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Editorial board member of *World Journal of Gastroenterology*, Saadi Berkane, MD, PhD, Chief Doctor, Professor, Internal Medicine, Hepatology and Gastroenterology, Bologhine Hospital, Algiers 16000, Algeria

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EDITORIAL OFFICE
Ze-Mao Gong, Director
World Journal of Gastroenterology
Baishideng Publishing Group Inc
7901 Stoneridge Drive, Suite 501,
Pleasanton, CA 94588, USA
Telephone: +1-925-2238242
Fax: +1-925-2238243
E-mail: editorialoffice@wjgnet.com
Help Desk: http://www.f6publishing.com/helpdesk
http://www.wjgnet.com

PUBLISHER
Baishideng Publishing Group Inc
7901 Stoneridge Drive, Suite 501,
Pleasanton, CA 94588, USA
Telephone: +1-925-2238242
Fax: +1-925-2238243
E-mail: bpgoffice@wjgnet.com
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EDITORIAL

Portal vein thrombosis in cirrhotic patients - it is always the small pieces that make the big picture

Irina Gîrleanu, Anca Trifan, Carol Stanciu, Cătălin Sfarti

Irina Gîrleanu, Anca Trifan, Carol Stanciu, Cătălin Sfarti, Department of Gastroenterology, "Grigore T Popa" University of Medicine and Pharmacy, Iași 700115, Romania

Irina Gîrleanu, Anca Trifan, Carol Stanciu, Cătălin Sfarti, Institute of Gastroenterology and Hepatology, "St. Spiridon" University Hospital, Iași 700115, Romania

ORCID number: Irina Gîrleanu (0000-0001-5925-1232); Anca Trifan (0000-0001-9144-5520); Carol Stanciu (0000-0002-6427-4049); Cătălin Sfarti (0000-0001-7074-5938).

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Correspondence to: Anca Trifan, MD, Doctor, Professor, Department of Gastroenterology, "Grigore T Popa" University of Medicine and Pharmacy, 16 Universitatii St, Iași 700115, Romania. ancatrifan@yahoo.com
Telephone: +40-72-6108428
Fax: +40-23-2211820

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Abstract

Portal vein thrombosis (PVT) is a frequent and serious complication in patients with liver cirrhosis (LC). Recently, a new classification of PVT was proposed, although the functional component was not completed included. The status of liver disease (compensated/decompensated) should be added to this classification. Reduced portal flow velocity and the acquired hypercoagulable status associated with LC are the main risk factors for PVT development, although endothelial dysfunction may play an important role that needs to be further evaluated. The European Association for the Study of the Liver and the American Association for the Study of Liver Disease recommend that the anticoagulant treatment should be consider in cirrhotic patients with PVT. Low molecular weight heparin and vitamin K antagonists proved their efficacy and relatively safety in PVT treatment, although in addition to recanalization rates, more complex end-points such as mortality and decompensation rate should be evaluated. The new oral anticoagulant therapies offers the advantage of oral administration in the absence of laboratory monitoring, however, there are a few reports regarding their use in cirrhotic patients, most of them referring to compensated isolated cases. Transjugular intrahepatic portosystemic shunt could be an alternative if thrombosis progresses despite anticoagulatant therapy and/or when PVT is associated with portal hypertension complications. The aim of this editorial is to discuss the different aspects of pathophysiology, clinical relevance, diagnosis and management of PVT in patients with LC.

Key words: Portal vein thrombosis; Liver cirrhosis; Classification; Risk factors; Anticoagulation

Core tip: Portal vein thrombosis is a frequent and serious complication in patients with liver cirrhosis. The new classification needs to be validated and should contain the pattern of thrombus evolution and the status of liver cirrhosis- compensated or decompensated. The two main risk factors - reduced portal flow velocity and the hypercoagulable state should be addressed more extensively in large studies, considering the stage of liver disease. The anticoagulant treatment could be considered in cirrhotics with portal vein thrombosis. The end-points of the anticoagulant treatment should consider the recanalization, decompensation, and the mortality rates.

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INTRODUCTION

Portal vein thrombosis (PVT) is a frequent and serious complication in patients with liver cirrhosis (LC).The prevalence of PVT in patients with LC ranges from 0.6% to 26%[1] compared to 0.7 -1/100000 in the general population[2]. PVT has been increasingly diagnosed in LC using noninvasive imaging techniques such as ultrasound (US), computed tomography (CT) or magnetic resonance imaging (MRI), with the highest prevalence at the time of liver transplantation[3]. PVT mechanisms in cirrhotic patients shifted from a hypocoagulable state, due to thrombocytopenia and decreased coagulation factors levels, towards an acquired hypercoagulable state characterized by decreased protein C, protein S and antithrombin III levels and increased factor VIII levels[4].

PVT clinical presentation in cirrhotic patients is heterogenous ranging from incidental diagnosis by US during routine follow-up screening for hepatocellular carcinoma (HCC) to life-threatening complications such esophageal/gastric variceal bleeding or intestinal infarction[5].

The diagnosis of PVT is based on imaging techniques: Doppler US the first choice method (widely available, cheap, without irradiation) or contrast enhanced US. Contrast enhanced CT and MRI are superior to Doppler US for the assessment of thrombotic extension to venous branches difficult to be assessed by US exam[6]. The optimal treatment of nonmalignant PVT in cirrhotic patients remains an unmet need. The European Association for the Study of the Liver (EASL)[7] guideline for vascular diseases of the liver, the American Association of the Study of the Liver Diseases (AASLD)[6] and BAVENO VI consensus[8] recommend that the anticoagulant treatment should be considered, without any strong clinical evidence The aim of this editorial is to discuss the different aspects of pathophysiology, clinical relevance, diagnosis and management of non-malignant PVT in patients with LC.

DEFINITIONS AND CLASSIFICATIONS: OLD AND NEW

PVT refers to partial or complete occlusion of the portal vein trunk which can includes its right and/or left intrahepatic branches, with the possibility to extend either to the superior mesenteric vein or to the splenic vein.

PVT includes two different entities: the first one is acute PVT defined by the sudden formation of a thrombus within portal vein and often involving mesenteric or splenic veins, and the second is chronic PVT (also known as cavernoma). The AASLD defined acute PVT as the sudden formation of a thrombus within the portal vein lumen, and chronic PVT as the replacement of the obstructed portion is replaced network of collaterals resulting in the cavernomatous transformation of the portal vein[6]. The EASL defined recent PVT as a recent formation of a thrombus within the portal vein and/or right or left branches, while chronic PVT is characterized by the absence of recanalization and development of porto-portal collaterals resulting in a cavernomatous transformation of the portal vein[7].

These definitions, otherwise simple and easily interpreted, are based only on anatomic findings, lacking any clinically significant consequences of thrombotic occlusion of the portal vein such as portal hypertension and ascites. Taking into account this aspect, Sarin *et al*[9] proposed that PVT should be defined as a clinical syndrome presenting itself either as an incidental finding or with variable signs and symptoms such as: abdominal pain, new onset of ascites, variceal bleeding or intestinal infarction.

During the past two decades at least eight classifications of PVT have been proposed; the first one by Stieber *et al*[10] in 1991, another by Yerdel *et al*[11] in 2000, and the last by de Franchis (Baveno VI classification) in 2015 (Table 1). All these classifications have several limitations: they are purely anatomic, with no functional relevance, or clear delineation between acute and chronic forms, no etiology assessment and, no clinical therapeutic decisiveness.

Sarin *et al*[9] have proposed a new classification of PVT in cirrhosis which is an anatomico-functional classification including the site of PVT, degree of portal venous system occlusion, extend of PVT, duration and presentation (recent, chronic asymptomatic, symptomatic), type and presence of underlying liver disease (cirrhotic, non-cirrhotic, post-transplant, HCC) (Table 2).

The prognostic value and the influence of this new

Table 1 Portal vein thrombosis - Baveno VI - classification[8]

Site of PVT	Type 1: Only trunk
	Type 2: Only branch: 2a - one branch, 2b - both branches
	Type 3: Trunk and branches
Presentation	R: Recent
	Ch: Chronic
Type of underlying liver disease	C: Cirrhotic
	N: Non-cirrhotic liver disease
	H: HCC and other local malignancies
	L: Post-liver transplant
	A: Absence of underlying liver disease
Degree of portal venous system occlusion	I: Incomplete: Flow visible in PV lumen through imaging
	T: Total: No flow visible in PV lumen on imaging
Extent of PV system occlusion	Splenic vein (S)
	Mesenteric vein (M)
	Both (SM)

PVT: Portal vein thrombosis; HCC: Hepatocellular carcinoma; PV: Portal vein.

Table 2 Anatomico-functional classification of portal vein thrombosis in cirrhosis[9]

Site of PVT	Type 1: Only trunk
	Type 2: Only branch: 2a - one branch, 2b - both branches
	Type 3: Trunk and branches
Duration and presentation	R: Recent (first time detected in previously patent PV)
	Asymptomatic: (As)
	Symptomatic: (S)- acute PVT features (with or without ABI)
	Ch: Chronic (previously diagnosed PVT on follow-up, portal cavernoma and clinical features of PHT)
	Asymptomatic
	Symptomatic: Features of portal hypertension
Type of underlying liver disease	Cirrhotic
	Non-cirrhotic liver disease
	HCC and other local malignancies
	Post-liver transplant
	Local malignancies
	Associated conditions
Degree of portal venous system occlusion	O: Occlusive: No flow visible in PV lumen on imaging/Doppler study
	NO: Nonocclusive: Flow visible in PV lumen through imaging/Doppler study
Extent of PV system occlusion	Splenic vein (S)
	Mesenteric vein (M)
	Both (SM)

PVT: Portal vein thrombosis; ABI: Acute bowel infarction; PHT: Portal hypertension; HCC: Hepatocellular carcinoma; PV: Portal vein.

classification in therapeutic decision remains to be confirmed by future prospective studies. In our opinion it is important to add the pattern of PVT evolution (spontaneous recanalization, extension or stable) with or without anticoagulant treatment, and the status of the liver cirrhosis (compensated or decompensated) in order to personalize the therapeutic approach.

PREVALENCE AND PREDICTORS FOR NON-MALIGNANT PVT: ETIOLOGY OF LIVER CIRRHOSIS

PVT prevalence is estimated 0.6%-26% in patients with liver cirrhosis, increasing proportionally with LC severity[1]. In patients with compensated cirrhosis reported prevalence ranges from 1% to 8%-26% in candidates for LT[3,4]. However, there are few studies that reported PVT incidence in LC. Thus, Nery *et al*[12] demonstrated a 5-year cumulative PVT incidence in LC of 10.7%, while Maruyama *et al*[13] performed a retrospective analysis on 150 patients with LC followed up for a median period of 66 mo and reported a 12.8% cumulative overall incidence of PVT at 1 year, 18.6% at 3 years, 20% at 5 years, and 38.7% at 8-10 years.

Multiple studies evaluated the predictive factors for PVT development in cirrhotic patients. Prior PVT[12], severe liver disease (Child-Pugh class A and B)[14], hypercoagulable status[15-17], recent surgical or invasive interventions of the abdomen[18], portal flow velocity < 15 cm/s[16], and HCC[12], were described as having predictive value for PVT development in cirrhotic patients. In a recent Italian national multicenter study, including 753 cirrhotic patients, Violi *et al*[19], demonstrated that previous portal vein thrombosis, Child-Pugh class B and C, HCC, prior upper gastrointestinal bleeding, and older age were independently associated with the presence of PVT.

The influence of cirrhosis ethiology on development

of PVT has not been yet clearly defined. Nonami *et al*[20] in a research on 885 candidates for LT with PVT demonstrated that alcoholic and hepatitis B virus related cirrhosis were found to be the most frequent etiologies of LC. The association between PVT and alcoholic etiology was recently confirmed by Scheiner *et al*[21]. Cruz *et al*[22] demonstrated that non-alcoholic steato-hepatitis was more frequently associated with PVT (40.48%), followed by hepatitis C virus (23.81%) and autoimmune hepatitis (19.05%), all of these etiologies being characterized by a significant pro-inflammatory status. By contrast, in another study with 199 candidates for LT, no relation was found between the etiology of liver disease and PVT prevalence[23].

MECHANISMS LEADING TO PVT IN LIVER CIRRHOSIS

The physiopathological mechanisms of PVT remain controversial, although many of them have been by now demonstrated. Even if, the interest in LC associated PVT have been increasing during these last years, considering the complex tests, such as the global test for coagulation assessment -thrombin generation assays or thrombelastometry used to characterize PVT[24-26] in cirrhotic patients, there are still a lot of missing pieces from the big picture of PVT.

PVT is a disease with multifactorial causes and, in some particular cases it is triggered by a genetic predisposition. The components of Virchow's triad (venous stasis, hypercoagulable state and endothelial dysfunction) are recognized as the main factors involved in PVT development in cirrhotic patients[4,13,15,16].

Reduced portal flow velocity was admitted to be as the most important risk factor for PVT development in LC, although this parameter varies significantly according to the degree of liver disease severity[16,19]. Zocco *et al*[16] demonstrated for the first time that portal vein velocity under 15 cm/s predisposes to PVT development and, recently, Stine *et al*[27] confirmed these results in a match case-control study. This theory started a long-debated argument that non-selective β-blockers (NSBBs) may induce PVT in liver cirrhosis. In a small study on 56 patients with liver cirrhosis, evaluated for PVT every 6 mo, Zampino *et al*[28] demonstrated that the use of NSBBs could be an independent predictor for PVT development, although no other study has yet confirmed this hypothesis.

Liver cirrhosis is associated with profound and complex coagulation defects, involving platelets number and function, pro- and anticoagulant factors, as well as fibrinolytic system[4].

It's a well known fact that patients diagnosed with LC present thrombocytopenia, mostly secondary to increased splenic destruction, but also due to thrombopoetin deficiency[29]. Although the platelet number is low, their function is not impaired, moreover platelet hyperreactivity is associated with increased levels of von Willebrand factor and factor VIII[30].

There is growing evidence that hypercoagulability is an important part of the hematological spectrum in cirrhosis. Tripodi *et al*[25] demonstrated, using global hemostasis assays, that in cirrhotic patients there is a normal or even increased thrombin generation. Liver cirrhosis is characterized by a decrease in procoagulant factors (fibrinogen, factor II, V, X, VII, IX, XI, XII) and anticoagulant factors (protein C, protein S and antithrombin III)[4,31,32]. In another study Tripodi *et al*[33] confirmed that protein C deficiency is the most important factor that contributes to the procoagulant status in LC. Rossetto *et al*[34] performed a more complex analysis of the coagulation cascade in cirrhotics with PVT and demonstrated that the complex factor VIIa-antithrombin was significantly higher in PVT patients compared to healthy volunteers. These data were not confirmed by two recent studies conducted by Chen *et al*[35] and Tang W *et al*[36], the results of their case-control analysis concluded that there was no difference regarding the pro- and anticoagulant factors between patients with and without PVT matched for age, sex and Child-Pugh score.

The fibrinolytic system also is involved in PVT development in cirrhotic patients. LC is characterized by increased tissue-type plasminogen activator and plasminogen activator inhibitor-1 levels, and decreased plasminogen, alpha 2-antiplasmin and thrombin-activable fibrinolysis inhibitor levels[37]. This abnormalities in the fibrinolytic cascade could explain the spontaneous recanalization of PVT as described in almost a quarter of the cirrhotic patients[38].

Inherited thrombophilic disorders are reported in up to 70% of patients with cirrhosis and PVT. The most important genetic abnormalities are factor II mutation (G20210A), factor V mutation and the homozygous polymorphisms of methylenetetrahydrofolate reductase (MTHFR) C677T gene mutation[39,40]. D'Amico *et al*[17] confirmed the influence of MTHFR gene mutation in PVT pathogenesis along with the plasminogen activator inhibitor-type 1 4G-4G mutation. Although, it should be mentioned that the prospective longitudinal found studies no clear relationship between inherited factors and PVT development.

Other inherited prothrombotic conditions as hyperhomocysteinemia[40] antiphospholipid syndrome[41] or myeloprolipherative disorders[42] were evaluated, but did not proved as major risk factors for PVT development in cirrhotic patients.

There is evidence that in cirrhotic patients, markers of endothelial dysfunction, including von Willebrand factor, P-selectin and isoprostanes, are up-regulated, suggesting that endothelial cells may favor the PVT development in cirrhosis[4]. Also, Carnevale *et al*[43] demonstrated that the lipopolysaccharide from *Escherichia coli* stimulates factor VIII production from the endothelial cells. Endotoxemia may play an important role in activating the clotting system in portal and systemic circulation and could represent an underlying mechanism for PVT.

The bacterial translocation determines inflammation which leads to hemodynamic alterations and ultimately to an increase in portal pressure[44]. There are studies that describe portal endotoxemia as a triggering factor of the coagulation cascade in cirrhotic patients, although a recent small study on 49 patients with cirrhosis found that endotoxemia and platelet activity were not associated to PVT[45]. Vascular endothelial dysfunction may play a role in the pathogenesis of PVT. All these risk factors could explain the favorable role of prophylactic administration of enoxaparin in delaying the hepatic decompensation and improving survival[46].

The two main risk factors for PVT in LC-reduced portal flow velocity and the procoagulant status should be addressed more extensively in large studies, considering two different scenarios: compensated and decompensated liver disease. This discrimination could influence not only the understanding of the physiopathological mechanism of PVT development, but also the indication for a certain anticoagulant therapy.

Obviously, data received while using the *in vitro* complex coagulation assessment should be considered carefully and not used for generalization[25]. Furthermore, data provided by the use of only one type of coagulation parameter should be partially considered, as there are several studies with different results in regard to pro- and anticoagulant factors levels in PVT[35,36]. As we advanced in understanding the underlying molecular mechanism of thrombosis, the coagulation investigation in cirrhotic patients becomes more complicated, time-consuming, and expensive, thus affordable only to large clinical laboratories. Unfortunately, this kind of comprehensive specific analysis of coagulation disorders in cirrhotic patients with PVT has not yet been conducted, while most of PVT and liver cirrhosis studies remain inconclusive, being based on a small sample size.

The screening for underlying thrombophilic conditions should be considered especially in patients with compensated liver disease in whom the vascular component of the Virchow's triad is not so important. A special category of cirrhotic patients with PVT is represented by those patients in whom PVT extends despite the administration of anticoagulant therapy or reappears after spontaneous recanalization. In such patients there are other risk factors which should be identified such as endothelial dysfunction, genetic thrombophilic disorders or undiagnosed neoplasia that could predispose to PVT.

WHEN AND HOW TO TREAT PVT IN LIVER CIRRHOSIS

The main goal of PVT treatment is to restore the portal blood flow and prevent the thrombus extension.

The Baveno VI Consensus[8], published in 2015, recommends the anticoagulant treatment in cirrhotic patients with PVT who are potential candidates for LT, while no recommendation is made for non-candidates, thus highlighting the need for individualized treatment and randomized trials on the benefit/risk ratio of anticoagulation in cirrhotic patients.

The EASL 2015[7] and 2018[47] guidelines for vascular diseases of the liver and for the management of patients with decompensated liver cirrhosis state that anticoagulant treatment must be considered in cirrhotic patients with PVT following the implementation of an adequate prophylaxis for gastrointestinal bleeding, while in 2009 the AASLD[6] recommended at least three months of anticoagulant use in the treatment of PVT, irrespective of the presence of cirrhosis.

Although the guidelines accepted the anticoagulant treatment or TIPS as therapeutic option for PVT in LC not all centers accepted the idea in the daily clinical practice, so that to treat or not to treat PVT in LC it still remains an open issue.

Low-molecular-weight heparin and vitamin K antagonists

The uncertainty regarding the real efficacy of an anticoagulant treatment derives from the data reporting the natural history of PVT in LC. Studies evaluating the anticoagulant treatment have reported that spontaneous recanalization of the portal vein in the absence of anticoagulant treatment is unusual[12,13]. In the study by Francoz *et al*[48] no patient achieved recanalization in the absence of anticoagulation, while 42% achieved recanalization while under anticoagulant therapy. Senzolo *et al*[49] reported thrombus progression in 75% of patients who did not receive anticoagulant treatment, compared to only 15% of treated patients. There are limited studies reporting on the use of anticoagulation for PVT in patients with cirrhosis. In all these studies, complete recanalization has been described in 33%-45% of cases, while partial portal vein recanalization was observed in 15%-35% of cases[48-53]. Small sample size is one of the major problems of nearly all such investigations. The most cited side effect was the bleeding from different sites: gastrointestinal (variceal bleeding, postligation ulcer, peptic ulcer), intracerebral hemorrhages, epistaxis and hematuria[48-53].

In order to overcome the small sample size bias and increase the efficacy and safeness of the anticoagulant treatment in patients with PVT and LC, two meta-analysis have recently been published[54,55]. Qi *et al*[54] concluded in 2015 that anticoagulation could achieve a relatively high rate of portal vein recanalization in cirrhotic patients with PVT, information confirmed by another meta-analysis published by Loffredo *et al*[55] in 2017.

The attendant optimism is, at least in part, based on the relatively safeness of the anticoagulant treatment, including the pleiomorphic effect of reducing fibrogenesis by thrombin antagonism[56]. For a better evaluation of the anticoagulant treatment in patients with LC other end-points should be established such as short-term and long-term mortality and decompensation or further

decompensation rate. Achieving PVT recanalization is only one of the goals of anticoagulant therapy in cirrhotics with PVT, and it is far more important to document the real impact of recanalization on LC evolution in order to confirm the benefits of this controversial treatment.

If the anticoagulant treatment is the first therapeutic option for cirrhotic patients with PVT, the ideal anticoagulanthas not been developed yet. Low-molecular-weight heparin (LMWH) and vitamin K antagonists (VKAs) are the anticoagulant drugs recommended for PVT treatment, but they have some disadvantages: efficacy of LMWH may be significantly decreased (up to 40%) due to lower levels of antithrombin III synthesis by the liver, and the coagulopathy secondary to liver disease frequently results in an elevated International Normalized Ratio (INR) and thus utilizing the INR to guide dosing of VKAs is particularly challenging[6-8].

Direct oral anticoagulants and PVT treatment

The direct oral anticoagulants (DOACs) - thrombin inhibitors (dabigatran) and activated factor X inhibitors (rivaroxaban, apixaban or edoxaban) overcame the numerous drawbacks of traditional anticoagulants and proved their efficacy and saffness in stroke prophylaxis in nonvalvular atrial fibrillation, venous thrombembolism prophylaxis in orthopaedic patients, and the treatment of acute pulmonary embolism and deep vein thrombosis[57]. DOACs offer the advantage of oral administration, the absence of laboratory monitoring, and an antithrombin III independent mechanism of action. Rivaroxaban and apixaban are 67% metabolized in the liver, with half-lives of 5-9 h and 12 h respectively[58], their concentration depending on the plasma bounding proteins. Edoxaban is 50% metabolized by the liver with a half-live of 10-15 h[58]. Dabigatran has limited hepatic metabolism, minimal binding to plasma proteins, and longer half-life (12-14 h)[57]. Another advantages of dabigatran is the development of an antidote - idarucizumab - monoclonal inhibitor antibody[59].

However, there are few reports regarding their use in cirrhotic patients, most of which in compensated isolated cases. Rivaroxaban is the most studied DOACs for the treatment of PVT[60]. There is little scientific evidence regarding the use of DOACs in cirrhosis with or without PVT, and even fewer well-designed prospective studies

In the VALDIG study, major bleeding requiring discontinuation of DOACs was seen in two of 258 (0.71%) patients without cirrhosis and in one of 36 (2.7%) patients with cirrhosis[61]. Intagliata *et al*[62] retrospectively evaluated class Child-Pugh A and B cirrhotic patients having received DOACs treatment for different conditions. Two thirds of the patients received DOACs for PVT treatment. There are no data reported on the recanalization rate. Major bleeding events occurred in 5% of the patients and a paradoxically PVT recurrence during the anticoagulant treatment was described. In a clinical trial assessing the efficacy of VKAs, Hafany *et al*[63] compared the DOAC rivaroxaban with warfarin in 80 patients with virus C compensated cirrhosis. They reported a 85% recanalization rate, in contrast with the 45% in patients treated with warfarin, higher short-term survival rate and fewer gastrointestinal bleeding events in patients treated with DOACs. Nagaoki *et al*[64] compared edoxaban and warfarin in cirrhotic patients with PVT and, concluded that edoxaban is an effective anticoagulant treatment, although most of the events involving the gastrointestinal bleeding were associated with the administration of edoxaban(15% *vs* 7%).

The recent literature does not establish with certainty the role of DOACs in treating PVT in cirrhotic patients, and further large clinical trials are needed confirm if the DOACs can be used effectively and safely in Child-Pugh A or B liver cirrhosis.

Transjugular intrahepatic portosystemic shunt

Classically considered contraindicated in PVT, TIPS could be an alternative particularly if thrombosis progresses despite satisfactory anticoagulation and/or when PVT is associated with severe portal hypertension complications[1,48]. However, in such cases, TIPS is expected to be technically challenging with a higher failure rate[48,65] and should be attempted only in experienced centres. TIPS may be a treatment option in patients with acute PVT. In chronic PVT or portal cavernoma TIPS is unsuccessful if the lumen of thrombosed portal vein is not catheterizable and cavernomatous vein is not amenable to dilatation.

FUTURES PERSPECTIVES: UNMET NEEDS

Although new data on the mechanisms of PVT development in cirrhotic patients was published and a new complex classification is proposed, there are still a lot of puzzle pieces missing in the big picture of PVT.

The prognostic value of the new PVT classification remains to be confirmed by future prospective studies, without omitting the pattern of PVT evolution and the status of the liver cirrhosis (compensated or decompensated).

Controversies persist regarding the mechanism leading to PVT in LC. The influence of each previously described risk factor, in the pathogenesis of PVT needs to be demonstrated. The role of microbiota and the influence of endotoxinemia in the development of PVT in compensated LC must also to be addressed. The natural history of PVT should be described in large multicenter studies in order to identify predictors for spontaneous recanalization and risk factors for rethrombosis. Updated complex and global dynamic coagulation tests should be developed and validated to assess the coagulation disorders in cirrhotic patients with PVT and even anticoagulant therapy monitoring.

The ideal anticoagulant treatment of PVT in cirrhotic patients is not yet described. DOACs are used off label for PVT treatment in LC despite the lack of randomized

control trials confirming the safety and efficacy. The end-points of these studies should also include short-term and long-term mortality rates together with decompensation outcomes.

No doubt, many advances have been made during the last decade regarding different aspects of PVT pathophysiology and treatment in cirrhotic patients, although this complication of liver cirrhosis still has more questions than answers.

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