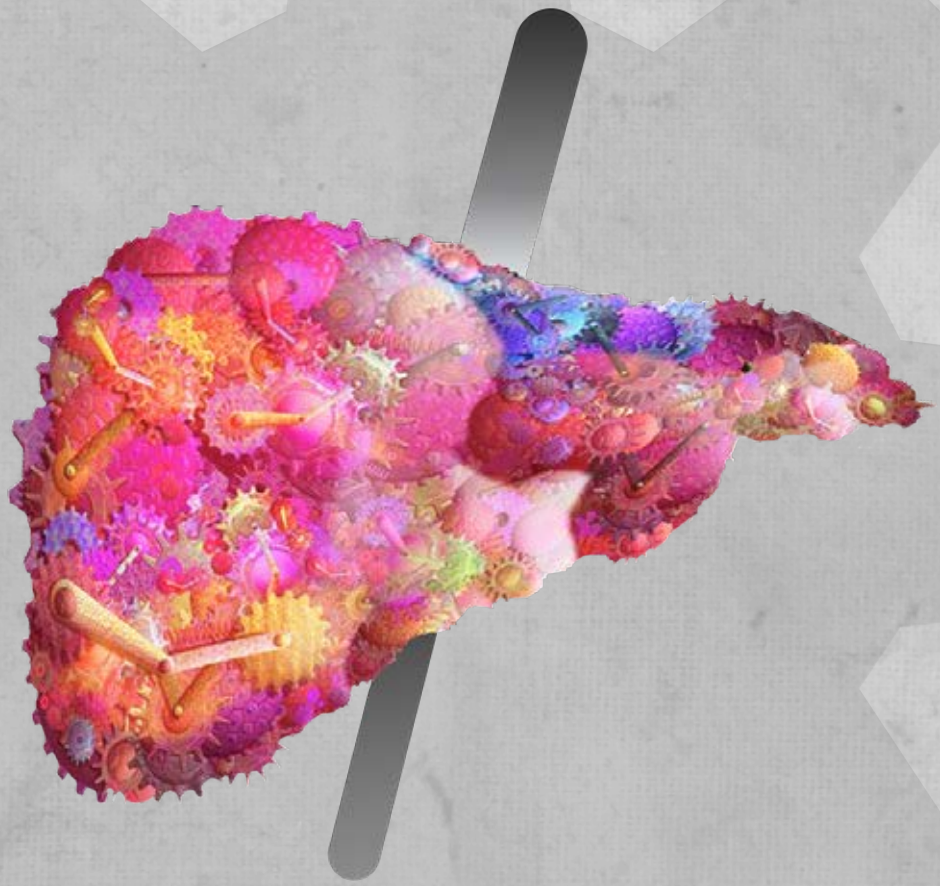
Cuidados Intermédios

C.I.P. | junho 2018 | Volume X

edição especial

- Monothematic Conference

VASCULAR LIVER DISEASES - Hot Topics and Controversies | resumos



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PROGRAMME

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Metabolic diseases and vascular liver involvement

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Cirrhosis and procoagulant environment

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Portal Vein Thrombosis in cirrhosis

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EM PERSPECTIVA

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Conteúdo WEB | **Ideoma**

Edição ACIM | **Associação de Cuidados Intermédios Médicos**

Associação de Cuidados Intermédios Médicos

For the 5th consecutive year, ACIM – Associação de Cuidados Intermédios Médicos (Intermediate Medical Care Association) – welcomes you to the Porto Liver Meeting. This time now dedicated to a very particular and mostly unrecognized subject by many physicians – vascular liver diseases. When we first thought about this subject it came obvious that it should be a Meeting with the scientific support of the VAscular Liver Disease Interest Group of EASL. Finally, we came, altogether, with this outstanding scientific program with a "deluxe" faculty.

Many of the subjects that will be approached are either in the field of investigation, either changing some old paradigms. This was made on purpose, in order to induce discussion and bring more knowledge and "light".

Every year we have made our agenda coincident to S.João festivities. In 2019, as S.João' eve will be a Sunday, we will profit the occasion and will enter in a "holiday" season.

Have a wonderful meeting, and a most outstanding S.João.

Filipe Nery

AACIM is very pleased to be part of the 5th Porto Liver Meeting organizing committee in collaboration with VALDIG (Vascular Liver Disease Group). This year, Porto Liver Meeting is dedicated to the Liver Vascular Disease a peculiar and interesting field. This event as the endorsement of EASL (European Association of Study of Liver), as the recognition of an outstanding programme with great speakers. I believe this will be a splendid meeting!

Have a nice S. João evening! Enjoy Porto festivities!

Diana Valadares

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Metabolic Diseases and Vascular Liver Involvement

THE LIVER: A "NEW" TARGET-ORGAN FOR DIABETES?

Laure Elkrief

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Diabetes mellitus is a major risk factor for cardio-vascular morbidity and mortality [1]. In patients with diabetes mellitus, vascular diseases, include atherosclerosis, the so-called diabetic macroangiopathy, and microvascular diseases, the so-called diabetic microangiopathy, namely nephropathy, retinopathy, and diabetic neuropathy. Although the epidemiological link between blood glucose and HbA1c and the risk of vascular diseases is clear [2,3], the impact of glycemic control with the currently used drugs is modest at best [4]. In the past ten years, several studies have reported an associated between type 2 diabetes mellitus and venous thromboembolism [5]. However, the results are inconsistent, and recent data suggest that these positive association may be related to confounding factors [6].

The link between diabetes and various vascular liver diseases has been addressed in a limited number of cohort studies, and different contexts, which should be considered separately: (i) hepatic artery thrombosis in liver transplant recipients, (ii) idiopathic portal vein thrombosis, (iii) portal vein thrombosis in patients with cirrhosis, and (iv) refractory ascites complicating cirrhosis.

- Hepatic artery thrombosis in liver transplant recipients:

The rate of hepatic artery thrombosis occurring after liver transplantation was found to be higher in recipients with diabetes mellitus than in those without [7,8], However, the clinical impact of recipient's diabetes mellitus on the risk of hepatic artery thrombosis may be low, compared to that of surgical difficulties.

- Portal vein thrombosis unrelated to cirrhosis

Data support that metabolic risk factors, including diabetes, contribute to portal vein thrombosis. A recent case-control study found that the prevalence of central obesity was higher in patients with idiopathic (i.e with negative etiological work-up) portal vein thrombosis than in those without [9]. In the latter study, type 2 diabetes was also more frequent in patients with PVT than in those without. Diabetes mellitus was found to be associated with the risk of intestinal resection in patients with superior mesenteric vein thrombosis[10].

- Portal vein thrombosis in patients with cirrhosis

In candidates for liver transplantation, the prevalence of diabetes was found to be higher in patients with PVT than in those without [11–13]. This association between PVT and diabetes in cirrhosis is likely to be explained to liver diseases severity.

- Microvascular alterations associated with refractory ascites in patients with cirrhosis

Liver microvascular alterations, namely perisinusoidal fibrosis, the so-called diabetic hepatosclerosis, have been described in diabetic patients without cirrhosis. One study of liver explants found that such microvascular changes, including sinusoidal dilatation and perisinusoidal fibrosis, were more frequently observed in the livers of patients with refractory ascites. Furthermore, these lesions were more frequently observed in patients with concomitant alcohol as a causal factor for cirrhosis and diabetes. These results suggest that diabetic microangiopathy contribute to refractory ascites in patients with cirrhosis [14].

Conclusion

Observational studies found an association between diabetes and arterial, venous and intrahepatic microvascular liver diseases. The clinical relevance over known risk factors, as well as the beneficial impact of glycemic control on the incidence and outcome of vascular liver diseases remain to be evaluated.

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Cirrhosis and Procoagulant Environment

CIRRHOSIS AS A PROCOAGULANT STATE – WHAT IS KNOWN AND WHAT IS THERE TO COME?

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Cirrhosis is associated with profound changes in the hemostatic system including thrombocytopenia, decreased plasma levels of pro- and anticoagulant factors, and decreases levels of fibrinolytic proteins. Although historically, cirrhosis was thought to result in a bleeding tendency, it is now widely accepted that the net effect of all hemostatic changes is a hemostatic system that remains in balance due to the concomitant decline of both pro- and anticoagulant drivers [1]. The reset hemostatic balance in patients with cirrhosis, however, is much less stable than the hemostatic balance in individuals with intact liver function, explaining why patients with liver diseases can experience both bleeding and thrombotic complications. It is incompletely known whether patients with very advanced disease (e.g., patients with acute on chronic liver failure) remain in hemostatic balance, and the incidence of bleeding and thrombosis in these critically ill patients have not been firmly established. Nevertheless, initial laboratory studies indicate that hemostatic balance is maintained even in the sickest patients [2].

There is increasing awareness of the occurrence of thrombotic complications in patients with cirrhosis, which include venous thrombosis, portal vein thrombosis (PVT), arterial thrombosis, and intrahepatic thrombosis. It is likely that hemostatic unbalance contributes, at least partly, to all these thrombotic complications. Indeed, upon close inspection of the hemostatic system in patients with liver disease, one can identify clear prothrombotic features. Prothrombotic aspects of hemostasis in patients with liver disease include enhanced thrombin generating capacity [3], a prothrombotic structure of the fibrin clot [4], platelet hyperreactivity [5], and increased circulating levels of tissue factor [6].

There may be additional prothrombotic features of the hemostatic system in patients with liver disease, and identification of these may be important in determining optimal strategies for prevention or treatment of thrombotic complications in these patients. Such prothrombotic features may include a prothrombotic endothelium, which likely is activated and is defective in key anticoagulant mechanisms including the glycocalix. Also, the structure of the fibrin clot requires additional study, given recent findings on the role of platelets, coagulation factor XIII, and red blood cells in determining clot stability [7]. Finally, there may be a role for neutrophil extracellular traps (NETs), which are structures consisting of DNA and various proteins that are expelled by neutrophils upon activation, for example by platelets. Although these NETs have been identified as actors in host defense, there is abundant literature implying NETs in the pathogenesis of thrombotic complications [8].

Clinically, there are a number of open questions on management of thrombotic complications in patients with liver diseases. Not only do we need to study further which patients require prophylaxis (for example for venous thrombosis or PVT), it is also incompletely known which patients require treatment (for PVT, for example). Management of thrombotic complications in patients with liver disease is further complicated by issues with dosing and monitoring of anticoagulants [9], and clinical studies are required to determine which drug at which dose is most appropriate for management of the different thrombotic complications. Importantly, in vitro experiments indicate profound differences in the anticoagulant effects of various clinically used drugs between patients and individuals with intact liver function, and these differences are most pronounced in the sickest patients [10].

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EXTRASPLANCHNIC VEIN THROMBOSIS: FROM PREVENTION TO TREATMENT

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The association between liver cirrhosis and risk of pulmonary thromboembolism (PE) or deep vein thrombosis (DVT) amongst hospitalized patients with cirrhosis has been evaluated in retrospective case control studies in which 0.5–6.3% of cirrhotic patients presented with a thrombotic complication.

These patients do not demonstrate a reduced risk of PE/DVT when compared to patients without cirrhosis and, importantly, a prolonged INR does not negate a risk of venous thromboembolism (VTE).

In the retrospective study (case-control) performed by Northup et al., liver cirrhosis was recognized, for the first time, as a thrombophilic condition. In a tertiary-care teaching hospital, over an 8-yr period, a total of 113 hospitalized cirrhotic patients (0.5% of all hospitalized patients with cirrhosis) with a documented new VTE were included in the analysis and compared to controls (cirrhotic patients without VTE). Of the 113 events, 74 (65.5%) involved a DVT only, 22 (19.5%) involved a PE only, and 17 (15%) involved both a PE and DVT. Interestingly, traditional markers of coagulation impairment in liver disease (such as INR and platelet count) were not predictive of VTE. On the other hand, in the multivariate analysis, low serum albumin remained independently predictive of VTE, with an odds ratio of 0.25 (95% CI 0.10–0.56), possibly reflecting the low level of endogenous anticoagulants typically found in cirrhosis coagulopathy.

The importance of low level of albumin in predicting the risk of VTE in liver cirrhosis has been confirmed by Gulley et al, too. In their case-control study 963 cirrhotic hospitalized were included and well-matched patients with no known evidence of cirrhosis served as controls (12,405 patients). In the multivariate analysis partial thromboplastin time (PTT; OR 0.88, P = 0.04) and serum albumin (OR 0.47, P = 0.03) were the independent predictors of DVT/PE.

In a case-control Danish population-based study of 99,444 patients with thromboembolic disease, patients with cirrhosis had a 1.7-fold increased relative risk of venous thrombosis compared to the general population. This increased relative risk of VTE was similarly found in cirrhotic patients under the age of 45 years in a large US-based population study of hospitalised patients. Interestingly, in patients over 45 years of age, there was no significant increase in VTE risk observed in patients with cirrhosis, compared to matched non-cirrhotic control participants. However, this may have solely reflected age-related risk factors for VTE outweighing that of cirrhosis itself.

Validated risk stratification scores that predict VTE within a general population of hospitalized patients, also appear to accurately predict VTE amongst hospitalised patients specifically with chronic liver disease i.e., Padua Predictor Score, and can be used to decide if patients should be treated with primary prophylaxis or not.

Studies have looked at the role of anticoagulation in preventing thromboembolic disease in patients with chronic liver disease. Current guidelines do not recognise the thromboembolic risk associated with chronic liver disease, and do not make specific recommendations for the prophylaxis or treatment of thromboembolic disease. The reported use of prophylactic anticoagulation for VTE in patients with cirrhosis (21–25%) remains significantly lower than in other inpatient groups (30–70%) and studies investigating the relationship between the use of prophylactic anticoagulation in patients with cirrhosis and the risk of VTE have given contradictory results. This may be because they are predominantly retrospective studies with differences in coding and/or means of defining cases of chronic liver disease. More specifically, some studies have failed to demonstrate a significant difference in the incidence of venous thromboembolic events in people with chronic liver disease given prophylactic anticoagulation, compared to those who were not, or observed no significant difference between incidence of VTE in patients treated with pharmacological, mechanical or no prophylaxis. In contrast, Barclay et al. have shown a decreased incidence of VTE in patients with chronic liver disease given pharmacological prophylaxis. In this latter study, multivariate logistic regression analysis identified risk factors for VTE amongst hospitalized patients with cirrhosis. These included: active malignancy, trauma or surgery during hospitalisation, or previous history of VTE, and is in keeping with VTE studies from other hospitalized patient populations. It suggests that patients with cirrhosis and additional risk factors should not be precluded from receiving VTE prophylaxis.

Further prospective studies are required to determine not only if cirrhotic patients benefit from receiving prophylactic doses of anticoagulating therapy in preventing VTE, but also which prophylactic regimen is most appropriate. The interim suggestion is that VTE prophylaxis is considered on a case-by-case basis in hospitalised cirrhotic patients, based on risk factor assessment for VTE (particularly, the likelihood of prolonged immobilisation). If anticoagulation is contraindicated (e.g., because of the potential risk of bleeding), then mechanical prophylaxis should be considered.

The decision to use anticoagulation in cirrhosis patients requires a careful assessment of the perceived risks and benefits of anticoagulation. Initial studies in patients with cirrhosis reveal that traditional therapeutic and prophylactic anticoagulation with low molecular weight heparin (LMWH) or vitamin K antagonists (VKA) are potentially safe in compensated and selected patients. However, these studies are generally small, retrospective, with considerable variation in study design.

One major concern on the use of LMWH in liver cirrhosis is the reduction of anti-thrombin that is a typical feature of patients with advanced liver disease, owing to the fact that LMWH requires antithrombin to exert its anticoagulant function. Furthermore, a superimposed condition of renal failure that frequently occurs in cirrhotic patients can critically influence the catabolism of heparin. Finally, LMWH is administered as a subcutaneous injection and this can be cumbersome for some patients.

The two crucial questions regarding the use of heparins in cirrhotic patients remain to be answered: whether fixed or weight-adjusted LMWH doses that are effective/safe in non-liver disease patients are equally effective/safe in cirrhotic patients and if the use of LMWH in liver cirrhosis requires laboratory monitoring to adjust the dosage or not.

As far as the second point, the in vitro studies gave conflicting results. The anti-Xa assay is not the assay of choice to measure the LMWH anticoagulant effect. Recently, Bechmann et al. demonstrated that after LMWH administration, anti-Xa activity was lower in cirrhotics than in controls, correlating to the degree of disease severity. Despite this finding could suggest the need to increase LMWH dose in cirrhotics, Lisman et al. showed in vitro that the anti-Xa assay underestimates LMWH plasma levels in these patients. These data point at the probable inadequacy of anti-Xa level measurement for the determination of anticoagulant efficacy in cirrhosis patients. Firstly, the measured anti-Xa activity does not reflect the functional anticoagulatory effects of LMWH, but is a surrogate for LMWH concentration in the patient's blood. Anti-Xa is quantified by a chromogenic assay, in which a given amount of activated factor Xa as well as a chromogenic substrate is added to the undiluted plasma sample of a patient. Abundant LMWH will bind to AT in the plasma sample. When LMWH and AT are complexed, two competing reactions occur simultaneously: in first place, the externally added factor Xa is inhibited by the AT-LMWH complex; thereafter, the non-inhibited factor Xa reacts with the chromogenic substrate, which resembles the natural substrate of factor Xa, resulting in the cleavage of p-nitroaniline (pNA), which is inversely proportional to the LMWH level in the sample. Antithrombin-deficient plasma, such as that observed in cirrhosis, has been documented to yield false anti-Xa determinations, possibly as a result of a decrease in the accuracy of classical anti-Xa assays.

While VKA are desirable for their low cost and oral administration, close monitoring of the international normalized ratio (INR) is necessary to determine therapeutic range. Dosing of VKA in cirrhosis patients is particularly challenging due to pre-existing elevation of the INR. As the vitamin K-dependent anticoagulant factor protein C (also inhibited by VKA) is low in cirrhosis, VKA may not be particularly desirable agent.

Moreover, an early cohort study evaluating 29 000 INR measurements during a period of 6 months demonstrated that underlying liver disease or alcohol abuse was independently correlated with risk of excessive anticoagulation (INR > 6).

WORKUP TO DO IN THE SETTING OF A THROMBOTIC EVENT

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Cirrhosis presents with complex hemostatic abnormalities, which affect both levels of pro- and anticoagulants, promoting an unstable balance of hemostasis. In this setting patients may have, at same time, a tendency for bleeding and a tendency for thrombosis, a concept that has became evident in the last decade (*Tripodi et al. Am J Gastroenterol 2017*). The acquired decreased levels of Protein C, Protein S and Antithrombin are associated with risk of venous thromboembolism and although the portal system is the most commonly affected, thrombosis in other places such as lower limbs and pulmonary embolism may also occur (*Tripodi and Mannucci, N Engl J Med 2011*). Mechanisms associated with portal vein thrombosis (PVT) are likely to be multifactorial including local factors as reduced portal flow velocity, presence of neoplastic infiltration and other systemic factors. Beside acquired factors, the possible role of hereditary thrombophilia in this setting has been extensively studied, but no consistent association with genetic defects were found (*Tait et al. Br J Haematol 2012*). Screening for myeloproliferative neoplasms (MPNs) is recommended in cases of abdominal vein thrombosis without liver disease, with JAK2/CALR/MPL mutations. In the context of cirrhosis, although the association of PVT with MPNs is rare, it should be considered as a possible underlying diagnosis (*Tait et al. Br J Haematol 2012*).

When a thrombotic event outside the splanchnic veins occurs, as deep vein thrombosis or pulmonary embolism, additional etiological factors besides the liver disease are commonly found including immobilization, hospitalization, surgery or infection. In particular cases, where etiological factors for thrombosis are not clear and a positive family history was found, the screening for genetic thrombophilic conditions should be considered (*Amitrano et al. Hepatology 2000, Andriulli et al. Dig Liver Dis 2016*).

In case of a thrombotic event, anticoagulation is recommended and must be started immediately after evaluating patient bleeding risk. To prevent gastrointestinal bleeding variceal eradication should be performed. Platelet count and function, the degree of liver disease and other co-morbidities, as impaired renal function or prior major bleeding, should be taken into consideration (*Garcia-Pagàn et al. J Hepatol 2016*).

The recommended anticoagulants are low molecular weight heparins (LMWH) or vitamin-K antagonists (VKA), each drug with their own advantages and disadvantages. The main concern for the use of LMWH in cirrhosis is whether the reduction of antithrombin, typical in advanced liver disease, could interfere in the effective and safety of this heparin. The main concern for the use of VKA in cirrhosis is the use of INR for drug adjustment, a parameter based on prothrombin time (PT) determination, that is often prolonged in liver disease.

Duration of anticoagulation treatment depends largely on the place of thrombosis and of the presence of additional and/or temporary risk factors. In patients with PVT candidates to liver transplantation anticoagulation should be maintained until transplantation. If transplantation is not indicated, long term anticoagulation is controversial (*Garcia-Pagàn et al. J Hepatol 2016*).

Alternatives to the classical anticoagulation with LMWH and VKA are now available. Non-vitamin K oral anticoagulants (NOACs), as dabigatran, rivaroxaban, apixaban and edoxaban, are indicated in non-liver disease patients. Although recent studies showed that NOACs seemed as effective and safe as the classical anticoagulation (De Gottardi et al. 2017), randomized clinical trials are needed to clarify this issue.

In summary, management of patients with liver disease, with perturbations in the pathophysiology of hemostasis, constitutes an additional challenge for clinicians to deal with the bleeding and thrombotic risks.

Portal Vein Thrombosis in Cirrhosis

FROM KNOWN RISK FACTORS TO PREDICTIVE SCORES

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ICBAS-UP

Determination of predisposing factors for a clinical entity allows to establish not only patients at risk, but also to assess the probability of having the event at the time of diagnosis. This is even more important in the setting of clinically relevant events. For example, in acute pulmonary embolism, known and validated risk factors combined with some other clinical features, allow to apply a probabilistic diagnostic score (Wells and Geneva rules)[1].

The 1-year incidence of portal vein thrombosis (PVT) in cirrhosis, although already significant in stable Child-Pugh A and B patients (4.6%)[2], is even more relevant in those with more severe liver disease, achieving 16.4% per year [3]. It has a large spectrum of clinical presentation, with a yet not completely established impact on either progression or aggravation of liver disease. Yet, its presence in those submitted to liver transplantation (LT) relates to a poorer early post-LT mortality [4], reason why PVT early recognition is of major interest and efforts in finding potential risk factors must be made.

In 1856 it has been postulated that blood stasis, changes in blood and vessel wall, all together lead to venous thrombosis, known as the Virchow's triad [5].

A decreased blood flow in the portal vein trunk has been linked to PVT development when < 15cm/s[3]. Despite of being recently corroborated by other studies, these findings have not been consistently found[2]. The decreased blood flow would lead to blood stasis within portal vein driving, eventually, to higher local thrombin concentration and an increased propensity to PVT. The intrahepatic block that characterizes cirrhosis is not only responsible for lowering portal blood flow velocity, but also for the increase in the pressure at the splanchnic venous bed, which relates to the presence of oesophageal varices (OV) [6]. OV and its degree[2], the presence of large portal-collateral vessels[7], ascites[7] and thrombocytopenia[8], all of them known markers of portal hypertension have been related to PVT development. This means that blood stasis, reflected either by lower portal vein flow, either by direct or indirect markers of portal hypertension is one of the pillars driving to PVT. Yet, these findings have not been consensually reported.

PVT has been more frequently documented in more severe liver patients, namely in those in the waiting list for liver transplantation, as aforementioned described. Cirrhosis is currently seen as a prothrombotic condition, with clear recognition not only of PVT occurrence but also of extrasplanchnic venous thrombotic events [9]. The imbalance between pro- and anticoagulant factors, namely FVIII and Protein C aggravates with the severity of liver disease[10]. Lower levels of Protein C, S and antithrombin have been found to correlate to PVT occurrence in patients with higher MELD scores[3]. Thrombomodulin resistance has been seen as a predictor of PVT development in patients with cirrhosis 11]. Yet, this hypercoagulability state failed to relate to PVT by other groups [12]. Anticardiolipin antibodies, Factor V Leiden (FVL), Prothrombin G20210A (PTHR) or Methylenetetrahydrofolate reductase C677T (MTHFR) gene mutations are other coexistent prothrombotic factors that have been reported, although in a non consensually way [13-15].

PVT in cirrhosis arises most probably due to an interaction of multiple risk factors rather than an isolated one, giving strength to the multiple vectors already stated in Virchow's triad.

Many other factors may be implicated or at least theorized in PVT genesis, as the use of non-selective beta-blockers [16] or the well-known inflammatory environment in cirrhosis that arises from bacterial translocation with the resulting circulating endotoxin/lipopolysaccharide which, in other situations as the ones occurring in gram-negative sepsis, may contribute to the coagulation cascade activation and extrasplanchnic venous thrombosis and hepatic endothelial dysfunction [17-19].

The main goal of identifying PVT risk factors is to establish, in the future, a predictive score that precludes patients that are more prone to develop this thrombotic event, which may be the ones considered to i) avoid the modifiable risk factors; ii) prophylactic anticoagulation schemes; iii) enter regular PVT screenings with Doppler-US.

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FROM THEORY TO PRACTICE: DOES PORTAL VEIN THROMBOSIS LEAD TO LIVER DISEASE DECOMPENSATION

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In patients with cirrhosis, the deleterious impact that the development of portal vein thrombosis (PVT) might have on liver disease course and outcome is of importance. If one is to conclude that the impact is significant, antithrombotic therapy becomes logical; whereas if there is no influence of PVT on the natural history of liver disease, the discussion of antithrombotic therapy should be limited to other targets: e.g. for easing an eventual liver transplantation by maintaining or recovering a sufficient portal venous inflow to the graft. The issue is rendered particularly crucial, as cirrhosis is associated with an increased risk of bleeding prior to any introduction of antithrombotic therapy, mostly due to portal hypertension.

What is the strength of the evidence that PVT induces an aggravation of the underlying liver disease?

The view that portal vein thrombosis occurring in a patient with underlying cirrhosis could lead to liver disease decompensation has emerged from 2 different kinds of clinical observations.

First, cross sectional studies have shown that patients with PVT at inception had more advanced liver disease than those without, as reflected by more common complications (ascites, encephalopathy, variceal bleeding), higher Child Pugh scores and MELD scores; and smaller livers [1-8]. However, cross sectional studies, even when performed prospectively, are unable to demonstrate that the association is causal. Furthermore, even if a causal relationship is present, such studies are unable to indicate its direction – the egg and chicken story.

Second, early retrospective clinical studies pointed to a strong association between the occurrence of a complication (e.g recent ascites, gastrointestinal bleeding, encephalopathy or abdominal pain), and the apparent de novo development of PVT [2-6]. However, if portal vein thrombosis can develop asymptomatically in some patients with cirrhosis, and if dating a thrombus is difficult or impossible based only on imaging or serum biomarkers, the "presenting" complication could only constitute the opportunity of

performing abdominal imaging and to finding PVT that would otherwise had gone unrecognized. Actually, at variance with patients without underlying liver disease, many if not most cases of PVT develop in patients with cirrhosis in the absence of detectable clinical manifestations [7-8]. Furthermore, again at variance with patients without underlying liver disease, imaging or laboratory tests are not able to differentiate a recent from a longstanding thrombus in the portal vein in patients with cirrhosis. Therefore, it is not surprising that the manifestations temporally associated with the discovery of the portal vein thrombus has largely varied with the context of the study: hospitalized patients, outpatients with advanced cirrhosis, or outpatients included in prospective ultrasound surveillance for hepatocellular carcinoma or for portal vein thrombosis itself [2,7,8].

Longitudinal studies support the view that patients who will develop PVT during follow-up actually have more severe liver disease at inception.

Several longitudinal studies, retrospective or prospective, differing by the cause and the average severity of liver disease at inception, showed that large size of gastroesophageal varices and increased severity of liver dysfunction are independently related to the subsequent development of portal vein thrombosis [7,8]. When the velocity of portal vein blood flow was considered however, results were less consistent in showing a relationship between a decreased initial velocity and the subsequent development of PVT [4,7,9,10]. Future studies will have to overcome the limitations arising from inter- and intra-observer variability in velocity assessment using Doppler ultrasound. This is a pressing issue as it would be most logical that the connection between severe liver disease and PVT development is through an increased intrahepatic block and thus a decreased portal venous blood flow velocity, precipitating in turn thrombus formation.

Several longitudinal studies are available to assess longitudinally the variation in the severity of liver disease and the development of PVT. These studies have not been able to disclose any relationship between the development of PVT and the later progression of liver disease (e.g. de novo decompensation) [4,5,7].

Therefore, available clinical epidemiology data indicate that PVT is a specific complication of severe liver disease both through portal hypertension and liver dysfunction. As yet, however, there is no evidence that PVT per se is inducing an aggravation of liver disease.

What is the hemodynamic impact of portal vein thrombosis in patients with cirrhosis?

In 85% of patients with cirrhosis and PVT, lumen occupancy by the thrombus is limited ("partial thrombosis") [6]. Furthermore, spontaneously, portal vein thrombus is transient in half the cases [5,7]. Cavernous transformation is rare in patients with cirrhosis, which suggests that the increase in portal pressure secondary to PVT is limited. Solid hemodynamic data are missing. Doppler ultrasound is predictably not appropriate to evaluate the impact of thrombosis on portal blood flow due to the interference with the thrombus itself. Hepatic venous pressure changes that parallel the development of the thrombus, if any, are unlikely to reflect the effective portal perfusion to the liver. The impact of PVT on portal hemodynamics and liver blood perfusion might well be limited in most patients. However, studies focusing on patients with occlusive PVT are needed.

What is the evidence that portal vein thrombosis affects liver function and structure?

In the cirrhotic liver, portal and hepatic veins thrombosis is associated with parenchymal extinction [11]. Procedures that deprive portal venous blood inflow to a part of the liver induce an atrophy of the corresponding parenchyma together with a hypertrophy of the unobstructed territories – the so-called atrophy-hypertrophy complex [13]. There has been no study documenting a decrease in liver size following development of an occluding thrombus in the main portal vein, in patients with or without cirrhosis. Still in patients with a normal liver developing thrombosis of the portal vein trunk, subtle consequences may be shown including liver remodeling (hypertrophy of the central part and atrophy of the periphery) and a mild decrease in synthetic function [12]. Therefore, a mild to moderate impact of occlusive PVT on liver function in patients with cirrhosis cannot be fully ruled out.

Last, using enoxaparin to prevent PVT in patients with cirrhosis did show an improvement in patients' outcome. This improvement was uncoupled however from the prevention of extrahepatic PVT [13].

Conclusion

Although it is clear that patients with advanced cirrhosis develop more commonly PVT than those with less advanced liver disease, there is no evidence that the development of PVT is directly precipitating an

accelerated course in such patients. Further studies are needed to explore this apparent paradox and also to assess whether portal vein recanalization is instrumental in improving liver disease.

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ANTICOAGULATION TREATMENT FOR PVT IN PATIENTS WITH CIRRHOSIS: DOACS – ARE WE STILL FAR FROM USING THEM?

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A large amount of data about the use of direct oral anticoagulants (rivaroxaban, edoxaban, apixaban and dabigatran) for the prevention and treatment of thrombotic events is currently available. Advantages including oral administration, no need for monitoring, and the availability of antidotes have made their use very popular. However clinical evidence about their efficacy and safety in patients with advanced chronic liver disease remains limited.

Major concerns are related to their pharmacokinetic in patients with significantly decreased liver function and portosystemic shunts or in those with acute or chronic kidney injury.

The risk of major gastrointestinal bleeding is higher with the dabigatran or rivaroxaban, while the risk of major intracranial bleeding is lower with all DOACs compared to vitamin K antagonists.

Current data from observational studies or case reports suggest that the use of DOACs is safe in patients with cirrhosis Child-Pugh A and B, but there are no data from Child-Pugh C patients, while comparative studies about their efficacy are not available.

Anticoagulant treatment is only recommended in cirrhotic patients with portal vein thrombosis, who are on the liver transplant waiting list. Since the natural history of portal vein thrombosis in this population is highly variable in terms of resolution, stability or progression, the indication for anticoagulation remains controversial. Currently ongoing studies aim to clarify whether, similarly to low molecular weight heparins, DOACs can be associated with beneficial effects in terms of prevention of portal vein thrombosis and decompensation of cirrhosis. Indeed, experimental evidence suggests that DOACs may have an antifibrotic effect.

When treating cirrhotic patients with DOACs, particular caution is needed in the following situations:

1) in kidney injury, consider decreasing the dose if CrCl<50 mL/min and stopping if CrCl< 30 mL/min, in particular for dabigatran

2) in concomitant medication with carvedilol, simvastatin or PPI, dabigatran needs dose adaptation

3) in drug-induced liver injury, in particular with rivaroxaban

4) in deterioration of liver function: stop DOACs in CHILD C patients

5) in BMI>40 Kg/m2 (use of DOACs not recommended)

Plasma levels of DOACs can be monitored, but the interpretation of the results is particularly difficult due to overlap between through and peak levels. Additionally, DOACs may increase INR and aPTT values.

Current data are preliminary and suggest that apixaban or dabigatran may be safer in patients at risk of gastrointestinal bleeding and that a dose adaptation is required in patients with significantly impaired renal injury or liver function.

More data from large cohorts of patients with cirrhosis are needed before strong recommendations may be formulated.

Portal Hypertension

HOW TO MEASURE IT: DIRECT AND INDIRECT TOOLS

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Complications of portal hypertension are the leading cause of death and of liver transplantation in patients with cirrhosis. Assessment of portal hypertension in patients with cirrhosis, stratifies patients according to their risk of clinical decompensation and death, correlates with morbidity and mortality after hepatocellular carcinoma resection and predicts the risk of treatment failure and death in patients with esophageal variceal bleeding.

The presence of portal hypertension in a patient with a chronic liver disease can be estimated by means of clinical, biochemical, endoscopic and imaging data. However, portal pressure can be measured using direct or indirect methods.

Clinical, Biochemical and endoscopic data

Physical examination

The cheapest and readily available information to detect cirrhosis and/or of portal hypertension is that obtained by physical examination. Physical stigmata of liver cirrhosis are: gynaecomastia, testicular atrophy, parotidomegaly, features of hepato-cellular failure such as jaundice, vascular spiders, leuconykia, palmar erythema or of hepatic encephalopathy, presence of abdominal wall collateral circulation, ascites, leg oedema and splenomegaly (which can be considered the single most important clinical diagnostic sign of portal hypertension). In addition, hypotension and tachycardia may be found reflecting the frequent hyperdynamic circulation found in patients with cirrhosis.

All these findings are highly specific of the syndrome. However, the sensitivity of physical signs is low.

Laboratory tests

Child-Pugh score and its objective component (albumin, bilirubin, INR) correlate with the severity of portal hypertension in cirrhotic patients. Platelet count is independently correlated with the presence of portal hypertension in patients with cirrhosis.

- Endoscopy

Presence of esophageal or gastric varices are patognomonic signs of the presence of portal hypertension. This is especially true when varices are of large size or with red signs on the wall.

- Transient Elastography (TE)

Liver stiffness correlates with fibrosis severity. The best cut-off to detect cirrhosis varies according to the etiology of liver disease; however, values over 12.5 kPa strongly suggested cirrhosis.

The value of TE in the non-invasive prediction of portal hypertension has also been evaluated. A liver stiffness value ≥8.74 kPa had a sensitivity and specificity of 90% and 81% for the diagnosis of any grade of portal hypertension (HVPG ≥6 mm Hg). In addition a value lower than 13.6 Kpa is highly specific ruling out clinically significant portal hypertension (CSPH) while a value higher than 20.1 Kpa is highly specific rule in CSPH.

- Ultrasound and color-Doppler-ultrasound

US signs of portal hypertension are very specific, while their sensitivity is low, especially in compensated cirrhosis. Spleen dimension is the US sign most commonly associated to the presence of portal hypertension; contrarily to other signs its sensitivity is high, while its specificity ranges 50-80% according to different series. It is an independent predictor of esophageal varices, and is associated to CSPH in compensated cirrhotic patients. The presence of porto-collateral circulation such as paraumbilical vein, spontaneous spleno-renal circulation, dilated left and short gastric veins, and the inversion of flow within the portal system are 100% specific US signs of CSPH.

Other US signs of CSPH include dilatation of portal vein (diameter >13 mm); lack or reduced respiratory variations of splenic and superior mesenteric vein diameter; reduced portal vein velocity (maximal and mean velocimetry of portal vein flow, respectively < 16 cm/s and < 10-12 cm/s).

Direct and Indirect Methods of Measure Portal Pressure

Hepatic vein catheterisation with HVPG measurement is currently the preferred technique to determine portal pressure, and has almost totally replaced the direct measurement of portal pressure by more invasive techniques (percutaneous transhepatic or transvenous catheterisation of the portal vein, splenic pulp puncture). Direct techniques (except for the transjugular approach) require the simultaneous puncture of a hepatic vein to be able to determine the portal pressure gradient, and are at present used only in selected cases, mostly in presinusoidal portal hypertension or in cholestatic disorders, where wedged hepatic venous pressure (WHVP) may underestimate portal pressure. The portal

pressure gradient is estimated as the hepatic venous pressure gradient, the difference between WHVP and free hepatic venous pressure (FHVP). WHVP is measured by occluding the hepatic vein. When blood flow is stopped the static column of blood transmits the pressure existing in the preceding communicated vascular territory, in this case the hepatic sinusoids. Thus, the WHVP is a measurement of the hepatic sinusoidal pressure, and not of portal pressure itself. In the normal liver, due to pressure equilibration through the interconnected sinusoids, WHVP is slightly lower than portal pressure. In liver cirrhosis, the static column created by hepatic vein occlusion cannot be decompressed at the sinusoidal level due to the disruption of the connections between sinusoids due to fibrous septa and nodule formation. Therefore, in cirrhosis, WHVP gives an accurate estimation of portal pressure. The FHVP is measured by maintaining the tip of the catheter "free" in the hepatic vein, at 2-4 cm from its opening into the IVC. FHVP is close to IVC pressure (the difference between both should be less than 2 mmHg). Occasionally the difference between FHVP and IVC is greater than 2 mmHg. In these situations, inadequate placement of the catheter or a hepatic vein obstruction must be discarded. WHVP is measured by occluding the hepatic vein, either by advancing the catheter until it becomes "wedged" into a small branch of a hepatic vein or by inflating a balloon at the tip of the catheter. Adequate occlusion of the hepatic vein should be checked by the slow injection of 5 ml of contrast dye with the balloon inflated. This should show the typical "wedged" pattern, without reflux of the contrast or wash-out through communications with other hepatic veins. The "balloon occlusion" technique is preferred since the volume of the liver circulation being sensed is much larger than by "wedging" the catheter, which reduces the variability of the measurements. In fact, a high variability of HVPG between different hepatic veins has been reported with end-hole, non-balloon catheters. Measurement of WHVP is not instantly obtained, the pressure should be recorded until the tracing is well stable, which usually require over 40 seconds. All measurements are performed at least by duplicate and permanent tracings should be obtained using a multichannel recorder and adequately calibrated transducers.

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CONTROVERSIES WITH THE USE OF BETA-BLOCKERS – FROM THE PRESENT TO THE FUTURE

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Non-selective beta-blockers (NSBBs) are the treatment of portal hypertension and its complications. The evidence for their efficacy to prevent variceal bleeding is derived from prospective trials, most of them have excluded decompensated patients with refractory ascites or renal failure. In parallel to the increasing knowledge on portal hypertension-induced changes in systemic hemodynamic, cardiac function, and renal perfusion, emerging studies have raised concerns about harmful effects of NSBBs, like a study by Mandorfer et al (Gastroenterology 2014), which revealed an increased mortality for patients under NSBBs developing spontaneous bacterial peritonitis. Physicians are facing an ongoing controversy on the use of NSBBs in patients with advanced cirrhosis. On the one hand, NSBBs are effective in preventing variceal bleeding and might also have beneficial non-hemodynamic effects. Non-selective β-blockers (NSBBs) have been shown to effectively reduce the risk of variceal bleeding and rebleeding due to a reduction of portal pressure. Thus, Baveno VI and AASLD guidelines recommend NSBBs for primary prophylaxis and for secondary prophylaxis (in combination with EBL) of variceal bleeding in patients with cirrhosis and oesophageal varices.

However, they also potentially induce hypotension and limit the cardiac reserve, and therefore close a window of opportunity for beneficial effects of NSBB therapy in portal hypertension. Severe hyponatremia, low arterial blood pressure, or cardiac output, and increasing serum creatinine as a marker of renal failure indicate a worse prognosis in patients with decompensated cirrhosis, in whom a dose reduction or (temporal) discontinuation of NSBB treatment might be considered. Thus the last Baveno VI consensus proposed that in patients with refractory ascites and (i) systolic blood pressure <90 mmHg, or (ii) serum creatinine >1.5 mg/dL, or (iii) hyponatremia <130 mmol/L the NSBB dose should be reduced or NSBB treatment discontinued.

An individualized NSBB regimen tailored to the specific pathophysiological stage of cirrhosis might optimize patient management at this point. In primary prophylaxis several studies have demonstrated the superiority of carvedilol over propranolol in reducing portal pressure. However, it is important to point out that carvedilol is also associated with a stronger decrease in arterial blood pressure, increased need for diuretics and potentially less survival benefit (when compared to propranolol) in patients with cirrhosis and ascites on the transplant waiting list. While we prefer to use carvedilol in primary prophylaxis for compensated patients we avoid the use of carvedilol in patients with severe or refractory ascites, as well as patients with progressive arterial hypotension. For primary prophylaxis in patients with severe ascites we would recommend low doses of propranolol (≤80 mg/d) or repetitive EBL until variceal eradication. This strategy is supported by meta-analysis data showing similar survival with EBL or NSBB in primary prophylaxis and a potentially higher risk of HRS and mortality in patients with ascites treated with NSBBs if they develop hypotension or have advanced liver dysfunction.

In secondary prophylaxis, NSBB treatment does not only decrease the risk of rebleeding but might also exert non-hemodynamic effects. At the same time, there is no convincing evidence of detrimental effects in uncomplicated (non-refractory, no SBP) ascites. Thus, NSBB treatment can be maintained in secondary prophylaxis for patients with ascites, but high doses of propranolol (>80 mg/d) and carvedilol in patients with severe or refractory ascites should be avoided.

In a study by Villanueva et al (Hepatology 2017), HVPG guided treatment resulted in lower mortality, rebleeding and decompensation rates compared to standard secondary prophylaxis of BB+EBL, suggesting a further role for HVPG measurement in expert centres. A study presented at this years EASL underlines the possible advantage of Cardiac output measurements to monitor treatment with NSBBs.

Rare Vascular Liver Diseases: Practical Flowchart From Diagnosis treatment

PORTO SINUSOIDAL DISEASE (IDIOPATHIC PORTAL HYPERTENSION)

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Idiopathic portal hypertension (IPH) is a rare disorder consisting of intrahepatic portal hypertension in the absence of other recognizable liver disease such as cirrhosis or portal vein thrombosis. The exact pathophysiology of the disease remains largely unknown although it is linked with several conditions such as underlying immunological disorders, chronic infections, exposure to medication or toxins, genetic predisposition or prothrombotic disorders.

The nomenclature of this entity has been very ambiguous and has made difficult the advance in the knowledge of its pathophysiology. For years it has been variable termed such as hepatoportal sclerosis, non-cirrhotic portal fibrosis, idiopathic portal hypertension, incomplete septal cirrhosis and regenerative nodular hyperplasia. These entities share histopathological characteristics and clinical presentation. Moreover, some of typical histological features observed in IPH have been also described in patients without portal hypertension and only some of them will develop portal hypertension during follow-up. Indeed, it has been suggested that it reflects different stages of a single entity rather than different diseases. This problem had been issued during the monothematic conference organized by VALDIG (Vascular Liver Disease group) in Ascona in 2017 in order to uniform nomenclature and unify the diagnostic criteria, and a new name had been proposed: Porto Sinusoidal Disease (PSD). This new term for the disease has the advantage of not referring the presence of portal hypertension and mentioning the anatomical site where the injury is thought to occur.

The diagnosis of PSD is based on a high index of suspicion, a set of clinical criteria and exclusion of other causes of liver disease and/or portal hypertension. Liver biopsy is considered mandatory to establish the diagnosis of PSD in order to rule out other causes of liver disease and portal hypertension, mainly cirrhosis. Liver histology may only show subtle or mild changes and the definite diagnosis often requires an experienced pathologist and a high-quality and large liver specimen. Liver biopsy should demonstrate the presence of the typical lesions such as phlebosclerosis, nodular regenerative hyperplasia, sinusoidal dilatation and/or perisinusoidal fibrosis. In patients with PSD-associated portal hypertension, it is mandatory to exclude other causes of portal hypertension and to demonstrate a patent portal venous axis in addition to the findings of the liver biopsy.

As previously mentioned, the clinical presentation of PSD varies from asymptomatic patients submitted to a liver biopsy for the study of mild liver test abnormalities or for the investigation of thrombocytopenia and/or splenomegaly to patients with severe complications of portal hypertension. In symptomatic cases, variceal bleeding is the most frequent initial complication, mainly due to esophageal varices. Ascites development is rarely observed initially and is associated with bad prognosis. Hepatic encephalopathy is rare and usually is due to the massive presence of porto systemic collaterals. Portal vein thrombosis is a complication frequently observed in PSD with portal hypertension. Other portal hypertension complications rarely occur.

Liver function tests are usually preserved. Anemia, leukopenia, and thrombocytopenia can be present due to splenomegaly. Imaging studies reveal signs of portal hypertension such as splenomegaly or collaterals whereas liver stiffness and hepatic venous pressure gradient (HVPG) values are usually normal or slightly elevated.

The long-term prognosis of patients with IPH is generally good and is better than in patients with cirrhosis. However some patients may develop liver-related complications that would eventually require liver transplantation. Presence of ascitis and underlying conditions are important prognostic factors in these patients. There is no specific treatment to modify natural history of the disease and treatment is based on managing portal hypertension complications.

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ABERNETHY MALFORMATION

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Congenital extrahepatic portosystemic shunts (CEPS), also known as Abernethy malformation, is a rare condition in which most of the intestinal and splenic venous blood bypasses the portal vein and the liver, draining directly into systemic veins through abnormal communications. The development of the portal vein and inferior vena cava is a complex process that takes place simultaneously during the fourth and tenth weeks of embryonic life, the portal venous system arising from the extraembryonic and umbilical veins [1] and the systemic veins developing from intraembryonic structures. The complicated process and the close relationship between the systemic and portal system may explain the occurrence of abnormal communications [2].

CEPS was first described in 1793 by John Abernethy [3] and since then, to our knowledge, less than 300 cases of congenital extrahepatic portosystemic shunts have been reported in the literature.

Morgan and Superina [4], and afterwards Howard and Davenport [2], classified CEPS into two types according to its anatomical morphology. The main feature of Type I CEPS is the absence of intrahepatic portal vein branches with end-to-side portocaval shunt, while in Type II the intrahepatic veins are hypoplastic but patent and important collateral circulation diverts blood from portal vein to the inferior vena cava with a side-to-side shunt. Type I can be further classified into Type Ia and Type Ib, based on whether the superior mesenteric and splenic vein drain separately into inferior cava vein (ICV) (Type Ia) or the superior mesenteric and splenic vein form a common trunk before draining into the ICV (Type Ib). More recently, other more detailed anatomical subclassifications by Lautz [5] and Blanc [6] have been described correlating the anatomy of the shunt to the surgical approach required for its closure, but the main classifying feature is still whether the intrahepatic veins are patent or not.

In countries routinely perfoming nenonatal screening for hereditary galactosemia, it has been estimated that the incidence of congenital portosystemic shunts is around 1 in 30.000 births [7,8] but these data are probably not accurate and may underestimate its real incidence since not all patients with CEPS present galactosemia (high levels of galactose milk can be found in new-borns with CEPS because galactose bypasses the liver).

The vast majority of CEPS reported were single case reports providing only a transversal description without

follow up and, although some series have been reported [9,5,10,6], most of them are small and mix patients with both CEPS and intrahepatic congenital portosystemic shunts (IPSS). However the natural history of the two entities is quite different and should be studied separately; IPSS is more frequently asymptomatic, can undergo spontaneous closure during infancy (<2 years old) and there are no reports of malignant liver tumours [11,12] .

The initial diagnosis is suspected through Doppler ultrasonography (US) finding the absence or nonvisibility of intrahepatic portal branches as well as slow or absent portal flow and a compensatory dilatation of the hepatic artery. The imaging evaluation should be completed to further assess the anatomy and location of the shunt with a computed tomography (CT) with contrast injection or a magnetic resonance imaging (MRI), that will moreover evaluate and characterize liver nodules [13, 14]. Angiography with temporary balloon occlusion is an invasive imaging technique that better depicts the presence and pattern of the hypoplastic portal vein, and may detect intrahepatic branches not visible on CT or MRI, but as it involves radiation exposure, requires anaesthesia and a vascular puncture with possible complications it is not recommended as a diagnostic technique.

Abernethy malformation is usually diagnosed during childhood, sometimes even by prenatal ultrasound [15], but its diagnosis can be delayed up to the adult age as patients may remain asymptomatic for long periods of time. CEPS can present with a wide range of manifestations, from completely asymptomatic patients or with only mild hepatic dysfunction to severe porto-systemic shunt related complications. Toxic compounds generated in the gastrointestinal tract that are normally metabolized in the liver are diverted into systemic circulation with accumulative deleterious effects. Hepatic encephalopathy (HE) is due to venous shunting of circulating ammonia not metabolized by the liver [13,16,17] resulting in abnormal neurologic symptoms, behaviour (irritability, agitation, disorientations) or learning impairment among others. The risk of encephalopathy is related to the degree of portosystemic shunting [11]. Effects of circulating toxins can also cause hepatopulmonary syndrome (HPS) with chronic hypoxemia or pulmonary hypertension (PaHT). The development of HPS and PH, although not fully understood, could be in relation to intestinal vasoactive mediators [18,19, 20] that, having bypassed the liver and not being properly metabolized, reached the pulmonary vascular bed inducing a long-standing pulmonary vasoconstriction in the case of PH [21,20] or, on the contrary, pulmonary vasodilation in the case of HPS. It is also known that CEPS predisposes to the apparition of different nodular liver lesions, probably due to the misbalanced excessive increase of arterial blood flow as a way to compensate the diminished portal blood flow. Most of these nodules are benign but malignant nodules as hepatocellular carcinoma and adenomas have also been reported [22-24]. Moreover, CEPS is usually associated with other congenital anomalies, being the most frequent malformations biliary atresia, cardiac abnormalities and musculoskeletal defects [25-30]. Cardiac anomalies are present in approximately one third of patients and include ventricular and atrial septal defects, patent ductus arteriosus and foramen ovale [31]. The presence of other vascular anomalies and chromosomal anomalies have also been reported [32].

The only known curative treatments of CEPS are liver transplantation and shunt closure. Lately, shunt closure (either a surgical or radiological procedure) has been proposed as the best approach to manage CEPS complications [6].

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BUDD-CHIARI SYNDROME: PRACTICAL FLOWCHART FROM DIAGNOSIS TO TREATMENT

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Primary Budd-Chiari syndrome (BCS) is defined as hepatic venous outflow obstruction from small hepatic veins to the inferior vena cava (IVC), due to thrombosis or fibrous stenosis of these veins. [1]

It is a rare disease in Europe, with a prevalence of 4 pmi, and an incidence 0.6-0.8 pmi, affecting in the majority middle-aged women [2-5]. In Europe, one or multiple prothombotic diseases are usually identified mainly myeloproliferative neoplasms, antiphospholipid syndrome, thrombophilia, and paroxysmal nocturnal hemoglobinuria. Other causes are more frequently encountered in the Mediterranean area or in Asia, and practical flowchart screening may vary accordingly. New noninvasive diagnostic tools facilitate the diagnosis of these causes, which may be difficult in the presence of portal hypertension (PH) or liver failure.

The spectrum of symptoms ranges from an absence of signs to fulminant hepatic failure. Specific and sensitive criteria for the diagnosis of BCS have been described with Doppler ultrasound or contrast imaging (CT or MRI) and liver biopsy is not necessary in most situations.

A minimally invasive therapeutic strategy is currently proposed for BCS patients in Europe [1], and may be somehow differ in Asia, where angioplasty recanalization performed in the vast majority of patients [6-8] :

1. The first step includes anticoagulant therapy and treatment of the identified cause when appropriate, to avoid the recurrence or extension of thrombosis; associated to nonspecific management of the complications of portal hypertension symptoms (diuretics, beta blockers, variceal banding,…).

2. The second step includes an attempt to recanalize and reestablish physiological venous outflow, with angioplasty/stenting. Recanalization seems to be feasible in only 20-40% of patients in Europe, whereas it is performed in 80-99%% of the patients in Asia.

3. When symptoms are not resolved by this approach, the disease is managed by TIPS.

4. If TIPS fails, or in patients with HCC, liver transplantation is performed.

Long-term management includes:

- Close follow-up of the cause (especially when a treatment is available), of liver disease (including nodule screening,...), and of treatment complications,
- Anticipation of pregnancy with preconception counseling,
- Patient's association support,

As part of a long list of the "practical flowchart".

A multidisciplinary approach including hematologist, internist, experts in anticoagulation, radiologist, and gynecologist should therefore be included in the practical flowchart, to manage patients thoroughly.

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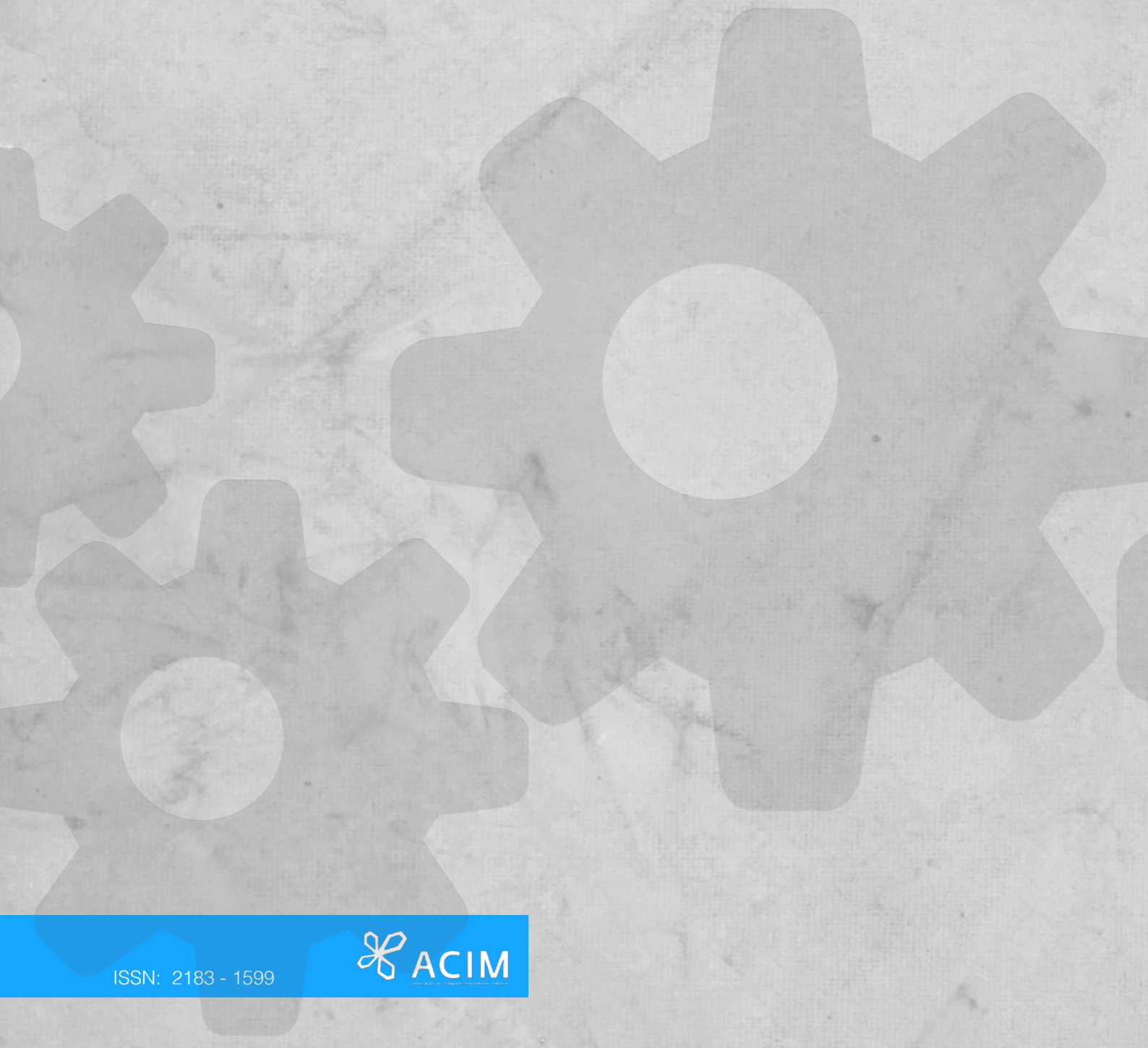

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