interactions between iron itself and the etiological agent (hepatotropic virus, alcohol, increased supply of free FA to the liver or insulin resistance), might be responsible. In addition, it must be considered that in end-stage liver disease, regardless of its cause, a decreased hepcidin synthesis due to the reduced hepatocytic mass might also lead to excess iron deposition [7]. These factors may cause or contribute to iron overload, and damage the liver itself and likely peripheral organs and extra-hepatic tissues (cardiovascular system, endocrine system, immune system…).

The clinical relevance of iron excess in different liver diseases, in terms of fibrosis development and cancer risk, is still debated. However increasing data from experimental and clinical studies indicate that iron might sustain disease activity and/or contribute to its progression. In fact, it has been demonstrated that iron-driven oxidative stress may cause or contribute to hepatocellular damage and necrosis, leading to activation of classic fibrogenic cascade. Moreover iron-loaded macrophages and Kupffer cells, even if constitutively prone to iron handling, could have impaired their functions (e.g. cytokine production, immunosurveillance, or pathogens clearance) and contribute to reactive oxygen species and cytokines production [8]. Also epidemiological data and mechanistic studies suggest a role for iron in cardiovascular diseases, cancer, neurodegeneration and aging.

In this context, the discovery that the liver is the main source of the key iron hormone, hepcidin, has shed new light on its pivotal role both in the regulation of body iron homeostasis and in the pathogenesis of numerous human diseases apparently unrelated to iron [1]. Giving the significant recent advances in the iron field, it is easy to understand that manipulations of hepcidin-ferroportin axis or hepcidin hormone-replacing strategies may represent a future therapeutic approach not only to iron-related disorders but also to human pathologic conditions, not primarily related to iron, where tissue iron misdistribution may contribute to disease perpetuation and progression.

References
ABacterial infection is the leading cause for morbidity and mortality in cirrhosis. Cirrhotic patients have a particular risk for infection, because of immune dysfunction, bacterial translocation and systemic inflammatory response with circulatory dysfunction; spontaneous or associated with predisposing iatrogenic factors. Spontaneous bacterial peritonitis (SBP) and other infections are important in decompensated cirrhosis, as urinary tract, respiratory, skin and soft tissues, bacteremia and sepsis, but also catheters and other medical devices associated (ex: mechanical ventilation).

The use of antibiotics in cirrhosis is frequent and it was demonstrated that preventive use has change the survival of this patients.

Since many years, prophylactic use in SBP is recommended either as primary or secondary. Norfloxacin 400mg daily was show to reduce episodes of SBP through selective intestinal decontamination, reducing gram negative bacteria from intestinal lumen. Prophylactic strategies are also indicated for prevention of infection during/after upper gastrointestinal bleeding and for prevention of hepatic encephalopathy (HE)

Usually prevention is done using norfloxacin, however, ciprofloxacin and trimethoprim-sulfamethoxazole could be an option (less strong evidence) as well as ceftriaxone for upper gastrointestinal bleeding; and for HE rifaximin as show efficacy with better tolerance than disaccharides. However, these strategies can select organisms for causing infection and many of these agents, particularly in healthcare units but even in community develop drug/antibiotics resistance.

According to the guidelines whenever infection is suspected in a cirrhotic patient empirical antibiotic therapy should be prescribe. Infection type should be screened and the prescription should be directed for the most probable agent. Fernandez (2012) published a paper where the best option for empirical antibiotics use is discussed. Concerning each type of infection, the most probable agents and anticipated resistances this author propose Gut microflora, E.Coli, Klebsiella spp, Enterobacter spp, enterococci and streptococci are frequence agents. The choice of the antibiotic should have in mind the origin of infection, individual risk factors and resistance profile epidemiology.

Community acquired, healthcare-associated (within 48h of hospital admission of any healthcare contact in prior 90days) or nosocomial (after 48h of admission) stratifies the risk for resistant agents and are associated with the outcome.

In nosocomial SBP (and in some places where quinolone resistance is high as occurs for E Coli in Portugal) first choice recommended antibiotics could be associated with high failure treatment rates. Gram positive agents and resistant bacteria SBP are reported with frequency, mainly in healthcare and nosocomial settings.

Angelo de Mattos (2014) propose to use beta lactams in community acquired or healthcare associated without signs of severity. In nosocomial acquired or healthcare associated with signs of severity the better option would be the use of carbapenems with or without glycopeptides or piperacillin-tazobactam.

However, infections other than SBP are also frequent in cirrhotic patients. Empirical use for community-acquired urinary tract infections are ciprofloxacin, cotrimoxazol or amoxicillin/clavulanic acid, considering that the most frequent agents are E Coli, Klebsiella pneumoniae and enterococcus spp.

And for community-acquired pneumonia (Streptococcus pneumoniae; Staphylococcus aureus and E Coli) the proposed antibiotics are amoxillin/clavulanic acid and macrolide or moxifloxacin (a fluoroquinolone).
Empiric antibiotic therapy is useful in treatment of the infection in cirrhotic patients and the appropriate use is associated with an increase of survival in this population.

However, clinical data concerning symptoms or risk factors or laboratory isolation of the infectious agent may indicate a specific treatment.

Among those *Clostridium difficile* diarrhea and colitis is associated with the use of antibiotics, namely broad spectrum. It has been describe associated with the use of quinolones in SBP prophylaxis.

Other agents should be suspected according the disease, for example, in a hemochromatosis cirrhotic patient with diarrhea Vibrio spp should be considered or in an alcoholic pneumonia probably is associated with *Streptococcus pneumoniae* and a specific treatment should be prescribe.

Multidrug resistant infections are getting more frequent, in community acquired agents (because of the misuse of antibiotics in community setting) but mainly in healthcare and nosocomial infection.

This situation is associated with treatment failure and poor outcome in cirrhotic patients. There are studies showing that those patients have a higher mortality rate.

From patients with infection those that receive an inappropriate antibiotic treatment have a longer stay in intensive care unit, and have more frequent treatment escalation.

In a large study, having cirrhosis is associated with the increase risk of infection, receiving inappropriate initial antibiotic treatment and in-hospital mortality rate.

Cirrhotic patients have a higher probability of infection and sepsis. And this infections are in about in one third of cases by multiresistant agents, as extended spectrum beta lactamase (ESBL) enterobacteriaceae, methicilline resistant streptococcus aureus (MRSA) and vancomycin-resistant enterococcus (VRE). The most important for this patients are identification of infection and of risk factors, appropriated antibiotic prophylaxis / treatment, recognition of local resistance epidemiology and adequate treatment strategy.

References

Factors associated/inducing decompensation in cirrhosis
Changing the paradigm: shall cirrhosis be really seen as a prothrombotic condition?

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Cirrhosis is characterized by a complex derangement of hemostasis including platelet vessel wall interaction (primary hemostasis) and coagulation (thrombin generation and fibrin formation). Coagulation is in particular characterized by a relative deficiency of most of the procoagulants factors (except factor VIII and von Willebrand factor, which are increased) [1]. This derangement makes the prothrombin time to be prolonged in these patients. However, the anticoagulant factors are also reduced in cirrhosis and this is consistent with the hypothesis that the balance of coagulation is restored. Evidence for this hypothesis have been provided by in vitro studies, which showed that thrombin generation in patients with cirrhosis is normal [2, 3]. More recently, it was shown that thrombin generation assays performed in the presence-vs-the absence of thrombomodulin (the main physiological activator of protein C) were able to detect a certain degree of hypercoagulability in patients with cirrhosis. This hypercoagulability is correlated with the (decreased) levels of protein C, with the (increased) levels of factor VIII and with the ratio factor VIII/protein C [4, 5]. What are the consequences of this hypercoagulability? Cirrhosis was recognized as a condition unprotected from venous thromboembolism notwithstanding the partial deficiency of procoagulant factors and the prolongation of the PT [6]. A population case-control study showed that patient with cirrhosis had a risk to develop venous thrombosis that was nearly 2-times greater than that of the normal population [7]. Portal vein thrombosis might also be triggered at least in part by this plasma hypercoagulability. Finally, it has been shown that increased thrombin generation may be responsible for the progression of liver fibrosis [8]. If these hypotheses hold true, cirrhosis should no longer be seen as an auto-anticoagulated condition as it was believed for many decades and patients are candidate to anticoagulation for both prophylaxis and treatment of venous thromboembolism [9, 10].

References

Portal vein thrombosis: shall we screen? Shall we treat?

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Screening is a strategy used in a population to identify the possible presence of an undiagnosed condition in individuals without signs or symptoms. This can include individuals with an unrecognized disease where screening tests are performed on persons apparently in good health. In addition, screening interventions can be designed to identify a possible asymptomatic complication of an already known disease. In both situations, screening is recommended if it benefits the person being screened. Then, screening for asymptomatic PVT should be recommended if the recognition of its presence will benefit the patient either because it gives additional information on the prognosis or because it changes the management of the patient.

Incidence and prevalence of PVT in cirrhosis

PVT is the most common of thrombotic events occurring in cirrhotic patients, with a reported prevalence ranging from 2.1% to 23.3% in published series of transplant candidates without HCC [1]. Incidence of PVT at 1 year has been described to range from 4 to 16% in different cohort studies. Therefore chances to detect asymptomatic PVT is relatively high if screening for its identification is performed. Doppler ultrasound is the screening technique used for PVT diagnosis. However, PVT may also be found during the development of liver decompensation. In the study by Amitrano et al. 43% of patients with cirrhosis were in stable condition when PVT was diagnosed, in 39% PVT was diagnosed during the admission of the patients because a portal hypertension-related gastrointestinal bleeding and in the remaining 18% patients during the study of an episode of acute abdominal pain [2]. However, whether PVT is the cause, the consequence or just and associated event to these last 2 manifestations (bleeding/pain) is not known. Indeed, the larger prospective study performed up to now including 1278 patients with Child A and B cirrhosis and without PVT showed a 1 year actuarial incidence of PVT of 4.6%. PVT developed more frequently in patients with more severe disease. However, PVT development had no impact on liver disease progression or in survival [3].

It is, however, important to point out that in this study most were partial non-occlusive PVTs. Therefore, this study does not allow answering whether occlusive PVT has also no impact in the outcome of patients with cirrhosis. Additionally, it has been shown that, although the reported progression of partial PVT is variable and in some cases there is even spontaneous regression, it is estimated that in more than 40% of patients partial PVT will progress over time (months or years) if no intervention is done. Thus, the potential impact of PVT on the natural history of cirrhosis may need to be evaluated after a much longer follow-up to what it has been evaluated up to now.

Some studies have suggested that PVT is independently associated with a higher risk of variceal bleeding, failure of endoscopic control of bleeding and rebleeding, leading to an increased 6 week mortality (36% in PVT versus 16% in non-PVT patients) [4-6]. However, these studies were small sized and no conclusive statement about the potential impact of PVT on the outcome of variceal bleeding can be done.

The impact of PVT seems clearer in the setting of liver transplantation. Thus, Englesbe et al. showed an increased mortality in cirrhotic patients with occlusive PVT listed for liver transplantation, independently from transplant (HR 1.99) [7]. Moreover, the presence of PVT was associated with a significant increase in 30-day and 1-year mortality post-LT when compared to patients without PVT [1]. However, only complete PVT accounted for this increased mortality [7]. Altogether these data suggests that, at least, in patients with cirrhosis that are in the waiting list or that are potential future candidates for liver transplantation to perform screening for PVT may change its outcome. In patients with cirrhosis it is recommended to perform HCC screening by Doppler-US every 6 months. This seems to be also an appropriate time frame to screen for PVT. Operators performing US need to be advice that PVT most be specifically discarded. Then, screening for PVT will not add costs to the current management strategy of patients with cirrhosis.

It is not yet clear whether PVT screening needs to be performed in patients with cirrhosis that will never be potential candidates for liver transplantation (old patients, with severe comorbidities, etc.).

The main reason to perform screening is to detect PVT with the aim to treat these patients to achieve PVT recanalization or at least to prevent its extension to superior mesenteric vein a situation associated with the highest risk of morbidity and mortality post-liver transplantation. When deciding the therapeutic strategy to follow when PVT is found, it is important to know that spontaneous complete recanalisation of
the portal vein may occur, mainly when thrombosis is partial [3, 8] but progression of thrombosis is reported in 48% up to 70% of patients at 2 years follow-up [8, 9].

Although there are currently no clinical guidelines addressing the management of PVT in this setting, either anticoagulation [10, 11], transjugular portosystemic shunts [12, 13], or non-intervention [10, 14, 15] have been applied in different case series.

Data on the efficacy of medical anticoagulation to treat PVT come from five cohort studies [9-11, 16, 17] which included 163 anticoagulated patients, most with partial PVT, with different regimens (LMWH or VKA). Repermeation rate ranged from 55% to 75% with a mean interval time of about 6 months. Time interval between diagnosis of PVT and start of anticoagulation treatment less than 6 months, seems to be the most important factor able to predict the chance of response to anticoagulation [9]. When anticoagulation has been stopped soon after repermeation of the PV recurrence of thrombosis has been reported in up to 38% of cases after a few months [16]. This observation suggests that the prolongation of anticoagulation treatment after repermeation of the PV may prevent rethrombosis. Overall, bleeding complications were seen in 9/163 (5%) patients and correlated with PH in three cases. A multicentre study showed a correlation between platelet count less than 50 x 10^9/L and risk of bleeding [16]. Either beta blockers or band ligation can be used to prevent variceal bleeding before anticoagulation.

TIPS is feasible and may be effective in patients with PVT and cirrhosis and, in fact, can be successfully placed in 75-100% of patients with PVT [18, 19]. However, the feasibility of this procedure is reduced in patients with portal cavernoma, the success rate ranging between 53% and 63% [18, 19]. Indeed, it is extremely difficult, if not impossible, when no patent intrahepatic portal vein branches are available. In the study by Luca et al, TIPS achieved complete or partial recanalization of the portal venous system in 57% and 30% of patients, respectively, without anticoagulation agents [13]. Predictors of complete recanalization were a less extensive PVT, de novo PVT, and the absence of gastroesophageal varices [13]. Thus, TIPS could represent an alternative to anticoagulants in patients with cirrhosis and PVT, and offers the additional advantage of ameliorating portal hypertension-related complications. However, one must take into account the fact that, in most cases, the indication for using TIPS was a severe complication of portal hypertension; only in a few cases was the indication PVT itself. In addition, all of the published studies are retrospective in nature and therefore the number of patients for whom TIPS was not even considered due to the presence of PVT is unknowable. This makes it difficult to estimate the real applicability of TIPS in the management of PVT in patients with cirrhosis. Studies specifically designed to compare the effectiveness of anticoagulation vs. TIPS for the treatment of PVT in cirrhotic patients are needed.

Clinical data on thrombolysis in patients with cirrhosis and PVT is very limited, and the attendant complications can be severe [20-22].

Despite the absence of strong evidence, we recommend that in cases of recent thrombosis, anticoagulation should be considered for all patients with the aim of achieving repermeabilization. If thrombosis is diagnosed during a chronic phase or when a portal cavernoma is present, we recommend anticoagulation only for those patients who have an underlying prothombotic disease, or when there is evidence of progressive thrombosis to other segments of the splanchnic venous system; this is especially true of patients who are potential candidates for LT. In all cases, prior to anticoagulation, adequate prophylactic therapy (with NSBB or endoscopic band ligation in cases of contraindications or an intolerance to NSBB) should be undertaken in any patients with high-risk varices. TIPS should be reserved for patients in whom anticoagulation fails or for those presenting concomitant severe complications of portal hypertension, such as variceal bleeding or refractory ascites.

References
EXTRA-HEPATIC INVOLVEMENT IN CHRONIC LIVER DISEASES


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**Extraspaticnal vein thrombosis – are patients with cirrhosis at risk?**

From prophylactic measures to specific treatments

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Extraspaticnal vein thrombosis refers to vascular occlusion that occurs out of the splanchnic bed, therefore, excluding portal and hepatic vein thrombosis. Herein, only venous thromboembolism (VTE), a syndrome that includes deep vein thrombosis (DVT) and/or pulmonary embolism (PE) in cirrhosis will be focused.

VTE occurs in the general population in more than 1 in 1000 people/ year. [1] Although an ancient retrospective case-control study reported that patients with “serious liver disease”, defined as active or chronic hepatitis, had a 90% less probability to develop VTE, [2] more recent and robust studies have shown an opposite tendency, showing that these patients are not protected against VTE, with incidences that may reach 6.3%. [3]

In fact, patients with cirrhosis share the same known risk factors for VTE as the general population namely surgery, trauma, oral contraceptives, cancer [4] and may even add others more “specific of liver diseases” such as hypoalbuminemia, elevated partial thromboplastin time/ INR and higher Child-Pugh classes. [5-7]

Scores, as the “Padua Predict Score”, may be useful to stratify patients with cirrhosis in order to predict the development of VTE. [8] Due to the aforementioned, patients with cirrhosis may be at risk to develop thrombotic events out of the splanchnic vascular bed and, therefore, measures to prevent it must be implemented, although current guidelines do not specifically refer patients with cirrhosis as a target population. Mechanic prophylactical measures are known not to increase the risk of haemorrhage. Instead, the use of pharmacological prophylactic measures such as low molecular weight heparins (LMWH), are still avoided by the physician community because of the fear of increased haemorrhagic events. This is
well expressed in the low percentage of hospitalized patients with cirrhosis that undergoes prophylaxis of VTE (around 25%). [9]

Anticoagulation in prophylactic doses has been done in patients with cirrhosis; it is safe and does not increase bleeding complications or death. [10] Another retrospective study also reported no higher incidence of bleeding (gastrointestinal or not) under LMWH prophylaxis but did not show any efficacy of the use of LMWH in preventing VTE events. [11] But these results are not consensual, as there are others that show an increased risk of haemorrhage when prophylactic anticoagulation is started. [12] Studies do not address to oesophageal varices grade as well as if they have, or not, been treated or if are under beta-blocker in order to avoid bleeding. Prospective randomized trials must be conducted in order to evaluate i) the real advantage in starting prophylactic pharmacological measures; ii) the ideal prophylactic measure. For now, a rational strategy may be followed using the knowledge of the existence, or not, of oesophageal varices, its grade and which prophylactic measures are under way to avoid gastrointestinal bleeding [figure 1]. [13]

If data concerning prophylactic measures for VTE are not abundant, studies concerning treatment options when the thrombotic event occurs are even scarcer. Systemic thrombolysis has been evaluated in a group of nine patients with cirrhosis that developed splanchnic vein thrombosis, as being safe. [14] But the dose of r-tPA (0.25mg/Kg/day) was not the consensually used for acute and severe pulmonary embolism treatment, for example.

But anticoagulation remains the mainstay of treatment for VTE in unselected patients. When considering the bleeding risk, the scores that are daily used, as HEMORR2HAGES, RIETE or HAS-BLED were not conceived for cirrhosis and even if some of them use “liver disease” as a marker of higher bleeding risk, the defined criteria for “liver disease” are not very clear, as they do not express the severity of cirrhosis or even its presence. The HAS-BLED score, for example, uses as criteria for “abnormal liver function”, the presence of “chronic liver disease” or the biological criteria of BT > 2 times the ULN (upper limit normal) with transaminases or alkaline phosphatase > 3 times ULN which, themselves, do not correlate with severe liver disease. [15]

The use of anticoagulation in patients with cirrhosis has been addressed in some studies, mainly in the context of splanchnic vein thrombosis and its safety must be extrapolated for extrasplanchinc vein thrombosis, as reports in this context are extremely scarce. A study, which included 17 patients with VTE treated with anticoagulation, revealed that 14 patients had some kind of haemorrhagic event, but it is retrospective, and lacks enormous amount of information as the origin of bleeding, grade of oesophageal varices, goal surveillance of INR.

Nowadays, direct acting anticoagulants (DOACs) are generally the accepted treatment for VTE in patients other than cirrhotic ones, but its use has never been addressed in the latter patients. Rivaroxaban has been reported to treat acute portal vein thrombosis in cirrhosis in 3 distinct cases, without bleeding complications. [17-19] Also, some recent data indicate that this new class of anticoagulants is being increasingly used in patients with cirrhosis and thrombosis, mostly in the context of splanchnic vein thrombosis, also with a low incidence of bleeding events and no mortality related to its use.

Thus, if DOAC’s safety and effectiveness is proven in future studies, its use may be generalized to patients with cirrhosis and extrasplanchic thrombotic events. An actuation flowchart for the treatment of extrasplanchnic vein thrombosis is proposed [Figure 2]. [13]
References


Hepatitis C
Cryoglobulinemia and systemic repercussion

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Chronic infection with the hepatitis C virus (HCV) leads to excess mortality due to liver complications, cirrhosis and hepatocellular carcinoma. However this excess mortality was long underestimated because it did not include the weight of the many extrahepatic HCV-related manifestations. Recent studies have shown, after a follow up of fifteen years, an extra hepatic origin excess mortality among patients HCV RNA positive (19.8%) versus the HCV RNA negative (11%) or HCV negative patients (12.2%). The excess mortality was mainly due to cardiovascular, renal and neoplastic diseases. Until recently, the most often described extrahepatic manifestations were auto-immune and/or lymphoproliferative diseases. More recently, many other extrahepatic injury has been reported, i.e. cardiovascular, renal, metabolic, neurological... The approval of new HCV combinations without interferon, very effective virologically (> 90% recovery), short (12 weeks) and very well tolerated are likely to change in the short term management of extrahepatic attacks that appear for a large part of them reversible after achieving a sustained virological response (viral cure).

Cryoglobulinemic vasculitis (CryoVas) is a small vessel vasculitis involving mainly the skin, the joints, the peripheral nerve system and the kidneys. The clinical expression is variable, of pauci-symptomatic forms (arthralgia, purpura) to more severe forms of life-threatening manifestations (membranoproliferative glomerulonephritis, vasculitis digestive, heart or central neurological). Type I CryoVas are single monoclonal immunoglobulins related to an underlying B-cell lymphoproliferative disorder. Type II and III cryoglobulins, often referred to as mixed cryoglobulinemia, consist of polyclonal IgG with or without monoclonal IgM with rheumatoid factor activity. Hepatitis C virus (HCV) infection represents the main cause of mixed CryoVas. The 10-year survival rates are 63%, 65% and 87% in HCV-positive mixed CryoVas, HCV-negative mixed CryoVas and type I CryoVas patients, respectively. In HCV-positive patients, baseline poor prognostic factors include the presence of severe liver fibrosis, and central nervous system, kidney, and heart involvement. Treatment with antivirals is associated with a good prognosis whereas use of immunosuppressant (including corticosteroids) is associated with a poor outcome. In HCV-negative patients, pulmonary and gastrointestinal involvement, renal insufficiency and age>65 years are independently associated with death. Increased risk of lymphoma should also be underlined. Treatment of type I CryoVas is that of the hemopathy; specific treatment also include plasma exchange, corticosteroids, rituximab and ilomedine. In HCV-CryoVas with mild to moderate disease, an optimal antiviral treatment should be given. For HCV-CryoVas with severe vasculitis (i.e. worsening of renal function, mononeuritis multiplex, extensive skin disease, intestinal ischemia…) control of disease with rituximab, with or without plasmapheresis, is required before initiation of antiviral therapy. Other immunosuppressants should be given only in case of refractory forms of CryoVas, frequently associated with underlying B-cell lymphoma. Therapeutic advances for HCV vasculitis followed the progress of HCV treatments, with clinical remission >10% during the era of antiviral interferon alpha monotherapy for 6-12 months, 35% with interferon alpha plus ribavirin for 6-12 months, and up to 55% with Peg-interferon alpha plus ribavirin for 6-12 months. The first combination with Peg-interferon alpha/ribavirin and a protease inhibitor NS5/NS4A (boceprevir or telaprevir) for 48 weeks brought a complete remission of the vasculitis in 65% of patients. However side effects are very common (50%) and sometimes severe. The more recent combination of sofosbuvir and ribavirin for 6 months has achieved a complete remission of the vasculitis in 85% of patients, with a very good tolerability.

Finally, meta-analyzes have confirmed the excess risk for B-NHL marginal zone [Odds ratio (OR) 2.47] and for B-NHL diffuse large cell (OR: 2.24). Effective antiviral treatment has permitted a complete remission of certain B-NHL (without chemotherapy) while a virological relapse was followed by a relapse of the hematologic disease. Recent data have shown that HCV cure after antivirals was correlated with hematologic response, and also for the progression free survival of lymphoma and overall survival.

References

Immunological manifestations beyond cryoglobulinemia

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Abstract

Hepatitis C virus (HCV) infection is usually correlated with chronic liver complications. However, extrahepatic manifestations of chronic hepatitis C virus infection are numerous and potentially disabling conditions. All these conditions are now called the HCV syndrome. The cryoglobulinaemic vasculitis will not be addressed in this overview, but many other hepatitis C virus-associated immune disorders have been reported. These can be classified in two subtypes. The first one refers to classic immune-mediated disorders including arthritis, sicca syndrome, auto-antibody production (i.e. cryoglobulins, rheumatoid factor, and antinuclear, anticardiolipin, anti-thyroid and anti-smooth muscle antibodies), monoclonal gammopathies, immune thrombocytopenia, porphyria cutanea tarda and lichen planus. The other subtype includes non-classic or potentially immune-mediated manifestations such as cardiovascular disorders (i.e. stroke, ischemic heart disease), renal, metabolic and central nervous system diseases. This conference will focus on the clinic-diagnostic assessments and therapeutical approaches of these immune-mediated disorders as well as the impact of new therapies and the sustained virological response on their prognosis.
Numerous extra-hepatic manifestations and immune-mediated conditions have been reported in patients with hepatitis C virus (HCV) infection including thyroid disease (Hashimoto’s thyroiditis, Graves disease, and thyroid cancer), cardiovascular disease (atherosclerosis, carotid artery disease, and coronary artery disease), renal disease (membranoproliferative glomerulonephritis and glomerulosclerosis), eye disease (Moore’s ulcers and sicca syndrome), skin disease (porphyria cutanea tarda – PCT -, vasculitis, and lichen planus), lymphomas (Non-hodgking lymphoma and splenic T-cell), and diabetes. Indeed, changes in dermatological, metabolic, endocrine, renal, cardiovascular and/or neurological systems are present in a high proportion of infected persons, may be the cause of diagnosing HCV infection and ultimately, may be responsible for most clinical symptoms and patient outcome [1]. Although cirrhosis-related death is the dominant cause of mortality in all studies, the presence of these conditions is thought to contribute to increased rates of morbidity and all-cause mortality. Furthermore, chronic hepatitis C (CHC) is associated with decreased quality of life [2] with increased prevalence of fatigue, depression, and cognitive impairment among HCV patients.

It is estimated that 40–74 % of patients with CHC may develop at least one extra-hepatic manifestation during the course of the disease [1]. Mixed cryoglobulinemia-MC- is the dominant extra-hepatic manifestation because it can be detected in half of all HCV-infected patients, yet less than 5% of the affected subjects develop a cryoglobulinemic syndrome [3]. The degree of association vary from strong (MC and non-Hodgkin B-cell lymphoma) where there is significant prevalence and interventional data supporting a causal relationship to a more moderate - mild association where large registries show a higher prevalence in HCV infected patients but there is lack of additional data supporting a causal link (PCT, fatigue, cardiovascular disease and neurological disorders).

The mechanisms causing the extra-hepatic effects of HCV are incompletely understood. HCV drives clonal expansion of B cells (3) to generate immunoglobulin (Ig) M rheumatoid factor in susceptible people that results in immune complex deposition in small vessels and vasculitis, although susceptibility factors are unknown. In addition, there is growing evidence that tissues other than liver can support limited replication of HCV. These infections may be quite significant in the development and modulation of systemic extra-hepatic disease disorders. In addition, immune response to HCV viral proteins may result in immune-mediated processes that can result in injury to distant organs. Finally, the direct effects of HCV on hepatic metabolism may have a significant impact on lipids, hormones, and other peptides that contribute to systemic disease states associated with the metabolic syndrome [4].

Evidence supporting the association between these extra-hepatic manifestations and chronic HCV infection mainly comes from large registry data together with systematic reviews and meta-analysis. A large, prospective cohort study found that patients with chronic HCV infection have an elevated risk of death from both hepatic and non-hepatic diseases, including cardiovascular and renal diseases, compared with uninfected patients and those with antibodies to HCV (anti-HCV) but no detectable HCV RNA in serum. [5]. In this study (REVEAL-C study), 23,820 adults were followed for a mean of 16.2 years in Taiwan. HCV antibodies were found at baseline in 1,095 of them (4%), of whom 69% were positive for serum HCVRNA (true chronic hepatitis C patients). There were a total of 2,394 deaths during the study period. When comparing individuals with and without HCV antibodies, the likelihood of death was nearly 2-fold in the former. Although hepatic complications were by far the most frequent cause of mortality in patients with HCV antibodies, deaths due to kidney disease and cardiovascular events were also more frequent in HCV-seropositive individuals. Moreover, deaths due to some cancers, i.e., esophagus, prostate and thyroid, were also more frequent in HCV antibody carriers than in the general population. All ratios were even more pronounced when comparisons only considered HCV viremic versus non-viremic individuals.

The strongest support for the association between chronic HCV infection and many extra-hepatic conditions though comes from studies showing that HCV eradication improves some extra-hepatic manifestations of HCV independently of the severity of the underlying liver disease. The evidence is strongest for MC, which often resolves entirely with viral clearance [3]. In addition, recent (mostly registry) studies have also demonstrated an association between sustained viral response (SVR) and a decreased not only in both liver-related death but also in all-cause mortality and specifically in non-liver related mortality. In a Scottish cohort followed for a median time of 7.5 years, non-

DAAs for chronic hepatitis C with and without extrahepatic involvement: same options, same lengths, same responses?

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liver mortality was reduced significantly with an adjusted hazard ratio of 0.68 compared to those who did not achieve viral clearance [6]. Using the Veteran’s Administration (VA) database, the authors demonstrated that non-liver-related mortality was significantly reduced among SVR patients who had comorbidities that included coronary artery disease, diabetes, and hypertension. It was suggested that decreased chronic inflammation associated with HCV was a key factor in mortality decline [7]. In a recent multinational study that included all consecutive F3-F4 patients enrolled between 1990 and 2003 with a median follow-up of 8.4 years, SVR was associated not only with a reduction in liver-related death but also with an all-cause mortality hazard ratio of 0.26 [8].

Most of the interventional studies showing an association between viral eradication and improvement in the extra-hepatic manifestations of chronic HCV infection come from the IFN-era. Thus, a lower incidence of malignant lymphoma [9], reduced risk of type 2 diabetes mellitus [10], and insulin resistance [11-14], improved cognitive performance [15], reduction in fatigue and improvement in health-related quality of life (16-19), Improved work productivity [18, 19], reduced depression [20], resolution of dermatological conditions including PCT [21-23], improvement in myocardial perfusion defects [24], reduced incidence of stroke [25-26], reduced renal and cardiovascular outcomes in the presence of diabetes [27], complete resolution of MC-related complications [3, 28] and regression or complete remission of HCV-associated lymphoma [29] or improvement in eGFR and proteinuria among patient with MC [30] have been described in patients achieving a viral cure compared to those left untreated or not achieving sustained viral eradication.

Data on the impact of the recently available and well-tolerated, interferon-free direct antiviral agents regimens are overall still lacking but emerging data support the notion that they will positively impact the outcome of patients with extrahepatic conditions.

A recent study showed decreased fatigue at SVR 12 compared to baseline in patients treated with ledipasvir/sofosbuvir [31]. Also, viral eradication with the same therapy has also been associated with improvement in health-related quality of life and work productivity [32]. Finally, recent data has shown an excellent toxicity and efficacy profile in patients with HCV-associated MC. In this study [33], the cohort of treated patients displayed similar viral kinetics, with all patients’ HCV RNA becoming undetectable within 4 weeks, no on-therapy viral breakthrough, and an SVR rate of 83%, a rate that, despite wide confidence intervals (55%-95%), is comparable to the SVR12 rate reported with similar regimens in other non-cryoglobulinemic real-world cohorts. Interestingly, previous studies suggested that kidney involvement is frequently associated with unfavorable clinical response in HCV-MCS. In this series though, six of seven (86%) patients with kidney involvement achieved SVR12. Furthermore, patients with active glomerulonephritis who were successfully treated with DAA therapy experienced an improvement in eGFR and a reduction in proteinuria, particularly in those whose onset of proteinuria was recent.

A few cases of complete remission of hematologic lymphomas have also been reported [34, 35]. These new therapies have the potential to significantly broaden the spectrum of patients eligible for anti-HCV treatment. Indeed, immune stimulation induced by IFN was a deterrent to the treatment of HCV-patients with various immunologic manifestations. In addition, patients with common comorbid conditions, such as depression, cardiovascular disease, and/or debilitating fatigue were typically considered poor candidates for IFN-based therapies. The new direct antiviral agents are now approved for candidates historically considered interferon-ineligible or intolerant, including most of those with extrahepatic manifestations associated with chronic HCV infection. There are no reasons to consider that patients with extrahepatic manifestations need to be treated with regimes different than those used in the general population. Sofosbuvir use is not approved for patients with severe renal insufficiency (estimated glomerular filtration (eGFR) rate below 30 ml/min) or end-stage renal disease (ESRD) based on concerns raised during premarket animal testing over hepatobiliary and cardiovascular toxicity in this population, which may be a limitation for those with renal disease secondary to MC. Reports of the use of this agent in patients with ESRD including those on hemodialysis have however been recently reported with excellent outcome both in terms of efficacy and toxicity [36-38].

References


