Management of splanchnic vein thrombosis

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Summary

The expression splanchnic vein thrombosis encompasses Budd-Chiari syndrome and portal vein thrombosis. These disorders have common characteristics: they are both rare diseases which can cause portal hypertension and its complications. Budd-Chiari syndrome and portal vein thrombosis in the absence of underlying liver disease share many risk factors, among which myeloproliferative neoplasms represent the most common; a rapid comprehensive work-up for risk factors of thrombosis is needed in these patients. Long-term anticoagulation is indicated in most patients. Portal vein thrombosis can also develop in patients with cirrhosis and in those with porto-sinusoidal vascular liver disease. The presence and nature of underlying liver disease impacts the management of portal vein thrombosis. Indications for anticoagulation in patients with cirrhosis are growing, while transjugular intrahepatic portosystemic shunt is now a second-line option. Due to the rarity of these diseases, studies yielding high-grade evidence are scarce. However, collaborative studies have provided new insight into the management of these patients. This article focuses on the causes, diagnosis, and management of patients with Budd-Chiari syndrome, portal vein thrombosis without underlying liver disease, or cirrhosis with non-malignant portal vein thrombosis.

Keywords: Cavernoma; Portal biliopathy; Direct oral anticoagulants; Portal vein recanalisation; Vascular liver diseases

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Introduction

The expression splanchnic vein thrombosis (SVT) encompasses Budd-Chiari syndrome (BCS) and portal vein thrombosis (PVT). PVT can develop in patients without underlying liver disease or affect patients with cirrhosis. BCS and PVT in the absence of underlying liver disease share several similarities. First, they belong to rare disorders since they affect fewer than 1 in 2,000 people in the general population.[1] Second, they are commonly associated with risk factors for thrombosis. Third, portal hypertension is a common consequence. PVT can also occur in patients with cirrhosis, where it is usually non-occlusive and found in the absence of symptoms. Risk factors for thrombosis in patients with PVT and cirrhosis are uncommon. However, PVT in cirrhosis carries specific challenges, especially in liver transplant candidates.

The present review focuses on recent findings on the management of BCS and PVT without underlying liver disease or with underlying cirrhosis. PVT occurring in patients with porto-sinusoidal vascular liver disorder will not be discussed here, since it has recently been reviewed elsewhere.[2] Management of BCS and PVT is multidisciplinary, with a growing place for interventional radiology. Importantly, besides treating portal hypertension-related complications, managing patients with SVT largely depends on associated risk factors for thrombosis or extrahepatic conditions. Indeed, the prognosis of patients with vascular liver diseases differs according to the causal factors.

Causes of SVT in the absence of underlying liver diseases

Causes for SVT include general risk factors for thrombosis, namely systemic acquired prothrombotic diseases and inherited thrombophilia, and local factors. General risk factors for thrombosis are found in approximately 70% of patients with SVT, while local factors are identified in 20% and 5% of patients with PVT and BCS, respectively.

A combination of two or more genetic or acquired risk factors is found in 26%–46% and 10–23% of patients with BCS or PVT, respectively.[3–6] Furthermore, 36% of patients with PVT and a local factor also have a general risk factor for thrombosis.[5,7] These results justify comprehensive investigations, even when predisposing or precipitating factors have already been identified (Table 1). This work-up should be performed at the diagnosis of SVT since control of some conditions (*e.g.*, myeloproliferative neoplasms [MPNs], Behcet's disease, paroxysmal nocturnal hemoglobinuria [PNH]) influences patient outcomes.[8–11]

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Myeloproliferative neoplasms

MPNs represent the most common risk factor for BCS and PVT in Europe and Asia. In Europe, the reported prevalence of MPNs in patients with BCS and PVT is 30-57% and 21-25%, respectively.[4–7,12–14] In Asia, the prevalence of MPNs among patients with BCS or PVT ranges from 5–28%.[15,16] The Janus kinase 2 (*JAK2*) V617F mutation can be detected in over 90% of patients with SVT and a MPN. Thus, routine screening for the *JAK2* V617F mutation should be performed in all patients with SVT. Somatic mutations of the gene encoding calreticulin (*CALR*) are identified in about 2% of patients with SVT without the *JAK2 V617F* mutation. *CALR* mutations should be searched for in patients with spleen height ≥16 cm and a platelet count ≥200x 10^9/L since 33-56% of patients who meet both these criteria have *CALR* mutations.[6,13,14] *MPL* exon 10 and *JAK2*-exon 12 mutations are even less common in patients with SVT.[6,10,12] Next-generation sequencing (NGS) could play a role in diagnosing an underlying MPN in patients without *JAK2 V617F* or *CALR* mutations.[10,17,18] Moreover, in patients with SVT, molecular profiling by NGS carries prognostic information since some molecular risk factors predict the risk of thrombosis recurrence in patients without MPN[10] and the risk of haematological transformation and poorer survival in patients with MPN.[17] Portal hypertension, by causing hypersplenism and haemodilution, often masks increased blood cell counts and makes the diagnosis of MPN challenging.[19] Therefore, given the frequency of MPN in patients with SVT and the consequences of its diagnosis, referral to a haematologist should be systematically considered to discuss NGS and/or bone marrow biopsy (Table 1).

Key points

- Patients with Budd-Chiari syndrome or portal vein thrombosis in the absence of underlying liver disease should be systematically screened for myeloproliferative neoplasms.
- The diagnosis of Budd-Chiari syndrome or portal vein thrombosis is suspected using abdominal Doppler ultrasonography and confirmed using contrast-enhanced CT or MRI; liver biopsy is generally not necessary.
- In patients with Budd-Chiari syndrome, long-term anticoagulation is recommended; prompt identification and treatment of the causal factor have a beneficial impact on patient outcomes.
- Spontaneous recanalization is rare in patients with portal vein thrombosis in the absence of underlying liver disease but occurs in ∼40% of patients with cirrhosis.
- In patients with portal vein thrombosis in the absence of underlying liver disease, long-term anticoagulation is generally recommended.
- In patients with portal vein thrombosis in the absence of underlying liver disease, preliminary data suggest that portal vein recanalization with or without TIPS is a safe option for the treatment of refractory complications of portal hypertension or portal cavernoma cholangiopathy when performed in expert centres.
- In patients with cirrhosis and portal vein thrombosis, anticoagulation is recommended for all liver transplant candidates and, among those who are not candidates, for those with recent (<6 months) thrombosis occluding >50% of the lumen of the main portal vein.
- In patients with cirrhosis, TIPS can be considered as the second-line option for the treatment of portal vein thrombosis, especially in case of significant concomitant complications of portal hypertension.
- There is growing evidence demonstrating that DOACs are a safe and effective option, though high-grade evidence is still needed before making strong recommendations on the use of DOACs in patients with splanchnic vein thrombosis.

Other acquired prothrombotic disorders

Antiphospholipid antibodies are reportedly present in between 5% and 30% of patients with SVT,[4–6,13,14] while these antibodies can be found in the absence of antiphospholipid syndrome in up to 5% of healthy individuals.[20] A meta-analysis did not show an association between antiphospholipid antibodies and BCS or PVT, except for IgG anticardiolipin antibodies.[21] Therefore, if antiphospholipid antibodies are detected at the diagnosis of SVT, repeat testing 12 weeks after the diagnosis is recommended.

The association between Behcet's disease and SVT mainly concerns BCS and is especially relevant in the Mediterranean population.[9,22] Behcet's disease should be suspected in case of inferior vena cava obstruction, oral and/or genital ulcers, male sex, deep venous thrombosis in other territories, and systemic inflammatory syndrome.[9] Early medical therapy, including anticoagulation and immunosuppressive agents, may improve symptoms of BCS (including requirement of invasive treatments) in patients with Behcet's disease.[9]

PNH has been observed in up to 10% of patients with BCS.[4,23] Conversely, PNH appears extremely rare (less than 2%) among patients with PVT.[5,6] Still, systematic screening for PNH is recommended in all patients with SVT since specific therapies, especially eculizumab, have been shown to decrease the recurrence of thrombosis and mortality in this setting.[11]

In a cohort of 115 Algerian patients with BCS, coeliac disease was found in 11% of patients.[24] This association is less common in European countries.[4,13] Cytomegalovirus (CMV) disease is another recently highlighted rare (<5%) risk factor for PVT. This association should be suspected in patients with recent PVT displaying features of mononucleosis syndrome. CMV disease should not deter a complete work-up since a general risk factor for thrombosis (especially the G20210A prothrombin gene mutation) was found in 50% of patients with CMV.[25] CMV disease does not influence thrombosis extension or recanalization. In addition, acute SVT has been reported in patients with SARS-CoV-2 infection. Although rare, SVT may be severe in this setting, suggesting that patients with SARS-CoV-2 infection and severe gastrointestinal symptoms should be screened for SVT.[26] Although rare cases of SVT occurring after COVID-19 vaccination were reported, the risk of thrombosis is higher after SARS-CoV-2 infection than after COVID-19 vaccination.[27] Furthermore, since SARS-CoV-2 infection seems to be more frequent and severe in patients with vascular liver diseases than in the general population,[28] a history of SVT should not contraindicate COVID-19 vaccination.

Inherited thrombophilia

Factor V Leiden and G20210A prothrombin gene mutations have been reported in 12% and 4% of patients with BCS, respectively. In patients with PVT, the prevalence of Factor V Leiden and G20210A prothrombin gene mutations are 5% and 8%, respectively.[6,14] Compared to healthy individuals, the Factor V Leiden mutation is associated with an increased risk of both BCS and PVT, whereas the G20210A prothrombin gene mutationis associated with PVT but not with BCS.[29]

The prevalence of deficiency in antithrombin, protein C or protein S is 3%, 2% and 2% in BCS, respectively, and 5%, 1% and 2% in those with PVT, respectively.[6,14] Diagnosis of inherited deficiencies in antithrombin, protein C, and protein S may be difficult to establish because liver dysfunction can induce a non-specific decrease in these natural anticoagulants, as recently highlighted with antithrombin deficiency.[30,31] Although not widely available, genetic testing might be considered in cases of

Table 1. Prevalence of risk factors for BCS and PVT in the absence of underlying liver disease and proposed diagnostic work-up and specific management (see[4–7,13,14]).

Condition	Prevalence		Recommended work-up
	BCS	PVT	
Myeloproliferative neoplasm	**30–57%**	**21–25%**	Systematic genetic testing of the V617F mutation of the *JAK2* gene in all patients.
JAK2 V617F	28–45%	15–21%	
CALR mutation	1–3%	1–2%	If negative: - Genetic testing of the *CALR* gene if platelet count ≥200 $\times 10^9$/L and/or spleen length ≥16 cm - Discuss next-generation sequencing - Discuss bone marrow biopsy
Inherited thrombophilic disorders			Genetic testing for prothrombin G202101A and Factor V Leiden mutations
G20210A prothrombin gene mutation	12%	5%	Protein S activity
Factor V Leiden mutation	4%	8%	Protein C activity
Antithrombin deficiency	3%	5%	Antithrombin activity
Protein C deficiency	2%	1%	*Protein S, C and antithrombin activities should be assessed in the absence of VKAs. Cautious interpretation of impaired liver function*
Protein S deficiency	2%	2%	
Acquired thrombophilic disorders			
Antiphospholipid antibody syndrome	5%	5%	Lupus anticoagulant, anti-cardiolipin, and anti-beta2 glycoprotein 1 antibody testing *Repeat testing after 12 weeks in case of positive testing*
Paroxysmal nocturnal hemoglobinuria	10%	0-0.5%	Flow cytometry analysis
Behcet's disease	1-2%	Uncommon	No specific testing, clinical diagnosis *Suspect Behcet's disease if: male sex, Mediterranean origin IVC stenosis, genital/oral ulcers, deep vein thrombosis in other sites, arterial thrombosis*
Coeliac disease	1.4%	0.7%	Anti-transglutaminase antibody +/- duodenal biopsies
Other systemic factors			Search clinical and/or laboratory features CMV IgM and CMV PCR (blood)
Auto-immune disease			
Inflammatory bowel disease			
Vasculitis			
Sarcoidosis			
Connective tissue disease			
CMV disease			
Hormonal factors	∼**30%**	∼**20%**	Clinical context
Oral contraceptive or pregnancy			*Search for introduction/modification of oral contraception within* 6 months *before diagnosis*
Local factors	**0-3%**	**20 %**	CT scan Colonoscopy
Pancreatitis			
Diverticulitis			
Cholecystitis			
Appendicitis			
Intra-abdominal surgery			
Hydatid cyst			
No identified factor	10-29%	15-40%	

BCS, Budd-Chiari syndrome; CMV, cytomegalovirus; IVC, inferior vena cava; PVT, portal vein thrombosis; VKAs, vitamin K antagonists.

re-thrombosis, family history of deep vein thrombosis or doubtful interpretation of antithrombin, protein C, and protein S concentrations.

Hyperhomocysteinemia and/or homozygous C677T methylene-tetrahydrofolate reductase (*MTHFR*) gene polymorphisms have been observed in 22% of patients with BCS[4] and 11% of those with PVT.[5] However, the role of hyperhomocysteinemia as a risk factor for SVT is difficult to assess because homocysteine levels are highly influenced by diet and by vitamin B6, B12, or B9 deficiencies. The role of homozygous C677T *MTHFR* mutations as a risk factor for BCS seems more relevant in Asia than in Europe.[15,32] The prevalence of the C677T MTHFR mutation does not differ between patients with PVT and healthy individuals[32]

Hormonal factors

Pregnancy and oral contraceptives have been associated with BCS. Up to 74% of western women with BCS have been using oral contraceptive agents and a temporal link between pregnancy and BCS has been described.[3,4,33] Local or other general prothrombotic factors are commonly associated with pregnancy or oral contraceptives in women with BCS. Regarding PVT, exposure to female hormones does not appear to cause PVT, as illustrated by the absence of a female predominance among patients with PVT (contrary to BCS).[5,34,35]

Local factors

Local risk factors for SVT include abdominal surgery and infectious or inflammatory conditions involving splanchnic organs, such as

cancer or inflammatory bowel disease[5] (Table 1). Certain local factors can be identified on the CT scan performed at SVT diagnosis. In PVT, colonoscopy is recommended to screen for colon cancer or inflammatory bowel disease, although the level of evidence is low.[36] PVT associated with alcoholic pancreatitis has some specificity since it does not seem to be favoured by general risk factors for thrombosis, so whether a comprehensive work-up for risk factors of thrombosis is warranted in this setting remains questionable.[37] Visceral adipose tissue might also promote PVT. Indeed, in a retrospective case-control study of 79 patients with PVT and 79 healthy individuals, features of the metabolic syndrome were more frequent in those with "idiopathic PVT" (*i.e.* no risk factor for PVT identified) than in those with either secondary PVT (*i.e.* risk factor for PVT identified) or healthy individuals. Specifically, increased waist circumference was observed in ~75% of patients with "idiopathic PVT" *vs.* ~30% of patients with either secondary PVT or healthy individuals, pointing to visceral adipose tissue as a potential risk factor for PVT.[7] Confirmatory studies addressing the link between visceral obesity and PVT are needed.

In patients with BCS, local factors appear to be rare. However, in countries with a high prevalence of *Echinococcus granulosus*, liver hydatid cysts have been associated with BCS in up to 4% of patients.[24]

Budd-Chiari syndrome

BCS is caused by hepatic venous outflow tract obstruction, originating anywhere from the small hepatic veins to the entry of the inferior vena cava into the right atrium. BCS is usually caused by thrombosis. Heart failure, constrictive pericarditis, and sinusoidal obstruction syndrome/veno-occlusive disease are differential diagnoses.

Diagnosis

BCS should be considered in patients with any acute or chronic liver disease. The clinical presentation of BCS varies from asymptomatic (3% of cases) to severe portal hypertension or liver insufficiency. In most patients, clinical manifestations include abdominal pain and ascites.[4]

The diagnosis of BCS is based on radiological findings on Doppler ultrasonography and contrast-enhanced CT or MRI. Because the diagnosis of BCS can be difficult, radiologists should be experienced and aware of the clinical suspicion of BCS. Radiological features of BCS include (i) direct evidence of obstruction, including solid non-enhancing endoluminal material or transformation of the veins into a cord devoid of flow signal, and (ii) indirect evidence of outflow obstruction, including dilatation of the vein upstream of the obstruction, inter-hepatic venous collateral or inverted venous flow, atrophy/hypertrophy of affected/unaffected segments.[38] "Classical" forms of BCS do not require liver biopsy for diagnosis, whereas it can be helpful in the rare cases where the obstruction is located in small hepatic veins and the large hepatic veins remain patent. Variations in the anatomical location of obstruction have been observed between regions: 62% of BCS in Western countries are pure hepatic vein obstruction, whereas membranous obstruction of the inferior vena cava is more common in Asia.[39] The difficulty of diagnosing BCS is illustrated by a French epidemiological study where the duration between first clinical manifestations and diagnosis of primary BCS exceeded 6 months in 15% of patients and 1 year in 6% of patients.[40]

Management

BCS requires referral to centres with expertise in managing patients with vascular liver diseases; access to interventional radiology and liver transplantation is crucial. The approach should be multidisciplinary, including specialists in haemostasis, haematology, diagnostic and interventional radiology, and liver transplantation. For more than 15 years, a stepwise treatment strategy, according to response to previous therapy (from less to more invasive), has been proposed and is now used worldwide.[41–43] With this strategy, patient outcomes have dramatically improved, with 5-year overall survival ranging from 77% to 87%.[44–46] Among patients alive at 5 years, BCS is controlled with medical therapy alone in ~30%, interventional radiology in 35% and liver transplantation in 10%.[45] The exact timings for treatment escalation have not been defined. Improvement (with no need for further intervention) is characterised by the presence of a combination of several of the following features: decreasing rate of ascites formation, decreasing serum bilirubin, decreasing serum creatinine and decreasing international normalised ratio (INR) (or increasing factor V in patients receiving vitamin K antagonists [VKAs]).[43] Several prognostic indices have been proposed for all patients with BCS (Child-Pugh score, model for end-stage liver disease (MELD), Clichy prognostic index, Rotterdam BCS index, New Clichy prognostic index) and one for patients with BCS in whom transjugular intrahepatic portosystemic shunt (TIPS) is being considered as a therapeutic option (BCS-TIPS). These prognostic indices are accurate to assess transplant-free survival and invasive therapy-free survival. However, because they were derived from retrospective cohorts collected over several decades (with drastically different therapeutic options and outcomes) and because they exhibited low prognostic accuracy in most recent studies, they are considered insufficiently accurate to guide the management of individual patients with BCS.[45,47–49]

Medical therapy

Prompt identification of MPN, PNH, or Behcet's disease associated with BCS is essential since targeting the underlying condition positively influences patient outcomes.[8–11] Anticoagulation should be started at BCS diagnosis, even in the absence of an identified prothrombotic disorder. Despite the absence of a randomised study comparing anticoagulation *vs.* no treatment, long-term anticoagulation is currently recommended for all patients with BCS based on survival *vs.* historical comparators.[50] Only a few cases of anticoagulation interruption have been described in patients with BCS in whom the prothrombotic factor was treated.[3,51] However, there is no clear or sufficient argument currently to stop anticoagulation once BCS is stabilised and the causal factor adequately treated. Because of a high rate of heparin-induced thrombocytopenia, mainly observed with unfractionated heparin (15%), low-molecular-weight heparin (LMWH) is currently recommended.[41,43,52,53] LMWH is usually substituted with VKA in patients with stable disease, with a target INR between 2 and 3. Although experience is limited, direct oral anticoagulants (DOACs) seem safe and effective in patients with BCS, but larger prospective studies are needed[54,55] (Table 2). A recent retrospective case-control study found that dabigatran was associated with similar stent patency and complication rates after endovascular intervention as VKAs.[56] DOACs are currently not recommended in patients with antiphospholipid syndrome as they have been associated with an

Table 2. Considerations for the choice of anticoagulant to treat splanchnic vein thrombosis and suggestion of doses (adapted from[149]).

Considerations	Low-molecular-weight heparin	Vitamin K antagonists	Direct oral anticoagulants			
			Apixaban	Rivaroxaban	Edoxaban	Dabigatran
Liver function						
Child-Pugh class A	No action needed	No action needed Target INR 2-3	No action needed 5 mg *twice a day*	No action needed 20 mg *once a day*	No action needed 60 mg *once a day*	No action needed 150 mg *twice a day*
Child-Pugh class B	No action needed	Possible Target INR 2-3	Use with caution 2.5 mg *twice a day*	Use with caution 15 mg *once a day*	Use with caution 30 mg *once daily*	Use with caution 110 mg *twice a day*
Child-Pugh class C	No action needed	Possible Target INR 2-3	Contraindicated	Contraindicated	Contraindicated	Contraindicated
Renal function						
eGFR 30-50 ml/min	No action needed	Possible Target INR 2-3	No action needed 5 mg *twice a day*	Use with caution 15 mg *once a day*	Use with caution 30 mg *once daily*	Use with caution 110 mg *twice a day*
eGFR <30 ml/min	Use with caution	Possible Target INR 2-3	Use with caution 2.5 mg *twice a day*	Use with caution 15 mg *once a day*	Use with caution 30 mg *once daily*	Contraindicated
eGFR <15 ml/min	Contraindicated	Possible Target INR 2-3	Contraindicated	Contraindicated	Contraindicated	Contraindicated
Other considerations						
Drug-drug interaction Other medication with P-gp protein or Cytochrome 3A4 metabolism	No action needed	No action needed Target INR 2-3	No action needed	Use with caution 15 mg *once a day*	No action needed	Use with caution 110 mg *twice a day*
History of peptic ulcer disease with or without gastrointestinal bleeding			No action needed	Use with caution *Consider* 15 mg *once a day*	No action needed	Use with caution *Consider* 110 mg *twice a day*
Specific consideration		Monitoring may be difficult in patients with liver insufficiency Factor II concentration may be useful in this setting				Contraindicated in patients with antiphospholipid syndrome No data on pharmacokinetics after TIPS placement

eGFR, estimated glomerular filtration rate; INR, international normalised ratio; P-gp, Permeability glycoprotein; TIPS, transjugular intrahepatic portosystemic shunt.

increased risk of recurrent arterial thrombosis.[57] Ascites, gastrointestinal bleeding, infections, renal failure, and encephalopathy should be treated as recommended for patients with cirrhosis, due to an absence of specific data in the BCS population. Severe bleeding related to paracentesis has been reported in patients with BCS receiving anticoagulation. Thus, a brief interruption of anticoagulation could be considered before paracentesis.[58]

Interventional radiology

Short-length hepatic vein stenosis should be systematically searched for to re-establish the physiological drainage of portal and sinusoidal blood. When identified, *i.e.* in ~15% of patients, percutaneous transluminal angioplasty of accessible stenosis should be performed as this procedure is associated with good efficacy and low morbidity.[39,41,44,45,59] In a recent Chinese randomised-controlled trial including 88 patients with BCS and short-length stenosis, stent placement improved hepatic vein patency and reduced symptom recurrence over percutaneous transluminal angioplasty alone.[60]

TIPS has become the standard of care for patients with BCS and incomplete response to medical therapy and/or angioplasty.[45,46,48] TIPS is currently needed in 40% of patients with BCS, persistent ascites being the most common indication.[45] The technical success rate exceeds 90% in expert centres, with 10-year liver transplantation-free survival rates reaching 76%. Long-term anticoagulation should be maintained after TIPS placement.[44] TIPS dysfunction occurs in 42% and was mostly due to re-thrombosis of the stent which can be managed with TIPS revision, leading to a secondary patency rate close to 100%. Late hepatic encephalopathy, which is mostly transient and easily medically controlled with no reappearance, occurs at an incidence of 25% in these patients.[61]

Surgery

Surgical portosystemic shunt placement for BCS has now been almost completely abandoned because of high perioperative mortality, averaging 25%,[62] and a high rate of shunt dysfunction due to early or late thrombosis or late stenosis, reaching 30% in series with long-term follow-up.[63]

Liver transplantation

Despite medical therapy and interventional radiology, liver transplantation is necessary for ~10% of patients with BCS. Previous TIPS does not compromise the results of liver transplantation.[64]

Specific issues

Pregnancy

Pregnancy is not contraindicated in women with controlled BCS. Three retrospectives studies, including 55 pregnancies completed between 1985 and 2015, reported no maternal death.[65–67] Liver-related complications were rare in women with BCS that had been diagnosed and treated before pregnancy. Bleeding events occurred in women receiving anticoagulation and were unrelated to portal hypertension. The reported rate of miscarriages or ectopic pregnancies before the 20th week of pregnancy was about 30%, higher than in healthy women of

Table 3. Practical management of pregnancy in patients with vascular liver diseases.

	Advice
Before conception	Early counselling should always be proposed before conception. Pregnancy should be planned when the liver disease and the prothrombotic condition are well-controlled. Cytoreductive treatments for myeloproliferative neoplasms should be stopped before conception as they are teratogenic.
Anticoagulation	VKAs must be switched to LMWH before the 6th week of amenorrhea, as they cross placenta and can cause foetal warfarin syndrome or warfarin embryopathy. LMWH are then continued during the whole pregnancy. DOACs are contraindicated during the whole pregnancy.
Portal hypertension	Gastroesophageal varices should ideally be investigated in the year before conception or during the second trimester of pregnancy. Variceal haemorrhage occurring during pregnancy should be prevented and managed as in non-pregnant patients.
Delivery	Vaginal delivery should be preferred even in case of portal hypertension. Caesarean section reserved only for obstetrical indications. Platelet count >20 × 10^9/L and >50 × 10^9/L considered as safe for vaginal delivery and caesarean section respectively. Platelet counts >75 × 10^9/L are considered safe for epidural anaesthesia and over 50 × 10^9/L for spinal anaesthesia. Stop anticoagulation therapy 24 h before epidural analgesia
Post-partum	Oestrogen-derived oral contraceptives are contraindicated. Breastfeeding is possible with beta-blocker therapy and warfarin but not with other VKA molecules or DOACs.

DOACs, direct oral anticoagulants, LMWH, low-molecular-weight heparin; VKAs, vitamin K antagonists.

similar age. On the other hand, after 20 weeks of pregnancy, 93% of children were healthy, but the prematurity rate was high. Practical management of pregnancy in women with vascular liver diseases is described in Table 3. All VKAs must be switched to LMWH before the 6th week of gestation as VKAs cross the placenta and can cause foetal haemorrhage and foetal VKA syndrome, especially between 6 to 12 weeks of gestation.[68]

Liver nodules

An early decrease in portal perfusion associated with a compensatory increase in hepatic arterial perfusion is thought to contribute to the development of liver nodules in chronic BCS. Most liver nodules are benign regenerative nodules, also called focal nodular hyperplasia-like nodules, but hepatocellular adenomas or hepatocellular carcinoma (HCC) can also arise.[69–73] The cumulative incidence of HCC is about 4%,[69,74] which is similar to that reported in other chronic liver diseases; so, like for cirrhosis, screening for liver nodules every 6 months can be proposed.[43] When liver nodules are detected, MRI is the imaging procedure of choice, ideally with the injection of hepatobiliary contrast agent, to distinguish malignant from benign nodules. The vast majority of nodules show arterial phase hyper-enhancement.[73,75] Washout is observed in 75% of HCC *vs.* 29% of benign lesions and is thus not specific for HCC. Additional features are helpful to differentiate benign nodules from HCC, including serum alpha-fetoprotein >15 ng/ml, fat content, capsule, hypo-intensity on T1-weighted sequence, hyper-intensity on T2-weighted sequence, hyper-intensity on high b value diffusion-weighted imaging, or hypo-intensity on hepatobiliary phase.[69,73,75] The combination of a hyper-enhanced nodule with washout and one of these features reaches a specificity of between 88% and 100% for HCC.[73] A liver biopsy is required in case of suspicion of HCC (Fig. 1). Management of hepatocellular adenoma and HCC should be discussed on a case-by-case basis in specialised centres. Ablation, transarterial chemoembolisation, and liver transplantation can be considered.[69,70]

PVT in patients without underlying cirrhosis

Diagnosis

Recent PVT refers to the recent formation (<6 months) of a thrombus within the portal vein and/or its branches and/or radicles. Abdominal pain is the most frequent clinical feature (91%); high leukocyte count and C-reactive protein levels are common.[5] Conversely, signs of peritoneal irritation, organ failure, clinical ascites, and/or high lactate levels are rare and should raise suspicion of PVT complicated with intestinal necrosis, *i.e.* a complication requiring emergency surgery (see below).[76]

The diagnosis of recent PVT is based on imaging. Ultrasound coupled with Doppler is usually the first-line approach, allowing for the direct detection of the thrombus in the portal vein and the absence of flow in case of complete PVT. Contrast-enhanced CT or MRI is recommended to (i) confirm the diagnosis of PVT, showing a hyperattenuating (hyperintense) thrombus on unenhanced CT (MRI) and a lack of enhancement of the lumen in the contrast-enhanced portal venous phase; enlargement of the portal vein can be observed when PVT is complete; (ii) determine the extension of the thrombus to splenic and mesenteric veins; (iii) identify potential local factors; and (iv) search for complications including signs of acute mesenteric ischaemia and intestinal necrosis.[77] Bowel wall thickening, mesenteric fat stranding, and ascites are common both in patients without acute mesenteric ischaemia and those with acute mesenteric ischaemia and intestinal necrosis.[76,78] By contrast, decreased bowel wall enhancement (especially of the mucosa) is more suggestive of intestinal necrosis.[76]

Chronic extrahepatic portal vein obstruction (EHPVO) in the absence of underlying liver disease refers to incomplete resolution of the portal vein obstruction 6 months after recent PVT or to portal cavernoma (Fig. 2). Portal cavernoma is a network of porto-portal collaterals that develop following portal vein obstruction. Obstruction leading to cavernoma is mainly related to thrombosis in adults and is less likely in children and young adults.[43] The main signs of EHPVO include gastroesophageal varices (80%), splenomegaly (70%), and thrombocytopenia (30%).[79] The diagnosis of EHPVO is based on an inability to visualise the portal vein on contrast-enhanced CT or MRI, which is usually associated with cavernoma enhancement after contrast injection.[80] A liver biopsy is needed when an underlying chronic liver disease (cirrhosis or porto-sinusoidal vascular liver disorder) is suspected based on abnormal liver morphology and/or increased liver stiffness measurement. Liver stiffness measurement <10 kPa can rule-out underlying cirrhosis in this setting.[81]

Management

Medical therapy

In patients with recent PVT, immediate initiation of anticoagulation is recommended because it has been associated with the prevention of thrombus extension and a reduction in the incidence of intestinal infarction to only 2%, compared with 30% in patients not receiving anticoagulants.[5,82] In a study on 67 patients with acute mesenteric ischaemia (arterial and venous), administration of oral antibiotics (gentamicin 80 mg/day + metronidazole 1.5 g/day) was associated with a decreased incidence of intestinal necrosis.[83]

Recanalization of the thrombosed veins is achieved in ~30% of patients treated with anticoagulation and takes place within the first 6 months of therapy.[5,84,85] Spontaneous recanalization is uncommon.[84] Factors associated with recanalization include the site of thrombosis (splenic or superior mesenteric veins having a higher rate of recanalization than the main portal vein) and early anticoagulation (<15 days after first symptoms).[5,84,86] By contrast, in patients with recent PVT, ascites, an occluded splenic vein, and underlying prothrombotic disorders have been associated with failure to recanalize the portal vein.[5] Accordingly, anticoagulants should be given for at least 6 months in patients with recent PVT.[43] In most studies, unfractionated heparin or LMWH were used initially, before being substituted for VKAs, with a target INR between 2 and 3.[5,35,86] Unfractionated heparin should be avoided because of the high risk (up to 20%) of heparin-induced thrombocytopenia, especially in patients with MPNs.[43,52] Although mostly derived from small retrospective unselected cohort studies, DOACs are now part of the therapeutic arsenal in patients with recent PVT. Despite the absence of direct comparison between LMWH or VKA and DOACs, the rates of PVT recanalization seem similar, without a higher risk of bleeding in patients receiving DOACs. Dedicated studies are still needed to assess the efficacy and safety of each DOAC in patients with PVT in the absence of underlying liver disease. The choice of anticoagulant therapy in PVT should be individualised, considering comorbidities and risk factors for PVT (Table 2).

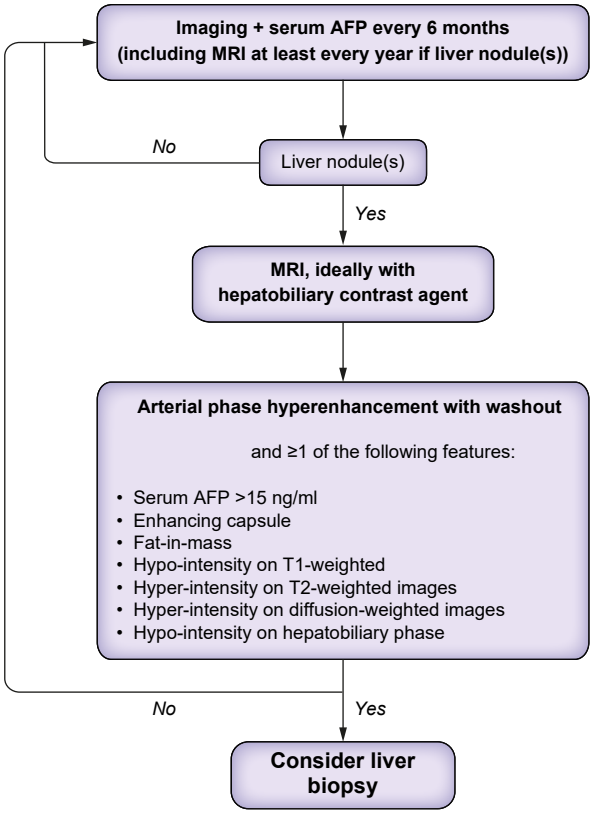

Fig. 1. Management of liver nodules in patients with Budd-Chiari syndrome. AFP, alpha-fetoprotein.

In patients with past PVT (*i.e.* who achieved recanalization after 6 months of anticoagulation) or in patients with chronic EHPVO, long-term anticoagulation is indicated in most cases since it decreases the incidence of recurrent thrombosis.[87,88] Recently, the Baveno VII consensus conference recommended adapting the dosage of anticoagulants according to the aetiologic work-up (grade B recommendation). In patients with a permanent and strong risk factor for thrombosis (MPN, PNH, Behcet's diseases, antiphospholipid syndrome, personal or first degree familial history of spontaneous venous thrombosis or a history of intestinal necrosis due to mesenteric ischaemia), full-dose long-term oral anticoagulation should be maintained.[42,43] VKAs targeting an INR between 2 and 3 have long been used in this situation.[43] Although solid data are still lacking, DOACs at therapeutic dosage (*e.g.*, rivaroxaban 20 mg once a day or apixaban 5 mg twice a day) appear an attractive alternative in patients without antiphospholipid syndrome.[57,87] In patients without underlying permanent and strong risk factors for thrombosis, the recent RIPORT randomised-controlled trial found that rivaroxaban at the dose of 15 mg per day decreased the incidence of recurrent thrombosis from 19/100 patient-years to 0/100 patient-years. Of note, in this trial, plasma D-dimer concentrations <500 ng/ml 1 month after interruption of anticoagulation were predictive of a low risk of recurrence.[88] Furthermore, recurrence of thrombosis was uncommon in patients with an isolated transient local factor for PVT. Therefore, in patients with no general risk factor for thrombosis and a transient local factor, anticoagulation might be discontinued, with D-dimer monitoring 1 month later to determine whether or not to resume anticoagulation[43] (Fig. 3A).

In patients with recent PVT or chronic EHPVO, endoscopy should be performed within the first months after diagnosis to screen for gastroesophageal varices. In patients with recent PVT, varices mainly develop during the first year of follow-up,[85] so endoscopy should be repeated 1 year after the diagnosis of PVT.[43] Non-invasive methods, including transient elastography, are not accurate to rule-out large varices.[81] In patients with chronic EHPVO, a study on 178 patients showed that the course of gastroesophageal varices is similar to that in patients with cirrhosis. Therefore, primary prophylaxis is usually based on non-selective beta-blockers or endoscopic band ligation, and secondary prophylaxis on the combination of both.[79] A study of 471 endoscopies showed that endoscopic band ligation is safe in patients with EHPVO treated with VKAs.[43,89] This suggests that oral anticoagulation can be maintained in patients undergoing scheduled endoscopic variceal band ligation.

Radiology

In patients with recent PVT, invasive strategies including transjugular or transhepatic thrombus aspiration, local fibrinolysis, and/or TIPS have been proposed in the first weeks after the PVT diagnosis in highly selected patients, namely those with PVT and

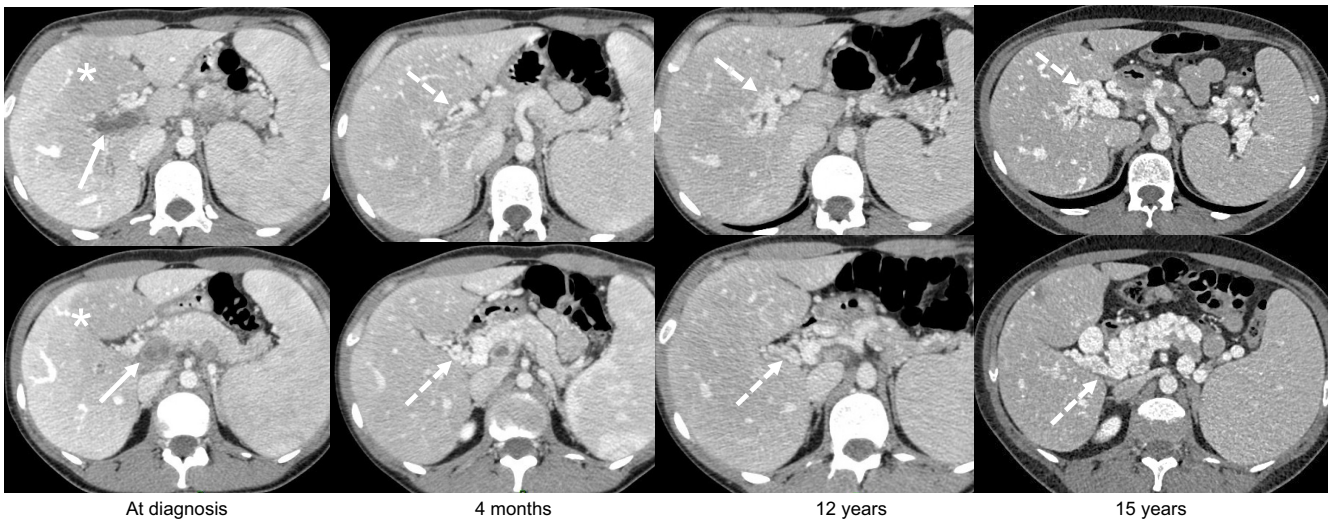

Fig. 2. Example of acute portal vein thrombosis with progressive development of a cavernous transformation. A female patient presented with abdominal pain. Contrast-enhanced CT (all portal venous phase, axial view) showed a complete occlusion of an enlarged portal trunk and intrahepatic portal branches by non-enhancing and hypoattenuating material (arrow) consistent with an acute portal vein thrombosis. Note the heterogeneous enhancement of the hepatic parenchyma with central hypoenhancement relative to the liver periphery (zonal perfusion, *). Over time, CT shows the progressive development of numerous tortuous veins in the hepatic pedicle and the hepatic hilum corresponding to a cavernous transformation of the portal vein (dashed arrows). Note the absence of recanalization of the portal veins and the progressive enlargement of the cavernoma, with progressive extension to the pancreas. No bile duct dilatation was noted.

extension to the superior mesenteric vein, particularly when features predictive of intestinal necrosis are present.[90,91] However, further studies are needed to clarify indications and patient outcomes.

In patients with chronic EHPVO, portal vein recanalization with or without TIPS can be considered in patients with portal hypertension-related bleeding not controlled with endoscopic treatment or in patients with symptomatic portal cavernoma cholangiopathy. Various approaches to shunt placement have been reported, including transjugular, transhepatic and transsplenic. This procedure is technically successful in more than 80% of cases when performed in expert centres if intrahepatic portal branches are patent.[92] The usefulness of long-term anticoagulation after portal vein recanalization is unknown. Maintaining anticoagulation seems reasonable, especially in patients with risk factors for thrombosis. The clinical outcome seems favourable. Recent data suggest successful portal vein recanalization is associated with increased muscle mass and decreased spleen volume.[92–95] However, these results are mainly based on small, retrospective, mostly single-centre, unselected cohort studies. Dedicated comparative studies are needed to evaluate the impact of portal vein recanalization on long-term outcome and to determine the best technical approach.

Surgery

In patients with acute mesenteric ischaemia and signs suggestive of intestinal necrosis, emergency surgery is indicated to assess bowel viability. Patients should be transferred to a referral centre to enable multidisciplinary management.[43] Shunt surgery to treat portal hypertension-related complications is increasingly being replaced by radiological portal vein recanalization.

Specific issues

Pregnancy

Pregnancy is not contraindicated in women with stable chronic EHPVO. The best information stems from three series of patients, two Indian and one European, including 104 pregnancies.[33,96–98] Anticoagulation was administered on a case-by-case basis. Rates of miscarriage and preterm birth were 14% and 14%, respectively. Foetal and maternal outcomes were favourable for most pregnancies. Only five episodes of variceal haemorrhage were reported, including three among patients without adequate prophylaxis for portal hypertension-related bleeding. This highlights the importance of upper gastrointestinal endoscopy before conception or during the second trimester of pregnancy in women not receiving beta-blockers (Table 2). Thrombotic events occurred in two patients.

Portal cavernoma cholangiopathy

"Portal cavernoma cholangiopathy" refers to abnormalities of the biliary tract in patients with chronic EHPVO.[99] These abnormalities are due to the pressure of dilated collaterals on the bile ducts or their lumen and ischaemic damage to the biliary tree.[100,101] Magnetic resonance cholangiography coupled with MR angiography is the reference technique for diagnosing portal cavernoma cholangiopathy.[100,102] MR cholangiography shows bile duct changes, including stenoses, upstream dilatation, and irregularities in the calibre of bile ducts; MR angiography shows cavernomatous veins in the vicinity of stenoses.[102,103] At MRI, bile duct changes are common (found in 80% of patients).[102–104] However, the clinical impact is much more limited than morphologic changes: moderate liver enzyme abnormalities are observed in 50% of patients;[103] severe biliary complications,

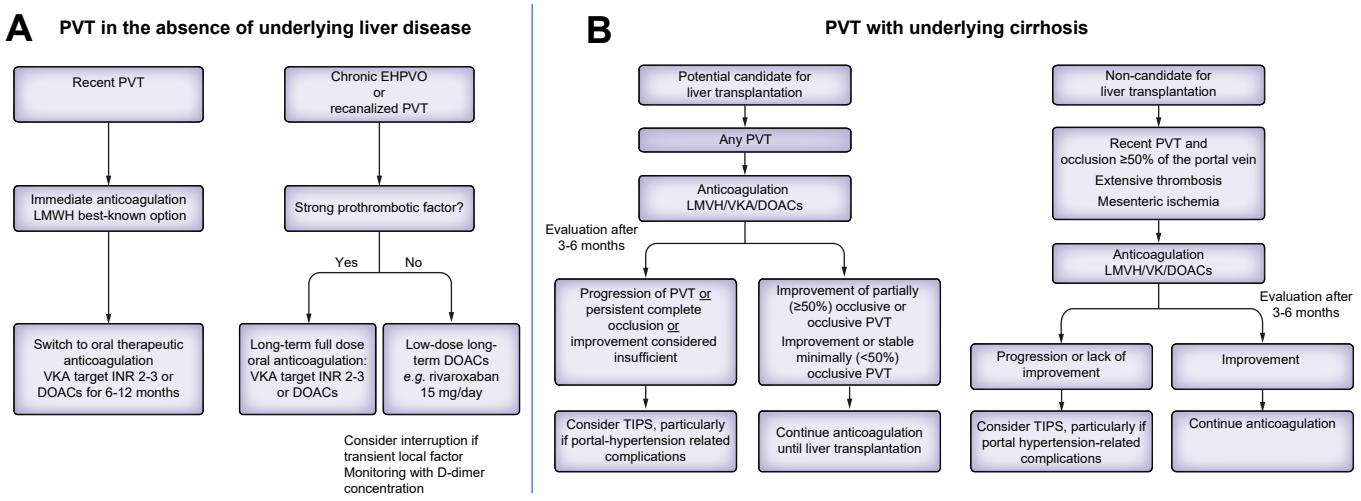

Fig. 3. Proposed algorithm for anticoagulant therapy in patients with portal vein thrombosis with and without cirrhosis. DOACs, direct-acting oral anticoagulants; EHPVO, extrahepatic portal vein obstruction; LMWH, low-molecular-weight heparin; PVT, portal vein thrombosis; TIPS, transjugular intrahepatic portosystemic shunt; VKAs, vitamin K antagonists.

including cholangitis, pancreatitis, jaundice, and pruritus, occur in ~10% of patients.[102–104] Such complications were described only in patients with grade III cholangiopathy (namely strictures with dilations), in whom the risk was 41%.[104]

Treatment of portal cavernoma cholangiopathy should be discussed on an individual basis at referral centres. Specific treatments of portal cavernoma cholangiopathy include endoscopic retrograde cholangiopancreatography and portal vein recanalization. These treatments should be considered only in patients with cholangitis, pancreatitis, jaundice, or pruritus. Endoscopic retrograde cholangiopancreatography enables bile stone extraction and temporary stenting of biliary strictures.[100] The risk of bleeding from bile duct varices should be kept in mind. Treatment with ursodeoxycholic acid following endoscopic therapy was associated with a reduction of symptoms in ~50% of patients.[102,104] Portal vein recanalization may also be helpful in this setting.[95] Bilio-enteric by-pass in the absence of portal decompression is not recommended because it is associated with high morbidity and mortality.[100]

Non-malignant portal vein thrombosis in patients with cirrhosis

Cirrhosis accounts for ~40% of unselected cases of PVT.[35] The prevalence of PVT increases in parallel with the severity of cirrhosis: 10% in patients with compensated cirrhosis, 17% in patients with decompensated cirrhosis, and up to 26% in liver transplant candidates.[105] Longitudinal studies reported an incidence of PVT ranging from 11% at 5 years in patients with compensated cirrhosis[106] to 24% per year in patients awaiting liver transplantation.[105,107]

Causes

In patients with cirrhosis and PVT, systematic screening for factor V Leiden and G20210A prothrombin gene mutations is not systematically recommended because their prevalence is low in this setting.[29,108,109] Features of metabolic syndrome, including higher body mass index,[106] obesity[110] and diabetes[110,111] have been associated with the occurrence of PVT, although the impact of these features on PVT development might be limited. Local risk factors, such as abdominal surgery, have also been reported.[112]

The main risk factors for PVT are features reflecting the severity of portal hypertension, including large oesophageal varices and low platelet count.[106,108,111,113] Low portal vein flow velocity (<15 cm/s) has also been reported in several large studies, although not systematically.[106,108,113] The link between non-selective beta-blockers and PVT occurrence remains debated.[108,114,115] The only study to include a time-dependent analysis of the association between beta-blockers and PVT occurrence did not find any association.[108]

Diagnosis

In patients with cirrhosis, PVT is usually found either in the absence of symptoms during HCC screening or following a decompensating event.[43,106] Although PVT is generally recognised on ultrasound, CT or MR angiography are recommended to assess the degree and extent of obstruction. In contrast to findings in patients without cirrhosis, non-occlusive PVT is the predominant form in patients with cirrhosis, accounting for around 70% of cases.[105] Recent recommendations concur regarding the need to provide information on the following characteristics as part of the description of PVT: time course (recent, *i.e.* <6 months, or chronic, *i.e.* ≥6 months), degree of occlusion (minimally occlusive, *i.e.* <50% of the lumen obstructed, partially occlusive, *i.e.* ≥50% of the lumen obstructed, or completely occlusive, *i.e.* no persistent lumen), and response to treatment or interval change (progression, stability or regression).[42,43] Patients with HCC are at risk of tumoral invasion of the portal vein but also at higher risk of non-tumoral PVT since HCC may tilt the haemostatic balance towards hypercoagulability.[116]

The presence of three or more features among serum alpha-fetoprotein concentrations >1,000 μg/L, venous expansion, thrombus enhancement at arterial phase, neovascularity, and PVT adjacent to HCC have a 100% sensitivity and 94% specificity

for the diagnosis of tumoral invasion of the portal vein.[117] In the absence of these specific features, fine needle ultrasound-guided biopsy of the thrombi may be safe and useful to obtain a definitive diagnosis.[118]

Natural history of PVT and impact on patient outcomes

Spontaneous regression or even recanalization of PVT may occur in ~40% of patients, mainly in those with non-occlusive PVT and compensated cirrhosis.[106,119,120] By contrast, the rate of spontaneous recanalization is very low in patients with occlusive PVT.[121] In patients with cirrhosis, with recent PVT and extension to the superior mesenteric vein, acute mesenteric ischaemia or intestinal necrosis can occur, though they are uncommon in this context.[122]

The link between PVT and decompensation of cirrhosis has been analysed in several studies,[123–125] including a large prospective study in over 1,200 patients with compensated cirrhosis: occurrence of PVT was not associated with subsequent decompensation of cirrhosis,[106] suggesting that PVT is a marker but not a direct cause of the progression of liver disease. By contrast, the impact of PVT in the context of liver transplantation is significant. Pre-transplantation PVT has been associated with increased short-term mortality and graft failure after transplantation in large databases.[126] However, in the latter studies, the link between the size and extent of PVT and post-transplant outcomes was not evaluated. The impact of PVT appears to depend on the possibility of restoring physiologic portal perfusion to the graft using anatomical (physiological) procedures. Good results are obtained when the superior mesenteric vein is patent. By contrast, an irremovable thrombus occluding the superior mesenteric vein requires left renal to portal vein anastomosis, or portocaval hemi-transposition. These interventions that do not relieve portal hypertension and do not restore graft perfusion with portal blood are associated with a high rate of failure or complications.[127] Thus, persistent complete extensive thrombosis may preclude liver transplantation.

Management

Medical therapy

In patients with cirrhosis and PVT who are potential candidates for liver transplantation – meaning those without a definitive contraindication to liver transplantation – the main objective of anticoagulation is to maintain or obtain a patent portal vein trunk to enable liver transplantation. The efficacy of anticoagulants in this setting has been evaluated in several cohort studies, mostly retrospective.[105] In a meta-analysis of eight studies involving 353 patients, PVT progression was observed in 9% of treated patients compared to 33% of untreated patients. Portal vein recanalization was achieved in 71% of treated patients compared to 42% of untreated patients.[119] A detailed analysis of the structure and composition of portal vein thrombi showed that portal vein obstruction consists of intimal fibrosis with an additional fibrin-rich thrombus in only one-third of cases, which may account for the unsystematic recanalization observed after anticoagulation[128] (Fig. 4). Likewise, factors associated with recanalization in patients receiving anticoagulants include recent PVT and a duration between PVT diagnosis and treatment initiation of <6 months.[129] Less severe liver disease and a non-occlusive PVT are also associated with a higher rate of recanalization.[129]

In patients with cirrhosis and PVT who are not candidates for liver transplantation, the beneficial effect of anticoagulation might go beyond its impact on PVT. A landmark prospective randomised-controlled trial in 70 patients with cirrhosis without PVT showed that treatment with 4,000 IU/day enoxaparin for 48 weeks effectively prevented PVT occurrence and, more importantly, decreased decompensation of cirrhosis and death.[130] In a large individual patient data meta-analysis of five studies, including 500 patients with cirrhosis and PVT, anticoagulation increased overall survival, and the beneficial effect was independent of portal vein recanalization.[131] Based on these data, the recent Baveno VII consensus conference recommended initiating anticoagulation (i) in all patients with cirrhosis and PVT who are potentially candidates for liver transplantation, independently of the degree of occlusion and extension and (ii) in patients with cirrhosis and recent (<6 months) completely or partially occlusive (>50%) thrombosis of the portal vein trunk even if not a candidate for liver transplantation.[43] Recanalization is usually achieved within 6 months.[132] Therefore, anticoagulants should be maintained until portal vein recanalization or for a minimum of 6 months.[43] After that, the decision to maintain anticoagulation depends on the response to therapy and the prospect of liver transplantation. Anticoagulation is generally maintained until liver transplantation, except if a TIPS is performed in potential liver transplant candidates. In other patients, the continuation of anticoagulation should be considered in patients without complete PVT based on regular evaluation and consideration of the benefits and risks of anticoagulation (Fig. 3B).

Bleeding events not related to portal hypertension occur in ~10% of patients with cirrhosis receiving anticoagulation.[119] This rate does not seem to be higher than that observed in patients with cirrhosis and PVT not receiving anticoagulation nor in patients without cirrhosis receiving anticoagulation.[119,133] In patients with cirrhosis treated with VKAs, platelet count <50x 10^9/L was predictive of bleeding.[132] Data obtained in the setting of atrial fibrillation suggest that VKAs are associated with a higher risk of major bleeding events than DOACs in patients with cirrhosis.[133] Bleeding events related to portal hypertension are actually less frequent in patients receiving anticoagulants, possibly due to the beneficial effect of anticoagulation on intrahepatic vascular resistance.[119,133,134] Therefore, administering anticoagulation does not imply a more frequent screening for gastroesophageal varices nor more intense prophylaxis for portal hypertension-related complications.[43]

The best type of anticoagulation in patients with cirrhosis and PVT remains to be defined. LMWH is the best-known option in this setting. LMWH should be used cautiously in patients with moderate kidney dysfunction (glomerular filtration rate [GFR] <30 ml/min) and is contraindicated in patients with a GFR <15 ml/min. Although data are scarce, especially on safety, fondaparinux might be an option in patients with PVT and cirrhosis.[135] An alternative option consists of oral VKAs targeting an INR between 2 and 3. However, the accuracy of INR for VKA monitoring is uncertain in patients with liver insufficiency. Experience with DOACs in patients with cirrhosis is growing. The main advantages of DOACs over VKAs are that they are given at fixed doses without laboratory monitoring. The liver disease could influence several aspects of DOAC pharmacokinetics, including systemic elimination, plasma protein binding,

cytochrome P450-mediated metabolism, and biliary excretion.[136] The Child-Pugh score is used to guide dosing and the use of DOACs. In the context of PVT treatment, all DOACs can be used in patients with Child-Pugh A cirrhosis; DOACs can be used with caution and/or adjusted doses in patients with Child-Pugh class B cirrhosis; DOACs are usually not recommended in patients with Child-Pugh class C cirrhosis or coagulopathy.[43,137,138] Renal insufficiency (GFR <30 ml/min), potential drug-drug interactions, and previous gastrointestinal bleeding should be evaluated before introducing DOACs[139] (Table 2). Although limited, available data suggest that the efficacy of DOACs in patients with cirrhosis and PVT is at least equivalent to that of LMWH or VKAs in achieving portal vein recanalization.[54,140–142]

Transjugular intrahepatic portosystemic shunt

PVT is no longer considered a contraindication to TIPS, which has been reported to be feasible in 73-100% of patients with PVT.[124,143–145] In patients with either completely occlusive PVT or cavernoma, TIPS might still be feasible through a transjugular or trans-splenic approach, although the technical success rate is lower.[143,146] Indeed, factors associated with technical failure of TIPS insertion are cavernomatous transformation, inability to identify intrahepatic portal vein branches, and extension to the superior mesenteric vein.[105] In a recent meta-analysis collating data on 367 patients with cirrhosis and PVT treated with TIPS, the 12-month recanalization rate was 84%[145] (Fig. 5). Importantly, these procedures were performed in expert centres, which may explain these promising results. After successful TIPS insertion, a randomised-controlled trial did not find any advantage of maintaining anticoagulation; recanalization was achieved in most patients even without anticoagulation.[147] Most patients included in the latter study had non-occlusive PVT, and only 3 out 64 had cavernoma. This suggests that long-term anticoagulation is not necessary after successful TIPS placement in patients with non-occlusive PVT. Further studies are needed to make broad recommendations against long-term anticoagulation after TIPS insertion, irrespective of the type of PVT. Severe procedural complications occur in 10% of patients with cirrhosis and PVT following TIPS placement.[145] Catheter-directed thrombolysis with or without thrombus aspiration have been associated with higher rates of bleeding complications. The rate of hepatic encephalopathy is similar to that observed in patients without PVT at around 25%.[145] Based on these data, beyond the usual indications for TIPS (refractory ascites and recurrent variceal bleeding), TIPS can be considered as a second-line option for the treatment of PVT, especially in case of significant concomitant complications of portal hypertension or after lack of improvement (*i.e.* persistent complete occlusion or progression) after anticoagulation[43] (Fig. 3B). In liver transplant candidates with complete or extensive PVT, TIPS (transjugular or trans-splenic) may improve transplantation feasibility if it leads to portal vein recanalization.[146] In patients with complete PVT, reno-portal anastomosis during liver

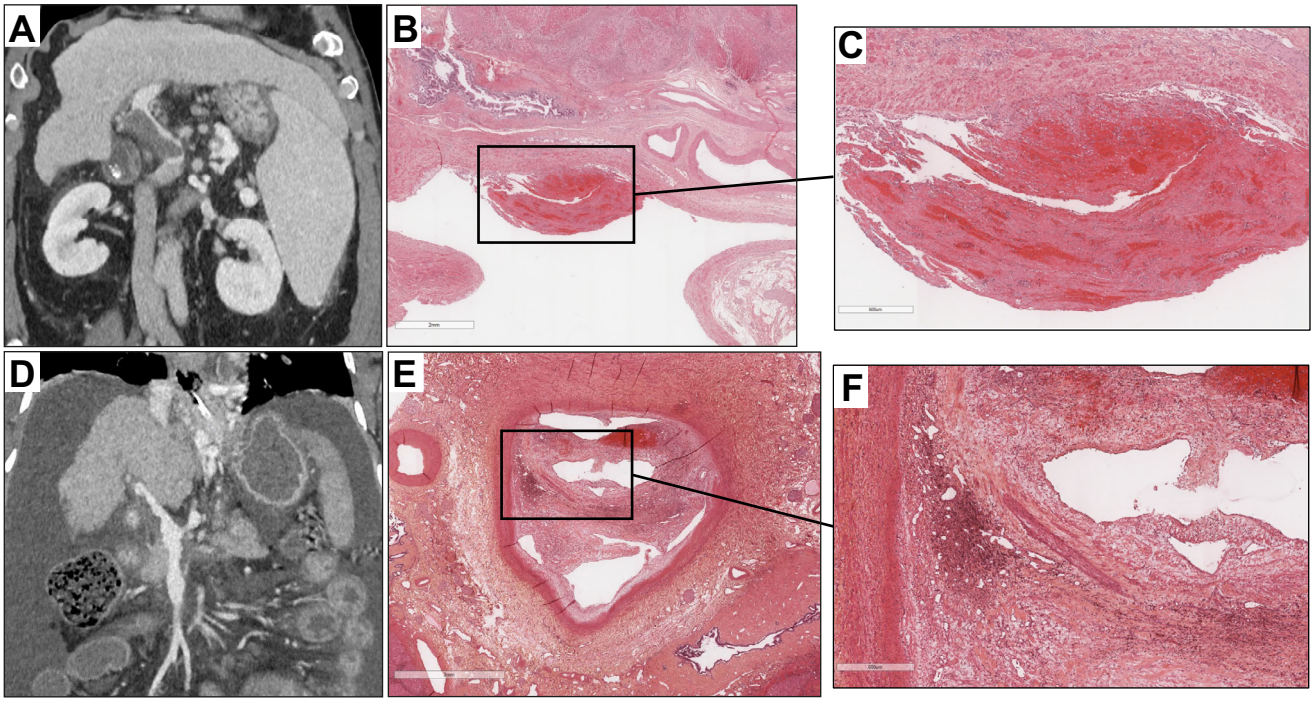

Fig. 4. Correlation between radiological findings and pathology. (A) Recent portal vein thrombosis in a 59-year-old man with viral cirrhosis. Contrast-enhanced CT (coronal view, portal venous phase) shows partially occlusive non-enhancing material corresponding to the clot in the lumen of the portal trunk (arrows). The downstream venous branches are patent. (B) HES staining. Low magnification. Recent portal vein partial thrombosis. (C) HES staining. Higher magnification. Recent portal vein thrombi composed of fibrinous deposits associated with red blood cells. (D) Chronic portal vein thrombosis in a 52-year-old man with alcohol-related cirrhosis. Contrast-enhanced CT (coronal view, portal venous phase) shows minimally occlusive non-enhancing material corresponding to the incorporation of the clot in the wall of the portal trunk and the superior mesenteric vein (arrows). (E) HES staining. Low magnification. Non-malignant chronic portal vein thrombi. (F) HES staining. Higher magnification. Chronic portal vein thrombi with fibro-oedematous intimal thickening with numerous siderophagous and neovessels partially repermeabilizing the lumen.

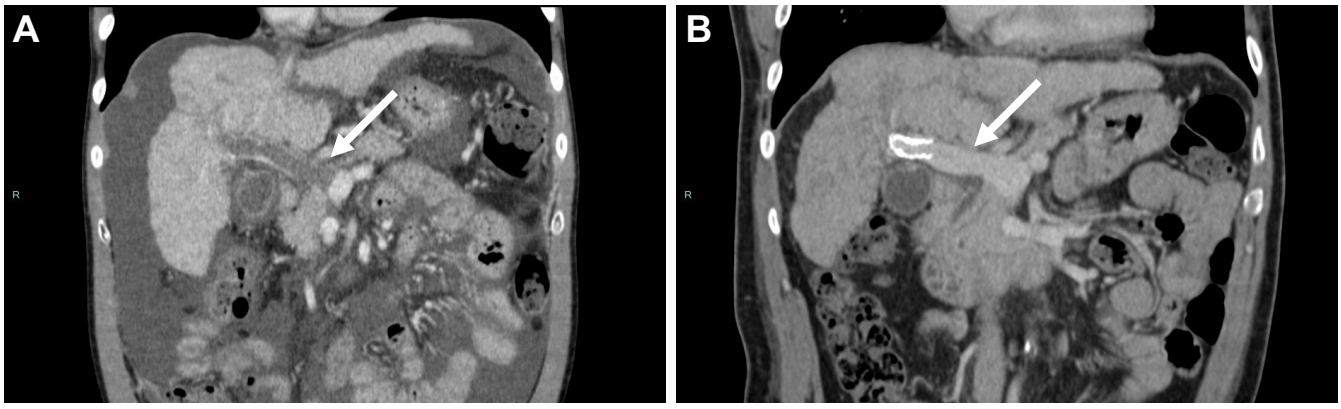

Fig. 5. CT scan showing a patient with decompensated cirrhosis and occlusive portal vein thrombosis in whom portal vein recanalization was achieved after TIPS insertion. Patient with (A) occlusive portal vein thrombosis (arrow) despite anticoagulation for 3 months, in whom (B) portal vein recanalization was achieved after TIPS insertion. TIPS, transjugular intrahepatic portosystemic shunt.

transplantation is another option, since it has been reported to be feasible in 89% of patients, and is associated with a 1-year survival rate of 87%.[148]

Conclusion

In patients without underlying cirrhosis, medical management of SVT is based on a complete aetiological work-up, specific aetiological treatment, and generally long-term anticoagulation. Interventional radiology, performed in expert centres, is the second-line therapy for both BCS and chronic EHPVO. In patients with cirrhosis and PVT, recent guidelines have extended the indications for anticoagulation, even to some patients who are not candidates for liver transplantation. Beyond its usual indications in cirrhosis (refractory ascites or recurrent variceal bleeding), TIPS is a second-line therapy for PVT, especially in patients with concomitant complications of portal hypertension. Although the use of DOACs is growing, further studies are needed to clarify the best option, considering both patient and disease heterogeneity.

Abbreviations

BCS, Budd-Chiari syndrome; CALR, calreticulin; DOACs, direct-acting oral anticoagulants; EHPVO, extrahepatic portal vein obstruction; GFR, glomerular filtration rate; JAK2, Janus kinase 2; LMWH, low-molecular-weight heparin; MPN, myeloproliferative neoplasm; MTHFR, methylenetetrahydrofolate reductase; PNH, paroxysmal nocturnal hemoglobinuria; PVT, portal vein thrombosis; SVT, splanchnic vein thrombosis; TIPS, transjugular intrahepatic portosystemic shunt; VKAs, vitamin K antagonists.

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Conflicts of interest

The authors declare no conflicts of interest that pertain to this work.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

Concept and writing of the original draft: LE, AP, PER. Critical revision: MR, DV, AP, VP, LDA.

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Supplementary data

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References

Author names in bold designate shared co-first authorship

[1] Jones DEJ, Sturm E, Lohse AW. Access to care in rare liver diseases: new challenges and new opportunities. J Hepatol 2018;68:577–585. https://doi.org/10.1016/j.jhep.2017.11.004.

[2] De Gottardi A, Sempoux C, Berzigotti A. Porto-sinusoidal vascular disorder. J Hepatol 2022;77:1124–1135. https://doi.org/10.1016/j.jhep.2022.05.033.

[3] Denninger MH, Chaït Y, Casadevall N, Hillaire S, Guillin MC, Bezeaud A, et al. Cause of portal or hepatic venous thrombosis in adults: the role of multiple concurrent factors. Hepatology 2000;31:587–591. https://doi.org/10.1002/hep.510310307.

[4] Darwish Murad S, Plessier A, Hernandez-Guerra M, Fabris F, Eapen CE, Bahr MJ, et al. Etiology, management, and outcome of the Budd-Chiari syndrome. Ann Intern Med 2009;151:167–175.

[5] Plessier A, Darwish-Murad S, Hernandez-Guerra M, Consigny Y, Fabris F, Trebicka J, et al. Acute portal vein thrombosis unrelated to cirrhosis: a prospective multicenter follow-up study. Hepatology 2010;51:210–218. https://doi.org/10.1002/hep.23259.

[6] Poisson J, Plessier A, Kiladjian J-J, Turon F, Cassinat B, Andreoli A, et al. Selective testing for calreticulin gene mutations in patients with splanchnic vein thrombosis: a prospective cohort study. J Hepatol 2017;67:501–507. https://doi.org/10.1016/j.jhep.2017.04.021.

[7] Bureau C, Laurent J, Robic MA, Christol C, Guillaume M, Ruidavets JB, et al. Central obesity is associated with non-cirrhotic portal vein thrombosis. J Hepatol 2016;64:427–432. https://doi.org/10.1016/j.jhep.2015.08.024.

[8] Chagneau-Derrode C, Roy L, Guilhot J, Goria O, Ollivier-Hourmand I, Bureau C, et al. Impact of cytoreductive therapy on the outcome of patients with myeloproliferative neoplasms and hepato-splanchnic vein thrombosis. Hepatology 2013;58:847A–898A. https://doi.org/10.1002/hep.26866.

[9] Desbois AC, Rautou PE, Biard L, Belmatoug N, Wechsler B, Resche-Rigon M, et al. Behcet's disease in Budd-Chiari syndrome. Orphanet J Rare Dis 2014;9:104. https://doi.org/10.1186/s13023-014-0153-1.

[10] Magaz M, Alvarez-Larrán A, Colomer D, López-Guerra M, García-Criado MÁ, Mezzano G, et al. Next-generation sequencing in the diagnosis of non-cirrhotic splanchnic vein thrombosis. J Hepatol 2021;74:89–95. https://doi.org/10.1016/j.jhep.2020.06.045.

[11] Plessier A, Esposito-Farèse M, Baiges A, Shukla A, Pagan JCG, De Raucourt E, et al. Paroxysmal nocturnal hemoglobinuria and vascular liver disease: eculizumab therapy decreases mortality and thrombotic complications. Am J Hematol 2022. https://doi.org/10.1002/ajh.26474.

[12] Smalberg JH, Arends LR, Valla DC, Kiladjian J-J, Janssen HLA, Leebeek FWG. Myeloproliferative neoplasms in Budd-Chiari syndrome and portal vein thrombosis: a meta-analysis. Blood 2012;120:4921–4928. https://doi.org/10.1182/blood-2011-09-376517.

[13] Turon F, Cervantes F, Colomer D, Baiges A, Hernández-Gea V, Garcia-Pagán JC. Role of calreticulin mutations in the aetiological diagnosis of splanchnic vein thrombosis. J Hepatol 2015;62:72–74. https://doi.org/10.1016/j.jhep.2014.08.032.

[14] Plompen EPC, Valk PJM, Chu I, Darwish Murad S, Plessier A, Turon F, et al. Somatic calreticulin mutations in patients with Budd-Chiari syndrome and portal vein thrombosis. Haematologica 2015. https://doi.org/10.3324/haematol.2014.120857.

[15] Qi X, Han G, Guo X, De Stefano V, Xu K, Lu Z, et al. Review article: the aetiology of primary Budd-Chiari syndrome - differences between the West and China. Aliment Pharmacol Ther 2016;44:1152–1167. https://doi.org/10.1111/apt.13815.

[16] Fan J, Wang Q, Luo B, Chen H, Wang Z, Niu J, et al. Prevalence of prothrombotic factors in patients with Budd-Chiari syndrome or non-cirrhotic nonmalignant portal vein thrombosis: a hospital-based observational study. J Gastroenterol Hepatol 2020;35:1215–1222. https://doi.org/10.1111/jgh.14925.

[17] Debureaux P-E, Cassinat B, Soret-Dulphy J, Mora B, Verger E, Maslah N, et al. Molecular profiling and risk classification of patients with myeloproliferative neoplasms and splanchnic vein thromboses. Blood Adv 2020;4:3708–3715. https://doi.org/10.1182/bloodadvances.2020002414.

[18] Kiladjian J-J, Debureaux P-E, Plessier A, Soret-Dulphy J, Valla D, Cassinat B, et al. Benefits of molecular profiling with next-generation sequencing for the diagnosis and prognosis of myeloproliferative neoplasms in splanchnic vein thrombosis. J Hepatol 2021;74:251–252. https://doi.org/10.1016/j.jhep.2020.07.043.

[19] **Chait Y**, **Condat B**, Cazals-Hatem D, Rufat P, Atmani S, Chaoui D, et al. Relevance of the criteria commonly used to diagnose myeloproliferative disorder in patients with splanchnic vein thrombosis. Br J Haematol 2005;129:553–560. https://doi.org/10.1111/j.1365-2141.2005.05490.x.

[20] Levine JS, Branch DW, Rauch J. The antiphospholipid syndrome. New Engl J Med 2002;346:752–763. https://doi.org/10.1056/NEJMra002974.

[21] Qi X, De Stefano V, Su C, Bai M, Guo X, Fan D. Associations of antiphospholipid antibodies with splanchnic vein thrombosis: a systematic review with meta-analysis. Medicine (Baltimore) 2015;94:e496. https://doi.org/10.1097/MD.0000000000000496.

[22] Sakr MA, Reda MA, Ebada HE, Abdelmoaty AS, Hefny ZM, Ibrahim ZH, et al. Characteristics and outcome of primary Budd-Chiari syndrome due to Behçet's syndrome. Clin Res Hepatol Gastroenterol 2020;44:503–512. https://doi.org/10.1016/j.clinre.2019.10.006.

[23] Hoekstra J, Leebeek FWG, Plessier A, Raffa S, Darwish Murad S, Heller J, et al. Paroxysmal nocturnal hemoglobinuria in Budd-Chiari syndrome: findings from a cohort study. J Hepatol 2009;51:696–706. https://doi.org/10.1016/j.jhep.2009.06.019.

[24] Afredj N, Guessab N, Nani A, Faraoun SA, Ouled Cheikh I, Kerbouche R, et al. Aetiological factors of Budd-Chiari syndrome in Algeria. World J Hepatol 2015;7:903–909. https://doi.org/10.4254/wjh.v7.i6.903.

[25] De Broucker C, Plessier A, Ollivier-Hourmand I, Dharancy S, Bureau C, Cervoni J-P, et al. Multicenter study on recent portal venous system thrombosis associated with cytomegalovirus disease. J Hepatol 2022;76:115–122. https://doi.org/10.1016/j.jhep.2021.09.011.

[26] Buso G, Becchetti C, Berzigotti A. Acute splanchnic vein thrombosis in patients with COVID-19: a systematic review. Dig Liver Dis 2021;53:937–949. https://doi.org/10.1016/j.dld.2021.05.021.

[27] Hippisley-Cox J, Patone M, Mei XW, Saatci D, Dixon S, Khunti K, et al. Risk of thrombocytopenia and thromboembolism after covid-19 vaccination and SARS-CoV-2 positive testing: self-controlled case series study. BMJ 2021;374:n1931. https://doi.org/10.1136/bmj.n1931.

[28] Baiges A, Cerda E, Amicone C, Téllez L, Alvarado-Tapias E, Puente A, et al. Impact of SARS-CoV-2 pandemic on vascular liver diseases. Clin Gastroenterol Hepatol 2022;20:1525–1533.e5. https://doi.org/10.1016/j.cgh.2021.12.032.

[29] Qi X, Ren W, De Stefano V, Fan D. Associations of coagulation factor V Leiden and prothrombin G20210A mutations with Budd-Chiari syndrome and portal vein thrombosis: a systematic review and meta-analysis. Clin Gastroenterol Hepatol 2014;12:1801–1812.e7. https://doi.org/10.1016/j.cgh.2014.04.026.

[30] Fisher NC, Wilde JT, Roper J, Elias E. Deficiency of natural anticoagulant proteins C, S, and antithrombin in portal vein thrombosis: a secondary phenomenon? Gut 2000;46:534–539. https://doi.org/10.1136/gut.46.4.534.

[31] **Baiges A**, **de la Morena-Barrio ME**, Turon F, Miñano A, Alberto Ferrusquía J, Magaz M, et al. Congenital antithrombin deficiency in patients with splanchnic vein thrombosis. Liver Int 2020;40:1168–1177. https://doi.org/10.1111/liv.14342.

[32] Qi X, Yang Z, De Stefano V, Fan D. Methylenetetrahydrofolate reductase C677T gene mutation and hyperhomocysteinemia in Budd-Chiari syndrome and portal vein thrombosis: a systematic review and meta-analysis of observational studies. Hepatol Res 2014;44:E480–E498. https://doi.org/10.1111/hepr.12348.

[33] Bissonnette J, Durand F, de Raucourt E, Ceccaldi P-F, Plessier A, Valla D, et al. Pregnancy and vascular liver disease. J Clin Exp Hepatol 2015;5:41–50. https://doi.org/10.1016/j.jceh.2014.12.007.

[34] Janssen HL, Meinardi JR, Vleggaar FP, van Uum SH, Haagsma EB, van Der Meer FJ, et al. Factor V Leiden mutation, prothrombin gene mutation, and deficiencies in coagulation inhibitors associated with Budd-Chiari syndrome and portal vein thrombosis: results of a case-control study. Blood 2000;96:2364–2368.

[35] Rajani R, Björnsson E, Bergquist A, Danielsson A, Gustavsson A, Grip O, et al. The epidemiology and clinical features of portal vein thrombosis: a multicentre study. Aliment Pharmacol Ther 2010;32:1154–1162. https://doi.org/10.1111/j.1365-2036.2010.04454.x.

[36] Soret J, Debray D, de Fontbrune FS, Kiladjian J-J, Saadoun D, de Latour RP, et al. Risk factors for vascular liver diseases: vascular liver diseases: position papers from the francophone network for vascular liver diseases, the French Association for the Study of the Liver (AFEF), and ERN-rare liver. Clin Res Hepatol Gastroenterol 2020;44:410–419. https://doi.org/10.1016/j.clinre.2020.03.010.

[37] Rebours V, Boudaoud L, Vullierme M-P, Vidaud D, Condat B, Hentic O, et al. Extrahepatic portal venous system thrombosis in recurrent acute and chronic alcoholic pancreatitis is caused by local inflammation and not thrombophilia. Am J Gastroenterol 2012;107:1579–1585. https://doi.org/10.1038/ajg.2012.231.

[38] Van Wettere M, Bruno O, Rautou P-E, Vilgrain V, Ronot M. Diagnosis of Budd-Chiari syndrome. Abdom Radiol (NY) 2018;43:1896–1907. https://doi.org/10.1007/s00261-017-1447-2.

[39] Valla D-C. Budd-Chiari syndrome/hepatic venous outflow tract obstruction. Hepatol Int 2018;12:168–180. https://doi.org/10.1007/s12072-017-9810-5.

[40] Ollivier-Hourmand I, Allaire M, Goutte N, Morello R, Chagneau-Derrode C, Goria O, et al. The epidemiology of Budd-Chiari syndrome in France. Dig Liver Dis 2018;50:931–937. https://doi.org/10.1016/j.dld.2018.04.004.

[41] Plessier A, Sibert A, Consigny Y, Hakime A, Zappa M, Denninger M-H, et al. Aiming at minimal invasiveness as a therapeutic strategy for Budd-Chiari syndrome. Hepatology 2006;44:1308–1316. https://doi.org/10.1002/hep.21354.

[42] Northup PG, Garcia-Pagan JC, Garcia-Tsao G, Intagliata NM, Superina RA, Roberts LN, et al. Vascular liver disorders, portal vein thrombosis, and procedural bleeding in patients with liver disease: 2020 practice guidance by the American association for the study of liver diseases. Hepatology 2021;73:366–413. https://doi.org/10.1002/hep.31646.

[43] de Franchis R, Bosch J, Garcia-Tsao G, Reiberger T, Ripoll C, Abraldes JG, et al. Baveno VII - renewing consensus in portal hypertension. J Hepatol 2021:S0168827821022996. https://doi.org/10.1016/j.jhep.2021.12.022.

[44] Eapen CE, Velissaris D, Heydtmann M, Gunson B, Olliff S, Elias E. Favourable medium term outcome following hepatic vein recanalisation and/or transjugular intrahepatic portosystemic shunt for Budd Chiari syndrome. Gut 2006;55:878–884. https://doi.org/10.1136/gut.2005.071423.
[45] Seijo S, Plessier A, Hoekstra J, Dell'era A, Mandair D, Rifai K, et al. Good long-term outcome of Budd-Chiari syndrome with a step-wise management. Hepatology 2013;57:1962–1968. https://doi.org/10.1002/hep.26306.
[46] Tripathi D, Macnicholas R, Kothari C, Sunderraj L, Al-Hilou H, Rangarajan B, et al. Good clinical outcomes following transjugular intrahepatic portosystemic stent-shunts in Budd-Chiari syndrome. Aliment Pharmacol Ther 2014;39:864–872. https://doi.org/10.1111/apt.12668.
[47] Rautou P-E, Moucari R, Escolano S, Cazals-Hatem D, Denié C, Chagneau-Derrode C, et al. Prognostic indices for Budd-Chiari syndrome: valid for clinical studies but insufficient for individual management. Am J Gastroenterol 2009;104:1140–1146. https://doi.org/10.1038/ajg.2009.63.
[48] Garcia-Pagán JC, Heydtmann M, Raffa S, Plessier A, Murad S, Fabris F, et al. TIPS for Budd-Chiari syndrome: long-term results and prognostics factors in 124 patients. Gastroenterology 2008;135:808–815. https://doi.org/10.1053/j.gastro.2008.05.051.
[49] EASL Clinical Practice Guidelines. Vascular diseases of the liver. J Hepatol 2016;64:179–202. https://doi.org/10.1016/j.jhep.2015.07.040.
[50] Zeitoun G, Escolano S, Hadengue A, Azar N, El Younsi M, Mallet A, et al. Outcome of Budd-Chiari syndrome: a multivariate analysis of factors related to survival including surgical portosystemic shunting. Hepatology 1999;30:84–89. https://doi.org/10.1002/hep.510300125.
[51] Al-Jafar HA, AlDallal SM, Askar HA, Aljeraiwi AM, Al-Alansari A. Long standing eculizumab treatment without anticoagulant therapy in high-risk thrombogenic paroxysmal nocturnal hemoglobinuria. Hematol Rep 2015;7:5927. https://doi.org/10.4081/hr.2015.5927.
[52] Randi ML, Tezza F, Scapin M, Duner E, Scarparo P, Scandellari R, et al. Heparin-induced thrombocytopenia in patients with Philadelphia-negative myeloproliferative disorders and unusual splanchnic or cerebral vein thrombosis. Acta Haematol 2010;123:140–145. https://doi.org/10.1159/000280466.
[53] Zaman S, Wiebe S, Bernal W, Wendon J, Czuprynska J, Auzinger G. Increased prevalence of heparin-induced thrombocytopenia in patients with Budd-Chiari syndrome: a retrospective analysis. Eur J Gastroenterol Hepatol 2016;28:967–971. https://doi.org/10.1097/MEG.0000000000000632.
[54] De Gottardi A, Trebicka J, Klinger C, Plessier A, Seijo S, Terziroli B, et al. Antithrombotic treatment with direct-acting oral anticoagulants (DOACs) in patients with splanchnic vein thrombosis and cirrhosis. Liver Int 2016. https://doi.org/10.1111/liv.13285.
[55] Semmler G, Lindorfer A, Schaefer B, Bartl S, Hametner-Schreil S, Gensluckner S, et al. Outcome of Budd-Chiari syndrome (BCS) patients treated with direct oral anticoagulants (DOACs) - an Austrian multicenter study. Clin Gastroenterol Hepatol 2022;S1542–3565(22):449. https://doi.org/10.1016/j.cgh.2022.04.024. -9.
[56] Sharma S, Kumar R, Rout G, Gamanagatti SR, Shalimar Null. Dabigatran as an oral anticoagulant in patients with Budd-Chiari syndrome post-percutaneous endovascular intervention. J Gastroenterol Hepatol 2020;35:654–662. https://doi.org/10.1111/jgh.14843.
[57] Dufrost V, Wahl D, Zuily S. Direct oral anticoagulants in antiphospholipid syndrome: meta-analysis of randomized controlled trials. Autoimmun Rev 2021;20:102711. https://doi.org/10.1016/j.autrev.2020.102711.
[58] Rautou P-E, Douarin L, Denninger M-H, Escolano S, Lebrec D, Moreau R, et al. Bleeding in patients with Budd–Chiari syndrome. J Hepatol 2011;54:56–63. https://doi.org/10.1016/j.jhep.2010.06.019.
[59] Mukund A, Sarin SK. Budd–Chiari syndrome: a focussed and collaborative approach. Hepatol Int 2018;12:483–486. https://doi.org/10.1007/s12072-018-9900-z.
[60] Wang Q, Li K, He C, Yuan X, Luo B, Qi X, et al. Angioplasty with versus without routine stent placement for Budd-Chiari syndrome: a randomised controlled trial. Lancet Gastroenterol Hepatol 2019;4:686–697. https://doi.org/10.1016/S2468-1253(19)30177-3.
[61] Hayek G, Ronot M, Plessier A, Sibert A, Abdel-Rehim M, Zappa M, et al. Long-term outcome and analysis of dysfunction of transjugular intrahepatic portosystemic shunt placement in chronic primary Budd-Chiari syndrome. Radiology 2017;283:280–292. https://doi.org/10.1148/radiol.2016152641.
[62] Langlet P, Valla D. Is surgical portosystemic shunt the treatment of choice in Budd-Chiari syndrome? Acta Gastroenterol Belg 2002;65:155–160.
[63] Bachet J-B, Condat B, Hagège H, Plessier A, Consigny Y, Belghiti J, et al. Long-term portosystemic shunt patency as a determinant of outcome in Budd-Chiari syndrome. J Hepatol 2007;46:60–68. https://doi.org/10.1016/j.jhep.2006.08.016.
[64] Segev DL, Nguyen GC, Locke JE, Simpkins CE, Montgomery RA, Maley WR, et al. Twenty years of liver transplantation for Budd-Chiari syndrome: a national registry analysis. Liver Transplant 2007;13:1285–1294. https://doi.org/10.1002/lt.21220.
[65] Rautou P-E, Angermayr B, Garcia-Pagan J-C, Moucari R, Peck-Radosavljevic M, Raffa S, et al. Pregnancy in women with known and treated Budd-Chiari syndrome: maternal and fetal outcomes. J Hepatol 2009;51:47–54. https://doi.org/10.1016/j.jhep.2009.02.028.
[66] Khan F, Rowe I, Martin B, Knox E, Johnston T, Elliot C, et al. Outcomes of pregnancy in patients with known Budd-Chiari syndrome. World J Hepatol 2017;9:945–952. https://doi.org/10.4254/wjh.v9.i21.945.
[67] Shukla A, Sadalage A, Gupta D, Gupte A, Mahapatra A, Mazumder D, et al. Pregnancy outcomes in women with Budd Chiari Syndrome before onset of symptoms and after treatment. Liver Int 2018;38:754–759. https://doi.org/10.1111/liv.13552.
[68] Bates SM, Greer IA, Middeldorp S, Veenstra DL, Prabulos A-M, Vandvik PO, et al. VTE, thrombophilia, antithrombotic therapy, and pregnancy: antithrombotic therapy and prevention of thrombosis, 9th ed: American college of chest physicians evidence-based clinical practice guidelines. Chest 2012;141:e691S–e736S. https://doi.org/10.1378/chest.11-2300.
[69] **Moucari R**, **Rautou P-E**, Cazals-Hatem D, Geara A, Bureau C, Consigny Y, et al. Hepatocellular carcinoma in Budd-Chiari syndrome: characteristics and risk factors. Gut 2008;57:828–835. https://doi.org/10.1136/gut.2007.139477.
[70] Gwon D, Ko G-Y, Yoon H-K, Sung K-B, Kim JH, Lee SS, et al. Hepatocellular carcinoma associated with membranous obstruction of the inferior vena cava: incidence, characteristics, and risk factors and clinical efficacy of TACE. Radiology 2010;254:617–626. https://doi.org/10.1148/radiol.09090738.
[71] Sempoux C, Balabaud C, Paradis V, Bioulac-Sage P. Hepatocellular nodules in vascular liver diseases. Virchows Arch 2018;473:33–44. https://doi.org/10.1007/s00428-018-2373-6.
[72] Vilgrain V, Paradis V, Van Wettere M, Valla D, Ronot M, Rautou P-E. Benign and malignant hepatocellular lesions in patients with vascular liver diseases. Abdom Radiol (NY) 2018;43:1968–1977. https://doi.org/10.1007/s00261-018-1502-7.
[73] Van Wettere M, Purcell Y, Bruno O, Payancé A, Plessier A, Rautou P-E, et al. Low specificity of washout to diagnose hepatocellular carcinoma in nodules showing arterial hyperenhancement in patients with Budd-Chiari syndrome. J Hepatol 2019;70:1123–1132. https://doi.org/10.1016/j.jhep.2019.01.009.
[74] Paul SB, null Shalimar, Sreenivas V, Gamanagatti SR, Sharma H, Dhamija E, et al. Incidence and risk factors of hepatocellular carcinoma in patients with hepatic venous outflow tract obstruction. Aliment Pharmacol Ther 2015;41:961–971. https://doi.org/10.1111/apt.13173.
[75] Van Wettere M, Paulatto L, Raynaud L, Bruno O, Payancé A, Plessier A, et al. Hepatobiliary MR contrast agents are useful to diagnose hepatocellular carcinoma in patients with Budd-Chiari syndrome. JHEP Rep 2020;2:100097. https://doi.org/10.1016/j.jhepr.2020.100097.
[76] Nuzzo A, Maggiori L, Ronot M, Becq A, Plessier A, Gault N, et al. Predictive factors of intestinal necrosis in acute mesenteric ischemia: prospective study from an intestinal stroke center. Am J Gastroenterol 2017;112:597–605. https://doi.org/10.1038/ajg.2017.38.
[77] Berzigotti A, García-Criado Á, Darnell A, García-Pagán J-C. Imaging in clinical decision-making for portal vein thrombosis. Nat Rev Gastroenterol Hepatol 2014;11:308–316. https://doi.org/10.1038/nrgastro.2013.258.
[78] Elkrief L, Corcos O, Bruno O, Larroque B, Rautou P-E, Zekrini K, et al. Type 2 diabetes mellitus as a risk factor for intestinal resection in patients with superior mesenteric vein thrombosis. Liver Int Off J Int Assoc Study Liver 2013. https://doi.org/10.1111/liv.12386.
[79] **Noronha Ferreira C**, **Seijo S**, Plessier A, Silva-Junior G, Turon F, Rautou P-E, et al. Natural history and management of esophagogastric varices in chronic noncirrhotic, nontumoral portal vein thrombosis. Hepatology 2016;63:1640–1650. https://doi.org/10.1002/hep.28466.
[80] De Gaetano AM, Lafortune M, Patriquin H, De Franco A, Aubin B, Paradis K. Cavernous transformation of the portal vein: patterns of intrahepatic and splanchnic collateral circulation detected with Doppler sonography. AJR Am J Roentgenol 1995;165:1151–1155. https://doi.org/10.2214/ajr.165.5.7572494.

[81] Sharma P, Mishra SR, Kumar M, Sharma BC, Sarin SK. Liver and spleen stiffness in patients with extrahepatic portal vein obstruction. Radiology 2012;263:893–899. https://doi.org/10.1148/radiol.12111046.

[82] Acosta S, Alhadad A, Svensson P, Ekberg O. Epidemiology, risk and prognostic factors in mesenteric venous thrombosis. Br J Surg 2008;95:1245–1251. https://doi.org/10.1002/bjs.6319.

[83] Nuzzo A, Maggiori L, Paugam-Burtz C, Cazals-Hatem D, Ronot M, Huguet A, et al. Oral antibiotics reduce intestinal necrosis in acute mesenteric ischemia: a prospective cohort study. Am J Gastroenterol 2019;114:348–351. https://doi.org/10.1038/s41395-018-0389-9.

[84] Condat B, Pessione F, Helene Denninger M, Hillaire S, Valla D. Recent portal or mesenteric venous thrombosis: increased recognition and frequent recanalization on anticoagulant therapy. Hepatology 2000;32:466–470. https://doi.org/10.1053/jhep.2000.16597.

[85] Turnes J, García-Pagán JC, González M, Aracil C, Calleja JL, Ripoll C, et al. Portal hypertension-related complications after acute portal vein thrombosis: impact of early anticoagulation. Clin Gastroenterol Hepatol 2008;6:1412–1417. https://doi.org/10.1016/j.cgh.2008.07.031.

[86] Amitrano L, Guardascione MA, Scaglione M, Pezzullo L, Sangiuliano N, Armellino MF, et al. Prognostic factors in noncirrhotic patients with splanchnic vein thromboses. Am J Gastroenterol 2007;102:2464–2470. https://doi.org/10.1111/j.1572-0241.2007.01477.x.

[87] Valeriani E, Di Nisio M, Riva N, Cohen O, Garcia-Pagan J-C, Magaz M, et al. Anticoagulant therapy for splanchnic vein thrombosis: a systematic review and meta-analysis. Blood 2020. https://doi.org/10.1182/blood.2020006827.

[88] Plessier A, Goria O, Cervoni JP, Ollivier-Hourmand I, Bureau C, Poujol-Robert A, et al. Rivaroxaban prophylaxis in noncirrhotic portal vein thrombosis. NEJM Evid 2022;1(12). https://doi.org/10.1056/EVIDoa2200104.

[89] Guillaume M, Christol C, Plessier A, Corbic M, Péron J-M, Sommet A, et al. Bleeding risk of variceal band ligation in extrahepatic portal vein obstruction is not increased by oral anticoagulation. Eur J Gastroenterol Hepatol 2018;30:563–568. https://doi.org/10.1097/MEG.0000000000001061.

[90] Hernández-Gea V, De Gottardi A, Leebeek FWG, Rautou P-E, Salem R, Garcia-Pagan JC. Current knowledge in pathophysiology and management of Budd-Chiari syndrome and non-cirrhotic non-tumoral splanchnic vein thrombosis. J Hepatol 2019;71:175–199. https://doi.org/10.1016/j.jhep.2019.02.015.

[91] Benmassaoud A, AlRubaiy L, Yu D, Chowdary P, Sekhar M, Parikh P, et al. A stepwise thrombolysis regimen in the management of acute portal vein thrombosis in patients with evidence of intestinal ischaemia. Aliment Pharmacol Ther 2019;50:1049–1058. https://doi.org/10.1111/apt.15479.

[92] Marot A, Barbosa JV, Duran R, Deltenre P, Denys A. Percutaneous portal vein recanalization using self-expandable nitinol stents in patients with non-cirrhotic non-tumoral portal vein occlusion. Diagn Interv Imaging 2018. https://doi.org/10.1016/j.diii.2018.07.009.

[93] Fanelli F, Angeloni S, Salvatori FM, Marzano C, Boatta E, Merli M, et al. Transjugular intrahepatic portosystemic shunt with expanded-polytetrafuoroethylene-covered stents in non-cirrhotic patients with portal cavernoma. Dig Liver Dis 2011;43:78–84. https://doi.org/10.1016/j.dld.2010.06.001.

[94] Knight GM, Clark J, Boike JR, Maddur H, Ganger DR, Talwar A, et al. TIPS for adults without cirrhosis with chronic mesenteric venous thrombosis and EHPVO refractory to standard-of-care therapy. Hepatology 2021;74:2735–2744. https://doi.org/10.1002/hep.31915.

[95] Artru F, Vietti-Violi N, Sempoux C, Vieira Barbosa J, Becce F, Sah N, et al. Portal vein recanalisation alone to treat severe portal hypertension in non-cirrhotic patients with chronic extrahepatic portal vein obstruction. JHEP Rep 2022;4:100511. https://doi.org/10.1016/j.jhepr.2022.100511.

[96] Aggarwal N, Chopra S, Raveendran A, Suri V, Dhiman RK, Chawla YK. Extra hepatic portal vein obstruction and pregnancy outcome: largest reported experience. J Obstet Gynaecol Res 2011;37:575–580. https://doi.org/10.1111/j.1447-0756.2010.01407.x.

[97] Mandal D, Dattaray C, Sarkar R, Mandal S, Choudhary A, Maity TK. Is pregnancy safe with extrahepatic portal vein obstruction? An analysis. Singapore Med J 2012;53:676–680.

[98] Hoekstra J, Seijo S, Rautou PE, Ducarme G, Boudaoud L, Luton D, et al. Pregnancy in women with portal vein thrombosis: results of a multicentric European study on maternal and fetal management and outcome. J Hepatol 2012;57:1214–1219. https://doi.org/10.1016/j.jhep.2012.07.034.

[99] Dhiman RK, Saraswat VA, Valla DC, Chawla Y, Behera A, Varma V, et al. Portal cavernoma cholangiopathy: consensus statement of a working party of the Indian national association for study of the liver. J Clin Exp Hepatol 2014;4:S2–S14. https://doi.org/10.1016/j.jceh.2014.02.003.

[100] Dhiman RK, Behera A, Chawla YK, Dilawari JB, Suri S. Portal hypertensive biliopathy. Gut 2007;56:1001–1008. https://doi.org/10.1136/gut.2006.103606.

[101] Puri P. Pathogenesis of portal cavernoma cholangiopathy: is it compression by collaterals or ischemic injury to bile ducts during portal vein thrombosis? J Clin Exp Hepatol 2014;4:S27–S33. https://doi.org/10.1016/j.jceh.2013.05.015.

[102] Condat B, Vilgrain V, Asselah T, O'Toole D, Rufat P, Zappa M, et al. Portal cavernoma-associated cholangiopathy: a clinical and MR cholangiography coupled with MR portography imaging study. Hepatology 2003;37:1302–1308. https://doi.org/10.1053/jhep.2003.50232.

[103] Malkan GH, Bhatia SJ, Bashir K, Khemani R, Abraham P, Gandhi MS, et al. Cholangiopathy associated with portal hypertension: diagnostic evaluation and clinical implications. Gastrointest Endosc 1999;49:344–348.

[104] Llop E, de Juan C, Seijo S, García-Criado Á, Abraldes JG, Bosch J, et al. Portal cholangiopathy: radiological classification and natural history. Gut 2011;60:853–860. https://doi.org/10.1136/gut.2010.230201.

[105] Senzolo M, Garcia-Tsao G, García-Pagán JC. Current knowledge and management of portal vein thrombosis in cirrhosis. J Hepatol 2021;75:442–453. https://doi.org/10.1016/j.jhep.2021.04.029.

[106] Nery F, Chevret S, Condat B, de Raucourt E, Boudaoud L, Rautou P-E, et al. Causes and consequences of portal vein thrombosis in 1,243 patients with cirrhosis: results of a longitudinal study. Hepatology 2015;61:660–667. https://doi.org/10.1002/hep.27546.

[107] Francoz C, Valla D, Durand F. Portal vein thrombosis, cirrhosis, and liver transplantation. J Hepatol 2012;57:203–212. https://doi.org/10.1016/j.jhep.2011.12.034.

[108] Turon F, Driever EG, Baiges A, Cerda E, García-Criado Á, Gilabert R, et al. Predicting portal thrombosis in cirrhosis: a prospective study of clinical, ultrasonographic and hemostatic factors. J Hepatol 2021;75:1367–1376. https://doi.org/10.1016/j.jhep.2021.07.020.

[109] **Fortea JI**, **Carrera IG**, Puente Á, Cuadrado A, Huelin P, Tato CÁ, et al. Portal thrombosis in cirrhosis: role of thrombophilic disorders. J Clin Med 2020;9:E2822. https://doi.org/10.3390/jcm9092822.

[110] Ayala R, Grande S, Bustelos R, Ribera C, García-Sesma A, Jimenez C, et al. Obesity is an independent risk factor for pre-transplant portal vein thrombosis in liver recipients. BMC Gastroenterol 2012;12:114. https://doi.org/10.1186/1471-230X-12-114.

[111] Abdel-Razik A, Mousa N, Elhelaly R, Tawfik A. De-novo portal vein thrombosis in liver cirrhosis: risk factors and correlation with the Model for End-stage Liver Disease scoring system. Eur J Gastroenterol Hepatol 2015;27:585–592. https://doi.org/10.1097/MEG.0000000000000325.

[112] Mangia A, Villani MR, Cappucci G, Santoro R, Ricciardi R, Facciorusso D, et al. Causes of portal venous thrombosis in cirrhotic patients: the role of genetic and acquired factors. Eur J Gastroenterol Hepatol 2005;17:745–751.

[113] Zocco MA, Di Stasio E, De Cristofaro R, Novi M, Ainora ME, Ponziani F, et al. Thrombotic risk factors in patients with liver cirrhosis: correlation with MELD scoring system and portal vein thrombosis development. J Hepatol 2009;51:682–689. https://doi.org/10.1016/j.jhep.2009.03.013.

[114] Nery F, Correia S, Macedo C, Gandara J, Lopes V, Valadares D, et al. Nonselective beta-blockers and the risk of portal vein thrombosis in patients with cirrhosis: results of a prospective longitudinal study. Aliment Pharmacol Ther 2019;49:582–588. https://doi.org/10.1111/apt.15137.

[115] Xu X, Guo X, De Stefano V, Silva-Junior G, Goyal H, Bai Z, et al. Nonselective beta-blockers and development of portal vein thrombosis in liver cirrhosis: a systematic review and meta-analysis. Hepatol Int 2019;13:468–481. https://doi.org/10.1007/s12072-019-09951-6.

[116] Zanetto A, Campello E, Pelizzaro F, Farinati F, Burra P, Simioni P, et al. Haemostatic alterations in patients with cirrhosis and hepatocellular carcinoma: laboratory evidence and clinical implications. Liver Int 2022;42:1229–1240. https://doi.org/10.1111/liv.15183.

[117] Sherman CB, Behr S, Dodge JL, Roberts JP, Yao FY, Mehta N. Distinguishing tumor from bland portal vein thrombus in liver transplant candidates with hepatocellular carcinoma: the A-VENA criteria. Liver Transpl 2019;25:207–216. https://doi.org/10.1002/lt.25345.

[118] Dodd GD, Carr BI. Percutaneous biopsy of portal vein thrombus: a new staging technique for hepatocellular carcinoma. AJR Am J Roentgenol 1993;161:229–233. https://doi.org/10.2214/ajr.161.2.8392785.

[119] Loffredo L, Pastori D, Farcomeni A, Violi F. Effects of anticoagulants in patients with cirrhosis and portal vein thrombosis: a systematic review and meta-analysis. Gastroenterology 2017. https://doi.org/10.1053/j.gastro.2017.04.042.
[120] Qi X, Guo X, Yoshida EM, Méndez-Sánchez N, De Stefano V, Tacke F, et al. Transient portal vein thrombosis in liver cirrhosis. BMC Med 2018;16:83. https://doi.org/10.1186/s12916-018-1069-8.
[121] Francoz C, Belghiti J, Vilgrain V, Sommacale D, Paradis V, Condat B, et al. Splanchnic vein thrombosis in candidates for liver transplantation: usefulness of screening and anticoagulation. Gut 2005;54:691–697. https://doi.org/10.1136/gut.2004.042796.
[122] Amitrano L, Guardascione MA, Brancaccio V, Margaglione M, Manguso F, Iannaccone L, et al. Risk factors and clinical presentation of portal vein thrombosis in patients with liver cirrhosis. J Hepatol 2004;40:736–741. https://doi.org/10.1016/j.jhep.2004.01.001.
[123] Maruyama H, Okugawa H, Takahashi M, Yokosuka O. De novo portal vein thrombosis in virus-related cirrhosis: predictive factors and long-term outcomes. Am J Gastroenterol 2013;108:568–574. https://doi.org/10.1038/ajg.2012.452.
[124] Luca A, Caruso S, Milazzo M, Marrone G, Mamone G, Crinò F, et al. Natural course of extrahepatic nonmalignant partial portal vein thrombosis in patients with cirrhosis. Radiology 2012;265:124–132. https://doi.org/10.1148/radiol.12112236.
[125] Zhang Y, Xu B-Y, Wang X-B, Zheng X, Huang Y, Chen J, et al. Prevalence and clinical significance of portal vein thrombosis in patients with cirrhosis and acute decompensation. Clin Gastroenterol Hepatol 2020;18:2564–2572.e1. https://doi.org/10.1016/j.cgh.2020.02.037.
[126] Englesbe MJ, Schaubel DE, Cai S, Guidinger MK, Merion RM. Portal vein thrombosis and liver transplant survival benefit. Liver Transpl 2010;16:999–1005. https://doi.org/10.1002/lt.22105.
[127] Hibi T, Nishida S, Levi DM, Selvaggi G, Tekin A, Fan J, et al. When and why portal vein thrombosis matters in liver transplantation: a critical audit of 174 cases. Ann Surg 2014;259:760–766. https://doi.org/10.1097/SLA.0000000000000252.
[128] Driever EG, von Meijenfeldt FA, Adelmeijer J, de Haas RJ, van den Heuvel MC, Nagasami C, et al. Nonmalignant portal vein thrombi in patients with cirrhosis consist of intimal fibrosis with or without a fibrin-rich thrombus. Hepatology 2022;75:898–911. https://doi.org/10.1002/hep.32169.
[129] Rodriguez-Castro KI, Vitale A, Fadin M, Shalaby S, Zerbinati P, Sartori MT, et al. A prediction model for successful anticoagulation in cirrhotic portal vein thrombosis. Eur J Gastroenterol Hepatol 2019;31:34–42. https://doi.org/10.1097/MEG.0000000000001237.
[130] Villa E, Cammà C, Marietta M, Luongo M, Critelli R, Colopi S, et al. Enoxaparin prevents portal vein thrombosis and liver decompensation in patients with advanced cirrhosis. Gastroenterology 2012;143:1253–1260.e1-4. https://doi.org/10.1053/j.gastro.2012.07.018.
[131] Guerrero A, DelCampo L, Piscaglia F, Reiberger T, Han G, Violi F, et al. OS-1544 Anticoagulation improves overall survival through portal vein recanalization in patients with cirrhosis and portal vein thrombosis: individual patient data meta-analysis (IMPORTAL study). J Hepatol 2021;75(SUPPLEMENT 2):S191–S866.
[132] Delgado MG, Seijo S, Yepes I, Achécar L, Catalina MV, García-Criado A, et al. Efficacy and safety of anticoagulation on patients with cirrhosis and portal vein thrombosis. Clin Gastroenterol Hepatol 2012;10:776–783. https://doi.org/10.1016/j.cgh.2012.01.012.
[133] Intagliata NM, Davitkov P, Allen AM, Falck-Ytter YT, Stine JG. AGA technical review on coagulation in cirrhosis. Gastroenterology 2021;161:1630–1656. https://doi.org/10.1053/j.gastro.2021.09.004.
[134] La Mura V, Braham S, Tosetti G, Branchi F, Bitto N, Moia M, et al. Harmful and beneficial effects of anticoagulants in patients with cirrhosis and portal vein thrombosis. Clin Gastroenterol Hepatol 2018;16:1146–1152.e4. https://doi.org/10.1016/j.cgh.2017.10.016.
[135] Senzolo M, Piano S, Shalaby S, Tonon M, Tonello S, Zanetto A, et al. Comparison of fondaparinux and low-molecular-weight heparin in the treatment of portal vein thrombosis in cirrhosis. Am J Med 2021;134:1278–1285.e2. https://doi.org/10.1016/j.amjmed.2021.05.013.
[136] Turco L, de Raucourt E, Valla D-C, Villa E. Anticoagulation in the cirrhotic patient. JHEP Rep 2019;1:227–239. https://doi.org/10.1016/j.jhepr.2019.02.006.
[137] Mort JF, Davis JPE, Mahoro G, Stotts MJ, Intagliata NM, Northup PG. Rates of bleeding and discontinuation of direct oral anticoagulants in patients with decompensated cirrhosis. Clin Gastroenterol Hepatol 2020. https://doi.org/10.1016/j.cgh.2020.08.007.
[138] Semmler G, Pomej K, Bauer DJM, Balcar L, Simbrunner B, Binter T, et al. Safety of direct oral anticoagulants in patients with advanced liver disease. Liver Int 2021;41:2159–2170. https://doi.org/10.1111/liv.14992.
[139] European Association for the Study of the Liver. Electronic address: easloffice@easloffice.eu, European Association for the Study of the Liver. EASL Clinical Practice Guidelines on prevention and management of bleeding and thrombosis in patients with cirrhosis. J Hepatol 2022;S0168–8278(21):02033. https://doi.org/10.1016/j.jhep.2021.09.003. -X.
[140] Intagliata NM, Henry ZH, Maitland H, Shah NL, Argo CK, Northup PG, et al. Direct oral anticoagulants in cirrhosis patients pose similar risks of bleeding when compared to traditional anticoagulation. Dig Dis Sci 2016;61:1721–1727. https://doi.org/10.1007/s10620-015-4012-2.
[141] Nagaoki Y, Aikata H, Daijyo K, Teraoka Y, Shinohara F, Nakamura Y, et al. Efficacy and safety of edoxaban for treatment of portal vein thrombosis following danaparoid sodium in patients with liver cirrhosis. Hepatol Res 2018;48:51–58. https://doi.org/10.1111/hepr.12895.
[142] Hanafy AS, Abd-Elsalam S, Dawoud MM. Randomized controlled trial of rivaroxaban versus warfarin in the management of acute non-neoplastic portal vein thrombosis. Vascul Pharmacol 2019;113:86–91. https://doi.org/10.1016/j.vph.2018.05.002.
[143] Perarnau J-M, Baju A, D'alteroche L, Viguier J, Ayoub J. Feasibility and long-term evolution of TIPS in cirrhotic patients with portal thrombosis. Eur J Gastroenterol Hepatol 2010;22:1093–1098. https://doi.org/10.1097/MEG.0b013e328338d995.
[144] Harding DJ, Perera MTPR, Chen F, Olliff S, Tripathi D. Portal vein thrombosis in cirrhosis: controversies and latest developments. World J Gastroenterol 2015;21:6769–6784. https://doi.org/10.3748/wjg.v21.i22.6769.
[145] Rodrigues SG, Sixt S, Abraldes JG, De Gottardi A, Klinger C, Bosch J, et al. Systematic review with meta-analysis: portal vein recanalisation and transjugular intrahepatic portosystemic shunt for portal vein thrombosis. Aliment Pharmacol Ther 2019;49:20–30. https://doi.org/10.1111/apt.15044.
[146] Thornburg B, Desai K, Hickey R, Hohlastos E, Kulik L, Ganger D, et al. Pretransplantation portal vein recanalization and transjugular intrahepatic portosystemic shunt creation for chronic portal vein thrombosis: final analysis of a 61-patient cohort. J Vasc Interv Radiol 2017;28:1714–1721.e2. https://doi.org/10.1016/j.jvir.2017.08.005.
[147] Wang Z, Jiang M-S, Zhang H-L, Weng N-N, Luo X-F, Li X, et al. Is post-TIPS anticoagulation therapy necessary in patients with cirrhosis and portal vein thrombosis? A randomized controlled trial. Radiology 2016;279:943–951. https://doi.org/10.1148/radiol.2015150369.
[148] Azoulay D, Quintini C, Rayar M, Salloum C, Llado L, Diago T, et al. Renoportal anastomosis during liver transplantation in patients with portal vein thrombosis: first long-term results from a multicenter study. Ann Surg 2021. https://doi.org/10.1097/SLA.0000000000004797.
[149] Steffel J, Collins R, Antz M, Cornu P, Desteghe L, Haeusler KG, et al. 2021 European heart rhythm association practical guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation. EP Europace 2021;23:1612–1676. https://doi.org/10.1093/europace/euab065.