Seminar

JOURNAL OF HEPATOLOGY

Current knowledge in pathophysiology and management of Budd-Chiari syndrome and non-cirrhotic non-tumoral splanchnic vein thrombosis

Virginia Hernández-Gea[1], Andrea De Gottardi[2], Frank W.G. Leebeek[3], Pierre-Emmanuel Rautou[4,5], Riad Salem[6], Juan Carlos Garcia-Pagan[1,*]

Summary

Budd-Chiari syndrome and non-cirrhotic non-tumoral portal vein thrombosis are 2 rare disorders, with several similarities that are categorized under the term splanchnic vein thrombosis. Both disorders are frequently associated with an underlying prothrombotic disorder. They can cause severe portal hypertension and usually affect young patients, negatively influencing life expectancy when the diagnosis and treatment are not performed at an early stage. Yet, they have specific features that require individual consideration. The current review will focus on the available knowledge on pathophysiology, diagnosis and management of both entities.

Keywords: Portal vein thrombosis; Portal hypertension; Thrombophilia; Coagulopathy; Transplant; TIPS; Angioplasty.

Received 9 November 2018; received in revised form 15 February 2019; accepted 19 February 2019

Introduction

Budd-Chiari syndrome (BCS) is defined as the obstruction of hepatic venous outflow regardless of its causative mechanism or level of obstruction. This obstruction can be traced to the small hepatic venules up to the entrance of the inferior vein cava (IVC) into the right atrium. Hepatic outflow obstruction related to cardiac disease, pericardial disease or sinusoidal obstruction syndrome have different pathophysiological and clinical implications and are excluded from this definition. BCS is classified as primary when the obstruction originates in the vein and thrombosis is the main cause, or secondary when the vein is externally compressed (abscess, tumour). The focus of this review is on primary BCS. Non-cirrhotic non-tumoral portal vein thrombosis (NCPVT) refers to the presence of a thrombus in the main portal vein trunk and/or the left or right intrahepatic portal vein branches that may extend to the splenic vein and/or the superior or inferior mesenteric veins. Isolated splenic or mesenteric vein thrombosis are beyond the scope of this review.

BCS and NCPVT risk factors

The estimated incidence of BCS and NCPVT in the absence of cirrhosis and cancer is 1 per million per year and 0.35–2.5 cases per 100,000 per year, respectively.[1–3] Most patients with BCS and NCPVT have identifiable thrombotic risk factors. However, both entities represent only ~1% of all venous thromboembolic events, implying other local factors besides thrombophilic disorders for developing BCS or NCPVT.[4,5] Although some risk factors are shared by both entities, others are specifically related to one or the other. Indeed, myeloproliferative neoplasm (MPN) and factor V Leiden mutation are prothrombotic conditions strongly associated with BCS but less frequently observed in NCPVT.[6]

Risk factors for BCS and NCPVT and their prevalence in 3 large European studies, including patients enrolled between 2003–2005 and 2013–2014, are presented in Table 1. Compared with older multicentre European studies, including patients between 2003 and 2005, we observed an overall stability in the prevalence of these risk factors over the last 15 years.[7,8] Work-up for these risk factors is presented in Table 2. Multiple prothrombotic conditions are found in 15–20% of patients with BCS or NCPVT suggesting that, when one causal factor is identified, additional factors should be investigated. Conversely, in some patients, no risk factor is found. However, in population-based databases, the reported percentage of patients with no risk factor is variable and has significantly decreased in recent studies, suggesting an improvement in their detection. Indeed, in the European study performed in 2009, which analysed 157 patients with BCS, 16% of patients did not show any prothrombotic risk factor. Interestingly, when these patients were re-analysed during follow-up, additional aetiological factors were diagnosed in 12 previously unclassified patients. Nonetheless, recent data from France and Italy describe the absence of a prothrombotic factor in 30%[1] and 61%[2] of patients respectively, maybe due to the intrinsic limitations of population studies. Differences between Eastern and Western countries are found and the prevalence of prothrombotic disorders in China seems to be very low.[9] However, over the years a higher detection of hypercoagulability conditions has been described,[10] reinforcing the need for more studies aimed at uncovering the causes of BCS in Asia.[11] Up to 30% of patients with NCPVT have no identifiable aetiological factor.

[1]*Barcelona Hepatic Hemodynamic Laboratory, Liver Unit, Hospital Clínic de Barcelona, IDIBAPS, CIBERehd, European Reference Network for Rare Vascular Liver Diseases, Universitat de Barcelona, Spain*;
[2]*Hepatology, University Clinic of Visceral Medicine and Surgery, Inselspital, and Department of Biomedical Research, University of Bern, Bern, Switzerland*;
[3]*Department of Haematology, Erasmus University Medical Center, Rotterdam, the Netherlands*;
[4]*Service d'Hépatologie, Centre de Référence des Maladies Vasculaires du Foie, DHU Unity, Pôle des Maladies de l'Appareil Digestif, Hôpital Beaujon, AP-HP, Clichy, France*;
[5]*Inserm, UMR-970, Paris Cardiovascular Research Center, PARCC, Paris, France*;
[6]*Department of Radiology, Section of Interventional Radiology, Northwestern University, Chicago, IL, USA*

Table 1. Prevalence of acquired and inherited risk factors for BCS, NCPVT in 3 recent European cohort studies[32,34,55].

Underlying condition	NCPVT n = 432		BCS n = 168	
	n tested	% positive	n tested	% positive
Acquired conditions				
Myeloproliferative neoplasms	432	21%	168	41%
JAK2^{V617F}	432	16%	168	35%
Antiphospholipid syndrome	429	6%	165	10%
PNH	386	0.3%	152	7%
Inherited conditions				
Factor V Leiden	429	3%	165	8%
Factor II gene mutation	432	6%	168	3%
Protein C deficiency	404	5%	150	5%
Protein S deficiency	407	5%	147	4%
Antithrombin deficiency	416	1%	153	1%
External factors				
Recent pregnancy	353	2%	168	1%
Recent oral contraceptive use	353	14%	168	22%
Systemic disease*	432	3%	168	6%
Inflammatory intra-abdominal lesions**	432	11%	168	2%
Intra-abdominal surgery	432	10%	168	1%
Abdominal trauma	292	4%	168	2%
>1 risk factor	432	14%	168	19%
No cause***	219	42%	168	24%

BCS, Budd-Chiari syndrome; PNH, paroxysmal nocturnal haemoglobinuria; NCPVT, non-cirrhotic non-tumoral portal vein thrombosis.
*Including connective tissue disease, coeliac disease, Behçet's disease, mastocytosis, inflammatory bowel disease, human immunodeficiency virus infection, sarcoidosis, myeloma.
**Acute pancreatitis, biliary or intestinal infection or inflammation.
***Oral contraception and pregnancy were not considered risk factors for NCPVT in all studies.

In the following paragraphs we discuss the more relevant risk factors for developing BCS or NCPVT.

Local risk factors

In patients with BCS, abdominal infection or inflammation is more rarely identified than in patients with NCPVT,[8] possibly due to the impossibility of bypassing the liver. A complementary hypothesis could be that activated platelets and microvesicles generated at the site of inflammation/infection are cleared within the liver by liver endothelial cells and macrophages.[12,13] However, it is still not fully understood why, even in the setting of a general prothrombotic condition, thrombosis arises at such an unusual site without any inflammatory or mechanical injury. In the European BCS cohort, the presence of local trauma, inflammatory diseases and abdominal infections was only reported in 11% of patients,[8] although in more recent data from the French survey it was found in 25% of patients.[1]

In patients with NCPVT, a local cause should be exhaustively investigated, as it may be present in approximately 30% of cases. Initial imaging studies (CT or MRI) performed during the diagnostic work-up should be examined carefully as they may reveal signs of gastrointestinal (appendicitis, diverticulitis, intra-abdominal abscesses or infections) or biliopancreatic pathologies including pancreatic pseudocysts and gallbladder alterations.

Abdominal infection and inflammation

Although thrombosis by itself can induce systemic inflammatory responses, abdominal infection is a classical cause of PVT.[7] Together with the inflammatory response, activation of coagulation is an important response in the host's defence against infection, as it prevents the dissemination of microorganisms. This implication of coagulation in infection is illustrated by the improved survival of patients with sepsis carrying heterozygous factor V Leiden compared with those without, a finding confirmed in animal models.[14] Mechanisms by which infection triggers thrombosis have recently been reviewed in detail.[15] Briefly, monocytes and neutrophils play an important role: monocytes express tissue factor, the primary initiator of the coagulation cascade, and release tissue factor positive microvesicles; neutrophils release neutrophil extracellular traps (NETs), *i.e.* networks of extracellular fibres, primarily composed of DNA from neutrophils, which bind pathogens and activate coagulation and thrombosis by favouring FVIIa-mediated thrombin generation and activating the intrinsic pathway. Simultaneously, platelets are activated and contribute to clot formation. Endothelial cells lose their physiological antithrombotic phenotype following exposure to inflammatory mediators and to activated neutrophils, platelets, and other cells. In addition to the cellular components, alarmins such as histones, high mobility group box 1, microvesicles and secreted granule proteins, are all important for clot formation.[15] Inflammation without infection, *e.g.* acute pancreatitis or inflammatory bowel

* Corresponding author.
Address: Barcelona Hepatic Hemodynamic Laboratory, Liver Unit, Hospital Clinic, Villarroel 170, Barcelona 08036, Spain.
Fax: +34 932279856.
E-mail address: jcgarcia@clinic.cat (J.C. Garcia-Pagan).

Table 2. Investigations for thrombotic risk factors in patients with BCS or NCPVT.

Underlying disorders	Suggestive signs*	Work-up
Systemic		
Acquired conditions		
MPN	Normal platelet count Large spleen	- In all patients, test first *JAK2*^{V617F} in peripheral granulocyte DNA. - In patients without *JAK2*^{V617F}, but with spleen height ≥16 cm and platelet count >200 $\times$ 10^9/L, test for *CALR* mutations. Propose a bone marrow biopsy in patients without *CALR* mutations. - In the remaining patients, *i.e.* those without *JAK2*^{V617F} when spleen height is <16 cm and platelet count ≤200 $\times$ 10^9/L, MPNs are extremely uncommon. *MPL* and *JAK2* exon 12 mutations are very rare. MPN diagnosis relies on bone marrow biopsy performed on a case-by-case basis.
Antiphospholipid syndrome		Diagnosis based on repeatedly detectable anticardiolipin antibodies at high level, or lupus anticoagulant, or antibeta2 glycoprotein 1 antibodies. Many patients with vascular liver disease have nonspecific fluctuating, low titer antiphospholipid antibodies in the absence of antiphospholipid syndrome.
PNH	Small hepatic vein involvement	CD55 and CD59 deficient clone at flow-cytometry of peripheral blood cells.
Inherited conditions		
Factor V Leiden		Activated protein C resistance. To be confirmed in patients with positive results, by molecular testing for factor V Leiden mutation
Factor II gene mutation		Molecular testing for G20210A mutation
Protein C deficiency		Results can be interpreted only in patients with normal coagulation factor levels. Diagnosis based on decreased protein C activity levels. Inherited deficiency can be established only with a positive test in first degree relatives.
Protein S deficiency		Results can be interpreted only in patients with normal coagulation factor levels. Diagnosis based on decreased free protein S levels. Inherited deficiency can be established only with a positive test in first degree relatives.
Antithrombin deficiency		Results can be interpreted only in patients with normal coagulation factor levels. Diagnosis based on decreased antithrombin activity levels. Inherited deficiency can be established only with a positive test in first degree relatives.
Hyperhomocysteinemia		Increased serum homocysteine level prior to disease. Uncertain value of C677T homozygous polymorphism. In many patients, a definite diagnosis for underlying hyperhomocysteinemia will not be possible. Blood folate and serum vitamin B12 levels may be useful.
External factors		
Recent pregnancy		Medical history
Recent oral contraceptive use		Medical history
Systemic disease		
Behcet disease	Involvement of inferior vena cava	Diagnosis based on a set of conventional criteria. To be routinely considered in patients with inferior vena cava thrombosis, or originating from endemic areas, or having extrahepatic features suggestive of the disease.
HIV infection		Anti-human immunodeficiency virus antibodies
Celiac disease		Anti-transglutaminase antibodies
Sarcoidosis	Black patients; respiratory symptoms	Serum angiotensin-converting-enzyme level; Biopsy
Cytomegalovirus infection		Anti-CMV IgM
Local factor		
Inflammatory intra-abdominal lesions		Medical history. CT-scan. Increased circulating levels of C reactive protein and/or of fibrinogen and/or increased platelet count, although recent thrombosis can by itself induce systemic inflammation.
Abdominal surgery		Medical history
Abdominal trauma		Medical history

BCS, Budd-Chiari syndrome; NCPVT, non-cirrhotic non-tumoral portal vein thrombosis; PNH, paroxysmal nocturnal haemoglobinuria, MPN, myeloproliferative neoplasms.
*All causes should be tested in all patients. Do not restrict testing to patients displaying these signs.

disease, shares many of the aforementioned features with infection and may also contribute to thrombosis.[16] PVT induced by inflammation or infection can be seen close to the site of infection/inflammation and may extend and or embolise to the portal trunk and branches (Fig. 1).

Abdominal malignancies

Abdominal cancer is another common cause of NCPVT. The pathogenesis of the cancer-associated coagulopathy is complex and multifactorial.[17] Most importantly, tumour cells gain the capacity to activate the host haemostatic system, a phenomenon driven by the same oncogenes responsible for the cellular neoplastic transformation. Indeed, cancer tissues express different procoagulant proteins including tissue factor, factor VII and cancer procoagulant (a molecule that, unlike tissue factor, directly activates factor X independently of coagulation factor VII), which contribute to the occurrence of the overt symptomatic coagulopathy *in vivo*. The shedding of procoagulant microvesicles is also regulated by oncogenic events and further adds to the pathogenesis of the cancer-associated hypercoagulable state. It is important to note that in one-third of

Key point

Notably, in one-third of patients with NCPVT and a recognized local factor, additional general prothrombic risk factors are present.

patients with NCPVT exhibiting a recognized local factor, additional general prothrombotic risk factors are found.[7,18]

Myeloproliferative neoplasms

MPNs are chronic clonal haematopoietic stem cell disorders characterized by an overproduction of granulocytes, erythrocytes and/or platelets. Currently, 7 subcategories of MPN have been identified, of which polycythaemia vera (PV), essential thrombocythemia (ET) and primary myelofibrosis (PMF) have the highest prevalence. Patients with MPNs are at a high risk of arterial and venous thrombotic complications.[19] A recent meta-analysis revealed that MPNs are found in 40% of patients with BCS and 30% of those with NCPVT.[7,8,20–22] More impressively, NCPVT and BCS are 2,000 and 10,000 times more common in patients with MPN than in the general population.[23] This high prevalence is not restricted to Western patients, since similar figures have been reported in India, Turkey and Egypt,[24–27] although less common in Chinese patients with BCS or NCPVT.[9,28]

According to the current WHO 2016 guidelines, the diagnosis of PV is based on several criteria, the main criterion being an increased haemoglobin >16.5 g/dl in men or >16.0 g/dl in women, or a haematocrit >49% in men or >48% in women.[29] For ET the main criterion is a platelet count >450 $\times$ 10^9/L. In addition, typical bone marrow findings including hypercellularity and an increased number of mature, enlarged, pleomorphic megakaryocytes with hyperlobulated nuclei, are present.

In recent years, several underlying somatic mutations have been identified in MPN. In PV, the *JAK2*^{V617F} or *JAK2* exon 12 mutations are found in >95% of patients. In ET and PMF, *JAK2*^{V617F} mutations are found in 50%. More recently, mutations in the calreticulin gene (*CALR*), encoding a protein present in the endoplasmic reticulum and involved in regulation of the STAT-signalling pathway, have been identified in 80% of patients with MPN that are *JAK2*^{V617F} negative.[30,31] Based on these findings *JAK2*^{V617F}, *JAK2* exon 12 and *CALR* or thrombopoietin receptor (*MPL*) mutations have become major diagnostic criteria for MPNs.

Compared to other patients with MPNs, those with BCS or PVT with underlying MPN are typically younger and more frequently female. In patients with splanchnic vein thrombosis who were diagnosed with MPN based on clinical, laboratory and/or morphological features of MPN in the bone marrow, as well as *JAK2*^{V617F} mutation status, 80% of patients with BCS and 87% with PVT were *JAK2*^{V617F} positive.[22] *JAK2*^{V617F} mutation, irrespective of other MPN features, was present in 41% of patients with BCS and 28% with PVT. Subclassification of MPN in patients with BCS reveals 53% PV, 25% ET and 7% PMF. For patients with PVT and MPN this is 28% PV, 26% ET and 13% PMF, respectively. Other patients with MPN could not be classified. However, due to portal hypertension, leading to hypersplenism and haemodilution in patients with BCS or NCPVT, peripheral blood cell counts, haemoglobin or haematocrit can be normal or even reduced, even in the presence of other criteria for MPN. In patients without typical haematologic features, the *JAK2*^{V617F} mutation can be found in 17.1% and 15.4% of patients, respectively.[22] *CALR* mutations are less frequent in patients with splanchnic vein thrombosis (<5%), however they may be of help to diagnose underlying MPN.[32,33] Due to the low incidence of *CALR* mutations, only screening for *CALR* mutations in patients who are *JAK2*^{V617F} negative and have platelets >200 $\times$ 10^9/L with a spleen size of >16 cm has been suggested.[34] *MPL* mutations are rare, but they may be included in the diagnostic work-up, together with *JAK2*^{V617F}, *JAK2* exon 12 and *CALR* mutations.[35–38] In a small subset of patients with BCS or PVT, peripheral blood counts are normal and molecular markers for MPN are negative, with MPN diagnosis made by bone marrow biopsy.[22] The role of bone marrow biopsy to diagnose MPN in patients with BCS and NCPVT, when all previous molecular markers are negative, remains challenging. Currently, decisions are made on a case-by-case basis. In the near future, it is possible that the introduction of extensive molecular diagnostic panels, that are able to simultaneously analyse multiple mutations, will change these recommendations.

Over the last 10 years, several studies have shed light on the close relationship between MPN and BCS or NCPVT. A pivotal study reported on the existence of *JAK2*^{V617F} in endothelial cells from hepatic veins in 2 patients with BCS.[39] Subsequently, *JAK2*^{V617F} has also been detected in

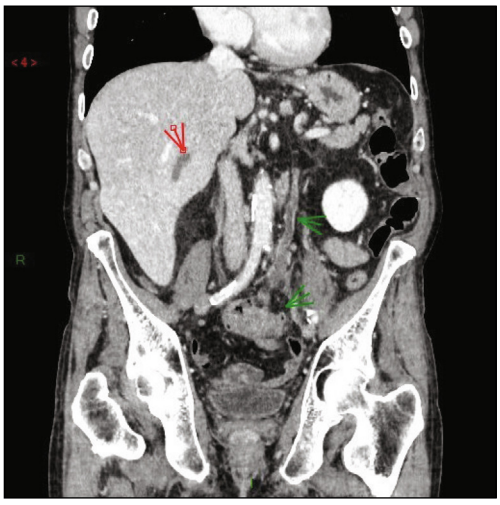

Fig. 1. 58-year-old male patient with a perforated sigmoid diverticulitis. This patient had an abscess (lower green arrow), complicated with an inferior mesenteric vein thrombus (upper green arrow) with extension into intrahepatic portal branches (red arrow). (Courtesy of Dr Onorina Bruno, Hôpital Beaujon, Clichy, France).

splenic endothelial cells from patients with myelofibrosis.[40] *JAK2*^{V617F} was found in circulating endothelial progenitor cells in 5 out of 17 patients with somatic *JAK2*^{V617F} expression.[41] Interestingly, patients harbouring *JAK2*^{V617F} in circulating endothelial progenitor cells were those with a history of thrombosis (splanchnic vein thrombosis, deep vein thrombosis or stroke).[41] Moreover, *JAK2*^{V617F} mutated circulating endothelial progenitor cells showed significantly higher adhesion proficiency to mononuclear cells than normal circulating endothelial progenitor cells.[41] The exact mechanism by which *JAK2*^{V617F} in the endothelium leads to BCS or NCPVT remains unclear. Recent results from experiments using cultured endothelial cells transduced with a lentivirus expressing *JAK2*^{V617F} and transgenic mice expressing *JAK2*^{V617F} in their endothelial cells have filled this gap in knowledge.[42] In this study, James and colleagues demonstrated that *JAK2*^{V617F} induces the exposure of P-Selectin at the surface of endothelial cells, increasing endothelial adhesion of platelets, of neutrophils and of mononuclear cells and inducing *in vivo* thrombus formation. Interestingly, in mice, small concentrations of TNFα were required to uncover this increased adhesion, suggesting that a low level of inflammation may trigger thrombosis in MPN. Similar results were obtained by an independent group using pluripotent stem cells from patients with MPN redirected towards the endothelial lineage.[43]

These results are a step forward in our understanding of the link between BCS or NCPVT and MPN. However, several questions remain unanswered: (a) Is *JAK2*^{V617F} expressed in endothelial cells only in the digestive vascular bed or ubiquitously? If ubiquitous, additional factors are needed and might be inflammatory mediators derived from the gut. (b) Why is the somatic myeloid mutation *JAK2*^{V617F} also found in endothelial cells? It is unlikely that endothelial *JAK2*^{V617F} is due to the occurrence of the mutation in a common cell of origin for endothelial cells and myeloid cells, called haemangioblasts. Indeed, haemangioblasts exist in embryos, but not in adults, and *JAK2*^{V617F} related BCS and NCPVT are rare in young children.[44] Patients with MPN and BSC or NCPVT are usually younger (≈30 years) than patients with MPN without thrombosis (≈60 years), suggesting the presence of haemangioblast mutations.

In BCS, *JAK2*^{V617F} is associated with worse prognostic features at presentation and the earlier requirement for hepatic decompression procedures.[21] To determine whether endothelial *JAK2*^{V617F} enhances liver injury and fibrosis induced by hepatic venous outflow obstruction, thus worsening BCS, a surgical model of BCS was applied to mice expressing endothelial *JAK2*^{V617F}. It was observed that the expression of *JAK2*^{V617F} in liver endothelial cells did not affect liver injury or liver fibrosis, meaning that endothelial *JAK2*^{V617F} does not explain the more severe presentation of patients with BCS and *JAK2*^{V617F}.[45] Therefore, the myeloid expression of *JAK2*^{V617F} should be explored as the most likely explanation for this.

Key point

NCPVT and BCS are 2,000 and 10,000 times more common in patients with MPN than in the general population, with *JAK2*^{V617F} mutations found in >95% of patients with MPN.

Other haematological conditions

Paroxysmal nocturnal haemoglobinuria (PNH) is a rare acquired haematological disorder of haematopoietic stem cells which leads to complement-induced haemolysis and is strongly associated with an increased risk of venous thrombosis.[46] BCS is one of the most common sites of thrombosis in patients with PNH, affecting 7–25%. More than one-fifth of the patients with PNH develop thrombosis in multiple sites.[47]

PNH has been reported in 9–19% of patients with BCS,[48] whereas a prevalence of 0–2% has been reported in patients with NCPVT.[7] Patients with a PNH cell population above 60% of the granulocytes are at a high risk of thrombosis.[49] Testing for PNH should routinely be performed in all BCS and considered in NCPVT.[46]

Systemic thrombophilic disorders

Factor V Leiden and factor II G20210A gene mutations are other frequently found prothrombotic factors in patients with BCS and NCPVT, respectively, with apparent site specificity. Indeed, the prevalence of factor V Leiden is twice as high in European patients with BCS (Table 1) than in the general population (∼4–5%), and is commonly associated with other risk factors for thrombosis.[6,33] Similar or even higher figures have been reported in India, Turkey and Egypt, but factor V Leiden is not found in Chinese patients with BCS.[27] The G20210A mutation of the factor II gene is more common in patients with NCPVT (Table 1) than in the general Caucasian population (∼2%).[50] By contrast, the role of factor V Leiden in patients with NCPVT and factor II gene mutation in patients with BCS appears to be negligible. The mechanism underlying this site specificity is unknown.

Antiphospholipid syndrome is a third common risk factor for BCS or NCPVT. However, its diagnosis is difficult because of the poor specificity of antiphospholipid antibodies in chronic liver disease.[51] Primary antiphospholipid syndrome affects males and females, but a large percentage of patients are women with recurrent pregnancy loss, while secondary antiphospholipid syndrome occurs mainly in lupus, and about 90% of lupus patients are female

Precise prevalence of inherited protein C, protein S or antithrombin deficiencies is difficult to estimate since the diagnosis of primary deficiencies is based on determination of plasma levels of these coagulation inhibitors that are synthesized by the liver. In patients with liver dysfunction, a non-specific decrease in plasma levels of these inhibitors makes interpretation of protein C, protein S or antithrombin levels quite challenging.[52]

Other systemic risk factors

Behçet's disease

Behçet's disease is a rare systemic disorder, clinically diagnosed by the presence of recurrent oral aphthous ulcers and genital ulcerations together with eye lesions, that may also be associated with the development of BCS.[53]

Obesity

In general, obesity is a risk factor for the first episode of venous thromboembolism (VTE) with an estimated overall odds ratio for VTE of 2.3.[54] Obesity is also a risk factor for recurrent VTE with an estimated hazard ratio of 1.6, a degree of risk similar to that of other risk factors for recurrent VTE.[54] In addition to clinical factors such as immobility, obstructive sleep apnoea, heart failure, and venous stasis, the major mechanisms proposed to be responsible for obesity-associated thrombosis are impaired fibrinolysis, and chronic inflammation.[54] Adipokines and proinflammatory cytokines secreted by M1 macrophages within adipose tissue contribute to the upregulation of procoagulant factors such as tissue factor and plasminogen activator inhibitor-1 (PAI-1), leading to increased thrombin generation, enhanced platelet activation, reduced fibrinolysis, and an increased risk of thrombosis.

This effect of obesity on venous thrombosis might be even more marked for NCPVT.[55] Indeed, concentrations of inflammatory molecules known to activate endothelial cells rendering them more prothrombotic, including interleukin 6, are higher in the portal vein than in the radial artery of obese patients.[56,57]

Acute cytomegalovirus infection

Acute cytomegalovirus (CMV) infection is a cause of NCPVT.[58] Several explanations have been put forward. One plausible mechanism of CMV-induced thrombosis involves formation of antiphospholipid syndrome antibodies observed in patients in response to CMV infection,[59] resulting in a transient hypercoagulable state. In mouse models, the immunological pathways have been studied in greater detail. Through this process, 1 CMV-derived peptide of particular interest, TIFI, was found to be an analogue of human beta-2-glycoprotein I (b2GPI). Mice injected with TIFI developed antiphospholipid antibodies and measurable lupus anticoagulant activity, resulting in more thrombotic events than controls. Translation to humans was postulated by formation of anti-b2GPI antibodies against TIFI which would bind endogenous human b2GPI on the surface of endothelial cells, leading to activation of the coagulation cascade.[58,60] The composition of the CMV envelope might also contribute to thrombosis. Indeed, the CMV surface contains the necessary procoagulant phospholipid for assembly of coagulation cascade proteins, thus favouring coagulation activation.[61] A third alternative or complementary mechanism relies on the ability of CMV to directly infect endothelial cells and induce endothelial tissue factor expression, as well as adhesion of monocytes and neutrophils to infected endothelial cells.[62,63]

Portosinusoidal vascular disease/Idiopathic portal hypertension

In the absence of an identifiable cause, especially when liver test abnormalities and/or hepatic dysmorphism on imaging are present, further aetiologic work-up may also include liver biopsy. In fact, idiopathic portal hypertension may be frequently associated with NCPVT. Among patients with idiopathic portal hypertension, the prevalence of NCPVT is 13–46% and the annual probability of developing NCPVT is 9%.[64] Such a high incidence might be due to reduced blood flow velocity secondary to the increase in intrahepatic resistance, together with portal vein wall abnormalities. Systematic analysis of abdominal imaging of patients with portosinusoidal vascular disease revealed that portal vein abnormalities are 3 times more common than in patients with cirrhosis.[65] However, more detailed analyses are lacking.

Natural history

BCS

Clinical manifestations of BCS are extremely heterogeneous and vary from severe forms of acute liver failure to asymptomatic forms incidentally diagnosed when studying mild alterations of liver enzymes. Generally, the diagnosis is made after portal hypertension related complications, mainly ascites. Ascites (83%), hepatomegaly (67%) and abdominal pain (61%) were the most frequent clinical manifestations in a European cohort of 163 patients with BCS. In this cohort, 58% of the patients had oesophageal varices[8] at diagnosis. Although less common, acute liver failure may be the initial presentation in around 5% of cases.[66,67] This wide range of clinical presentations probably correlates with both time to establishment and extension of the hepatic vein thrombosis. A slight and gradually-formed thrombosis may be accompanied by the development of hepatic venous collaterals able to, at least partially, decompress the portal venous system[68] and maintain the patient asymptomatic; a clinical form described in up to 15% of cases.[8,68] Conversely, an extensive and rapidly constituted thrombosis of the hepatic veins may produce a severe form of liver failure with renal impairment, coagulopathy and death if not adequately treated. However, in many instances, despite the initial form of presentation being acute, signs of chronic liver disease are frequently found (*i.e.* alterations of liver morphology with atrophy/hypertrophy of different liver segments at imaging studies). This results from hepatic veins (HV) being frequently

thrombosed at different time-points in a progressive manner. Obstruction of one hepatic vein can promote the development of intrahepatic or extrahepatic collateral circulation aimed at bypassing the occluded vein; thus, the patient may remain asymptomatic. However, imaging studies may reveal chronic morphological changes in the hepatic lobe drained by the occluded vein. If the patient is misdiagnosed and not adequately treated, recurrent thromboses in additional patent veins may happen, promoting severe hepatic congestion and appearance of symptoms, a clinical scenario potentially misdiagnosed as acute disease.

Typical laboratory findings are aminotransferase elevation, reflecting subjacent necrosis and a decrease in prothrombin time in severe cases. The biochemical characteristic of ascites are its low cellularity and high protein content.[69]

The site of occlusion and clinical presentation seem to be different in patients from Western countries and Asia. In the West, the available data suggest that the most frequent site of thrombosis is the hepatic veins,[8,70] whereas IVC obstruction (mainly from membrane or web) or combined IVC-HV obstruction prevails in most of the reported cases from Asia.[71] However, recent data from India indicates this is changing,[26] and more cases with HV obstruction have been identified in the last decade. Regarding clinical presentation, the most frequent clinical manifestation in the West is ascites and impaired liver function[8,70] compatible with an acute course. In China, it is often diagnosed when complications of portal hypertension arise; the presence of abdominal varices and lower limb oedema or ulcers[11] are more frequently described in Eastern patients.

Concomitant splanchnic vein thrombosis and BCS has also being described although the incidence varies from 3.8–21% in epidemiological studies.[1]

Another clinical finding in patients with chronic BCS is the presence of benign hepatic regenerative nodules.[72,73] Although the pathogenesis remains unclear, the coexistence of focal defects of portal perfusion and hypervascularized areas of preserved venous outflow may be involved in their development. The reported prevalence of these nodules is highly variable; they have been described in around 60–70% of patients in pathology studies,[74,75] but in only 36% in an imaging study.[76] Typically, benign nodules are small (under 3–4 cm in diameter), multiple (more than 10 lesions), hypervascularized and disseminated throughout the liver. Benign nodules may not only increase in number during follow-up, but may also increase in size.[73] Histologically, benign nodules have the macro and microscopic alterations of focal nodular hyperplasia (FNH) and they may display a map-like pattern of glutamine synthase expression.[77] However, because the underlying liver is not healthy, these lesions are usually called FNH-like lesions.[78] Similar to traditional FNH, these benign lesions are usually homogeneous and hypervascular at imaging and the presence of a central scar can be found in nodules larger than 1 cm in diameter.[79] However, other imaging characteristics may be different from those of typical FNH such as hyperintensity on T1-weighted and variable signal T2-weighted MR images. In addition, benign nodules may have washout on contrast-enhanced CT or MR imaging during portal venous and/or delayed phase.[79] Less frequently, patients with chronic BCS may also develop hepatocellular adenomas[80] and hepatocellular carcinoma (HCC).[81] Moucari *et al.* reported a 5-year cumulative incidence of HCC of 7% in a large cohort of patients with BCS.[81] A recent systematic review of 16 studies that reported HCC prevalence in BCS highlights the huge difference in the reported rates ranging from 2.0–46.2%. This is probably due, at least in part, to the heterogeneity of the studies included: geographical differences, dissimilar follow-up time (ranging from 4.5 to 11.6 years), diverse enrolment periods, different diagnostic tools and treatments, and different survivals rates.[82] Risk factors for developing HCC are not well defined, although a higher prevalence has been described in patients with long-term IVC obstruction when compared to patients with isolated HV involvement.[81,83] Frequently, HCC appears as a hypervascular lesion, which is heterogeneous at arterial phase and hypoechoic on portal and delayed phase. However, the radiological pattern of HCC in patients with BCS is heterogeneous and differential diagnosis with benign regenerative nodules remains a challenge. As previously mentioned, benign nodules in BCS may present the typical radiological appearance and vascular enhancement pattern of HCC in cirrhosis[81,84,85] and may increase in number and size over time as part of the natural history of the disease.[73] A recent study specifically evaluating the radiological pattern of nodules in BCS, showed that 29% of benign lesions presented washout and up to 18% of benign lesions greater than 1 cm showed both washout and arterial phase hyperenhancement.[86] Therefore, HCC diagnosis in BCS is always a challenge and should never rely only on imaging criteria but should require histological confirmation. Although alpha-fetoprotein above a cut-off value of 15 nm/ml has been suggested as a useful biomarker for HCC in the setting of BCS,[81] it needs to be validated in larger cohorts. Surveillance for HCC in patients with chronic BCS is recommended.[18] Although specific data are lacking, the most widely endorsed strategy is to perform ultrasound every 6 months, as in cirrhosis.

Key point

HCC surveillance is recommended in patients with chronic BCS; ultrasound every 6 months is the most widely endorsed strategy.

Recent NCPVT

Recent NCPVT relates to the new occurrence of a thrombus in the portal venous axis in a patient with a previous patent portal vein. However, it may also occur in patients who exhibit partial

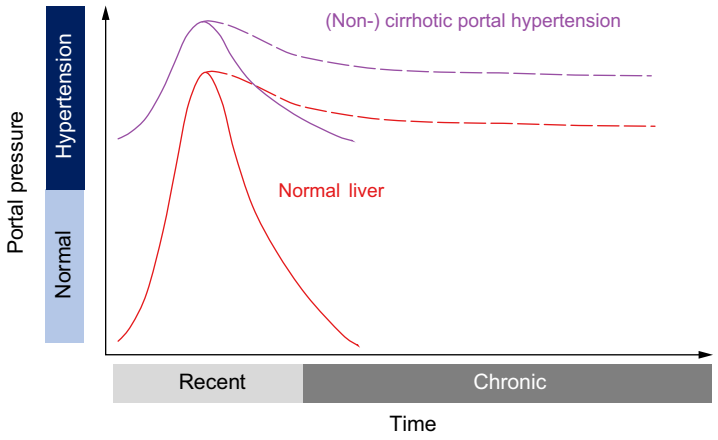

Fig. 2. Evolution of portal pressure in portal vein thrombosis. In recent portal vein thrombosis, the rapid rise in portal pressure (red line) may be associated with clinically relevant consequences including bowel infarction and ascites. However, when portal pressure is already increased due to cirrhotic or non-cirrhotic portal hypertension (violet line), the haemodynamic consequences of portal vein thrombosis are attenuated due to the presence of collateral vessels. When complete recanalization occurs, portal pressure returns to baseline levels (dashed lines).

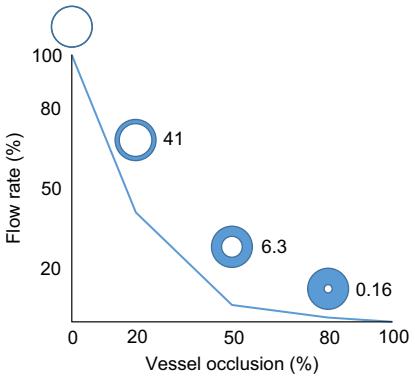

Fig. 3. Application of Poiseuille's law to blood flow. According to Poiseuille's law, and assuming that the portal vein is a rigid tube, following portal vein thrombosis, blood flow decreases proportionally to the fourth power of the vessel radius. For example, in the presence of a thrombus occupying 80% of the lumen, the blood flow is decreased by 98.4%.

PVT, where progression of the thrombus is noted. (Fig. 2). Various imaging modalities including colour Doppler ultrasound, computed tomography and MRI can be used to identify the presence of a thrombus, collateral circulation, or a dilated portal vein with accuracy rates ranging from 88–98%, with sensitivity and specificity of 80–100%. Using grey-scale ultrasound, an acute portal vein thrombus typically appears as heterogeneous, mainly hyperechoic material in the vessel lumen. The advantage of CT scan in this case relates to the improved ability to detect possible aetiologies or complications. On CT, acute PVT appears as increased attenuation and lack of enhancement, with or without inhomogeneities in portal venous and parenchymal hepatic perfusion. On MRI, the portal vein may appear with edge enhancement because of blood flow surrounding the thrombus or because of an inflammatory response of the venous wall. T1-weighted images may reveal an isointense thrombus compared to muscle, while T2 images may show a hyperintense signal.[87,88] The anatomical degree of occlusion of these vessels may be total or partial. While the occlusion by the thrombus may not be complete in imaging studies, the haemodynamic consequence of partial thrombosis may be relevant. Indeed, the portal vein can be compared to a relatively rigid tubular structure[89] in which the Poiseuille's law predicts a decreased blood flow rate proportional to the radius elevated to the fourth power. Thus, a thrombus maintaining 20% of the vessel radius free will result in a >98% decrease of the flow rate (http://hyperphysics.phy-astr.gsu.edu/hbase/ppois2.html). Consequently, partial PVT occupying more than 80% of the lumen corresponds to a nearly complete obstruction (Fig. 3).

At presentation, NCPVT may involve an extensive obstruction of the portal vein and its right and left branches, superior mesenteric vein, and splenic vein in approximately one-third of patients, while obstruction of the portal vein or of its 2 branches was found in 87% of cases. Moreover, only a single obstructed portal vein branch (with or without splenic or superior mesenteric vein obstruction) was reported in 12% of patients and the splenic or superior mesenteric vein were obstructed in 43% and 58% of patients, respectively.[7] Acute abdominal pain may be the initial manifestation of recent NCPVT. However, the intensity is variable among patients. Recent NCPVT may also be completely asymptomatic, delaying diagnosis for long periods until portal cavernoma develops. Liver function test abnormalities are usually mild and transient. A systemic inflammatory response syndrome is often present in cases of recent NCPVT due to inflammation related to thrombosis but recognized local or systemic infection is identified in only 20% of these cases. Transient ascites, often of low abundance (hence clinically non-relevant unless infection develops) and visible only using ultrasound, CT or MRI, is present in half of patients with NCPVT.[7]

Mesenteric infarction is the most severe and immediate complication of recent NCPVT. Its 60% mortality rate is high in the absence of anticoagulant treatment. Extended resection of the small bowel is sometimes necessary and is associated with a significant risk of short bowel syndrome. Early initiation of anticoagulant therapy is associated with a very low incidence of this complication.[7] The diagnosis of venous mesenteric infarction is difficult because the clinical, biological and radiological manifestations are not specific. Severe and persistent abdominal pain, despite full anticoagulant treatment, signs of organ failure (shock, renal failure, metabolic acidosis with elevated arterial lactate), abundant ascites, and/or the presence of blood in stool must evoke the diagnosis of mesenteric infarction. Type 2 diabetes has been identified as a risk factor for mesenteric infarction,[90] with a recent study identifying 3 read-

ily available criteria that predict irreversible intestinal ischaemic injury requiring resection in the setting of acute mesenteric ischaemia, namely organ failure, serum lactate levels >2 mmol/L and bowel loop dilation on CT scan. The presence of only one of these criteria was associated with a 40% risk of in irreversible intestinal ischaemic injury requiring resection at 2 months.[91]

The most common manifestations of chronic NCPVT are related to the presence of portal hypertension. Oesophageal varices may develop in nearly half of patients,[92] whereas other complications, including rectal or ectopic varices, large portosystemic collaterals and splenomegaly, frequently occur during the course of the disease. In general, hepatic function is preserved, in apparent contrast with obvious manifestations of portal hypertension. The most common complications are variceal bleeding, recurrent thrombosis and biliary complications. The risk of variceal bleeding is, as in cirrhosis, higher in medium or large varices and in the presence of red signs. The recurrence or extension of thrombosis may often be asymptomatic and is consequently not only underdiagnosed, but also poorly evaluated. In chronic NCPVT, ascites, hepatic encephalopathy, and bacterial infections are rare and most often transient. They occur preferentially as complications after gastrointestinal bleeding.[93] If specifically looked for, minimal hepatic encephalopathy is frequently present in patients with extrahepatic portal vein obstruction[94,95] but their clinical impact is unknown. Hepatic nodules of the "HNF-like" type were found in 21% of adult patients with cavernomatous transformation of the portal vein when studied by MRI.[96] However, the risk of HCC is low. Cardiovascular complications such as hepatopulmonary syndrome[97] and pulmonary arterial hypertension[98] have been reported.

Portal cavernoma cholangiopathy is characterized by abnormalities of the intrahepatic and extrahepatic bile ducts. It is the consequence of the extrinsic compression of bile ducts by portoportal collateral veins (cavernoma) and/or of an ischaemic injury of the bile ducts by thrombosis of the venous plexus of the biliary tree.[99] Biliary tract abnormalities may be observed at cholangio-MRI in 77–100% of patients. Portal cavernoma cholangiopathy is most frequently asymptomatic and can be associated with initially mild abnormalities of liver enzymes, particularly cholestatic markers alkaline phosphatase and gamma glutamyltransferase. Severe biliary manifestations including biliary colics, cholecystitis, obstructive jaundice, cholangitis, pancreatitis, are rare, occurring in only 5–30% of cases.[99–101]

Diagnostic strategy: staging and prognosis

BCS

Due to heterogeneous clinical presentation, BCS should be suspected and discarded in any patient with acute or chronic liver disease, especially when its aetiology is unknown and/or if there is an underlying prothrombotic condition. The key feature for the diagnosis of BCS is to demonstrate obstruction of the hepatic venous outflow. Non-invasive imaging techniques (Doppler ultrasound, CT or MRI) are the mainstay of an adequate diagnosis. Doppler ultrasound, performed by an experienced operator, has a sensitivity of >75% and should be the first choice option.[18] MRI and CT evaluation have a role in diagnostic confirmation or in the absence of an experienced ultrasound operator. Both CT and MRI are also useful for mapping intrahepatic and extrahepatic collateral networks, identifying associated PVT, and planning future treatment. Numerous imaging features have been described in patients with BCS.[102,103] Direct signs included visualization of the occluded veins, presence of endoluminal thrombus in HV, non-visualization of the HV, stagnant or inverted venous flow and collateral networks; these signs are more frequently found in acute BCS. Chronic forms are usually associated with indirect signs such as hypertrophy of the caudate lobe, and a caudate vein >3 mm and concomitant atrophic lobes, dysmorphic liver, parenchymal heterogeneity, heterogeneous enhancement and benign regenerative nodules. CT and MRI can also identify a rapid clearance of contrast from the caudate lobe and patchy hepatic enhancement due to uneven portal perfusion. Acutely occluded veins demonstrate no enhancement following contrast administration on CT scan, whereas on MRI they display hyperintensity on spin echo and signal void on gradient echo sequences. A multidisciplinary approach is essential, as diagnostic efficiency is augmented when the radiologist is aware of the suspected clinical diagnosis.

Liver damage in BCS is variable, and the histological changes (congestion, coagulative necrosis or simple loss of hepatocytes without inflammatory infiltrates and/or fibrosis) are not pathognomonic and do not reflect the severity of the disease. Therefore, liver biopsy is not usually necessary for the diagnosis. The sole scenario when biopsy is necessary is to confirm BCS due to small intrahepatic vein obstruction in the presence of preserved large veins on imaging techniques.[18]

Similarly, hepatic venography is only recommended if diagnosis remains uncertain despite the above investigations and classically reveals a spiderweb pattern, formed by a rich collateral circulation.

Key point

The most common complications of NCPVT are variceal bleeding, recurrent thrombosis and biliary problems, while cardiovascular complications have also been reported.

BCS staging: prognostic scores

The prognosis of BCS has dramatically changed in the last decade, with an improvement in survival as a consequence of a better management based on anticoagulation, transjugular intrahepatic portosystemic shunt (TIPS) and liver transplantation.[70] Better outcomes may also be related to a higher degree of suspicion leading to early stage

Table 3. BCS-specific prognostic index.

Score	Formula	Cut-off	Predicted survival rate	Reference
Clichy PI	(Ascites score[a] × 0.75) + (Child-Pugh score × 0.28) + (age × 0.037) + (creatinine × 0.0036)	5.4 (range from 3.4 to 9.1)	At 5 yr ≤5.4: 95% >5.4: 65%	104
New Clichy PI	0.95 × ascites score + 0.35 × Child-Pugh score + 0.0 47 × age + 0.0045 × serum creatinine + 2.2 × type III[b]—2.6	5.1 (range from 2.0 to 9.7)	At 5 y <5.1: 100% ≥5.1: 65%	67
Rotterdam BCS index	1.27 × encephalopathy + 1.04 × ascites + 0.72 × prothrombin time + 0.004 × bilirubin	Class I: 0–1.1 Class II: 1.1–1.5 Class III: ≥1.5 (range from 0.02 to 4.03)	At 5 y Class I: 89% Class II: 74% Class III: 42%	106
TIPS-BCS PI	Age (years) × 0.08 + bilirubin (mg/dl) × 0.16 + international normalized ratio (INR) × 0.63	7	1-year OLT-free survival ≤7 95% >7 12%	105
BCS-intervention-free survival prognostic score	Ascites [yes = 1, no = 0]*1.675 + ln creatinine [μmol/L]*0.613 + ln bilirubin [μmol/ L]*0.440)	Interval I: ≤5 Interval 2: 5–6 Interval 3: ≥6	Intervention-free survival Interval I: 78.3% Interval 2: 27.8% Interval 3: 6.8%	70
BCSurvival score	Age/10*0.370 + ln creatinine [μmol/L]*0.809 + ln bilirubin [μmol/L]*0.496)	Interval I: ≤7 Interval 2: 7–8 Interval 3 ≥8	Probability survival Interval I: 87.5% Interval 2: 63.3% Interval 3: 42.9%	70

[a] Ascites score: 1, absent with free sodium intake and no diuretic agents; 2, easy to control with sodium restriction or diuretic agents; and 3, resistant to this treatment because of hyponatremia or functional renal failure.
[b] Type III' is a binary variable coded as 1 for patients with clinicopathological findings of acute injury superimposed on chronic lesions, and 0 for the other patients. BCS, Budd-Chiari syndrome.

diagnosis and consequently superior treatment response. Indeed, 3-year mortality in the 60s reached 90%,[104] whereas the current expected 5-year survival is above 80%.[8,70] Information regarding the prognosis of BCS relies mostly on retrospective studies.[68,104–107] The largest prospective multicentre cohort of consecutive diagnosed patients with BCS comes from the European registry EN-Vie. 157 patients were prospectively diagnosed during a 2-year period and followed up for almost 5 years, reporting a 5-year survival of 85%.[70]

As shown in Table 3, there are several parameters or combinations of them that are used to predict BCS prognosis. Liver function tests such as Child-Pugh[108] and model for end-stage liver disease score[109] are able to predict outcomes in BCS. BCS-specific prognostic scores[67,104,106] are useful for predicting transplant-free survival and invasive therapy-free survival and have been externally validated[70,110]. The BCS-TIPS prognostic index score was developed to identify patients that would not tolerate TIPS. Indeed, this score identifies patients with poor outcomes despite TIPS, suggesting that liver transplant may be a better alternative. Nevertheless, despite showing a statistically significant association with survival and, permitting comparison among different cohorts, none of the BCS-specific prognostic indices has excellent discriminative capacity and none can be used to guide individualized management.[70,110]

Histological features and aminotransferase levels have also been evaluated as prognostic factors. Pathological lesions are not useful for predicting outcomes in BCS due to heterogeneity of the lesions and the non-homogeneous pattern.[67,108] The largest analysis of Western patients with acute liver failure due to BCS included 19 patients registered in the US Acute Liver Failure Study Group and showed poor outcomes. They evaluated patients from 1999–2015 and demonstrated that increased aminotransferases (aspartate aminotransferase [AST], alanine aminotransferase [ALT]) were predictors of poor outcomes, marking the severity and/or acuity of the damage. While mortality was high at 58%, cases reported after 2010 had a better outcome due to the improved diagnosis and management.[111] Moreover, in a retrospective study including 96 patients with primary BCS, ALT ≥5 × the upper limit of normal was associated with more severe clinical presentation, a higher Child-Pugh score, Clichy score, Rotterdam BCS score, and higher mortality. However high levels of ALT that decrease rapidly can be considered a marker of imminent improvement in liver function, reflecting a good outcome.[112]

NCPVT staging and prognosis

Following recent thrombosis of the portal vein, and in the absence of recanalization, a network of porto-portal collateral veins, defined as cavernoma, may develop within a few weeks. The presence of cavernoma is a direct consequence of NCPVT, and this term suggests that thrombosis of the portal vein was not recent. Moreover, the presence of portal vein cavernoma *per se* does

not imply chronicity of this condition. Portosystemic collateral veins may also develop and contribute to the complications of portal hypertension. An accurate diagnosis and staging of NCPVT is important, because it represents the basis for its management. In addition, the purpose of correct classification is to guide therapeutic decisions aimed at obtaining recanalization and at preventing the extension and/or the relapse of PVT and of possible complications. Given the complexity of the clinical picture related to NCPVT, including a high number of possible aetiologic factors and different degrees of obstruction and extension of the thrombosis, the need for an individualized yet precise approach appears crucial. For these reasons, several classification models have been proposed. One of the most frequently used systems is, however, only based on localization and extension of thrombosis.[113] More recently, Sarin *et al.* have proposed a new classification,[87] which takes into account not only the location and extension of the thrombus, but also the mode of onset and diagnosis of the thrombosis (recent or chronic), the type of presentation (signs and symptoms), and the possible underlying liver disease (cirrhosis or normal liver). The purpose of this classification (Box 1) is to serve as a starting point for the uniform reporting of NCPVT, to better define clinical endpoints, and to compare future studies. The prospective evaluation of this classification should allow a risk stratification to apply therapeutic or preventive strategies.

Treatment and management of complications

Stepwise treatment for BCS

Unfortunately, randomized clinical trials comparing different treatment options for BCS are still lacking. Recommendations are based on clinical experience, retrospective studies and expert consensus. Based on these, the current treatment strategy of BCS relies on progressively escalating invasiveness. The first step is based on medical management aimed at treating the complications of portal hypertension and the underlying disease. If no improvement or even further deterioration in BCS symptoms is observed, the next step is devoted to correcting hepatic venous outflow obstruction as described below.

Portal hypertension complications

Because no specific studies exist in patients with Budd-Chiari, the current recommendation is to treat and prevent complications related to portal hypertension, as recommended for patients with cirrhosis.[18,114]

Treatment of the underlying disease

The underlying disease should be promptly diagnosed and specifically treated. This usually requires a dedicated multidisciplinary team of hepatologist, haematologist and specialists in systemic disorders. As an example, early recognition and adequate treatment of underlying MPN, PNH or Behçet's syndrome may markedly influence the outcome of the patients and/or prevent thrombosis progression.[115,116]

Key point

The current treatment strategy for BCS involves a progressive escalation in invasiveness.

Correcting hepatic venous outflow obstruction: Stepwise treatment

Although there are small retrospective studies showing good outcomes after initial management with surgical shunts,[117–119] most recommendations support the gradual escalation of management from least to most invasive (Fig. 4).[18,107,114]

Anticoagulation

The stepped approach starts with medical treatment using anticoagulation, in an attempt to achieve recanalization but mainly to prevent thrombosis progression, together with the treatment or prevention of the complications of portal hypertension. Anticoagulation should be administered to all patients with BCS, even those without an underlying prothrombotic disorder or in those that are initially asymptomatic. Long-term anticoagulation, started as soon as possible after the diagnosis, achieves a 5-year intervention free survival with disease-control in 25–30% of patients, particularly in mild/moderate cases. This is observed both in Western and in Asian patients.[8,69,99,112] Either low molecular weight

Box 1. Morphological, functional, and clinical classification of NCPVT[87]. HCC, hepatocellular carcinoma; NCPVT, non-cirrhotic non-tumoral portal vein thrombosis; PHT, portal hypertension; PV, portal vein.

Site of NCPVT
- **Type 1**: trunk only
- **Type 2**: branch only: 2a, one branch; 2b, both branches
- **Type 3**: trunk and branches

Degree of portal venous system occlusion
- **O**: Occlusive: no flow visible in PV lumen on imaging/Doppler study
- **NO**: Non-occlusive: flow visible in PV lumen through imaging/Doppler study

Duration and presentation
- **R**: Recent (first time detected in previously patent PV, presence of hyperdense thrombus on imaging, absent or limited collateral circulation, dilated PV at the site of occlusion)
- **Ch**: Chronic (no hyperdense thrombus; previously diagnosed NCPVT on follow-up, portal cavernoma and clinical features of PHT)
- **As**: Asymptomatic
- **S**: Symptomatic: features of acute NCPVT (with or without acute bowel ischaemia) or features of portal hypertension

Extent of PV system occlusion (S, M, SM)
- **S**: Splenic vein, **M**: mesenteric vein or **SM**: both

Type and presence of underlying liver disease
Cirrhotic, non-cirrhotic liver disease, post-liver transplant, HCC, local malignancies, and associated conditions

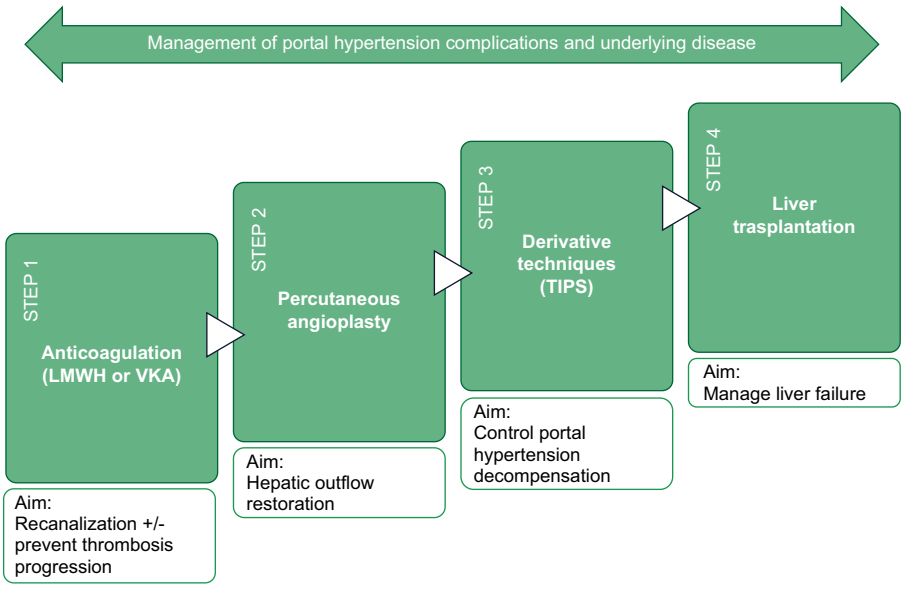

Fig. 4. Minimal Invasiveness therapeutic strategy for BCS. BCS, Budd-Chiari syndrome.

heparin (LMWH) or vitamin K antagonists (VKAs) are the treatment of choice to initiate anticoagulation. Therapeutic doses of LMWH should be given together with VKAs until the therapeutic range (international normalized ratio between 2–3) is achieved. It should be noted that long-term LMWH cannot be used in patients with severe renal failure and that unfractionated heparin should be avoided due to the high incidence of heparin-induced thrombocytopenia in patients with BCS.[107] Direct oral anticoagulants (DOACs) are used to treat thrombotic diseases in other vascular areas and, although there are currently only a few reports,[121] this option can also be considered in patients with BCS and normal liver function. However, DOACs are not registered for this indication, and therefore, if used, this must be done with caution, especially in patients with renal failure.

Restoring hepatic venous outflow

Thrombolysis. The experience of thrombolysis in BCS is limited. Recombinant tissue plasminogen activator, streptokinase or urokinase have been used. These agents can be instilled through a peripheral vein or locally after catheterization of the thrombosed vein. There are no studies comparing the efficacy of local *vs.* systemic infusion. No systematic reviews have been published to evaluate the efficacy and risks of thrombolysis in BCS. A narrative review by *Sharma et al.* indicates that the best results are achieved in patients with a recent and incomplete thrombosis who are treated with local and early infusion combined with another interventional procedure (*e.g.* angioplasty, stenting) to restore venous outflow.[122] In the published series, the bleeding complications of thrombolysis were major, with 2 fatal outcomes.[123] Hence, this therapeutic option is contraindicated in patients with a potentially haemorrhagic condition, or patients who have had an invasive procedure, including paracentesis, in the previous 24 hours. In summary, thrombolysis should only be attempted in select cases with acute or sub-acute BCS, at experienced centres.[18]

Percutaneous angioplasty. In some instances, BCS is due to partial or segmental stenosis in the cranial part of the HV or at the suprahepatic IVC.[124] In these cases, percutaneous transluminal angioplasty is an effective and safe approach for restoring the physiological hepatic outflow, with or without stenting. This makes it mandatory to try and identify these patients once the diagnosis of BCS is established. In European patients, segmental stenosis is only found in a small percentage of patients and therefore, this technique only benefits a small proportion of patients with BCS (10% in the EN-Vie cohort).[70] In Asia, where IVC obstruction predominates, the reported applicability is much higher, and combining angioplasty and stenting can achieve patency in >80% of patients at 5 years.[125]

Angioplasty is the first step to restore hepatic outflow. However, post-angioplasty re-stenosis may occur, necessitating subsequent angioplasties. While stenting may reduce re-stenosis, stent misplacement may make future TIPS or liver transplantation more challenging. In the European cohort, 22 patients underwent angioplasty, 13 patients were treated with angioplasty, 7 with thrombolysis and 2 with both as the first invasive treatment. In 6 of these 22 patients, a vascular stent was placed at the time of angioplasty and in total 14 patients (64%) required further treatment (TIPS in 12 and orthotopic liver transplant [OLT] in 2 patients).[70]

A recent retrospective study performed in China suggests higher efficacy and long-term patency of retrievable stents (retrieved after a median of 15 days). However, these results should be interpreted cautiously due to the short duration of stenting and because a significant number of patients with retrievable stents exhibited acute thrombosis (66.7% *vs.* 2.4%, $p = 0.0004$) and hence, were additionally treated with thrombolysis.[126]

Derivative techniques. When the aforementioned treatments are not possible or fail to solve the obstruction of the hepatic blood flow, the portal system can be converted into an outflow tract by derivative techniques.

Before the 90s, surgical shunts were the only derivative technique available. Mesocaval shunt was the most frequent shunt used, preferred to the porto-caval side-to-side shunt since it is easier to perform in the setting of caudate lobe hypertrophy.[127] In the setting of IVC compression, the presence of an infrahepatic caval pressure >20 mmHg or a gradient between it and the right atrium of 15 mmHg, are predictive of inadequate shunt function, unless the stenosis/compression of the IVC is simultaneously corrected.[127] In cases when the obstructed IVC cannot be bypassed, a meso-atrial shunt may be an alternative.[128] Decompressing the cava together with the portal venous system through a meso-cavo-atrial shunt has been proposed as a better alternative to a meso-atrial shunt.[129] Overall, surgical shunts are associated with significant morbidity-mortality, and have not demonstrated a clear survival advantage.[104,130] However, in patients surviving surgery in whom the shunt remains patent, the outcome is excellent.[119,131]

Since the 90s, surgical shunts have been replaced by the less-invasive TIPS in most places. TIPS has been demonstrated to be more effective in maintaining patency and is associated with lower morbidity and mortality than surgery in patients with failure on medical treatment or when recanalization has failed.[18,114] However, very good outcomes have been reported in selected patients with BCS treated with surgical portal decompression performed early after diagnosis.[132] Moreover, in cases with HV and concomitant IVC thrombosis or severe compression of the IVC by an enlarged liver, as mentioned, the traditional meso-caval surgical shunt may be ineffective and TIPS becomes a more feasible option.[119,133] TIPS primary patency rate using PTFE-covered stents is 67% at 2-year follow-up.[105] However, TIPS should be performed in experienced centres because of the increased difficulty and morbidity associated with the technique in patients with NCPVT compared to those with cirrhosis. Indeed, a transcaval approach for the portal vein puncture may be needed in up to 60% of patients given inaccessibility of the hepatic vein.[105,134] In a European prospective cohort of 157 patients with BCS, after 5 years of follow-up, 40% of patients required TIPS because of failed medical treatment, most of them (73%) during the first 6 months after diagnosis. In this cohort, 5-year survival without liver transplantation was 72%.[70] The use of TIPS at an earlier time point in the recommended stepwise management has recently been suggested.[135] However, there are no direct data supporting this recommendation. In addition, in the study by Seijo *et al.*[70] in the 62 patients receiving TIPS following the stepwise strategy, the median time from BCS diagnosis to TIPS was 1 month (range 0–38 months). Interestingly, no differences in survival were observed in patients receiving TIPS during or after the first months following diagnosis, with similar results observed when the cut-off time was 3 or 6 months after diagnosis. These results suggest that the stepwise strategy is effective and safe provided that patients are followed closely and TIPS is implemented soon after prior treatment ceases to confer an improvement or clinical deterioration hastens. no improvement, hastening further deterioration. In addition, instead of using TIPS for all patients with symptomatic BCS, following this strategy will prevent a significant number of patients from experiencing the potential side-effects of TIPS in cases of limited benefit. Evaluation of some criteria 2 weeks after treatment initiation has been proposed to identify the optimal point at which to move a given patient along the treatment algorithm (Table 4). However, this is always a challenge.[18] This is why these patients are best managed in referral centres.

Key point

Current results suggest that the stepwise strategy to BCS treatment is effective and safe, as long as patients are followed closely, and TIPS is implemented as soon as needed.

In Asian countries where IVC obstruction prevails, TIPS placement is not as frequent as in Europe. However, the use of TIPS in Asia is increasing, and available reports show similar positive results as in the West.[136–140]

Recent data suggest that liver elastography measurements may be a good non-invasive test to evaluate the effectiveness of liver decompression. Currently this has been evaluated after invasive techniques such as balloon angioplasty (with or without stenting) in a small number of patients, showing a reduction of elastography measurement when the liver is adequately decompressed.[141] It is possible that this technology can also be used to monitor the response to medical treatment, although more studies are needed.

Liver transplantation: indications and post-transplant approach. In patients with BCS, LT represents the last therapeutic option following treatment failure on other less-invasive therapies. Although it may be a first step in patients who initially present with acute hepatic failure,[142] TIPS should be considered while waiting for LT as it may foster fast improvement and potentially avoid transplantation. It may be acknowledged that LT in patients with BCS represents a technical challenge mainly because of the presence of retroperitoneal fibrosis

Table 4. Evaluation of the response to treatment (Adapted from Plessier A *et al.*[107].

	Ongoing treatment response (2 weeks)	Complete treatment response
Ascites	Yes	No clinically detectable*
Creatinine	Normal or decreasing	normal
Sodium	Normal or increasing	normal
Balance (water-Na)	negative	
NaCl intake	moderate	moderate
Factor V level	increasing	above 40% of normal value
Serum conjugated bilirrubin	Decreasing	below 15 μmol/L
PHT related bleeding		No
SB Infections		No
BMI		>20 kg/m^2

*Without diuretic treatment or low dose (spironolactone 75 mg/d or furosemide 40 mg/d).

related to HV thrombosis, liver enlargement and adhesions. In addition, the classical "piggyback" technique for anastomosis becomes more challenging due to the increased size of the caudate lobe and occlusion of the HV ostia. However, TIPS did not worsen prognosis after LT in patients with BCS.[105,143]

Key point

There is some evidence that living donor liver transplant is a viable choice for patients with BCS who have experienced treatment failure on other less-invasive therapies.

Five-year survival rate after LT has improved over the years.[144–147] A large European study showed actuarial overall survival of 76%, 71% and 68% at 1-year, 5-years and 10-years, respectively.[145] Notably, these outcomes are similar to those in patients treated with TIPS (88% and 78% OLT-free survival at 1 year and 5 years, respectively),[105] reinforcing the benefit of the stepwise approach for selecting patients who undoubtedly require LT and saving organs for other indications.

Once LT is considered, it will be the cure in cases of inborn errors of metabolism, such as antithrombin deficiency or homozygous factor V Leiden mutation. However, other prothrombotic disorders, such as MPN or PNH, can be a contraindication and/or impact post-LT outcome.

Key point

The general strategy for treating NCPVT is aimed at preventing the extension of the thrombus and achieving portal vein recanalization, to prevent portal hypertension and its complications.

MPN is not a contraindication for LT, since optimal treatment of these patients yields excellent long-term survival. Since patients with MPN have mature and well-differentiated granulocytes, the risk of infectious complications after LT is no higher than in LT patients without MPN. Several case series and retrospective studies[142,145,148] did not reveal evidence of accelerated MPN progression (leukemic transformation) after LT in a 10-year follow-up period, and the survival rates were excellent (71–>90% over 3 years, comparable to non-MPN patients with BCS).

Patients with MPN who have undergone liver transplantation for BCS should be treated with anticoagulant drugs and/or aspirin, and with anti-proliferative treatment (hydroxyurea). Several groups have reported excellent outcomes in patients with MPN treated only with hydroxyurea and aspirin after LT, without recurrence of BCS.[149,150] However, in another study, recurrence of BCS and other thrombotic complications were reported despite anticoagulant therapy with warfarin.[151] Based on the available data and the severity of thrombotic complications if they occur, it is advisable to treat patients with anticoagulants (warfarin), aspirin and hydroxyurea in order to prevent recurrent thrombotic complications after LT. In cases of high risk of bleeding or development of bleeding complications, it is suggested to give at least aspirin and anti-proliferative treatment, avoiding VKAs.

When the underlying disorder is PNH, LT may be more challenging, as patients may present or develop aplastic anaemia, requiring an allogenic stem cell transplant, thereby increasing the risk of infection. Some cases of liver transplantation for BCS in patients with PNH have been reported, sometimes complicated by the recurrence of BCS.[152,153]

Although the evidence comes from a small series of cases, living donor liver transplant is a viable choice with acceptable survival rates (>70% at 5 years).[154,155]

Treatment of recent NCPVT

The aim of therapy for recent NCPVT is to prevent the extension of the thrombus to mesenteric veins and intestinal infarction. In addition, therapy for recent NCPVT must try to achieve portal vein recanalization to prevent the development of portal hypertension.

Anticoagulation

Anticoagulation is the key treatment of recent NCPVT. Although randomized controlled trials are lacking, a landmark European prospective multicentre study reported no thrombus extension to the splenic or mesenteric vein in 95 patients with recent PVT. They were treated with early administration of LMWH, and rapidly replaced by oral anticoagulation with VKAs, targeting an international normalized ratio of 2–3.[7] Only 2/95 patients developed intestinal infarction. There was no mortality related to NCPVT or its treatment. Full recanalization of the vein was only obtained in one-third of patients following 6 months of continued anticoagulation therapy. Interestingly, with a prolongation of anticoagulation, there was no further recanalization of the portal vein, but continued recanalization of the splenic and superior mesenteric vein. A year after

the onset of NCPVT, 40% of the patients had a permanent obstruction of the portal vein and portal cavernoma.[7] These findings independently validated previous retrospective single centre studies.[156–159] Among baseline factors, splenic vein obstruction, ascites[7] and delays in initiating anticoagulation[159] have been associated with the absence of portal vein recanalization. Adverse events on anticoagulation therapy did not obviously differ from those expected from natural history.[7] The mortality rate was 2% and was not related to bleeding or NCPVT, with a median follow-up of 8 months after NCPVT diagnosis[7].

Recently, a few cases of initial treatment of recent NCPVT with DOACs instead of LMWH have been reported.[160–162] The largest study compared 26 patients treated with DOACs with 23 treated with enoxaparin. Although the data should be interpreted cautiously, since more than half of these thrombotic events occurred in a cancer setting, recurrence and major bleeding rates were not different between patients treated with DOACs and with enoxaparin.[162]

Antibiotics

Antibiotics are given in patients with NCPVT triggered by an abdominal infection. When septic pylephlebitis is diagnosed, prolonged treatment with antibiotics adapted to isolated bacteria or to anaerobic digestive flora is necessary.[18] Recent data suggest that oral antibiotics should be given in patients with acute mesenteric ischaemia, since their use is associated with a lower risk of irreversible transmural intestinal necrosis.[91]

Treatment of underlying causes

Retrospective studies suggested that rapid identification and treatment of risk factors for NCPVT might favourably influence NCPVT outcome. Indeed, in a retrospective multicentre study including 109 patients with MPN and NCPVT (n = 63) or BCS (n = 46), cytoreductive therapy was associated with less common severe liver-related events or vascular complications.[115] Although specific data on NCPVT are lacking, aetiological treatment in addition to anticoagulation in patients with other vascular liver diseases, such as corticosteroids and/or immunosuppressive therapy in Behçet's disease,[116] or eculizumab (a humanized monoclonal antibody directed against the terminal complement protein C5) in PNH,[163] improve patient outcomes.

Thrombolysis and/or interventional radiology

Pharmacological thrombolysis (local or systemic) has been proposed as an adjunct to anticoagulation. However, severe procedure-related morbidity and fatalities have been reported with recanalization rates similar to those achieved with anticoagulation alone.[123,164,165]

Recent reports suggest better results with a combination of transjugular thrombectomy, local fibrinolysis and/or TIPS, as summarized (Table 5). Interestingly, patients treated with this approach rarely developed portal cavernoma and signs of portal hypertension. This invasive strategy does not fit all patients with acute NCPVT, but might be useful in patients with progressive thrombosis, clinical deterioration despite anticoagulation, or with a low likelihood of recanalization following therapeutic anticoagulation. This strategy might also be considered in patients with superior mesenteric vein thrombosis and features predictive of irreversible intestinal ischaemic injury, as detailed above.[91]

Surgery

Surgical thrombectomy is currently not an option for NCPVT given the invasiveness of the procedure, the low rate of recanalization achieved, and the favourable outcome yielded using only anticoagulation.[18]

Surgery has 2 main indications in patients with acute NCPVT: (a) treatment of a local factor responsible for NCPVT; (b) suspicion of mesenteric infarction.[166]

Treatment of chronic NCPVT

Management of complications of portal hypertension

In general, the current recommendation is to treat and prevent complications of portal hypertension, as recommended for patients with cirrhosis.[18,114]

Oesophageal varices. In a recent study that included 178 non-cirrhotic patients with NCPVT, the natural history of oesophageal varices appeared similar to that observed in patients with cirrhosis.[92] In patients without varices at inclusion, the risk of developing them was 2% at 1 year and 22% at 3 years. Progression from small to medium or large varices was 13% at 1 year, and 54% at 5 years. In patients with medium or large varices, who received adequate prophylaxis, the risk of bleeding was 9% at 1 year and 32% at 5 years. Head to head comparison studies have never been conducted. Therefore, there are no strong data on the real impact of those treatments on the natural history of the disease.[18] However, it has been suggested that the use of non-selective beta-blockers was associated with a decreased risk of bleeding[167] and improved survival,[168] and that the incidence of bleeding was similar using beta-blockers or endoscopic band ligation (32% and 25%, respectively).[92,169] Currently, the same principles related to the use of beta-blockers and endoscopic therapy in patients with cirrhosis should also be applied in patients with extrahepatic portal vein obstruction.[114]

In patients treated with anticoagulants for extrahepatic portal vein obstruction, the incidence

Table 5. Interventional radiology treatment of acute extensive portal vein thrombosis without cirrhosis.

Reference Number of patients	Procedure	Long-term anticoagulation	Recanalization	Complications	Recurrence of thrombosis
Hollingshead, 2005 [164] n = 20	Local thrombolysis alone	Yes	-Complete: 3/20 -Partial: 12/20 -No: 5/20	-1 death 2 weeks after thrombolytic therapy.-11 major complications (bleeding) -2 liver transplantation	Not mentioned
Smalberg JH, 2008[123] n = 4	Local thrombolysis, combined (in 1 out of the 4 patients) with TIPS	Yes	-Complete: 1/4 -Partial: 1/4 -No: 2/4	2 major bleeding	Not mentioned
Cao, 2013[213] n = 12	Percutaneous transhepatic balloon angioplasty and/or stent placement without thrombolysis or thrombectomy	No	11/12	1 death from acute respiratory distress syndrome 8 days after the procedure	5/12
Rosenqvist, 2016[214] n = 4	Local thrombolysis, combined (in 3 out of the 4 patients) with TIPS	Not available	Limited data. "3 recovered and have survived more than 6 years."		
Klinger, 2017[64] n = 17	Combination of transjugular thrombectomy, local fibrinolysis and – depending on thrombus resolution – TIPS	Yes (≥12 months after recanalization)	-Complete: 9/17 -Partial: 7/17 -No: 1/17	-2 HIT, including 1 leading to segmental bowel resection) -1 additional bowel resection -1 hepatic artery pseudoaneurysm with spontaneous occlusion	-2/17 recurrence of NCPVT at 28 months (1 recanalized) -3 TIPS obstructions, all recanalized -1 portal cavernoma
Wolter, 2018[65] n = 9	Thrombectomy, local fibrinolysis and/or TIPS	Not available	-Partial or complete: 7/9-No: 2/9 (due to failure to access portal vein)	None	3 TIPS obstructions (1 recanalized)

HIT, heparin-induced thrombocytopenia; TIPS, transjugular intrahepatic portosystemic shunt.

(7.4%) and severity of bleeding after endoscopic band ligation were not significantly different compared to that observed in non-anticoagulated patients.[170] Similarly, 1 study in cirrhotic patients suggests that LMWH during prophylactic endoscopic band ligation does not increase the risk of bleeding and death.[171] Although more results on this issue are needed, these studies seem to challenge the currently accepted concept that anticoagulation should be delayed until adequate treatment of variceal bleeding has been established.

Anticoagulation. The indications for the administration of long-term anticoagulant therapy in patients with chronic NCPVT remain in part controversial and are based on retrospective series in adults.[172] Anticoagulants have been associated with decreased risk of thrombosis extension or recurrence in 3 studies and improved survival. Recurrence of thrombosis was associated with the presence of a prothrombotic condition. In patients with a history of intestinal infarction, long-term anticoagulation therapy was associated with a decreased risk of recurrent thrombosis.[167,168,173,174] No change,[167] or a mild increased risk of gastrointestinal bleedings,[175] in patients under anticoagulation treatment, has been reported, however without increasing bleeding severity.[167,175] The most commonly used anticoagulants are unfractionated heparin as initial anticoagulant treatment, LMWH and VKAs. One significant drawback of unfractionated heparin is the occurrence of heparin-induced thrombocytopenia that has been reported in up to 20% of patients with NCPVT associated with a myeloproliferative disorder.[176]

Derivative techniques. The insertion of a TIPS in patients with cavernoma may be indicated in cases of recurrent bleeding and of refractory ascites not manageable medically or endoscopically. TIPS in patients with chronic PVT is usually technically difficult or impossible to perform. Although this has been more extensively evaluated in patients with cirrhosis with associated PVT, risk factors for the failure of TIPS are the lack of identification of the intrahepatic portal vein branches, the presence of portal cavernoma without identification of the portal vein trunk, and the lack of a clear "landing" zone at mesenteric or splenic territories.[177] Long-term outcomes after TIPS in patients with chronic PVT are unknown. In some patients with chronic PVT, recanalization of the portal vein, restoring physiological portal blood flow without the need for TIPS, could be a better therapeutic strategy (Fig. 5). Contemporary imaging techniques now make recanalization of the portal vein more practical.

Invasive treatment: surgery/portal vein recanalization. Portal vein recanalization followed by TIPS (PVR-TIPS) was initially developed in LT candidates to allow a physiological anastomosis between the graft and the recipient portal vein.[182,183] The transplenic approach to access the thrombosed portal vein was shown to be superior to the transhepatic approach, achieving PVR with a high success rate and fewer side-effects.[183] The technique has been described in detail, with long-term patency of the recanalized vein demonstrated in the most recent report.[183,184] The technique for PVR-TIPS has now become perfected and it is easily reproducible. In brief, the films of a potential PVR-TIPS patient are reviewed and cavernoma and chronic NCPVT identified (Fig. 6A). In the coronal plane, an intraparenchymal splenic vein that flows inline to the main splenic vein is identified and punctured. A 5-French system is advanced to the junction of the splenic and portal vein, with subsequent splenoportography, confirming cavernomatous transformation (Fig. 6B). The diminutive portal "chord" is identified, with retrograde accessing through this chord into the right portal vein. A 10 mm snare is deployed and used as a target for standard TIPS puncture. An exchange length glide wire is used for through-and-through access out of the spleen. From there, proper measurement from the hepatic vein to 1 cm into the main PV is made followed by stent placement. Angioplasty of the chronically thrombosed PV will immediately re-establish flow (Fig. 7A). With time, the vein will remodel and

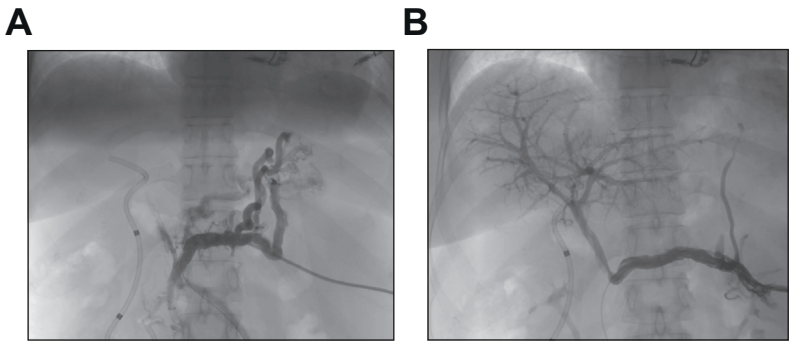

Fig. 5. Patient with NCPVT. (A) Before and (B) after angioplasty restoring physiological portal blood flow. NCPVT, non-cirrhotic non-tumoral portal vein thrombosis

Key point

While still slightly controversial, long-term anticoagulant therapy can be used in patients with chronic NCPVT, with some evidence of improved survival.

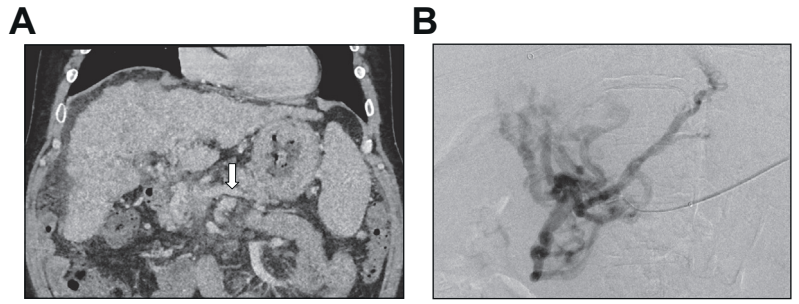

Fig. 6. Patient with cavernomatous transformation. (A) Coronal contrast-enhanced CT demonstrates cirrhotic liver, cavernomatous transformation and patent splenic vein (arrow), (B) trans-splenic splenoportography confirms absent main portal vein with cavernomas.

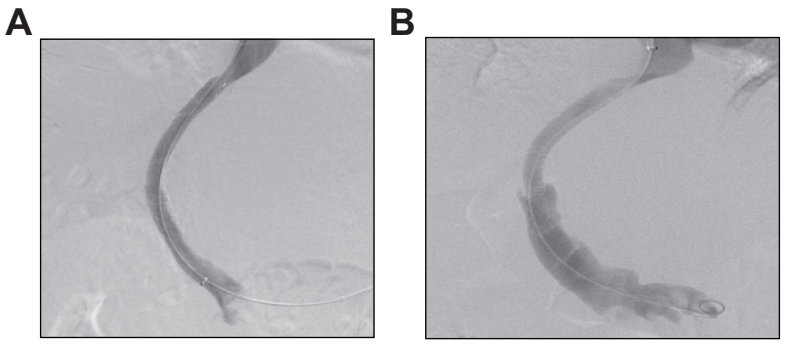

Fig. 7. Completed TIPS in patient on the liver transplant waiting list. (A) Completed TIPS demonstrates flow and 4 cm of unstented main portal vein, ready for transplantation, (B) TIPS venography after 2 months shows continued expansion of the main portal vein while the patient waits for liver availability. TIPS, transjugular intrahepatic portosystemic shunt.

behave normally (Fig. 7B). Most patients treated with PVR and TIPS have cirrhosis. However, some patients without cirrhosis have also been treated. Indeed, a recent study shows good results when performing PVR without the need for TIPS provided the PVT does not occlude distal intrahepatic portal vein branches.[185,186] However, the potential role of PVR-TIPS in this scenario should be further investigated.

Management of portal cavernoma cholangiopathy
The recommendations for the treatment of portal cavernoma cholangiopathy are based on expert opinions.[99] Specific treatment should only be considered in cases of jaundice, pruritus, or cholangitis.[18,99] Endoscopic treatment is indicated for main bile duct stones or biliary stenosis, however, the risk of bleeding is increased when varices are present around the bile ducts. After endoscopic treatment, the use of ursodeoxycholic acid may decrease the risk of recurrence of symptoms.[100,101,187] There are no data evaluating the efficacy of endoscopic treatment *vs.* ursodeoxycholic acid in these groups of patients. Shunt surgery may also be required in some selected cases of failure of other treatment modalities, while bilio-digestive anastomoses are associated with a high risk of severe complications (cholangitis and intraoperative bleeding) and recurrence of biliopathy in 30% and 70% of cases, respectively, according to a systematic review.[188] Overall, management of severe complications of portal cavernoma cholangiopathy is usually challenging and requires a individualized and multidisciplinary approach.

Management of NCPVT in the paediatric population
Chronic NCPVT in children is a severe condition even if symptoms are well tolerated. Medical care and hospitalizations are often required because of a number of possible complications including neurological or cognitive deficits, somatic growth retardation and progressive portal cavernoma cholangiopathy, which result in impaired quality of life.[178] In the paediatric population, the meso-Rex shunt or the mesenterico-left portal vein bypass, in contrast to portosystemic shunts which divert portal blood flow into the systemic circulation, may restore blood flow in the closest possible manner to the physiological state and have been associated with resolution of portal hypertension. In addition, other complications such as coagulopathy, neurocognitive defects from hepatic encephalopathy, growth retardation and portal cavernoma cholangiopathy, may be partially or completely corrected after this procedure.[179,180] As a consequence, the meso-Rex bypass should be considered the treatment of choice in children with chronic PVT, and its feasibility should be evaluated in tertiary hospitals. In children presenting with intrahepatic cavernoma, or with poor quality splanchnic veins, surgical options are limited, but since portal cavernoma is not a contraindication to LT, children with severe clinical manifestations of chronic NCPVT should be evaluated for LT, including living donor related procedures. While the preferred non-surgical options for the treatment of varices remain endoscopic band ligation and non-selective beta-blockers, no consensus is currently available.[181]

Specific considerations in the treatment of the associated condition

MPN

Diagnosing the underlying aetiological factor for developing NCPVT is important, since it may have therapeutic or prognostic implications. According to current MPN guidelines, patients diagnosed with MPN are treated prophylactically with low-dose aspirin. However, in many patients with MPN-associated NCPVT, the thrombotic event is the presenting symptom of the MPN. In case of NCPVT and underlying MPN, anticoagulant treatment with unfractionated heparin or LMWH should be started immediately. Long-term treatment with VKA should be given for NCPVT in patients with MPN, because of the high risk of recurrence.[18,189] The risk of recurrent thrombotic complications is associated with several factors, including history of previous thrombosis, splenomegaly and leukocytosis.[190] It is unknown whether aspirin should be added to treatment with VKAs in patients with NCPVT and MPN in order to reduce the high recurrence rate. In a retrospective study in 44 patients with NCPVT and MPN, the prevalence of recurrent thrombosis was higher in individuals treated with VKAs than in patients treated with aspirin or with combination therapy of VKAs and aspirin.[191] In a more recent study, these findings could not be confirmed, and recurrent thrombosis was not dependent upon the type of anticoagulant treatment.[190,192] Therefore, prospective studies are urgently needed to assess the benefit of combination anticoagulant therapy. Patients with MPN should also be treated with anti-proliferative therapy and/or phlebotomy

in case of elevated blood cell counts in order to normalize peripheral blood cell counts.[193] In general, in patients with PV, haematocrit <45% and platelet count $<400 \times 10^9$/L and white blood cell count $<10 \times 10^9$/L should be the therapeutic target.[194,195] In patients with ET, the aim is to maintain platelet counts $<400 \times 10^9$/L.[196] It is unclear whether these target values are also optimal in patients with NCPVT.

PNH

The diagnosis of underlying PNH in patients with NCPVT may have important implications for treatment. Patients with PNH and thrombotic events, who are known to have a high risk of recurrence even with VKA treatment, can be treated more effectively with eculizumab, an antibody directed to complement factor C5, which strongly reduces the risk of thrombotic events.[197]

Direct oral anticoagulants in patients with BCS and NCPVT

DOACs are direct-acting oral anticoagulant drugs, which target factor IIa (thrombin) (*e.g.* dabigatran) or factor Xa (*e.g.* rivaroxaban, apixaban and edoxaban). The advantages of DOACs compared to VKAs include reduced risk of major bleeding, fixed dose once or twice daily, fast action within 2–3 hours, short half-life, limited interaction with food and drugs, and no need for monitoring.[198] Possible disadvantages of DOACs are the lack of an antidote in Europe in case of bleeding associated with the use of factor Xa inhibitors, inability to routinely monitor these drugs, and the high costs.[198] The incidence of gastrointestinal bleeding may be slightly higher with DOACs compared to VKA treated patients, especially with dabigatran and rivaroxaban.[199–201] This is of importance because patients with BCS or PVT may be at an even higher risk of gastrointestinal bleeding.

No randomized clinical trials have been performed in patients with vascular liver disorders, including NCPVT or BCS. In addition, it is also still debated whether DOACs can be safely used in patients with liver disease, since these patients were not included in the large trials on venous thrombosis and atrial fibrillation. The label advice for using DOACs in patients with hepatic dysfunction suggests not to use DOACs in moderate to severe cirrhosis. Several cases or case series reported the use of DOACs in these patients.[160,202–205] The VALDIG study group recently reported results in 60 patients with NCPVT and 9 with BCS, some of whom also had cirrhosis, who were treated with DOACs.[206] They found a low rate of recurrent thrombosis and bleeding in 5% of patients, concluding that DOACs seemed safe and effective for individuals with NCPVT. Prospective randomized clinical trials are urgently needed to investigate the efficacy and safety of DOACs in comparison to current treatment in patients with BCS and NCPVT, before DOACs can be recommended for these patients.

Key point

In patients with NCPVT and MPN, anticoagulant therapy should be started immediately following diagnosis.

Pregnancy and splanchnic vein thrombosis

BCS and NCPVT frequently affect women of childbearing age who might desire pregnancy. In general, pregnancy and the postpartum are prothrombotic states. Moreover, haemodynamic changes occurring during pregnancy are reminiscent of the circulatory changes classically associated with portal hypertension and might thus further augment them. Pregnancy in women with BCS and NCPVT theoretically favours splanchnic vein thrombosis and complications of portal hypertension. However, data obtained by the VALDIG network were favourable and demonstrated that pregnancy should not be contraindicated in these women when the liver disease was stabilized, including, if needed, by the use of portal decompressive procedure.[207,208] Outcomes of pregnancy in women with vascular diseases of the liver and the management of pregnancy and delivery has been reviewed elsewhere in detail.[209] Briefly, the presence of oesophageal varices should be screened and adequate prophylaxis of bleeding applied in a manner similar to what is recommended for patients with cirrhosis. Portopulmonary hypertension should be searched for prior to conception, since pregnancy can worsen lung disease.[210] The risk of miscarriage and premature birth is heightened, particularly in women with BCS. Current management of these diseases makes it very likely to see the child carried to full term once the pregnancy reaches 20 weeks. Assisted vaginal delivery is the preferred mode of delivery. Caesarean section should be restricted to gynaecological indications. Indeed, caesarean section is known to carry a substantially increased risk of thromboembolic complications and may be hazardous in patients with portal hypertension due to large pelvic venous collaterals and postoperative ascites.[211,212] Most women likely benefit from anticoagulation during the postpartum and some during pregnancy. These women should be managed by a multidisciplinary team of hepatologists and obstetricians well-versed in high-risk pregnancies.

Future perspective

Improvement in the quality of imaging studies and awareness of BCS and NCPVT has increased the number of patients that are currently diagnosed with these conditions. Initiatives from the last decades, combining the efforts of dedicated groups comprised of hepatologists, haematologists, radiologists, surgeons and basic scientists have resulted in huge advances in knowledge on these disorders and an exponential increase in the number of publications on splanchnic vein thrombosis. Nevertheless, there are still a number

of questions that remain to be answered in relation to identification of the underlying causes promoting splanchnic vein thrombosis, prognosis of a given patient, and the choice of the best treatment for each individual patient. The development of new molecular diagnostic tools, prognostic models and pre-clinical models that can be used to test new therapies are unmet needs. Further studies are warranted to address these needs and improve the management of these patients.

Financial support

This study was supported by the Ministry of Education and Science (SAF-2016-75767-R), and Instituto de Salud Carlos III (PIE15/00027, PI17/00398), FEDER "Una manera de hacer Europa") in Spain. The Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBERehd) is funded by the Instituto de Salud Carlos III, Spain. REHEVASC is partially funded by Asociación Española para Estudio del Hígado (AEEH), Spain. VALDIG is partially funded by EASL and Stiftung für Leberkrankheiten, Bern. This work was also supported by the "Institut National de la Santé et de la Recherche Médicale", France, and the "Agence Nationale pour la Recherche", France (ANR-14-CE12-0011, ANR-14-CE35-0022, ANR-18-CE14-0006-01).

Conflict of interest

The authors who have taken part in this study declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2019.02.015.

References

[1] 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.

[2] Ageno W, Dentali F, Pomero F, Fenoglio L, Squizzato A, Pagani G, et al. Incidence rates and case fatality rates of portal vein thrombosis and Budd-Chiari syndrome. Thromb Haemost 2017;117:794–800. https://doi.org/10.1160/TH16-10-0781.

[3] Ki M, Choi HY, Kim K-A, Kim BH, Jang ES, Jeong S-H. Incidence, prevalence and complications of Budd-Chiari syndrome in South Korea: a nationwide, population-based study. Liver Int 2016;36:1067–1073. https://doi.org/10.1111/liv.13008.

[4] Heit JA. Epidemiology of venous thromboembolism. Nat Rev Cardiol 2015;12:464–474. https://doi.org/10.1038/nrcardio.2015.83.

[5] Smalberg JH, Kruip MJ, Janssen HL, Rijken DC, Leebeek FW, de Maat MP. Hypercoagulability and hypofibrinolysis and risk of deep vein thrombosis and splanchnic vein thrombosis: similarities and differences. Arter Thromb Vasc Biol 2011;31:485–493.

[6] Deltenre P, Denninger MH, Hillaire S, Guillin MC, Casadevall N, Briere J, et al. Factor V Leiden related Budd-Chiari syndrome. Gut 2001;48:264–268.

[7] 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.

[8] Murad SD, Plessier A, Hernandez-Guerra M, Fabris F, Eapen DE, Bahr MJ, et al. Etiology, management, and outcome of the Budd-Chiari syndrome. Ann Intern Med 2009;151:167–175, doi:151/3/167 [pii].

[9] Qi X, Wu F, Ren W, He C, Yin Z, Niu J, et al. Thrombotic risk factors in Chinese Budd-Chiari syndrome patients. An observational study with a systematic review of the literature. Thromb Haemost 2013;109:878–884.

[10] Pati HP, Dayal S, Srivastava A, Pande GK, Acharya SK. Spectrum of hemostatic derangements, in Budd-Chiari syndrome. Indian J Gastroenterol 2003;22:59–60.

[11] 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.

[12] Rautou P-E, Mackman N. Deletion of microvesicles from the circulation. Circulation 2012;125:1601–1604. https://doi.org/10.1161/CIRCULATIONAHA.112.094920.

[13] Ma R, Xie R, Yu C, Si Y, Wu X, Zhao L, et al. Phosphatidylserine-mediated platelet clearance by endothelium decreases platelet aggregates and procoagulant activity in sepsis. Sci Rep 2017;7:4978. https://doi.org/10.1038/s41598-017-04773-8.

[14] Kerlin BA, Yan SB, Isermann BH, Brandt JT, Sood R, Basson BR, et al. Survival advantage associated with heterozygous factor V Leiden mutation in patients with severe sepsis and in mouse endotoxemia. Blood 2003;102:3085–3092. https://doi.org/10.1182/blood-2003-06-1789.

[15] Iba T, Levy JH. Inflammation and thrombosis: roles of neutrophils, platelets and endothelial cells and their interactions in thrombus formation during sepsis. J Thromb Haemost 2018;16:231–241. https://doi.org/10.1111/jth.13911.

[16] De Caterina R, D'Ugo E, Libby P. Inflammation and thrombosis – testing the hypothesis with anti- inflammatory drug trials. Thromb Haemost 2016;116:1012–1021. https://doi.org/10.1160/TH16-03-0246.

[17] Falanga A, Russo L, Milesi V, Vignoli A. Mechanisms and risk factors of thrombosis in cancer. Crit Rev Oncol Hematol 2017;118:79–83. https://doi.org/10.1016/j.critrevonc.2017.08.003.

[18] Association E. 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.

[19] Marchetti M, Castoldi E, Spronk HM, van OR OR, Balducci D, Barbui T, et al. Thrombin generation and activated protein C resistance in patients with essential thrombocythemia and polycythemia vera. Blood 2008;112:4061–4068.

[20] Smalberg JH, Darwish MS, Braakman E, Valk PJ, Janssen HL, Leebeek FW. Myeloproliferative disease in the pathogenesis and survival of Budd-Chiari syndrome. Haematologica 2006;91:1712–1713.

[21] Kiladjian J-JJ, Cervantes F, Leebeek FWGW, Marzac C, Cassinat B, Chevret S, et al. The impact of JAK2 and MPL mutations on diagnosis and prognosis of splanchnic vein thrombosis: a report on 241 cases. Blood 2008;111:4922–4929. https://doi.org/10.1182/blood-2007-11-125328.

[22] Smalberg JH, Arends LR, Valla DC, Kiladjian JJ, Janssen HL, Leebeek FW. Myeloproliferative neoplasms in Budd-Chiari syndrome and portal vein thrombosis: a meta-analysis. Blood 2012;120:4921–4928.

[23] How J, Zhou A, Oh ST. Splanchnic vein thrombosis in myeloproliferative neoplasms: pathophysiology and molecular mechanisms of disease. Ther Adv Hematol 2017;8:107–118. https://doi.org/10.1177/2040620716680333.

[24] Shetty S, Kulkarni B, Pai N, Mukundan P, Kasatkar P, Ghosh K. *JAK2* mutations across a spectrum of venous thrombosis cases: table 1. Am J Clin Pathol 2010;134:82–85. https://doi.org/10.1309/AJCP7VO4HAIZYATP.

[25] Deepak A, Punamiya S, Patel N, Parekh S, Mehta S, Shah N. Prevalence of JAK29V617F) mutation in intra-abdominal venous thrombosis. Trop Gastroenterol 2011;32:279–284.

[26] Shukla A, Parikh H, Modi T, Abraham P, Kamble S, Majumder D. Hepatic vein obstruction is the most common type of hepatic venous outflow obstruction regardless of socioeconomic status. Ann Gastroenterol 2014;27:130–134.

[27] 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.

[28] Wang H, Sun G, Zhang P, Zhang J, Gui E, Zu M, et al. JAK2 V617F mutation and 46/1 haplotype in Chinese Budd-Chiari syndrome patients. J Gastroenterol Hepatol 2014;29:208–214. https://doi.org/10.1111/jgh.12379.
[29] Arber DA, Orazi A, Hasserjian R, Borowitz MJ, Le Beau MM, Bloomfield CD, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood 2016;127:2391–2406. https://doi.org/10.1182/blood-2016-03-643544.
[30] Klampfl T, Gisslinger H, Harutyunyan AS, Nivarthi H, Rumi E, Milosevic JD, et al. Somatic mutations of calreticulin in myeloproliferative neoplasms. N Engl J Med 2013;369:2379–2390. https://doi.org/10.1056/NEJMoa1311347.
[31] Nangalia J, Massie CE, Baxter EJ, Nice FL, Gundem G, Wedge DC, et al. Somatic CALR mutations in myeloproliferative neoplasms with non-mutated JAK2. N Engl J Med 2013;369:2391–2405. https://doi.org/10.1056/NEJMoa1312542.
[32] Turon F, Cervantes F, Colomer D, Baiges A, Hernandez-Gea V, Garcia-Pagan JC, et al. 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.
[33] Plompen EPC, Valk PJM, Chu I, Murad SD, Plessier A, Turon F, et al. Somatic calreticulin mutations in patients with Budd-Chiari syndrome and portal vein thrombosis. Haematologica 2015;100. https://doi.org/10.3324/haematol.2014.120857.
[34] Poisson J, Plessier A, Kiladjian JJ, 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.
[35] Karalus NC, Dunn PJ, Haslam AJ, Burroughs A. Outcome of diabetic pregnancies in Waikato: five year experience. New Zel Med J 1985;98:369–371.
[36] Akpan IJ, Stein BL. Splanchnic vein thrombosis in the myeloproliferative neoplasms. Curr Hematol Malig Rep 2018;13:183–190. https://doi.org/10.1007/s11899-018-0446-x.
[37] Iurlo A, Cattaneo D, Gianelli U, Fermo E, Augello C, Cortelezzi A. Molecular analyses in the diagnosis of myeloproliferative neoplasm-related splanchnic vein thrombosis. Ann Hematol 2015;94:881–882. https://doi.org/10.1007/s00277-014-2249-z.
[38] Langabeer SE, Haslam K. Incidence of CALR mutations in patients with splanchnic vein thrombosis. Br J Haematol 2015;168:459–460. https://doi.org/10.1111/bjh.13121.
[39] Sozer S, Fiel MI, Schiano T, Xu M, Mascarenhas J, Hoffman R. The presence of JAK2V617F mutation in the liver endothelial cells of patients with Budd-Chiari syndrome. Blood 2009;113:5246–5249. https://doi.org/10.1182/blood-2008-11-191544.
[40] Rosti V, Villani L, Riboni R, Poletto V, Bonetti E, Tozzi L, et al. Spleen endothelial cells from patients with myelofibrosis harbor the JAK2V617F mutation. Blood 2013;121:360–368. https://doi.org/10.1182/blood-2012-01-404889.
[41] Teofili L, Martini M, Iachininoto MG, Capodimonti S, Nuzzolo ER, Torti L, et al. Endothelial progenitor cells are clonal and exhibit the JAK2V617F mutation in a subset of thrombotic patients with Ph-negative myeloproliferative neoplasms. Blood 2011;117:2700–2707. https://doi.org/10.1182/blood-2010-07-297598.
[42] Guy A, Gourdou-Latyszenok V, Le Lay N, Peghaire C, Kilani B, Vieira Dias J, et al. Vascular endothelial cell expression of JAK2V617F is sufficient to promote a pro-thrombotic state due to increased P-selectin expression. Haematologica 2018;103:95321. https://doi.org/10.3324/haematol.2018.195321.
[43] Guadall A, Lesteven E, Letort G, Awan Toor S, Delord M, Pognant D, et al. Endothelial cells harbouring the JAK2V617F mutation display pro-adherent and pro-thrombotic features. Thromb Haemost 2018;118:1586–1599. https://doi.org/10.1055/s-0038-1667015.
[44] Poisson J, Lemoinne S, Boulanger C, Durand F, Moreau R, Valla D, et al. Liver sinusoidal endothelial cells: physiology and role in liver diseases. J Hepatol 2017;66:212–227. https://doi.org/10.1016/j.jhep.2016.07.009.
[45] Poisson J, Hilscher MB, Tanguy M, Hammoutene A, Boulanger CM, Villeval JL, et al. Endothelial JAK2V617Fdoes not enhance liver lesions in mice with Budd-Chiari syndrome. J Hepatol 2018;68:1086–1087. https://doi.org/10.1016/j.jhep.2018.01.010.
[46] van Bijnen STA, van Rijn RS, Koljenovic S, te Boekhorst P, de Witte T, Muus P. Possible high risk of thrombotic events in patients with paroxysmal nocturnal haemoglobinuria after discontinuation of eculizumab. Br J Haematol 2012;157:762–763. https://doi.org/10.1111/j.1365-2141.2012.09073.x.
[47] Hill A, Kelly RJ, Hillmen P. Thrombosis in paroxysmal nocturnal hemoglobinuria quiz 5105. Blood 2013;121:4985–4996. https://doi.org/10.1182/blood-2012-09-311381.
[48] Hoekstra J, Leebeek FWG, Plessier A, Raffa S, Murad SD, Hadengue A, 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.
[49] Brodsky RA. Narrative review: paroxysmal nocturnal hemoglobinuria: the physiology of complement-related hemolytic anemia. Ann Intern Med 2008;148:587–595.
[50] Plompen EPC, Darwish Murad S, Hansen BE, Loth DW, Schouten JNL, Taimr P, et al. Prothrombotic genetic risk factors are associated with an increased risk of liver fibrosis in the general population. J Hepatol 2015;63:1459–1465. https://doi.org/10.1016/j.jhep.2015.07.026.
[51] 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. https://doi.org/10.1097/MD.0000000000000496 e496.
[52] Janssen HL, Meinardi JR, Vleggaar FP, van Uum SH, Haagsma EB, 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.
[53] Seyahi E, Caglar E, Ugurlu S, Kantarci F, Hamuryudan V, Sonsuz A, et al. An outcome survey of 43 patients with Budd-Chiari syndrome due to Behçet's syndrome followed up at a single, dedicated center. Semin Arthritis Rheum 2015;44:602–609. https://doi.org/10.1016/j.semarthrit.2014.10.014.
[54] Lentz SR. Thrombosis in the setting of obesity or inflammatory bowel disease. Blood 2016;128:2388–2394. https://doi.org/10.1182/blood-2016-05-716720.
[55] 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.
[56] Fontana L, Eagon JC, Trujillo ME, Scherer PE, Klein S. Visceral fat adipokine secretion is associated with systemic inflammation in obese humans. Diabetes 2007;56:1010–1013. https://doi.org/10.2337/db06-1656.
[57] Magkos F, Fabbrini E, Patterson BW, Eagon JC, Klein S. Portal vein and systemic adiponectin concentrations are closely linked with hepatic glucose and lipoprotein kinetics in extremely obese subjects. Metabolism 2011;60:1641–1648. https://doi.org/10.1016/j.metabol.2011.03.019.
[58] Kelkar AH, Jacob KS, Yousif EB, Farrell JJ. Venous thromboembolism related to cytomegalovirus infection: a case report and literature review. Medicine (Baltimore) 2017;96. https://doi.org/10.1097/MD.0000000000009336 e9336.
[59] Uthman IW, Gharavi AE. Viral infections and antiphospholipid antibodies. Semin Arthritis Rheum 2002;31:256–263.
[60] Gharavi AE, Pierangeli SS, Espinola RG, Liu X, Colden-Stanfield M, Harris EN. Antiphospholipid antibodies induced in mice by immunization with a cytomegalovirus-derived peptide cause thrombosis and activation of endothelial cells in vivo. Arthritis Rheum 2002;46:545–552. https://doi.org/10.1002/art.10130.
[61] Pryzdial EL, Wright JF. Prothrombinase assembly on an enveloped virus: evidence that the cytomegalovirus surface contains procoagulant phospholipid. Blood 1994;84:3749–3757.
[62] Evans PC, Coleman N, Wreghitt TG, Wight DG, Alexander GJ. Cytomegalovirus infection of bile duct epithelial cells, hepatic artery and portal venous endothelium in relation to chronic rejection of liver grafts. J Hepatol 1999;31:913–920.
[63] Squizzato A, Gerdes VEA, Büller HR. Effects of human cytomegalovirus infection on the coagulation system. Thromb Haemost 2005;93:403–410. https://doi.org/10.1160/TH04-08-0523.
[64] Siramolpiwat S, Seijo S, Miquel R, Berzigotti A, Garcia-Criado A, Darnell A, et al. Idiopathic portal hypertension: natural history and long-term outcome. Hepatology 2014;59:2276–2285. https://doi.org/10.1002/hep.26904.
[65] Glatard A-S, Hillaire S, D'Assignies G, Cazals-Hatem D, Plessier A, Valla DC, et al. Obliterative portal venopathy: findings at CT imaging. Radiology 2012;263:741–750. https://doi.org/10.1148/radiol. 12111785.
[66] Dilawari JB, Bambery P, Chawla Y, Kaur U, Bhusnurmath SR, Malhotra HS, et al. Hepatic outflow obstruction (Budd-Chiari syndrome). Expe-

rience with 177 patients and a review of the literature. Medicine 1994;73:21–36.
[67] Langlet P, Escolano S, Valla D, Coste-zeitoun D, Denie C, Mallet A, et al. Clinicopathological forms and prognostic index in Budd-Chiari syndrome. J Hepatol 2003;39:496–501. https://doi.org/10.1016/S0168-8278(03)00323-4.
[68] Hadengue A, Poliquin M, Vilgrain V, Belghiti J, Degott C, Erlinger S, et al. The changing scene of hepatic vein thrombosis: recognition of asymptomatic cases. Gastroenterology 1994;106:1042–1047.
[69] Mitchell MC, Boitnott JK, Kaufman S, Cameron JL, Maddrey WC. Budd-Chiari syndrome: etiology, diagnosis and management. Medicine 1982;61:199–218.
[70] Seijo S, Plessier A, Hoekstra J, Era AD, 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.
[71] Okuda K. Inferior vena cava thrombosis at its hepatic portion (obliterative hepatocavopathy). Semin Liver Dis 2002;22:15–26.
[72] Sonomura T, Sato M, Kishi K, Terada M, Shioyama Y, Kimura M, et al. Balloon-occluded retrograde transvenous obliteration for gastric varices: a feasibility study. Cardiovasc Intervent Radiol 1998;21:27–30.
[73] Flor N, Zuin M, Brovelli F, Maggioni M, Tentori A, Sardanelli F, et al. Regenerative nodules in patients with chronic Budd-Chiari syndrome: a longitudinal study using multiphase contrast-enhanced multidetector CT. Eur J Radiol 2010;73:588–593. https://doi.org/10.1016/j.ejrad.2009.01.012.
[74] Tanaka M, Wanless IR. Pathology of the liver in Budd-Chiari syndrome: portal vein thrombosis and the histogenesis of veno-centric cirrhosis, veno-portal cirrhosis, and large regenerative nodules. Hepatology 1998;27:488–496.
[75] Wanless IR. Benign liver tumors. Clin Liver Dis 2002;6:513–526.
[76] Vilgrain V, Lewin M, Vons C, Denys A, Valla D, Flejou JF, et al. Hepatic nodules in Budd-Chiari syndrome: imaging features. Radiology 1999;210:443–450.
[77] Kim H, Nahm JH, Park YN. Budd-Chiari syndrome with multiple large regenerative nodules. Clin Mol Hepatol 2015;21:89–94. https://doi.org/10.3350/cmh.2015.21.1.89.
[78] Vilgrain V, Paradis V, Van Wettere M, Valla D, Ronot M, Rautou PE. Benign and malignant hepatocellular lesions in patients with vascular liver diseases. Abdom Radiol 2018;43:1968–1977. https://doi.org/10.1007/s00261-018-1502-7.
[79] Maetani Y, Itoh K, Egawa H, Haga H, Sakurai T, Nishida N, et al. Benign hepatic nodules in Budd-Chiari syndrome: radiologic-pathologic correlation with emphasis on the central scar. AJR Am J Roentgenol 2002;178:869–875.
[80] Sempoux C, Paradis VV, Komuta M, Wee A, Calderaro J, Balabaud C, et al. Hepatocellular nodules expressing markers of hepatocellular adenomas in Budd-Chiari syndrome and other rare hepatic vascular disorders. J Hepatol 2015;63:1173–1180. https://doi.org/10.1016/j.jhep.2015.06.017.
[81] Moucari R, Rautou PE, 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.
[82] Ren W, Qi X, Yang Z, Han G, Fan D. Prevalence and risk factors of hepatocellular carcinoma in Budd-Chiari syndrome: a systematic review. Eur J Gastroenterol Hepatol 2013;25:830–841. https://doi.org/10.1097/MEG.0b013e32835eb8d4.
[83] Paul SB, Sreenivas, Shalimar 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.
[84] Cazals-Hatem D, Vilgrain V, Genin P, Denninger MH, Durand F, Belghiti J, et al. Arterial and portal circulation and parenchymal changes in Budd-Chiari syndrome: a study in 17 explanted livers. Hepatology 2003;37:510–519.
[85] Brancatelli G, Federle MP, Grazioli L, Golfieri R, Lencioni R. Large regenerative nodules in Budd-Chiari syndrome and other vascular disorders of the liver: CT and MR imaging findings with clinicopathologic correlation. Am J Roentgenol 2002;178:877–883. https://doi.org/10.2214/ajr.178.4.1780877.
[86] van Wettere Morgane, Purcell Yvonne, Bruno Onorina, Payancé Audrey, Plessier Aurélie, Rautou Pierre-Emmanuel, 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.
[87] Sarin SK, Philips CA, Kamath PS, Choudhury A, Maruyama H, Nery FG, et al. Toward a comprehensive new classification of portal vein thrombosis in patients with cirrhosis 574–577.e3. Gastroenterology 2016;151. https://doi.org/10.1053/j.gastro.2016.08.033.
[88] Jha RC, Khera SS, Kalaria AD. Portal vein thrombosis: Imaging the spectrum of disease with an emphasis on MRI features. Am J Roentgenol 2018;211:14–24. https://doi.org/10.2214/AJR.18.19548.
[89] White D, Coombe D, Rezania V, Tuszynski J. Building a 3D virtual liver: methods for simulating blood flow and hepatic clearance on 3D structures. PLoS ONE 2016;11. https://doi.org/10.1371/journal.pone.0162215 e0162215.
[90] Elkrief L, Corcos O, Bruno O, Larroque B, Rautou P-EE, Zekrini K, et al. Type 2 diabetes mellitus as a risk factor for intestinal resection in patients with superior mesenteric vein thrombosis. Liver Int 2014;34:1314–1321. https://doi.org/10.1111/liv.12386.
[91] 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.
[92] Noronha Ferreira C, Seijo S, Plessier A, Silva-Junior G, Turon F, Rautou P-EP-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.
[93] Rangari M, Gupta R, Jain M, Malhotra V, Sarin SK, et al. Hepatic dysfunction in patients with extrahepatic portal venous obstruction. Liver Int 2003;23:434–439.
[94] Mínguez B, García-Pagán JC, Bosch J, Turnes J, Alonso J, Rovira A, et al. Noncirrhotic portal vein thrombosis exhibits neuropsychological and MR changes consistent with minimal hepatic encephalopathy. Hepatology 2006;43:707–714. https://doi.org/10.1002/hep.21126.
[95] Sharma P, Sharma BC, Puri V, Sarin SK. Minimal hepatic encephalopathy in patients with extrahepatic portal vein obstruction. Am J Gastroenterol 2008;103:1406–1412.
[96] Marin D, Galluzzo A, Plessier A, Brancatelli G, Valla D, Vilgrain V. Focal nodular hyperplasia-like lesions in patients with cavernous transformation of the portal vein: prevalence, MR findings and natural history. Eur Radiol 2011;21:2074–2082.
[97] Kaymakoglu S, Kahraman T, Kudat H, Demir K, Cakaloglu Y, Adalet I, et al. Hepatopulmonary syndrome in noncirrhotic portal hypertensive patients. Dig Dis Sci 2003;48:556–560.
[98] Saunders JB, Constable TJ, Heath D, Smith P, Paton A. Pulmonary hypertension complicating portal vein thrombosis. Thorax 1979;34:281–283.
[99] Dhiman RK, Saraswat VA, Valla DC, Chawla Y, Behera A, Varma V, Portal, et al. 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] Asselah T, Toole DO, Rufat P, Zappa M, Condat B, Moreau R, 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.
[101] 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;60:853–861. https://doi.org/10.1136/gut.2010.230201.
[102] Bargalló X, Gilabert R, Nicolau C, García-Pagán JC, Bosch J, Brú C, et al. Sonography of the caudate vein: value in diagnosing Budd-Chiari syndrome. Am J Roentgenol 2003;181:1641–1645. https://doi.org/10.2214/ajr.181.6.1811641.
[103] Miller WJ, Federle MP, Straub WH, Davis PL. Budd-Chiari syndrome: imaging with pathologic correlation. Abdom Imaging 1993;18:329–335.
[104] 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.
[105] Garcia-Pagan 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.
[106] Darwish Murad S, Valla DC, de Groen PC, Zeitoun G, Hopmans JAM, Haagsma EB, et al. Determinants of survival and the effect of portosystemic shunting in patients with Budd-Chiari syndrome. Hepatology 2004;39:500–508. https://doi.org/10.1002/hep.20064.
[107] Plessier A, Sibert A, Consigny Y, Hakime A, Zappa M, Denninger M-HH, 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.
[108] Tang TJ, Batts KP, de Groen PC, van Hoek B, Haagsma EB, Hop WC, et al. The prognostic value of histology in the assessment of patients with Budd-Chiari syndrome. J Hepatol 2001;35:338–343.
[109] Darwish MS, Kim WR, de Groen PC, Kamath PS, Malinchoc M, Valla DC, et al. Can the model for end-stage liver disease be used to predict the prognosis in patients with Budd-Chiari syndrome? Liver Transpl 2007;13:867–874. https://doi.org/10.1002/lt.
[110] Rautou PE, Moucari R, Escolano S, Cazals-Hatem D, Denie 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.
[111] Parekh J, Matei VM, Canas-Coto A, Friedman D, Lee WM. Acute Liver Failure Study Group. Budd-chiari syndrome causing acute liver failure: a multicenter case series. Liver Transpl 2017;23:135–142. https://doi.org/10.1002/lt.24643.
[112] Rautou P, Moucari R, Cazals-Hatem D, Escolano S, Denié C, Douarin L, et al. Levels and initial course of serum alanine aminotransferase can predict outcome of patients with Budd-Chiari syndrome. Clin Gastroenterol Hepatol 2009;7:1230–1235. https://doi.org/10.1016/j.cgh.2009.06.011.
[113] Yerdel MA, Gunson B, Mirza D, Karayalcin K, Olliff S, Buckels J, et al. Portal vein thrombosis in adults undergoing liver transplantation: risk factors, screening, management, and outcome. Transplantation 2000;69:1873–1881.
[114] De Franchis R, Abraldes JG, Bajaj J, Berzigotti A, Bosch J, Burroughs AK, et al. Expanding consensus in portal hypertension: report of the Baveno VI Consensus Workshop: stratifying risk and individualizing care for portal hypertension. J Hepatol 2015;63:743–752. https://doi.org/10.1016/j.jhep.2015.05.022.
[115] Chagneau-Derrode C, Roy L, Guilhot J, Gloria O, Ollivier-Hourmand I, Bureau C, et al. Impact of cytoreductive therapy on the outcome of patients with myeloproliferative neoplasms and hepatosplanchnic vein thrombosis. Hepatology 2013;58:857A.
[116] 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.
[117] Orloff MJ, Isenberg JI, Wheeler HO, Daily PO, Girard B. Budd-Chiari syndrome revisited: 38 years' experience with surgical portal decompression. J Gastrointest Surg 2012;16:286–300. https://doi.org/10.1007/s11605-011-1738-9.
[118] Montano-Loza AJ, Tandon P, Kneteman N, Bailey R, Bain VG. Rotterdam score predicts early mortality in Budd-Chiari syndrome, and surgical shunting prolongs transplant-free survival. Aliment Pharmacol Ther 2009;30:1060–1069.
[119] Bachet J, Condat B, Consigny Y, Belghiti J, Valla D. 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.
[121] Taguchi E, Koyama J, Kajiwara M, Inoue M, Horibata Y, Nishigami K, et al. Successful vascular intervention without embolic complications in Budd-Chiari syndrome. Circ J 2018;82:602–603. https://doi.org/10.1253/circj.CJ-17-0333.
[122] Sharma S, Texeira A, Texeira P, Elias E, Wilde J, Olliff SP. Pharmacological thrombolysis in Budd Chiari syndrome: a single centre experience and review of the literature. J Hepatol 2004;40:172–180.
[123] Smalberg JH, Spaander MV, Jie KS, Pattynama PM, van Buuren HR, van den BB, et al. Risks and benefits of transcatheter thrombolytic therapy in patients with splanchnic venous thrombosis. Thromb Haemost 2008;100:1084–1088.
[124] Valla D, Hadengue A, el Younsi M, Azar N, Zeitoun G, Boudet MJ, et al. Hepatic venous outflow block caused by short-length hepatic vein stenoses. Hepatology 1997;25:814–819. https://doi.org/10.1002/hep.510250405.
[125] Han G, Qi X, Zhang W, He C, Yin Z, Wang J, et al. Percutaneous recanalization for Budd-Chiari syndrome: an 11-year retrospective study on patency and survival in 177 Chinese patients from a single center. Radiology 2013;266:657–667.
[126] Bi Y, Chen H, Ding P, Ren J, Han X. Comparison of retrievable stents and permanent stents for Budd-Chiari syndrome due to obstructive inferior vena cava. J Gastroenterol Hepatol 2018. https://doi.org/10.1111/jgh.14295.
[127] Shaked A, Goldstein RM, Klintmalm GB, Drazan K, Husberg B, Busuttil RW. Portosystemic shunt versus orthotopic liver transplantation for the Budd-Chiari syndrome. Surg Gynecol Obstet 1992;174:453–459.
[128] Klein AS, Molmenti EP. Surgical treatment of Budd-Chiari syndrome. Liver Transpl 2003;9:891–896. https://doi.org/10.1053/jlts.2003.50156.
[129] Chen H, Zhang F, Ye Y, Cheng Y, Chen Y. Long-term follow-up study and comparison of meso-atrial shunts and meso-cavo-atrial shunts for treatment of combined Budd-Chiari syndrome. J Surg Res 2011;168:162–166. https://doi.org/10.1016/j.jss.2009.07.024.
[130] Langlet P, Valla D. Is surgical portosystemic shunt the treatment of choice in Budd-Chiari syndrome? Acta Gastroenterol Belga 2002;65:155–160.
[131] Panis Y, Belghiti J, Valla D, Benhamou JP, Fekete F. Portosystemic shunt in Budd-Chiari syndrome: long-term survival and factors affecting shunt patency in 25 patients in Western countries. Surgery 1994;115:276–281.
[132] Orloff MJS, Daily PO, Orloff SL, Girard B, Orloff MS. A 27-year experience with Surgical treatment of Budd-Chiari syndrome. Ann Surg 2000;232:340–352.
[133] Hemming AW, Langer B, Greig P, Taylor BR, Adams R, Heathcote EJ. Treatment of Budd-Chiari syndrome with portosystemic shunt or liver transplantation. Am J Surg 1996;171:176–180.
[134] 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.
[135] Mancuso A. In favour of early intervention for Budd-Chiari syndrome. Eur J Gastroenterol Hepatol 2016;28:850–851. https://doi.org/10.1097/MEG.0000000000000653.
[136] Shalimar, Gamanagatti SR, Patel AH, Kedia S, Nayak B, Gunjan D, et al. Long-term outcomes of transjugular intrahepatic portosystemic shunt in Indian patients with Budd-Chiari syndrome. Eur J Gastroenterol Hepatol 2017;29:1174–1182. https://doi.org/10.1097/MEG.0000000000000945.
[137] Rathod K, Deshmukh H, Shukla A, Popat B, Pandey A, Gupte A, et al. Endovascular treatment of Budd-Chiari syndrome: single center experience. J Gastroenterol Hepatol 2017;32:237–243. https://doi.org/10.1111/jgh.13456.
[138] Fan X, Liu K, Che Y, Wang S, Wu X, Cao J, et al. Good clinical outcomes in Budd-Chiari syndrome with hepatic vein occlusion. Dig Dis Sci 2016;61:3054–3060. https://doi.org/10.1007/s10620-016-4208-0.
[139] He F, Zhao H, Dai S, Wu Y, Wang L, Huang H, et al. Transjugular intrahepatic portosystemic shunt for Budd-Chiari syndrome with diffuse occlusion of hepatic veins. Sci Rep 2016;6:36380. https://doi.org/10.1038/srep36380.
[140] Qi X, Guo W, He C, Zhang W, Wu F, Yin Z, et al. Transjugular intrahepatic portosystemic shunt for Budd-Chiari syndrome: techniques, indications and results on 51 Chinese patients from a single centre. Liver Int 2014;34:1164–1175. https://doi.org/10.1111/liv.12355.
[141] Wang H-W, Shi H-N, Cheng J, Xie F, Luo Y-K, Tang J. Real-time shear wave elastography (SWE) assessment of short- and long-term treatment outcome in Budd-Chiari syndrome: a pilot study. PLoS ONE 2018;13. https://doi.org/10.1371/journal.pone.0197550 e0197550.
[142] Doğrul AB, Yankol Y, Mecit N, Kanmaz T, Acarlı K, Kalayoğlu M. Orthotopic liver transplant for Budd-Chiari syndrome: an analysis of 14 cases. Exp Clin Transplant 2016;14:641–645. https://doi.org/10.6002/ect.2015.0026.
[143] 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 2007;13:1285–1294. https://doi.org/10.1002/lt.
[144] Ulrich F, Pratschke J, Neumann U, Pascher A, Puhl G, Fellmer P, et al. Eighteen years of liver transplantation experience in patients with advanced Budd-Chiari syndrome. Transplantation 2008;14:144–150. https://doi.org/10.1002/lt.
[145] Mentha G, Giostra E, Majno PE, Bechstein WO, Neuhaus P, Grady JO, et al. Liver transplantation for Budd – Chiari syndrome: a European study on 248 patients from 51 centres. J Hepatol 2006;44:520–528. https://doi.org/10.1016/j.jhep.2005.12.002.
[146] Srinivasan P, Rela M, Prachalias A, Muiesan P, Portmann B, Mufti GJ, et al. Liver transplantation for Budd-Chiari syndrome. Transplantation 2002;73:973–977.
[147] Raza SM, Zainab S, Shamsaeefar AR, Nikeghbalian S, Malek Hosseini SA. Experience of liver transplant in patients diagnosed with Budd-Chiari syndrome. Exp Clin Transplant 2018;16:177–181. https://doi.org/10.6002/ect.2016.0129.

[148] Potthoff A, Attia D, Pischke S, Mederacke I, Beutel G, Rifai K, et al. Long-term outcome of liver transplant patients with Budd-Chiari syndrome secondary to myeloproliferative neoplasms. Liver Int 2015;35:2042–2049. https://doi.org/10.1111/liv.12816.
[149] Melear JM, Goldstein RM, Levy MF, Molmenti EP, Cooper B, Netto GJ, et al. Hematologic aspects of liver transplantation for Budd-Chiari syndrome with special reference to myeloproliferative disorders. Transplantation 2002;74:1090–1095.
[150] Chinnakotla S, Klintmalm GB, Kim P, Tomiyama K, Klintmalm E, Davis GL, et al. Long-term follow-up of liver transplantation for Budd-Chiari syndrome with antithrombotic therapy based on the etiology. Transplantation 2011;92:341–345. https://doi.org/10.1097/TP.0b013e3182247b05.
[151] Cruz E, Ascher NL, Roberts JP, Bass NM, Yao FY. High incidence of recurrence and hematologic events following liver transplantation for Budd-Chiari syndrome. ClinTransplant 2005;19:501–506.
[152] Singer AL, Locke JE, Stewart ZA, Lonze BE, Hamilton JP, Scudiere JR, et al. Successful liver transplantation for Budd-Chiari syndrome in a patient with paroxysmal nocturnal hemoglobinuria treated with the anti-complement antibody eculizumab. Liver Transpl 2009;15:540–543. https://doi.org/10.1002/lt.21714.
[153] Bahr MJ, Schubert J, Bleck JS, Tietge UJ, Boozari B, Schmidt RE, et al. Recurrence of Budd-Chiari syndrome after liver transplantation in paroxysmal nocturnal hemoglobinuria. Transpl Int 2003;16:890–894.
[154] Karaca C, Yilmaz C, Ferecov R, Iakobadze Z, Kilic K, Caglayan L, et al. Living-donor liver transplantation for Budd-Chiari syndrome: case series. Transplant Proc 2017;49:1841–1847. https://doi.org/10.1016/j.transproceed.2017.04.028.
[155] Ara C, Akbulut S, Ince V, Karakas S, Baskiran A, Yilmaz S. Living donor liver transplantation for Budd-Chiari syndrome: overcoming a troublesome situation. Medicine (Baltimore) 2016;95. https://doi.org/10.1097/MD.0000000000005136 e5136.
[156] 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.
[157] Condat B, Pessione F, Denninger MH, Hillaire S, Valla D, Condat B, et al. 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.
[158] Acosta S, Alhadad A, Svensson P, Ekberg O. Epidemiology, risk and prognostic factors in mesenteric venous thrombosis. Br J Surg 2008;95:1245–1251.
[159] Turnes J, García-Pagán JC, González M, Aracil C, Calleja JLJL, 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.
[160] Nery F, Valadares D, Morais S, Gomes MT, De Gottardi A. Efficacy and safety of direct-acting oral anticoagulants use in acute portal vein thrombosis unrelated to cirrhosis. Gastroenterol Res 2017;10:141–143. https://doi.org/10.14740/gr806w.
[161] Priyanka P, Kupec JT, Krafft M, Shah NA, Reynolds GJ. Newer oral anticoagulants in the treatment of acute portal vein thrombosis in patients with and without cirrhosis. Int J Hepatol 2018;2018. https://doi.org/10.1155/2018/8432781.
[162] Janczak DT, Mimier MK, McBane RD, Kamath PS, Simmons BS, Bott-Kitslaar DM, et al. Rivaroxaban and apixaban for initial treatment of acute venous thromboembolism of atypical location. Mayo Clin Proc 2018;93:40–47. https://doi.org/10.1016/j.mayocp.2017.10.007.
[163] Sicre de Fontbrune F, Peffault de Latour R. Ten years of clinical experience with eculizumab in patients with paroxysmal nocturnal hemoglobinuria. Semin Hematol 2018;55:124–129. https://doi.org/10.1053/j.seminhematol.2018.04.001.
[164] Hollingshead M, Burke CT, Mauro MA, Weeks SM, Dixon RG, Jaques PF. Transcatheter thrombolytic therapy for acute mesenteric and portal vein thrombosis. J Vasc Interv Radiol 2005;16:651–661. https://doi.org/10.1097/01.RVI.0000156265.79960.86.
[165] Liu K, Li W-D, Du X-L, Li C-L, Li X-Q. Comparison of systemic thrombolysis versus indirect thrombolysis via the superior mesenteric artery in patients with acute portal vein thrombosis. Ann Vasc Surg 2016;39:264–269. https://doi.org/10.1016/j.avsg.2016.06.029.
[166] Hmoud B, Singal AK, Kamath PS. Mesenteric venous thrombosis. J Clin Exp Hepatol 2014;4:257–263. https://doi.org/10.1016/j.jceh.2014.03.052.
[167] Condat B, Pessione F, Hillaire S, Denninger M-HH, Guillin MC, Poliquin M, et al. Current outcome of portal vein thrombosis in adults: Risk and benefit of anticoagulant therapy. Gastroenterology 2001;120:490–497. https://doi.org/10.1053/gast.2001.21209.
[168] Orr DW, Harrison PM, Devlin J, Karani JB, Kane PA, Heaton ND, et al. Chronic mesenteric venous thrombosis: evaluation and determinants of survival during long-term follow-up. Clin Gastroenterol Hepatol 2007;5:80–86. https://doi.org/10.1016/j.cgh.2006.09.030.
[169] Sarin SK, Gupta N, Jha SK, Agrawal A, Mishra SR, Sharma BC, et al. Equal efficacy of endoscopic variceal ligation and propranolol in preventing variceal bleeding in patients with noncirrhotic portal hypertension 1238–1245.e1. Gastroenterology 2010;139. https://doi.org/10.1053/j.gastro.2010.06.017.
[170] 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.
[171] Bianchini M, Cavani G, Bonaccorso A, Turco L, Vizzutti F, Sartini A, et al. Low molecular weight heparin does not increase bleeding and mortality post-endoscopic variceal band ligation in cirrhotic patients. Liver Int 2018;38:1253–1262. https://doi.org/10.1111/liv.13728.
[172] Spaander VMCW, van Buuren HR, Janssen HLA. Review article: The management of non-cirrhotic non-malignant portal vein thrombosis and concurrent portal hypertension in adults. Aliment Pharmacol Ther 2007;26:203–209. https://doi.org/10.1111/j.1365-2036.2007.03488.x.
[173] Amitrano L, Guardascione MA, Menchise A, Martino R, Scaglione M, Giovine S, et al. Safety and efficacy of anticoagulation therapy with low molecular weight heparin for portal vein thrombosis in patients with liver cirrhosis. J Clin Gastroenterol 2010;44:448–451.
[174] Holster IL, Kuipers EJ, van Buuren HR, Spaander MCW, Tjwa ETTL. Self-expandable metal stents as definitive treatment for esophageal variceal bleeding. Endoscopy 2013;45:485–488. https://doi.org/10.1055/s-0032-1326227.
[175] Spaander MCW, Hoekstra J, Hansen BE, Van Buuren HR, Leebeek FWG, Janssen HL. Anticoagulant therapy in patients with non-cirrhotic portal vein thrombosis: effect on new thrombotic events and gastrointestinal bleeding. J Thromb Haemost 2013;11:452–459. https://doi.org/10.1111/jth.12121.
[176] 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.
[177] Klinger C, Riecken B, Schmidt A, De Gottardi A, Meier B, Bosch J, et al. Transjugular portal vein recanalization with creation of intrahepatic portosystemic shunt (PVR-TIPS) in patients with chronic non-cirrhotic, non-malignant portal vein thrombosis. Z Gastroenterol 2018;56:221–237. https://doi.org/10.1055/s-0043-121348.
[178] Primignani M. Portal vein thrombosis, revisited. Dig Liver Dis 2010;42:163–170. https://doi.org/10.1016/j.dld.2009.08.003.
[179] Shneider B, Emre S, Groszmann R, Karani J, McKiernan P, Sarin S, et al. Expert pediatric opinion on the report of the Baveno IV consensus workshop on methodology of diagnosis and therapy in portal hypertension. PediatrTransplant 2006;10:893–907. https://doi.org/10.1111/j.1399-3046.2006.00597.x.
[180] Khanna R, Kumar S. Idiopathic portal hypertension and extrahepatic portal venous obstruction. Hepatol Int 2018;12:148–167. https://doi.org/10.1007/s12072-018-9844-3.
[181] Shneider BL, de Ville de Goyet J, Leung DH, Srivastava A, Ling SC, Duché M, et al. Primary prophylaxis of variceal bleeding in children and the role of MesoRex Bypass: summary of the Baveno VI Pediatric Satellite Symposium. Hepatology 2016;63:1368–1380. https://doi.org/10.1002/hep.28153.
[182] Salem R, Vouche M, Baker T, Herrero JI, Caicedo JC, Fryer J, et al. Pretransplant portal vein recanalization—transjugular intrahepatic portosystemic shunt in patients with complete obliterative portal vein thrombosis. Transplantation 2015;99:2347–2355. https://doi.org/10.1097/TP.0000000000000729.
[183] 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 1714–1721.e2. J Vasc Interv Radiol 2017;28. https://doi.org/10.1016/j.jvir.2017.08.005.
[184] Thornburg B, Desai K, Hickey R, Kulik L, Ganger D, Baker T, et al. Portal vein recanalization and transjugular intrahepatic portosystemic shunt

creation for chronic portal vein thrombosis: technical considerations. Tech Vasc Interv Radiol 2016;19:52–60. https://doi.org/10.1053/j.tvir.2016.01.006.
[185] Kallini JR, Gabr A, Kulik L, Ganger D, Lewandowski R, Thornburg B, et al. Noncirrhotic complete obliterative portal vein thrombosis: novel management using trans-splenic transjugular intrahepatic portosystemic shunt with portal vein recanalization. Hepatology 2016;63:1387–1390. https://doi.org/10.1002/hep.28429.
[186] 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.
[187] Perlemuter G, Bejanin H, Fritsch J, Prat F, Gaudric M, Chaussade S, et al. Biliary obstruction caused by portal cavernoma: a study of 8 cases. J Hepatol 1996;25:58–63.
[188] Franceschet I, Zanetto A, Ferrarese A, Burra P, Senzolo M. Therapeutic approaches for portal biliopathy: a systematic review. World J Gastroenterol 2016;22:9909–9920. https://doi.org/10.3748/wjg.v22.i45.9909.
[189] De Stefano V, Qi X, Betti S, Rossi E. Splanchnic vein thrombosis and myeloproliferative neoplasms: molecular-driven diagnosis and long-term treatment. Thromb Haemost 2016;115:240–249. https://doi.org/10.1160/TH15-04-0326.
[190] De Stefano V, Vannucchi AM, Ruggeri M, Cervantes F, Alvarez-Larrán A, Iurlo A, et al. Splanchnic vein thrombosis in myeloproliferative neoplasms: risk factors for recurrences in a cohort of 181 patients. Blood Cancer J 2016;6. https://doi.org/10.1038/bcj.2016.103 e493.
[191] Hoekstra J, Bresser EL, Smalberg JH, Spaander MCW, Leebeek FWG, Janssen HL. Long-term follow-up of patients with portal vein thrombosis and myeloproliferative neoplasms. J Thromb Haemost 2011;9:2208–2214. https://doi.org/10.1111/j.1538-7836.2011.04484.x.
[192] Lavu S, Szuber N, Mudireddy M, Yogarajah M, Gangat N, Pardanani A, et al. Splanchnic vein thrombosis in patients with myeloproliferative neoplasms: the Mayo clinic experience with 84 consecutive cases. Am J Hematol 2018;93:E61–E64. https://doi.org/10.1002/ajh.24993.
[193] Finazzi G, De Stefano V, Barbui T. Splanchnic vein thrombosis in myeloproliferative neoplasms: treatment algorithm. Blood Cancer J 2018;2018(8). https://doi.org/10.1038/s41408-018-0100-9.
[194] Marchioli R, Finazzi G, Specchia G, Cacciola R, Cavazzina R, Cilloni D, et al. Cardiovascular events and intensity of treatment in polycythemia vera. N Engl J Med 2013;368:22–33.
[195] Barosi G, Mesa R, Finazzi G, Harrison C, Kiladjian J-J, Lengfelder E, et al. Revised response criteria for polycythemia vera and essential thrombocythemia: an ELN and IWG-MRT consensus project. Blood 2013;121:4778–4781. https://doi.org/10.1182/blood-2013-01-478891.
[196] Tefferi A, Barbui T. Polycythemia vera and essential thrombocythemia: 2017 update on diagnosis, risk-stratification, and management. Am J Hematol 2017;92:94–108. https://doi.org/10.1002/ajh.24607.
[197] Van Bijnen STA, Van Heerde WL, Muus P. Mechanisms and clinical implications of thrombosis in paroxysmal nocturnal hemoglobinuria. J Thromb Haemost 2012;10:1–10. https://doi.org/10.1111/j.1538-7836.2011.04562.x.
[198] Yeh CH, Hogg K, Weitz JI. Overview of the new oral anticoagulants: opportunities and challenges. Arterioscler Thromb Vasc Biol 2015;35:1056–1065. https://doi.org/10.1161/ATVBAHA.115.303397.
[199] Holster IL, Valkhoff VE, Kuipers EJ, Tjwa ETTL. New oral anticoagulants increase risk for gastrointestinal bleeding: a systematic review and meta-analysis 105–112.e15. Gastroenterology 2013;145. https://doi.org/10.1053/j.gastro.2013.02.041.
[200] Abraham NS, Noseworthy PA, Yao X, Sangaralingham LR, Shah ND. Gastrointestinal safety of direct oral anticoagulants: a large population-based study 1014–1022.e1. Gastroenterology 2017;152. https://doi.org/10.1053/j.gastro.2016.12.018.
[201] Miller CS, Dorreen A, Martel M, Huynh T, Barkun AN. Risk of gastrointestinal bleeding in patients taking non-vitamin K antagonist oral anticoagulants: a systematic review and meta-analysis 1674–1683.e3. Clin Gastroenterol Hepatol 2017;15. https://doi.org/10.1016/j.cgh.2017.04.031.
[202] Intagliata NM, Maitland H, Northup PG, Caldwell SH. Treating thrombosis in cirrhosis patients with new oral agents: ready or not? Hepatology 2015;61:738–739. https://doi.org/10.1002/hep.27225.
[203] Martinez M, Tandra A, Vuppalanchi R. Treatment of acute portal vein thrombosis by nontraditional anticoagulation. Hepatology 2014;60:425–426. https://doi.org/10.1002/hep.26998.
[204] Pannach S, Babatz J, Beyer-Westendorf J. Successful treatment of acute portal vein thrombosis with rivaroxaban. Thromb Haemost 2013;110:626–627. https://doi.org/10.1160/TH13-05-0407.
[205] Simonetto DA, Wysokinski WE, Kamath PS. Use of nontraditional anticoagulants in portal vein thrombosis: a note of caution 2119–2119. Hepatology 2015;61. https://doi.org/10.1002/hep.27541.
[206] De Gottardi A, Trebicka J, Klinger C, Plessier A, Seijo S, Terziroli B, et al. Antithrombotic treatment with direct-acting oral anticoagulants in patients with splanchnic vein thrombosis and cirrhosis. Liver Int 2017;37:694–699. https://doi.org/10.1111/liv.13285.
[207] Rautou P-EE, Angermayr B, Garcia-Pagan J-CC, 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.
[208] Hoekstra J, Seijo S, Rautou PEE, 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.
[209] Bissonnette J, Durand F, de Raucourt E, Ceccaldi PF, 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.
[210] Andrade F, Shukla A, Bureau C, Senzolo M, D'Alteroche L, Heurgué A, et al. Pregnancy in idiopathic non-cirrhotic portal hypertension: a multicentric study on maternal and fetal management and outcome. J Hepatol 2018;69:1242–1249. https://doi.org/10.1016/J.JHEP.2018.08.007.
[211] Greer IA. Thrombosis in pregnancy: maternal and fetal issues. Lancet (London, England) 1999;353:1258–1265. https://doi.org/10.1016/S0140-6736(98)10265-9.
[212] d'Alteroche L, Perarnau J-M, Perrotin F, Bacq Y. Grossesse et hypertension portale. Gastroentérologie Clin Biol 2008;32:541–546. https://doi.org/10.1016/j.gcb.2008.02.028.
[213] Cao G, Ko GY, Sung KB, Yoon HK, Gwon D, Kim JH. Treatment of postoperative main portal vein and superior mesenteric vein thrombosis with balloon angioplasty and/or stent placement. Acta Radiol 2013;54:526–532.
[214] Rosenqvist K, Eriksson L-G, Rorsman F, Sangfelt P, Nyman R. Endovascular treatment of acute and chronic portal vein thrombosis in patients with cirrhotic and non-cirrhotic liver. Acta Radiol 2016;57:572–579. https://doi.org/10.1177/0284185115595060.