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PRACTICE GUIDELINES

# Risk factors for vascular liver diseases Vascular liver diseases: position papers from the francophone network for vascular liver diseases, the French Association for the Study of the Liver (AFEF), and ERN-rare liver

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*Abbreviations:* ACC, circulating anticoagulant; AT, antithrombin; BCS, Budd-Chiari Syndrome; CMV, cytomegalovirus; EHPVT, extrahepatic portal vein thrombosis; FOPV, familial obliterative portal venopathy; FV, factor V; GPI, glycosylphosphatidylinositol; LDH, lactate dehydrogenase; LMWH, low molecular weight heparins; MPN, Myeloproliferative neoplasms; PNH, Paroxysmal nocturnal hemoglobinuria; PC, protein C; PS, protein S; PSD, porto-sinusoidal diseases; UFH, unfractionated heparins; VKA, vitamin K antagonist; VLD, vascular liver disease; WHO, World Health Organization.

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## Introduction

Risk factors for vascular liver disease (VLD) are local and systemic. A systemic factor is identified in more than 50% and a combination of factors in more than one third of cases. Thus, the most frequent risk factors and/or those requiring specific therapeutic management should be systematically assessed. The presence of a local factor varies according to the location of thrombosis (infrequent in BCS), and may be associated with a systemic cause. For unexplained reasons, prothombotic disease and the site of thrombosis are specific features. In particular, myeloproliferative neoplasms are over-represented in VLD compared to the general population, with a decreasing frequency from hepatic vein obstruction, to obstruction of the portal system and of porto-sinusoidal disease. Factor V Leiden mutation is overrepresented in cases of inferior vena cava thrombosis and factor II Leiden mutation in extrahepatic portal vein thrombosis. Paroxysmal nocturnal hemoglobinuria is strongly associated with thrombosis of the small hepatic veins and Behçet's disease with inferior vena cava thrombosis.

In children, abdominal vein thrombosis is rare: according to data from a US registry of 4538 pediatric abdominal venous thromboses, 4.4% involved the inferior vena cava, 36% the portal vein, and 11% hepatic veins [1].

## What are the common systemic risk factors in adults?

### Philadelphia chromosome negative-myeloproliferative neoplasms (MPN)

Myeloproliferative neoplasms (MPN) are known to be the most common risk factors for splanchnic vein thrombosis (Table 1). They are found in 30 to 50% of patients with Budd-Chiari syndrome (BCS) or extrahepatic portal vein thrombosis (EHPVT) [2—6] and in 5 to 20% of porto-sinusoidal disease [7—9]. MPN are clonal proliferations of hematopoietic cells, resulting in hyperplasia of one or more myeloid lineages. This results in an increase in mature cells (red blood cells and hemoglobin, platelets, and/or white blood cells) in the blood. It may be associated with hyperplasia of fibroblastic populations and progression to bone marrow fibrosis and/or extramedullary hematopoiesis, with myeloid metaplasia (mainly in the liver and the spleen). The three main categories of MPN are polycythemia vera, essential thrombocythemia and primary myelofibrosis.

The main short-term risk of MPN is arterial and/or venous thrombosis, with a reported incidence of up to 40% [10]. The physiopathology of thromboses has not been clearly defined and is multifactorial: hyperviscosity, pro-thrombotic phenotype of abnormal cells (particularly platelet hyperaggregability), acquired resistance to activated protein C and increased thrombin generation, inflammation and activation of endothelial cells [11—13]. Endothelial cells carrying the JAK2 V617 F mutation have been reported in the liver [14].

Blood cell count abnormalities that are often at the origin of the diagnosis of these MPNs and are usually part of the diagnostic criteria [15] are often masked by portal hypertension in the case of splanchnic vein thrombosis [16]. The discovery of the JAK2 V617F mutation in 2005 changed the diagnostic management of MPN. This mutation is present in 95% of patients with polycythemia vera, 65% of those with myelofibrosis and 55% of those with essential thrombocythemia [17].

A recent meta-analysis reported a prevalence of MPN and the JAK2 V617F mutation of 40.9% and 41.1%, respectively in patients with BCS and 31.5% and 27.7% in patients with EHPVT [18]. In patients with no MPN-like blood count abnormality, screening for the JAK2 V617F mutation identifies an underlying MPN in 17.1% of patients with BCS and 15.4% of patients with EHPVT. It is therefore recommended to include the JAK2 V617F mutation in first-line investigations of patients with splanchnic thrombosis [19].

**Table 1** Identified risk factors and prevalences in adult vascular liver disease.

| Risk Factors | BCS (%) [2] | Thrombosis of the portal vein (%) [3] | PSD(%) [7] | Diagnosis |
|---|---|---|---|---|
| Myeloproliferative neoplasm | 40-50 | 21-31 | 10-15 | Mutations JAK2 V617F, mutation of *CALR*<br>Spleen size > 16 cm<br>and Platelets > $250 \times 10^9$/L<br>Osteomedullary biopsy |
| Antiphospholipid Syndrome | 4-25 | 8-12 | 4-8 | Antiphospholipid, Anti beta2 GP1 or Lupus anticoagulant antibodies |
| Paroxysmal nocturnal hemoglobinuria | 0-4 | 0-2 | NA | Deficit of GPI-anchored proteins: CD55 and CD59 |
| Behçet's disease | 0-33 | 12-22 | NA | Cerebral and thoracic injected imaging, HLA typing,<br>C-reactive protein |
| Factor V Leiden | 6-32 | 3-5 | 0 | rPCA mutation and factor V mutation |
| Mutation of prothrombin gene G202101 | 5-7 | 10-14 | 3 | mutation of the prothrombin gene G202101 |
| Protein C deficiency | 4-30 | 1 | 3 | Decreased activity/other coagulation factors |
| Protein S deficiency | 3-20 | 5 | 3 | Decreased activity/other coagulation factors |
| Antithrombin deficiency | 3-23 | 2 | 0 | Decreased activity/other coagulation factors |
| Recent pregnancy | 6-12 | 6-30 | 3 | Major risk 6 weeks postpartum |
| Recent oral contraception | 6-60 | 44 | NA | |
| Hyperhomocysteinemia | 11-37 | 15-22 | NA | Serum homocysteinemia assay |
| Systemic Disease | 4 | 23 | 17 | Transglutaminase antibodies |
| Local cause | 6 | 21 | 0 | Injected imaging + coloscopy and upper gastrointestinal endoscopy, especially in acute portal vein thrombosis |
| > 1 risk factor | 45 | 50 | 5-15 | |

Other molecular markers have also been associated with MPN. The somatic mutation of the gene encoding calreticulin (CALR), described in 2013, is found in 30 to 40% of patients with essential thrombocythemia or myelofibrosis but not in those with polycythemia vera [20,21]. Its estimated prevalence is between 0.7 and 2% in patients with splanchnic thrombosis, 2 and 7.5% in patients with MPN, and increases to 9 to 40% in patients with MPN without the JAK2 V617F mutation [22—24]. A recent study in 521 patients with splanchnic thrombosis [25] showed that all the patients with the CALR mutation as the cause of splanchnic vein thrombosis had a splenomegaly >16 cm and a platelet count >200 G/L (negative predictive value 100%).

The MPL W515 K mutation is rare [5,26] and the JAK2 exon 12 mutation has not yet been found in patients with splanchnic vein thrombosis [5,26—28].

In the 2016 World Health Organization (WHO 2016) classification, the histological criterion is a major criterion for the diagnosis of polycythemia vera, essential thrombocythemia and myelofibrosis. [15] Osteomedullary biopsy helps specify the MPN type in patients with VLD who don't have a characteristic blood cell count, and to identify MPN in JAK2 V617F-negative mutation patients. Osteomedullary biopsy confirmed the MPN diagnosis in 7 to 28% of patients with splanchnic thrombosis without the JAK2 V617F mutation [5]. Conversely, the JAK2 V617F mutation was found in 6% to 18% of patients with a normal osteomedullary biopsy. This reflects the limits of the osteomedullary biopsy because of medullary heterogeneity, sampling error and inter-individual variability of interpretation [29].

The red cell mass can help specify the type of MPN in case of masked polycythemia [5]. However, it is not useful in the absence of the JAK2 mutation with normal osteomedullary biopsy. The assessment of endogenous erythroid colony formation is no longer recommended.

## Importance of the underlying MPN diagnosis for treatment

Initial anticoagulant management of splanchnic vein thrombosis is the same with or without underlying MPN. Since the risk of heparin-induced thrombocytopenia is increased in this population, low molecular weight heparins (LMWH),

rather than unfractionated heparins (UFH), are recommended. Effective anticoagulation should be, in the absence of severe bleeding complications, a long-term treatment [30].

Some patients with splanchnic thrombosis are candidates for liver transplantation. It is important to highlight that the presence of MPN does not affect survival after liver transplantation, but increases the risk of thrombotic and hemorrhagic complications [27,31].

Secondary cardiovascular prevention with aspirin is usually indicated in patients with polycythemia vera or essential thrombocythemia. Under effective anticoagulation, the use of aspirin is controversial, due to the increase of bleeding events.

The presence of thrombosis is an indication for cytoreductive treatment in patients with MPN [32]. A combination of cytoreductive and anticoagulant treatments improves survival and decreases the risk of liver complications in patients with splanchnic thrombosis. [33] There are, however, no data on the benefit of cytoreductive therapy in patients with splanchnic thrombosis who harbor the JAK2 V617F mutation but who do not meet the criteria for MPN [14].

The proposed cytoreductive treatments are hydroxyurea, interferon alpha, or ruxolitinib [32,34]. The objective of cytoreductive treatment outside of splanchnic thrombosis is normalization of the blood cell count. The hematocrit should be reduced to < 45% and platelets to < 400 G/L [35]. During splanchnic thrombosis, the blood cell count may be normal despite confirmed MPN. In our experience, more stringent targets are often used in patients with splanchnic thrombosis taking into account hypersplenism and hemodilution: hematocrit < 42% and platelets < 250 G/L.

## Thrombophilia

There are numerous biological abnormalities that increase the thrombotic risk. The most extensively evaluated are the constitutional deficits in coagulation inhibitors: antithrombin (AT), protein C (PC), protein S (PS), factor V (FV) Leiden mutation that induces resistance to activated protein C, and the G20210A mutation of prothrombin, as well as acquired abnormalities: antiphospholipid antibodies (circulating anticoagulant (ACC), anti-beta-2-GP1 antibodies and anticardiolipids).

In patients with vascular liver disease the prevalence of constitutional deficits in coagulation inhibitors is difficult to assess because these inhibitors are decreased in case of liver injury. Moreover, PC and PS are vitamin K dependent and thus decreased during vitamin K antagonist (VKA) treatment.

According to several studies, the prevalence of AT deficiency, PC deficiency and PS deficiency varies from 0 - 5%, 4 - 20%, and 0-7%, respectively in case of BCS, and from 0 - 5%, 0-7%, and 0-30% respectively in EHPVT [2—4,36—38]. These prevalences are significantly higher than in the general population, thus deficits in AT, PC and PS are recognized as etiological factors for BCS and PVT and are usually investigated at diagnosis. However, in patients with liver impairment, the results should be interpreted in relation to the hemostatic results and the family history of thrombosis.

In patients with BCS, the prevalence of the FV Leiden mutation varies from 7% to 32% and is mostly heterozygous. Rare cases of homozygous mutation have been reported [39]. Patients with a homozygous mutation have a significantly higher risk of deep vein thrombosis than heterozygous cases, although this has not been confirmed in BCS. The prevalence of the FV Leiden mutation ranges from 3 to 9% in patients with EHPVT. Carriers of the FV Leiden mutation have an estimated 4- to 11-fold greater risk of BCS and 2—fold risk of EHPVT. Conversely, the G20210A prothrombin mutation is more frequent in EHPVT than BCS. A meta-analysis reports a 4 and 5-fold increased risk of EHPVT in G20210A prothrombin mutation carriers compared to a 2-fold risk of BCS. The reason for these differences in the prevalence of FV Leiden mutations and the prothrombin gene in EHPVT and BCS is unclear.

The prevalence of anti-phospholipid antibodies in EHPVT and BCS has been estimated to be between 5 and 15% [40]. However, the diagnostic criteria for the antibody positivity threshold are often poorly defined as are the techniques used for screening circulating anticoagulants. In addition, most studies only report the results of one test, while the diagnosis of antiphospholipid syndrome is based on the detection of anti-cardiolipin antibodies, anti-B2GP1 antibodies and/or a circulating anticoagulant of the lupus-positive type, to be confirmed in two blood samples at a 12-week interval.

Other less frequently investigated abnormalities have been described such as increased factor VIII in patients with EHPVT [40,42], increased thrombin generation during splanchnic thrombosis whatever the underlying prothrombotic factor [42,43], and fibrinolysis abnormalities.

## Paroxysmal nocturnal hemoglobinuria (PNH)

PNH is a rare condition with an estimated prevalence of 1/80,000 in France. PNH is due to a clonal somatic mutation of the PIGA gene in one or more hematopoietic stem cells. This mutation is responsible for a partial or complete deficiency in the synthesis of the glycosylphosphatidylinositol anchor (GPI) and thus for defective expression of a certain number of proteins on the hematopoietic cell surface. The expansion of this PNH clone occurs in association with a hematological disease (idiopathic aplastic anemia, and more rarely, myelodysplastic or myeloproliferative syndrome). These proteins include CD59 and CD55, which regulate the effector phase of the complement cascade. The deficiency of these 2 proteins on the surface of erythrocytes is responsible for intravascular hemolysis with hemoglobinuria. While hemolysis is permanent, paroxysms may occur especially in case of infection. While anemia and dystonia related to intravascular hemolysis are responsible for impaired quality of life, the particularly poor prognosis without treatment of this disease is related to the arterial and venous thrombosis observed in 30% of untreated patients. The pathophysiology of thrombosis has not been fully clarified and is multifactorial: hemolysis plays an important role and treating this condition reduces the thrombotic risk [44].

BCS accounts for 50% of the thrombotic events in PNH patients in the absence of treatment with eculizumab (Soliris®). The risk of death in these patients is 15 times

higher than in those without thrombosis. Receiving anticoagulant therapy before eculizumab was considered a risk factor and was not protective of thrombosis [45]. Recent data including patients managed with eculizumab show that the cumulative incidence of thrombotic events has been reduced to 0.8 - 3% [46]. Data from the three eculizumab registration studies have shown that this agent reduces the risk of the extension and recurrence of thrombosis. The occurrence of thrombosis in a patient with PNH is an indication to begin emergency eculizumab [47].

The prevalence of PNH in patients with BCS varies from 1.4 to 19% depending on the series and countries [2,48]. The prevalence of other forms appears to be much lower. Patients with BCS and PNH have more pronounced cytopenia, higher levels of lactate dehydrogenase (LDH) and more frequent portal or splanchnic thrombosis [49]. The PNH clone should be systematically evaluated in BCS because hemolysis may be difficult to interpret in patients with portal hypertension and liver failure. Thrombosis is an absolute indication for treatment with eculizumab [47]. Anticoagulant therapy alone does not reduce the thrombotic risk in patients with PNH [45].

Recent unpublished data from a multicenter cohort of 54 patients with PNH and BCS have shown that these patients have frequent thrombosis outside the splanchnic vascular bed as well as bleeding and severe septic complications. Patients treated with eculizumab in these cases have significantly better survival, less hemolysis and fewer complications of liver disease [50].

## What are the other identified risk factors in adults [51]?

### Overview

A familial or personal past history of thrombosis has been identified as a risk factor for deep vein thrombosis. This increases the risk of thrombosis by two fold [52]. Few studies have analyzed this in the presence of EHPVT or BCS. However, two studies on acute and chronic EHPVT have reported that 14 to 30% of patients had a personal or family history of extrasplanchnic thrombosis [3,53]. Similar results were reported in mesenteric thrombosis [54].

In a recent Italian epidemiological study [55], portal vein thrombosis was more frequent in older men, while there was no gender difference for BCS. Conversely, most epidemiological studies report a predominance of women with a male/female ratio of 2/3 in BCS.

The association of BCS with oral contraception was evaluated in two studies during two different periods: 1970-1983 (OR 2.37, 95% CI (1.05-5.34)) and 1985-2000 (OR 2,4, 95% CI (0.9-6.2)). Oral contraception was associated with an increased risk of thrombosis of the hepatic veins at a time when the estrogen content was much higher than it is at present. The impact of pregnancy as a causal factor is higher in BCS (because of the chronological relationship) than extrahepatic portal vein thrombosis.

Finally, central obesity and metabolic syndrome are risk factors for idiopathic EHPVT. In one study, the group of patients with idiopathic EHPVT had an increased abdominal circumference (105 cm) and an increased prevalence of metabolic syndrome (47%) compared to the EHPVT group from other causes (abdominal circumference 93 cm; metabolic syndrome, 26%) and to a control population (abdominal circumference 92 cm; metabolic syndrome, 18%) [56]. Similarly, in a recent epidemiological study, 50% of the patients with idiopathic BCS had a BMI (Body Mass index) > 25 $kg/m^2$ compared to only 27% when a cause was identified [57].

### Local risk factors

A local risk factor (splanchnic territory infection, splanchnic territory inflammation, splanchnic territory surgery, splanchnic territory cancer..) is common and often associated with a systemic risk factor in EHPVT. Conversely, local risk factors are not identified in most cases of BCS. Closed abdominal trauma, amoebic and bacterial abscess or polycystic liver disease may be risk factors for primary BCS. However, these local factors are only present in a minority of patients with thrombosis of the hepatic veins or vena cava.

The predisposition for hepatic vascularization in certain vascular diseases suggests local action on these vessels in certain diseases such as MPN, PNH or Behçet's disease. In MPN, the arguments for local action in hepatic venous endothelial cells are:

- a significantly higher prevalence of JAK2 V617F and MPN in the splanchnic veins other than deep vein thrombosis;
- The JAK2 mutation is present in the endothelial cells of patients with JAK2 V617F MPN, in particular the hepatic veins [58].

### Rare acquired diseases

Other possible risk factors for vascular liver disease include rare acquired diseases such as Behçet's disease, hypereosinophilic syndromes, granulomatous venulitis, ulcerative colitis, and celiac disease.

### Behçet's disease

BCS occurs in 2.4% of patients with Behçet's disease. There is a higher prevalence of Behçet's disease associated BCS in the Mediterranean basin which is found in 5, 9% and 13% of cases of BCS in Western Europe, Turkey and Egypt, respectively. The diagnosis of Behçet's disease is particularly difficult. Male gender, involvement of the inferior vena cava, other venous or arterial localizations, and a persistent inflammatory syndrome are strongly associated with the diagnosis in BCS.

The HLA B 51 allele is not a specific diagnostic marker because it is present in 20% of the general population and in only 50% of patients with Behçet's disease. Corticosteroids and immunosuppressive therapy can treat the complications of vasculitis. It must be discussed quickly because it improves the prognosis of patients and most often allows postponement of more invasive vascular management [59].

## Celiac disease

The diagnosis of celiac disease is frequent in North Africa, and identified in 11% of patients with BCS. There are arguments for a positive impact of the gluten-free diet on the progression of liver disease [60].

## Viral infections and toxic exposures

Some viral infections are associated with vascular liver diseases such as cytomegalovirus (CMV) infection, associated with EHPVT, or human immunodeficiency virus (HIV) infection frequently associated with PSD and EHPVT [61]. The first hypothesis to explain the HIV/PSD association is exposure to didanosine, an antiretroviral drug whose prolonged use has been associated with the development of PSD through suspected mitochondrial toxicity [62]. The second pathophysiological hypothesis is an acquired decrease in protein S activity, targeted by autoantibodies, which contributes to the venopathy of PSD [61].

In addition to didanosine, exposure to certain agents, such as 6-mercaptopurine, azathioprine, oxaliplatin and arsenic have been associated with the development of PSD. A direct correlation has not been found for purine analogues which are most often administered for the treatment of chronic inflammatory bowel disease. In addition to HIV infection, other immune problems including common variable immune deficiency and various autoimmune diseases have also been associated with PSD [63].

## Identified genes that may be associated with vascular liver disease

A French pediatric series of porto-sinusoidal disease reports 40% of associated syndromic diseases (Noonan syndrome, Turner syndrome,..) and 16% of familial involvement, some with nonsense mutations of Notch1, a gene involved in vascular remodeling [64,65] (Table 2). A recent study of two families, including 6 patients with porto-sinusoidal disease, reports a new mutation of the familial obliterative portal venopathy ''FOPV'' gene located in chromosome 4, with incomplete penetrance and variable expressivity [66].

In adults, porto-sinusoidal diseases are also reported in association with syndromic diseases such as Turner syndrome, genetic diseases such as cystic fibrosis, but also congenital dyskeratosis subtypes due to defective telomerase function [67,68].

Specific mutations should be assessed in patients with suggestive clinical phenotypes: Small size, infertility for Turner's syndrome, pulmonary, pancreatic or familial history of cystic fibrosis, thrombocytopenia, pancytopenia, macrocytosis, pulmonary fibrosis, dyskeratosis, early fracture osteoporosis, unexplained hypergammaglobulinemia, premature graying, for telomerase gene mutations.

**Table 2** Genetic abnormalities associated with MPN.

| Disease | Diagnosis | Symptoms |
|---|---|---|
| Turner [69] | Karyotype | Small size, infertility |
| Cystic Fibrosis [68] | CFTR gene, chromosome 7 | Pulmonary disease, pancreatic insufficiency or family history of cystic fibrosis |
| Defective telomerase function [67] | Genes: DKC1,TERC,TERT, TINF2,RTEL1,PARN,. Short telomere | Thrombocytopenia, pancytopenia, macrocytosis, pulmonary fibrosis, dyskeratosis, early osteoporosis, unexplained hypergammaglobulinemia, early hair greying/loss |
| Familial obliterative portal venopathy [66] | FOPV gene chromosome 4 | Familial MPN |

## What are the risk factors in children?

In contrast to adults, constitutional deficiencies in coagulation inhibitors such as protein C or S and antithrombin and acquired abnormalities (antiphospholipid antibody syndrome) appear to be rare in children. However, very few studies have been performed. A decrease in anticoagulant factors is difficult to interpret but seems to be more often acquired and secondary to thrombosis than primary [70—72]. Most vascular liver diseases are primary or congenital. The most common, although rare, diseases (Table 3) are:

- congenital porto systemic shunts, sometimes associated with other cardiac or vascular malformations, heterotaxis, polysplenia.. [73,74];
- extrahepatic PVT with the development of a cavernoma, most commonly neonatal umbilical vein catheterization. In these cases, the risk of EHPVT is increased by improper positioning of the catheter in the portal vein, blood transfusion or infusion of a hypertonic solution via the catheter, and the occurrence of infectious complications [70,71,76]. No cause is identified in approximately 50% of cases [77];
- porto-sinusoidal diseases (including OPV) whose causes in children are either genetic, including a newly identified OPV of autosomal dominant transmission related to mutations of the Familial Obliterative Portal Venopathy (FOPV) gene on chromosome 4 [78], or syndromic (Turner, Noonan, Adams Olliver syndromes (associated with Notch1 mutations) and the short telomere syndrome) [79—82]. OPV has also been observed in some children with cystic fibrosis [83];
- sinusoidal obstruction syndrome is toxic or drug-induced like in adults. There are, however, rare forms of the disease associated with T- and B- combined immunodeficiency linked to mutations in the SP110 gene of autosomal recessive transmission [84];

**Table 3** Risk factors for vascular liver diseases in children.

| Vascular Liver Diseases in children | Estimated incidence | Causes or Predisposing Factors |
|---|---|---|
| Congenital porto-systemic shunt | 1/30 000 | Malformative<br>Isolated<br>Or associated with congenital malformations: Heterotaxy, congenital heart diseases, polysplenia syndrome (with or without associated biliary atresia) |
| Exrahepatic Portal vein thrombosis (cavernoma) | 1,3/100 000 | Local cause:<br>Umbilical vein catheterization (30-40% of cases); Sepsis, omphalitis<br>Associated congenital malformations (17-24%)<br>Abnormal development of the portal vein (?)<br>Constitutional deficiency in coagulation inhibitors, (rare)<br>Splenectomy, abdominal surgery, pancreatitis |
| Obliterative Portal venopathy | No epidemiological data | Genetic: familial recurrence (FOVP, others)<br>Abnormal development of the portal vein?<br>Syndromic: Turner, Noonan, Adams Oliver, short telomeres.<br>Constitutional deficiency in coagulation inhibitors (rare) |
| Sinusoidal obstruction syndrome | No epidemiological data<br>1/2 500 in the Lebanese popuation | Toxic and drug induced (chemotherapy, immune suppressors, conditioning treatment for bone marrow transplant)<br>Genetic: associated with a combined T and B immune deficiency linked to mutations of SP110. |
| Budd Chiari syndrome | No epidemiological data | Constitutional deficit in coagulation inhibitors<br>Myeloproliferative Disease, Paroxysmal nocturnal hemoglobinuria, Behçet's disease<br>Local or malformative cause? |

- BCS is very rare in children and requires the same etiological investigations as in adults including a search for a prothrombotic promoting factor, a myeloproliferative disorder (JAK2 V617F mutation) and paroxysmal nocturnal hemoglobinuria, although this is rare children [71,85,86], and Behçet's disease in young adolescents.

## Conclusion

The identification of one or more etiological factors is crucial because when it can be treated, it improves the prognosis of liver injury and limits the risk of recurrence or the extension of thrombosis [33,59].

## Recommendations

In the case of BCS or EHPVT, the local and systemic risk factors listed in Table 1 should be looked for. The identification of a risk factor should not prevent searching for others (A1).

Refer patients with BCS or EHPVT to a specialist in thromboembolic diseases and hemostasis (A1).

Interpret abnormalities of coagulation tests in relation to non-specific changes induced by liver disease and portal hypertension (A1).

Screen for the JAK2 V617F mutation in all VLD patients (A1). Screen for the PNH clone in all patients with BCS (A1) and non-cirrhotic-associated EHPVT (B2).

Refer patients with BCS or EHPVT to a hematologist and/or an internist, even in the absence of blood cell count abnormalities or a JAK2 V617F mutation (A1).

Implement the management of risk factors without delay (B1).

Adapt contraception and anticipate questions regarding pregnancy (B2).

Discuss the discontinuation or continuation of anticoagulation in a multidisciplinary consultation, according to risk factor(s), to location of thrombosis and comorbidities (B1).

Provide information on patient associations as early as possible. Refer to social support initiatives and possibilities as appropriate (C2).

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